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## Paternal age and schizophrenia: a population based cohort study

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### Abstract

**Objective** To investigate the association of paternal age at conception with the risk of offspring developing schizophrenia.

**Design** A population based cohort study.  
**Setting** Sweden.

**Subjects** 754 330 people born in Sweden between 1973 and 1980 and still alive and resident in Sweden at age 16 years.

**Main outcome measures** Hospital admission with schizophrenia or non-schizophrenic non-affective psychosis.

**Results** After adjustment for birth related exposures, socioeconomic factors, family history of psychosis, and early parental death the overall hazard ratio for each 10 year increase in paternal age was 1.47 (95% confidence interval 1.23 to 1.76) for schizophrenia and 1.12 (0.98 to 1.29) for non-schizophrenic non-affective psychosis. This association between paternal age and schizophrenia was present in those with no family history of the disorder (hazard ratio for each 10 year increase in paternal age 1.60, 1.32 to 1.92), but not in those with a family history (0.91, 0.44 to 1.89) (P = 0.04 for interaction).

**Conclusions** Advancing paternal age is an important independent risk factor for schizophrenia. The stronger association between paternal age and schizophrenia in people without a family history provides further evidence that accumulation of de novo mutations in paternal sperm contributes to the overall risk of schizophrenia.

### Introduction

There is growing evidence that factors operating at different points in life contribute to an individual's risk of developing schizophrenia. Recent research interest has focused on the influence of paternal age at conception.<sup>1-6</sup> Advancing paternal age is known to be associated with several other disorders,<sup>7</sup> including cancer<sup>8-9</sup> and achondroplasia,<sup>10</sup> and is thought to be due to the age associated increase in sporadic de novo mutations in male germ cells.<sup>11</sup> One study estimated that about a quarter of cases of schizophrenia could be attributed to paternal age.<sup>5</sup> It has been suggested that if this association between paternal age and schizophrenia was due to accumulating de novo mutations,

sporadic cases of schizophrenia should show a stronger association with increased paternal age compared with cases in people with a known family history of the disorder.<sup>12</sup> Using a large Swedish record linkage database, we investigated the association between paternal age and schizophrenia in offspring. We also investigated whether any associations differed in relation to family history, sex, birth weight, and Apgar score. We investigated the latter two because they have been identified as possible environmental risk factors,<sup>13-14</sup> and it has been hypothesised that in the presence of genetic predisposition, exposure to such factors may lead to the clinical manifestation of schizophrenia.<sup>15-16</sup>

### Method

#### Sample

Our cohort comprised 754 330 people born in Sweden between 1973 and 1980 and still alive and resident in Sweden at the age of 16 years. Information on the study sample was obtained from linkage between Sweden's medical birth registry, its population and housing census of 1990, its inpatient discharge register (up to 31 December 2001), and its cause of death and emigration registers (up to 31 December 2001). Our analysis was based on records of people admitted to hospital between 1989 and 2001 with a diagnosis of schizophrenia (international classification of diseases, 10th revision, ICD-10: F20; ninth revision, ICD-9, Swedish version: all 295 except 295F and 295H) or other non-affective psychosis (ICD-10: F21-29; ICD-9 Swedish version: 295F, 295H, 297-8) (see table A on bmj.com).

Overall, 42 316 (5.6%) people were excluded from the main analysis because of missing data, or because they developed schizophrenia (68 cases) or other non-affective psychosis (141 cases) before the age of 16 years.

#### Variables examined

We examined the influence of seven possible confounding factors on the associations with paternal age. We controlled for: sex; calendar year; maternal age; place of birth; obstetric complications and fetal growth; family



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Two extra tables of data can be found on bmj.com

history of psychosis; and socio-economic position. For details of the variables used see [bmj.com](http://bmj.com).

### Data analysis

All statistical analysis was performed with Stata Release 8.0 (StataCorp, College Station, TX). We used Cox's proportional hazards models to assess the influence of paternal age on psychosis. People were censored at the time of first admission for schizophrenia, non-schizophrenic non-affective psychosis, death, or emigration. We used the cluster option in Stata to adjust standard errors for clustering of cases within families. We controlled all reported hazard ratios for sex, age, and maternal age, unless otherwise specified or stratified by sex. We tested the validity of the proportional hazards assumption graphically and used Wald tests to investigate interaction effects.

## Results

### Parental age

Subjects were followed up for a mean of nine years after the age of 16 years. During this follow up period 639 (0.09%) were admitted with a diagnosis of schizophrenia and 1311 (0.18%) with a diagnosis of non-schizophrenic non-affective psychosis. The estimated annual incidence rates were 0.10 and 0.21 per 1000 person years, respectively.

Table 1 shows the characteristics of subjects in relation to the age of their father. People with older fathers tended also to have older mothers and mothers who had had more pregnancies. People with older fathers were more likely to lose their parents before they reached the age of 18 years; they were more likely to have a family history of psychosis; and their parents were more likely to come from extreme ends of the distribution of the various measures of socioeconomic position.

Table 2 shows the hazard ratios for successive five year paternal age groups. In the basic model, adjusted for sex, age, and maternal age, there is a clear increase in the risk of schizophrenia with increasing paternal age. There is a suggestion that the offspring of younger fathers (<21 years) are also at somewhat greater risk than those with fathers aged 21-24 years (hazard ratio 1.34, 95% confidence interval 0.74 to 2.43), but there was no evidence of a non-linear association between paternal age and schizophrenia ( $P=0.39$ , quadratic). The strength of the association between paternal age and schizophrenia was only modestly reduced when controlled for possible confounding factors. The variable mostly responsible for this reduction was highest annual parental income.

Table 3 shows the results for the same series of models for non-schizophrenic non-affective psychosis. Overall, we found a much weaker association.

Maternal age showed a weak association with schizophrenia in the unadjusted model, but this association disappeared as soon as we controlled for paternal age, sex, and age (0.83, 0.64 to 1.07) (see table B on [bmj.com](http://bmj.com)). We found a similar pattern for non-schizophrenic non-affective psychosis. We calculated that the population attributable fraction of schizophrenia in this sample due to having a father aged >30 years at birth was 15.5%.

**Table 1** Characteristics of subjects according to paternal age groups. Figures are number (percentage) unless stated otherwise

	<30 years	30-39 years	≥40 years
Total	374 783 (52.6)	299 707 (42.1)	37 524 (5.3)
Schizophrenia	291 (0.08)	297 (0.10)	51 (0.14)
Non-schizophrenic non-affective psychosis	652 (0.17)	572 (0.19)	87 (0.23)
Male	192 411 (51.3)	153 794 (51.3)	19 138 (51.0)
Mean maternal age (SD) at birth (years)	24.30 (3.48)	29.70 (3.83)	34.26 (4.89)
Mean (SD) birth weight (g)	3475 (525)	3525 (541)	3519 (568)
Mean (SD) gestational age (weeks)	39.8 (1.8)	39.7 (1.8)	39.5 (1.8)
Season of birth:			
Winter	88 804 (23.7)	69 883 (23.3)	8 990 (24.0)
Spring	107 170 (28.6)	86 852 (29.0)	10 203 (27.2)
Summer	94 195 (25.1)	73 791 (24.6)	9 336 (24.9)
Autumn	84 614 (22.6)	69 181 (23.1)	8 995 (24.0)
Place of birth:			
Main cities and suburbs	97 662 (26.1)	89 858 (30.0)	11 208 (29.9)
Large cities and industry	237 286 (63.3)	177 743 (59.3)	21 389 (57.0)
Rural areas	39 835 (10.6)	32 106 (10.7)	4 927 (13.1)
Apgar score ≤6 at one minute	15 407 (4.1)	11 028 (3.7)	1 563 (4.2)
Parity of mother:			
1	213 752 (57.0)	83 645 (27.9)	9 246 (24.6)
2	130 110 (34.7)	129 786 (43.3)	11 357 (30.3)
≥3	30 921 (8.3)	86 276 (28.8)	16 921 (45.1)
Twin or multiple birth	5 320 (1.4)	5 294 (1.8)	754 (2.0)
Parent or sibling admitted with schizophrenia	1 670 (0.5)	1 527 (0.5)	312 (0.8)
Parent or sibling admitted with schizophrenia or non-schizophrenic non-affective psychosis	6 350 (1.7)	5 909 (2.0)	1 120 (3.0)
Father died before subject was aged 18	5 706 (1.5)	6 968 (2.3)	2 984 (8.0)
Mother died before subject was aged 18	2 665 (0.7)	3 391 (1.1)	639 (1.7)
Highest parental annual income*:			
<Kr100 000	18 720 (5.0)	13 532 (4.5)	4 199 (11.2)
Kr100 001-200 000	206 525 (55.1)	140 371 (46.8)	20 220 (51.6)
Kr200 001-300 000	116 983 (31.2)	103 040 (34.4)	9 815 (25.3)
>Kr300 000	32 555 (8.7)	42 764 (14.3)	3 290 (11.0)
Highest parental socioeconomic status:			
Blue collar	123 963 (33.1)	72 635 (24.2)	12 404 (33.1)
White collar	204 793 (54.6)	187 219 (62.5)	19 175 (51.1)
Self employed	42 409 (11.3)	37 514 (12.5)	5 304 (14.1)
Other	3 618 (1.0)	2 339 (0.8)	641 (1.7)
Highest parental education:			
<9 years	15 433 (4.1)	31 411 (10.5)	8 641 (23.0)
9-10 years	54 461 (14.5)	32 649 (10.9)	3 889 (10.4)
Full secondary school	187 186 (50.0)	110 398 (36.8)	12 150 (32.4)
Higher	117 703 (31.4)	125 249 (41.8)	12 844 (34.2)

\*Kr100 000=£7467, \$13 238, €10 953.

### Association with family history, sex, birth weight, Apgar scores, and age of onset

Associations with paternal age differed in those with and without a family history of schizophrenia ( $P=0.04$  for interaction). The hazard ratio for every 10 years of paternal age was 1.60 (1.32 to 1.92) in those with no family history of schizophrenia and 0.91 (0.44 to 1.89) in those with an affected first degree relative.

We found no strong evidence for any marked difference in the association between paternal age and schizophrenia by sex ( $P=0.20$  for interaction) or by birth weight ( $P=0.15$  for interaction). The association of paternal age with schizophrenia, however, differed in relation to the subjects' Apgar score at birth ( $P=0.02$  for interaction). In those with normal Apgar scores (7-10) at one minute hazard ratios increased by 1.60 for every 10 years of paternal age (1.33 to 1.92) but not in those with Apgar scores suggestive of the need for resuscitation (hazard ratios decreased by 0.92, 0.31 to 2.76).

**Table 2** Hazard ratios (with 95% confidence intervals) of schizophrenia in relation to paternal age (n=639 cases of schizophrenia)

	No of cases	Model 1: controlled for sex, age, and maternal age	Model 2: as model 1 plus birth related factors*	Model 3: as model 2 plus parental death and family history of schizophrenia	Model 4: as model 3 plus socioeconomic variables†
Paternal age groups (years):					
<21	15	1.34 (0.75 to 2.43)	1.33 (0.73 to 2.39)	1.33 (0.74 to 2.40)	1.31 (0.73 to 2.36)
21-24	72	1.00	1.00	1.00	1.00
25-29	204	1.22 (0.91 to 1.64)	1.24 (0.92 to 1.68)	1.25 (0.93 to 1.68)	1.26 (0.93 to 1.69)
30-34	194	1.62 (1.15 to 2.28)	1.67 (1.19 to 2.36)	1.66 (1.18 to 2.34)	1.66 (1.18 to 2.34)
35-39	103	2.33 (1.57 to 3.46)	2.42 (1.62 to 3.60)	2.37 (1.60 to 3.53)	2.32 (1.56 to 3.44)
40-44	32	2.23 (1.33 to 3.73)	2.30 (1.38 to 3.85)	2.22 (1.33 to 3.71)	2.08 (1.25 to 3.46)
45-49	7	1.50 (0.64 to 3.47)	1.53 (0.66 to 3.56)	1.47 (0.63 to 3.41)	1.30 (0.56 to 3.06)
≥50	12	5.85 (2.91 to 11.74)	5.85 (2.92 to 11.73)	5.46 (2.68 to 11.11)	4.62 (2.28 to 9.36)
Change per 10 year increase in paternal age	—	1.56 (1.30 to 1.88)	1.58 (1.32 to 1.89)	1.54 (1.29 to 1.85)	1.47 (1.23 to 1.76)

\*Birth weight, birth length, gestational age, place of birth, season, Apgar score at one and five minutes, parity, multiple birth.

†Three measures from Swedish housing and population census 1990: highest annual income of either parent, highest socioeconomic index of either parent, highest educational level of either parent.

## Discussion

Our findings confirm an association between increased paternal age and schizophrenia in offspring, which remained even after we controlled for a wide range of potential confounding factors. The association seems to be relatively specific to schizophrenia compared with non-schizophrenic non-affective psychosis and was stronger in those with no family history of the disorder and those with normal Apgar scores at birth.

### Strengths and weaknesses of study

We used routinely recorded data on variables related to birth, parents, and adulthood collected before the onset of disease. Furthermore, as cases were ascertained from a national inpatient register the possibility of selection bias was reduced. The large number of cases gives us statistical power to control for a wide range of important confounding factors and investigate whether the associations differ in relation to family history of psychosis or environmental risk factors.

The main limitation of our analysis is that case ascertainment was based on people admitted to hospital only with diagnoses recorded on an administrative database. Though we will have missed people who were not admitted to hospital, studies in the United Kingdom indicate that in the first three years after presentation over 80% of patients are admitted, even in areas with community oriented

services.<sup>17</sup> Furthermore, analyses of diagnoses recorded on the Swedish inpatient discharge register indicate that schizophrenia is diagnosed with reasonable accuracy.<sup>18,19</sup> Another limitation is that a family history of admission with schizophrenia is only a marker for and not the equivalent of genetic vulnerability.

### Comparison of findings with earlier research

In comparing our findings with those of earlier studies<sup>1-3,5,6</sup> it is important to bear in mind that we were able to distinguish between narrowly defined schizophrenia (ICD-10 F20) and other non-schizophrenic non-affective psychosis (ICD-10 F21-29). One previous study<sup>1</sup> also reported a stronger association with paternal age in relation to narrowly defined schizophrenia.

We found a pattern of association across the categories of paternal age that suggested a J shaped rather than a linear association, in line with the initial unadjusted findings of Byrne et al.<sup>2</sup> In our study this pattern remained even after we controlled for possible confounders. Two other studies also investigated the possibility that family history may modify the risk associated with paternal age. Malaspina et al showed that paternal age was significantly higher for people with schizophrenia without a family history in a small study that compared 35 familial cases with 68 sporadic cases.<sup>12</sup> Zammit et al found no evidence for such effects, but their study lacked statistical power.<sup>6</sup>

**Table 3** Hazard ratios (with 95% confidence intervals) of non-schizophrenic non-affective psychosis in relation to paternal age (n=1311 cases of non-schizophrenic non-affective psychosis)

	No of cases	Model 1: controlled for sex, age, and maternal age	Model 2: as model 1 plus birth related factors*	Model 3: as model 2 plus parental death and family history of schizophrenia	Model 4: as model 3 plus socioeconomic variables†
Paternal age groups (years):					
<21	35	1.58 (1.04 to 2.41)	1.56 (1.03 to 2.37)	1.57 (1.04 to 2.38)	1.55 (1.02 to 2.35)
21-24	168	1.00	1.00	1.00	1.00
25-29	449	0.99 (0.82 to 1.20)	1.01 (0.83 to 1.22)	1.01 (0.83 to 1.22)	1.01 (0.83 to 1.22)
30-34	404	1.15 (0.92 to 1.44)	1.19 (0.95 to 1.49)	1.17 (0.93 to 1.46)	1.17 (0.94 to 1.46)
35-39	168	1.29 (0.98 to 1.69)	1.34 (1.02 to 1.77)	1.28 (0.98 to 1.68)	1.27 (0.97 to 1.66)
40-44	49	1.18 (0.81 to 1.73)	1.24 (0.85 to 1.81)	1.14 (0.78 to 1.66)	1.10 (0.75 to 1.60)
45-49	30	2.30 (1.47 to 3.59)	2.37 (1.52 to 3.70)	2.15 (1.38 to 3.35)	2.00 (1.60 to 3.11)
≥50	8	1.40 (0.68 to 2.89)	1.40 (0.68 to 2.90)	1.12 (0.54 to 2.32)	1.01 (0.49 to 2.10)
Change per 10 year increase in paternal age	—	1.19 (1.03 to 1.38)	1.22 (1.06 to 1.41)	1.15 (1.00 to 1.32)	1.12 (0.98 to 1.29)

\*Birth weight, birth length, gestational age, place of birth, season, Apgar score at one and five minutes, parity, multiple birth.

†Three measures from Swedish housing and population census 1990: highest annual income of either parent, highest socioeconomic index of either parent, highest educational level of either parent.

### What is already known on this topic

Increased paternal age is associated with several diseases, possibly due to the age associated increase in sporadic de novo mutations in male germ cells

Several studies have reported an association between paternal age at conception and their offspring's risk of schizophrenia

If this association was due to de novo mutations one would expect to find a stronger association between paternal age and schizophrenia in cases with no family history of the disorder

### What this study adds

There is a strong positive association between paternal age and schizophrenia that is not due to sociodemographic, birth related, or socioeconomic factors or family history or early parental death

Paternal age is only weakly associated with other non-schizophrenic non-affective psychosis

This association is stronger in those with no family history of schizophrenia, supporting the hypothesis that accumulating de novo mutations in the germ lines of older fathers could play an important part in the aetiology of schizophrenia

### Conclusions

Our findings confirm advancing paternal age as a strong independent risk factor for schizophrenia and indicate that 15.5% of cases of schizophrenia in our cohort could be due to the patient having a father who was aged >30 years at birth. We found a stronger association in subjects without a family history of schizophrenia, providing further evidence to support the theory that accumulating de novo mutations in the germ cells of older fathers might contribute to an increased risk of schizophrenia in their offspring.

In England and Wales the average paternal age has increased from 29.2 years in 1980 to 32.1 in 2002.<sup>20</sup> Assuming a background annual incidence rate for schizophrenia of 10/100 000<sup>21</sup> and that the association is causal, our results suggest that the increase in paternal age since 1980 could account for 710 out of the 6633 new cases of schizophrenia diagnosed in the United Kingdom in 2002.

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### Corrections and clarifications

#### *ABC of preterm birth: Immediate care of the preterm infant*

A drug dosage cited in this article by Peter W Fowle and William McGuire substantially understated the correct dose (9 October, pp 845-8). In the box entitled "Drugs used in acute resuscitation of the preterm infant" (p 847), we correctly stated that the dosage of dextrose (in needed) is 2.5 ml/kg, but the amount of 10% dextrose to be given is in fact 250 mg/kg (not 250 µg/kg, as was stated).

#### *The PROGRESS trial three years later: time for more action, less distraction (commentary)*

A misspelling of someone's name was not picked up until after this commentary by Stephen MacMahon and colleagues had gone to press (23 October, p 970-1). In the contributors section, Jeffrey Cutler's name was misspelt.

#### *Second drug firm found guilty of "switching" patients to new drugs*

GlaxoSmithKline (GSK) wishes to point out that, contrary to what was reported in the opening section of this news article by Zosia Kmietowicz (16 October, p 875), the Airways Integrated Management Service (AIMS) was not found in breach of the Code of Practice of the Prescription Medicines Code of Practice Authority (set up by the Association of British Pharmaceutical Industry). GSK has not been told to withdraw the service. However, as was stated later in the article in a statement from GSK, "GSK accepts that the materials used to introduce [AIMS] to practices were, although unintentionally, in breach of the Code of Practice and has agreed to withdraw these materials." The company affirms that it has now withdrawn the materials and that it remains fully committed to the spirit and the letter of the Code of Practice.