Parental Age and Risk of Schizophrenia

A Case-control Study

Majella Byrne, MSc, PhD; Esben Agerbo, MSc; Henrik Ewald, MD, DMSc; William W. Eaton, PhD; Preben Bo Mortensen, MD, DMSc

Background: Advanced paternal age has been suggested as a possible risk factor for schizophrenia. It is not known whether this is explained by known risk factors for schizophrenia, including sibship characteristics, death of a parent before first hospital admission, season and place of birth, and family history of psychiatric illness, or by socioeconomic factors. We investigated the risk of schizophrenia associated with parental age, adjusting for known risk factors for schizophrenia, including family psychiatric history, and controlling for socioeconomic and demographic factors.

Methods: We performed a national population, nested, case-control study based on Danish longitudinal register data. The sample included 7704 patients with an ICD-8 or ICD-10 diagnosis of schizophrenia admitted to a psychiatric facility between 1981 and 1998 in Denmark, and 192,590 individually time-, age-, and sex-matched population controls, their parents, and siblings. The risk of schizophrenia associated with increasing parental age was investigated using conditional logistic regression and controlling for family socioeconomic and demographic factors and family psychiatric history.

Results: Advanced paternal and maternal age was associated with increased risk of schizophrenia in univariate analyses. Controlling for socioeconomic factors and family psychiatric history, increased risk of schizophrenia was identified in those with a paternal age of 50 years or older. Sex-specific analyses revealed that the risk of schizophrenia was increased for males with fathers 55 years or older (incidence rate ratio [IRR], 2.10; 95% confidence interval [CI], 1.35-3.28); for females, the risk associated with paternal age was substantial for fathers aged 50 to 54 years (IRR, 2.22; 95% CI, 1.44-3.44) and 55 years or older (IRR, 3.53; 95% CI, 1.82-6.83).

Conclusion: Increased risk of schizophrenia was associated with advanced paternal age, particularly in females, lending support to the theory that de novo mutations, possibly X-linked, associated with increased parental age might be responsible for some cases of schizophrenia.

Arch Gen Psychiatry. 2003;60:673-678

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be explained by any of the identified risk factors for schizophrenia, including family psychiatric history, sibship characteristics, death of a parent before admission, season of birth, and place of birth, while assessing the possible confounding or modifying effect of socioeconomic factors (parental wealth, education, and marital status).

METHODS

The data were based on Danish longitudinal registers that were merged using a unique personal identification number known as the CPR (central person registration) number, which 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. Parents’ date of birth was identified through the CPR register.

The Danish Psychiatric Central Register has monitored all psychiatric inpatient facilities in Denmark since 1969. There are no private psychiatric facilities in Denmark, and all treatment is free of charge. All diagnoses were according to International Classification of Diseases, 8th Revision (ICD-8) until December 31, 1993, and according to International Classification of Diseases, 10th Revision (ICD-10) beginning January 1, 1994. Parental and sibling psychiatric information relates to the status just before the date of first contact of the case. In this manner, only family members who are affected before this date contribute information to the calculation of the risk associated with family history.

The socioeconomic data were obtained from the Integrated Database for Longitudinal Labour Market Research, which includes linked information on employees and establishments and for which there is continuous annual information available from 1980 to 1998. The register covers the total population and includes detailed socioeconomic information. We obtained information on parental education, wealth status, and marital status. We also obtained information on number of siblings as a proxy for family size. For our purposes, a random 5% 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 extracted.

STUDY DESIGN

A time-matched, nested, case-control design was used to select the control sample. For each case, 25 controls were randomly selected from a subsample of all available controls fulfilling the matching criteria: born in the same calendar year, same age in days, same sex, no admissions to a psychiatric facility in Denmark, and alive on the date that the case was first admitted.

STUDY POPULATION

The study sample was composed of all persons older than 15 years admitted to a Danish psychiatric facility for the first time between 1981 and 1998 with a diagnosis of schizophrenia and known maternal identity. A total of 7704 persons with schizophrenia were identified, 92% had links to a father (that is, paternity was not known or declared in 8%), and 66% were male. The control sample consisted of 192,590 individuals, representing 25 controls per case. Of the controls, 96% had links to a father.

PARENTAL AGE

We defined parental age in a similar manner to Malaspina et al. Paternal age was categorized into the following age groups: younger than 20 years, 20 through 24 years, 25 through 29 years, 30 through 34 years, 35 through 39 years, 40 through 44 years, 45 through 49 years, and 50 years or older. Maternal age was defined as younger than 20 years, 20 through 24 years, 25 through 29 years, 30 through 34 years, 35 through 39 years, and 40 years or older. Because we had a substantial number of patients and controls, we were in a position to investigate the effect of paternal and maternal age on the risk for schizophrenia in greater detail than Malaspina et al. We extended the age categories to 50 through 54 years and 55 years or older for paternal age and 40 through 45 years and 45 years or older for maternal age.

FAMILY PSYCHIATRIC HISTORY

It was possible to obtain information relating to family history of psychiatric contact for mothers, fathers, and siblings by linking with the Danish Psychiatric Central Register. In line with previous studies using similar data, history of psychiatric disorders in family members was defined in a hierarchical manner as follows: (1) schizophrenia, schiz-affective disorder, and schizophrenia-like psychosis (ICD-8 codes: 295, 295.7, 297, 298.39, 301.83; ICD-10 codes: F20, F25, F21-F24, F28, F29); (2) bipolar illness and other affective illness (ICD-8 codes: 296.1, 296.3, 296, 300.4; ICD-10 codes: F30, F31, F34.0, F32-F39) and no history of disorders in category 1; and (3) other psychiatric disorder (any other diagnosis) but no history of disorders in either category 1 or 2. In addition, and not included in the hierarchy, we assessed the risk associated with a history of substance abuse disorders (ICD-8 codes: 303, 304; ICD-10 codes: 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 for mother, father, and siblings.

SOCIOECONOMIC AND DEMOGRAPHIC VARIABLES AND SEASON OF BIRTH

Socioeconomic and demographic variables included information about parental education level (organized according to 4 categories: basic/primary education, high school education and vocational training, university level education, and no available information) and information on parental wealth (organized into quartiles based on the distribution of these variables in the 5% sample of the Integrated Database for Longitudinal Labour Market Research). Other variables included were parental marital status, defined as single or married (including cohabiting); death of a parent or sibling before first hospital admission (not due to suicide); reference to father at birth; number of siblings (0, 1, 2, or 3 or more); and place of birth (defined as the capital [Copenhagen], capital suburbs, provincial city [population >100,000], provincial town [population <100,000], rural area, and birth outside Denmark, according to Pedersen and Mortensen). All variables were treated categorically and entered into the analysis as covariates.

We modeled month of birth as 11 dummy variables, with June as the reference category. The interaction between parental age and season of birth was modeled.

STATISTICAL ANALYSIS

The data were analyzed in a conditional logistic regression model using the PhReg procedure of SAS statistical software version 8.1 (SAS Institute Inc, Cary, NC), and asymptotic 95% con-
For all analyses, the reference group was parental age of 20 through 24 years. In Table 2, the IRRs for the unadjusted models are presented, where paternal (model 1a) and maternal (model 1b) age groups were modeled in separate univariate models (all models, including paternal age, controlled for whether there was a reference to father). These data were forced into the model regardless of significance of the estimates. Controlling for this range of factors (possible confounders), there remained a significantly increased risk in those with a paternal age of 30 years or older. We reanalyzed the data to include only those cases with schizophrenia (model 3). For paternal age a significant association remained for the age groups of 40 through 44 years and 50 years or older. We found a weak but significant association between the maternal age group of 30 through 34 years and risk of schizophrenia and a significant association for the maternal age group of 40 years or older. In the next model (model 4), we included the socioeconomic and demographic factors that might independently account for the relationship between parental age and risk of schizophrenia, including parental education, wealth, marital status, history of death before the case was first admitted, place of birth of cases and controls, family size, and, in addition to family psychiatric history, history of suicide and substance abuse in a parent or sibling and reference to father. These data were forced into the model regardless of significance of the estimates. Controlling for this range of factors (possible confounders), there remained a significantly increased risk in those with a paternal age of 30 years or older. We reanalyzed the data to include only those cases (n = 5413) and controls (n = 118930) without a family history of schizophrenia or other psychiatric admissions, and these are presented in Table 2 (model 5). The results are similar to those of model 4.

When the risks were estimated in the extended parental age groups (paternal age, 50-54 years and ≥55 years; maternal age, 40-44 years and ≥45 years), the increased risk was most marked in the oldest paternal age group. The increased risk of schizophrenia associated with
We investigated the interactions between parental age in each category and sex of the patients and between parental age and sex at first admission of the patients. We also included a 3-way interaction composed of age group of parent, sex, and age at first admission. Age at first admission was entered into the analysis as a mean-centered variable (the difference between age at first admission and mean age at first admission). We did not find any interactions between age at first admission and parental age in this sample. Significant sex interactions were observed for the paternal age groups of 35 through 39 years and 50 years or older, the extended age group of 50 through 54 years, and the maternal age group of 45 years or older. Analyses were conducted separately for males and females and the results are displayed in Table 2. The risk of schizophrenia was significantly increased in the 35- through 39-year age group of paternal age for females only. However, this effect was no longer significant once age of the other parent was controlled for (model 2; the models displayed in Table 3 are named to coincide with those in Table 2; for consistency, model 3 is not presented on this table). The risk associated with paternal age of 50 years or older was significantly increased for females in models 2 and 4. In the paternal age group of 50 through 54 years, the significant effect of paternal age on increased schizophrenia risk was present exclusively for females. The risk was higher for females in the paternal age group of 55 years or older than for males (model 4: IRR, 2.10; 95% CI, 1.35-3.28; vs IRR, 2.10; 95% CI, 1.35-3.28); however, the interaction was not significant. In terms of maternal age, there was a significant increase in the risk for males with mothers 45 years or older but not for females in all models. The estimates associated with the extended maternal age group (age, ≥45 years) were based on only a few cases (n=3 females; n=20 males).

There was no significant increase in the risk of schizophrenia for any month of birth. We did not find any significant interaction between month of birth and parental age.

Table 2. Incidence Rate Ratios (IRRs) for Schizophrenia Associated With Parental Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Unadjusted Model (Model 1)</th>
<th>Adjusted for Age of Both Parents (Model 2)</th>
<th>Adjusted for Age and Psychiatric History of Both Parents (Model 3)</th>
<th>Full Model Adjusted for Family Psychiatric History and Socioeconomic Factors (Model 4)</th>
<th>Full Model, Family History Negative Only (Model 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1.18 (1.01-1.39)</td>
<td>1.14 (0.97-1.35)</td>
<td>1.01 (0.93-1.30)</td>
<td>1.04 (0.88-1.23)</td>
<td>1.05 (0.85-1.29)</td>
</tr>
<tr>
<td>20-24</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>25-29</td>
<td>0.96 (0.90-1.03)</td>
<td>0.97 (0.90-1.04)</td>
<td>0.98 (0.91-1.05)</td>
<td>0.99 (0.92-1.07)</td>
<td>1.01 (0.93-1.11)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.02 (0.95-1.10)</td>
<td>1.01 (0.93-1.10)</td>
<td>1.02 (0.93-1.11)</td>
<td>1.04 (0.95-1.13)</td>
<td>1.03 (0.93-1.14)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.04 (0.95-1.13)</td>
<td>1.01 (0.91-1.12)</td>
<td>1.00 (0.90-1.11)</td>
<td>1.02 (0.91-1.13)</td>
<td>1.06 (0.93-1.20)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.20 (1.08-1.34)</td>
<td>1.16 (1.02-1.32)</td>
<td>1.14 (1.00-1.30)</td>
<td>1.15 (1.00-1.31)</td>
<td>1.21 (1.03-1.42)</td>
</tr>
<tr>
<td>45-49</td>
<td>1.20 (1.02-1.41)</td>
<td>1.14 (0.95-1.37)</td>
<td>1.10 (0.92-1.32)</td>
<td>1.09 (0.90-1.31)</td>
<td>1.22 (0.98-1.51)</td>
</tr>
<tr>
<td>≥50</td>
<td>1.75 (1.41-2.16)</td>
<td>1.65 (1.32-2.08)</td>
<td>1.64 (1.30-2.06)</td>
<td>1.51 (1.19-1.92)</td>
<td>1.61 (1.21-2.13)</td>
</tr>
<tr>
<td>50-54</td>
<td>1.42 (1.09-1.84)</td>
<td>1.32 (1.00-1.74)</td>
<td>1.29 (0.98-1.71)</td>
<td>1.22 (0.92-1.62)</td>
<td>1.33 (0.95-1.86)</td>
</tr>
<tr>
<td>≥55</td>
<td>2.90 (2.05-4.11)</td>
<td>2.71 (1.89-3.88)</td>
<td>2.76 (1.92-3.96)</td>
<td>2.45 (1.69-3.54)</td>
<td>2.42 (1.56-3.77)</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1.13 (1.04-1.23)</td>
<td>1.07 (0.98-1.18)</td>
<td>1.04 (0.95-1.14)</td>
<td>1.03 (0.94-1.13)</td>
<td>1.04 (0.93-1.16)</td>
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<td>1.02 (0.96-1.09)</td>
<td>1.05 (0.97-1.13)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.09 (1.02-1.17)</td>
<td>1.06 (0.98-1.15)</td>
<td>1.09 (1.00-1.18)</td>
<td>1.05 (0.97-1.14)</td>
<td>1.08 (0.98-1.20)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.15 (1.05-1.26)</td>
<td>1.05 (0.94-1.18)</td>
<td>1.11 (0.99-1.24)</td>
<td>1.07 (0.95-1.20)</td>
<td>1.08 (0.94-1.24)</td>
</tr>
<tr>
<td>≥40</td>
<td>1.39 (1.20-1.62)</td>
<td>1.15 (0.97-1.37)</td>
<td>1.23 (1.03-1.46)</td>
<td>1.18 (0.98-1.41)</td>
<td>1.21 (0.99-1.49)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.34 (1.14-1.58)</td>
<td>1.12 (0.94-1.34)</td>
<td>1.20 (1.00-1.44)</td>
<td>1.16 (0.96-1.39)</td>
<td>1.20 (0.97-1.48)</td>
</tr>
<tr>
<td>≥45</td>
<td>1.92 (1.26-2.94)</td>
<td>1.45 (0.93-2.26)</td>
<td>1.55 (0.99-2.42)</td>
<td>1.41 (0.90-2.24)</td>
<td>1.43 (0.86-2.39)</td>
</tr>
</tbody>
</table>

*Two separate models were conducted: model 1a for paternal age and model 1b for maternal age.
†Model adjusted for parental education, wealth, marital status, death before case admission not by suicide, family psychiatric history, history of suicide in parent or sibling, reference to father, place of birth, and sibship size.
‡Includes older age groups.

EFFECT OF SEX AND AGE AT FIRST ADMISSION

Table 3. The risk of schizophrenia was significantly increased in the 35- through 39-year age group of paternal age for females only. However, this effect was no longer significant once age of the other parent was controlled for (model 2; the models displayed in Table 3 are named to coincide with those in Table 2; for consistency, model 3 is not presented on this table). The risk associated with paternal age of 50 years or older was significantly increased for females in models 2 and 4. In the paternal age group of 50 through 54 years, the significant effect of paternal age on increased schizophrenia risk was present exclusively for females. The risk was higher for females in the paternal age group of 55 years or older than for males (model 4: IRR, 3.53; 95% CI, 1.82-6.83; vs IRR, 2.10; 95% CI, 1.35-3.28); however, the interaction was not significant. In terms of maternal age, there was a significant increase in the risk for males with mothers 45 years or older but not for females in all models. The estimates associated with the extended maternal age group (age, ≥45 years) were based on only a few cases (n=3 females; n=20 males).

There was no significant increase in the risk of schizophrenia for any month of birth. We did not find any significant interaction between month of birth and paternal age.

In this national, population-based, epidemiologic sample, controlling for a range of familial socioeconomic and psychiatric factors, advanced paternal age (≥50 years) was
associated with an increased risk of schizophrenia. In addition, we identified a sex effect, in which the increased risk associated with advanced paternal age was particularly prominent for females. A particular strength of our study was the ability to control for the presence of psychiatric disorders in the parents and siblings and for possible confounding due to family socioeconomic factors, family size, and whether a parent had died before the first hospital admission. The data are register based and so are bound by the same limitations of all register-based research, including the fact that the cases represent treated incidence cases.

In our analyses, unlike that of Malaspina et al, in which the authors found a monotonic relationship between paternal age and risk of schizophrenia, the increased risk was confined to the older (≥50 years) paternal ages in our final model (model 4). However, in our study, we were in a position to control for factors that Malaspina et al² could not control for, namely, parental psychiatric history and information relating to the death of the parents before admission. We identified a U-shaped distribution in the risk for schizophrenia associated with parental age in the initial models; however, after controlling for family psychiatric history and social factors, this U shape was no longer visible for paternal age, and only a weak and nonsignificant effect remained for maternal age. Furthermore, the present study did not find an increased risk in the relatively younger groups of parents. It is possible that environmental and genetic risk factors differ between the Danish population investigated by us and the Israeli population. A simple explanation might include the relatively higher ambient temperatures in Israel, since heat exposure may increase the exposure of spermatozoa to mutagenic metabolites, leading to more and earlier mutations among Israeli fathers and a paternal effect in younger age groups as well.

A variety of possible explanations for the association between risk of schizophrenia and paternal age have been discussed, including an increase in the rate of de novo genetic mutations in older fathers, attributes of the parents that lead to marriage at an older age than normal that are related to schizophrenia in the offspring, and the adverse psychological consequences of losing a parent by death because of the parents' increased age.

We examined the risk of schizophrenia associated with the death of a parent other than by suicide; however, no increase in risk was identified in the final model. This suggests that the psychological distress caused by the death of an aging parent does not account for the relationship between risk of schizophrenia and advanced paternal age. Although we could not control for birth order in this sample, we controlled for sibship size. In a previous study, sibship size but not birth order was associated with increased risk of schizophrenia. We found an independent, small but significant increase in the risk of schizophrenia among those from families with 3 or more siblings compared with being an only child (IRR, 1.15; 95% CI, 1.05-1.26), controlling for family history of psychiatric diagnoses in parents and siblings and socioeconomic factors. This finding suggests that the advanced paternal age effect is independent of factors operating in larger families, such as environmental exposure, perhaps to common infections in childhood, that may increase the risk of schizophrenia.

We found a sex difference insofar as there was a significant increase in the risk of schizophrenia in females with older fathers in all age groups 50 years or older (≥50 years, 50-54 years, ≥55 years) compared with males, for whom the increased risk was confined to the 55-year-
or older age group. Males had an increased risk associated with older mothers (≥45 years); however, the estimates were based on a small sample size. The de novo mutations that occur with advancing age in parents not only might be point mutations but also could involve trinucleotide repeated expansions, imprinting, or small structural chromosomal rearrangements.13 The data from the present study suggest that the parental effect is particularly related to paternal age in female cases. Therefore, a gene on the X chromosome might be involved, because these are always passed from fathers to daughters. It is well-known that the X chromosome contains a relatively high number of genes expressed in the central nervous system and that the gene for many diseases with cognitive impairment are located on the X chromosomes. Furthermore, a few linkage studies have suggested possible risk loci for schizophrenia on the X chromosome.13 However, the increased mutation rate in males can occur on 2 autosomes in each chromosome pair but only on 1 X chromosome, at least outside the pseudoautosomal region. Imprinted autosomal genes may also explain that an increased risk depends on the sex of the parent.

In our sample, the effect was not restricted to those with a family history of psychiatric illness. When we analyzed the data, including only those cases (n = 5413) with a family history of psychiatric illness. When we reanalyzed the data, including only those cases (n = 5413) and controls (n = 118930) without a family history of schizophrenia or any other psychiatric disorder, the results were similar (Table 2, model 5), indicating that the effect of parental age is not restricted to those with or without a family history of schizophrenia or other psychiatric disorders in this sample and suggesting that family history of psychiatric disorders does not explain the association.

Our findings support the theory that de novo mutations might occur in the offspring of older parents, particularly fathers, leading to an increased risk of schizophrenia and that this might help explain the fact that schizophrenia persists in the population despite reduced fertility levels.14 However, this effect seems to be restricted to fathers older than 50 years. The findings of interactions between sex and age of parent of origin lead to speculation about involvement of de novo genetic mutations occurring on the X chromosome in the etiology of schizophrenia, particularly in the female offspring of older fathers. However, males with older fathers (≥55 years) also had an increased risk. Focusing efforts on a specific chromosome may facilitate the final identification of risk genes possibly involved in the parental age effect. Such a risk gene might either be a gene of importance for brain development and function or might predispose to de novo mutations in such genes by causing decreased DNA repair and/or increased environmental susceptibility.

Submitted for publication May 7, 2002; final revision received December 20, 2002; accepted January 14, 2003.

This study was funded by the Stanley Medical Research Institute and by grant MH53188 from the National Institutes of Mental Health, Bethesda, Md. The National Centre for Register-based Research is supported by the Danish National Research Foundation, Copenhagen, Denmark.

Corresponding author and reprints: Majella Byrne, MSc, PhD, National Centre for Register-based Research, Aarhus University, Taasingeade 1, Aarhus 8000 C, Denmark (e-mail: mb@ncrr.dk).

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