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Psychotic Experiences Are Associated With Paternal Age But Not With Delayed Fatherhood in a Large, Multinational, Community Sample

Franck Schürhoff*[,1,2,3,4], Baptiste Pignon[1,2,3,4], Mohamed Lajnef[1], Romain Denis[1,2,3,4], Bart Rutten[5], Craig Morgan[6], Robin M. Murray[7], Marion Leboyer[1,2,3,4], Jim van Os[5,7], and Andrei Szöke[1,2,3,4]

[1]INSERM, U955, Translational Neuropsychiatry lab, Créteil, France; [2]AP-HP, DMU IMPACT, Psychiatry and Addictology Department, Mondor University Hospital, Créteil, France; [3]Fondation FondaMental, Créteil, France; [4]Univ Paris-Est Créteil, Faculté de médecine, Créteil, France; [5]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, South Limburg Mental Health Research and Teaching Network, Maastricht University Medical Centre, Maastricht, The Netherlands; [6]Department of Health Service and Population Research, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [7]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

*To whom correspondence should be addressed; Hôpital Albert Chenevier, Groupe hospitaliers Henri-Mondor, CHU de Créteil, Assistance Publique-Hôpitaux de Paris (AP-HP), 40 rue de Mesly, 94 000, Créteil, France; tel: + 33 1 49 81 32 90, fax: +33 1 49 81 30 59, e-mail: franck.schurhoff@inserm.fr

Advanced paternal age has been consistently associated with an increased risk of schizophrenia. It is less known if such an association also exists with subclinical/attenuated forms of psychosis. Additionally, it has been suggested that it is not paternal age per se, but rather delayed fatherhood, as a marker of a genetic liability of psychosis, that is the cause of the association. The aim of the current study was to examine whether paternal age and/or delayed fatherhood (paternity age) predict self-reported positive, negative, and/or depressive dimensions of psychosis in a large sample from the general population. The sample (*N* = 1465) was composed of control subjects from the 6 countries participating in the European Union Gene-Environment Interaction study. The CAPE, a self-report questionnaire, was used to measure dimensions of subclinical psychosis. Paternal age at the time of respondents' birth and age of paternity were assessed by self-report. We assessed the influence of the variables of interest (paternal age or paternity age) on CAPE scores after adjusting for potential confounders (age, gender, and ethnicity). Paternal age was positively associated with the positive dimension of the CAPE. By contrast, paternity age was not associated with any of the psychosis dimensions assessed by the CAPE. Thus, our results do not support the idea that delayed fatherhood explains the association between age of paternity and psychosis risk. Furthermore, our results provide arguments for the hypothesis of an etiologic continuum of psychosis.

Key words: paternal age/psychotic experiences/schizotypy/risk factors/CAPE/epidemiology

Introduction

Studies have consistently shown associations of advanced paternal age (APA) with an increased risk for schizophrenia. This association has been confirmed by 2 meta-analyses.[1,2] Moreover, a "dose-related" effect of paternal age on the risk of schizophrenia has been reported irrespective of the gender of the offspring.[3–5] These studies also demonstrated that the effect of APA on the risk of developing schizophrenia was not explained by confounding factors such as a family history of psychosis, maternal age, parental education, family social integration, social class, birth order, birth weight, or birth complications.[6] The mechanism through which the APA could predispose to the development of schizophrenia is unknown, but de novo mutations occurring in the male germ cell lines may represent the underlying causal mechanism, because these mutations tend to accumulate with advancing age.[7] Although de novo mutations are the most probable explanation, some alternative explanations have been proposed. Epigenetic factors such as DNA methylation abnormalities arising in the sperm of older fathers are also a plausible mechanism that could explain some of the risks associated with APA.[8] It has been suggested that the association between paternal age and schizophrenia may not be due to paternal age per se, but rather due to delayed fatherhood (ie, advanced age when the first child was born).[4,9,10] According to this hypothesis, delayed fatherhood is related to the presence of psychotic symptoms (such as the presence of schizotypal traits, social withdrawal, etc.) or psychotic disorders in fathers

due, at least in part, to genetic factors. These genetic factors transmitted from older fathers to their offspring would be the link between APA and risk for psychosis.[11] This association could also be due to the psychological impact of having older parents (including the probability of early parental death) and/or the decreasing capacity of older parents to provide an appropriate education to growing children.[12] These explanations are not mutually exclusive, and the different mechanisms could act in an additive way.

Several epidemiological and clinical studies suggest the existence of an extended spectrum of psychosis which encompasses the full range of psychotic manifestations from sub-syndromal or "subclinical" manifestations to clinically significant psychotic symptoms typically observed in individuals diagnosed with a psychotic disorder.[13] The set of subclinical psychotic experiences (PEs) and traits which do not reach clinical threshold and are distributed throughout the general population are usually known as schizotypal traits and PEs.[14] Epidemiological studies and meta-analyses have demonstrated that the mean prevalence of PEs in the general population is around 5%–8%.[15–17] A meta-analysis found 7.2% prevalence and 2.5% mean annual incidence.[15] Another study using a sample of 31 261 adults from 18 countries has found that the average prevalence is 5.8%, 5.2%, and 1.3% for PEs, hallucinatory experiences, and delusional experiences, respectively.[16] Overall, the estimated prevalence of these subclinical manifestations is clearly much higher than the lifetime morbid risk for an actual psychotic disorder. Aside from the positive psychotic manifestations, schizotypy also includes negative (ie, blunting of affect, loss of motivation, etc.) and disorganized (eg, formal thought disorder, inappropriate affects) psychotic manifestations. Schizotypy is a complex construct related to psychosis, particularly at phenotypic and genetic levels.[18–20] The fact that some of the previously identified risk factors for schizophrenia, including cannabis consumption, childhood traumatic experiences, and urbanicity, also increase the risk of PEs or attenuated psychotic manifestations in the nonclinical population[21–23] supports the extended-spectrum hypothesis. However, the existence of an etiological continuum is still debated in the literature.[24] Indeed, the fact that psychotic symptoms are continuously distributed in the general population does not mean that schizophrenia symptoms are not qualitatively different from normal experiences. The identification of other common risk factors (for schizophrenia and subclinical psychotic manifestations) could give support to the hypothesis of an etiological continuum of psychosis. The demonstration of the existence of such a continuum could provide a better understanding of the pathophysiology of schizophrenia.[25]

To date, the influence of APA on subclinical manifestations of psychosis has been the subject of very few studies. Among the 4 studies published to our knowledge, 3 have investigated PEs in different population samples. An association with positive symptoms has been found by some,[26,27] but not all authors.[28] The fourth study has examined schizotypal traits in relation to paternal age, in a sample of undergraduate students. This study shows an association between the positive dimension of schizotypy and paternal age.[29] Research to date has 2 main limitations: The first limitation is that the samples[27–29] were not representative of the general population in terms of age (only young subjects) and level of education. This might be problematic as, on the one hand, it might limit the variation of the range of psychotic manifestations, and on the other hand, the samples might include subjects that will develop schizophrenia (as the subjects have not fully passed through the developmental risk period for developing schizophrenia). With the exception of one study,[29] the second limitation is the evaluation of only one of the dimensions of psychosis, ie, the positive dimension.[26–28]

Building on the aforementioned observations, the aim of the current study was to examine whether paternal age and/or paternity age predict self-reported positive, negative, and/or depressive dimensions of psychosis in a sample of the general population. If confirmed, this could give support to a common etiology along the psychotic continuum.

Materials and Methods

General Background

Data were collected in the European Union Gene-Environment Interaction (EU-GEI) study (*www.eu-gei.eu*): a major multicenter case-sibling-control study of genetic and environmental determinants of the occurrence, severity, and outcome of psychotic disorders. For the second work-package of the study (WP2—Functional Enviromics), 3 different samples of subjects were recruited: subjects with a first-episode psychotic disorder (FEP), control subjects, and siblings of FEP cases. They were recruited across 6 different countries: Brazil, France, Italy, the Netherlands, Spain, and the United Kingdom.[30,31] Ethical approval was obtained from local research ethics committees in each country and written informed consent was obtained from every participant. The EU-GEI Project is funded by the European Community's Seventh Framework Programme. The funder had no involvement in study design, data collection, analysis, interpretation of findings, manuscript preparation, or the decision to submit the article for publication.

Subjects

The sample was comprised of the control subjects of the WP2 of the study. Quota sampling strategies were used to guide their recruitment. Accurate local demographic data were used to ensure the samples' representativeness of each catchment area's population in terms of age, gender,

and ethnicity. Participants were between 18 and 65 years old and were excluded if they had received a diagnosis of, or treatment for, a psychotic disorder. Subjects were recruited over periods of 2–4 years (depending on the including center) in the interval between May 1, 2010 and April 1, 2015. First- and second-generation migrants were oversampled 2-fold.[32]

Materials

Community Assessment of Psychic Experiences. All subjects completed (among other questionnaires) the Community Assessment of Psychic Experiences (CAPE). The CAPE, a self-report questionnaire, uses a 4-point Likert scale (1–4) to indicate symptom frequency ("Never," "Sometimes," "Often," and "Nearly Always") of the 42 items.[33] It has been constructed to assess 3 dimensions: positive experiences (20 items), negative experiences (14 items), and depressive experiences (8 items), representing the magnitude of attenuated depressive and psychotic manifestations over the lifetime. As with several other studies using the CAPE,[34,35] given that scores of 3 or 4 are very rare, we decided to dichotomize each item of the CAPE to reflect the presence or absence of the condition as follows: "never" was rated as "0" and "sometimes, often, and nearly always" as "1." We used the sum of endorsed items to quantify the psychotic dimensions, which is usually done in studies using other similar questionnaires,[36,37] and has also been advocated by other researchers using the CAPE.[38–41] A total score representing the sum of all items was calculated for each dimension. There is also a 4-point Likert "distress" assessment for each symptom. As for several other analyses of the CAPE,[38–41] the distress assessment was not used in the present study.

The CAPE used in this dichotomized version has shown equivalent factorial structure, factor loadings, and thresholds across the 6 countries.[42] Thus, cross-national variability can be considered negligible and data from different countries can be pooled.

Other Variables

Maternal and paternal age at the time of respondents' birth and age of paternity (the age when the first child of the subject's father was born) were assessed by self-report. In addition, a number of socio-demographic variables considered as potential confounders were recorded: gender, age at interview, and ethnicity.

Data Analyses

We assessed the association between demographic variables (potential confounders) and CAPE scores (positive, negative, depressive, and total) expressed as correlations (Kendall's Tau) for continuous variables (ie, age, maternal age, paternal age, and age of paternity) and means comparison for categorical variables (eg, gender, ethnicity).

The main analyses assessed the influence of the variables of interest (paternal age or paternity age) on CAPE scores after adjusting for a priori potential confounders.

To choose the best suited model, we used the following general strategy based on testing the structure of the data and requirements of the different models/statistical methods. First, we tested if missing data were missing completely at random (MCAR) using Little's MCAR test.[43] If the MCAR was not confirmed, we imputed the missing data using k-Nearest Neighbor Imputation.[44]

Second, we tested if conditions for Poisson regression (the standard option for count data) were met. To do this, we assessed the presence of overdispersion using the AER package.[45] When overdispersion was present, we used the negative binomial function to model the data.

The third step was to test for variance inflation, ie, a measure of collinearity of variables. The Variation Inflation Factor (VIF) was calculated using "car" package.[46]

We were especially concerned with the risk of collinearity between parental characteristics (paternal/paternity, maternal age). When there were suggestions of significant collinearity, we restricted the main analyses to models using a single parental variable.

Finally, because we were concerned with the risk of frequent zero-valued observations, we compared the fit of the model selected previously to the corresponding zero-inflated model using Vuong's procedure (from "pscl" package).[47]

Whenever 2 alternative models could be used, we chose the one that ensured homogeneity in the treatment of data and thus comparability of results. Thus, for example, if one analysis could be done using a Poisson or a binomial negative function but for other analyses, the binomial negative function was mandatory, we used the binomial negative function for all analyses.

Separate analyses were performed for each of the CAPE scores (positive, negative, depressive, and total) and for each of the variables of interest (paternal age or paternity age). This resulted in 8 different analyses. A P-value of ≤.05 was considered statistically significant. Analyses were performed using R software (version 3.6).[48]

Results

Descriptive Statistics

The sample was comprised of 1465 subjects (685 men and 780 women, mean age (SD) = 36 (13) years). The number of subjects per country was as follows: United Kingdom (n = 332, 22% of the total sample), the Netherlands (n = 214, 14,6%), Spain (n = 218, 14.9%), France (n = 140, 9.6%), Italy (n = 261, 17.8%), and Brazil (n = 310, 21.2%).

The mean and standard deviation for paternal age and age of paternity were 31.7 ± 6.9 and 28.1 ± 5.9, respectively.

The mean and standard deviation for positive, negative, and depressive scores of the CAPE were 3.9 ± 2.9, 6.1 ± 3.6, and 4.3 ± 1.9, respectively. Demographic characteristics and CAPE scores of the sample are summarized in table 1.

There were few missing data. Missing data were primarily CAPE items (see table 1). The number of subjects with complete data varied between 1204 (82%) for CAPE full scores and paternity age and 1400 (96%) for CAPE depressive scores and paternal age. Details on missing data, by country, are provided in supplementary table S1. Paternal, paternity, and maternal age were fairly similar between countries (see supplementary table S2).

Associations of CAPE Scores With Potential Confounders

The CAPE scores did not differ according to gender except for the depressive dimension, which showed significantly higher scores in women. We found significant differences for each CAPE score according to ethnicity status (with minority subjects having higher scores on the positive dimension, and lower scores on the negative and depressive dimensions). We also found a significant negative correlation between age at interview and the positive and total scores of the CAPE (lower scores in older subjects). Maternal age was positively associated with the negative dimension and total score. Paternal and paternity age showed a similar association, but for paternity age and total score, it did not reach a significant threshold (see table 2 for details).

Table 1. Demographic and Clinical Variables of the Sample

Sample size (number of subjects and % of the whole population)	1465 (100%)
Brazil	310 (21.3%)
France	140 (9.6%)
UK	322 (22%)
Netherlands	214 (14.6%)
Spain	218 (14.9%)
Italy	261 (17.8%)
Paternal age (years (SD))	31.7 (6.9)
Age of paternity (years (SD))	28.1 (5.9)
Maternal age (years (SD))	28.2 (5.8)
Gender (% of females)	53.4%
Ethnicity (% of "white")	73.8%
CAPE scores	
CAPE positive dimension (SD)	3.9 (2.9)
CAPE negative dimension (SD)	6.1 (3.6)
CAPE depressive dimension (SD)	4.3 (1.9)
CAPE full score (SD)	14.3 (7.0)
CAPE—No items endorsed (N)	
CAPE positive dimension	121
CAPE negative dimension	68
CAPE depressive dimension	27
CAPE full score	6

Associations of CAPE Dimensions With Paternal and Paternity Age (Main Analyses)

Little's MCAR test suggested that variables used for positive and total scores calculations were not missing at random (see supplementary table S3). Thus, we decided to impute all missing CAPE values and use, in all analyses, the scores calculated using the imputed data.

The next step was to test for overdispersion of data, to select the most appropriate statistical model. With the exception of depressive data, significant overdispersion was present (see supplementary table S4). Thus, we decided to use the binomial negative function for the analyses.

The next step was to test for potential collinearity—variance inflation. For paternal age, in all models using maternal age (ie, for the 3 dimensions and the total scores), there were more than a 2 times increase in VIF suggesting potential collinearity problems. Thus, we decided to analyze data without maternal age as a covariate (see supplementary tables S5 and S6). Although the increase in VIF for models using paternity and maternal age was less important, we decided to also analyze the role of paternity without adjusting for maternal age in order to facilitate comparison with results for paternal age.

Finally, using the Vuong procedure, we compared the standard (non-ZIP) models with ZIP models. In all comparisons, except for the negative dimension, negative binomial (non-ZIP) models performed better than ZIP models. Thus, a ZIP model was used only for the negative score.

The whole procedure of selection of the best fitted model is summarized in supplementary table S7.

The results of the analyses are summarized in table 3. Both paternal variables were associated with an increase in the CAPE total score. Paternal age was also associated with a significant increase in the positive CAPE score. Age of paternity, however, was not associated with any CAPE dimension.

Discussion

We report an association between paternal age and the positive dimension of schizotypy in a nonclinical general population sample. In contrast, paternal age was not associated with the negative and depressive dimensions of the CAPE. Paternity age was not associated with any of the dimensions of schizotypy explored by the CAPE but was associated with the CAPE total score.

Our findings are in line with former studies on paternal age and schizophrenia, which had found that APA is associated with an elevated risk for schizophrenia.[5,49–53] Our data are also in accordance with other studies.[26,29] In particular, Grattan et al,[29] using a schizotypy questionnaire, found that APA is associated with PEs but not with other

Table 2. CAPE Scores According to Gender, Ethnicity, Age at Interview, and Maternal Age at Birth

	Gender (Mean, SD)		Ethnicity (Mean, SD)		Age at Interview (Tau)	Maternal Age at Birth (Tau)
	Females	Males	White	Other		
CAPE positive	3.74 (2.85)	4.01 (2.98)	3.70 (2.82)***	4.52 (3.20)***	−0.10***	0.024
CAPE negative	6.14 (3.56)	6.12 (3.66)	6.24 (3.59)*	5.68 (3.65)*	−0.0088	0.045*
CAPE depressive	4.65 (1.98)***	4.02 (1.86)***	4.43 (1.92)**	4.04 (2.03)**	0.0054	0.026
CAPE full score	14.44 (7.00)	14.12 (7.08)	14.32 (6.89)	14.16 (7.58)	−0.047	0.044*

Note: Levels of *P*-values of associations with CAPE scores: *$P < .05$; **$P < .01$; ***$P < .001$.

Table 3. Paternal Age and Age of Paternity Influence on CAPE Scores

	Paternal Age	Age of Paternity
CAPE	β (95% CI)[a]	β (95% CI)[a]
Positive	0.0063 (.0008 to 0.0119)*	0.0029 (−.0039 to .0098)
Negative	−0.0298 (−.0783 to .0187)	−0.0531(−.0115 to .0083)
Depressive	0.0026 (−.0010 to .0062)	0.0038 (−.0005 to .0082)
Total	0.0051 (.0012 to .0090)*	0.0048 (.0000 to .0096)*

Note: [a]Adjusted for age, gender, ethnicity, maternal age.
*$P < .05$.

dimensions of psychosis. Thus, our results provide arguments for similar etiology across the phenotypic continuum that includes PEs and psychosis.

Our results are in apparent contradiction with those of Vreeker et al[28] and Zammit et al,[27] who did not find any association between APA and subclinical manifestations of psychosis. A possible explanation is that the samples of these 2 studies were composed of young or very young people (mean ages of participants were 20.8 and 12.9 years, respectively), which are known to exhibit more psychotic symptoms compared to adults.[54–56] Furthermore, PEs in children and adolescents are not always related to the presence of psychotic symptoms in adults but may also be related to other psychiatric manifestations or disorders.[57–60] This suggests that in these populations, in contrast to adult populations, PEs are not phenomenologically related to psychosis.

Our analyses were intended to test 2 alternative explanations of the association between APA and subclinical manifestations of psychosis. The first explanation is the accumulation of novel mutations in paternal germ cells over time.[61] The alternative explanation proposed that delayed fatherhood occurs as a result of impaired social functioning, schizotypal traits in the father and that these heritable traits are transmitted to the child and lead to schizophrenia in the offspring.[4] Because of the lack of association between delayed fatherhood and any of the schizotypal dimensions, our results are not in favor of this alternative hypothesis, but rather consistent with the notion that the paternal age association arises from the greater opportunity for de novo mutations in spermatogenesis and is a risk factor for psychotic disorders. An alternative, more direct way to test these 2 hypotheses would be to perform polygenic risk score profiling. With genetic data, polygenic risk scores can be determined and used to investigate whether men with higher polygenic risk scores for schizophrenia have children at later ages.[62,63]

After adjustment for demographic potential confounders, paternal age was unrelated to negative and depressive features. Given the large sample size, it is unlikely that these results are due to a lack of statistical power. As we controlled for several possible sources of bias, it is also unlikely that the result was due to statistical confounders. Regarding the negative dimension, we found similar results to Grattan et al,[29] which was the only study we found that explored this relationship.

Thus, the association between paternal age and attenuated psychotic dimensions seems to be specific to the positive dimension. Concerning the positive dimension, our data suggest an underlying dimensional process or processes present in all individuals and associated with a quantitative variation in the clinical phenotype.

Conversely, there was no association between paternal age and the negative dimension. It is possible that schizotypal dimensions may have different underlying pathophysiological mechanisms and, therefore, are associated with different risk factors. For example, it is possible that only positive symptoms (hallucinations and delusions) are dimensional phenomena lying on a continuum with normal experiences, and the other psychotic symptoms (eg, negative) are qualitatively (and etiologically) different from the attenuated symptoms measured by the CAPE. However, we cannot rule out an etiological continuity between subclinical and clinical manifestations for the negative dimension. Indeed, we cannot exclude that different risk factors for psychotic disorders are differently associated with the 2 dimensions (positive and negative). For example, data from brain imaging studies have suggested that there may be overlap in the structural and functional correlates of negative symptoms across the psychosis continuum suggesting a common

pathophysiological mechanism.[64,65] More generally, our results suggest the need for further study of the specific etiological and pathophysiological correlates of psychotic dimensions.

Our study has several strengths: a multi-site study (including several countries), a very large sample size with subjects drawn from a population-based sample and thus our findings can be generalized more confidently to the population as a whole, and analyses of both paternal age and paternity age (ie, delayed fatherhood) at birth.

Some limitations of this study should also be taken into account. Although we included several potential confounders in our analyses, we did not control for parental history of psychotic disorders and for the exposure to other risk factors such as cannabis, childhood trauma, etc. However, it seems unlikely that our findings (an association with APA but not with age of paternity) could be explained by these confounders. We studied the association between CAPE dimensions and paternal characteristics in an international and culturally diverse sample. The sample size and diversity are among the strong points of our study. However, although we have no reason to believe that there are significant differences in the associations in different countries, we did not formally test it. The national sample sizes were not sufficient for separate analyses and thus, further studies in larger national samples are necessary to reproduce our findings. Similarly, although we do not have reasons to believe that the oversampling of migrant subjects impacted the results observed, it must be kept in mind that our results might not be generalized to the entire general population of the countries included. Finally, the association of paternal age and the positive dimension of the CAPE was relatively weak. Its statistical significance might even be disputed, given the number of associations tested. However, our results are similar to those already reported in the literature[26] and the fact that association with paternal age was stronger than with paternity age is independent of the arbitrary choice of a significant threshold.

The fact that APA is associated with an increased risk of psychosis is of concern, given the worldwide tendency toward an increase in paternal age.[66] However, APA is also associated with potentially positive outcomes; for example, in an analysis of a historical database, we found that APA was also associated with exceptional achievement.[67] Thus, before drawing any final conclusions, the whole spectrum of consequences of APA (ie, positive and negative) should be carefully examined.

As it is likely that subclinical manifestations of psychosis are associated with some, but not necessarily all, established risk factors for schizophrenia, future studies on risk factors in relation to dimensions of psychosis will increase our understanding of mechanisms underlying the development of schizophrenia.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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