ORIGINAL ARTICLE

Advancing Paternal Age and Bipolar Disorder

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Context: Advancing paternal age has been reported as a risk factor for neurodevelopmental disorders.

Objectives: To determine whether advanced paternal age is associated with an increased risk of BPD in the offspring and to assess if there was any difference in risk when analyzing patients with early-onset BPD separately.

Design: A nationwide nested case-control study based on Swedish registers was performed. Risk for BPD in the offspring of older fathers was estimated using conditional logistic regression analysis controlling for potential confounding of parity, maternal age, socioeconomic status, and parental family history of psychotic disorders.

Setting: Identification of 7 328 100 individuals and their biological parents by linking the nationwide Multigeneration Register and the Hospital Discharge Register.

Participants: A total of 13 428 patients with a BPD diagnosis on at least 2 separate hospital admissions was identified. Five healthy control subjects matched for sex and year of birth were randomized to each case.

Main Outcome Measure: Bipolar disorder based on *ICD* codes at discharge from hospital treatment.

Results: An association between paternal age and risk for BPD in the offspring of older men was noted. The risk increased with advancing paternal age. After controlling for parity, maternal age, socioeconomic status, and family history of psychotic disorders, the offspring of men 55 years and older were 1.37 (95% confidence interval [CI], 1.02-1.84) times more likely to be diagnosed as having BPD than the offspring of men aged 20 to 24 years. The maternal age effect was less pronounced. For early-onset (<20 years) cases, the effect of paternal age was much stronger (odds ratio, 2.63; 95% CI, 1.19-5.81), whereas no statistically significant maternal age effect was found.

Conclusions: Advanced paternal age is a risk factor for BPD in the offspring. The results are consistent with the hypothesis that advancing paternal age increases the risk for de novo mutations in susceptibility genes for neurodevelopmental disorders.

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BIPOLAR DISORDER (BPD) IS A common clinically severe and episodic mood disorder. The disorder is a serious health problem associated with suicidality,[1] comorbidity,[2] and substance abuse.[3]

Bipolar disorder has few, if any, established risk factors other than a markedly increased risk for individuals with a family history of psychotic disorders.[4] However, many patients with BPD do not have family members with psychotic disorders[5]; hence, other factors likely contribute to maintaining BPD in the population.

Advancing paternal age has been reported as a risk factor for complex neurodevelopmental disorders (eg, schizophrenia[6-9] and autism spectrum disorder[10]). Similar to BPD, these disorders are mental disorders with a substantial genetic influence. Despite the robust evidence supporting the association between paternal age and severe mental disorders, the association between advanced paternal age and BPD has not been investigated, to our knowledge.

Bipolar disorder is a heterogeneous syndrome with various clinical presentations. The heterogeneity of BPD has resulted in efforts to dissect BPD into subcategories. For instance, subcategorization based on age at onset has been suggested,[11,12] supported by the clinical homogeneity within the subgroups. For example, early-onset BPD is associated with poor prognosis, greater hereditability, poor response to lithium, and increased risk for comorbidity.[13-16] Because early-onset BPD displays homogeneous characteristics, it is plausible that specific risk factors might operate in this subgroup.

The first objective of this study was to determine whether advanced paternal age is associated with an increased risk of BPD in the offspring. A second objective was to assess if there was any difference in risk when analyzing patients with early-onset BPD separately.

METHOD

NATIONAL REGISTERS

A population-based nested case-control study was conducted using Swedish national registers. The primary key of the register linkage is the unique personal identification number (national regis-

tration number) assigned to each Swedish citizen dating back to 1947. The Hospital Discharge Register contains the admission and discharge dates, the main discharge diagnosis, and up to 8 secondary diagnoses assigned by the treating physician. Diagnoses are coded according to the 8th, 9th, and 10th *ICD* editions.[17-19] This register includes data on practically all psychiatric inpatient care in Sweden since 1973. Admissions occurring before December 31, 2001, were included in the register. The Multigeneration Register enables identification of biological parents of an "index person" and information on maternal and paternal ages. A prerequisite for being included in the registry is that the index person was born after January 1, 1932, and was ever registered as living in Sweden after 1960. For immigrants to Sweden, similar information exists for those who became citizens before age 18 years together with 1 or both parents. The biological father of the offspring was assumed to be the husband of the mother at the time of birth or "by acknowledgment" for unwed mothers. Ethical approval was given by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

SELECTION OF STUDY SUBJECTS

Linkage of the Hospital Discharge Register and the Multigeneration Register resulted in a study base of 7 739 202 individuals. Of these, 411 102 (5.3%) were excluded because of missing parental data, resulting in 7 328 100 persons with known biological mothers and fathers. Patients with episodes of BPD were identified in the Hospital Discharge Register by *ICD-8* and *ICD-9* code 296 and by *ICD-10* codes F30 and F31. Admissions with *ICD* codes for unipolar depression (ie, *ICD-8* code 296.2 and *ICD-9* code 296B) were excluded. This resulted in 23 278 individuals (0.3%) with known biological parents who on 1 or more occasions had been diagnosed as having BPD. So far, the validity of BPD diagnoses has not been thoroughly investigated. Therefore, to avoid inclusion of individuals incorrectly diagnosed as having BPD and to reduce the risk of incorrect diagnoses because of simple coding or transcription errors, 9850 persons diagnosed as having BPD but with only 1 hospitalization were excluded. Therefore, the main analyses were performed on the remaining 13 428 individuals (0.2%) with 2 or more BPD diagnoses and 2 known parents. The sample consisted of 5626 men (41.9%) and 7802 women (58.1%) born between 1932 and 1991.

Subanalyses were conducted on a patient subgroup having early-onset BPD identified by age at onset of their first hospital discharge. Because there is no established cutoff for early-onset BPD, we evaluated the distribution of onset age after rounding off to the closest birth date. We a priori decided that the bottom 5% of the distribution of onset age would represent a conservative estimate for the subanalysis of early-onset cases. Individuals with onset before age 20 years corresponded to 5.3% of the total study group; therefore, we chose age 20 years as the cutoff level.

Cases who had received 1 or more diagnoses of schizophrenia after their BPD diagnoses were identified in our data set. In an attempt to reduce the risk of including misclassified individuals with schizophrenia, we conducted a subanalysis that excluded cases diagnosed as having schizophrenia (*ICD-8* and *ICD-9* code 295 and *ICD-10* code F20) after their last BPD diagnosis.

We aimed to explore how our narrow definition of BPD might have affected the results. Therefore, an additional analysis was performed with all cases who had ever been diagnosed as having BPD during hospitalization.

STUDY DESIGN

A nested case-control study design was applied. For each BPD case, 5 control subjects were randomly selected from all 7 328 100 individuals in the Multigeneration Register with known biological parents. Individuals without a BPD diagnosis in the Hospital Discharge Register at the time of the case's first admission were eligible as controls. Controls were matched for sex and year of birth. To ensure an equivalent period of risk, each control had to be alive at the date of the case's first hospitalization.

PARENTAL AGE

Paternal and maternal ages were categorized into 5-year intervals similar to the methods by Malaspina et al[7] and Byrne et al.[6] Fathers and mothers aged 20 to 24 years at the offspring's birth constituted the reference category.

STATISTICAL ANALYSIS

The main method of analysis was conditional logistic regression analysis fitted by using commercially available statistical software (PROC TPHREG procedure in SAS version 9.1.3; SAS Institute Inc, Cary, North Carolina). Odds ratios (ORs) and 95% 2-sided confidence intervals (CIs) were calculated. Tests of statistical hypotheses were based on the 2-sided 5% level of significance. Paternal and maternal ages were treated as categorical variables. The following 4 models were used: (1) unadjusted analyses on paternal and maternal ages, (2) analyses on paternal and maternal ages adjusted for age of the other parent, (3) analyses on paternal and maternal ages adjusted for age of the other parent and for family history of psychotic disorders, and (4) analyses on paternal and maternal ages adjusted for age of the other parent, family history of psychotic disorders, socioeconomic status (SES), and parity. Information about the potential confounders (SES, parity, and family history of psychotic disorders) was obtained from the Hospital Discharge Register, the Education Register, and the Multigeneration Register. **Table 1** gives the distribution of the potential confounders for cases and controls. Family history of psychotic illness was defined as having a parent or sibling who had received a diagnosis of BPD, schizophrenia, or schizoaffective disorder during at least 2 separate hospitalizations. These individuals were identified from the Hospital Discharge Register by *ICD-8* and *ICD-9* codes 295 and 296 and by *ICD-10* codes F20, F21, F23.1, F23.2, F25, F30, and F31. Education was used as a proxy measure of SES and was categorized into 7 groups. Highest obtained education within the family (ie, of the father, mother, or proband) was selected as the SES indicator. A fraction of the study subjects (96 cases [0.7%] and 1752 controls [2.6%]) for whom no information about highest education could be obtained was excluded in the analyses adjusted for SES. Parity was defined as the total number of live births by the biological mother of each subject.

RESULTS

EFFECTS OF PARENTAL AGE

Table 2 gives the numbers of cases and controls in each parental age category together with the unadjusted and adjusted analyses. Risk for BPD increased with advancing paternal age. In the unadjusted analyses (model 1), an increased risk for BPD was found in all age categories older than 24 years. After adjusting for maternal age (model 2), there was a significant increase in risk for BPD in all age categories in which fathers were older than 29 years. The highest risk estimate was found in the offspring of fathers older than 54 years (OR, 1.38; 95% CI,

Table 1. Distribution of Potential Confounders

Variable	No. (%) Cases (n=13 428)	No. (%) Controls (n=67 140)
Family history of psychotic disorders		
Family member with a history of psychosis	1873 (13.9)	1607 (2.4)
Family member with only BPD, >1 diagnosis	1120 (8.3)	853 (1.3)
Family member with only psychotic disorders other than BPD, >1 diagnosis	482 (3.6)	617 (0.9)
Family member with >1 BPD diagnosis and >1 other psychotic disorders	257 (1.9)	128 (0.2)
Family member with 1 BPD diagnosis and 1 other diagnosed psychotic disorder	14 (0.1)	9 (0.0)
Highest education within family, parents, or proband		
Elementary school, <9 y	1893 (14.1)	8756 (13.0)
Compulsory school, 9 y	1255 (9.3)	5056 (7.5)
Upper secondary, <3 y	4417 (32.9)	21 373 (31.8)
Upper secondary, 3 y	1598 (11.9)	8665 (12.9)
Postsecondary	1706 (12.7)	9102 (13.6)
University undergraduate	2301 (17.1)	11 570 (17.2)
University graduate	162 (1.2)	866 (1.3)
Missing data	96 (0.7)	1752 (2.6)
Parity, No. of live births to the mother, including the proband		
1	6166 (45.9)	32 529 (48.4)
2	4074 (30.3)	20 576 (30.6)
3	1912 (14.2)	8536 (12.7)
4	763 (5.7)	3259 (4.9)
5	289 (2.2)	1282 (1.9)
6	120 (0.9)	539 (0.8)
7	63 (0.5)	246 (0.4)
8	25 (0.2)	92 (0.1)
9	9 (0.1)	49 (0.1)
≥10	7 (0.1)	32 (0.0)

Abbreviation: BPD, bipolar disorder.

1.04-1.84). The association between maternal age and BPD was significant in the unadjusted analysis in all age categories older than 24 years. After controlling for paternal age (model 2), a significantly increased risk was found for mothers aged 35 to 39 years.

Adjustment for family history of psychotic disorders (model 3) did not have a substantive effect on the results. Statistical significance was observed in the same parental age categories as in model 2. Model 4 was fitted by excluding individuals with missing SES data. Again, there were only trivial changes in point estimates. The highest risk for BPD was found in the offspring of fathers 55 years and older (OR, 1.37; 95% CI, 1.02-1.84) (Table 2). The results of model 4 indicated statistically significant maternal age effects in 2 age categories, namely, maternal ages 30 to 34 years and 35 to 39 years.

Models 1 through 3 were refitted on the subsample used in model 4 to detect potential effects of the exclusion of study individuals missing SES data. The results of these analyses for paternal age showed similar but slightly lower risks as in models 1 through 3 (data not shown).

To evaluate the paternal and maternal age effects overall and without focusing on individual age categories, we compared models using likelihood ratio tests. The analyses were conducted on the entire study sample and did not include the SES and parity variables. Given that the model included family history of psychotic disorder and maternal age, there was statistically significant support for adding paternal age to the model (P=.04). In contrast, given that the model included family history of psychotic disorders and paternal age, there was no statistically significant support for adding maternal age (P=.09).

PARENTAL AGE EFFECTS ON EARLY-ONSET BPD

Results of parental age effects on early-onset BPD are given in **Table 3**. In total, 715 cases and 3575 controls were included in these analyses.

In the unadjusted analyses (model 1), a statistically significant increased risk for BPD was present in the offspring of fathers younger than 20 years or 30 years and older. There was also a statistically significant increased risk for BPD in the offspring of mothers older than 29 years. After adjusting for age of the other parent (model 2), the increased risks were still statistically significant in the same paternal age groups as in the unadjusted analyses, whereas the associations with maternal age and risk for BPD in the offspring were no longer statistically significant. The highest risk was found for fathers 50 years and older (OR, 2.63; 95% CI, 1.19-5.81) (Table 3).

SPECIFICITY FOR THE PARENTAL AGE EFFECTS ON BPD

Among our cases, 1567 individuals (11.7%) had been diagnosed as having schizophrenia after their last BPD diagnosis. After excluding these cases, the remaining 11 861 cases were analyzed separately with their corresponding controls (**Table 4**). The association between risk for

Table 2. Associations Between Parental Age and Bipolar Disorder

Variable	No. (%)		Odds Ratio (95% Confidence Interval)			
	Cases (n=13 428)	Controls (n=67 140)	Model 1	Model 2[a]	Model 3[b]	Model 4[c]
Paternal age, y						
<20	176 (1.3)	938 (1.4)	1.07 (0.90-1.26)	1.08 (0.91-1.28)	1.13 (0.95-1.35)	1.12 (0.94-1.34)
20-24	1774 (13.2)	10 090 (15.0)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
25-29	3518 (26.2)	18 697 (27.8)	1.07 (1.01-1.14)	1.05 (0.98-1.12)	1.05 (0.98-1.12)	1.04 (0.97-1.11)
30-34	3522 (26.2)	17 126 (25.5)	1.18 (1.10-1.25)	1.13 (1.05-1.21)	1.12 (1.03-1.20)	1.11 (1.02-1.19)
35-39	2371 (17.7)	11 344 (16.9)	1.20 (1.12-1.28)	1.12 (1.03-1.22)	1.11 (1.01-1.21)	1.09 (1.00-1.19)
40-44	1319 (9.8)	5810 (8.7)	1.30 (1.20-1.41)	1.19 (1.08-1.32)	1.17 (1.06-1.30)	1.15 (1.04-1.28)
45-49	508 (3.8)	2200 (3.3)	1.32 (1.18-1.47)	1.21 (1.06-1.37)	1.18 (1.04-1.35)	1.14 (1.00-1.30)
50-54	172 (1.3)	679 (1.0)	1.45 (1.22-1.73)	1.32 (1.09-1.59)	1.24 (1.02-1.50)	1.21 (1.00-1.48)
≥55	68 (0.5)	256 (0.4)	1.53 (1.16-2.00)	1.38 (1.04-1.84)	1.37 (1.03-1.83)	1.37 (1.02-1.84)
Maternal age, y						
<20	792 (5.9)	4439 (6.6)	0.97 (0.89-1.05)	0.99 (0.90-1.08)	0.98 (0.89-1.08)	0.96 (0.88-1.06)
20-24	3262 (24.3)	17 747 (26.4)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
25-29	3991 (29.7)	20 140 (30.0)	1.08 (1.03-1.14)	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.04 (0.99-1.11)
30-34	3020 (22.5)	14 494 (21.6)	1.14 (1.08-1.20)	1.06 (0.99-1.13)	1.07 (1.00-1.15)	1.08 (1.01-1.16)
35-39	1752 (13.0)	7673 (11.4)	1.25 (1.17-1.33)	1.13 (1.04-1.23)	1.15 (1.05-1.25)	1.16 (1.06-1.26)
40-44	561 (4.2)	2459 (3.7)	1.25 (1.13-1.38)	1.10 (0.97-1.23)	1.10 (0.98-1.25)	1.12 (0.99-1.27)
≥45	50 (0.4)	188 (0.3)	1.46 (1.06-1.99)	1.23 (0.89-1.71)	1.22 (0.87-1.71)	1.23 (0.88-1.72)

[a] Adjusted for age of other parent.
[b] Adjusted for age of other parent and family history of psychotic disorders.
[c] Adjusted for age of other parent, family history of psychotic disorders, socioeconomic status, and parity. Only includes patients with present socioeconomic status.

Table 3. Associations Between Parental Age and Early-Onset (<20 Years) Bipolar Disorder

Variable	No. (%)		Odds Ratio (95% Confidence Interval)	
	Cases (n=715)	Controls (n=3575)	Model 1	Model 2[a]
Paternal age, y				
<20	18 (2.5)	62 (1.7)	1.97 (1.13-3.47)	1.85 (1.04-3.30)
20-24	104 (14.5)	699 (19.6)	1 [Reference]	1 [Reference]
25-29	195 (27.3)	1198 (33.5)	1.10 (0.85-1.43)	1.16 (0.87-1.54)
30-34	192 (26.9)	866 (24.2)	1.50 (1.16-1.96)	1.58 (1.15-2.17)
35-39	108 (15.1)	449 (12.6)	1.65 (1.23-2.23)	1.66 (1.14-2.42)
40-44	62 (8.7)	205 (5.7)	2.06 (1.45-2.93)	1.96 (1.25-3.08)
45-49	25 (3.5)	70 (2.0)	2.44 (1.48-4.02)	2.32 (1.28-4.19)
≥50	11 (1.5)	26 (0.7)	2.81 (1.35-5.86)	2.63 (1.19-5.81)
Maternal age, y				
<20	54 (7.6)	274 (7.7)	1.18 (0.85-1.64)	1.18 (0.82-1.69)
20-24	193 (27.0)	1157 (32.4)	1 [Reference]	1 [Reference]
25-29	214 (29.9)	1143 (32.0)	1.12 (0.91-1.39)	0.96 (0.76-1.22)
30-34	144 (20.1)	641 (17.9)	1.35 (1.07-1.72)	1.00 (0.74-1.33)
35-39	84 (11.7)	288 (8.1)	1.76 (1.32-2.35)	1.15 (0.80-1.67)
≥40	26 (3.6)	72 (2.0)	2.17 (1.36-3.49)	1.24 (0.71-2.19)

[a] Adjusted for age of other parent.

BPD and increased paternal age was still evident after adjusting for maternal age, although the adjustment resulted in a wider confidence interval because of fewer study individuals. A maternal age effect was still statistically significant in 2 of the age group categories.

A total of 23 278 patients met our broader inclusion criteria (ie, requiring only 1 BPD discharge diagnosis). The results of these subanalyses (**Table 5**) were generally consistent with the results given in Table 2, although highest risk was found for offspring of fathers aged 50 to 54 years.

COMMENT

We found evidence of an association between paternal age and risk of BPD in the offspring of older fathers. We also found some support for a maternal age effect. The highest risk was observed for offspring of fathers 55 years and older and remained after controlling for maternal age. Although the adjustment for family history of psychotic disorders slightly reduced the risk of BPD with advancing paternal age, the risk persisted. Adjustment for SES

Table 4. Specificity Analysis on Paternal Age and Bipolar Disorder in 11 861 Patients Without a Schizophrenia Diagnosis After Their Bipolar Diagnoses

Variable	Odds Ratio (95% Confidence Interval)	
	Model 1	Model 2[a]
Paternal age, y		
<20	1.13 (0.94-1.35)	1.14 (0.95-1.37)
20-24	1 [Reference]	1 [Reference]
25-29	1.08 (1.01-1.15)	1.06 (0.98-1.13)
30-34	1.20 (1.13-1.29)	1.15 (1.06-1.25)
35-39	1.22 (1.13-1.31)	1.14 (1.04-1.25)
40-44	1.32 (1.21-1.43)	1.21 (1.09-1.35)
45-49	1.33 (1.19-1.50)	1.22 (1.07-1.40)
50-54	1.39 (1.15-1.68)	1.27 (1.04-1.56)
≥55	1.52 (1.14-2.03)	1.39 (1.03-1.87)
Maternal age, y		
<20	0.98 (0.89-1.07)	0.99 (0.90-1.10)
20-24	1 [Reference]	1 [Reference]
25-29	1.09 (1.04-1.15)	1.04 (0.98-1.11)
30-34	1.16 (1.09-1.23)	1.07 (0.99-1.15)
35-39	1.25 (1.17-1.34)	1.13 (1.03-1.23)
40-44	1.24 (1.11-1.37)	1.08 (0.95-1.23)
≥45	1.45 (1.04-2.01)	1.23 (0.87-1.73)

[a] Adjusted for age of other parent.

Table 5. Specificity Analysis on Paternal Age and Bipolar Disorder in 23 278 Individuals With 1 or More Admissions Having Bipolar Diagnoses

Variable	Odds Ratio (95% Confidence Interval)	
	Model 1	Model 2[a]
Paternal age, y		
<20	1.19 (1.05-1.35)	1.19 (1.04-1.35)
20-24	1 [Reference]	1 [Reference]
25-29	1.06 (1.01-1.11)	1.05 (1.00-1.11)
30-34	1.15 (1.10-1.20)	1.11 (1.05-1.18)
35-39	1.18 (1.12-1.24)	1.12 (1.05-1.19)
40-44	1.24 (1.17-1.32)	1.16 (1.08-1.25)
45-49	1.31 (1.20-1.42)	1.22 (1.10-1.34)
50-54	1.48 (1.30-1.69)	1.37 (1.19-1.58)
≥55	1.38 (1.12-1.70)	1.28 (1.03-1.59)
Maternal age, y		
<20	1.01 (0.95-1.08)	1.02 (0.95-1.09)
20-24	1 [Reference]	1 [Reference]
25-29	1.06 (1.02-1.10)	1.03 (0.98-1.07)
30-34	1.13 (1.08-1.18)	1.06 (1.01-1.11)
35-39	1.22 (1.16-1.28)	1.12 (1.05-1.19)
40-44	1.20 (1.12-1.30)	1.07 (0.97-1.17)
≥45	1.46 (1.15-1.86)	1.23 (0.96-1.58)

[a] Adjusted for age of other parent.

and parity had little effect on the paternal age estimates. The lack of an effect of potential confounders suggests that the paternal age effect is an independent risk factor for BPD. Furthermore, our results indicate that the paternal age effect might be most evident in patients with an early onset of the disorder.

RELATION TO PREVIOUS KNOWLEDGE

Increasing paternal age has been found to be associated with the risk of developing neurodevelopmental disorders. These include schizophrenia[6-8] and autism spectrum disorder.[10]

Zammit et al[8] reported an association of older paternal age with schizophrenia but not with other psychoses. However, the definition of "other psychoses" was broad and included drug-induced, paranoid, and affective psychoses. The causes of these disorders are likely to differ; therefore, it seems plausible that the results would have been different if the other psychoses group had been categorized into subcategories.

Malaspina et al[7] compared the paternal age effect on risk for schizophrenia with the paternal age effect on risk for other psychiatric conditions. The other category included 679 patients with affective disorder, anxiety, substance abuse, personality disorder, and eating disorders. The analyses showed an increased risk for these disorders in the offspring of fathers older than 49 years. The association between paternal age and other psychiatric conditions was explained as the result of including patients with misclassified schizophrenia. To reduce the risk for false-positive results in our study, subanalyses were performed that excluded cases who had been hospitalized with a diagnosis of schizophrenia after their last BPD diagnosis. We found no indication that misclassification had influenced the results.

METHODOLOGICAL ASPECTS

The main strengths of the study are that it is a large population-based sample of individuals, it covers practically all inpatient care, and routines for psychiatric care are standardized across Sweden. Validation studies confirm few false-positive diagnoses. Ekholm et al[20] conducted a validation study on patients with schizophrenic psychoses showing that the Hospital Discharge Register had high positive power to predict a standard research *DSM-IV* diagnosis of schizophrenic psychosis obtained by using the Operational Criteria (OPRICT) algorithm.[21] The validity of a discharge diagnosis of BPD was not examined, which we consider a limitation. However, the validity of BPD diagnoses is likely high because of the conservative and restrictive diagnostic culture for psychoses in Sweden. Validation of the clinical diagnoses of BPD in the Danish Psychiatric Central Register against the research criteria diagnoses of BPD demonstrated high agreement between them.[22] We believe that this gives support to the validity of BPD diagnoses in the Swedish Hospital Discharge Register because Denmark and Sweden have similar routines for registering psychiatric inpatient care. Furthermore, the definition of BPD used in this study required 2 or more inpatient hospitalizations for a core BPD diagnosis (the reasoning being that diagnostic precision would be greater if 2 admissions were required). When analyses were conducted using a broader inclusion criteria (ie, requiring only 1 BPD discharge diagnosis), the results mirrored those in the analyses using our narrow definition of BPD. Excluding patients with BPD who were diagnosed as having schizophrenia on their last admission did not materially change our results.

Our sample of patients admitted for BPD covers *ICD* diagnoses comparable with bipolar types I and II. Most cases in our sample have classic bipolar type I or bipolar diag-

nosis not otherwise specified, and the generalizability to the narrower category of bipolar type II is unknown. During the case inclusion period used in this study, diagnostic traditions regarding BPD have evolved in Sweden and elsewhere in the world. At the inception of the period, BPD referred primarily to the classic bipolar type I. During the past 15 years, the importance of bipolar spectrum disorders became increasingly recognized.[23] For this reason, a slight shift in the meaning of a bipolar diagnosis might have occurred such that a greater proportion of individuals with diagnoses pertaining to the wider bipolar spectrum was included during the latter phase of the study. However, during the past 15 years, the incidence of BPD has not increased, indicating that a possible widening of the bipolar diagnosis could not have been substantial. Furthermore, this study included only readmitted inpatient cases, which diminishes the likelihood of including individuals with milder forms of BPD.

The *ICD-8* and *ICD-9* codes of BPD do not reliably distinguish between patients with and without psychotic features. Therefore, a comparison between individuals with vs without psychosis is not possible, which is a limitation to the study. An additional limitation is the lack of personality trait data.

The father of the offspring was assumed to be the husband of the mother at the time of birth or by acknowledgment of the mother. In a study[24] examining published evidence on levels of false paternity, the median discrepancy was estimated to be 3.7% (interquartile range, 2.0%-9.6%) for studies based on populations chosen for reasons other than disputed paternity. The accuracy of paternity in the Multigeneration Register has not been investigated (to our knowledge), but this type of misclassification should most likely only dilute the results.

In this study, highest education within the family was used as the SES indicator. Critics might claim that occupational status is a more accurate measurement of SES. Still, there are several advantages of using education over occupational social class as a measure of social status, one of which is better comparability internationally and over time. The drawback might be that educational structures change over time and that the general education level has increased, which could have contributed to skewness in birth cohorts. However, our matched case-control design reduces this skewness in that all cases are compared with controls born the same year.

In our study, parity was defined as the number of live births to the mother, including the study infant. We acknowledge the limitation that stillborn children do not receive a personal identification number and are not included in the Multigeneration Register. However, stillbirths are rare in Sweden. Fellman and Eriksson[25] estimated the rate of stillbirths in Sweden from 1991 to 2001 as 3.4 per 1000 births for singletons. Adjusting for parity did not affect the analyses; therefore, it is unlikely that the exclusion of stillbirths would have had a meaningful effect on our results.

Age at onset was defined as the age at which a case first was admitted and met the criterion for a BPD diagnosis. Age at first hospitalization is highly correlated with onset of acute symptoms and is considered a fairly objective measure of age at onset.[26] Our definition of early age at onset included only the individuals hospitalized at an early age and might represent patients with a more severe form of early-onset BPD and not patients who at an early age experienced milder BPD symptoms not requiring hospitalization. Patients born before 1953 with early-onset BPD might not be included in the early-onset subanalyses if their first admission occurred before the register covered all inpatient care in Sweden. To summarize, all individuals included in the early-onset subanalyses were truly early-onset cases, but it is likely that some individuals with early-onset BPD were not included.

POSSIBLE EXPLANATIONS OF THE FINDINGS

Our results reveal an association between paternal age and risk for BPD in the offspring. Personality of older fathers has been suggested to explain the association between mental disorders and advancing paternal age.[8] However, the mental disorders associated with increasing paternal age are under considerable genetic influence. Advanced paternal age is known to be associated with autosomal dominant disorders and with disorders having a more complex genetic cause. Therefore, it is possible that the effect of increasing paternal age is genetically mediated. Because spermatogonial cells replicate every 16th day, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years,[27] the risk of DNA copy errors increases with advancing age. Therefore, it has been suggested that the disorders associated with advancing paternal age could partially result from de novo mutations. This conjecture is further supported by recent reports of high evidence of de novo mutations in autism.[28] Although the results are inconclusive concerning the association between paternal age and nonfamilial schizophrenia compared with familial schizophrenia,[29] de novo mutations might be a possible explanation for the paradox of common heritable severe mental disorders not being eliminated from the general population, despite generally low fertility.[30]

As men age, successive germ cell replications occur, and de novo mutations accumulate monotonously as a result of DNA copy errors.[31] Women are born with their full supply of eggs that have gone through only 23 replications, a number that does not change as they age. Therefore, DNA copy errors should not increase in number with maternal age. Consistent with this notion, we found smaller effects of increased maternal age on the risk of BPD in the offspring.

Because altered regulation has been associated with increasing paternal age,[32] epigenetic regulation (such as DNA methylation), in addition to the de novo mutations, could be involved in mediating the paternal age effect. This argument finds further support from evidence suggesting that de novo mutations cannot fully explain the association between advancing paternal age and genetic disorders.[33]

To test the hypothesis of genetically mediated causes, we performed a subanalysis on cases with early-onset BPD. Because early-onset BPD has shown greater heritability than BPD that occurs later in life,[13,14] it is evident that this subgroup is under a greater genetic influence. If the paternal age effect is genetically mediated, it should be more likely to cause BPD earlier than later in life, similar to BPD that

is genetically inherited within affected families. Therefore, we believe that our finding of a strong association between advancing paternal age and early-onset of BPD provides additional support for the mutation hypothesis.

There was also an association between the risk of early-onset BPD and teenage fathers. A similar association has been reported in investigations of schizophrenia and paternal age.[9] Although some evidence suggests that the offspring of very young fathers might have an increased risk for de novo genetic disorders as a result of immature sperm, contributing to a U-shaped curve for the association between paternal age and offspring risk for genetic disorder,[34] other factors might underlie this association. For instance, teenage fathers are more likely to have experienced a stressful environment and to have conduct problems.[35] Moreover, they are more likely to come from disadvantaged families and to lack education,[36] 2 conditions associated with inadequate prenatal care.[37] Finally, teenage fathers are more likely to smoke and to abuse alcohol and other drugs[38,39] compared with older fathers. Previous studies[40,41] have reported associations between paternal smoking or alcohol use and adverse reproductive outcomes.

CONCLUSIONS

The risk of BPD was significantly higher in the offspring of older men compared with the offspring of younger men. This difference was stronger in early-onset BPD, which supports the notion that, similar to other neurodevelopmental disorders, older paternal age increases the risk for de novo mutations in susceptibility genes for BPD.

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