



Parental age and risk of bipolar disorder in offspring



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ABSTRACT

We investigated prospectively documented parental age and bipolar disorder (BD) in a multi-ethnic birth cohort. The study was based on a nested case–control design from the Child Health and Development Study (CHDS) birth cohort from 1959 to 1966. Potential cases with BD were ascertained by database linkages between CHDS, Kaiser Permanente Medical Care Plan (KPNC), and Alameda County Behavioral Health Care Services, and mailed questionnaires. Consensus diagnoses with the SCID for DSM-IV-TR were made. The total number of BD cases was 94. Controls ($N=746$) were selected from the birth cohort and matched on date of birth, sex, and KPNC membership or residence in Alameda County. For every 10-year increment of paternal age, there was no significant association with BD, adjusting for maternal age. There was also no significant association between maternal age, modeled in 10-year increments, and risk of BD after adjustment for paternal age and maternal race, although there was a suggestion for a protective relationship between increasing maternal age and BD with psychotic features. These findings suggest that if advanced paternal age is a risk factor for BD, the strength of the relationship is small.

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1. Introduction

Advanced paternal age is a well-replicated risk factor for schizophrenia (Brown et al., 2002; Malaspina et al., 2001; Zammit et al., 2003; Dalman and Allebeck, 2002). Bipolar disorder (BD) shares several features with schizophrenia, including susceptibility genes, familial aggregation (Lichtenstein et al., 2009), psychotic symptoms, and response to antipsychotic medications (Craddock et al., 2006; Farmer et al., 2007). To date, however, relatively few previous studies have specifically investigated the question of an association between paternal age and risk of BD. Frans et al. (2008), in a nested case–control study based on a Swedish national cohort, found an association ($OR=1.37$ for fathers aged >54) between paternal age and BD which was statistically significant following adjustment for covariates, including maternal age. A U-shaped distribution for associations between both teenage and older fathers and early onset ($<age 20$) BD in offspring was also observed in that study; moreover, the paternal age and BD associations for fathers in these subgroups were particularly robust. Paternal age and BD was investigated in a second study of a Swedish birth cohort (Menezes et al., 2010), which overlapped in time

with the sample of Frans et al. (2008). The authors observed a non-significant, 1.2-fold increase in risk of BD for every 10-year increase in paternal age, following adjustment for maternal age and other potential confounders. There were, however, significant increases in BD for the 35–39 and 40–44 year age groups, though not in fathers older than age 44.

Buizer-Voskamp et al. (2011), in a register-based study from the Netherlands, did not find an association between increasing paternal age and risk of BD. While Laursen et al. (2007), in a study from Denmark, observed a significantly increased risk of BD for offspring of fathers aged 51–55, and in two other younger age categories, the risk of BD was not consistently increased across paternal age categories. The authors of the latter study also appeared to have interpreted this finding as indicative of no association.

Previous studies of paternal age at offspring birth and schizophrenia have generally revealed stronger effects than corresponding studies of BD. In a meta-analysis by Miller et al., the risk of schizophrenia was increased 1.66-fold for offspring of fathers aged 50 or greater. Individual positive studies frequently reported even larger effect sizes. For example, in the Prenatal Determinants of Schizophrenia (PDS) Study (Susser et al., 2000), based on the Child Health and Development Study (CHDS) birth cohort, the risk of schizophrenia and other schizophrenia spectrum disorders (SSD) in offspring was increased by a factor of nearly 1.9-fold for every 10 year increase in paternal age, adjusting for maternal age, and

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offspring of fathers aged over 45 evidenced a 2.7-fold increased risk of SSD (Brown et al., 2002), consistent with other studies (Malaspina et al., 2001; Zammit et al., 2003; Dalman and Allebeck, 2002). In two of the negative studies of paternal age and BD cited above (Laursen et al., 2007; Buizer-Voskamp et al., 2011), associations were observed between paternal age and risk of schizophrenia.

In the present study, we therefore aimed to examine the relationship between paternal age at time of the offspring's birth and risk of BD in offspring. We also assessed maternal age and risk of BD. In one of the previous studies cited above, advanced maternal age was associated with an increased risk of BD, but the association became attenuated and non-significant following adjustment for paternal age (Menezes et al., 2010). In the second study cited above, there was no significant relationship between maternal age and risk of BD, though slightly increased, significant risks were observed for mothers aged 30–39 (Frans et al., 2008).

The present study was based on a follow-up investigation of BD in the CHDS birth cohort. The study featured three advantages to previous work. First, the diagnoses were obtained following directly administered research-based assessments and consensus diagnosis, in contrast to previous studies which relied upon registry-based diagnoses. This is expected to have diminished the potential for diagnostic misclassification as compared to the previous studies, which were based on registry diagnoses. It also allowed for exploratory analyses of whether paternal or maternal age was related to specific subtypes of BD, though power was compromised due to the small sample sizes for each subtype (see Section 4). Second, this is the first study of paternal age and BD to be conducted in the USA, and featured a multi-ethnic cohort, in contrast all previous studies, in which the vast majority of subjects were Caucasian due to their having been conducted in European countries.

2. Method

2.1. Description of the cohort

Cases and controls were drawn from the Child Health and Development Study (CHDS) birth cohort (van den Berg, 1979). During 1959–1966, the CHDS recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) in Alameda County, California. Their liveborn offspring ($N=19,044$) were automatically enrolled in KPNC. Approximately 30% of the population of the county was enrolled in KPNC. The KPNC membership was largely representative of the population of the Bay Area of California at the time, based on ethnicity, education, and occupation.

2.2. Collection of parental age data

Each gravida in the CHDS was administered an interview that included questions on parental birth dates at the time of enrollment of the pregnancy in the cohort. Data on parental age were only recorded for gravidae who were married, which included nearly the entire sample. Biological paternity of offspring was recorded for the vast majority of subjects.

2.3. Case ascertainment and diagnosis

Cases with potential DSM-IV BD (BD I, BD II, BD NOS, BD with psychotic features) were ascertained using screening procedures from three sources: the KPNC electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailed survey to the entire living CHDS birth cohort (mothers and offspring). These methods of ascertainment were used to maximize identification of patients with BD. CHDS cohort members who belonged to KPNC at the date of first treatment would have been ascertained from this source. Subjects who left KPNC before the first treatment for BD and who did not have other health insurance, but still lived in Alameda County would have likely been treated by ABHCS if they sought treatment. Subjects who were not ascertained by these two approaches were identified by a mailed survey including questions on mental health treatment sent out to all living mothers and cohort members in the CHDS, and followed up by a diagnostic screening interview.

2.3.1. Ascertainment by KPNC

Subjects with potential BD were identified by screening the inpatient and outpatient databases of KPNC. Computerized record linkages between the CHDS and KPNC identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of KPNC members, whether in KPNC or as referrals to non-KPNC hospitals, and covered the period from 1981 to 2010. The maximum duration of follow-up by this source was 29 years. Subjects from the KPNC inpatient database were considered to screen positive for potential BD based on discharge diagnoses of ICD-9 295–298. A database of outpatient treatment was introduced in 1981, but does not contain searchable codes for diagnoses until 1995. Potential BD cases from the outpatient database were considered to screen positive based on ICD-9 diagnoses of 295–298 excluding unipolar major depressive disorder. Case ascertainment was complemented by the outpatient pharmacy database of KPNC, which commenced in 1992. Cases screened positive from this source based on prescriptions for mood stabilizing medications for BD (lithium, carbamazepine, valproic acid).

Subjects identified by any of these methods were invited to participate in the study by a letter to the most recent address, and were sent a postcard indicating if they did not wish to be contacted. Those who did not return the postcard were contacted to arrange an appointment for a diagnostic interview. Repeat appointments were scheduled for subjects who failed to show up for the initial and/or subsequent interviews. Extensive efforts were made to locate individuals no longer living at the most recent known address, including Department of Motor Vehicles records, telephone directories, and the subjects' parents or siblings from CHDS or KPNC files.

2.3.2. Ascertainment by Alameda County Behavioral Health Care Services (ABHCS) database

Subjects with potential BD treated as outpatients were ascertained by electronic record linkage between the CHDS and ABHCS identifiers; the ABHCS database included treatment from 1993 to 2009; thus the maximum duration of follow-up from this source was 16 years. These subjects screened positive based on ICD-9 outpatient diagnoses of 295–298, excluding unipolar major depressive disorder. Procedures for recruitment and location of subjects were similar to those described above for ascertainment by KPNC, except that mailings were conducted by staff members from ABHCS rather than KPNC.

2.3.3. Ascertainment of CHDS birth cohort by mailed questionnaire and follow-up

The third method of ascertainment was initiated by letters mailed to all living mothers ($N=6971$) and cohort members ($N=13,009$) with known addresses in the whole CHDS cohort accompanied by a questionnaire on mental and physical health. This protocol was conducted from 2009 to 2011. Questionnaire respondents who reported "mental health problems" in an eligible cohort member (including the respondent him or herself) were contacted by a trained KPNC study interviewer (see Section 2.3.4 for qualifications of interviewers), who administered the Family Interview for Genetic Studies (FIGS) in order to screen for possible BD or psychotic illness in the cohort member. If the interview indicated at least one bipolar and/or psychotic symptom (delusions/hallucinations), then the cohort member was considered to have screened positive, and was invited to participate in the diagnostic interview. If the respondent (mother or sibling) described symptoms of BD or psychosis in a birth cohort member, the respondent was asked about willingness to have the study contact the affected family member about participation in the study. If the respondent agreed, the affected cohort member was invited to participate in the interview.

The total number of potential cases of BD identified from these three sources (KPNC, ABHCS, cohort mailing) was 448 (see Fig. 1).

2.3.4. Diagnostic protocol

We sought all potential cases identified from the above ascertainment procedures to schedule a diagnostic interview with the Structured Clinical Interview for DSM-IV TR (SCID). A total of 214 identified subjects (48% of those ascertained) were interviewed. The reasons that interviews were not conducted are given in Fig. 1. Study interviewers were required to have a minimum of a master's degree in a mental health field and were trained to reliability on this instrument. DSM-IV-TR diagnoses including diagnostic qualifiers representing subtypes of BD (BD I, BD II, BD NOS, BD with psychotic features) were systematically assigned by consensus of three doctoral-level experienced clinicians including research psychiatrists. Information was supplemented with inpatient and outpatient psychiatric records for potential cases in whom a definitive diagnosis could not be made from the SCID. This protocol yielded 72 total BD cases.

2.3.5. Ascertainment from PDS I study

Additional cases of BD ascertained by KPNC records as part of an earlier study (Prenatal Determinants of Schizophrenia I, PDS I) (Susser et al., 2000), in which case ascertainment ended in 1998, were included in the present study. Although the aim of PDS I was to identify schizophrenia and other schizophrenia spectrum disorder cases, BD cases were also diagnosed by interview. The protocol for PDS I included the same electronic linkages with the KPNC inpatient, outpatient, and pharmacy

databases, and used the same ICD-9 diagnostic codes of 295–298. Ascertainment included the period from 1981–1998. The only other differences in the ascertainment/screening methods between the PDS I and the protocol described above for potential BD cases identified from KPNC, are that the former did not include review of pharmacy records for treatment with mood stabilizers and the PDS I included a second screening step, which consisted of review by a research psychiatrist of abstracted data from inpatient/outpatient records for psychotic symptoms. The Diagnostic Interview for Genetic Studies (DIGS), rather than the SCID, was used to diagnose cases in the PDS I, and consensus diagnoses were based on review of the DIGS and psychiatric records by three research psychiatrists. There were 23 BD cases diagnosed from the PDS I study. Therefore, in total, there were 95 BD cases diagnosed following interview and ascertainment from all sources (KPNC, ABHCS, CHDS mailing, PDS I).

Following complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and KPNC.

The numbers of subjects ascertained, sought for interview, interviewed, and diagnosed with BD are provided in Fig. 1. The reasons for lack of participation are also included in the figure.

2.4. Selection of matched controls

The first step in selection of controls was exclusion of CHDS cohort members who screened positive for potential bipolar or psychotic disorders ($N=448$) in this study or the prior PDS I study; that is, they did not meet any of the screening criteria described above (see Section 2.3.5). In order to ensure that controls would have been equally likely (as their matched cases) to be ascertained if they had received treatment for BD in KPNC or ABHCS, controls were matched to cases on membership in KPNC (for cases identified by KPNC records) or residence in Alameda County (for cases identified by ABHCS or CHDS mailing survey and protocol) in the year the case was first treated. For KPNC, membership in the health plan at the time of first treatment of the case was used for control matching. For cases treated by ABHCS, controls were ascertained using DMV records indicating residence in Alameda County at the time of case diagnosis. For cases ascertained by the mailed survey, controls were also defined by DMV records indicating residence in Alameda County. The vast majority of the subjects who received the mailed questionnaire were Alameda County residents. Potential controls who belonged to KPNC at the time of case ascertainment were excluded from the control pool for cases ascertained from ABHCS or the mailed survey. Siblings of selected controls

were excluded from further control selection, such that all controls were independent observations, each of which represented a single family or pregnant woman.

Controls were also matched to cases on date of birth (± 30 days), sex, and availability of maternal archived sera (for serologic studies). An 8:1 ratio of controls to cases was selected as it represented the maximum number of controls that could be successfully matched to cases on all criteria in the study and in order to maximize statistical power.

This protocol yielded 754 matched controls. The corresponding cases and matched controls are termed a “matched set.”

2.5. Description of the analytic sample

One family had two siblings with BD; one of these siblings was randomly excluded, since these two cases represented non-independent observations. This resulted in 94 cases. This sample was composed of 78 with BD I, 12 with BD II, and 4 with BD NOS. Among these, 83 had data on paternal age (69 BD I, 10 BD II, 4 BD NOS). There were 92 BD cases with maternal age data (76 BD I, 12 BD II, 4 BD NOS). For BD with psychotic features, there were 39 cases in the overall sample, 38 cases with maternal age data and 34 cases with paternal age data.

Eight matched controls corresponding to the case that was excluded were also excluded, yielding 746 matched controls. There were 679 matched controls with paternal age data and 746 matched controls with maternal age data.

2.6. Statistical analysis

Appropriate to the nested case-control study design, point and interval estimates of odds ratios were obtained by fitting conditional logistic regression models for matched sets. Statistical significance was judged at $\alpha=0.05$. The primary exposure variables were parental ages (paternal and maternal ages were examined separately) at the time of the offspring's birth. We examined parental age first in 10 year age increments and then as a categorical measure (to allow for a general, non-linear effect of parental age on the risk of BD). For the categorical analyses, paternal age was classified into four age categories: 15–24, 25–34 (the referent category), 35–44, and ≥ 45 . Maternal age was classified as < 20, 20–29 (the referent category), 30–39, and ≥ 40 . This scheme afforded natural groupings by decade of age.

2.6.1. Covariates

Given the high correlation between paternal and maternal age, we adjusted for these covariates, in analyses of paternal, and maternal age, respectively. We classified paternal age and maternal age into two categories based on the median values (paternal age < 31 and ≥ 31 ; maternal age < 27, ≥ 27).

Other covariates selected *a priori* as potential confounders included paternal/maternal education, paternal/maternal ethnicity, and gestational age at the time of birth. Data on these factors were included in the CHDS database. Paternal/maternal race was defined as white (referent category), black, and other. Education was defined categorically: less than high school, high school graduate (referent category), some college/college graduate. Gestational age at time of birth was classified in days. Bivariate analyses were conducted to determine the association between these covariates and the outcome (BD). In accord with standard epidemiologic practice, covariates were included in the final model based on all of the following criteria: (1) associations with the primary exposure ($p < 0.10$); (2) associations with BD ($p < 0.10$); (3) a $> 10\%$ reduction in the odds ratio following inclusion of each covariate, individually, in the statistical model (Greenland, 1989).

All statistical analyses were performed using SAS 9.2© (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Comparisons of covariates between cases and controls (Table 1)

Maternal race was related to BD risk, though the result fell short of statistical significance ($p=0.07$). The association appeared to have been accounted for predominantly by a decrease in prevalence of BD in the “other” category, which includes a heterogeneous mixture of ethnicities. There were no statistically significant differences between BD cases and controls on any of the other covariates.

3.2. Covariates in relation to paternal and maternal age (Tables 2a and 2b)

Paternal age was associated with paternal race, though the effect appeared to be accounted for by increased paternal age among a modest number of subjects in the “other” category, and

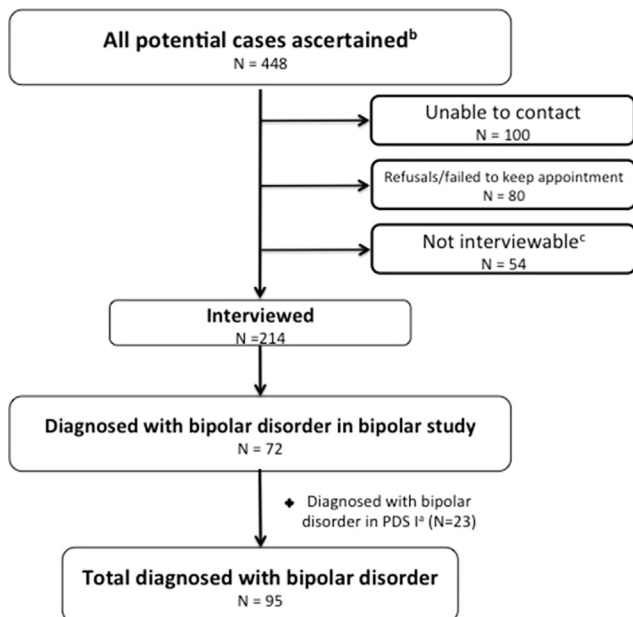


Fig. 1. ^aPDS I=Prenatal Determinants of Schizophrenia I Study.

^bFrom database linkages between CHDS cohort and Kaiser Permanente Medical Care Plan (KPNC), Alameda County Behavioral Health Care Services (ABHCS) (see Section 2 for further description of database diagnoses) and subjects screening positive by mailed questionnaire on mental health to offspring and mothers in CHDS cohort. For subjects ascertained by mailing to offspring and mothers in CHDS cohort, surveys indicating mental health problems were returned from 535 subjects. Of these, DIGS were completed on 376 subjects, and among these, 80 subjects screened positive for bipolar disorder or psychosis. All 80 were targeted for interview.^cIncludes deceased, incarcerated, no physician permission, too ill (psychosis, severe mental disability).

the result fell short of statistical significance; there was no difference in paternal age between whites and blacks (Table 2a). Paternal age was associated with paternal education, with somewhat higher paternal ages for the less than high school group. There was no association between paternal age and gestational age at birth. Hence, the analyses of paternal age in relation to BD were adjusted only for maternal age in the main analyses, since no covariate tested was related to both paternal age and BD.

Maternal age was associated with maternal race; blacks had decreased maternal age (Table 2b). Maternal age was also associated with maternal education, though the effect was curvilinear, with greater maternal age at the extremes of education. Of all covariates tested, only maternal race was associated with both maternal age and BD (Tables 2a and 2b). Consequently, in the main analyses, maternal age was adjusted for both paternal age and maternal race.

3.3. Comparison of interviewed and non-interviewed ascertained cases (Table 3)

Potential cases who were interviewed, compared to potential cases who were not interviewed, demonstrated a significant increase in paternal age and a trend for increased maternal age. Interviewed potential cases also had significantly increased gestational age at birth. There were no differences between interviewed and non-interviewed potential cases with regard to maternal race and maternal education. The implications of these results are provided in Section 4.

3.4. Paternal age and risk of BD

The proportions of cases and controls by paternal age category were similar. For every 10 year increment of paternal age, there was no association with BD (OR=1.04, 95% CI=0.75–1.44, $p=0.83$). Adjusting for maternal age had no appreciable effect on this result (OR=1.30, 95% CI=0.80–2.12, $p=0.29$). For further reassurance, we adjusted for paternal race, paternal education, and gestational age at birth, in addition to maternal age. There was only a negligible change in the result (OR=1.28, 95% CI=0.73–2.26, $p=0.39$). In the analyses of individual paternal age categories, there was no relationship between this exposure and risk of BD in the model adjusting for maternal age; though the odds ratios ranged from 1.16 for the youngest category and 1.45 for the oldest category, the findings were well short of statistical significance (Table 4). The findings were also not appreciably altered adjusting for the other covariates (data available on request).

We then assessed whether paternal age was related to two specific subtypes of BD, bipolar I disorder (BD I) and BD with psychotic features. For every 10 year increment of paternal age, there was no association with BD I in both the crude analysis (OR=1.01, 95% CI=0.71–1.44, $p=0.96$) and adjusting for maternal age (OR=1.20, 95% CI=0.68–2.10, $p=0.53$). There was also no association between every 10-year increment of paternal age and BD with psychotic features in both the crude analysis (OR=0.77, 95% CI=0.46–1.27, $p=0.30$) and in the analysis that adjusted for maternal age (OR=1.57, 95% CI=0.70–3.52, $p=0.28$).

3.5. Maternal age and risk of BD

There was no association between maternal age, modeled in 10-year increments, and risk of BD (OR=0.83, 95% CI=0.57–1.20, $p=0.31$). Adjusting for paternal age and maternal race did not appreciably alter this result (OR=0.64, 95% CI=0.34–1.19, $p=0.16$). Adjustment for these covariates as well as maternal education and gestational age at birth also did not alter the result (OR=0.68, 95% CI=0.37–1.28, $p=0.24$). The individual maternal age categories were not significantly associated with BD, with odds ratios ranging

Table 1

Comparison of covariates between bipolar cases and matched controls.

Parental demographics	Cases (N=94)	Controls (N=746)	P
Paternal race, N (%)			0.14
White	55 (69.6)	387 (59.1)	
Black	19 (24.1)	189 (28.9)	
Other	5 (6.3)	79 (12.0)	
Paternal education, N (%)			0.51
Less than high school	12 (14.6)	134 (29.8)	
High school graduate	26 (31.7)	292 (28.4)	
Some college/college graduate	44 (53.7)	350 (51.8)	
Maternal race, N (%)			0.07
White	64 (68.8)	435 (58.6)	
Black	24 (25.8)	215 (29.0)	
Other	5 (5.4)	92 (12.4)	
Maternal education, N (%)			0.85
Less than high school	18 (20.9)	128 (18.5)	
High school graduate	32 (37.2)	271 (39.2)	
Some college/college graduate	36 (41.9)	293 (42.3)	
Gestational age at birth (days)			0.33
Mean (S.D.)	281.4 (15.8)	279.8 (14.1)	

Table 2a

Relationship between paternal age and paternal demographic variables.

	N	Paternal age, Mean (S.D.)	P
Paternal race			0.08
White	424	31.6 (6.7)	
Black	204	31.6 (7.5)	
Other	84	33.2 (8)	
Paternal education			0.02
Less than high school	140	34 (8.6)	
High school graduate	214	30.4 (7.1)	
Some college/college graduate	383	31.5 (6.3)	
	β	Standard error	P
Gestational age at birth	–0.009	0.018	0.60

from 1.29 for the youngest age category and 1.46 for the oldest, adjusting for paternal age and maternal race (see Table 5). Maternal age modeled in 10-year age increments was not associated with BD I in the crude analyses (OR=0.84, 95% CI=0.57–1.26, $p=0.41$) and the analysis adjusting for paternal age (OR=0.77, 95% CI=0.39–1.53, $p=0.45$), nor were there any associations between individual maternal age categories and risk of BD I (results available on request).

Interestingly, maternal age analyzed in 10-year age increments demonstrated a protective relationship with BD with psychotic features (OR=0.51, 95% CI=0.28–0.94, $p=0.03$). The finding persisted after adjustment for paternal age (OR=0.32, 95% CI=0.10–0.98, $p=0.046$).

4. Discussion

In the present study, we found no relationship between paternal age and risk of BD in offspring. Maternal age was also not associated with this outcome. There was also no association between paternal or maternal age and risk of BD I disorder, the more narrow phenotype. The study benefited from a population-based birth cohort with prospectively obtained measures of paternal and maternal age and rigorous diagnoses from a direct interview with a structured research instrument developed for DSM-IV criteria, complemented by psychiatric records. The latter of these strengths most likely provided greater diagnostic validity than in previous studies and allowed for the novel exploratory investigation of relationships between parental age and subtypes

Table 2b
Relationship between maternal age and maternal demographic variables.

	N	Maternal age, Mean (S.D.)	P
Maternal race			0.047
White	498	28.1 (5.8)	
Black	239	27.1 (6.7)	
Other	97	28.6 (5.8)	
Maternal education			< 0.001
Less than high school	146	28.9 (7.1)	
High school graduate	303	27 (5.9)	
Some college/college graduate	329	28.7 (5.2)	
	β	Standard error	P value
Gestational age at birth	0.002	0.015	0.91

Table 3
Characteristics of potential case subjects interviewed and not interviewed.

Characteristic	Potential cases interviewed (N=214)	Potential cases not interviewed (N=234)	P
Paternal age (years)			0.01
Mean (S.D.)	32.2 (7.7)	30.1 (7.5)	
Maternal age (years)			0.06
Mean (S.D.)	27.7 (6.7)	26.5 (6.5)	
Maternal race, N (%)			0.48
White	119 (55.9)	118 (51.1)	
Black	76 (35.7)	87 (37.7)	
Other	18 (8.4)	26 (11.2)	
Maternal education, N (%)			0.75
Less than high school	47 (24.2)	52 (25.2)	
High school graduate	76 (39.2)	86 (41.8)	
Some college/college graduate	71 (36.6)	68 (33.0)	
Gestational age at birth (days)			0.03
Mean (S.D.)	282.5 (17.7)	278.6 (19.5)	

of BD, discussed further below. In addition, to our knowledge, this is the first investigation of this question in a multi-ethnic sample.

Compared to a previous study of paternal age and schizophrenia, which was based on the PDS study (Brown et al., 2002), the odds ratio for the association with BD was markedly lower than for schizophrenia. Although a previous study, in Sweden, that specifically examined this question yielded significant findings, the relationships between paternal age and BD were also considerably attenuated compared to two previous studies of schizophrenia in Sweden (Zammit et al., 2003; Dalman and Allebeck, 2002). In the first, offspring of fathers ≥ 55 at the time of birth had a fourfold increased risk of schizophrenia, and in the latter study there was a nearly threefold increased risk for offspring of fathers ≥ 45 . In the CHDS cohort, the risk of schizophrenia was increased nearly threefold for fathers above this age (Brown et al., 2002), and most, though not all, previous studies of schizophrenia documented significant associations, though effect sizes have not always been this large (Miller et al., 2011).

Our findings are consistent with two previous studies of BD, from the Netherlands (Buizer-Voskamp et al., 2011) and Denmark (Laursen et al., 2007), discussed above, which found no clear evidence for associations between paternal age and BD. However, the only previous study to show a consistent, significant overall association following adjustment for confounding factors also had the largest

sample size ($> 13,000$ cases) (Frans et al., 2008), suggesting that the greater statistical power may have been responsible.

A third finding, which is novel, is that older maternal age had a protective effect on risk of BD with psychotic features in this study. Although this may be a chance finding, as it was observed *post-hoc*, previous studies suggest that advanced maternal age is protective of adverse externalizing behaviors (Saha et al., 2009) and decreased risk of several mental health problems (Fergusson and Woodward, 1999). In two previous studies, maternal age was related to slight but generally non-significant increases in risk of BD (Frans et al., 2008; Menezes et al., 2010). However, neither of these studies specifically examined BD with psychotic features.

One limitation of the present study that may have reduced the potential to detect significant associations is the modest sample size, which was considerably smaller than previous studies. Consequently, we investigated the statistical power to detect an effect of paternal age on BD (Stevenson, 2012). Statistical power to detect a twofold effect of paternal age ≥ 35 , as compared to < 35 was 0.83, while the power to demonstrate a 1.5-fold effect was 0.40. Hence, it is likely that power in this study was not adequate to detect the observed effects within the range of Frans et al. (2008). Hence, we cannot rule out a small effect of paternal age on BD risk.

A second limitation is the possibility that cases of BD in the cohort may have been missed. To obviate this, we identified cases not only using KPNC records, but also by ABHCS records and a direct mailing of the entire surviving cohort and their mothers. These procedures would have captured cases who left KPNC before they could have been ascertained. Moreover, to diminish the potential for bias, controls were selected who represented the source population that gave rise to cases. Nonetheless, we found that interviewed potential cases had significantly greater paternal age, and a trend for increased maternal age, than non-interviewed potential cases. Since we did not identify our cases based on the receipt of treatment, we believe that some of the key reasons for not having been interviewed included factors that are often associated with BD, including psychosis or mental disability, deceased status, and inability to keep appointments; this is expected to lead to underascertainment of BD. Hence, if a greater proportion of ascertained potential cases were interviewed, this would tend to increase the number of BD cases with younger fathers. Assuming that older paternal age is related to BD, this would have diminished the association observed in our study. Under this same assumption, one would have also expected that the diminished risk of BD with psychotic features with increased maternal age would have been even lower if more ascertained subjects had been interviewed, given that this would have led to a greater number of younger mothers with BD in the sample.

We also wish to comment on potential explanations for the observed differences in the effects of paternal age on schizophrenia and BD. One potential explanation for the paternal age associations with schizophrenia, BD, and other neuropsychiatric disorders including autism (Reichenberg et al., 2006) is a heightened occurrence of *de novo* mutations due to DNA copy errors in spermatogonia of older fathers. These mutations were strongly associated with increasing paternal age in a recent study (Kong et al., 2012). A second proposed explanation is a disruption in epigenetic regulation. If these mechanisms are *bona fide* explanations of the effect of paternal age, however, it will be necessary to account for a greater effect on genes that confer risk for schizophrenia compared to BD. Interestingly, a recent study found that large and rare copy number variants (CNVs) were significantly more common in schizophrenia cases than BD cases, and there were no significant differences in CNV burden between BD and controls (Grozeva et al., 2010). If advanced paternal age was related to increased large and rare CNVs, this may contribute to observed differences in effects of this risk factor in schizophrenia

Table 4
Paternal age by category and bipolar disorder.

Paternal age (years)	Cases (N, %)	Controls (N, %)	OR (95% CI)	P	OR (95% CI) ^a	P ^a
15–24	14, 16.87%	97, 14.29%	1.30 (0.68, 2.49)	0.44	1.16 (0.57, 2.34)	0.68
25–34	41, 49.40%	366, 53.90%	1	NA	1	NA
35–44	23, 27.71%	180, 26.51%	1.11 (0.65, 1.92)	0.70	1.25 (0.67, 2.31)	0.48
≥45	5, 6.02%	36, 5.30%	1.27 (0.47, 3.41)	0.64	1.45 (0.51, 4.11)	0.49

^a Adjusted for maternal age.

Table 5
Maternal age by category and bipolar disorder.

Maternal age (years)	Cases (N, %)	Controls (N, %)	OR (95% CI)	P	OR (95% CI) ^a	P ^a
< 20	9, 9.78%	44, 5.90%	1.56 (0.71, 3.40)	0.27	1.29 (0.46, 3.58)	0.63
20–29	54, 58.70%	428, 57.37%	1	NA	1	NA
30–39	23, 25.00%	247, 33.11%	0.72 (0.44, 1.20)	0.21	0.60 (0.31, 1.16)	0.13
≥40	6, 6.52%	27, 3.62%	1.78 (0.69, 4.57)	0.23	1.46 (0.52, 4.11)	0.47

^a Adjusted for paternal age and maternal race.

and BD. That said, an increase in CNVs in certain genes has been demonstrated in BD (Lee et al. 2012).

In a recent study from Denmark, paternal age at the time of birth of the first child, rather than age at birth of the subject under study accounted for the association between paternal age and schizophrenia (Petersen et al., 2011). As noted by the authors, that finding is consistent with heritable personality traits related to delayed childbearing. Yet, patients without a family history of schizophrenia had older fathers than familial patients (Malaspina et al., 2002). Moreover, some animal studies of paternal age effects on offspring, which are unconfounded by such genotypes, have suggested that advanced paternal age is associated with impaired learning, diminished exploration (Bradley-Moore et al., 2002), diminished social behaviors (Smith et al., 2009), increased anxiety-related behaviors in female offspring, and thinner cortices at birth (Foldi et al., 2010). In addition, as noted above, several studies have demonstrated strong associations between advanced paternal age and autism (Reichenberg et al., 2006; Hultman et al., 2011) in which social deficits are characteristic of the disorder, and CNVs have been prominently demonstrated (Sanders et al., 2011).

On a broader note, studies that compare risk factors between schizophrenia and BD may help to address the Kraepelinian dichotomy. If schizophrenia is more likely due to an influence of *de novo* mutations or epigenetic factors, this may facilitate efforts to dissect these two disorders from one another at the etiopathogenic level, with potential preventive and treatment implications.

5. Conclusion

No association was observed between increasing paternal age and BD among offspring. Further studies on the effects of advanced paternal age on the male germ line and translational epidemiologic research may shed further light on these findings.

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