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Advanced paternal age and risk of psychotic-like symptoms in adult offspring

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ABSTRACT

Between 2% and 12% of adults in the general population report experiencing psychotic-like symptoms, and there is suggestive evidence that these symptoms are associated with risk of schizophrenia and other forms of psychopathology. Older parental age is an established risk factor for schizophrenia, however few studies have attempted to extend this relationship to psychotic-like symptoms. Data come from the National Comorbidity Survey—Replication and analysis is restricted to a subset of respondents who completed questions on psychosis ($N = 924$). Lifetime occurrence of six psychotic-like symptoms (i.e., see a vision others couldn't see, hear voices others couldn't hear) was assessed by self-report. These symptoms were combined into a single binary (any vs. none) variable and analyzed using logistic regression, accounting for the complex survey design. Models were adjusted for age, sex, race/ethnicity, socioeconomic status, marital status, birth order, and history of mood, anxiety, and substance use disorders. Approximately 9% ($n = 103$) of respondents reported at least one psychotic-like symptom. In fully-adjusted models, paternal age was significantly associated with experiencing psychotic-like symptoms ($\chi^2 = 13.34$, $p = .010$). Relative to respondents whose fathers were aged 25 to 29 at the time of their birth, those with fathers aged >35 had 2.12 times higher odds (95% confidence interval: 1.08–4.16) of psychotic-like symptoms. There was no relationship between maternal age (younger or older) and psychotic-like symptoms ($\chi^2 = 0.54$, $p = .909$). Older paternal, but not maternal, age at birth is associated with psychotic-like symptoms in adult offspring.

1. Introduction

Worldwide prevalence estimates of schizophrenia range from 0.5% to 1% (Messias et al., 2007; Centers for Disease Control and Prevention, 2013). One of the most distinct clinical features of schizophrenia is the experience of positive psychotic symptoms, including delusions and hallucinations (National Institute of Mental Health, 2014). Although schizophrenia is a rare condition, experiences of psychotic-like symptoms (PLS) are relatively common in the general population. The lifetime prevalence of experiencing PLS in the general adult population ranges from 1.5% to 12% when ascertained using interview-administered questionnaires (Eaton et al., 1991), and estimates from self-administered questionnaires are often higher (Verdoux et al., 1998; Peters et al., 1999). While it is unclear how PLS relate to schizophrenia, there is suggestive evidence that these symptoms increase the risk of developing psychotic disorders, including schizophrenia, later in life (Hanssen et al., 2005). If risk factors for schizophrenia are shared with non-pathological experiences such as PLS, this would support the hypothesis that these symptoms lie on a continuum of risk with psychotic disorders more generally (Schultze-Lutter, 2009; Kaymaz et al., 2012). Finally, as schizophrenia is a rare disorder, if these more common symptoms are an early indicator of increased risk then investigating psychotic experiences in the general population may inform targeted intervention efforts (Kaymaz et al., 2012; DeVylder et al., 2014b).

Studies as early as the 1950s indicated older paternal age at birth was related to schizophrenia (Johanson, 1958). In the decades since these initial investigations, both advanced maternal age (generally defined as ≥35 years) (Gregory, 1959) and paternal age (generally defined as ≥40, but with more robust findings age ≥55 years) (Gregory, 1959; Malaspina et al., 2001; Zammit et al., 2003; Sorensen et al., 2014) have been associated with elevated risk of psychosis. However, many studies indicate that the observed association between advanced maternal age and schizophrenia is largely confounded by advanced paternal age (Hare and Moran, 1979; Byrne et al., 2003). In contrast, when controlling for paternal age, studies generally indicate that younger maternal age (generally defined as <20 years) is associated with increased risk of psychosis (El-Saadi et al., 2004; McGrath et al., 2014).

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Finally, some studies report a "J-shaped" relationship between paternal age and schizophrenia, with younger paternal age (<20 years) associated with modestly elevated risk, and advanced paternal age (≥45 years) associated with substantially elevated risk, relative to typical-age (e.g., 25–29) (McGrath et al., 2014).

The mechanisms underlying this purported relationship between parental age and schizophrenia risk are not well understood. Several recent studies have implicated de novo germ cell mutations (Malaspina et al., 2001, 2002; Byrne et al., 2003; Sipos et al., 2004), whereas others argue that this association is largely a function of selection factors (e.g., individuals with a genetic predisposition, have schizotypal personality traits, or who are socially reclusive may not have the opportunity to conceive children, particularly their first child, until later in life) (Petersen et al., 2011; Jaffe et al., 2014; Pedersen et al., 2014). The mechanisms underlying the association between younger parental, particularly younger maternal age, and risk of schizophrenia in offspring are also unclear. Again, several studies have pointed to the possibility of de novo mutations due to immature spermatids or from low activity of DNA repair or antioxidant enzymes (Malaspina, 2001), however environmental factors young parents often face (i.e., financial, residential, and/or relationship instability) are also likely relevant (McGrath et al., 2014).

While parental age is a well-established risk factor for the development of schizophrenia, few studies have attempted to extend these findings to PLS. The handful of studies that have investigated this relationship have found weak or null associations between parental age and elevated risk of PLS (Zammit et al., 2008; Vreeker et al., 2013). However, these reports have important limitations, including relatively young samples that have not fully passed through developmental risk period for delusions and hallucinations (Zammit et al., 2008; Vreeker et al., 2013), as well as examining only recent (e.g., past 6 months), not lifetime, occurrence of these symptoms (Zammit et al., 2008).

Building on this research, the aim of this study is to examine the relationship between parental age and risk of PLS in a nationally-representative sample of adults.

2. Methods

2.1. Data

Data come from the National Comorbidity Survey Replication (NCS-R), a nationally representative cross-sectional household survey of adults aged ≥18 conducted between 2001 and 2003. 9282 respondents completed Part I of the survey, and the Part I sample was approximately 72% non-Hispanic White, 12% non-Hispanic Black, and 52% female; approximately one-third of respondents were aged 18–34 or aged 35–49, 21% were aged 50–64, and 16% were aged 65 and older. Part I was administered to all respondents, and included the World Health Organization Composite International Diagnostic Interview (WHO-CIDI), a fully-structured diagnostic instrument administered by lay interviewers (Kessler and Ustun, 2004). To reduce participant burden, only a subset of respondents ($N = 5692$) were asked Part II of the survey, which included assessments of risk factors. Additional details of the study design are described elsewhere (Kessler et al., 2004). This analysis is limited to respondents who had complete data on parental age at birth and psychotic-like symptoms ($N = 924$); the sample size is due to skip patterns in the survey that restricted the number of respondents who were asked all relevant items.

The NCS-R was approved by the IRB at the University of Michigan and all respondents provided informed consent.

2.2. Exposure

Maternal and paternal age at the time of respondents' birth were assessed by self-report. Consistent with prior studies and accounting for the range of these variables in the sample (Malaspina et al., 2001; Byrne et al., 2003; El-Saadi et al., 2004; Petersen et al., 2011; McGrath et al., 2014), maternal and paternal ages were categorized as 13–19 years, 20–24 years, 25–29 years, 30–34 years old, and ≥35 years. Due to a limited number of respondents with mothers in the oldest age group ($n = 41$), the ≥35 and 30–34 categories were collapsed. The 25–29 year age group was used as the reference group for analysis for both maternal and paternal age.

2.3. Outcome

Lifetime occurrence of six PLS were assessed by self-report using the WHO-CIDI Non-Affective Psychosis (NAP) screener: "Did you…" 1) ever see a vision others couldn't see?, 2) ever hear voices others couldn't hear?, 3) ever have a mind control experience?, 4) ever feel your mind taken over by strange forces?, 5) ever experience communication attempts from strange voices?, and 6) ever experience an unjust plot to harm you or have people follow you?. Respondents were instructed to only report on symptoms that were experienced while they were alert (e.g., not while sleeping, dreaming, or under the influence of drugs and alcohol). Each item was assessed as a dichotomous (ever/never) variable, which were then combined into a single dichotomous variable indicating any symptoms vs. no symptoms for analysis.

2.4. Confounders

Covariates included age at interview (in years), sex, race, education, household income, marital status, birth order, and psychiatric disorders. Race was categorized as White (reference group), Black, and other (predominantly Hispanic). Education was dichotomized as less than high school (reference group) vs. high school graduate or more. Household income categorized <$30,000/year (reference group), $30,000–$60,000/year, and >$60,000/year based on the distribution of this variable in the sample. Marital status was dichotomized as currently married (reference group) vs. not currently married (e.g., divorced, widowed, never married).

Prior reports have found that risk of schizophrenia was only associated with paternal age for first-born children of older fathers, but not later-born children of older fathers (Petersen et al., 2011), and thus birth order was included as a covariate as a continuous variable indicated by the number of full siblings older than the respondent (e.g., only children and first-born = 1, one older sibling = 2, etc.).

PLS are more common among individuals with a history of psychopathology, including depressive, anxiety, and substance use disorders (Johns et al., 2004; DeVylder et al., 2014a; Stochl et al., 2014). Thus we included these lifetime history of these conditions, assessed according to DSM-IV criteria using the WHO-CIDI, as covariates. Depressive disorders included major depressive disorder (with hierarchy) and dysthymia (with hierarchy). Anxiety disorders included generalized anxiety disorder (with hierarchy), social phobia, panic disorder, and posttraumatic stress disorder. Substance use disorders included both drug and alcohol abuse and dependence.

2.5. Analysis

We examined differences in demographic characteristics for respondents who reported at least one PLS as compared to those who reported none using Rao–Scott Chi-square tests for categorical variables and *t*-tests for continuous variables. We also examined gender differences in the experiences of specific psychotic-like symptoms using this approach. Logistic regression was used to assess the relationship between parental age and PLS. Separate models were fitted for maternal age, paternal age, and finally maternal and paternal age in the same model. Two sets of regression models were fit. In the first set, models were adjusted for demographic characteristics and birth order. In the second set, lifetime history of depressive, anxiety, and substance use disorders were included as additional covariates. Point estimates and