



Effects of paternal age and offspring cognitive ability in early adulthood on the risk of schizophrenia and related disorders



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ABSTRACT

Advanced paternal age (APA) and intelligence quotient (IQ) are both associated with the risk of schizophrenia spectrum disorder (SSD) in young adult offspring. We hypothesized that the offspring SSD risk gradient associated with paternal age is mediated by offspring IQ. We investigated joint and separate associations of paternal age and offspring IQ with the risk of SSD. We used IQ routinely measured at conscription in Danish males ($n = 138,966$) from cohorts born in 1955–84 and in 1976–1993 and followed them from a year after the conscription through 2010. We used Cox regression to estimate the incidence rate ratio (IRR) of SSD. During the follow-up, 528 men developed SSD (incidence rate [IR] 5.2 and 8.6 per 10,000 person-years in the first and second cohorts, respectively). APA was associated with higher risk of SSD (IRR, 1.32; 95% CI, 1.10–1.60 per a ten-year increase in paternal age). A higher IQ was associated with lower SSD risk (IRR, 0.68; 95% confidence interval [CI], 0.63–0.74 per one SD increase). The IR of SSD was higher among persons who were draft-exempt for health reasons (<20% of the men). Overall, there was little evidence of lower premorbid IQ in APA-related SSD (individuals who developed SSD and were also offspring of older fathers). Our results do not support the notion that risk gradient for offspring SSD associated with paternal age is mediated by offspring IQ.

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1. Introduction

Studies have consistently shown associations of advanced paternal age (APA) with an increased risk of schizophrenia (Miller et al., 2011a) and associations with a range of other psychiatric morbidities in offspring have also been found (D'Onofrio et al., 2014). Furthermore, associations between APA and lower offspring general cognitive ability (IQ) have been observed in some (Malaspina et al., 2005; Saha and McGrath, 2012), but not all (Svensson et al., 2011; Myrskylä et al., 2013; McGrath et al., 2013), published studies. It is uncertain whether, and to what extent, APA, offspring IQ and offspring risk of schizophrenia are interrelated. The association between APA and offspring psychiatric morbidity might involve de novo mutations (Goriely et al., 2013) and if offspring of older fathers perform worse on tests of general cognitive ability (Malaspina et al., 2005; Saha and McGrath, 2012), then offspring of older fathers who develop schizophrenia may display more signs of abnormal neurodevelopment, for instance manifested by lower level of premorbid general cognitive ability.

Several studies suggest that lower IQ is associated with an increased risk of subsequent schizophrenia (Mortensen et al., 2005; Reichenberg et al., 2006; Meier et al., 2014; Kahn and Keefe, 2013). To our knowledge, no large-scale study on the association between APA and risk of schizophrenia has previously taken IQ into account as a possible mediator. We hypothesized that the association between APA and schizophrenia spectrum disorders (SSD) in offspring is mediated by a lower offspring IQ. Thus, we expected the premorbid IQ to be lower in individuals with SSD who were also the offspring of older fathers (“APA-related SSD”) compared with SSD patients born to younger fathers. We addressed this hypothesis using data combined from two cohorts of Danish male draftees (Norgaard et al., 2009; McGrath et al., 2013).

2. Materials and methods

2.1. Procedure

Denmark maintains mandatory military conscription for all men, and they become draft-liable at age 18 years. Recently, the Danish National Board of Health has established a nationwide Draft Board register of everyone evaluated for by the Draft Board from 2006 onwards. The present study was based on data from this register, which presently

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contains records of men born 1976–1993 who appeared before the Draft Board in 2006–2010, combined with data from the North Jutland birth cohort of men born 1955–1984, who appeared before the Draft Board 1974–2002 (Sørensen et al., 1997; Norgaard et al., 2009). The pooled data from both cohorts encompasses records of 176,454 men who born between 1955–1984 and 1976–1993. To ensure the availability of information of the men and their parents, we used the Danish Civil Registration System (Pedersen, 2011) to restrict the study population to Danish men with Danish-born parents. After this restriction, the dataset contained 152,506 men. Men with preexisting conditions such as severe mental retardation, asthma and extreme myopia mental health conditions, musculoskeletal disorders and earlier injury/trauma are exempted from conscription. Not all mental health problems are regarded as disqualifiers for military service (Osler et al., 2007; Teasdale, 2009). Exemption rates for health reasons have varied between 10 and 15% (Norgaard et al., 2009) and about 80% of all Danish males born 1976–1993 have appeared before the Draft Board in 2006–2010.

2.2. Assessment of schizophrenia spectrum disorders in cohort members and family members

Due to considerations regarding statistical power, we decided to examine schizophrenia spectrum disorders (SSD). Records of the cohort members and their mothers and fathers were linked with information from the Danish Psychiatric Central Register (Mors et al., 2011). This register has been computerized since 1969 and contains data on all admissions to Danish psychiatric in-patient facilities, and, from 1995 onwards, information on outpatient visits to psychiatric departments. To code diagnoses, the registry used the Danish modification of the International Classification of Diseases, 8th revision (ICD-8) in 1969–1993 and the International Classification of Diseases, 10th revision (ICD-10) thereafter. Schizophrenia spectrum disorder (SSD) was defined for study population members and their parents as a psychiatric hospitalization or an outpatient visit with a diagnosis in the schizophrenia spectrum (ICD-8 code 295 [schizophrenia], 296.89 [schizoaffective disorder], 297, 298.39, 301.83 [schizophrenia-like]) or ICD-10 code F20–29 (including F20 [schizophrenia], F25 [schizoaffective disorder], F21 [schizotypal personality] and other spectrum diagnoses such as F23 [acute psychoses] and F22 [paranoid psychoses]).

2.3. Parental age, parental education, and birth order

Variables for maternal and paternal age and education at conscripts' birth were obtained from Statistics Denmark. Variables for paternal and maternal education were categorized, separately for fathers and mothers, into basic, high school, vocational, medium or higher education (corresponding to university level). Birth order was defined using maternal parity.

2.4. Assessment of intelligence in early adulthood

The Danish Military Draft Board has used the Børge Priens test (Børge Priens Prøve [BPP]) since 1956 (Reinisch et al., 1995). The BPP is a 45-minute 78-item group intelligence test consisting of 4 subtests (logical, verbal, numerical, spatial reasoning). The test score is the number of correct answers across subtests (range 0–78). The BPP score has a correlation of 0.82 with the full-scale WAIS IQ (Mortensen et al., 2002; Teasdale et al., 2011).

2.5. Study design and statistical analyses

We restricted our cohort to persons with available BPP data and excluded 118 men with a diagnosis within the schizophrenia spectrum within 1 year after appearing before the Draft Board. The final analysis dataset contained 138,966 men. The cohort members were followed until the first diagnosis with SSD, death, emigration from Denmark, or

Dec. 31, 2011, whichever came first. Incidence rate ratios were estimated using Cox regression in Stata 10 (Stata, College Station, Texas, United States). The basic model was adjusted for age in the non-parametric part of the Cox model, and for calendar time as a time dependent variable. The periods were categorized in groups: 1970–79, 1980–89, 1990–91, 1992–93, 1994–95, 1996–97, 1998–99, 2000–03, 2004–07, and 2008–10. The use of two-year intervals from 1990 to 1999 was due to the change in diagnostic classification system which took place in 1993–94. The change in registration practice from 1995 to include outpatient visits necessitated the use of two-year intervals up to 1999. The use of three-year intervals from 2000 and onwards was due to a rise in the incidence of schizophrenia and related disorders in Denmark during this period. Year of birth was categorized to include approximately equal number of persons: 1960–64, 1965–69, 1970–74, 1975–79, 1980–84, 1985–86, 1987, 1988, 1989, 1990, 1991, and 1992–93. Paternal age at conscript's birth was categorized as below 24, 25–29 (ref), 30–34, 35–39, 40–44, and above 45 years, and maternal age at conscript's birth was categorized as below 20, 20–24, 25–29 (ref), 30–34, and above 35 years as elsewhere (Pedersen and Mortensen, 2001; Sørensen et al., 2014). We examined the effects of paternal age as a categorical as well as a continuous variable.

For the study population, the mean BPP score was 41.7 and the standard deviation (SD) was 10.0. In the analyses, we estimated effects associated with 1 SD increase in BPP. We also adjusted for the degree of urbanicity of the place of birth (capital, capital suburb, towns with more than 100,000 inhabitants, towns with more than 10,000–100,000 inhabitants, and rural areas). Familial psychiatric history was analyzed separately for mothers, fathers and siblings as a time-dependent variable. Birth order was categorized as first, second, third, fourth or higher.

Cognitive performance is not measured in the men exempted before the Draft Board evaluation. To assess the impact of a potential selection bias, the IRs of developing SSD were calculated among the exempted in the two cohorts and sensitivity analyses were carried out to compare the IRs of the exempted to those of Danish men in either a provincial rural area (the North Jutland cohort) or all Danish males of similar age distributions.

3. Results

During a follow-up of 847,466 person-years, 528 persons were registered with a SSD, predominantly a diagnosis of schizophrenia ($n = 337$, 64%) or schizoaffective disorder ($n = 16$, 3%). The remaining 175 persons were registered with schizotypal personality disorder, brief psychotic disorder, or delusional disorder. The North Jutland cohort contributed approximately 596,000 person-years and 312 SSD cases (IR = 5.23 per 10,000 person-years). The younger nationwide cohort of males who appeared before the Draft Board during 2006–2010 contributed 251,000 person-years and 216 SSD cases (IR = 8.61 per 10,000 person-years).

Table 1 shows descriptive characteristics of the 138,966 Danish male conscripts born 1955–1993 according to paternal age at conscripts' birth. As expected, parental age directly correlated with educational length. Compared with conscripts born to younger fathers, conscripts born to fathers aged 40 or older had a higher proportion of schizophrenia spectrum disorder and psychiatric admissions among their siblings. Schizophrenia and psychiatric admissions in general were more common in mothers than in fathers, reflecting known reproductive patterns in people with psychosis (Laursen and Munk-Olsen, 2010). Compared with conscripts born in the capital, conscripts born in rural areas had greater prevalence of the youngest and the oldest fathers. Proportion of firstborns was inversely associated with the age of the father.

3.1. Effects of IQ, parental age and parental education on the risk of SSD

Table 2 shows unadjusted and adjusted incidence rate ratios (IRR) for developing SSD ($n = 528$) according to BPP score at Draft Board assessment; paternal and maternal age, and paternal and maternal

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