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Paternal age and mortality in nonaffective psychosis

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ABSTRACT

Introduction: Advanced paternal age (APA) is associated with an increased mortality in the general population, and is a risk factor for schizophrenia. We aimed to test if APA is associated with increased mortality in people with nonaffective psychosis.
Methods: Subjects with nonaffective psychosis who were born in Helsinki, Finland, between 1951 and 1960 ($n=529$) were followed until June 2006 (age 46 to 55). Hazard ratios were calculated, adjusting for subject age, age of the other parent, and gender.
Results: In *females* but not males, there was a significant increase in all-causes mortality (HR = 7.04, 95% CI 1.60–31.04, $p=0.01$) and natural deaths (HR = 7.64, 95% CI 1.20–48.66, $p=0.03$) in offspring of fathers age ≥40, after adjustment for potential confounders. In *males* but not females, there was a significant decrease in suicides (HR = 0.89, 95% CI 0.81–0.97, $p=0.01$) with increasing maternal age (as a continuous variable). In the entire sample, there was also a trend for decreased all-cause mortality (HR = 0.96, 95% CI 0.92–1.01, $p=0.08$) with increasing maternal age (as a continuous variable).
Discussion: Both paternal and maternal age may affect mortality risk in offspring with psychosis. The specific disorders and pathway(s) associated with the increase in natural cause mortality remain to be determined.

1. Introduction

Evidence is accumulating that advanced paternal age may exhibit a wide range of effects on the health and development of the offspring. Advanced paternal age is a risk factor for childhood conditions such as cleft lip and palate, cancer, congenital heart defects, and neuropsychiatric conditions such as autism, epilepsy, and bipolar disorder (Bray et al., 2006; Cannon, 2009). Advanced paternal age has also been associated with poorer intellectual performance in the offspring (Malaspina et al., 2005; Saha et al., 2009). The best replicated of these associations is that between advanced paternal age and risk of schizophrenia in offspring (Granville-Grossman, 1966; Bojanovsky and Gerylovova, 1967; Costello et al., 1968; Hare and Moran, 1979; Gillberg, 1982; Kinnell, 1983; Malama et al., 1988; Bertranpetit and Fananas, 1993; Raschka, 1998; Malaspina et al., 2001; Dalman and Allebeck, 2002; Brown et al., 2002; Byrne et al., 2003; Zammit et al., 2003; Sipos et al., 2004; El-Saadi et al., 2004; Tsuchiya et al., 2005; Laursen et al., 2007; Torrey et al., 2009; Lopez-Castroman et al., 2009).

Paternal age also appears to affect offspring mortality. Gavrilov and Garvrilova (2000) found that increasing paternal age was associated with increased mortality in daughters, but not sons, in a study of genealogical and longevity data on European royal and noble families. Robine and Allard (1997)

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did not find a relationship between paternal age and mortality, but the findings may have been biased due to incomplete data. A large Danish register based study found a U-shaped association between paternal age and all-cause childhood mortality (Zhu et al., 2008). In our previous work (Miller et al., in press), we have found that increasing paternal age was associated with increased suicides and all-cause mortality in a large Finnish register study with follow-up to age 39. Findings were adjusted for subject age, maternal age, paternal social class, and maternal parity. A study of male inpatients with psychosis found that paternal age was positively correlated with completed suicides, but did not consider the relationship between paternal age and other causes of death (Axelsson and Lagerkvist-Briggs, 1992).

In the present study, we tested the hypothesis that increasing paternal age is associated with increased mortality in subjects with nonaffective psychosis, from age of onset of psychosis up to age 46 to 55. The broader category of nonaffective psychosis appears to share family history and other characteristics of schizophrenia (Lichtermann et al., 2000; Niemi et al., 2004).

2. Methods

2.1. Study population and study sample

The study population consisted of all individuals with nonaffective psychosis who were born in Helsinki, Finland, between January 1, 1951 and December 31, 1960. We did not have any data on subjects without nonaffective psychosis who were born during this ten-year period. Risk factors for schizophrenia in this cohort have been investigated in two previous studies (Cannon et al., 1999; Cannon et al., 2002). Individuals with a diagnosis of schizophrenia spectrum psychosis (International Classification of Diseases, Eighth Revision [ICD-8] and Ninth Revision [ICD-9] diagnostic code 295.x, including schizophrenia, schizophreniform disorder, and schizoaffective disorder), born during this ten-year period were ascertained from three nationwide healthcare registers: 1) the Finnish Hospital Discharge Register (FHDR), and two registers of the Social Insurance Institution, namely, 2) the Pension Register and 3) the Medication Reimbursement Register.

The FHDR was founded in 1967 and covers all mental, general and private hospitals in Finland. It contains the unique social security number for each individual and the hospital identification code, and it lists data on date of birth, gender, admission and discharge dates, and primary plus up to three subsidiary diagnoses for each inpatient stay. For all disability pensions, the pension register includes their beginning dates and the diagnoses on which the pension was granted. The Medication Reimbursement Register includes the diagnoses of persons receiving free outpatient medication, and the type of medication the benefit concerns. All health care registers were computerized in 1968, and used the ICD-8 diagnostic criteria and codes before 1987 (WHO 1967). Between 1987 and 1995 psychiatric diagnoses were coded according to ICD-9 (WHO 1977), applying the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) diagnostic criteria (APA 1987). ICD-10 diagnostic codes and criteria have been used since 1996 (WHO 1994). The data in all registers were linked by means of each individual's unique social security number. Information from these registers was available for the period January 1, 1969, through December 31, 1991. In order to facilitate the case note collection, the FHDR information was later extended to cover years 1992–1998, with year 1998 being the latest available year in the FHDR at the time the case note collection was started.

The search of all three registers identified 928 individuals with a diagnosis of schizophrenia-spectrum psychosis, of whom 877 (94.5%) had at least one psychiatric hospitalisation for psychosis according to FHDR. All of the available hospital case notes were collected from the archives of the hospitals ($n=834$, or 95.1% of those hospitalized). Of the remaining 43 case notes, 8 had been destroyed, 27 were lost, and 8 were not given for research purposes.

As described in detail elsewhere (Pihlajamaa et al., 2008), all hospital case notes were carefully examined by five experienced psychiatrists who extracted clinical information from the case notes and filled the Operational Criteria (OPCRIT) checklist. The OPCRIT-system (version 3.4) consists of checklist of 90 items and a computer program, which generates psychiatric diagnoses based on 13 different diagnostic classifications and sub-classifications (McGuffin et al., 1991). In the present study, we used the DSM-IV diagnoses given by the OPCRIT program. Of those $n=834$ individuals with available case notes, $n=679$ (81.4%) met criteria for a DSM-IV nonaffective psychotic disorder (schizophrenia, schizophreniform disorder, brief psychotic disorder, delusional disorder, or psychotic disorder not otherwise specified) given by the OPCRIT program.

The study was approved by the Ethics Committee of the National Public Health Institute, and the case notes were collected with permission from the Finnish Ministry of Social Affairs and Health. The study was also overseen by the Human Assurance Committee of the Medical College of Georgia.

2.2. Information on parents

Parents and their dates of birth were identified from the Population Register Centre. Maternal information was found for all $n=679$ persons with nonaffective psychosis, while information on father was missing for $n=150$ subjects (22.1% of the study sample). Family information was linked into the register at the beginning of the 1970s for persons alive at that time. Missing paternal information means that the father had died before 1970, or that the father's identity was unknown.

2.3. Information on socioeconomic status

Information on the socioeconomic status (SES) of the family of origin, based on paternal occupation, was obtained from either obstetric ($n=435$) or school ($n=76$) records. These data were missing for $n=168$ subjects (24.7% of the study sample). We coded SES according to the Rauhala scale. This classification results from sociological studies in Finland at the time of the study (Rauhala, 1966), and was formed on the basis of education, occupation, industrial status, and industry groupings (Central Statistical Office of Finland, 1974). The Rauhala scale is coded from 1 to 9, with 1 being the highest. In the analyses, we trichotomized SES into high (Rauhala scale scores 1–3), middle (4–6), and low (7–9).