Differences in maternal and paternal age between schizophrenia and other psychiatric disorders

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ABSTRACT

Advanced parental age has been shown to increase offspring risk for a number of neuropsychiatric disorders including schizophrenia and Down's syndrome. Other psychiatric disorders have been less studied with respect to the effect of parental age on offspring risk. In this study we examine if advanced parental age increased risk for ICD-10 diagnoses. We hypothesized that advanced parental age would increase risk for offspring psychotic disorders and mental retardation but not other ICD-10 diagnoses. We examined follow-up data for 30,965 subjects treated in outpatient psychiatric facilities between 1980 and 2007. Subjects were younger than 18 years of age at their first outpatient visit. A comparison group was obtained from data on registered births in Spain from 1975.

We compared parental age (maternal, paternal, combined) across diagnostic categories using ANOVA and logistic regression was used to estimate the risk of psychopathology in the offspring with advanced parental age (maternal, paternal, combined). Maternal and paternal ages were higher for subjects diagnosed with mental retardation. Risk for psychotic disorders showed a significant linear increase only with advancing maternal age, and not paternal age as is more often reported.

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1. Introduction

Demographic changes in the age of childbearing in past decades have led to investigation of advanced parental age as a putative risk factor for neuropsychiatric disorders in offspring (Cannon, 2009; Heffner, 2004). Advanced paternal

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age has been associated with increased offspring risk for autism (Larsson et al., 2005), schizophrenia (Zammit et al., 2003), and bipolar disorder (Frans et al., 2008), and has also been associated with neurocognitive (Saha et al., 2009), developmental (Mannerkoski et al., 2007) and social (Weiser et al., 2008) impairment. Advanced maternal age is an important risk factor for chromosomal abnormalities, including Down's syndrome (Roizen and Patterson, 2003), however, its association with other neuropsychiatric disorders, such as autism (Durkin et al., 2008; Reichenberg et al., 2006) and schizophrenia (Ekeus et al., 2006), remains controversial. A number of mechanisms have been proposed for the differential effects of maternal and paternal age including disparities in the ratio and type of mutations during gametogenesis (Arnheim and Calabrese, 2009; Malaspina et al., 2005). Accumulated mutations and chromosomal anomalies in reproductive germ cells might account for the largest part of the risk for mental disorders associated with advanced parental age (Heffner, 2004; Malaspina et al., 2002). Other factors might be personality traits (Zammit et al., 2003), physical disease in elderly parents (Malaspina et al., 2005) and social characteristics (Saha et al., 2009).

Research in this area has been focused on a specific subset of disorders and genetic causality. We found only two studies that compared parental age and psychopathology across multiple diagnostic categories. Gillberg (1982) reported that advanced parental age was associated with psychotic disorders and mental retardation but not emotional disorders, and Ekeus et al (2006) found an increased risk of schizophrenia, but not drug abuse or suicide, in offspring with elderly parents. Neither study systematically assessed the effect of parental age across ICD-10 diagnostic categories as one used a non-systematic diagnostic classification (Gillberg et al) and the other examined only a small subset of ICD-10 diagnoses (Ekeus et al 2006).

This study examines the association of offspring disorder and advanced parental age across all ICD-10 psychiatric diagnoses. We hypothesized that subjects with psychotic disorders and mental retardation would have a greater likelihood of having advanced parental age (maternal, paternal, mean parental) than subjects with other ICD-10 diagnoses and population based controls.

2. Material and methods

2.1. Sample

Data was available for 30,965 psychiatric outpatients attending community Mental Health Centers in the province of Madrid, Spain. Approximately 85% of Mental Health Centers in Madrid province are included. All subjects were younger than 18 years at the time of their first outpatient visit, and follow-up data was collected from January 1st 1980 to December 31st 2007. Subjects were followed for a mean of 2.56 ± 3.7 years. On a subject's initial outpatient visit the date of birth of their parents and other sociodemographic data was recorded by clinic staff. A population based comparison group was derived from the historical registry of births in Spain (Instituto Nacional de Estadistica, 2009) in order to calculate yearly population means and standard deviations for maternal and paternal ages. For each year of the inclusion period a population-based sample was generated matched in size to the outpatient sample. Prior to 1975 parental age data was not collected, and population data from 2002 onwards was excluded to reduce the bias that would produce the increasing age of childbearing along that period; the excluded data represented less than 1% of the clinical sample. The mean age of parents in the general population over the inclusion period was calculated weighting each yearly mean with the number of outpatient cases that year.

2.2. Diagnosis

Mental disorders were recorded in clinic records according to the International Classification of Disease (ICD), 10th version. Diagnoses were assigned by attending clinicians reflecting real world conditions. Diagnosis and treatment information were recorded at all follow-up visits. To maximize reliability, in analyses we examined 1) diagnosis at last visit as it was thought likely to be more reliable due to better knowledge of the patient and their history by clinicians; and 2) diagnostic mode, the most frequent diagnosis assigned throughout the follow-up. Concordance rate between last diagnosis and diagnostic mode was calculated using Cohen's kappa coefficient (Altman et al., 2000).

2.3. Statistical analysis

Analyses were conducted using Matlab software. For each diagnostic category we used ANOVAs comparing mean parental age and maternal and paternal age with respect to diagnostic category for both last diagnosis and diagnostic mode. We used the Bonferroni correction for multiple testing and an α level .005 was required for statistical significance in individual comparisons. Due to the later age of onset of psychotic disorders (ICD-10 code F2) we conducted separate analyses for subjects who had reached the age of 25 years ($n = 5,236$) by December 31st 2007 (Kessler et al 2007). All patients were included regardless of recent visits being registered for the following reasons: i) over 85% of Spaniards receive mental health care in public healthcare facilities (Instituto Nacional de Estadistica, 2006); and ii) the rates of residential changes to other provinces in Spain or other countries among young people are estimated annually at less than 2% (Ministerio de Sanidad y Consumo, 2007).

For diagnostic categories where there was an association between paternal age and likelihood of offspring diagnosis in ANOVA, we used logistic regression to measure the risk associated with advancing age. Maternal and paternal ages were modelled separately (Reichenberg et al. 2006) using seven age categories (<25 years, 25–29, 30–34, 35–39, 40–44, 45–49, $\geq$50 years). Parental age <25 years was the reference group. In the analysis of F2 diagnoses only subjects older than 25 years on 31st December 2007 were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Wald χ^2 test was used to determine p values, and the significance level was set at $\alpha = .05$ (2-sided).

3. Results

Subjects were on average 8.9 ± 3.8 years of age at the time of their first diagnosis, and 11.7 ± 5.1 years at their last