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Paternal age and psychiatric disorders: Findings from a Dutch population registry

Jacobine E. Buizer-Voskamp [a,b], Wijnand Laan [c], Wouter G. Staal [d], Eric A.M. Hennekam [e], Maartje F. Aukes [a,c], Fabian Termorshuizen [c], René S. Kahn [a,1], Marco P.M. Boks [a,c], Roel A. Ophoff [a,b,f,*]

[a] Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[b] Department of Medical Genetics, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
[c] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
[d] Department of Child and Adolescent Psychiatry, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[e] Department of Clinical Genetics, University Medical Center Utrecht, Postbus 85090, 3508 AB Utrecht, The Netherlands
[f] Center for Neurobehavioral Genetics, University of California, 695 Charles E. Young Drive South, Los Angeles, CA 90095-1761, USA

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ABSTRACT

Background: We measured the association between paternal age and schizophrenia (SCZ), autism spectrum disorders (ASD), major depressive disorder (MDD), and bipolar disorder (BPD) in the Dutch population.
Methods: In total, 14231 patients and 56924 matched controls were collected and analyzed for an association with paternal age by logistic regression.
Results: ASD is significantly associated with increased paternal age: Older fathers >40 years of age have a 3.3 times increased odds of having a child with ASD compared to young fathers <20 years of age. SCZ has significant associations for fathers aged >35 years (OR = 1.27, 95% Confidence Interval: 1.05 and 1.53). For MDD, both younger and older fathers have increased odds. No association was found for BPD.
Conclusions: The effects of paternal age as a risk factor are different for ASD and SCZ on one hand, and the affective disorders on the other hand. Different types of association might indicate different biological or psychosocial mechanisms. Late paternity (associated with predispositions to psychiatric disorders) seems the most probable explanation for the association with paternal age.

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1. Introduction

Psychiatric disorders show substantial similarities in symptoms. Also, it is increasingly clear that they share genetic and environmental risk factors (Hyman, 2007), which likely operate through mediating characteristics that alter risk for a number of different outcomes (Dick et al., 2010). One of those possible shared vulnerability factors is increased paternal age. Accumulating evidence from epidemiological studies has suggested an association between increased paternal age and complex disorders, such as autism, schizophrenia, and bipolar disorder (Dalman and Allebeck, 2002; Frans et al., 2008; Malaspina et al., 2001; Shelton et al., 2010; Sipos et al., 2004). Different associations have been found between paternal age and psychiatric disorders in the offspring. So, the question remains whether paternal age has different risk effects for major psychiatric disorders such as autism spectrum disorders (ASD), schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BPD) in the offspring.

In total, 17 cohort studies and 10 case–control studies investigated the association between increased paternal age and SCZ, ASD, MDD and/or BPD in the offspring (Brown et al., 2002; Byrne et al., 2003; Croen et al., 2007; Dalman and Allebeck, 2002; Durkin et al., 2008; Ekeus et al., 2006; Frans et al., 2008; Gillberg, 1982; Glasson et al., 2004; Grether et al., 2009; King et al., 2009; Lauritsen et al., 2005; Laursen et al., 2007; Lopez-Castroman et al., 2009; Malaspina et al., 2002; Malaspina et al., 2001; Menezes et al., 2010; Petersen et al., 2011; Rasmussen, 2006; Reichenberg et al., 2006; Sasanfar et al., 2010; Shelton et al., 2010; Sipos et al., 2004; Torrey et al., 2009; Tsuchiya et al., 2008; Tsuchiya et al., 2005; Zammit et al., 2003). Several studies with up to 13297 patients (Miller et al., 2010) found that higher paternal age doubles or triples the risk for SCZ in the offspring of men above 40 years of age (Brown et al., 2002; Byrne et al., 2003; Dalman and Allebeck, 2002; Laursen et al., 2007; Malaspina et al., 2002; Malaspina et al., 2001; Rasmussen, 2006; Sipos et al., 2004; Torrey et al., 2009; Tsuchiya et al., 2005; Zammit et al., 2003). ASD was reported to be associated with both increased maternal and paternal age, with a recent emphasis for an increased paternal age (Croen et al., 2007; Durkin et al., 2008; Glasson et al., 2004; Grether et al., 2009; King et al., 2009; Lauritsen et al., 2005; Reichenberg et al., 2006; Sasanfar et al., 2010; Shelton et al., 2010; Tsuchiya et al., 2008). The

* Corresponding author at: Center for Neurobehavioral Genetics, University of California, Gonda Center #4357C, Box 951761, 695 Charles E. Young Drive South, Los Angeles, CA 90095-1761, USA. Tel.: +1 310 794 9602; fax: +1 310 794 9613.
E-mail addresses: J.E.Buizer@umcutrecht.nl (J.E. Buizer-Voskamp), Wijnand.Laan@gmail.com (W. Laan), W.Staal@umcutrecht.nl (W.G. Staal), F.A.M.Hennekam@umcutrecht.nl (E.A.M. Hennekam), M.Aukes@umcutrecht.nl (M.F. Aukes), F.Termorshuizen@umcutrecht.nl (F. Termorshuizen), R.Kahn@umcutrecht.nl (R.S. Kahn), M.P.M.Boks@umcutrecht.nl (M.P.M. Boks), ROphoff@mednet.ucla.edu (R.A. Ophoff).
[1] For GROUP Consortium.

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number of ASD patients ranged from a few hundreds for case–control studies to thousands of patients within birth cohort studies. However, for both SCZ and ASD the results remain inconsistent. Results include reports that the age of both parents is associated, that only one is associated (maternal or paternal), and that there is no association of SCZ and ASD with parental age. In contrast to the large number of studies investigating the association between paternal age and SCZ and ASD, data on the association with BPD or MDD are rare (Menezes et al., 2010). Two studies reported an association between increased paternal age and the risk of BPD in the offspring ((Frans et al., 2008): 13 428 BPD patients and (Menezes et al., 2010): 493 BPD patients), but we are not aware of studies that investigate the relation between paternal age and MDD.

A systematic analysis of paternal age is necessary to assess its relevance as risk factor for SCZ, ASD, MDD, and BPD in the offspring. On one hand, lack of specificity in the association between increased paternal age and psychiatric diagnoses suggests that paternal age is related to phenotypes shared among disorders or associated with common – perhaps genetic – etiology (Smith et al., 2009). On the other hand, diverse associations between paternal age and psychiatric diagnoses may reflect different risk effects and therefore other biological or psychosocial mechanisms. Few studies examined the effect of paternal age across different diagnostic categories simultaneously (Ekeus et al., 2006; Gillberg, 1982; Lopez-Castroman et al., 2009), but none of these included different DSM-IV-TR diagnoses. In this study we examine the association between paternal age and SCZ, ASD, MDD, and BPD in a single large Dutch population-based sample. As far as we are aware, this is the first large-scale population-based study to compare the four main DSM-IV-TR psychiatric diagnoses on paternal age in a single homogeneous cohort.

2. Materials and methods

2.1. Subjects

Patients were collected through the Psychiatric Case Registry Middle Netherlands (PCR-MN), a case registry from the central part of the Netherlands. The PCR-MN contains data on psychiatric in- and outpatient admissions and diagnoses. Currently over 175 000 cases are registered in the PCR-MN. Patients diagnosed with SCZ, ASD, MDD, or BPD between January 1999 and December 2008 were identified and included in the study. Each diagnosis was defined by the corresponding codes from DSM-IV-TR. Disorders were categorized as schizophrenia spectrum disorder if they were given a DSM-IV code of 295.1–295.4, 295.6, 295.7, 295.9, 298.8, and 298.9; as autism spectrum disorder if they received a DSM-IV code of 299.00, 299.10, or 299.80; as major depressive disorder if they were given a DSM-IV code of 296.20–296.26, 296.30–296.36 or 311.00; and as bipolar disorder if they received a DSM-IV code of 296.00–296.06, 296.40–296.46, 296.50–296.56, 296.60–296.66, 296.70, 296.80, and 296.89. Patients were linked to a record in the civil registry of Statistics Netherlands (CBS) based upon gender, date of birth, and postal code. CBS makes individual, but anonymous data of the Dutch population available for scientific research. Among these characteristics is the parent–children registry. The likelihood to identify both parents of a patient within the civil registry decreases from 90% for those born after 1987 to about zero percent for those born before 1947. Therefore we only included those who were born after 1947. Twins were excluded because it is not possible to differentiate between these two siblings if they live in the same postal-code area. A fourfold number of matched control subjects were collected from the CBS database for each diagnostic group, matched for year of birth, place of birth, and gender. The data available in the PCR-MN is processed in accordance with its security and confidentiality policy. The use of data linked to the civil registry is allowed by Dutch CBS-law article 41 (Statistics-Netherlands, 2004). The use of the civil registry is approved by the Dutch law for the protection of privacy and is monitored by the Central Commission for Statistics of the CBS.

2.2. Parental age determination and statistical analyses

Parental age at time of birth of the proband was calculated in months. We investigated paternal age as a categorical measure by logistic regression (using Statistical Package for the Social Sciences (SPSS), 14th edition). The level of significance was set to 5% and the test was performed two-tailed. The reference group was set at age 25–29 years (in accordance to a recent meta-analysis by Miller et al. (2010)).

Social economic status and ethnic background were considered as confounders. The average income of the residential area at time of birth of the patient was taken as a proxy for social economic status. The ethnic background was categorized into three groups: native Dutch, non-Dutch Western European, or non-Western European.

We investigated the possible influence of maternal age by performing different analyses for mothers aged <30 years and >30 years. We also performed separate analyses for male and female offspring, as it has been suggested that paternal age has a sexually dimorphic effect for psychiatric traits (Miller et al., 2010).

3. Results

Of all patients with a SCZ, ASD, MDD or BPD diagnosis identified in the PCR-MN database, 79.6% could be uniquely linked to a record in the CBS database. Of the 20.4% that could not be linked 11.9% gave more than one unique match and 8.5% gave no match to a record in the civil registry. Of those who were linked to a unique record we could identify both parents for 69.7% of cases. This resulted in a final sample of 2564 SCZ patients, 2262 ASD patients, 8284 patients with MDD and 1121 patients with BPD. A total of 56 924 matched controls were included through the CBS database for the different diagnostic groups (Table 1).

Several studies report age of the other parent as a strong confounder. However, paternal and maternal ages are suggested to be highly related (Fokkema et al., 2008; Olsen and Zhu, 2009). We examined this by computing the Pearson's correlation coefficient. Paternal and maternal ages were highly correlated for all diagnostic groups, with all coefficients between the 0.7 and 0.8 (fathers are 2–3 years older than mothers). Because of this strong relatedness it is not possible to investigate both age effects in the continuous model. We therefore focused on paternal age effects only. The strong correlation makes it also conceivable that paternal age effects can be caused by factors associated with an increased age difference between father and mother instead (Durkin et al., 2008). We therefore also adjusted for the age difference between parents (together with social economic status and ethnic background). This would cover both the confounders of age difference and age of the other parent.

Logistic regression shows a significant association between increased paternal age and ASD risk in the children: older fathers at 40 years of age have a 3.3 times increased odds ratios (OR) of having a child with ASD compared to young fathers <20 years of age. Also the prevalence of SCZ in the offspring is significantly associated with increased paternal age. Older fathers of 35 years of age and above show significant odds ratios compared to fathers at 25–29 years of age. MDD shows a different pattern of association compared to SCZ and ASD. There is not a linear association with paternal age, but a U-shaped relationship: both the youngest and oldest paternal age categories show significantly increased odds ratios of MDD in their offspring. Our results provide no evidence for any association between BPD and paternal age (Table 2). Maternal age shows no additional association effects for any diagnostic category for the separate analyses of younger (<30 years of age) and older (>30 years of age) mothers. Also gender

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