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

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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.

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

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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

Table 1
Demographic characteristics of patients with schizophrenia (SCZ), autism spectrum disorders (ASD), major depression disorder (MDD), or bipolar disorder (BPD) and matched controls.

		Cases	Controls
SCZ	N	2564	10 256
	Mean age (SD)	36.66 (9.69)	36.74 (9.66)
	Male/female ratio	64.8% / 35.2%	64.9% / 35.1%
	Ethnicity: *Native Dutch (%)*	1737 (67.7)	8316 (81.1)
	Non-Dutch Western European (%)	52 (2.0)	192 (1.9)
	Turkey (%)	82 (3.2)	247 (2.4)
	Morocco (%)	225 (8.8)	426 (4.2)
	Surinam/Netherlands Antilles/Aruba (%)	147 (5.7)	278 (2.7)
	Other (%)	321 (12.5)	797 (7.8)
	Mean paternal age (SD)	30.84 (5.84)	30.56 (5.47)
ASD	N	2262	9048
	Mean age (SD)	19.38 (11.28)	19.33 (11.23)
	Male/female ratio	80.9% / 19.1%	80.7% / 19.3%
	Ethnicity: *Native Dutch (%)*	1911 (84.5)	7080 (78.2)
	Non-Dutch Western European (%)	48 (2.1)	176 (1.9)
	Turkey (%)	25 (1.1)	227 (2.5)
	Morocco (%)	35 (1.5)	497 (5.5)
	Surinam/Netherlands Antilles/Aruba (%)	51 (2.3)	252 (2.8)
	Other (%)	192 (8.5)	816 (9.0)
	Mean paternal age (SD)	32.96 (5.53)	32.47 (5.51)
MDD	N	8284	33 136
	Mean age (SD)	37.23 (10.54)	37.32 (10.52)
	Male/female ratio	34.2% / 65.8%	34.3% / 65.7%
	Ethnicity: *Native Dutch (%)*	6429 (77.6)	27 566 (83.2)
	Non-Dutch Western European (%)	149 (1.8)	618 (1.9)
	Turkey (%)	316 (3.8)	651 (2.0)
	Morocco (%)	615 (7.4)	1130 (3.4)
	Surinam/Netherlands Antilles/Aruba (%)	197 (2.4)	735 (2.2)
	Other (%)	578 (7.0)	2436 (7.4)
	Mean paternal age (SD)	30.54 (5.76)	30.48 (5.39)
BPD	N	1121	4484
	Mean age (SD)	40.71 (10.03)	40.71 (10.02)
	Male/female ratio	46.1% / 53.9%	46.1% / 53.9%
	Ethnicity: *Native Dutch (%)*	937 (83.6)	3749 (83.6)
	Non-Dutch Western European (%)	26 (2.3)	80 (1.8)
	Turkey (%)	15 (1.3)	76 (1.7)
	Morocco (%)	24 (2.1)	147 (3.3)
	Surinam/Netherlands Antilles/Aruba (%)	27 (2.4)	105 (2.3)
	Other (%)	92 (8.2)	327 (7.3)
	Mean paternal age (SD)	30.75 (5.41)	30.54 (5.50)

N: number and SD: standard deviation.

Table 2
Multivariate Logistic Regression for paternal age as a categorical measurement.

Paternal age	<20 yr		20–24 yr		25–29 yr		30–34 yr		35–39 yr		≥40 yr	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
SCZ												
N Cases	36		324		874		751		380		199	
N Controls	87		1271		3840		3146		1293		619	
OR-crude	1.82	1.22, 2.70	1.12	0.97, 1.29	Ref		1.05	0.94, 1.17	1.29	1.13, 1.48	1.41	1.19, 1.68
OR-adjusted	1.47	0.98, 2.21	1.05	0.91, 1.22	Ref		1.04	0.94, 1.17	**1.24**	**1.07, 1.42**	**1.27**	**1.05, 1.53**
ASD												
N Cases	3		108		576		846		505		224	
N Controls	40		623		2345		3375		1886		779	
OR-crude	0.31	0.09, 0.99	0.71	0.56, 0.88	Ref		1.02	0.91, 1.15	1.09	0.95, 1.25	1.17	0.98, 1.39
OR-adjusted	0.37	0.11, 1.20	**0.75**	**0.60, 0.95**	Ref		1.00	0.89, 1.13	1.07	0.93, 1.23	**1.23**	**1.01, 1.50**
MDD												
N Cases	125		1148		2871		2454		1136		550	
N Controls	299		4160		12 382		10 151		4364		1780	
OR-crude	1.80	1.46, 2.23	1.19	1.10, 1.29	Ref		1.04	0.98, 1.11	1.12	1.04, 1.21	1.33	1.20, 1.48
OR-adjusted	**1.65**	**1.33, 2.05**	**1.15**	**1.07, 1.24**	Ref		1.04	0.98, 1.11	**1.09**	**1.01, 1.18**	**1.22**	**1.09, 1.36**
BPD												
N Cases	17		117		406		364		149		68	
N Controls	43		583		1645		1328		630		255	
OR-crude	1.60	0.90, 2.84	0.81	0.65, 1.02	Ref		1.11	0.95, 1.30	0.96	0.78, 1.18	1.08	0.81, 1.44
OR-adjusted	1.68	0.94, 3.01	0.82	0.65, 1.03	Ref		1.12	0.96, 1.32	0.99	0.80, 1.22	1.14	0.84, 1.55

OR: Odds-ratio; N: Number; and Yr: Years; Odds-ratios are presented with corresponding 95% confidence intervals. Adjusted OR were corrected for average income of the neighborhood, difference in age between the father and the mother and the ethnic background. Bold values indicate significant adjusted odds-ratios.

has no impact on the rate of any psychiatric disorder in the model (data not shown).

It is possible that these paternal age effects in patients from the case registry are not generalizable to differently collected samples (Berkson, 1946; Parkes et al., 2006). We investigated possible differences between these population-based patients and those collected in hospitals with the use of two available clinical samples for SCZ and ASD. We found both clinic-based samples to differ significantly in paternal age from our patients from the population-based registry, showing that the way in which subjects are collected can be a source of bias (see Supplemental Information for methods and results).

4. Discussion

In this study we investigated 14231 patient and 56924 controls from the Dutch population on the relevance of paternal age as a risk factor for psychiatric disorders in the offspring. We find significant associations between paternal age and autism spectrum disorders (ASD), schizophrenia (SCZ), and major depressive disorder (MDD), but not for bipolar disorder (BPD). Interestingly, population demographics in the Western world show a clear increase in father's mean age at childbirth. Dutch fathers have one of the highest ages at birth in Europe: 34.2 years of age in 2006 (Fokkema et al., 2008). Our analysis shows that the prevalence of ASD in the offspring is significantly associated with an increased paternal age. Older fathers (>40 years of age) have a 3.3 times increased odds for having a child with ASD compared to younger fathers (<20 years of age). A similar trend is seen for SCZ: fathers above 35 years of age have significantly higher odds ratios of having a child with the disorder. The relationship between MDD in the offspring and paternal age is U-shaped, meaning that both younger and older fathers are associated with a higher prevalence of MDD in the offspring. This is a markedly different pattern from that observed for ASD and SCZ. It is noteworthy that we find no evidence that BPD is associated with paternal age.

The linear association between increased paternal age and ASD and SCZ in the offspring is most commonly found in literature (Miller et al., 2010). For the affective disorders the evidence for paternal age as a risk factor is less pronounced. We found only one study to describe a U-shaped relationship as we found for MDD (Krishnaswamy et al., 2009). However, this study describes the relation between younger and older fathers with increased rate of common mental disorders. Our negative findings for BPD contrast with two previous studies (Frans et al., 2008; Menezes et al., 2010) reporting increased paternal age to be associated with BPD in the offspring.

Our clearly different effects for paternal age as a risk factor for ASD and SCZ on one hand and the affective disorders on the other hand are striking. Gillberg (1982) described already in 1982 that increased parental age might have different effects on the risk of psychiatric disorders in the offspring. Our results for ASD and SCZ contrasting MDD and BPD are another indication that paternal age might have different risk effects for the major psychiatric disorders.

Different types of association could reflect different biological or psychosocial mechanisms. A molecular mechanism for the associations could be the occurrence of *de novo* mutations or epigenetic changes in the germline (Crow, 2003; McClellan et al., 2007). Diminished DNA repair mechanisms, declining testosterone levels and other circumstances during mitotic divisions associated with late paternal age could lead to new mutations arising in sperm (Bassett et al., 2010; Lopez-Castroman et al., 2009). The fact that neuropsychiatric disorders are influenced by a large number of individually rare deleterious mutations, many of which have occurred in the present or recent generations, may favor this hypothesis (Carroll and Owen, 2009; McClellan et al., 2007). However, it is not clear how a biological explanation would only apply to ASD and SCZ (and possibly MDD), but not to BPD.

Another important explanation could be confounding by genetic vulnerability. Older fathers may have personality traits (such as schizotypal or autistiform traits), which would result in difficulty in establishing relationships and thereby an increased age of parenthood. Because of the high heritability, the presence of these personality traits in the fathers could result in an increased risk of developing a psychiatric disorder in the offspring (Zammit et al., 2003). The finding that ASD, SCZ, and MDD, but not BPD are associated with increased paternal age supports this hypothesis, since recent findings show that patients in the premorbid phase of BPD have improved social and cognitive functions. Also, in contrast to ASD and SCZ, BPD is not associated with reduced fecundity (MacCabe et al., 2010). These findings suggest that fathers with bipolar sub clinical symptoms may not suffer from diminished social functioning explaining the lack of an increased paternal age of patients with BPD.

The hypothesis of an association between late paternity and predisposition to psychiatric disorders is supported by a recent study by Petersen et al. (2011). They confirm the association between paternal age and schizophrenia. However, they also show that the risk of SCZ did not depend on paternal age at birth of the proband, but rather on the age at which the father had his first child. The findings of Petersen et al. (2011) are the opposite of what would be predicted if de novo mutations or epigenetic changes were a major reason for the effect of paternal age.

It is possible that multiple exposures may increase the risk of psychiatric disorders through shared pathways (i.e. genetics, epigenetics, hormonal alterations and environmental factors). This will be represented as a generalized increased risk with paternal age (Shelton et al., 2010). In accordance to recent findings, our results suggest that the association with increased paternal age is due to factors related to higher paternal age at first fatherhood.

An important strength of our study is that we investigated the four major psychiatric disorders simultaneously, with large sample sizes for each diagnostic group. We used data from a psychiatric case registry, which records all psychiatric diagnoses of the complete population living in the study area. Therefore there is little risk of selection bias, which may occur in clinically selected samples. However, some residual bias may still be present. As can be seen in Table 1, the ASD subjects are from a younger generation than the other diagnostic groups, which could bias our results. These different generations reflect the rising of father's mean age at childbirth during the past decades, with older fathers in the ASD group compared to the other groups. However, the age of fathers from the ASD matched controls is also higher compared to the other matched control groups. This generation effect for ASD should therefore have no effect on the outcome of the analyses. Even with the recently highlighted underdiagnosis of ASD there is no reason to assume that this bias is systematic towards children with younger parents, although it would be very interesting to investigate this in more detail. Secondly, diagnoses within the PCR-MN are not based on standardized interviews that are ordinarily used for research purposes. However, because the diagnoses are made in a clinical context by experienced psychiatrists trained to use DSM-IV diagnostic criteria, we do not expect diagnoses to be much different when based on standardized questionnaires and interviews and we particularly do not expect a systematic bias in diagnosis related to paternal age. Finally, the absence of information on non-paternity is a limitation. However, we expect this to be equal for cases and controls.

In conclusion, in this large-scale population-based study we report an association between paternal age and the prevalence of ASD, SCZ, and MDD, but not BPD in the offspring. Whatever the cause behind paternal age as risk factor for psychiatric traits in the children, our results show clear differences between ASD and SCZ compared to the affective disorders. This could reflect different biological or psychosocial mechanisms. Most likely the results can be explained by social selection as pointed out by Petersen et al. (2011) who reported that not

age at birth of the schizophrenia patient but rather paternal age at birth of the first child explains the association. Our differential effects of paternal age in SCZ, ASD, and affective disorders are in line with this finding.

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Contributors

J.E. Buizer-Voskamp carried out part of the data collection and analyses and drafted the manuscript. W. Laan and F. Termorshuizen carried out the data collection from the PCR-MN and CBS databases and performed the statistical analyses. W.G. Staal supervised the collection of the ASD clinic-based sample and participated in the design of the study. E.A.M. Hennekam did part of the parental age data collection. M.F. Aukes participated in the design of the study. R.S. Kahn carried out the data collection of the SCZ clinic-based sample, on behalf of the GROUP consortium. M.P.M. Boks participated in the design of the study and helped to draft the manuscript. R.A. Ophoff supervised the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.schres.2011.03.021.

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