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ORIGINAL PAPER

Parental Age and Risk of Autism Spectrum Disorders in a Finnish National Birth Cohort

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Abstract Aim of the study was to examine the associations between parental age and autism spectrum disorders (ASD). Data were based on the FIPS-A (Finnish Prenatal Study of Autism and Autism Spectrum Disorders), a case-control study with a total of 4,713 cases with childhood autism (n = 1,132), Asperger's syndrome (n = 1,785) or other pervasive developmental disorder (PDD) (n = 1,796), which were ascertained from the Finnish Hospital Discharge Register. Controls were selected from the Finnish Medical Birth Register. Conditional logistic regression models were used for statistical analyses. Advanced paternal age (35–49 years) was associated with childhood autism in offspring, whereas advanced maternal age was associated with both Asperger's syndrome and PDD in offspring (35 years or more and 40 years or more, respectively). Teenage motherhood (19 years or less) was associated with PDD in offspring. The main finding was that maternal and paternal ages were differentially associated with ASD subtypes. In addition to advanced parental age, teenage pregnancy seems to incur a risk for PDD in offspring.

Keywords Epidemiology · Autism spectrum disorders · Parental age

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Introduction

Autism spectrum disorders (ASD) represent a group of psychiatric syndromes characterized by qualitative abnormalities in reciprocal social interactions, in language and patterns of communication, and by a restrictive, stereotyped, repetitive repertoire of interests and activities (World Health Organization 1992). Specific diagnostic criteria for childhood autism, which is the most severe disorder of the subtypes, include all three of these criteria and onset by the age of 3 years. The majority of individuals diagnosed with childhood autism have significant cognitive problems or intellectual disability (Fombonne et al. 1997; Haglund and Kallen 2011). Asperger's syndrome differs from childhood autism mainly in the absence of significant delay in language development and cognitive functioning. Intellectual capacity is expected to be age-appropriate in Asperger's syndrome; therefore, it can be considered as a milder variant of autism, although deficits in pragmatic language and social interaction are often present. Other pervasive developmental disorders (PDD) are the least well

defined but yet the most frequently diagnosed subtypes of these disorders. In Finland, the diagnosis of PDD may often be received if a child does not meet specific diagnostic criteria for childhood autism or Asperger's syndrome. Children with PDD usually have multiple developmental delays in learning, communication and socialization skills, though the phenotype exhibits significant variation between cases. Based on current diagnostic classifications and considering the heterogeneity of ASD, it can be difficult to distinguish ASD subtypes from each other (e.g. Mahoney et al. 1998). In the forthcoming DSM -5, some changes are likely to replace the current categorical classifications based on the severity of ASD symptomology with what equates to an ASD severity continuum covering largely the same clinical population. We acknowledge this plan, however, even if the diagnostic classifications for ASD will be different in the DSM 5, several studies (Lampi et al. 2012; Haglund and Kallen 2011; Glasson et al. 2004; Tran et al. 2013) suggest that the use of different subtypes or symptom severity continue to have value with regard to the investigation of prenatal risk factors.

The possibility that autism is more common in children of older parents has been of considerable interest. Both genetic and environmental factors are thought to contribute to the development of ASD. Genomic alterations have been found in autistic children (Christian et al. 2008) and epigenetic dysfunction has been associated with several neuropsychiatric disorders (Mill et al. 2008). However, it is unclear whether these are specifically related to advanced parental age. The findings from population-based studies investigating the association between parental age and risk of autism are inconsistent. A case–control study from Australia (Glasson et al. 2004) and three birth cohort studies from the United States (Croen et al. 2007; Durkin et al. 2008; Grether et al. 2009) suggested an association between both maternal and paternal age and ASD. Population-based studies from Denmark (Lauritsen et al. 2005), Israel (Reichenberg et al. 2006), Iran (Sasanfar et al. 2010), China (Zhang et al. 2010) and Sweden (Hultman et al. 2011) have shown that high paternal age is associated with increased risk of ASD in offspring. In contrast to these findings, two large case–control studies from Sweden (Hultman et al. 2002) and Denmark (Larsson et al. 2005) reported no association between parental ages and risk of autism after adjusting for prenatal factors and parental psychiatric history. There are several methodological issues which may explain the inconsistency of previous research findings. First, there is large variation in sample sizes; in most studies the number of cases is less than one thousand. Second, most of the previous register-based studies have been based on children admitted to hospitals and do not include outpatient care. In the two Danish studies (Lauritsen et al. 2005; Larsson et al. 2005) outpatient visits in psychiatric departments were included. Third, there is a considerable amount of variation between studies on confounding factors. For example, among previous population-based studies, only the Swedish and Danish studies (Hultman et al. 2011; Larsson et al. 2005) included both maternal and paternal psychiatric history in the analyses. Finally, in previous population-based studies the case definition for autistic disorders has been relatively broad, usually including the whole autism spectrum or different combination of ASD diagnoses (Croen et al. 2007; Durkin et al. 2008; Reichenberg et al. 2006; Sasanfar et al. 2010), or the studies focused on the severe end of the autism spectrum (Grether et al. 2009; Lauritsen et al. 2005; Hultman et al. 2002, 2011; Larsson et al. 2005). Therefore, it is unclear if the associations between parental ages and ASD differ by diagnostic subtype or severity of the disorder. Given the likely multifactorial etiology of ASD, it is conceivable that different etiologic factors (in this case parental ages) could be related to different symptoms within the spectrum. In our previous study (Lampi et al. 2012), ASD subtypes were different in birth weight characteristics: low birth weight and being small for gestational age were associated with childhood autism and PDD, but not with Asperger's syndrome. A Swedish study reported similar findings (Haglund and Kallen 2011). Also a large Australian population-based study reported that subtypes differed in types of obstetric complications (Glasson et al. 2004). These findings suggest that different prenatal risk factors need to be examined separately for ASD subtypes or based on the severity of the disorder.

In the present study, we aimed to examine the association between maternal and paternal age and risk of ASD, separately for the three main subtypes, namely childhood autism, Asperger's syndrome and PDD. The study is based on a large, ongoing epidemiological study of autism and autism spectrum disorders in Finland, the Finnish Prenatal Study of Autism and autism spectrum disorders (FIPS-A). Unlike most previous investigations on this topic, this study included both inpatient and outpatient diagnoses based on nationwide register information and controlled for the effects of prenatal/perinatal factors and maternal and paternal psychiatric history.

Materials and methods

Study Design

The FIPS-A is a nested case–control study of all live singleton births in Finland between January 1, 1987 and December 31, 2005 (n = 1,149,271). The nesting is a consequence of selecting cases and a sample of matched controls from a defined birth cohort. Specifically, cases consisted of all offspring born in Finland who were diagnosed with ASD by December 31, 2007. Controls were

selected from the remainder of the national cohort who were resident of Finland at the time of case diagnosis and were born during the specified years, and who were without ASD or severe/profound mental retardation. Excluding these forms of mental retardation was justified by considerable diagnostic overlap with infantile/childhood autism, particularly during the earlier years of the study period. Each case was individually matched to four controls on date of birth, sex, and place of birth. If the birth place was a very small community and a control could not be found, the first option was to match by birth hospital and the second by regional hospital district. A total of 18,777 control subjects were matched from the nationwide medical birth register. A full description of the study methodology is provided in a previous publication (Lampi et al. 2011). This study was authorized by the Ministry of Social Affairs and Health in Finland (STM/2593/2008) with the approval from the ethics committee of the hospital district of Southwest Finland and the National Institute for Health and Welfare, and approved by the Institutional Review Board of the New York State Psychiatric Institute.

Nationwide Registers

This study is based on information from three nationwide registers: the Finnish Hospital Discharge Register (FHDR) the Finnish Medical Birth Register (FMBR), and the Finnish Central Population Register (CPR). The FHDR was established in the 1960s and computerized data with personal identity codes are available from 1969 to the present. All psychiatric and other medical diagnoses, based on the International Classification of Diseases (ICD: ICD-8 (World Health Organization 1967) from 1969 to 1986, ICD-9 (World Health Organization 1977) from 1987 to 1995 and ICD-10 (World Health Organization 1992) from 1996 to the present), are included in the FHDR, which covers all somatic and psychiatric hospitals, inpatient wards of local health centers, military wards, prison hospitals and private hospitals. Since 1998, the FHDR has covered all outpatient care in public hospitals as well. Past diagnoses are available in the FHDR, and at each visit, the current diagnosis is registered on a computer by health care personnel. The registration routines are standardized across Finland. In this study, the most recent diagnosis was used for diagnostic classification. The Finnish public health care system includes primary health care, district and central hospitals as well as university hospitals. Primary health care doctors are gatekeepers for referral to the more specialized services where the assessment is led by a child neurologist or child psychiatrist. Usually ASD cases are diagnosed in specialized services within the public health care system and receive care free of charge. The FMBR was established in 1987 and includes comprehensive data on all live births and stillbirths (22 gestational weeks and/or 500 grams) and the neonatal period up to the age of 7 days of all births in Finland. The CPR is a computerized national register that contains basic information about Finnish citizens and foreign citizens residing permanently in Finland, including name, personal identity code, address, municipality of residence, citizenship, family relations and date of birth and death. All data from the registers used in the study were linked using the child's personal identity code which remains unchanged throughout the person's lifetime and is unique for each person. The Finnish personal identity code is issued to all Finnish citizens and permanent residents at birth or at migration.

Case Identification

Cases with ASD diagnoses during the 21-year follow-up period were identified from the FHDR by ICD-criteria with diagnostic codes 299x (ICD-9) or F84x (ICD-10). In Finland, access to special health care services is equal to all citizens and free of charge. All diagnostic codes given in any health care unit by the attending physician are entered into the FHDR. The majority of cases were diagnosed in accord with ICD-10 while only 19 cases were diagnosed by ICD-9. Since the most recent registry diagnosis was used for classification, those 19 cases with only ICD-9 diagnoses represent a rare group of individuals, who do not have any diagnoses registered after 1996 (e.g. most likely have deceased or moved out of Finland). In this study, we examined the association between parental age and three different diagnostic subgroups of ASD: childhood autism (F84.0), Asperger's syndrome (F84.5) and other pervasive developmental disorders/pervasive developmental disorder, unspecified (PDD, F84.8/F84.9). In this study, "PDD" refers to cases that had received either a diagnosis of "other pervasive developmental disorder" or "pervasive developmental disorder, unspecified". Register-based diagnoses of childhood autism have been validated against the Autism Diagnostic Interview-Revised (ADI-R) (Lampi et al. 2010). A total of 4,713 cases were found in the FHDR: 1,132 were diagnosed with childhood autism, including 894 (79 %) boys and 238 (21 %) girls; 1,785 with Asperger's syndrome, including 1,506 (84 %) boys and 279 (16 %) girls; and 1,796 with PDD, including 1,353 (75 %) boys and 443 (25 %) girls. Based on these data (Lampi et al. 2010), the prevalence of childhood autism in Finland among children 19 years or younger was 9 per 10,000 by the end of 2005. The respective prevalences of Asperger's syndrome and PDD are 14.5 and 14.6 per 10,000. In a previous review, Williams et al. (2006) reported an estimate of prevalence of ASD across different studies by the end of 2004. Based on their review, prevalence for "typical autism" was 7.1 per 10,000 and for "all ASD" the

prevalence was 20 per 10,000. Our estimates are similar to these overall values, although our prevalence rates for Asperger's syndrome and PDD are slightly lower than those estimated for "all ASD" by Williams et al. (2006) Some studies have reported a higher prevalence for ASD. For example, a review by Elsabbagh et al. (2012) reports the median estimate of ASD to be as high as 62 per 10,000, whereas a Korean population-based study (Kim et al. 2011) reported the prevalence of ASD to be as high as 264 per 10,000.

Maternal and Paternal Age

Data on maternal age were obtained from the FMBR; data on paternal age were obtained from the CPR. Data on maternal age were available for all subjects, whereas data on paternal age were available for 98.3 % of the subjects. The data on paternal age were missing only if the paternity was unknown. In Finland, it is mandatory to have an acknowledgement of paternity outside marriage. If the child's parents are officially married, the husband of the mother is automatically registered as the father. In other situations, e.g. cohabiting relationships, the child welfare officer of the municipality establishes the paternity. Free-of-charge DNA- testing for paternity by a court decision can be proposed by the child welfare officer or required by either of the parents. However, the alleged father usually acknowledges his paternity without need for court decision (Forss and Säkkinen 2012). In this sample, 98.3 % of the cases had a registered father. Cases without information on paternity (1.7 %) were excluded in the statistical analyses. Maternal age was classified into the following categories: below 20, 20–24, 25–29, 30–34, 35–39 and 40 years or more. Paternal age was categorized as below 20, 20–24, 25–29, 30–34, 35–39, 40–49 and 50 years or more. Parental ages of 25–29 years were chosen as reference categories. Similar categories have been used in previous studies (E.g. Croen et al. 2007; Larsson et al. 2005).

Confounding Factors

The following potential confounding variables were included in the analyses: maternal socioeconomic status (SES), based on maternal occupation at birth, number of previous births (i.e. birth order), child's weight for gestational age (WGA), child's intellectual disability, and maternal and paternal psychiatric history. These factors have been associated with both ASD and parental age in previous studies (Kolevzon et al. 2007; Gardener et al. 2009; Cleary-Goodman et al. 2005; Croen et al. 2002; Lampinen et al. 2009). Data on maternal SES, number of previous births, and WGA were obtained from the FMBR, whereas data on intellectual disability and parental psychiatric history were obtained from the FHDR. Maternal SES was classified into four categories: upper white collar workers, lower white collar workers, blue collar workers, and others who do not belong to any of the previous categories (e.g. students, housewives). These SES categories were based on existing national classifications that are included in the FMBR. Data on maternal SES are available from October, 1990 to the present. The number of previous births was categorized as 0, 1, 2, 3 or 4 or more. WGA was estimated according to Finnish birth weight standards, based on a sex-specific weight distribution in a sample (Pihkala et al. 1989) of children born in Finland ($n = 75{,}061$), and was categorized into three groups: small for gestational age (SGA, <-2 SD), appropriate for gestational age (AGA, -2 SD to $+2$ SD) and large for gestational age (LGA, $>+2$ SD). In the FMBR, the best clinical estimation of gestational age at birth is registered, which has been based on ultrasound since the late 1980s, prior to that, it was based on the last menstrual period. Cases were defined as having intellectual disability if they had received a diagnosis for that based on the FHDR (F70–79 in the ICD-10). Corresponding diagnoses based on the ICD-9 (317–319) were also included. Parents were defined as having a psychiatric history if they had any of the following diagnoses recorded in the FHDR during their lifetime: mental and behavioural disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related and somatoform disorders; behavioural syndromes associated with physiological disturbances and physical factors; disorders of adult personality and behaviour; disorders of psychological development; behavioural and emotional disorders with onset usually occurring in childhood and adolescence and unspecified mental disorder (including autism spectrum disorders) (F10–F99 in the ICD-10). Corresponding diagnoses based on the ICD-9 and the ICD-8 were also included: psychosis; neurotic disorders, personality disorders, and other nonpsychotic mental disorders (ICD-9: 291–316 and ICD-8: 291–309). Parental psychiatric history was classified as a binary variable (yes/no).

Statistical Analyses

Conditional logistic regression was used to examine the association between the ASD outcome and parental age. Unadjusted odds ratios (OR) and 95 % confidence intervals (CI) were first calculated separately for maternal and paternal age. In the age-adjusted model, maternal and paternal ages were both included. The final model included maternal and paternal age, maternal SES, number of previous births, WGA, intellectual disability and parental psychiatric history. In all analyses, a two-sided p value of

<0.05 was considered statistically significant. Statistical analyses were performed with SAS statistical software (SAS Institute Inc. SAS Version 9.2. Cary, NC). Of note, we analysed maternal and paternal age also as continuous variables to test for the linearity between maternal and paternal age and ASD. The associations were not linear indicating that adoption of any decomposition strategies developed for continuous variables was not applicable.

Results

In the total sample of cases, maternal age ranged from 15 to 48 years (mean 29.6, SD 5.3). Paternal age ranged from 17 to 72 years (mean 32.0, SD 6.0). Descriptive characteristics of cases and controls are presented in Table 1.

Childhood Autism

In the unadjusted analysis, both high maternal and paternal ages (35 years or more) were associated with an increased risk of childhood autism in offspring (Table 2). However, after adjusting for the other parent's age, only the effect of high paternal age remained statistically significant. In the final model, the effect persisted: for fathers aged 35–39 and 40–49 years old, the risk of childhood autism was increased by 40, and 50 %, respectively.

Asperger's Syndrome

In the unadjusted analysis, both high maternal (35 years or more) and paternal ages (40–49 years) were associated with having offspring with Asperger's syndrome (Table 2). However, after adjustment for the other parent's age, only the two highest maternal age categories (35–39 and 40 years or more) were statistically significantly associated with Asperger's syndrome. The effect remained statistically significant in the final model with a nearly twofold increased risk.

PDD

In the unadjusted analysis, all maternal ages compared to 25–29 years were associated with an increased risk of PDD (Table 2). Moreover, both low (less than 25 years) and high (40 years or more) paternal ages were associated with PDD in offspring in the unadjusted model. After adjusting for the other parent's age, these results were slightly attenuated. In the final model, the strongest association was found for the teenage mothers (15–19 years), the offspring of whom had a statistically significant, greater than twofold increase in risk of PDD. For mothers aged 40 years or more, there was a statistically significant 60 % increase in PDD risk among offspring. No statistically significant associations were found between paternal age and PDD in the final model.

Table 1 Maternal and paternal age distributions in autism spectrum disorder cases and matched controls among all children born in Finland 1987–2005

	Childhood autism		Asperger's syndrome		PDD[a]	
	Cases n (%)	Controls	Cases n (%)	Controls	Cases n (%)	Controls
Maternal age (years)						
19 or less	15 (1.3)	103 (2.3)	30 (1.7)	120 (1.7)	66 (3.7)	118 (1.7)
20–24	158 (14.0)	685 (15.2)	247 (13.8)	1,123 (15.7)	311 (17.3)	1,065 (15.0)
25–29	364 (32.2)	1,551 (34.4)	618 (34.6)	2,558 (36.0)	522 (29.1)	2,502 (35.0)
30–34	346 (30.6)	1,368 (30.2)	508 (28.4)	2,121 (29.8)	535 (29.8)	2,213 (31.0)
35–39	201 (17.8)	672 (14.9)	307 (17.3)	972 (13.7)	269 (15.0)	1,002 (14.0)
40 or more	48 (4.2)	136 (3.0)	75 (4.2)	220 (3.1)	93 (5.2)	248 (3.5)
Paternal age (years)						
19 or less	22 (1.9)	71 (1.8)	46 (2.6)	122 (2.1)	65 (3.6)	121 (2.1)
20–24	84 (7.4)	373 (8.2)	124 (6.9)	558 (7.8)	170 (9.5)	545 (7.6)
25–29	261 (23.1)	1,204 (26.6)	508 (28.4)	2,030 (28.4)	433 (24.1)	1,959 (27.3)
30–34	359 (31.7)	1,517 (33.5)	575 (32.2)	2,380 (33.3)	551 (30.7)	2,373 (33.1)
35–39	252 (22.3)	888 (19.6)	307 (17.2)	1,333 (18.7)	344 (19.2)	1,417 (19.7)
40–49	136 (12.0)	429 (9.5)	210 (11.8)	633 (8.9)	212 (11.8)	683 (9.5)
50 or more	18 (1.6)	33 (0.7)	15 (0.8)	58 (0.8)	21 (1.17)	50 (0.7)

[a] Other pervasive developmental disorder/pervasive developmental disorder, unspecified

Table 2 Parental age and risk of childhood autism, Asperger's syndrome, and other pervasive developmental disorders (PDD) in Finland from 1987 to 2005

	Childhood autism (n = 1,132)			Asperger's syndrome (n = 1,785)			PDD[a] (n = 1,796)		
	Unadjusted OR (95 % CI)	Age adjusted[b]	Final adjusted[c]	Unadjusted OR (95 % CI)	Age adjusted	Final adjusted	Unadjusted OR (95 % CI)	Age adjusted	Final adjusted
Maternal age (years)									
19 or less	0.6 (0.3, 1.1)	0.5 (0.3, 1.0)	0.7 (0.3, 1.8)	1.0 (0.7, 1.6)	0.9 (0.6, 1.4)	0.5 (0.3, 1.0)	2.7 (2.0, 3.7)***	2.2 (1.6, 3.2)***	2.1 (1.2, 3.6)**
20–24	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.1 (0.8, 1.5)	0.9 (0.8, 1.1)	0.9 (0.7, 1.0)	0.7 (0.6, 0.9)*	1.4 (1.2, 1.6)***	1.4 (1.1, 1.6)***	1.2 (0.98, 1.5)
25–29	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
30–34	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.0 (0.9, 1.1)	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)	1.2 (1.01, 1.3)*	1.1 (1.0, 1.3)	1.2 (0.99, 1.4)
35–39	1.3 (1.1, 1.6)*	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)	1.3 (1.1, 1.5)***	1.4 (1.2, 1.7)***	1.8 (1.4, 2.3)***	1.3 (1.1, 1.5)**	1.2 (1.0, 1.4)	1.2 (0.97, 1.6)
40 or more	1.5 (1.1, 2.2)*	1.2 (0.8, 1.7)	0.9 (0.5, 1.6)	1.4 (1.1, 1.9)*	1.4 (1.02, 1.9)*	1.8 (1.2, 2.7)**	1.8 (1.4, 2.3)***	1.5 (1.1, 2.0)**	1.7 (1.2, 2.5)**
Paternal age (years)									
19 or less	1.4 (0.9, 2.4)	1.7 (1.0, 2.8)	0.4 (0.1, 2.4)	1.5 (1.1, 2.2)*	1.4 (1.00, 2.1)	0.7 (0.2, 2.3)	2.5 (1.8, 3.4)***	2.0 (1.4, 2.8)**	1.6 (0.7, 3.8)
20–24	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.7, 1.6)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	1.4 (1.2, 1.7)***	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)
25–29	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
30–34	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.2 (0.9, 1.5)	1.0 (0.8, 1.1)	0.9 (0.8, 1.0)	1.0 (0.9, 1.3)	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.9, 1.3)
35–39	1.3 (1.1, 1.6)**	1.3 (1.00, 1.6)	1.4 (1.1, 2.0)*	0.9 (0.8, 1.1)	0.8 (0.6, 0.9)**	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.8, 1.3)
40–49	1.5 (1.2, 1.9)**	1.4 (1.03, 1.8)*	1.6 (1.1, 2.3)*	1.3 (1.1, 1.6)**	1.0 (0.8, 1.3)	1.3 (0.98, 1.7)	1.4 (1.2, 1.7)***	1.3 (1.03, 1.6)*	1.2 (0.9, 1.6)
50 or more	2.5 (1.4, 4.5)**	2.3 (1.2, 4.2)**	1.7 (0.6, 4.6)	1.0 (0.6, 1.8)	0.8 (0.4, 1.4)	1.1 (0.5, 2.2)	2.0 (1.2, 3.3)*	1.7 (1.0, 3.0)	1.6 (0.8, 3.2)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] Other pervasive developmental disorder/pervasive developmental disorder, unspecified

[b] Adjusted for the other parent's age

[c] Adjusted for the other parent's age, number of previous births, weight for gestational age, intellectual disability, maternal socioeconomic status and maternal and paternal psychiatric history

Discussion

The main finding of the present study is that maternal and paternal ages were differentially associated with subtypes of autism spectrum disorders. Paternal age was independently associated only with the outcome of childhood autism, whereas high maternal age was independently associated with both Asperger's syndrome and PDD. Moreover, teenage motherhood was associated with PDD.

The finding that high paternal age was associated with autism in offspring is consistent with at least five population-based studies from Israel (Reichenberg et al. 2006), Denmark (Lauritsen et al. 2005), Iran (Sasanfar et al. 2010), China (Zhang et al. 2010) and Sweden (Hultman et al. 2011). Although some of the previous studies, as described earlier, had broader or otherwise different definitions of cases than our study, our results further substantiate the finding that advanced paternal age has an independent effect on the development of autism in offspring. The magnitude of the risk in our study was lower than reported in the Israeli study (Reichenberg et al. 2006), in which offspring of men 40 years or older had an almost sixfold increased risk of ASD. However, our results and odds ratios are almost identical to the recent Swedish study (Hultman et al. 2011). The paternal age effect has been hypothesized to be related to greater cumulative spermatogonial cell divisions as men age, resulting in higher rates of de novo mutations (Croen et al. 2007; Reichenberg et al. 2006; Malaspina 2001; Kong et al. 2012; Amaral and Ramalho-Santos 2009; Smith et al. 2009). Another explanation is epigenetic modifications, which are heritable but reversible modifications to the genome caused by mechanisms other than changes in the underlying DNA sequence (Grafodatskaya et al. 2010; Schanen 2006). An example of an epigenetic mechanism is DNA methylation-mediated imprinting, which is involved in parent-specific gene silencing. In the case of paternal imprinting, the gene inherited from the father is silenced by methylation and only the maternal allele is expressed. Changes in methylation patterns influenced by paternal age could therefore have significant effects in the expression of the gene concerned (Sartorius and Nieschlag 2010).

Advanced maternal age was independently associated with Asperger's syndrome and PDD. Explanations for the association include age-related genetic factors, higher risk of pregnancy complications and the role of personality traits (Rutter 2011). The increased risk of chromosomal abnormalities in older women has been suggested as an explanation for an independent maternal age effect in ASD (Reichenberg et al. 2006; Gardener et al. 2009). There is also evidence that advanced maternal age can increase the risk of pregnancy and obstetric complications. Older women are known to have a higher risk for maternal hypertension, pre-eclampsia, caesarean section, placental pathology, and other pre- and perinatal complications. These conditions can lead to fetal hypoxia which has been associated with ASD in some studies (Glasson et al. 2004; Kolevzon et al. 2007; Gardener et al. 2009; Juul-Dam et al. 2001). There are very few studies that have examined prenatal risk factors separately for Asperger's syndrome (Haglund and Kallen 2011; Glasson et al. 2004; Eaton et al. 2001; Gillberg and Cederlund 2005) and the studies have been limited to relatively small numbers of cases. Our results are consistent with the Danish study (Eaton et al. 2001) which reported for the first time an association between high maternal age and Asperger's syndrome. However, in that study the definition of Asperger's syndrome was notably broader than in our study, since it was based on the older version of the ICD (World Health Organization 1967) in which the diagnosis was not yet explicitly described.

To our knowledge, this is the first population-based study reporting an association between teenage motherhood and PDD. The finding of a nearly three-fold increased risk for PDD in offspring of very young mothers has not been shown previously. Future population-based studies are warranted on this topic. However, this finding adds to the previous literature showing that teenage motherhood is associated with psychiatric outcomes in offspring, for example externalizing behavior problems such as inattention, hyperactivity and aggressive behaviour (Moffitt and E-Risk Study Team 2002; Trautmann-Villalba et al. 2004). These types of disorders are often comorbid with PDD (Harada et al. 2009; Gadow et al. 2006). One possible explanation for the association between teenage motherhood and PDD is that certain risk behaviors of teenage mothers during pregnancy, such as smoking, are greater than in older women (Vuori and Gissler 2010; Langley et al. 2005; Linnet et al. 2003; Boden et al. 2010; Savio Beers and Hollo 2009; Cunnington 2001). Maternal smoking has been associated with several risk factors e.g. low birth weight, hypoxia, premature birth, pregnancy complications, that have been associated with ASD in some studies (Glasson et al. 2004; Kolevzon et al. 2007; Gardener et al. 2009). However, research findings regarding maternal smoking and ASD have been inconsistent (Ekblad et al. 2010; Johnson and Leff 1999).

Strengths and Limitations of the Study

The large sample size allowed us to assess not only associations between ASD and advanced maternal and paternal ages, but also the relation of ASD to young parenthood. The universal health care system in Finland, as in other Nordic countries such as Denmark and Sweden, reduces the possibility of selection bias due to socioeconomic differences,

which are present in some countries in which families with higher income may have better access to special health care services, or other forms of selection bias, increasing the probability that autism will have been detected in the offspring. In Finland, equal access to both primary and specialized health care services is available to all citizens free of charge. Children under school age (i.e. until the age of 7 years) visit child health clinics at least once a year where physical, cognitive and social development is assessed. This comprehensive monitoring system means that the majority of children with moderate or severe symptoms of ASD, or intellectual disabilities will have been detected in the study population and subsequently referred to more specialized services for diagnostic assessment.

However, there are several limitations that need to be considered. First, in the present study direct assessment with structured research interviews of ASD cases was not performed, possibly resulting in some degree of diagnostic misclassification. Register-based diagnoses of childhood autism, though not Asperger's syndrome or PDD, in the FHDR have been validated by the ADI-R (Lampi et al. 2010). Therefore, findings regarding the associations between parental age and Asperger's syndrome and PDD may be viewed with less confidence than those regarding the associations with childhood autism. While the ADI-R is regarded as the gold standard in autism research, a study including both the ADI-R and, for example, the Autism Diagnostic Observation Schedule (ADOS) would have strengthened the validation of diagnoses. However, since in Finland the clinical assessment of any ASD is done in specialized services (and led by an experienced physician), we believe that the validity of the diagnoses is at least acceptable. In addition, to receive disability benefits from the Social Insurance Institution, an independent evaluation by another physician is required. The validity of register-based diagnoses in Finland has also been shown to correlate well with information based on hospital records in studies of other psychiatric disorders, including schizophrenia and bipolar disorders (Isohanni et al. 1997). Second, a study design based on screening an entire population with research assessments, rather than relying on registers of treated cases, may have allowed for more complete detection of cases with mild/subclinical symptoms of ASD. Third, since inclusion of outpatient diagnoses in the FHDR began in 1998, we were not able to ascertain cases diagnosed and treated only in outpatient services prior to that year. However, since the most recent diagnosis was used for case identification, and ASD is generally a chronic condition, we expect that this would have captured many cases treated exclusively as outpatients with onset prior to 1998 in our study sample. Fourth, our sample included only singleton births, and therefore, our findings apply mainly for singletons and the findings may not be generalizable for twins. Finally, it is conceivable that residual confounders may have contributed to our results (Thapar and Rutter 2009).

Conclusions

The results of this study substantiate the finding that advanced paternal age is an independent risk factor for childhood autism, whereas advanced maternal age was found to be a risk factor for Asperger's syndrome and PDD. Furthermore, this study shows that in addition to advanced parental age, teenage pregnancy incurs a risk for one of the ASD subtypes, namely PDD in offspring. Further studies that incorporate genetic vulnerability and epigenetic effects into studies of paternal and maternal age in autism may lead to an improved understanding of the pathogenic mechanisms. Our findings suggest that parental age and perhaps other putative developmental risk factors should be examined separately for each diagnostic subtype or symptom severity of ASD.

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