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Parental psychiatric disorders and autism spectrum disorders

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Abstract

The present population-based, case-control study examines associations between specific parental psychiatric disorders and autism spectrum disorders (ASD) including childhood autism, Asperger's syndrome and pervasive developmental disorder (PDD-NOS). The cohort includes 4713 children born between 1987 and 2005 with diagnoses of childhood autism, Asperger's syndrome or PDD-NOS. Cases were ascertained from the Finnish Hospital Discharge Register, and each was matched to four controls by gender, date of birth, place of birth, and residence in Finland. Controls were selected from the Finnish Medical Birth Register. Parents were identified through the Finnish Medical Birth Register and Finnish Central Population Register. Parental psychiatric diagnoses from inpatient care were collected from the Finnish Hospital Discharge Register. Conditional logistic regression models were used to assess whether parents' psychiatric disorders predicted ASD after controlling for parents' age, smoking during pregnancy and weight for gestational age. In summary, parental schizophrenia spectrum disorders and affective disorders were associated with the risk of ASD regardless of the subgroup. PDD-NOS was associated with all parental psychiatric disorders investigated. Further studies are needed to replicate these findings. These results may facilitate the investigation of shared genetic and familial factors between ASD and other psychiatric disorders.

Keywords

Schizophrenia; affective; childhood autism; Asperger's syndrome; pervasive developmental disorders—unspecified; risk factors; epidemiology

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Introduction

Autism spectrum disorders (ASD) have been considered highly heritable (Folstein and Rutter, 1977; Steffenburg et al., 1989; Bailey et al., 1995; Lichtenstein et al., 2010), even though environmental factors may account for at least some of the variance to develop ASD (Hallmayer et al., 2011). In a recent study, Hallmayer et al (2011) demonstrated that approximately 55% of the variance in liability to ASD may be accounted for by environmental factors, though many studies show a much stronger genetic contribution. The most common subgroups of ASD are childhood autism, Asperger's syndrome and pervasive developmental disorders – unspecified (PDD-NOS) (World Health Organization, 1992). The diagnostic criteria for childhood autism include abnormalities in language, reciprocal social interactions, and the presence of a restricted repertoire of behavior and interests. The symptoms are required to emerge before age three to fulfill the diagnostic criteria (World Health Organization, 1992). Intellectual disability and cognitive problems are common in childhood autism. The diagnostic criteria for Asperger's syndrome include deficits in social interaction and behaviour, while language development and intellectual capacity are required to be normal. Asperger's syndrome is seldom diagnosed before age seven. The diagnostic criteria for PDD-NOS are heterogeneous and less well defined. These children have multiple developmental delays in cognitive functioning, social interactions, motor skills and learning, but the symptomatology does not fulfil the criteria for any other ASD subgroup.

Clinical studies have demonstrated that psychiatric disorders are more common among relatives of children with ASD (Bolton et al., 1998; Piven and Palmer, 1999; Bölte et al., 2007; Mouridsen et al., 2007; Ingersoll et al., 2011). This has led to the assumption that ASD and several other psychiatric disorders may share common genetic/familial factors (Daniels et al., 2008). However, only three population-based studies have examined the association between ASD and parental psychiatric disorders (Larsson et al., 2005; Lauritsen et al., 2005; Daniels et al., 2008). Two of these studies assessed the relationship between ASD and specific parental psychiatric disorders (Larsson et al., 2005; Daniels et al., 2008) while in the third study parental psychiatric disorders were not specified (Lauritsen et al., 2005). In the Danish study (Larsson et al., 2005), parental schizophrenia, affective disorders and substance abuse were associated with childhood autism. That study, however, did not examine the association between childhood autism and maternal and paternal psychiatric disorders separately. In the Swedish study (Daniels et al., 2008) maternal and paternal schizophrenia spectrum, maternal depression, and non-psychotic personality disorders were associated with ASD. None of these previous studies (Larsson et al., 2005; Lauritsen et al., 2005; Daniels et al., 2008) have examined the associations among ASD subgroups (childhood autism, Asperger's syndrome and PDD-NOS).

The aims of the current study are: 1. to examine whether diagnosed psychiatric disorders are more common among mothers and fathers of children diagnosed with ASD compared to controls; and, 2. if so, to determine which psychiatric disorders are the most associated with ASD. Based on the previous studies showing a strong association between parental psychopathology and ASD we hypothesized that ASD would be associated with one or more parental psychiatric disorders, particularly with affective and schizophrenia spectrum disorders. We acknowledge the possible plan to subsume all autism spectrum disorders under one category in the DSM-V and therefore the analyses include a total ASD group combining childhood autism, Asperger's syndrome and PDD-NOS under one category. However, as at present there remain separate diagnostic criteria for each of these disorders, the examination is also made separately for these subgroups of ASD (childhood autism, Asperger's syndrome and PDD-NOS). Regardless of current diagnostic categories, ASD as a group encompass significant phenotypic heterogeneity, which is believed to stem from

substantial etiologic heterogeneity. Observing associations with parental psychopathology that are consistent across subgroups would suggest factors common to both parental psychopathology and ASD as a whole, whereas differences in parental psychopathology between subgroups may suggest these factors are specific to certain subsets of ASD symptoms.

2. Material and methods

2.1 Study design

The Finnish Prenatal Study of Autism Spectrum Disorders (FIPS-A) is based on a nested case-control design that relies upon linkages between several nationwide Finnish registries. The sample includes all singleton live births born in Finland between January 1, 1987 and December 31, 2005 ($n = 1\,149\,271$). These children were followed until December 31, 2007 for the diagnosis of ASD ($n = 4713$). A total of 18 849 control subjects were matched from the nationwide medical birth register. The identification of cases and controls, as well as the linkages between several registries is based on a unique identity code, which every Finnish resident has. This identity code remains the same through a person's lifetime. The full description of the study design and data sources is available (Lampi et al., 2011) and will therefore be only summarized herein. The FIPS-A has been authorized by the Ministry of Social Affairs and Health in Finland (STM/2593/2008). The ethics committees of the hospital district of Southwest Finland and the Finnish National Institute for Health and Welfare and the Institutional Review Board of the New York State Psychiatric Institute have given approval for the study.

2.2 National registries

The data were collected from three nationwide registries: the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR) and the Finnish Central Population Register (CPR). The FHDR is maintained by the National Institute of Health and Welfare (THL) and includes all inpatient diagnoses since January 1, 1967 and outpatient diagnoses since January 1, 1998. It contains the personal identity code unique for every person, dates of admission and discharge, primary diagnosis of discharge, and three possible subsidiary diagnoses. It covers all hospitals (somatic, psychiatric, military, prison, private, local health centres) in Finland. FHDR was used to identify ASD cases and parents' psychiatric diagnoses. The diagnostic classification is based on the International Classification of Diseases (ICD). The 8th revision (World Health Organization, 1967) was used from 1969 to 1986, the 9th (World Health Organization, 1977) from 1987 to 1995 and the 10th revision (World Health Organization, 1992) has been used since January 1, 1996. The FMBR is also maintained by THL and includes comprehensive and standardised data on every pregnancy, the prenatal period and the neonatal period up to 7 days on all births in Finland. The FMBR was established in 1987 and it includes the personal identity codes of mothers and every live born child. The FMBR was used to identify the controls and mothers as well as to obtain data on potential confounders as discussed below. 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. The CPR was used to identify the fathers.

2.3 Case definition

Cases with ASD were identified through the FHDR using ICD-9 (299x) and ICD-10 (F84x) codes. The most recent diagnosis was used in the classification. Therefore there were only 19 cases which had a diagnosis based on ICD-9. No limitations were applied for age at first diagnosis beyond the age attained at the end of follow-up in 2007. Matching criteria assured

that cases and matched controls had equivalent follow-up time. We examined the association between parental psychiatric diagnosis and three different subgroups of ASD: childhood autism (F84.0) (n = 1132), Asperger's syndrome (F84.5) (n = 1785), and other pervasive developmental disorders/pervasive developmental disorders, unspecified (PDD-NOS) (F84.8/F84.9) (n = 1796). The total ASD group combines childhood autism, Asperger's syndrome and PDD-NOS under one category (n = 4713). In Finland, the diagnosis of ASD is usually made in specialized care units of child neurology, child or adolescent psychiatry or paediatrics. The Finnish register-based diagnosis of childhood autism including children diagnosed after either outpatient or inpatient care alike, has been validated previously (Lampi et al., 2010).

2.4 Control inclusion criteria

All cases were matched to four controls by date of birth (+/- 30 days), gender, residence in Finland, and place of birth (birth hospital; secondly, regional hospital district if a birth hospital control could not be found). A child is automatically defined to be a resident of Finland if his mother is a citizen of Finland or has a permanent residence permit. Controls were identified through the FMBR and did not meet criteria of ASD or profound/severe intellectual disability according to the FHDR. Overall 18 849 control subjects were matched from the FMBR.

2.5 Maternal and paternal psychiatric disorders

Mothers were identified through the FMBR; fathers from the CPR. Paternity was based on an individual's status as a husband of the mother at the time of the child's birth. If the mother was unmarried, paternity was confirmed by acknowledgment of the father. In this study paternity was established in 98.3 % of the subjects, including DNA testing if the father agreed to such testing.

Parents' psychiatric diagnoses from inpatient care were obtained from the FHDR, which includes inpatient diagnoses since January 1, 1967. We included only parents' inpatient care, because there is no information on outpatient diagnoses prior to 1998.

Psychiatric diagnoses were classified into four categories in order of most to least severe. These categories included *schizophrenia spectrum; affective disorders; neurotic and personality disorders and other nonpsychotic disorders (for convenience referred to as anxiety and personality disorders group); alcohol and drug addiction/abuse (for convenience referred to as substance disorders group)* (see Appendix). To avoid correlation across diagnoses driven by co-morbidity, parents were assigned to only one diagnostic category. The assignment was based on a hierarchical structure, in the order presented in the preceding sentence; therefore, schizophrenia spectrum disorders were given highest priority and substance disorders the lowest. For example, if the parent had been diagnosed both with severe depression and schizophrenia, she/he was assigned to the schizophrenia spectrum category; a substance disorders diagnosis is interpretable as a diagnosis of substance disorder without history of additional recorded psychiatric diagnosis.

The category of *disorders usually diagnosed in childhood or in adolescence (for convenience referred to as childhood disorders)* was examined separately. Therefore a parent diagnosed with disorders in this category (e.g. ASD, attention deficit hyperactivity disorder, oppositional and conduct disorders, learning disabilities, see Appendix) could also belong to any of the four above-mentioned categories. The separate analysis enables one to isolate the association for childhood- and adolescent-onset psychiatric disorders. Similar systems of classification and hierarchical categorization (Appendix) have been used in previous studies (Daniels et al., 2008; Larsson et al., 2005).

2.6 Confounding factors

Potential confounding factors that have been associated with both ASD and psychiatric disorders were: maternal and paternal age (Fergusson et al., 2005; Colman et al., 2009; Hultman et al., 2011; Sandin et al., 2012), smoking during pregnancy (Hultman et al., 2002; Maughan et al., 2004; Larsson et al., 2009) and weight for gestational age (WGA) (Bennedsen et al., 1999; Hultman et al., 2002; Lampi et al., 2012). Data on maternal socioeconomic status (SES) were not available prior to October, 1990. Maternal SES and smoking during pregnancy were, however, multicollinear ($p < 0.001$, data available on request) and therefore the variable of smoking during pregnancy serves as a good proxy measure for maternal SES status (Jaakkola et al., 2001; Gissler et al., 2003; Gissler et al., 2009). Data on maternal age was obtained from the FMBR; data on paternal age was obtained from the CPR. Maternal age was categorized into the following categories: 15–19, 20–24, 25–29, 30–34, 35–39 and over 40 years. Paternal age was categorized as 15–19, 20–24, 25–29, 30–34, 35–39, 40–49 and over 50 years. A similar age categorization has been used in previous studies (Larsson et al., 2005; Lauritsen et al., 2005; Daniels et al., 2008). Data on smoking during pregnancy as reported by the mother at the first antenatal visit was obtained from the FMBR. A dichotomous variable was used. Information on WGA was collected from the FMBR. It was categorized into three groups: small for gestational age (SGA), < -2 SD, appropriate for gestational age (AGA), -2 SD - $+2$ SD and large for gestational age (LGA), $> +2$ SD. These categories were derived from Finnish birth weight standards (Pihkala et al., 1989).

2.7 Statistical methods

Conditional logistic regression analysis was used to examine the association between parental psychiatric disorder and ASD. Associations were quantified using odds ratios (ORs) with 95 % confidence intervals (CIs). P-values were calculated by the χ^2 -test with a significance threshold of $p < 0.05$. The model was adjusted for maternal and paternal age, smoking during pregnancy, and WGA. To compare the magnitude of risk between different ASD subgroups, pairwise comparisons between subgroups were conducted. To evaluate whether parent's psychiatric disorders are relative to child's disorder, the associations were stratified by timing of the parent's diagnosis before or after the child's birth. The statistical analyses were carried out using SAS statistical software (SAS Version 9.2; SAS Institute Inc., Cary, NC).

3. Results

The mean age of childhood autism diagnosis was 5.5 years (standard deviation 3.6 years) while in the Asperger's syndrome the mean age was 9.6 years (standard deviation 3.3 years). In PDD-NOS the mean age of diagnosis was 7.3 years (standard deviation 3.4 years). Descriptive characteristics of mothers' and fathers' psychiatric diagnoses among cases and controls are presented in Table 1. The results of associations between ASD subgroups and maternal psychiatric disorders were very similar between unadjusted and adjusted analyses and therefore only adjusted analyses are shown in the tables. As shown in Table 2, total ASD was associated with maternal schizophrenia spectrum, affective, anxiety and personality, substance and childhood disorders group status. Childhood autism was associated with maternal affective disorders, but not with any other categories of disorders. The association with schizophrenia spectrum disorders was the same magnitude as for Asperger's and close to statistical significance ($p = 0.07$). Asperger's syndrome and PDD-NOS were associated with maternal schizophrenia spectrum disorders, affective disorders, anxiety and personality and childhood disorders. Additionally, PDD-NOS was associated with maternal substance disorders.

The results of associations between ASD subgroups and paternal psychiatric disorders were also very similar between unadjusted and adjusted analyses. Total ASD was associated with paternal schizophrenia spectrum, affective, anxiety and personality and childhood disorders group status. Childhood autism was associated with paternal schizophrenia spectrum and affective disorders. Asperger's syndrome was associated with paternal affective and anxiety and personality disorders. PDD-NOS was associated with schizophrenia spectrum, affective, anxiety and personality, substance and childhood disorders group status.

As shown in Table 2, maternal and paternal schizophrenia spectrum disorders were most strongly associated with PDD-NOS. Pairwise analysis showed that schizophrenia spectrum disorders were more common among mothers of a child with PDD-NOS than mothers of a child with childhood autism ($p < 0.01$) or Asperger's syndrome ($p < 0.01$). Significant differences were not found among fathers.

Table 3 depicts the results of parental psychiatric disorders and ASD stratified by parental diagnosis and by timing of the psychiatric diagnosis before or after the birth of the child. As shown in the table, the proportion of those mothers' and fathers' who received the psychiatric diagnosis before versus after child's birth did not differ significantly between cases and controls. An additional analysis showed that the proportion of those mothers' and fathers' receiving a diagnosis of affective disorders before versus after child's birth was also quite similar between cases and controls regardless of the subgroup of ASD ($p > 0.05$, data not shown).

Table 4 shows the associations of any psychiatric disorder in parents (separately reported as "only mother", "only father", "either parent", and "both parents") with total ASD, childhood autism, Asperger's syndrome or PDD-NOS in offspring. As shown in the table, maternal and paternal disorders had a similar effect on the risk of ASD. If both parents were affected, the risk of total ASD was over threefold. The risks of childhood autism and Asperger's syndrome were over twofold compared to parents which neither were affected. The risk of PDD-NOS was over fourfold when both parents had a psychiatric disorder. An additional analysis was made to examine whether two affected parents increase the risk of ASD compared to only one affected parent (data not shown). An additional analysis showed that two affected parents did not increase statistically the risk of total ASD (1.5 [0.9, 2.3]), childhood autism (1.7 [0.5, 5.2]) or the risk of Asperger's syndrome (0.7 [0.2, 2.0]) compared to only one affected parent. There was an additive effect in the risk of PDD-NOS in that two affected parents were related to statistically significant ($p < 0.01$) increase in the risk of PDD-NOS compared to the presence of a psychiatric disorder in one parent but not the other (3.0 [1.4, 6.5]).

4. Discussion

The present study is based on a large, population-based sample including cases drawn from both inpatient and outpatient settings. These design strengths increase the generalizability of the findings and reduce the potential for bias. The results support our hypothesis that a wide range of parental psychiatric disorders are associated with ASD. Both maternal and paternal affective disorders were associated with all ASD subgroups. All examined maternal and paternal psychiatric disorders were associated with PDD-NOS. Furthermore, the strongest association was found between parental schizophrenia spectrum disorders and PDD-NOS.

Affective disorders were the only group of psychiatric disorders which were associated with every examined subgroup of ASD. This finding is consistent with prior studies showing associations between ASD and affective disorders in relatives (Bolton et al., 1998; Piven and Palmer, 1999; DeLong et al., 2002; Cederlund and Gillberg, 2004; Ghaziuddin, 2005; Larsson et al., 2005; Daniels et al., 2008; Morgan et al., 2012). Moreover, affective

disorders are common co-morbid disorders among subjects with ASD (Lainhart, 1999). A recent study suggested that use of selective serotonin reuptake inhibitors (SSRI's) during pregnancy may modestly increase the risk of ASD (Croen et al., 2011). However, our finding that paternal affective disorders are also associated with about two-fold elevated risks of having offspring with childhood autism, Asperger's syndrome or PDD-NOS suggests a shared genetic background for ASD and affective disorders.

Previous meta-analysis suggests that parents (mothers in particular) of children with developmental disabilities are at increased risk for affective disorders, as negative maternal psychological well-being has been associated with the high levels of challenging behaviors present in this group of children (Singer, 2006). Limitations of these studies include small, clinical samples and use of screens or other descriptive measures of symptomatology rather than psychiatric diagnoses (Bailey et al., 2007). Our study overcame these limitations while finding that the proportion of cases receiving a diagnosis of affective disorder after (versus before) a child's birth was similar to that among controls, suggesting against the interpretation that the association between parents' affective disorder and ASD was due to the increased demands of caregiving for these children.

Our findings that schizophrenia spectrum disorders are more common among parents who have a child with ASD are consistent with the Swedish and Danish population-based studies (Larsson et al., 2005; Daniels et al., 2008). Clinical studies report co-morbidity between schizophrenia and ASD (Larsen and Mouridsen, 1997; Konstantareas and Hewitt, 2001; Ståhlberg et al., 2004; Billstedt et al., 2005) while genetic studies suggest that schizophrenia, affective disorders and ASD share common genetic factors (Burbach and van der Zwaag, 2009; Carroll and Owen, 2009). With regard to the ASD subgroups, the strongest association with schizophrenia spectrum disorders was for PDD-NOS in offspring. Earlier report (Rapoport et al., 2009) suggested that PDD might both precede and be comorbid with childhood-onset or later-onset schizophrenia. Consistent with these findings, some symptoms in PDD-NOS (e.g. multiple developmental delays in cognitive functioning, social interactions and motor skills) are similar to symptoms common in the premorbid or prodromal phases of schizophrenia (Isohanni et al., 2000).

Maternal and paternal substance disorders were associated with PDD-NOS but not with childhood autism or Asperger's syndrome. Three previous population-based studies have examined the association between parents' substance abuse and ASD (Larsson et al., 2005; Daniels et al., 2008; Eliassen et al., 2010) though the results are inconsistent. This finding might be accounted for by fetal exposure to alcohol, which has been associated with ASD in some clinical studies (Nanson, 1992; Harris et al., 1995). However, paternal substance disorders were also associated with PDD-NOS. One explanation is that fathers' and mothers' substance use are correlated although may not be severe enough in both parents to warrant hospital admission.

While both maternal and paternal childhood disorders were associated with PDD-NOS, only mothers' childhood disorders were associated with Asperger's syndrome. Since there were only a few parents with ASD diagnoses ($n = 7$ among controls; $n = 6$ among cases, $p > 0.05$), the associations were mainly accounted for by other childhood and adolescent disorders (see Appendix). Prior studies indicate that some childhood-onset disorders (e.g. language delay, learning deficits) are more common among relatives of a child with ASD (Bailey et al., 1998; Cederlund and Gillberg, 2004). Co-morbid behavioural disorders are common among subjects with ASD (Simonoff et al., 2008; Kanne et al., 2009). In addition, a recent twin study showed that there is a high co-morbidity between ASD and other neuropsychiatric disorders (e.g. attention deficit hyperactivity disorder, tic and developmental coordination disorder) (Lichtenstein et al., 2010). Moreover, monozygotic

twins had higher concordance rates than dizygotic twins ASD and other neuropsychiatric disorders indicating some common genetic etiology for different neuropsychiatric disorders (Lichtenstein et al., 2010). Taken together, these findings may indicate common genetic factors for ASD and some other childhood and adolescent-onset disorders.

The present study is the first population-based study which has examined the associations between parental psychiatric disorders and offspring's PDD-NOS status. Because of the lack of other studies, we can only speculate as to the possible explanations for the associations observed. One explanation is that children diagnosed with PDD-NOS constitute a more heterogeneous group because of the diagnostic criteria; while the diagnostic criteria for childhood autism and Asperger's syndrome are quite strictly defined, the criteria for PDD-NOS are more heterogeneous and less well defined. Another explanation might be that PDD-NOS reflects greater heterogeneity in etiology including genetic factors and possible prenatal exposures (i.e. drugs or alcohol) than other ASDs.

There are several limitations which need to be considered. The first is that cases and parents were not directly ascertained for psychiatric diagnoses and therefore some diagnostic misclassification may exist. However, as reported previously (Lampi et al., 2010), the validity of register-based diagnosis of childhood autism is high. Moreover, the validity of parental psychiatric diagnosis is assumed to be good, since Finnish register-based diagnoses agree well with information based on hospital records (Isohanni et al., 1997). At present, validation studies for Asperger's syndrome or PDD-NOS have not been conducted. Therefore the associations with these diagnoses may be viewed with somewhat less confidence compared to the associations with childhood autism. However, because in Finland the clinical assessment of any ASD is done in specialized services, primarily by specialists in child psychiatry or pediatric neurology, we believe that the validity of the diagnoses of Asperger's syndrome and PDD-NOS is at least satisfactory. Furthermore, in Finland the diagnosis of any ASD is usually evaluated by two independent physicians, as a requirement for receiving disability benefits from the Social Insurance Institution. Second, the FHDR includes outpatient diagnoses since 1998 and therefore we were not able to ascertain cases diagnosed and treated only in outpatient services prior to that year. However, because ASD is generally a chronic condition, the most recent diagnosis should have captured many cases treated as outpatients with onset prior to 1998. Third, since the FHDR includes children who were referred to specialized services some children with mild ASD symptoms may not have been ascertained in our study sample. We expect, however, that coverage of moderate and severe ASD cases is high, for two reasons. First, before the beginning of school at age seven, all children visit child health clinics at least once a year where the child's health is assessed comprehensively. Second, like other Nordic countries such as Sweden and Denmark, Finland has a universal health care system that covers the cost of treatment for ASD. Thus, parental education is not associated with child mental health service use (Sourander et al., 2001; Sourander et al., 2004). Therefore children with moderate or severe symptoms of ASD will most likely be referred to specialized services and subsequently become registered in the FHDR. Fourth, the variable for smoking during pregnancy was included in the model to test for potential confounding instead of maternal SES because the data on maternal SES is not complete. However, these variables were multicollinear and therefore the variable of smoking during pregnancy serves as a good proxy measure for maternal SES status. In addition, several studies based to the Finnish Medical Birth Register – which was also used in this study – show that in Finland prenatal smoking is associated with maternal SES status (Jaakkola et al., 2001; Gissler et al., 2003; Gissler et al., 2009). To further address potential confounding by SES in this population, a sub-analysis was conducted for the associations of any maternal or any paternal psychiatric diagnosis with ASD subgroups adjusting for maternal SES in the observations where data was available. After adjusting for maternal SES, all statistically significant associations

remained and adjustment did not have any influence on the observed odd ratios. Fifth, parental psychiatric diagnoses were based only on inpatient care. Consequently, the findings cannot be generalized to cover all psychiatric disorders, because some, such as mild anxiety, are usually managed in outpatient care. Sixth, compared to studies made prior to the 1990's, the prevalence of ASD has increased substantially (Fombonne, 2009). Some of the increase can be explained by improved awareness of ASD, changes in diagnostic criteria and the development of services (Fombonne, 2009). In the present study there were only a few parents with the diagnosis of ASD and therefore the sample possibly includes parents with undiagnosed ASD. However, the clinical study of Nylander and Gillberg (2001) showed that in an adult psychiatric population many undiagnosed ASD cases had another psychiatric diagnosis reflecting mostly co-morbidity rather than misdiagnosis. Thus, even though the sample possibly includes undiagnosed ASD parents, they are likely included in to some examined psychiatric disorders category. Finally, the influence of emigration in the present cohort can be viewed as a potential cause of selection bias, if it was related to parental psychiatric disorders and ASD. In Finland, however, the emigration rate is very low; during the study the annual rate varied between 0.2–0.4 % (Statistics Finland). Therefore, emigration is expected to have played a very small role in influencing the findings.

To conclude, the present study provides evidence that parental psychopathology is associated with ASD. For PDD-NOS, significant relationships were demonstrated for all maternal and paternal psychiatric disorders, with the strongest associations for schizophrenia spectrum disorders. For childhood autism, relationships were demonstrated for parental schizophrenia spectrum and affective disorders. For Asperger's syndrome, relationships with most maternal psychiatric diagnoses were observed. Associations between parental schizophrenia spectrum disorders and affective disorders and ASD are supported by prior population-based studies (Larsson et al., 2005; Daniels et al., 2008).

The observed familial aggregation between various psychiatric disorders and ASD suggests that these syndromes may have shared genetic susceptibility and familial environmental factors. This is consistent with some molecular genetic studies of ASD, including those investigating copy number variants (Cook and Scherer, 2008; Pinto et al., 2010) and polymorphisms in genes such as DISC1 (Ekelund et al., 2001; Ekelund et al., 2004; Hodgkinson et al., 2004; Kilpinen et al., 2008) which have been related to several psychiatric diagnoses, including ASD, schizophrenia, bipolar disorder, and major affective disorders. Although familial environmental factors have been less well investigated in ASD, the results of this study suggest that future investigations should examine whether some of the same risk factors that aggregate in families with one or more members afflicted by psychiatric disorders other than ASD should be investigated in ASD probands. Moreover, as our knowledge of risk factors for ASD increases, these findings may ultimately benefit genetic counseling strategies.

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Abbreviations

ASD	Autism spectrum disorder
PDD – NOS	Pervasive developmental disorder, unspecified

FMBR	Finnish Medical Birth Register
FHDR	Finnish Hospital Discharge Register
CPR	Finnish Central Population Register
FIPS-A	Finnish Prenatal Study of Autism and Autism Spectrum Disorders
ICD	International Classification of Diseases
WGA	Weight for gestational age

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Appendix. Detailed description of psychiatric categories

Diagnostic group	Current classification ICD-10 (1996 to present)	Previous Classifications	
		ICD-9 (1987–1995)	ICD-8 (1969–1986)
Schizophrenia and other nonaffective psychoses	F20 schizophrenia, F21 schizotypal disorder, F22 delusional disorder, F23 acute polymorphic psychotic disorder without symptoms of schizophrenia, F24 induced delusional disorder, F25 schizoaffective disorder, F28 other nonorganic psychotic disorders, F29 unspecified nonorganic disorders	295, 297, 2989X, 3012C	295, 297, 298.20, 298.30, 298.99, 299
Affective disorders	F30 hypomania, F31 bipolar affective disorder, F32 depressive episode, F33 recurrent depressive episode, F34 cyclothymia and dysthymia, F38 other single mood (affective) disorder, F39 unspecified mood (affective) disorder	296, 3004A, 2988A	296, 298.00, 298.10, 300.41
Neurotic and personality disorders and other nonpsychotic disorders	F40 phobic anxiety disorders, F41 other anxiety disorders, F42 obsessive-compulsive disorders, F43 reaction to severe stress and adjustment disorders, F44 dissociative amnesia, F45 somatoform disorders, F48 other neurotic disorders, F50 eating disorders, F51 nonorganic sleep disorders, F52 lack or loss of sexual desire, F53 mental and behavioural disorders associated with the puerperium, not elsewhere classified, psychological and behavioural factors associated with disorders or diseases classified elsewhere, F55 abuse of nondependence producing substances, F59 unspecified behavioural syndromes associated with physiological disturbances, F60 specific personality disorders, F61 mixed and other personality disorders, F62 enduring personality changes, not attributable to brain damage and diseases, F63 habit and impulse disorders, F64 gender identity disorders, F65 fetishism, F66 psychological and behavioural disorders associated with sexual development and orientation, F68 other disorder of adult personality and behaviour, F69 unspecified disorder of adult personality and behaviour, F99 mental disorder not otherwise specified	300–302 (excluding 3004A and 3012C), 3071A, 3074A, 3074F, 3074H, 3075A, 3075B, 3075C, 3075E, 3078A, 3079X, 309 (excluding 3092A, 3092B, 3093A and 3094A), 312 (excluding 3120A and 3123D)	300–302, (excluding 300.41), 305, 306.40, 306.50, 306.98, 307.99
Alcohol and drug addiction/abuse	Mental and behavioural disorders due to use of... F10 alcohol, F11 opioids, F12 cannabinoids, F13 sedatives or hypnotics, F14 cocaine, F15 other stimulants, including caffeine, F16 hallucinogens, F17 tobacco, F18 volatile	303–305, 291–292	303–304, 291

Diagnostic group	Current classification ICD-10 (1996 to present)	Previous Classifications	
		ICD-9 (1987–1995)	ICD-8 (1969–1986)
	solvents, F19 multiple drug use and use of other psychoactive substances		
Disorders usually diagnosed in childhood or in adolescence	F70–F79 intellectual disability, F84 pervasive developmental disorders (F84.0 childhood autism, F84.5 Asperger syndrome, F84.8 other pervasive developmental disorders, F84.9 pervasive developmental disorders, unspecified), F80 specific developmental disorders of speech and language, F81 Specific developmental disorders of scholastic skills, F82 specific developmental disorder of motor function, F83 mixed specific developmental disorders, F88 other disorders of psychological development, F89 unspecified disorder of psychological development, F90 hyperkinetic disorders, F91 conduct disorders, F92 mixed disorders of conduct and emotions, F93 emotional disorders with onset specific to childhood, F94 disorders of social functioning with onset specific to childhood and adolescence, F95 tic disorders, F98 other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	299, 313–315, 317–319, 3120A, 3123D, 3070A, 3070B, 3072A, 3072B, 3072C, 3072D, 3073A, 3074G, 3075D, 3076A, 3076B, 3076C, 3077A, 3092A, 3092B, 3093A, 3094A	306.00, 306.10, 306.20, 306.30, 306.60, 306.70, 308.99, 310–315

Table 1

Frequencies and percentages for mother's and father's psychiatric diagnosis

	Total ASD		Childhood autism		Asperger's syndrome		PDD-NOS	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)
Psychiatric diagnosis in mother								
No	4197 (89.1)	17748 (94.5)	1040 (92.0)	4290 (95.0)	1619 (90.7)	6697 (94.1)	1538 (85.6)	6761 (94.6)
Yes	516 (10.95)	1025 (5.5)	92 (8.1)	225 (5.0)	166 (9.3)	417 (5.9)	258 (14.4)	387 (5.4)
Schizophrenia spectrum	114 (2.4)	191 (1.02)	17 (1.5)	42 (0.9)	31 (1.7)	76 (1.1)	66 (3.7)	73 (1.0)
Affective disorders	211 (4.5)	405 (2.2)	37 (3.3)	78 (1.7)	77 (4.3)	185 (2.6)	97 (5.4)	143 (2.0)
Neurotic and personality disorders and other nonpsychotic disorders	121 (2.6)	280 (1.5)	23 (2.0)	62 (1.4)	40 (2.2)	107 (1.5)	58 (3.2)	111 (1.6)
Alcohol and drug addiction/abuse	53 (1.1)	103 (0.6)	11 (1.0)	32 (0.7)	13 (0.7)	33 (0.5)	29 (1.6)	38 (0.5)
Disorders usually diagnosed in childhood or in adolescence	57 (1.2)	85 (0.5)	6 (0.5)	19 (0.4)	19 (1.1)	27 (0.4)	22 (1.8)	39 (0.6)
Psychiatric diagnosis in father								
No	4031 (87.5)	17093 (92.1)	998 (89.8)	4121 (92.1)	1549 (88.7)	6448 (91.8)	1484 (84.8)	6524 (92.4)
Yes	578 (12.5)	1465 (7.9)	114 (10.3)	353 (7.9)	198 (11.3)	575 (8.2)	266 (15.2)	537 (7.6)
Schizophrenia spectrum	76 (1.7)	145 (0.8)	18 (1.6)	39 (0.9)	20 (1.1)	56 (0.8)	38 (2.2)	50 (0.7)
Affective disorders	183 (4.0)	416 (2.2)	35 (3.2)	84 (1.9)	79 (4.5)	169 (2.4)	69 (4.0)	163 (2.3)
Neurotic and personality disorders and other nonpsychotic disorders	199 (4.3)	506 (2.7)	37 (3.3)	131 (2.9)	64 (3.7)	186 (2.7)	98 (5.6)	189 (2.7)
Alcohol and drug addiction/abuse	104 (2.3)	353 (1.9)	19 (1.7)	86 (1.9)	30 (1.7)	145 (2.1)	55 (3.1)	122 (1.7)
Disorders usually diagnosed in childhood or in adolescence	50 (1.1)	105 (0.6)	8 (0.7)	31 (0.7)	13 (0.7)	44 (0.6)	29 (1.7)	30 (0.4)

Table 2

Adjusted OR's with 95 % CI's for mother's and father's psychiatric diagnosis

	Total ASD		Childhood autism		Asperger's syndrome		PDD-NOS	
	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)
Maternal diagnosis								
Adjusted^x (any psychiatric diagnosis)[†]	2.0	(1.8, 2.3)	1.6	(1.3, 2.1)	1.7	(1.4, 2.0)	2.7	(2.2, 3.2)
Schizophrenia spectrum	2.5	(1.9, 3.2)	1.7	(0.96, 3.1)	1.7	(1.1, 2.6)	3.8	(2.7, 5.5)
Affective disorders	2.1	(1.8, 2.5)	1.9	(1.3, 2.9)	1.7	(1.3, 2.3)	2.7	(2.1, 3.6)
Neurotic and personality disorders and other nonpsychotic disorders	1.8	(1.4, 2.4)	1.5	(0.9, 2.6)	1.7	(1.1, 2.4)	2.1	(1.5, 3.0)
Alcohol and drug addiction/abuse	1.9	(1.8, 2.5)	1.3	(0.6, 2.7)	1.7	(0.9, 3.3)	2.6	(1.5, 4.3)
Disorders usually diagnosed in childhood or in adolescence	2.5	(1.8, 3.6)	1.1	(0.4, 2.9)	3.1	(1.7, 5.7)	2.8	(1.7, 4.7)
Paternal diagnosis								
Adjusted^x (any psychiatric diagnosis)[†]	1.7	(1.5, 1.8)	1.3	(1.1, 1.7)	1.5	(1.3, 1.8)	2.0	(1.7, 2.4)
Schizophrenia spectrum	2.2	(1.7, 3.0)	1.8	(1.02, 3.3)	1.4	(0.8, 2.5)	3.4	(2.2, 5.4)
Affective disorders	1.8	(1.5, 2.2)	1.6	(1.1, 2.5)	2.0	(1.5, 2.6)	1.7	(1.3, 2.3)
Neurotic and personality disorders and other nonpsychotic disorders	1.7	(1.4, 2.0)	1.2	(0.8, 1.8)	1.6	(1.2, 2.2)	2.1	(1.6, 2.8)
Alcohol and drug addiction/abuse	1.2	(0.9, 1.5)	0.9	(0.5, 1.6)	0.9	(0.6, 1.3)	1.7	(1.2, 2.4)
Disorders usually diagnosed in childhood or in adolescence	2.1	(1.4, 2.9)	0.9	(0.4, 2.2)	1.6	(0.8, 3.0)	3.4	(2.0, 6.0)

* p < 0.05;

** p < 0.01;

*** p < 0.001

^x Adjusted for maternal age, paternal age, smoking during pregnancy, weight for gestational age

[†] The psychiatric diagnosis can be any examined psychiatric diagnosis, analyzed without hierarchical structure

Note: Specific psychiatric disorders have been analyzed hierarchically from most severe (schizophrenia spectrum) to least (alcohol and drug addiction/abuse). Also separately category *Disorders usually diagnosed in childhood or in adolescence*

Table 3

Frequencies, percentages and OR's with 95 % CI's for psychiatric diagnosis before or after a child's birth

		Total ASD		Childhood autism		Asperger's syndrome		PDD-NOS	
		Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)
Psychiatric diagnosis in mother									
Before child's birth		207 (40.1)	361 (35.1)	41 (44.6)	90 (40.0)	60 (36.1)	126 (30.2)	106 (41.1)	145 (37.5)
After child's birth		309 (59.9)	668 (64.9)	51 (55.4)	135 (60.0)	106 (63.9)	291 (69.8)	152 (58.9)	242 (62.5)
OR (95 %)		0.8 (0.6, 1.0)		0.8 (0.5, 1.4)		0.8 (0.5, 1.1)		0.9 (0.6, 1.2)	
Psychiatric diagnosis in father									
Before child's birth		287 (49.7)	741 (50.6)	60 (52.6)	188 (53.3)	91 (46.0)	277 (48.2)	136 (51.1)	276 (51.4)
After child's birth		291 (50.4)	724 (49.4)	54 (47.4)	165 (46.7)	107 (54.0)	298 (51.8)	130 (48.9)	261 (48.6)
OR (95 %)		1.1 (0.7, 1.6)		1.0 (0.7, 1.6)		1.1 (0.8, 1.5)		1.0 (0.8, 1.4)	

*
p < 0.05;
**
p < 0.01;

p < 0.001

Table 4

Frequencies, percentages and adjusted OR's with 95 % CI's for mother, father, only other parent or both of the parents diagnosed

	Total ASD		Childhood autism		Asperger's syndrome		PDD-NOS	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)	Control n (%)
	OR (95 %)		OR (95 %)		OR (95 %)		OR (95 %)	
No psychiatric dg in either parent	3673 (79.7)	16281 (87.7)	937 (84.3)	3945 (88.2)	1424 (81.6)	6119 (87.1)	1312 (75.0)	6217 (88.1)
Mother yes, father no	358 (7.8)	811 (4.4)	61 (5.5)	175 (3.9)	125 (7.2)	329 (4.7)	172 (9.8)	307 (4.4)
Adjusted ^x	1.9 (1.7, 2.2)	***	1.4 (1.02, 1.9)	*	1.7 (1.3, 2.1)	***	2.4 (2.0, 3.0)	***
Father yes, mother no	447 (9.7)	1277 (6.9)	90 (8.1)	308 (6.9)	163 (9.3)	500 (7.1)	194 (11.1)	469 (6.6)
Adjusted ^x	1.6 (1.4, 1.8)	***	1.2 (0.95, 1.6)		1.5 (1.2, 1.8)	***	1.9 (1.6, 2.4)	***
Yes in either parent	805 (17.5)	2088 (11.3)	151 (13.6)	483 (10.8)	288 (16.5)	829 (11.8)	366 (20.9)	776 (11.0)
Adjusted ^x	1.7 (1.5, 1.9)	***	1.3 (1.1, 1.6)	*	1.5 (1.3, 1.8)	***	2.1 (1.8, 2.4)	***
Yes in both parents	130 (2.8)	188 (1.0)	24 (2.2)	45 (1.0)	34 (2.0)	75 (1.1)	72 (4.1)	68 (1.0)
Adjusted ^x	3.1 (2.4, 4.0)	***	2.3 (1.3, 4.1)	**	2.4 (1.5, 3.7)	***	4.3 (2.9, 6.3)	***

* p < 0.05;

**

p < 0.01;

p < 0.001

^x Adjusted for maternal age, paternal age, smoking during pregnancy, weight for gestational age

Note: Includes only parents which the complete data of both maternal and paternal psychiatric disorders are available