

Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study

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Background: The etiology of autism is unknown. A strong genetic component has been detected but non-genetic factors may also be involved in the etiology. **Methods:** We used data from the Danish Psychiatric Central Register and the Danish Civil Registration System to study some risk factors of autism, including place of birth, parental place of birth, parental age, family history of psychiatric disorders, and paternal identity. **Results:** A total of 943,664 children younger than ten years were followed from 1994 to 2001; of those, 818 children developed autism. The highest risks of autism were found in siblings of children with autism, or Asperger's syndrome and other pervasive developmental disorders (PDDs), with relative risks of 22 and 13, respectively. The relative risk of autism in the child was about twice as high if the mother had been diagnosed with a psychiatric disorder. The risk of autism was associated with increasing degree of urbanisation of the child's place of birth and with increasing paternal, but not maternal, age. An increased relative risk of 1.4 was found if the mother was born outside Europe, and in children of parents who were born in different countries. **Conclusions:** The highest risk of autism was found in families with a history of autism, or Asperger's syndrome and other PDDs in siblings, supporting the commonly accepted knowledge that genetic factors are involved in the etiology of autism. **Keywords:** Autism, Asperger's syndrome, PDD, family history, risk factors, place of birth, maternal age, paternal age, parental age, psychiatric disorders, immigrants.

Autism is a pervasive developmental disorder characterised by qualitative impairments in social interaction and communication, and stereotyped repetitive behaviour. In order to fulfil the diagnostic criteria of childhood autism, the symptoms must be apparent before three years of age. In contrast, when symptoms are present after the age of three, or impairments in all three areas of behaviour are lacking, the criteria of atypical autism are fulfilled (World Health Organization, 1993). A strong genetic component has been established (Folstein & Rutter, 1977; Steffenburg et al., 1989; Bolton et al., 1994) but the mode of inheritance appears to be complex, and a polygenic model with interaction of three to more than 15 genes has been suggested (Pickles et al., 1995; Risch et al., 1999). However, interaction with environmental risk factors has also been proposed. Several risk factors have been investigated, e.g., maternal obstetrical complications (Burd, Severud, Kerbeshian, & Klug, 1999; Eaton, Mortensen, Thomsen, & Frydenberg, 2001; Hultman, Sparren, & Cnattingius, 2002; Glasson et al., 2004), viral infections during pregnancy (Chess, 1971; Wilkerson, Volpe, Dean, & Titus, 2002), maternal age (Burd et al., 1999; Croen, Grether, & Selvin, 2002), immunological abnormalities (Korvatska, Van de Water, Anders, & Gershwin, 2002), vaccines (Wakefield et al., 1998; Madsen et al., 2002), and season of birth (Bolton, Pickles, Harrington, Macdonald, & Rutter, 1992), but the specific etiology remains unknown.

Most studies investigating risk factors of autism are based on prevalence rather than incidence. We used data from the Danish Psychiatric Central Register (Munk-Jørgensen & Mortensen, 1997) and the Danish Civil Registration System (Malig, 1996) to investigate the effects of potential risk factors of autism, of which some are related to family factors. The risk factors studied are family history of psychiatric disorders, place of birth of the child and parents, paternal identity, and parental age. We used an incidence study design where each individual contributes years at risk since the incidence rates are more sensitive with respect to changes in etiological factors compared to prevalence rates.

Methods

Study design

All live-born children and immigrants to Denmark are assigned a unique personal identification number (the CPR-number) which is stored in the Danish Civil Registration System (Malig, 1996) along with information about date and place of birth, gender, vital status (alive, dead, immigrated), parental identity, and parental place of birth. The CPR-number is used in all national registers, which ensures accurate linkage between registers. We used data from the Danish Civil Registration System to establish a population-based cohort of children younger than ten years born in Denmark. The study population and

their mothers, fathers, and siblings were linked with the Danish Psychiatric Central Register (Munk-Jørgensen & Mortensen, 1997) to obtain information on history of psychiatric disorders. The Danish Psychiatric Central Register is a nationwide computerised register established in 1969 which contains information about all admissions to Danish psychiatric inpatient facilities since April 1969, and outpatients' visits to psychiatric departments since 1995. In Denmark, both children who stay at the hospital overnight and children who come to the hospital on a daily basis for evaluation and treatment are registered as inpatients, whereas outpatients represent visits to an outpatient clinic on a less regular basis. There are no private psychiatric hospitals in Denmark, and all treatment is free of charge. The register diagnoses are clinical, and are reported to the register by the psychiatric departments. Before 1 January 1994 diagnoses were classified according to the International Classification of Diseases, 8th Revision (ICD-8) (World Health Organisation, 1967) and from 1 January 1994 according to the International Classification of Diseases, 10th Revision (ICD-10) (World Health Organization, 1993).

Study population

The population-based cohort consisted of all children born in Denmark between 1 January 1984 and 31 December 1998. The children were followed from their 1st birthday or 1 January 1994, whichever came later, until onset of autism, their 10th birthday, death, emigration, or 31 December 2001, whichever came first. We chose to follow children from their 1st birthday as no children were diagnosed with autism prior to this date. Cohort members were recorded with autism if they had been registered as inpatients or received outpatient care at a psychiatric hospital with the diagnoses childhood autism (ICD-10: F84.0) or atypical autism (ICD-10: F84.1). Onset was defined as the first day of the first contact leading to a diagnosis of autism. Owing to incomplete registration of people with autism in the Danish Psychiatric Central Register during the period when the ICD-8 was used (Lauritsen, Pedersen, & Mortensen, in press), the first analyses included only children born 1993 or later. However, in order to achieve a sample size as large as possible, we expanded the study population to children younger than ten years of age diagnosed during the period when ICD-10 was used. For children born prior to the period of ICD-10 (i.e., 1984–92), we do not have complete information on admissions with autism, while this is the case for children who were aged one year during the period of ICD-10. In order to evaluate the impact of this incomplete registration of children with autism, we subdivided the study population into children born 1993–8 for whom we have complete information on first admission, and children born 1984–92 for whom we do not have complete information on first admission with autism. We evaluated if the effect of any variable in the model was modified by completeness of follow-up. The advantages of this procedure are that we both maximise the power of our study and minimise the risk of bias caused by incomplete registration of children with autism.

Classification of exposure variables

Cohort members were classified hierarchically with a history of autism (ICD-10 codes F84.0, F84.1) or with the broader autism diagnoses (Asperger's syndrome or other or unspecified pervasive developmental disorders (PDDs) (ICD-10 codes F84.5, F84.8, F84.9)) in a sibling if the sibling had been admitted or received outpatient care with one of these diagnoses. Cohort members were classified with a history of psychiatric disorder in a parent if the parent had been admitted or received outpatient care with any psychiatric disorders prior to the child's birth. The restriction prior to the child's birth was chosen to avoid bias resulting from dependence between outcome (autism in cohort members) and exposure (psychiatric disorder in a parent). Further subdivision in order to test hypotheses about association between autism and specific psychiatric disorders was done using the following diagnoses: schizophrenia and other paranoid psychoses (ICD-10 codes F20–29 and ICD-8 codes 295, 297, 298.39, and 301.83), mood disorders (ICD-10 codes F30–39 and ICD-8 codes 296, 298.09, 298.19, 300.49, and 301.19), and nervous conditions and personality disorders (ICD-10 codes F40, F60 and ICD-8 codes 300 except 300.49, 301 except 301.83 and 301.19).

The place of birth of the child was defined as maternal place of residence at child's birth. The degree of urbanisation of place of birth was classified according to capital, capital suburb, provincial city with more than 100,000 inhabitants, provincial towns with more than 10,000 inhabitants, or rural areas (Statistics Denmark, 1997).

Maternal country of birth was classified into the categories Denmark, other Scandinavian and European countries, outside Europe, or unknown. Outside Europe includes Asia, The Middle East, Australia, Africa, North and South America, and Greenland. Uniformity of parental country of birth was classified according to whether mother and father were born in the same country, mother and father were not born in the same country, or one of the parents had unknown country of birth.

Maternal age at time of child's birth was classified as 12–19, 20–24, 25–29, 30–34, 35–39, or 40+ completed years, while paternal age at time of child's birth was classified as 12–24, 25–29, 30–34, 35–39, 40–44, or 45+ completed years.

Statistical analyses

The relative risk of autism was estimated by log-linear Poisson regression (Breslow & Day, 1987) with the SAS GENMOD procedure (SAS Institute Inc., 1999). Estimates of relative risks were adjusted for age, sex, interaction between age and sex, calendar period, and all other characteristics used in this study. Age, calendar year, and history of autism or the broader autism diagnoses in a sibling were treated as time-dependent variables (Breslow & Day, 1980), whereas all other variables were treated independent of time. Age and calendar year were categorised in one-year age bands.

Although tests for a large number of variables were performed, no correction for multiple testing was done.

The epidemiological approach and the large sample size support the validity of the findings.

This study was approved by the Danish Data Protection Agency.

Results

Our study included 818 incident cases of autism in a population of 943,664 children representing 4,456,453 person years of follow-up. Figure 1 shows the crude incidence of autism according to age and gender. In our study, the incidence of first admission or outpatient contact with a diagnosis of autism peaked at age 3 for boys at 5.12 cases per 10,000 person years at risk, and at age 4 for females at 1.79 cases per 10,000 person years at risk. The male-female ratio was 2.86:1 at these ages.

Table 1 shows the estimated relative risks associated with the risk factors investigated in this study.

The highest relative risk was found for individuals with a sibling also diagnosed with autism, and the risk was increased by about 22 times compared to individuals without a history of autism or the broader autism diagnoses in a sibling. Moreover, the risk of autism was increased by about 13 times in siblings of individuals diagnosed with the broader autism diagnoses compared to individuals without a history of autism or the broader autism diagnoses in a sibling.

The risk of autism was twice as high in patients with a maternal history of admission with a psychiatric disorder compared to no history of maternal psychiatric admission. However, only very few mothers have been admitted with only one psychiatric diagnosis (see Appendix 1) and we did not have enough statistical power to subdivide this variable into specific psychiatric disorders. There was no

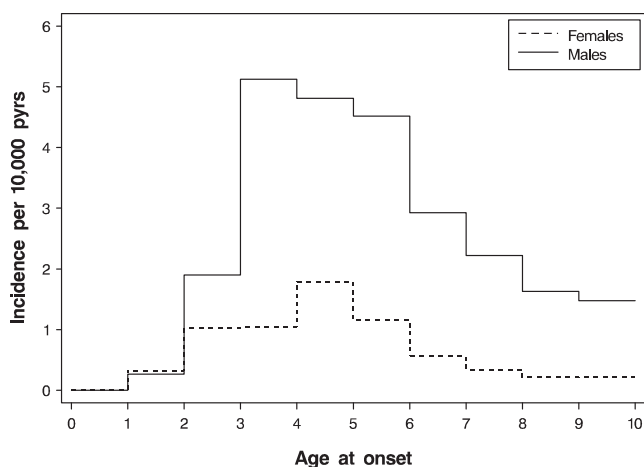


Figure 1. Incidence of autism per 10,000 person years at risk according to age and gender in a Danish population-based cohort of 943,664 children of whom 818 developed autism during the 4,46 million person years of follow-up. The incidence indicated the number of new cases occurred per time period

significant association between paternal history of a psychiatric disorder and the risk of autism.

Adjusted for maternal age, the risk of autism increased with increasing paternal age. Children with fathers 35 years or older had a risk of 1.39 (95% CI: 1.12–1.73) compared to children with fathers who were 25–29 years at child's birth. Adjusting the effect of paternal age for maternal age, the effect of paternal age measures the effect of paternal age for any fixed maternal age. This is almost the same as the effect of paternal age stratified by maternal age. Maternal age had no significant influence on the risk of autism when adjusted for paternal age (Table 1). However, without adjustment for paternal age, maternal age had a significant effect ($p = .02$), which indicates that maternal age is a proxy variable for paternal age. The relative risks associated with maternal age without adjustment for paternal age were 1.68 (95% CI: 1.07–2.63), 1.19 (95% CI: .96–1.47), 1.00 (reference category), 1.07 (95% CI: .89–1.29), 1.19 (95% CI: .93–1.54), and 1.19 (95% CI: .72–1.98) for the age categories 12–19, 20–24, 25–29, 30–34, 35–39, and 40+ completed years, respectively.

Among other risk factors for autism, we studied place of birth of the parents. As a single effect, the maternal region of birth was important since we found that the risk of autism increased by 1.42 times when the mother was born outside Europe compared to mothers born in Denmark. Owing to lack of power, further subdivision by country could not be performed. Paternal country of birth did not increase the risk of autism when adjusted for maternal country of birth. However, when we combined the countries of birth of both parents we found that the risk of autism increased by 1.36 times when the mother and the father were born in different countries compared to individuals with parents from the same country (for combinations of countries, see Appendix 2). Additional analyses investigating the effect of maternal and paternal region of birth were performed. The risk of autism was 1.17 (.90–1.51) if both parents were born abroad, 1.15 (.84–1.58) if only the father was born abroad, 1.77 (1.22–2.34) if only the mother was born abroad as compared to children where both parents were born in Denmark. Note that, as we only study children born in Denmark, children with foreign parental place of birth are 2nd generation immigrants. We also investigated the risk of autism among persons with unknown fathers and found no significant effect associated with unknown fathers compared to known identity of the father.

As noted earlier, we may not have complete information on the date of first admission with autism for children who entered the study during the ICD-8 period (i.e., 1992 or earlier). In order to evaluate the potential impact of this incomplete registration, we investigated whether the effect of all variables in the model presented in Table 1 was modified by

Table 1 Distribution of 818 cases of autism and adjusted relative risks of autism in a Danish population-based cohort of 943,664 people constituting 4.46 million person years of follow-up during the ICD-10 classification

Variable ^a	No. cases	Incidence ^b	Relative risk (95% CI) ^c
Total	818	1.84	–
Maternal age (yrs), $p = .25$			
12–19	24	2.24	1.68 (1.07, 2.63)
20–24	144	1.65	1.19 (.96, 1.47)
25–29	285	1.58	1.00 (ref)
30–34	246	2.01	1.08 (.89, 1.29)
35–39	102	2.59	1.18 (.92, 1.53)
40+	17	2.87	1.17 (.70, 1.97)
Paternal age (yrs) ^d , $p = .007$			
12–24	66	1.41	.81 (.60, 1.09)
25–29	225	1.57	1.00 (ref)
30–34	251	1.74	1.08 (.89, 1.30)
35–39	165	2.34	1.35 (1.07, 1.70)
40–44	71	2.94	1.61 (1.19, 2.18)
45+	26	2.51	1.21 (.78, 1.86)
Maternal history of psychiatric disorder, $p = .0003$			
History	37	4.05	1.97 (1.41, 2.74)
No history	781	1.79	1.00 (ref)
Paternal identity ^e , $p = .87$			
Father unknown	14	2.51	1.11 (.32, 3.79)
Father known	804	1.83	1.00 (ref)
Paternal history of psychiatric disorder ^d , $p = .51$			
History	18	1.86	.86 (.54, 1.37)
No history	786	1.83	1.00 (ref)
History of psychiatric disorder in siblings, $p < .0001$			
History of autism	14	54.92	22.27 (13.09, 37.90)
History of broader autism diagnoses	9	27.50	13.40 (6.93, 25.92)
No history in a sibling	795	1.79	1.00 (ref)
Degree of urbanisation of place of birth, $p < .0001$			
Capital	176	3.20	2.05 (1.67, 2.51)
Capital suburb	148	2.46	1.67 (1.35, 2.06)
Provincial city	74	1.35	.92 (.70, 1.20)
Provincial town	211	1.71	1.22 (1.00, 1.47)
Rural area	209	1.37	1.00 (ref)
Maternal country of birth ^d , $p = .03$			
Denmark	688	1.72	1.00 (ref)
Scandinavia and Europe (except Denmark)	50	2.36	1.02 (.75, 1.39)
Outside Europe	78	3.51	1.42 (1.10, 1.83)
Parental countries of births ^d , $p = .01$			
Mother and father not born in the same country	109	3.00	1.36 (1.08, 1.71)
Mother and father born in the same country	690	1.72	1.00 (ref)

^a P -values measure whether the effect of each variable included in the model has a significant effect ($p < .05$) when adjusted for all other variables included in the model.

^bIncidence of autism per 10,000 person years at risk. The incidence indicates the number of new cases per time period.

^cEstimates of relative risks were adjusted for age and its interaction with gender, calendar year of diagnosis, and for all variables in the table.

^dCategories with missing information are not shown.

^eEstimate associated with an unknown father was based on a model not adjusting for paternal age and paternal history of a psychiatric disorder.

completeness of follow-up (classified as born 1984–92, or 1993–8). We found no significant interaction between any variable in the model and completeness of follow-up, except for the variable place of birth. As shown in Table 2, the effect of degree of urbanisation was influenced by completeness of follow-up of the cohort member.

In the study cohort born 1993 or later, an increasing risk of autism was found with increasing degree of urbanisation, while in the cohort born 1984–92 there was no clear dose–response relationship between degree of urbanisation and risk of autism. Overall, a two-fold increase in the risk of

autism was found among those born in the capital or suburb compared to other places of birth (combined effect is shown in Table 1). Excluding outpatient activities had no impact on these results.

Discussion

Psychiatric disorders in siblings and parents

Our study provides further evidence of the involvement of genetic factors in the etiology of autism based on the significant findings of very high relative risks of autism in the siblings of children with

Table 2 Estimates of relative risks of autism by degree of urbanisation of place of birth subdivided by completeness of our study cohort

Degree of urbanisation of place of birth ^a	Born 1984–92, i.e., incomplete follow-up Relative risk (95% CI) ^b	Born 1993 or later, i.e., complete follow-up Relative risk (95% CI) ^b
Capital	1,54 (1.10, 2.15)	2,44 (1.88, 3.17)
Capital suburb	2,01 (1.49, 2.71)	1,41 (1.04, 1.90)
Provincial city	0,52 (.31, .86)	1,23 (.89, 1.70)
Provincial town	1,13 (.84, 1.50)	1,29 (1.00, 1.67)
Rural area	1 (ref)	1 (ref)

^aThe effect of the degree of urbanisation of place of birth was modified significantly by completeness of follow-up ($p < .0001$).

^bEstimates of relative risks were adjusted for age and its interaction with gender, calendar year of diagnosis, and for all variables in Table 1 (excluding degree of urbanisation of place of birth).

autism or the other PDDs studied compared to the other risk factors investigated. In contrast to the literature in which most family studies are clinically based, we used an epidemiological approach. We found that the relative risk of autism in siblings of children affected with autism is increased by about 22 times, and increased by about 13 times in siblings of children with the broader autism diagnoses. Furthermore, in a previous study we found that the prevalence of autism is about 15 per 10,000 children (Lauritsen et al., in press). Therefore, although these estimated relative risks associated with affected siblings are extremely high, the absolute individual risk that children with an affected sibling will develop autism is limited. The probability that siblings to children with autism and siblings to children with the broader autism diagnoses will develop autism is about 3% and 2%, respectively, which is in line with the literature (Bolton et al., 1994; Rutter, 2000).

Furthermore, we found gradations in the relative risk for autism in siblings from families with the sibling affected with autism to families with the other PDDs in the child and this provides evidence from an epidemiological study that PDDs are spectrum disorders with the same genetic liability.

We found a higher risk of autism if the mother had a psychiatric disorder. The finding that very few mothers were admitted with only one psychiatric diagnosis most likely reflects the diagnostic practice in Denmark. However, we were unable to find differential effects according to specific psychiatric disorders, whereas higher rates of affective disorders and social phobia in relatives of people with autism compared to a control group have been found in other studies (Piven et al., 1991; DeLong & Nohria, 1994; Smalley, McCracken, & Tanguay, 1995; Bolton, Pickles, Murphy, & Rutter, 1998; Piven & Palmer, 1999; Wilcox, Tsuang, Schnurr, & Baida-Fragoso, 2003).

Parental age

We found an increasing risk of autism with increasing paternal age when adjusting for maternal age and this is consistent with the study by Burd et al. (1999). In some studies where no adjustment for paternal age was done, the risk of autism increased with increased maternal age (Finegan & Quarrington, 1979;

Hoshino, Kumashiro, Yashima, Tachibana, & Watanabe, 1982; Tsai & Stewart, 1983; Gillberg & Gillberg, 1983; Hultman et al., 2002; Croen et al., 2002). These studies may support our finding since, in our study, maternal age is a proxy variable for paternal age. However, in other studies no significant difference between a group of children with autism and a control group was found for maternal age (Mason Brothers et al., 1987; Piven et al., 1993; Cryan, Byrne, O'Donovan, & O'Callaghan 1996; Burd et al., 1999; Eaton et al., 2001; Juul-Dam, Townsend, & Courchesne, 2001). Advanced paternal age has been linked to a variety of diseases, e.g., childhood cancers (Dockerty, Draper, Vincent, Rowan, & Bunch, 2001), achondroplasia (McIntosh, Olshan, & Baird, 1995), Apert syndrome (Tolarova, Harris, Ordway, & Vargervik, 1997), and schizophrenia (Malaspina et al., 2002; Byrne, Agerbo, Ewald, Eaton, & Mortensen, 2003). Among these diseases, at least some of the congenital malformations are known to be caused by single-gene mutations, and in human beings, the male is believed to contribute the majority of new mutations into the human gene pool due to the constantly dividing reproductive stem cell division (Crow, 1997). Older fathers may therefore more often than older mothers have children with new inheritable-mutation disorders due to exposure to agents like ionising radiation and chemical mutagens, and older fathers might have increased risk of having a child with autism due to increasing frequency of mutant sperm as they grow older. With respect to structural chromosome abnormalities, some support for increasing frequency of chromosomal abnormalities with increasing paternal age has been found (Sartorelli, Mazzucatto, & Pina-Neto, 2001), and it is well known that some individuals with autism have structural chromosome anomalies although some of these are maternally derived.

Place of birth of the cohort members and their parents

The higher risk of having a child with autism in the capital or suburb, and to some extent in families with unknown father, may indicate that lower socioeconomic status and educational level were seen in the families with a child with autism. Note that

place of birth refers to maternal residence at time of child's birth. However, in a Danish study, Larsson et al. (accepted) concluded, after adjusting for some perinatal factors and parental psychiatric history, that socioeconomic status plays little or no role in the etiology of autism in Denmark. Furthermore, most studies have not been able to find any difference regarding the socioeconomic status in autistic families compared to controls (Schopler, Andrews, & Strupp, 1979; Tsai, Stewart, Faust, & Shook, 1982). Other causes, e.g., obstetric complications, infections, diet, toxic exposures, household crowding, breast feeding, or an artefact due to migration, have been hypothesised as underlining causes for the urban-rural differences for schizophrenia (Mortensen, 2000), and some of these mechanisms may also be important for the development of autism.

We found an increased risk of autism among children of mothers born outside Europe, which is in concordance with the findings from Sweden by Gillberg, Schaumann, and Gillberg (1995) and Hultman et al. (2002). Since Denmark and Sweden receive immigrants from nearly the same countries, these studies are largely comparable. Gillberg et al. (1995) outlined the theory that the mother and/or child are not immunised against infectious agents in the new country, resulting in increased susceptibility to relatively harmless infections. However, this hypothesis cannot be tested in this study because we have no information about exposure to infectious agents. Gillberg et al. (1995) also suggested that males with traits of social disability, perhaps due to mutant genes, have more difficulties in finding a partner from their own country. They may more easily establish an intimate relationship with a person from another country and have children. The genetic liability may then be transmitted to the child together with other autism susceptibility genes. However, based on our data, the effect of the mother born abroad was more important than the effect of the father born abroad, which may confirm the hypothesis by Gillberg et al. (1995).

Strengths and limitations

This incidence study of autism is among the largest with respect to number of incident cases included. Overall, we found a male-female ratio of 2.86:1 which is similar to most other studies, and the prevalence rate of autism narrowly defined, calculated from the same population-based data as those used in the present study (Lauritsen et al., in press), is comparable to the prevalence rates of at least some other studies (Fombonne, 2003; Croen et al., 2002).

Owing to the register-based design, the study is not prone to recall bias because the diagnoses were made independently of this study by clinicians. Potential misclassification of the variables studied is not considered to have any impact on the findings of this study because even though, e.g., some family

members with a psychiatric disorder are misclassified as not having a psychiatric disorder they would contribute very little to the incidence in the large group of unexposed individuals, and the rate ratio would not change considerably. Another strength of the study is that the risks were adjusted for factors like age, gender, time of diagnosis of the disorder, parental age, place of birth, etc. However, it is worth mentioning that because we did not adjust for socioeconomic status we are unable to detect confounding by these and other unmeasured factors. The validity of the diagnosis of childhood autism in the Danish Psychiatric Central Register is believed to be very high (Madsen et al., 2002), but we cannot rule out that some individuals with autism are missed. However, we believe that most autistic individuals will be diagnosed owing to the severity of the handicap and because a diagnosis made by specialists is necessary to be enrolled with the special education services in most regions in Denmark. Moreover, in Denmark all treatment in psychiatric wards is free of charge. However, in 1993 a private diagnostic service was established which in recent years has diagnosed some individuals with autism and other PDDs.

Conclusion

The purpose of this study was to study some potential risk factors of autism. Overall, the strongest risk factor in terms of relative risk was a family history of autism and the broader autism diagnoses in siblings, supporting the strong genetic involvement in the etiology of autism. This may be supported by the finding of an increased risk of autism with increasing paternal age, since the risk of some genetic defects increases with paternal age. However, the influence of non-genetic factors on the development of autism cannot be ruled out, and variables like place of birth of child and parents may represent proxy variables for environmental risk factors of autism. The identification of risk factors is relevant with respect to etiology, intervention or prevention of autism and further studies are needed to replicate the importance of the risk factors investigated in the present study.

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Appendix 1. The psychiatric diagnoses among mothers of children with autism

Maternal psychiatric disorder	No. of cases
Only a diagnosis of schizophrenia and other paranoid psychoses	1
Both a diagnosis of schizophrenia and nervous conditions and personality disorders	4
A diagnosis of schizophrenia, mood disorder, and nervous conditions and personality disorders	3
Only mood disorder	2
Mood disorder and nervous conditions and personality disorders	2
Nervous conditions and personality disorders	11
Other psychiatric disorders than the above psychiatric diagnoses	14

Appendix 2. Incidence rates of combinations of parental place of birth per 10,000 person years according to region of birth of parents (only combinations based on ≥ 5 cases and $\geq 5,000$ person years are shown)

Father Mother	Denmark	Europe	Scandinavia	Asia	Middle East	Africa	Unknown
Denmark	1.7	2.8	3.2	–	–	–	1.9
Europe	4.3	1.4	–	–	–	–	–
Scandinavia	2.2	–	–	–	–	–	–
Asia	6.9	–	–	3.5	–	–	–
Middle East	–	–	–	–	1.9	–	–
Africa	–	–	–	–	–	5.9	–