Risk factors for autism and Asperger syndrome Perinatal factors and migration

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Risk Factors for Autism and Asperger Syndrome: Perinatal Factors and Migration.

Abstract

Using the Swedish Medical Birth Registry (MBR), obstetrical and demographic information was retrieved for 250 children with autism or Asperger syndrome who were born in Malmoe, Sweden, and enrolled at the local Child- and Youth Habilitation Center. The reference group consisted of all children born in Malmoe during 1980 – 2005. Obstetric sub-optimality (prematurity, low Apgar scores, growth restriction, or macrosomia) was positively associated with autism but not with Asperger syndrome. Maternal birth outside the Nordic countries was positively associated with autism (adjusted OR:2.2; 95%CI: 1.6-3.1) and negatively associated with Asperger syndrome (OR:0.6; 95%CI: 0.3-0.97). The highest risk estimate for autism was found among children to women who were born in Africa south of Sahara (OR:7.3), or East Asia (OR:3.4).

Key words: Autism, Asperger Syndrome, Perinatal factors, Migration

Introduction

Autism is a developmental condition that is characterized by impairment in socialization, abnormalities of verbal and nonverbal communication, and a pattern of repetitive, stereotypical interests and behaviours. Autism is diagnosed by clinical criteria, DSM IV (Diagnostic and Statistical Manual of Mental Disorders, *American Psychiatric Association,* 1994) or ICD-10 (International Clarification of Diseases, 10th edition). Autism is a part of a spectrum disorder that also includes Asperger Syndrome and pervasive developmental disorder – not otherwise specified (PDD-NOS), the latter two diagnoses include individuals with fewer or milder symptoms. Autism is usually diagnosed at 3 to 5 years, but the symptoms of autism are often noticed already at 9 to 15 months (Filipek et al., 1999). Individuals with Asperger syndrome are usually diagnosed in late childhood or in the adolescence, and are seldom diagnosed before the age of 7 years. About two thirds of the individuals with autism are affected with mental retardation, whereas a normal intellectual capacity is required for a diagnosis of Asperger syndrome. Autism was previously reported to affect approximately 5 of every 10 000 children (Fombonne et al. 1997). The prevalence of all autism spectrum disorders (ASD) today are estimated at approximately 60 per 10,000 (Fombonne, 2003; Yeargin-Allsopp et al. 2003; Bertrand et al. 2001). The increase of diagnosed ASD has been hypothesised to mostly depend on a better knowledge of autism and a higher detection rate of the milder forms (Asperger Syndrome and PDD-NOS) over the last decade. However, the rising figures could also to some extent reflect a true increase where environmental causes may play an important role (Kolevzon et al. 2007).

The aetiology of autism spectrum disorders is to a large extent not known, but it is likely to be multi-factorial and the hypothesis of a genetic component is supported by clustering in families and higher concordance in monozygotic twins than in dizygotic twins (Muhle et al., 2004). In 1999, Wakefield (1999) reported a possible association between autism and measles-mumps-rubella–vaccine (MMR). Since then, numerous negative studies on this topic have been published, and the suspected association between MMR and autism has not been verified (Demicheli et al. 2005)

In a recent review (Kolevzon et al. 2007), three parental characteristics and 2 obstetric conditions emerged as potential risk factors for autism; advanced paternal and maternal age, maternal immigration, growth restriction, and newborn hypoxia. One study found advanced maternal age to be specifically associated only with Aspergers syndrome (Eaton et al. 2001), but most studies did not report the risk factors for Asperger syndrome and autism separately. Several investigators have reported an increased risk for autism in children whose mothers were born outside Europe or North America (Hultman et al., 2002; Gillberg & Gillberg, 1996; Maimburg & Vaeth 2006; Williams et al. 2008). Lauritsen et al. (2005) found an association between immigration from outside Europe when investigating the whole group of ASD, and in a recent Swedish study, Barnevik-Olsson et al. (2008) found a strong association between maternal immigration from Somalia and risk of autism or PDD-NOS, respectively. Maternal immigration was not found to be a risk factor for autism in an American study, but maternal black ethnicity was (Croen et al. 2002). To our knowledge, no study on the risk factors for autism has reported estimates according to country of origin for different groups of immigrants, and no study has evaluated maternal immigration as a risk factor for Asperger syndrome separately.

The current study was designed to investigate, and to compare, the pre- and perinatal risk factors for autism and Asperger syndrome in a population in the south of Sweden.

Material and Methods

Malmoe is the largest town in the south of Sweden, and the third largest town in the country. All children suspected of having ASD are admitted to the Malmoe child psychiatric clinic and examined by a multidisciplinary diagnostic team. Children or adolescents fulfilling the criteria for ASD below the age of 20 and living in the surroundings of Malmoe are offered free treatment and support at the Malmoe Habilitation Center.

Case participants were children diagnosed with autism or Asperger syndrome at the Malmoe Child Psychiatric Clinic, who were born in 1980-2005, and attended the Child- and Youth Habilitation Center in Malmoe for a period during 1997-2007. Cases of autism were diagnosed according to DSM-IV (earlier cases DSM-III) (Autistic Disorder, 29900), or ICD-10 (Childhood autism, F840). Individuals with Asperger syndrome were diagnosed according to DSM-IV (29980), ICD-10 (F985), or Gillberg & Gillberg criteria (1989). Cases of PDD-NOS who were enrolled at the habilitation centre were rather few (n=74 of whom 49 were born in Malmoe), and were excluded. The diagnostic instruments, ADOS-G (Autism Diagnostic Observation Schedule-Generetic) (Lord et al. 1989) and the ADI-R (Autism Diagnostic Interview- Revised) (Lord et al. 1994) were used in the majority of the cases (approximately 75%) to ensure that the core symptoms of autism were present. A diagnosis of autism required that symptoms were present before three years of age. Asperger syndrome was seldom diagnosed before the age of seven, and seldom if symptoms were present before three years of age.

Intellectual capacity in the children with autism was usually assessed with WPPSI-R (Wechler Preschool and Primary Scale of Intelligence) or WISC-III (Wechler Intelligence Scale for Children). When children had severe retardation or were non-verbal, the PEP-R

(Psychoeducational profile- Revised) or Leiter International Performance scale was used as a complement. Children with Asperger syndrome were intellectually assessed in childhood or adolescence with WISC-III. Language development in these cases was estimated through standardized parental- or ADI-interviews. Mental retardation was defined as measured intellectual capacity below IQ 70 and significant limitations in adaptive behavior and functioning in daily life. The limited mental resources should be detected before 18 years of age in order to fulfill the criteria for mental retardation.

Children with autism are usually enrolled at the Child and Youth Habilitation Center at the age of 2.5 years to 8 years. Approximately 75% of the individuals with Asperger syndrome were enrolled at the age of 8 to 15 years. The date of the first diagnosis was not available in the database.

The control group was identified from the Swedish Medical Birth Registry (MBR), and consisted of all individuals who were born in Malmoe during the study period, and were not included in the case group. Infants who died before one year of age were excluded.

Using the personal identification number of each individual, the case group was linked to the MBR in order to obtain demographic and obstetrical information. Individuals for whom no linkage was possible (e.g., were born abroad) were not included in the final analyses. The MBR contains medical information on nearly all deliveries in Sweden (coverage about 99%) (Cnattingius et al. 1990). Standardized record forms are used at all antenatal clinics, all delivery units, and at all paediatric examinations of newborn infants. Copies of these forms are sent to the National Board of Health where they are computerized. Nearly all pregnant women receive free

antenatal care. The MBR is annually linked with Statistics Sweden to, among other things; obtain information on the infant's identification numbers, date of death, and parental citizenship.

Intrauterine growth was evaluated in accordance with the national fetal weight-based growth standard (Marsal et al., 1996) and expressed in standard deviation (SD) scores. Infants with birth weight of more than 2 SD below the expected weight for gestational age were classified as small for gestational age, whereas infants weighing more than 2 SD above expected were considered large for gestational age.

Maternal parity was defined as the number of previously born children at birth of the study child. Thus, the parity information used in the current study reflects birth order.

Statistical analyses

Odds ratios (OR) and 95 % confidence intervals (CI) for autism or Asperger syndrome, respectively, were calculated using multiple logistic regression analyses (Gauss^{TM}, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com). Throughout the analyses, the mentioned groups were analyzed separately. The details of each model are specified in text and table headings. In order to determine the best multivariate model the following steps were taken: First, for each outcome (autism or Asperger syndrome) the best model for each investigated variable (linear, quadratic, or divided into designed class variables) was determined by investigating the level of significance and goodness of fit according to the Hosmer-Lemoshov test. Variables with p-values below 0.20 in the final univariate models were initially included in the multivariate models and excluded if the p-values exceeded 0.20 in the multivariate analyses. In order to make it possible for the reader to compare the results for the study groups, one

exception was made for primiparity, which was included in the multivariate model for autism even though the p-value exceeded 0.20 in the univariate as well as in the multivariate model. Birth weight was entered to the multivariate model expressed as SD-scores. In all multivariate models, year of birth was controlled for using class variables divided into 6- or 7-year-periods (1980-1986, 1987-92 [reference], 1993-98, and 1999-2005). For each model, the number of investigated factors never exceeded 1/10 of the number of cases. When comparing two adjusted ORs, two-tailed *z* tests were carried out. Tests of homogeneity of the odds ratios across strata were based on weighted sums of the squared deviations of the stratum specific log-odds ratios from their weighted means (Hosmer & Lemeshow 1989).

Time trends for the incidence of autism were investigated using linear regression analyses, and were restricted to individuals born in 1980 – 1998 in order to minimize the problem with different lengths of follow-up. Individuals who were born during this time span were followed to at least 9 years of age. As autism is rarely diagnosed after this age, the follow up time was sufficient for all study participants, and the time trend results were unlikely to be severely biased by different lengths of follow up.

Results

Table 1 shows the number of patients with Autism or Asperger syndrome who were enrolled at the Child- and Youth habilitation center in Malmoe during 1997-2007. Among 376 patients with Autism or Asperger syndrome, 14% were born outside Sweden, and 19% were born in Sweden but outside Malmoe. In total, 250 patients with Autism or Asperger syndrome were born in Malmoe and constituted the final study group.

Information on presence of mental retardation was lacking in 19 individuals with autism. Among the remaining 138 infants with autism, 92 (67%) were reported to have a mental retardation.

The population characteristics of the study group and the controls (all children born in Malmoe between 1980 and 2005) are displayed in Table 2. The annual number of births increased slightly during the study period. Compared to the total number of birth, the individuals within the Autism study group were more often born during the latter 10-year period, whereas individuals with Asperger syndrome were born during the first years of the study period. The OR for one-year-increase for year of birth in the autism group was 1.13 (95% 1.08 – 1.17) among children born between 1980 and 1998 (children who were followed until at least 9 years of age). The estimate changed marginally when adjustments were made for maternal country of birth, age, parity, and smoking (OR: 1.11, 95%CI: 1.06-1.16).

The factors listed in Table 2 were evaluated as possible risk factors (univariate) for autism or Asperger syndrome. The univariate results for both conditions are shown in Table 3. The most significant risk factors were selected (forward selection) and were included in a multivariate model as specified in Table 4.

Maternal age 40 years or above was a significant risk factor for autism. A possible U-shaped relationship between maternal age and risk of autism was indicated but could not be verified in an analysis including a second grade term for maternal age (p=0.12). For Asperger syndrome, an association with maternal age 40 years or above was indicated but not statistically significant. For both Asperger and autism, the OR for maternal age ≥ 40 years did not change when adjustments for the other possible risk factors were made (Table 4).

No relationship between maternal parity and autism could be detected, whereas a significant association between primiparity and Asperger syndrome was found in the univariate analysis (Table 3), a finding that only reached borderline significance in the multivariate analysis (Table 4). Among the 55 first-born individuals with Asperger syndrome, 15 (27%) had no younger brothers or sisters. The corresponding percentage among all first-born individuals in Malmoe was 35%.

A strong positive association between autism and maternal birth outside Sweden was found, the magnitude of the association was similar across the time periods (p-value for homogeneity=0.44), and the association remained significant in the multivariate analysis. Quite contrary to this, a significant negative relationship between Asperger syndrome and maternal birth outside Sweden was detected (p-value for homogeneity across time periods=0.85). Maternal smoking was positively related to Asperger syndrome (univariate analysis, Table 3), but negatively associated with autism (univariate analyses, Table 3, and multivariate analyses, Table 4). Male gender was a strong risk factor for autism and Asperger syndrome, but multiple birth was not. Premature birth (birth before 37 gestational weeks), elective caesarean section, and low birth weight (below 2500g) was associated with autism but not with Asperger syndrome. No association between small-for-gestational-age and risk for autism or Asperger syndrome could be

detected, but when standard-deviations-score (SD-score) was modelled as a continuous variable, significant negative relationships between increasing SD-scores and risk of autism or Asperger syndrome were found (Table 3). As evident from Table 4, the decreased risk for Asperger syndrome with increased birth weight for gestational age remained significant in the multivariate analysis, could partly be explained by the increased smoking during pregnancy in the mothers of individuals with Asperger syndrome.

In order to evaluate the overall impact of obstetrical risk factors in the aetiology of autism or Asperger syndrome, birth before 37 weeks of pregnancy, Apgar score at 5 minutes below 7, small-for-gestational-age, and large-for-gestational-age, were combined into a designed dichotomous variable (see Tables 2, 3, and 4). Adjusting for year of birth, maternal age 40 years or older, primiparity, maternal birth outside Sweden, and gender, the ORs (with 95% CI) for 'any obstetrical risk factor', defined as above, was 1.7, and no heterogeneity over the time periods could be detected (p-value for homogeneity=0.33). The corresponding OR for Asperger syndrome was 0.7, and the p-value for homogeneity over time periods was 0.42. The difference between the estimates for autism and Asperger syndrome was statistically significant (p=0.02). The adjusted OR for 'any obstetrical risk factor' was 1.3 (95%CI: 0.3- 2.2) for autism with mental retardation, and 3.1 (95%CI: 1.7- 5.7) for autism without cognitive impairment. The difference between the estimates among individuals with or without mental retardation was not significant (p for homogeneity =0.28), but the estimate for 'any obstetrical risk factor' was significantly higher among individuals with autism without mental retardation than among individuals with Asperger syndrome (p for homogeneity =0.0004, results not shown).

The relationship between maternal country of birth and autism in the offspring was investigated in detail (Table 5). Except for immigrants from the other Nordic countries, women who were not

born in Sweden had significantly more often than Swedish women given birth to a child with autism. The highest OR for autism was found for children of women who were born in Africa south of Sahara, and this estimate differed significantly from the estimates for the other groups of women born outside of Nordic countries ($p=0.007$). The estimates changed marginally when adjustments were made for year of birth, maternal age, and perinatal risk factors. Table 5 also shows the risk of autism in relation to paternal nationality and maternal birth outside Sweden. As evident from the table, maternal origin outside Sweden was a significant risk factor for autism irrespective of paternal Swedish citizenship.

Among individuals with autism whose mothers were born outside Sweden, 19 (22%) were the first-born child in Sweden, but had older brothers or sisters who were born abroad. The corresponding percentage among all children to immigrant women giving birth in Malmoe was 21%.

Discussion

Few previous studies have reported the risk factors for autism and Asperger syndrome separately. The results from the current study suggest that aetiology for these conditions differ. Maternal immigration outside the Nordic countries was positively associated with autism and negatively associated with Asperger syndrome. Furthermore, for autism, a significant association with 'any obstetrical risk factor' was found, and the estimate differed significantly from the corresponding estimate for Asperger syndrome, suggesting a truly different role of obstetric sub-optimality in the genesis of the two conditions. Thus, the results of the current study stress the importance of analysing the different groups within the autism spectrum separately. In a review from 2004, MacIntosh and Dissanayake (2004) conclude that there is currently insufficient evidence to establish the validity of Asperger disorder as a syndrome distinct from high-functioning autism. However, Rinehart et al. (2006), found qualitative differences in executive dysfunction between cases of Asperger syndrome and cases of high-functioning autism which may implicate differential disruption within the fronto-striatal circuitry. In the current study, a significant difference was found between the odds ratio for 'any obstetrical risk factor' among cases of autism without mental retardation, and the corresponding odds ratio among cases of Asperger syndrome. If not due to chance, the results could indicate that a true difference exist, at least with regard to aetiology, between Asperger syndrome and autism without intellectual impairment.

One challenge when comparing the results from studies investigating risk factors for ASD is that the studied case groups substantially differ with regard to diagnostic criteria. E.g., several investigators reported the risk estimates for the combined ASD-case group (Lauritsen et al. 2005; Reichenberg et al. 2006), others have reported the Asperger group together with PDD-NOS

(Croen et al. 2007). Furthermore, within the autism group, the diagnostic criteria may differ between studies. In order to ensure that the agreed core symptoms of ASD are truly identified, a certain degree of diagnostic conformity is required. Discrimination from other psychiatric and developmental disorders becomes more challenging as the spectrum becomes broader. In the current study, the diagnostic instruments, ADOS-G and the ADI-R were used in the majority of the cases to ensure that the core symptoms of autism were present. The mentioned instruments have been used to identify ASD-cases in former studies (Juul-Dam et al. 2001), some investigators have used the Childhood Autism Rating Scale (CARS) (Mesibov et al. 1989), the Asperger Syndrome Diagnostic Interview (ASDI) (Gillberg et al. 2001), and/or the Asperger Syndrome Screening Questionnaire (ASSQ) (Ehlers & Gillberg 1993), but in most studies, the examination protocol to establish the diagnostic criteria for ADS have not been fully described. In the present study the case groups consisted of individuals who met all criteria for autism or Asperger syndrome, respectively.

The majority of children in the Asperger study group were born in the eighties or early nineties, whereas children with autism were born towards the end of the study period. The distribution of year of birth reflects the fact that the individuals with Asperger are often diagnosed in their adolescence. Thus, affected children who were born towards the end of the study period were, at least to a large extent, not yet diagnosed with Asperger syndrome when data were retrieved. For autism, a significant association with increasing year of birth was found among individuals born between 1980 and 1998. The mentioned sub analysis was restricted to children who were followed to at least 9 years of age, keeping cases of autism lost to follow-up to a minimum, and reflects an annual increase of children with autism who were enrolled at the Child- and Youth Habilitation Center during the time span. The increase could partly be explained by population changes, but is likely to mainly reflect a gradual broadening of the diagnostic criteria combined

with an increasing detection rate. In order to avoid confounding due to the different distribution of year of birth, no analysis was performed directly comparing the risk factors for autism and Asperger syndrome. Instead, the risk factors for autism and Asperger syndrome were evaluated separately, using controls matched by year of birth. The risk estimates for various factors among cases of autism and Asperger syndrome were then compared in order to investigate whether the risk panorama for the conditions was truly different. In order to study the stability of the risk factors for autism and Asperger syndrome, respectively, the risk estimates were checked for heterogeneity over time period strata. No heterogeneity was indicated.

A significant association with advanced maternal age at delivery and the risk of Asperger syndrome or autism have been reported by several investigators, at least in univariate analyses (Croen et al. 2002; Hultman et al. 2002; Glasson et al. 2004; Larsson et al. 2005; Maimburg and Vaeth 2006; Reichenberg et al.2006; Croen et al. 2007; Williams et al. 2008). Fewer investigators have analyzed the influence of paternal age, but all of these reported a significantly increasing risk for Asperger syndrome or autism with increasing paternal age (Burd et al. 1999; Croen et al. 2002; Larsson et al. 2005; Lauritsen et al. 2005; Reichenberg et al. 2006; Glasson et al. 2004; Croen et al. 2007). In the studies that considered the simultaneous effect of maternal and paternal age, increasing maternal age and paternal age were both found to be independent risk factors in one study (Croen et al. 2007). However, in three studies (Larsson et al. 2005; Lauritsen et al. 2005; Reichenberg et al. 2006), advanced paternal age, but not maternal age, was found to be a significant independent risk factor for Aspergers syndrome or autism. In the present study, information on paternal age was not available. In concordance with most previous studies, a significant association with maternal age ($\geq$ 40 years) and autism was found. For Asperger syndrome (putatively due to small numbers), no significant effect of maternal age could be detected, but the point estimates for autism and Asperger syndrome were almost identical,

suggesting that no true difference in the relationship between maternal age and the two conditions exists.

The relationship between birth order and the risk for autism remains unclair. Eaton et al. (2001) and Larsson et al. (2005) could not detect any significant association. Hultman et al. (2002) found an increased risk in individuals fourth-born or later compared to second- and third born, whereas Croen et al. (2007) found a significant negative association between birth order and autism when birth order was modelled as a continuous variable. In the current study, no relation between parity and the risk for autism could be detected whereas a significant association between primiparity and the risk for Asperger syndrome was found. This finding of the current study is in concordance with Croen et al. (2007), who found a negative association between parity and the risk for Asperger syndrome or PDD-NOS combined, and Eaton et al. (2001), who found an increased risk in first-born children compared to children with older brothers and sisters when investigating the relationship between parity and infantile psychosis (judged to be corresponding to Asperger syndrome). To our knowledge, no study investigating the association between parity and Asperger syndrome has been previously published. It could perhaps be hypothesized that the existence of brothers or sisters could improve social and communicative skills, and perhaps to some extent 'protect' against communicative disorders like Asperger syndrome. However, in the current study, first-born children with Asperger syndrome had younger brothers and sisters to the same extent as first-born children in the comparison group. Thus, we found no evidence for the detected association between primiparity and Asperger syndrome to be due to an increased proportion of individuals without brothers and sisters in the Asperger syndrome group.

Several investigators have reported significant associations between autism and sub optimal pre- or perinatal conditions such as low birth weight (Burd et al. 1999; Eaton et al. 2001; Hultman et al. 2002; Mainburg & Vaeth 2006), low Apgar score (Eaton et al. 2001; Hultman et al. 2002; Glasson et al. 2004; Larsson et al. 2005), low gestational age (Eaton et al. 2001; Williams et al. 2008), and low birth weight for gestational age (Hultman et al. 2002; Larsson et al. 2005). However, the mentioned studies differ considerably in design and number of possible confounders included in the final analyses. In the study of Hultman et al. (2002) birth before 37 weeks was reported to be a significant risk factor for autism in the univariate analyses, but in the final model when several putative risk factors were included, no association between prematurity and autism was indicated.

As pointed out above, there are not many studies on the association between perinatal risk factors and the risk of Asperger syndrome. Evaluating several factors during pregnancy and labour, Glasson et al. (2004), found statistically significant associations between Asperger syndrome and use of epidural anesthesia, induced labour, delivery with forceps or vacuum extractor, or elective caesarean section. An association between Asperger syndrome and low Apgar score was indicated, but far from statistically significant. Gillberg and Cederlund (2005), investigating risk factors for 100 individuals with Asperger syndrome, estimated that 13% of the cases had e pre- or perinatal aetiology and 11% of the cases had a genetic, prenatal, or perinatal origin. However, as the investigators of the former study did not include any comparison group, their results are difficult to evaluate and compare to the results of the present study.

In the current study, autism was significantly associated with prematurity, low birth weight, caesarean section, and decreasing weight-for-gestational-age (SD-scores) in the univariate analyses. For both autism and Asperger syndrome, a negative association with increasing SD-

scores was the only single perinatal risk factor that remained significant in the multivariate analysis. In order to evaluate the overall influence of perinatal health on the aetiology of autism and Asperger syndrome, respectively, a composite variable 'any obstetrical risk factor' was developed and evaluated. This composite variable was positively associated with autism but not with Asperger syndrome, and the difference between the risk estimates was statistically significant. We found no significant evidence that the association between autism and "any obstetrical risk factor" was influenced by the presence or absence of mental retardation. However, the numbers within the subgroups regarding mental capacity were low, and a true discrepancy may be present even though it could not be statistically proven.

The results suggest that obstetrical risk factors may play significantly different roles in the aetiology of autism and Asperger syndrome, respectively. However, even if a statistically significant association between obstetric sub-optimality and autism exists, perinatal hazards are unlikely to be major causes of autism as only 34 out of 157 cases of autism were affected in the current material, and the attributable fraction due to any obstetrical risk factor among cases of autism could be estimated to be about 4%.

Quite contrary to the increased risk for autism in the children of immigrant mothers, we found a significant negative association between immigrant status and Asperger syndrome. To our knowledge, no previous study investigating the relationship between migration and Asperger syndrome has been published. The observed low prevalence of Asperger syndrome in children to immigrant mothers found in the current study may be due to possible under-reporting of Asperger syndrome in children to immigrant parents.

Several investigators have reported an increased risk for autism in the children of immigrant women born outside Europe, USA or Australia (Gillberg & Gillberg 1996; Hultman et al. 2002; Maimburg & Vaeth 2006; Williams et al. 2008). Furthermore, investigating the ethnicity among 4,356 cases of autism in California, USA, Croen et al. (2002) found an increased risk for autism in children of black women. This finding could perhaps be considered to have been confirmed by a recent Swedish study (Barnevik-Olsson et al., 2008), reporting an increased risk for autism or PDD-NOS in infants born in Sweden of women who originated from Somalia. However, this latter study population consisted of the children in an already observed cluster of children with autism born to parents with a Somali origin, a fact that must be considered when the level of statistical significance of this finding is evaluated. To our knowledge, no study has been published with attempts to systematically compare the composition of the autism case group regarding maternal origin with reference population.

In 1996, Gillberg and Gillberg (1996) suggested that the increased risk that they had found for autism in children who were born in Sweden of mothers who were born abroad, may have been due to a possible increased vulnerability to intrauterine infections in non-immunized immigrant mothers. Their alternative hypothesis was that inborn men affected with autistic traits would be inclined to travel abroad in order to find female partners. The results of the current study, in which the maternal country of origin was divided into 9 major groups and compared to a reference population, suggest that maternal migration from any group of countries outside the Nordic region was associated with an increased risk for autism in the offspring. The highest risk estimate was found among children to women who were born in Africa south of Sahara (OR: 7.3), among the other groups the estimated ORs varied from 2.2 (previous Eastern Europe) to 3.4 (East Asia), and no substantial heterogeneity was indicated. The risk estimates for autism for maternal country of origin were only marginally influenced by paternal citizenship. Thus, we

found no support for the hypothesis that a substantial mechanism behind the elevated risk for autism in the offspring of migrated women from outside Europe would be due to the fact that men with autistic traits would seek partners in a foreign country where their lack of social skills would perhaps be less apparent. Also, we found no evidence for the increased risk for autism in second generation immigrants being due to the fact that immigrant mothers from non-Nordic countries may lack immunity to certain infections during pregnancy that are uncommon in their country of origin. Under such a hypothesis, one would expect children who were born in Sweden close to the date of maternal immigration to Sweden to be at an increased risk for autism. Date of immigration was not available in the current data set. Instead we evaluated the hypothesis by investigating the country of birth of brothers and sisters to the children with autism. Children with older sisters or brothers to mothers who had no previous delivery in Sweden were regarded to have been conceived close to the date of maternal immigration to Sweden, and thus they would have been conceived before their mothers had gained the required immunity against potential foetes-damaging infections that may be prevalent in their new country. We found no evidence suggesting that the risk for autism in children to immigrant women was influenced by the country of birth (Sweden or other) of older brothers or sisters. However, the above mentioned piece of evidence is speculative, and future studies for which information on date of immigration is available are needed for a proper evaluation of the role of perinatal infection on the incidence of autism.

Recently, Cannell (2008) released a hypothesis of an association between vitamin D deficiency and autism. However, no evidence for such an association was ever presented, and although the hypothesis may be consistent with the reports of increased risk for autism in black or dark-skinned children (Croen et al. 2002; Barnevik-Olsson et al., 2008), no convincing evidence has

been published suggesting that vitamin D-deficiency could be a major contributor to the observed increased risk for autism in children of women from Africa south of Sahara.

Although many genes have been implicated as causes of autism, single-gene defects are rare within multiplex families with the broader autism phenotypes. Still too little is known about their functions in brain development to generate hypotheses about the brain dysfunction that underlie autism (Muhle et. al 2004). Future studies may show if the observed risk increase for autism in the children of immigrant women born outside Europe, USA or Australia is due to factors influenced by the migration itself, or may reflect different incidence of autism in different populations. Such differences may be potentiated by high rates of consanguineous marriages in some ethic groups. A specific mutation or unique set of genetic polymorphism may determine each individual's susceptibility to autism, however environmental triggers may modify the phenotypic expression of the condition. In the current study, we had no access to familial/genetic information. Thus, we were not able to investigate if the association between immigrant status and autism may have been due to consanguineous marriages in immigrant couples, or to selective migration of people with genetic vulnerability to autism. Also, we could not investigate a possible interaction between genetic and perinatal factors in the aetiology of autism.

The results of the present study stress the importance of analyzing risk factors for autism and Asperger syndrome separately and to investigate the role of migration in the aetiology of autism in detailed with the aid of systematic grouping and a robust comparison group. Future studies may have the opportunity to study the interplay between genetic and perinatal factors in the aetiology of autism or Asperger syndrome, respectively.

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Table 1

Number of patients (born 1980-2005) with autism or Asperger syndrome enrolled at the child and youth habilitation center in Malmo (1997-2007) by location of birth.

	Autism		Asperger syndrome	
	n=241	(%)	n=135	(%)
Born in Malmoe	157	(65.1)	93	(68.9)
Born in Sweden outside Malmoe	42	(17.4)	30	(22.2)
Not born in Sweden	42	(17.4)	12	(8.9)

Table 2

Demographic characteristics of patients in the study group and the total population (children born in Malmoe between 1980 and 2005).

	Autism n=157		Asperger syndrome n=93		Total population n=68 964	
	n	(%)	n	(%)	n	(%)
Year of birth						
1980-86	17	(10.8)	22	(23.7)	16567	(24.0)
1987-92	28	(17.8)	53	(57.0)	17622	(25.6)
1993-98	60	(38.2)	15	(16.1)	17054	(24.7)
1999-05	52	(33.1)	3	(3.2)	17721	(25.7)
Maternal age at delivery (years)						
<20	8	(5.1)	4	(4.3)	2343	(3.4)
20-24	29	(18.5)	21	(22.6)	14555	(21.1)
25-29	57	(36.3)	24	(25.8)	24170	(35.0)
30-34	39	(24.8)	29	(31.2)	18887	(27.4)
35-39	16	(10.2)	12	(12.9)	7706	(11.2)
40+	8	(5.1)	3	(3.2)	1303	(1.9)
Maternal parity at delivery						
1	68	(43.3)	55	(59.1)	32944	(47.8)
2	58	(36.9)	22	(23.7)	22814	(33.1)
3	16	(10.2)	10	(10.8)	8526	(12.4)
4+	15	(9.6)	6	(6.5)	4680	(6.8)
Maternal country of birth						
Sweden	72	(45.9)	77	(82.8)	47868	(69.4)
Other Nordic countries	2	(1.3)	2	(2.2)	1764	(2.6)
Western Europe / USA	6	(3.8)	1	(1.1)	1332	(1.9)
Previous Eastern Europe	24	(15.3)	8	(8.6)	7199	(10.4)
Sub-Saharan Africa	11	(7.0)	1	(1.1)	1019	(1.5)
Middle East / north Africa	24	(15.3)	2	(2.2)	6064	(8.8)
East Asia	8	(5.1)	1	(1.1)	1574	(2.3)
South- Central America	6	(3.8)	1	(1.1)	1229	(1.8)
Unknown / other	4	(2.5)	0	(0.0)	915	(1.3)
Maternal country of birth and paternal nationality						
Mother born in Sweden, Father Swedish	69	(43.9)	74	(79.6)	45252	(65.6)
Mother born in Sweden, Father not Swedish	3	(1.9)	3	(3.2)	2616	(3.8)
Mother not born in Sweden, Father Swedish	49	(31.2)	13	(14.0)	12879	(18.7)
Mother not born in Sweden, Father not Swedish	36	(22.9)	3	(3.2)	8217	(11.9)
Maternal smoking in early pregnancy						
Not known	*7*		*9*		*8867*	

Non smoking	133 (88.7)	52 (61.9)	46417 (77.2)
Smoking 1-9 cigarettes/day	8 (5.3)	17 (20.2)	8092 (13.5)
Smoking ≥10 cigarettes/day	9 (6.0)	15 (17.9)	5588 (9.3)
Gender			
Male	125 (79.6)	72 (77.4)	35359 (51.3)
Female	32 (20.4)	21 (22.6)	33603 (48.7)
Singleton / multiple pregnancy			
Singleton	151 (96.2)	92 (98.9)	67268 (97.5)
Multiple	6 (3.8)	1 (1.1)	1696 (2.5)
Gestational age at birth			
Not known			*48*
<32v	2 (1.3)	2 (2.2)	511 (0.7)
32-36v	14 (8.9)	1 (1.1)	3508 (5.1)
37-41v	128 (81.5)	79 (84.9)	59660 (86.6)
42+v	13 (8.3)	11 (11.8)	5237 (7.6)
Mode of delivery			
Vaginal, non-instumental	121 (77.1)	80 (86.0)	58751 (85.2)
Elective cesarean section	10 (6.4)	4 (4.3)	2006 (2.9)
Emergency cesarean section	16 (10.2)	6 (6.5)	5428 (7.9)
Forceps/vacuum extraction	10 (6.4)	3 (3.2)	2779 (4.0)
Apgar scores at 5 minutes after birth			
0	2 (1.3)	2 (2.2)	2228 (3.2)
1-6	7 (4.5)	0 (0.0)	2136 (3.1)
7+	148 (94.3)	91 (97.8)	64600 (93.7)
Birth weight (gram)			
<2500g	15 (9.6)	6 (6.5)	3486 (5.1)
2500-4000g	117 (74.5)	73 (78.5)	54887 (79.6)
>4000g	25 (15.9)	14 (15.1)	10591 (15.4)
Standard deviation scores (birth weight) (SD)			
<-2SD	13 (8.3)	7 (7.5)	3393 (4.9)
-2 - -1.1SD	38 (24.2)	24 (25.8)	12092 (17.5)
-1 - 1SD	83 (52.9)	52 (55.9)	43225 (62.7)
1.1 - 2SD	16 (10.2)	9 (9.7)	7521 (10.9)
>2SD	7 (4.5)	1 (1.1)	2733 (4.0)
Existence of any obstetrical risk factor*			
Yes	34 (21.7)	12 (12.9)	12534 (18.2)
No	123 (78.3)	81 (87.1)	56430 (81.8)

* <37 weeks of gestational age, SGA, LGA, or Apgar <7 at five minutes.

Table 3.

Perinatal factors and risk for autism and Asperger syndrome, respectively, versus controls (children born in Malmoe without autism or Asperger syndrome as specified in Table 2). Odds Ratio (with 95%CI) obtained using univariate logistic regression analyses as specified.

	Autism		Asperger syndrome	
	OR	(95% CI)	OR	(95% CI)
Maternal age at delivery (years)				
<20	1.4	(0.7-3.0)	1.7	(0.6-5.0)
20-24	0.8	(0.5-1.3)	1.5	(0.8-2.6)
25-29	Reference		Reference	
30-34	0.9	(0.6-1.3)	1.5	(0.9-2.7)
35-39	0.9	(0.5-1.5)	1.6	(0.8-3.1)
40+	2.6	(1.2-5.5)	2.3	(0.7-7.7)
Maternal parity at delivery				
1	0.8	(0.5-1.1)	1.7	(1.0-2.6)
2	Reference		Reference	
3	0.7	(0.4-1.2)	1.2	(0.6-2.4)
4+	0.8	(0.3-1.8)	1.1	(0.3-3.5)
Mother born outside Sweden	2.7	(2.0- 3.7)	0.5	(0.3- 0.8)
Maternal smoking in early pregnancy				
Non smoking	Reference		Reference	
Smoking 1-9 cigarettes/day	0.3	(0.2-0.7)	1.9	(1.1-3.2)
Smoking ≥10 cigarettes/day	0.6	(0.3-1.1)	2.4	(1.4-4.3)

Smoking quasi-continuous	0.6	(0.4- 0.9)	1.6	(1.2-2.1)
Gender				
Male	3.7	(2.5-5.5)	3.3	(2.0-5.3)
Female	Reference		Reference	
Singleton / multiple pregnancy				
Singleton	Reference		Reference	
Multiple	0.6	(0.3-1.4)	2.3	(0.3-16.6)
Gestational age at birth				
<37v	1.8	(1.1-3.1)	0.6	(0.2-1.8)
37-41v	Reference		Reference	
42+v	1.2	(0.7-2.0)	1.6	(0.8-3.0)
Mode of delivery				
Vaginal, non-instumental	Reference		Reference	
Elective cesarean section	2.4	(1.3-4.6)	1.5	(0.5-4.0)

Emergency cesarean section	1.4	(0.8 – 2.4)	0.8	(0.4-1.9)
Forceps/vacuum extraction	1.8	(0.9-3.3)	0.8	(0.3-2.5)
Birth weight (gram)				
<2500g	2.0	(1.2-3.5)	1.3	(0.6-3.0)
2500-4000g	Reference		Reference	
>4000g	1.1	(0.7-1.7)	1.0	(0.6-1.8)
Standard deviation scores (birth weight) (SD)				
Small for gestational age	1.5	(0.7-3.3)	1.5	(0.7-3.3)
Adequate for gestational age	Reference		Reference	
Large for gestational age	0.3	(0-1.9)	0.3	(0 -1.9)

SD-scores, linear model				
(1-step increase)	0.8	(0.7-0.9)	0.8	(0.7-1.0)*
Apgar scores at 5 minutes after birth[a]				
1-6	1.4	(0.7-3.1)	-	
7+	Reference			
Any obstetrical risk factor[b]				
Yes	1.4	(1.0 – 2.0) NS	0.7	(0.4 – 1.3)
No	Reference		Reference	

[a]Apgar scores= 0 at five minutes were interpreted as missing data and were excluded.
[b] <37 weeks of gestational age, SGA, LGA, or Apgar <7 at five minutes.
*Significant, $p<0.05$
NS=Not significant

Table 4.

Perinatal factors and risk for autism and Asperger syndrome, respectively, versus controls (children born in Malmoe without autism or Asperger syndrome as specified in Table 2). Odds Ratio (with 95%CI) obtained using multivariate logistic regression analyses as specified.

	Autism		Asperger syndrome	
	OR [a]	(95% CI)	OR [a]	(95% CI)
Maternal age at delivery ≥ 40 years versus <40 years	2.5	(1.2–5.1)	2.3	(0.7 – 7.4)
Parity 1 versus parity 2+	0.9	(0.6 – 1.2)	1.5	(1.0 - 2.3) NS
Mother born outside Sweden versus mothers born in Sweden	2.2	(1.6 – 3.0)	0.6	(0.3 –1.0)*
Maternal smoking in early pregnancy quasi-continuous variable[c] (1-step increase)	0.7	(0.5 – 1.0)*	1.3	(1.0 – 1.7) NS
Male gender versus female gender	3.8	(2.5 – 5.5)	3.3	(2.0 – 5.3)
Gestational age at birth < 37 weeks Versus gestational age ≥ 37 weeks	1.7	(1.0 – 2.8) NS		
SD-scores, linear model,(1-step increase)	0.8	(0.7 – 0.9)	0.8[b]	(0.7 – 1.0)*
			0.9	(0.7 – 1.0) NS
Any obstetrical risk factor[d] versus no obstetrical risk factor	1.7[e]	(1.2 – 2.4)	0.7[e]	(0.4 – 1.2)

[a]Multivariate model including year of birth and the variables specified in the column.
[b]Multivariate model including year of birth and the variables specified in the column except of maternal smoking information.
[c] 1= Non smoking, 2= smoking 1-9 cigarettes/day, 3=smoking ≥10 cigarettes/day
[d] <37 weeks of gestational age, SGA, LGA, or Apgar <7 at five minutes.
[e]Multivariate model including year of birth, primi-parity, maternal birth outside Sweden, maternal smoking, and gender.

*Significant, $p<0.05$
NS=Not significant

Table 5.
Detailed analysis on the relationship between maternal country of birth, and maternal country of birth and paternal nationality, respectively, and risk for autism in the offspring. The reference population consisted of children born in Malmoe without autism or Asperger syndrome as specified in Table 2. Odds Ratio (with 95%CI) obtained from multivariate logistic regression analyses.

	Crude OR for autism OR (95% CI)	Adjusted* OR for autism OR (95% CI)
Maternal country of birth		
Sweden	Reference	Reference
Other Nordic countries	0.8 (0.2 -3.1)	0.8 (0.2-3.3)
Western Europe / USA	3.0 (1.3-6.9)	2.8 (1.2-6.5)
Previous Eastern Europe	2.2 (1.4-3.5)	2.1 (1.3-3.3)
Sub-Saharan Africa	7.3 (3.8-13.7)	5.6 (2.9-10.6)
Middle East / north Africa	2.6 (1.7-4.2)	2.0 (1.2-3.2)
East Asia	3.4 (1.6-7.1)	2.9 (1.4-6.1)
South- Central America	3.3 (1.4-7.5)	3.1 (1.3-7.1)
Unknown / other	2.9 (1.1-8.0)	3.0 (1.1-8.3)
Maternal country of birth and paternal nationality		
Mother born in Sweden, Father Swedish	Reference	Reference
Mother born in Sweden, Father not Swedish	0.8 (0.2-2.4)	0.7 (0.2-2.2)
Mother not born in Sweden, Father Swedish	2.5 (1.7-3.6)	2.1 (1.4-3.1)
Mother not born in Sweden, Father not Swedish	2.9 (1.9-4.3)	2.6 (1.7-3.9)

*Adjusted for year of birth, maternal age ≥ 40 years, birth <37 weeks, and gestational age-adjusted weight Standard Deviation- (SD-) scores (continuous).