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Risk of Autism Spectrum Disorders in Low Birth Weight and Small for Gestational Age Infants

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Abstract

Objective—To examine the relationship between birth weight, gestational age, small for gestational age (SGA), and three most common autism spectrum disorder (ASD) subtypes.

Study design—In this population-based case-control study conducted in Finland, 4713 cases born between 1987 and 2005 with ICD-diagnoses of childhood autism, Asperger syndrome or PDD, were ascertained from the Finnish Hospital Discharge Register. Four controls, individually matched on sex, date of birth, and place of birth, were selected from the Finnish Medical Birth Register for each case. Conditional logistic regression models were used to assess whether birth weight and gestational age information predicted ASD after controlling for maternal age, parity, smoking during pregnancy and psychiatric history, as well as for infant's major congenital anomalies.

Results—Very low (<1500g) and moderately low (<2500g) birth weight, very low gestational age (less than 32 weeks), and SGA increased risk of childhood autism (adjusted OR 3.05, 95% CI 1.4–6.5; 1.57, 1.1–2.3; 2.51, 1.3–5.0 and 1.72, 1.1–2.6, respectively). Very low and moderately low birth weight, very low gestational age, and SGA were also associated with increase in PDD risk (OR 3.44, 95% CI 1.9–6.3; 1.81, 1.4–2.4; 2.46, 1.4–2.3 and 2.24, 1.7–3.0, respectively). No associations were found between the perinatal characteristics and Asperger syndrome. The increased risks persisted after controlling for selected potential confounders.

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Conclusions—The finding that low birth weight, prematurity and SGA were related to childhood autism and PDD but not to Asperger syndrome suggests that prenatal factors related to these exposures may differ for these ASD subtypes, which may have preventive implications.

Keywords

Epidemiology; Risk Factors

Associations between autism spectrum disorders (ASD) and birth weight, gestational age, and small for gestational age (SGA) status have remained inconsistent. Associations between low birth weight (< 2500g) and childhood autism or ASD were shown in population-based studies from Sweden[1] and the US[2] as well as in three studies from Denmark.[3–5] However, in one study[2] the association between low birth weight and ASD was statistically significant only among girls. Furthermore, several population-based studies have reported no association between low birth weight and autism or ASD, after adjusting for potential confounders.[6–9]

Studies examining gestational age at birth and ASD have also yielded mixed findings. A population-based study from Denmark[4] showed an association between low gestational age (< 35 weeks) and childhood autism. Studies from the USA[2] and Australia[10] found associations between preterm birth and the broader group of ASD in children born below 37 and 33 gestational weeks, respectively. In contrast, population-based studies from Australia,[8] Denmark,[5] the USA[6] and two studies from Sweden[1,11] reported no association between gestational age and autism or ASD after adjusting for maternal, pregnancy and birth characteristics.

Small for gestational age (SGA) status is a distinct risk factor from birth weight or gestational age, and reflects fetal growth and well-being. Among population-based studies including SGA in their analyses, four have found an association between SGA and childhood autism or ASD after adjusting for maternal, pregnancy and birth characteristics.[1,4,5,11] In the study by Larsson et al.,[4] the increased risk for SGA infants was observed when adjusted for perinatal factors, but the risk did not remain statistically significant when adjusted for parental psychiatric history and socioeconomic characteristics.

Methodological issues may at least partly explain the inconsistency of previous research findings. First, in most of the previous register-based studies, data from outpatient care available and analyses were usually limited to ASD cases receiving inpatient care. Second, there are large variations between studies in sample sizes and on confounding factors. Third, despite the increasing number of population-based studies examining the risk of ASD following low birth weight, prematurity, or SGA, few studies have directly examined ASD by subtype. Investigators have usually either pooled all cases into the broad category of ASD[2,6,8,11] or have only examined the relation of these exposures and risk of childhood/infantile autism.[1,4,5,7] Even though we acknowledge the possible plan to subsume all autism spectrum diagnoses under one category in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), at present there remain separate diagnostic criteria for each of these disorders providing sufficient rationale for separate examination of these disorders by subtype.

It is unclear if these ASD subtypes are associated similarly with prematurity, low birth weight and SGA. In the Australian study,[8] the pattern of pregnancy and labor complications differed between ASD subtypes. The autism group had the greatest number of complications compared with Asperger syndrome and PDD. In their study, however, birth weight itself was not compared between subtypes. In the recent Swedish study,[12] low birth weight and

low gestational age were associated with autism, but not with Asperger syndrome. However, PDD was not investigated in this study. Given the lack of population-based studies examining the associations between birth weight and gestational age and these three most commonly diagnosed subtypes of ASD, we sought to address this question in the current study.

METHODS

The present study was based on a large, ongoing epidemiological study of autism and autism spectrum disorders in Finland, the Finnish Prenatal Study of Autism and Autism Spectrum Disorders (FIPS-A). The FIPS-A is a nested case-control study derived from all singleton live births (n= 1 149 271) in Finland between January 1, 1987 and December 31st, 2005. The sampling frame included all children in Finland followed up for ASD diagnoses until the end of 2007. Cases were identified from the Finnish nationwide Hospital Discharge Register, including both inpatient and outpatient diagnoses, and matched controls were representative of the source population that gave rise to the cases. A full description of the study design and sources of data is available,[13] and will therefore be only summarized here. This study was authorized by the Ministry of Social Affairs and Health in Finland (STM/2593/2008) with the approval from the ethics committee of the hospital district of Southwest Finland and the National Institute for Health and Welfare, and approved by the Institutional Review Board of the New York State Psychiatric Institute.

This study is based on data from three nationwide registers: the Finnish Hospital Discharge Register (FHDR), Finnish Medical Birth Register (FMBR) and the Register of Congenital Malformations (RCM). All medical diagnoses from 1969 to the present are available in the FHDR. In Finland, diagnostic classification is based on the International Classification of Diseases (ICD); the 10th Revision is used since 1996.

Finland has universal health coverage; the Finnish public health care system includes primary health care (child welfare clinics, school health care services and health care centers), district and central hospitals as well as university hospitals. The visits to child welfare clinics and school health care services are free-of-charge, and practically all children in Finland use these services. Primary health care doctors are gatekeepers for referral to the more specialized services provided in hospitals. Children suspected to have ASD are referred from primary health care to more specialized services to be fully assessed by a multiprofessional, specialized team including e.g. child neurologists or psychiatrists, psychologists and speech therapists using standardized methods. Furthermore, in order to receive disability benefits from the Social Insurance Institution, an independent evaluation by another physician is required. In Finland, the private health care system is small and it mainly focuses on acute primary care in pediatric patients and is does not significantly overlap with the public health care system in the area of specialized health care.

The FHDR covers all somatic and psychiatric hospitals, inpatient wards of local health centers, military wards, prison hospitals and private hospitals. In 1998, diagnoses from outpatient care in public hospitals were added to the FHDR. Past diagnoses are available in the FHDR, and at each visit, the current diagnosis is registered and reported by health care personnel, and controlled by the register keeper. In this study, the most recent diagnosis was used for diagnostic classification. The FMBR includes detailed data on pregnancies and the neonatal period up to the age of seven days. The linkage between registers was conducted using a unique personal identity code assigned to all residents in Finland. The RCM contains information on all infants with a congenital anomaly or birth defect. Data are received from several sources, including a data collection form completed by delivery hospitals, neonatal,

pediatric and pathology departments and cytogenetic laboratories, and by linkage to other nationwide registers.[e.g.14]

Case identification

Cases with ASD diagnoses during the 21-year follow-up period (from January 1st, 1987 to December 31st, 2007) were identified from the FHDR. Diagnostic codes 299x (ICD-9) and F84.x (ICD-10) were used. In this study, the majority of cases were diagnosed with ICD-10, and only 19 cases (0.4%) were diagnosed according to the ICD-9. Because the most recent registry diagnosis was used for classification, these 19 cases represent a rare group with no ASD diagnosis registered after 1996. The majority (94%) of all ASD cases registered during the study period belonged to one of the three subtypes: childhood autism (F84.0, n=1132), Asperger syndrome (F84.5, n=1785), and other pervasive developmental disorders/pervasive developmental disorder – unspecified, PDD (F84.8/F84.9, n=1796). Cases receiving either a diagnosis of "other pervasive developmental disorder or "pervasive developmental disorder, unspecified" were pooled together, and they are referred to as "PDD". The less common ASD subtypes, which are rare diseases such as Rett syndrome, were excluded in this study.

Controls were drawn from the population at risk (born in Finland 1987–2005 and resident in Finland at the time of first diagnosis of cases) and who were without ASD or severe/profound intellectual disability according to the FHDR. Each case was individually matched to four controls on date of birth, place of birth and sex. If the birth place was a very small community and a control could not be found, the first option was to match to birth hospital and the second to regional hospital district.

Birth weight and gestational age information

Data on birth weight and gestational age were obtained from the FMBR. Birth weight categories were: < 1500, 1500 to 2499, 2500 to 3999, 4000 to 4499 and ≥ 4500 grams. Gestational age was classified into four categories: ≤ 31, 32 to 37, 38 to 41 and ≥ 42 weeks. The best clinical estimation of gestational age at birth is registered, which has been based on ultrasound since the late 1980s and early 1990s; prior to that it was based on the last menstrual period. Birth weight for gestational age (SGA/AGA/LGA status) was calculated according to national sex-specific weight distribution standards at a given gestational age in a sample of children (n= 75 061) born in Finland between 1979 and 1983.[15] SGA/AGA/LGA status 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).

Confounding factors

Six potential confounding factors that have been associated with both ASD and birth weight characteristics were considered for inclusion in the analyses: maternal age,[8,16] smoking during pregnancy,[1,17] number of previous births,[18,19] maternal psychiatric history,[4,20] congenital anomalies[21] and maternal socioeconomic status (SES) based on maternal occupation at birth.[7,22] Data on these variables were obtained from the FMBR and the FHDR. Maternal age was classified into the following categories: less than 20, 20–24, 25–29, 30–34, 35–39 and 40 years or more. Maternal smoking during pregnancy was classified as a binary variable (yes/no). The number of previous births was categorized as 0, 1, 2, 3 or 4 or more. A mother was defined as having a psychiatric history if she had any of the following diagnoses registered in the FHDR during her lifetime: F10-F99 based on the ICD-10 (mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related and somatoform disorders; behavioral syndromes associated with physiological disturbances and physical factors; disorders of adult personality and behaviour; disorders of psychological

development; behavioral and emotional disorders with onset usually occurring in childhood and adolescence and unspecified mental disorder). Corresponding diagnoses based on the ICD-9 (291–316) and the ICD-8 (291–309) were also included: psychosis, neurotic disorders, personality disorders, and other nonpsychotic mental disorders. Maternal psychiatric history was classified as a binary variable (yes/no). Major congenital anomalies as defined by the RCM were classified as a binary variable (yes/no). Only major congenital anomalies detected before the age of one year were included. Minor anomalies were excluded according to the exclusion list of European Registration of Congenital Anomalies (EUROCAT). If a child had more than one major congenital anomaly of one organ system, those anomalies were treated as one outcome of the organ system. Maternal SES categories were based on existing national classifications that are used in the FMBR: upper white collar workers, lower white collar workers, blue collar workers and others (e.g. students and housewives).

Statistical analyses

Conditional logistic regression models were used to examine the association between the ASD outcome and birth weight factors. In the first stage we estimated unadjusted odds ratios (OR) and 95% confidence intervals (CI). As maternal SES and smoking during pregnancy were considered to be potentially collinear, we assessed for this by fitting a model with both maternal SES and smoking during pregnancy as potential confounding factors (model I), followed by models with only smoking (model II) and only maternal SES (model III). When comparing the results between model I and II, and between model I and model III, we noticed large changes in the estimated ORs due to large standard errors when either smoking or maternal SES was excluded from the models. Smoking during pregnancy and maternal SES were highly correlated ($p<.001$, data available on request), and were therefore considered to be multicollinear. Hence, we excluded maternal SES from the adjusted model and treated smoking during pregnancy as a potential confounding factor, given that the latter variable served as an excellent proxy measure for maternal SES. Furthermore, there was a statistically significant correlation between maternal smoking and low birth weight, very preterm birth and SGA. The correlations between maternal smoking and low birth weight, very preterm birth, and SGA, respectively, were 0.084, −0.056, and −0.027. Maternal smoking accounted for 0.07% ($p<.0001$), 0.31% ($p<.0001$) and 0.70% ($p<.0001$) of the variability in low birth weight, very preterm birth and SGA, respectively. Thus, statistical significance was considered to be mainly a result of the large sample size. The correlation between maternal smoking and maternal psychiatric diagnoses was 0.092 and smoking explained 0.85% of the variability in maternal psychiatric diagnosis ($p<.0001$). These variables are not considered as multicollinear and were therefore included in the same model. In the second stage of the analysis we estimated the ORs and 95% CIs for birth weight, gestational age and SGA/AGA/LGA-status on ASD risk, adjusting for smoking during pregnancy, maternal age, and number of previous births, maternal psychiatric history and major congenital anomalies. As low birth weight can be a consequence of both prematurity and poor intrauterine growth, we estimated the ORs and 95% CIs for gestational age, adjusting for SGA/AGA/LGA-status as an additional covariate. In all analyses, a two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SAS statistical software.[23]

RESULTS

Frequencies of ASD cases and controls according to birth weight, gestational age and SGA/AGA/LGA status are shown in Table I. Based on these data,[13] the prevalence of childhood autism among children 19 years or younger was 9 per 10 000 by the end of 2005. The prevalences of Asperger syndrome and PDD were 14.5 and 14.6 per 10 000. Table II gives

the associations between childhood autism, Asperger syndrome and PDD and birth weight characteristics. In unadjusted analyses, low birth weight (< 2500 grams), very low gestational age (< 32 weeks) and SGA were associated with both childhood autism and PDD, and high gestational age (42 weeks or more) and SGA were associated with Asperger syndrome.

When the results were adjusted for the effects of potential confounders, i.e. maternal age, smoking during pregnancy, maternal psychiatric history, number of previous births and major congenital anomalies, the associations between low birth weight, low gestational age, and SGA and childhood autism remained statistically significant (Table II). Very low birth weight (VLBW, < 1500g) infants had a greater than three-fold increased odds of autism compared with the normal birth weight (2500–3999g) infants (OR 3.1, CI 1.4, 6.5, p=.004). Low birth weight infants (< 2500g) had a 60% increased odds of autism (OR 1.6, CI 1.05, 2.3, p=.029). Very low gestational age infants (less than 32 weeks) were two and one half times more likely to develop autism compared with term infants (OR 2.5, CI 1.3, 5.0, p=.009). SGA infants had a 70% increased odds for childhood autism compared with AGA infants (OR 1.7, CI 1.1, 2.6, p=.009). Prematurity was an independent risk factor for childhood autism and PDD even after adjustment for impaired fetal growth (data available on request). There were no significant associations between Asperger syndrome and birth weight, gestational age or SGA/AGA/LGA status. PDD was statistically significantly associated with very low birth weight, low gestational age, and SGA. VLBW infants had a greater than threefold increased odds for PDD (OR 3.4, CI 1.9, 6.3, p<.001) compared with normal birth weight infants. Low birth weight infants had a nearly two-fold increased odds for PDD (OR 1.8, CI 1.4, 2.4, p<.001) compared with the normal birth weight infants. In addition, very low gestational age infants had a greater than two-fold increased odds for PDD compared with term infants (OR 2.5, CI: 1.4, 4.3, p<.001). SGA infants were over twice more likely to develop PDD compared with AGA infants (OR 2.2, CI 1.7, 3.0, p<.001). Due to an increased vulnerability of males to ASD, we conducted a secondary analysis including only males. The same risk factors remained statistically significant (data available on request).

DISCUSSION

This population-based study examined the association between three birth characteristics (birth weight, gestational age and SGA/AGA/LGA status) and each of the three most common subtypes of ASD, childhood autism, Asperger syndrome and PDD. Childhood autism and PDD were associated with all three factors. No associations were found between Asperger syndrome and birth weight, gestational age or SGA/AGA/LGA-status after controlling for potential confounders. Our findings indicate that risk factors might be different for ASD subtypes. The autism spectrum is usually defined based on similarities in symptoms. Given the likely multifactorial etiology of ASD, it is conceivable that different etiologic factors (in this case birth characteristics) can be related to different syndromes within the spectrum.

These findings indicate that both intrauterine growth restriction and very preterm birth are related to risk of childhood autism and PDD. Based on this study, prematurity was an independent risk factor for childhood autism and PDD even after adjustment for impaired fetal growth. There appeared to be dose-response effects between prematurity and both childhood autism and PDD as the risk ratios increased with decreasing gestational age. Our findings confirm the results of previous studies showing an association between childhood autism and low birth weight[1,3–5] and prematurity.[4] Furthermore, VLBW and prematurity are associated with neurodevelopmental and intellectual disabilities, such as learning

disabilities, attention problems and poor executive function[24–27] that are often present in children diagnosed with ASD.[28]

Premature infants with very low birth weight often need long hospitalizations in the neonatal intensive care unit (NICU). The infants in the NICU are treated with highly advanced medical technology and the number of survivors has increased, but neurodevelopmental consequences still exist.[29] The NICU infants may experience postnatal complications such as intraventricular hemorrhages and white matter injuries, which may mediate the effects of intrauterine growth restriction and prematurity on the risks of autism and PDD. It has been suggested that the proportion of NICU infants that are later classified with ASD has increased.[30] It is also possible that the environment of the NICU adversely affecting physiological, emotional and social maturation may result in negative effects on child neurodevelopment.[29,31–33] Another possibility is that prematurity/VLBW and ASD may share similar neurodevelopmental antecedents, including exposure to adverse prenatal factors such as infection, nutritional deficits, hypoxia, and other obstetric insults, as well as genetic susceptibilities.

Both childhood autism and PDD were associated with SGA. The association between childhood autism and SGA is consistent with findings from previous population-based studies from the Nordic countries[1,4,5], and there is a lack of previous studies of the association between SGA and PDD. The finding that SGA incurs over a two-fold increased risk specifically for PDD has not been demonstrated in previous research. Consistent with our results, the magnitude of the association between SGA and childhood autism in previous studies was rather low; odds ratios have varied between one and two. Additionally, in the study by Buchmayer et al[11] a similar association was found between SGA and the broader group of ASD.

There are several possible explanations for the findings related to SGA. First, there may be shared genetic mechanisms for SGA and ASD.[2] Recently, a polymorphism in the gene for insulin-like growth factor-I (IGF-I) was found to be associated with lower birth weight (weight reduction of 215 g compared with subjects without the polymorphism).[34] Conceivably, this or other genes that predispose to low birth weight may also account for part of the association between this exposure and childhood autism and PDD. Second, parallel to VLBW, SGA is a marker of several prenatal risk factors that may be associated with autism such as fetal hypoxia, placental pathology, pre-eclampsia or infections during pregnancy.[1,2,22,35,36] Third, maternal risk behaviours, such as smoking, alcohol or other substance use, have been associated with low birth weight, prematurity[37] and neuropsychiatric morbidity.[38,39]

Asperger syndrome was not associated with birth weight, gestational age or SGA status when adjusted for confounding factors. Our results are similar to a recent Swedish study[12] which found no associations between obstetric risk factors (prematurity, low Apgar scores, growth restriction, or macrosomia) and Asperger syndrome. Most previous studies of risk factors for Asperger syndrome, however, have been either clinic-based or limited to rather small sample sizes.[40,41] These findings suggest that susceptibility genes and/or prenatal risk factors for retarded fetal growth or prematurity may have a lower prevalence in Asperger syndrome than other ASD.

The main strengths of this study include: (1) a large, population-based sample of 1.1 million births, yielding high statistical power to demonstrate associations; (2) inclusion of cases treated in both inpatient and outpatient settings, which increases the generalizability of the findings and may reduce bias; (3) high quality and completeness (eg, <0.1% missing of birth weight and gestational age information, limiting the potential for diagnostic

misclassification).[42,43] In Finland, most hospitals follow the VLBW infants up to 2 years of age and thereafter according to clinical judgment. This follow-up, unfortunately, is not sufficient to diagnose all ASD. However, all children are also followed by child welfare clinics that are responsible for screening developmental problems, such as symptoms of ASD. As noted before, child welfare clinics are an important part of primary health care settings, referring children with ASD symptoms to more specialized services. However, this study has limitations that need to be considered. First, cases were classified based on discharge diagnoses from the FHDR. Consequently, some diagnostic misclassification is likely to exist. However, as reported previously,[44] 77 of 80 subjects with register-based diagnoses of childhood autism fulfilled the diagnostic criteria according to the Autism Diagnostic Interview – Revised (ADI-R), indicating high validity of register-based diagnoses of childhood autism. At present, validation studies for the other diagnoses (Asperger syndrome or PDD) have not been conducted. Thus, results regarding these diagnoses may be viewed with somewhat less confidence than those regarding the associations with childhood autism. However, because in Finland the clinical assessment of any ASD is done in specialized services mostly by specialists in child psychiatry or pediatric neurology, we believe that the validity of the diagnoses of Asperger syndrome and PDD is at least satisfactory. Second, because the FHDR includes children who have been referred from the child health clinics to specialized services; it is probable that many cases with mild symptoms are missing. However, we expect the coverage of moderate and severe ASD cases to be good, for three reasons. First all children in Finland under school age (7 years) visit child health clinics at least once a year. Second, similar to other Nordic countries such as Sweden and Denmark, Finland has a public health system which covers for all treatments for ASD. Third, all inpatient treatment for ASD and all outpatient treatment for these disorders since 1998 are coded in the FHDR. Therefore, a child with moderate or severe symptoms of ASD will most likely be referred to specialized services for diagnostic assessment and possible treatment, and subsequently become registered in the FHDR. Since the inclusion of outpatient diagnoses in the FHDR began in 1998, we were not able to include cases that were diagnosed and treated only in outpatient units prior to that year. However, since the most recent diagnosis was used for case identification, and ASD is generally a chronic condition, we expect that this would have captured many cases treated exclusively as outpatients with onset prior to 1998 in our study sample. Finally, the issue of emigration from the cohort needs to be considered. Although emigration can be viewed as a potential cause of selection bias, if it is related to birth complications and ASD, it should be noted that the emigration rate is very low in Finland; during the study period the annual rate has varied between 0.2–0.4%.[58] Hence, emigration is expected to have played a very small role, if at all, in influencing the findings.

We have demonstrated that low birth weight, very low gestational age and SGA are related to increased risks of childhood autism and PDD. The findings may have important implications for understanding prenatal risk factors and susceptibility genes for ASD that may impair fetal growth and/or lead to premature birth. The fact that different risk factors were found for childhood autism and PDD on the one hand, and Asperger syndrome on the other, suggests that different vulnerability factors and their interactions may be responsible. These findings stimulate search for specific environmental factors and genes that act during the prenatal period to increase the susceptibility for ASD.

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Abbreviations

ASD	autism spectrum disorder
PDD	pervasive developmental disorder
SGA	small for gestational age
OR	odds ratio
CI	confidence interval

References

1. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology (Cambridge, Mass). 2002; 13:417–23.
2. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics. 2008; 121:1155–64. [PubMed: 18519485]
3. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. J Autism Dev Disord. 2001; 31:279–85. [PubMed: 11518482]
4. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005; 161:916–25. discussion 926–8. [PubMed: 15870155]
5. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand. 2006; 114:257–64. [PubMed: 16968363]
6. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009; 123:1293–300. [PubMed: 19403494]
7. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: Who is at risk? J Autism Dev Disord. 2002; 32:217–24. [PubMed: 12108623]
8. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: A population study. Arch Gen Psychiatry. 2004; 61:618–27. [PubMed: 15184241]
9. Stein D, Weizman A, Ring A, Barak Y. Obstetric complications in individuals diagnosed with autism and in healthy controls. Compr Psychiatry. 2006; 47:69–75. [PubMed: 16324905]
10. Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child Care Health Dev. 2008; 34:249–56. [PubMed: 18257794]
11. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparen P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics. 2009; 124:e817–25. [PubMed: 19841112]
12. Haglund NG, Kallen KB. Risk factors for autism and Asperger syndrome: Perinatal factors and migration. Autism. 2010; 15:163–83. [PubMed: 20923887]
13. Lampi KM, Banerjee PN, Gissler M, Hinkka-Yli-Salomäki S, Huttunen J, Kulmala U, et al. Finnish prenatal study of autism and autism spectrum disorders (FIPS-A): Overview and design. J Autism Dev Disord. 2011; 41:1090–6. [PubMed: 21082229]
14. Artama M, Gissler M, Malm H, Ritvanen A. the Drugs and pregnancy –pilot study group. Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996–2006. Pharmacoepidemiol Drug Saf. 2011; 20:729–38. [PubMed: 21626607]
15. Pihkala J, Hakala T, Voutilainen P, Raivio K. Uudet suomalaiset sikiön kasvukäyrät. Duodecim. 1989; 105:1540–6. [PubMed: 2680445]
16. Newburn-Cook CV, Onyskiw JE. Is older maternal age a risk factor for preterm birth and fetal growth restriction? A systematic review. Health Care Women Int. 2005; 26:852–75. [PubMed: 16214797]

17. Agrawal A, Scherrer JF, Grant JD, Sartor CE, Pergadia ML, Duncan AE, et al. The effects of maternal smoking during pregnancy on offspring outcomes. Prev Med. 2010; 50:13–8. [PubMed: 20026103]
18. Aliyu MH, Salihu HM, Keith LG, Ehiri JE, Islam MA, Jolly PE. High parity and fetal morbidity outcomes. Obstet Gynecol. 2005; 105(5 Pt 1):1045–51. [PubMed: 15863543]
19. Maimburg RD, Bech BH, Vaeth M, Moller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. Pediatrics. 2010; 126:872–8. [PubMed: 20937652]
20. Lee HC, Lin HC. Maternal bipolar disorder increased low birthweight and preterm births: A nationwide population-based study. J Affect Disord. 2010; 121:100–5. [PubMed: 19501914]
21. Wier ML, Yoshida CK, Odouli R, Grether JK, Croen LA. Congenital anomalies associated with autism spectrum disorders. Dev Med Child Neurol. 2006; 48:500–7. [PubMed: 16700944]
22. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: A review and integration of findings. Arch Pediatr Adolesc Med. 2007; 161:326–33. [PubMed: 17404128]
23. SAS Version 9.2. SAS Institute Inc; Cary, NC:
24. Aarnoudse-Moens CSH, Weisglas Kuperus N, van Goudoever J, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009; 124:717. [PubMed: 19651588]
25. Aram DM, Hack M, Hawkins S, Weissman BM, Borawski-Clark E. Very-low-birthweight children and speech and language development. J Speech Hear Res. 1991; 34:1169–79. [PubMed: 1749247]
26. McCormick MC, Gortmaker SL, Sobol AM. Very low birth weight children: Behavior problems and school difficulty in a national sample. J Pediatr. 1990; 117:687–93. [PubMed: 2231200]
27. Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age. the collaborative project on preterm and small for gestational age infants (POPS) in the Netherlands. Lancet. 1991; 338:33–6. [PubMed: 1711644]
28. Gadow KD, DeVincent CJ, Pomeroy J. ADHD symptom subtypes in children with pervasive developmental disorder. J Autism Dev Disord. 2006; 36:271–83. [PubMed: 16477513]
29. Vandenberg KA. Individualized developmental care for high risk newborns in the NICU: A practice guideline. Early Hum Dev. 2007; 83:433–42. [PubMed: 17467932]
30. Karmel BZ, Gardner JM, Meade LS, Cohen IL, London E, Flory MJ, et al. Early medical and behavioral characteristics of NICU infants later classified with ASD. Pediatrics. 2010; 126:457–67. [PubMed: 20679296]
31. Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, et al. Early experience alters brain function and structure. Pediatrics. 2004; 113:846–57. [PubMed: 15060237]
32. Gooding JS, Cooper LG, Blaine AI, Franck LS, Howse JL, Berns SD. Family support and family-centered care in the neonatal intensive care unit: Origins, advances, impact. Semin Perinatol. 2011; 35:20–8. [PubMed: 21255703]
33. Latva R, Lehtonen L, Salmelin RK, Tamminen T. Visiting less than every day: A marker for later behavioral problems in Finnish preterm infants. Arch Pediatr Adolesc Med. 2004; 158:1153–7. [PubMed: 15583100]
34. Vaessen N, Janssen JA, Heutink P, Hofman A, Lamberts SW, Oostra BA, et al. Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. Lancet. 2002; 359:1036–7. [PubMed: 11937187]
35. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics. 2001; 107:E63. [PubMed: 11335784]
36. Burstyn I, Wang X, Yasui Y, Sithole F, Zwaigenbaum L. Autism spectrum disorders and fetal hypoxia in a population-based cohort: Accounting for missing exposures via estimation-maximization algorithm. BMC Med Res Methodol. 2011; 11:2. [PubMed: 21208442]
37. Kelly RH, Russo J, Holt VL, Danielsen BH, Zatzick DF, Walker E, et al. Psychiatric and substance use disorders as risk factors for low birth weight and preterm delivery. Obstet Gynecol. 2002; 100:297–304. [PubMed: 12151153]

38. Ekblad M, Gissler M, Lehtonen L, Korkeila J. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Arch Gen Psychiatry. 2010; 67:841–9. [PubMed: 20679592]

39. Johnson JL, Leff M. Children of substance abusers: Overview of research findings. Pediatrics. 1999; 103(5 Pt 2):1085–99. [PubMed: 10224196]

40. Gillberg C. Asperger syndrome in 23 Swedish children. Dev Med Child Neurol. 1989; 31:520–31. [PubMed: 2680690]

41. Gillberg C, Cederlund M. Asperger syndrome: Familial and pre- and perinatal factors. J Autism Dev Disord. 2005; 35:159–66. [PubMed: 15909402]

42. Gissler M, Shelley J. Quality of data on subsequent events in a routine medical birth register. Med Inform Internet Med. 2002; 27:33–8. [PubMed: 12509121]

43. Teperi J. Multi method approach to the assessment of data quality in the Finnish medical birth registry. J Epidemiol Community Health. 1993; 47:242–7. [PubMed: 8350040]

44. Lampi KM, Sourander A, Gissler M, Niemelä S, Rehnström K, Pulkkinen E, et al. Brief report: Validity of Finnish registry-based diagnoses of autism with the ADI-R. Acta Paediatr. 2010; 99:1425–8. [PubMed: 20412100]

Table 1

Birth weight, gestational age, and weight for gestational age in ASD cases and controls

	Childhood Autism		Asperger Syndrome		PDD	
Risk factors	**cases (*n*=1132)**	**controls (*n*=4515)**	**cases (*n*=1785)**	**controls (*n*=7114)**	**cases (*n*=1796)**	**controls (*n*=7148)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Birth weight (g)						
<1500	18 (1.6)	36 (0.8)	15 (0.8)	61 (0.9)	34 (1.9)	56 (0.8)
1500–2499	41 (3.6)	105 (2.3)	45 (2.5)	146 (2.1)	85 (4.7)	159 (2.2)
2500–3999	829 (73.2)	3396 (75.2)	1348 (75.5)	5316 (74.7)	1324 (73.7)	5359 (75.0)
4000–4499	189 (16.7)	799 (17.7)	305 (17.1)	1278 (18.0)	283 (15.8)	1274 (17.8)
4500 or more	55 (4.9)	179 (4.0)	72 (4.0)	313 (4.4)	70 (3.9)	300 (4.2)
Gestational age (weeks)						
≤ 31	14 (1.3)	26 (0.6)	8 (0.5)	41 (0.6)	24 (1.4)	34 (0.5)
32–37	108 (9.6)	405 (9.0)	179 (10.1)	596 (8.4)	199 (11.2)	652 (9.2)
38–41	946 (84.2)	3851 (85.9)	1473 (83.1)	6083 (86.0)	1472 (82.7)	6103 (85.9)
42 or more	56 (5.0)	202 (4.5)	113 (6.4)	352 (5.0)	84 (4.7)	315 (4.4)
Weight for gestational age *						
SGA	39 (3.5)	94 (2.1)	41 (2.3)	113 (1.6)	82 (4.6)	123 (1.7)
AGA	1050 (93.4)	4258 (95.0)	1671 (94.3)	6717 (95.0)	1632 (91.9)	6736 (94.8)
LGA	35 (3.1)	129 (2.9)	61 (3.4)	241 (3.4)	62 (3.5)	245 (3.5)

* SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age

Table 2

Associations between ASD subtypes and birth weight, gestational age and weight for gestational age

	Childhood Autism						Asperger Syndrome						PDD					
	Unadjusted analysis			Adjusted analysis**			Unadjusted analysis			Adjusted analysis**			Unadjusted analysis			Adjusted analysis**		
Risk factors	**OR**	**95 %CI**	**p**	**OR**	**95 %CI**	**p**	**OR**	**95 %CI**	**p**	**OR**	**95 %CI**	**p**	**OR**	**95 %CI**	**p**	**OR**	**95 %CI**	**p**
Birth weight (g)																		
<1500	2.03	1.1, 3.6	.02	3.05	1.4, 6.5	.004	0.97	0.5, 1.7	.92	0.90	0.4, 2.0	.79	2.54	1.6, 4.0	<.001	3.44	1.9, 6.3	<.001
1500–2499	1.62	1.1, 2.3	.01	1.57	1.05, 2.3	.03	1.22	0.9, 1.7	.25	0.99	0.7, 1.4	.96	2.17	1.7, 2.9	<.001	1.81	1.4, 2.4	<.001
2500–3999	REF			REF			REF			REF			REF			REF		
4000–4499	0.97	0.8, 1.2	.69	0.92	0.8, 1.1	.40	0.94	0.8, 1.1	.39	1.07	0.9, 1.2	.38	0.90	0.8, 1.03	.13	0.97	0.8, 1.1	.72
4500 or more	1.26	0.9, 1.7	.14	1.26	0.9, 1.7	.16	0.91	0.7, 1.2	.47	1.11	0.8, 1.5	.46	0.95	0.7, 1.2	.68	1.01	0.8, 1.3	.94
Gestational age (weeks)																		
≤ 31	2.16	1.1, 4.2	.02	2.51	1.3, 5.0	.009	0.80	0.4, 1.7	.56	0.73	0.3, 1.6	.43	2.88	1.7, 4.9	<.001	2.46	1.4, 4.3	.001
32–37	1.11	0.9, 1.4	.38	1.12	0.9, 1.4	.36	1.24	1.04, 1.5	.02	1.15	0.96, 1.4	.14	1.26	1.1, 1.5	.007	1.14	0.95, 1.4	.15
38–41	REF			REF			REF			REF			REF			REF		
42 or more	1.13	0.8, 1.5	.42	1.16	0.8, 1.6	.37	1.34	1.1, 1.7	.01	1.15	0.9, 1.4	.24	1.11	0.9, 1.4	.40	1.10	0.9, 1.4	.47
Weight for gestational age *																		
SGA	1.69	1.2, 2.5	.007	1.72	1.1, 2.6	.009	1.46	1.02, 2.1	.04	1.29	0.9, 1.9	.18	2.76	2.1, 3.7	<.001	2.24	1.7, 3.0	<.001
AGA	REF			REF			REF			REF			REF			REF		
LGA	1.10	0.7, 1.6	.64	1.12	0.8, 1.7	.57	1.01	0.8, 1.3	.95	1.23	0.9, 1.7	.18	1.05	0.8, 1.4	.72	1.04	0.8, 1.4	.79

*SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age

**Adjusted for maternal age, maternal psychiatric history, previous births, congenital anomalies and smoking during pregnancy.