

Perinatal Risk Factors for Infantile Autism

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Background. Etiologic hypotheses in infantile autism suggest a strong genetic component, as well as possible environmental risks linked to early fetal development. We evaluated the association of maternal, pregnancy, delivery, and infant characteristics and risk of infantile autism.

Methods. We conducted a case-control study nested within a population-based cohort (all Swedish children born in 1974–1993). We used prospectively recorded data from the Swedish Birth Register, which were individually linked to the Swedish Inpatient Register. Cases were 408 children (321 boys and 87 girls) discharged with a main diagnosis of infantile autism from any hospital in Sweden before 10 years of age in the period 1987–1994, plus 2,040 matched controls. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results. The risk of autism was associated with daily smoking in early pregnancy (OR = 1.4; CI = 1.1–1.8), maternal birth outside Europe and North America (OR = 3.0; CI = 1.7–5.2), cesarean delivery (OR = 1.6; CI = 1.1–2.3), being small for gestational age (SGA; OR = 2.1; CI = 1.1–3.9), a 5-minute Apgar score below 7 (OR = 3.2, CI = 1.2–8.2), and congenital malformations (OR = 1.8, CI = 1.1–3.1). No association was found between autism and head circumference, maternal diabetes, being a twin, or season of birth.

Conclusions. Our findings suggest that intrauterine and neonatal factors related to deviant intrauterine growth or fetal distress are important in the pathogenesis of autism.

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Key words: infantile autism, perinatal, risk factors, maternal, intrauterine growth.

Autistic disorder in children is manifested by impaired social interactions; communication deviance; and restricted, stereotypical behavioral patterns. Autism occurs at a rate of at least 1/1,000 births.^{1,2} The etiology of the disorder is thought to be largely genetically determined,³ although early environmental insults affecting brain development (such as intrauterine exposure to rubella, thalidomide, or valproate) may also be associated with autism.^{4,5} Infants with autism have been reported to have an increased frequency of pre- and perinatal complications compared with unaffected siblings or unrelated controls.^{6–8} The incidence of autistic disorder in survivors of neonatal

intensive care appears to be elevated.⁹ It has been hypothesized that pregnancy, delivery, or neonatal complications may act through independent etiologic pathways to increase the risk of autism or may interact with a genetic disposition to increase the risk by interfering at critical times in the developmental process.¹⁰ However, there has been no consistent pattern of specific prenatal and perinatal risk factors associated with autism.^{10,11} Small samples, different types of control group, variations in diagnostic criteria, and distribution of gender may partially account for contradictory findings. We used nationwide Swedish registers of births and hospital admissions to study the question of whether unfavorable perinatal conditions and aberrations in physical size at birth predispose to infantile autism.

Methods

Register Merging

The Swedish National Board of Health and Welfare gave access to data from the Medical Birth Register and the Inpatient Register. Individual record linkage was possible through the unique personal identification number assigned to each Swedish resident. The Inpatient Register includes data on hospital discharges and diagnoses classified by the treating physician according

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to the ninth revision of the *International Classification of Diseases* (ICD-9) from 1987 to 1996. The treating psychiatrist (usually the consultant or a junior physician in collaboration with a senior physician) completes the assessment of main diagnosis (and secondary diagnoses if occurring) at the time of discharge from hospital. The diagnostic assessment is then forwarded on a computer medium to the Inpatient Register. These routines are standardized across Sweden. The register provides nationwide coverage from 1986 onward.¹² The register does not cover outpatient care.

We obtained exposure information from the Medical Birth Register, established in 1973. This register includes information collected prospectively, starting with the first antenatal visit through the time when mother and child are discharged from the hospital after delivery. This information is provided through antenatal, obstetrical, and neonatal records, which have been in common use in Sweden since 1973. Antenatal care routines are standardized. More than 95% of pregnant women receive antenatal care before the fifteenth gestational week, and 90% of the pregnant population have at least nine visits for antenatal care.¹³ Complications during pregnancy, delivery, and the neonatal period are classified according to ICD-8 from 1983 to 1986, and ICD-9 thereafter. More than 99% of all births in Sweden are included in the Medical Birth Register.¹⁴

Study Sample

We designed a case-control study nested in a population-based cohort defined by all infants born alive in Sweden from 1974 through 1993. The case sample was composed of 408 children (321 boys and 87 girls) registered in the Medical Birth Register who, at the age of 9 years or younger, had been discharged from a Swedish psychiatric or general hospital with a main diagnosis of infantile autism (ICD-9 code 299A). Pervasive developmental disorders not otherwise specified are not included. As no ICD-9 code of autism was available before ICD-9 was introduced in 1987, the study was restricted to include subjects diagnosed from 1987 through 1994. For each case, we selected from the Medical Birth Register five controls who were individually matched by sex, year, and hospital of birth, resulting in a control sample of 2,040 infants. The controls were all alive and had no diagnosis of autism in the Inpatient Registry at the time of diagnosis of the case subject. The study was approved by the Research Ethics Committee at the Karolinska Institutet (Stockholm, Sweden).

Risk Factors

We selected the following potential prenatal and neonatal risk factors for infantile autism.

Maternal Characteristics

Maternal characteristics were mother's age (in completed years at the birth of the infant), parity (including present birth), maternal cigarette smoking during pregnancy (categorized into daily and nondaily smoking, as collected by midwives at registration for antenatal care), and mother's country of birth (categories were Nordic countries [Sweden, Norway, Denmark, Finland, and Iceland], other European countries and North America, and countries outside Europe and North America).

Pregnancy and Delivery Complications

We selected the following pregnancy and delivery complications as potential risk factors for infantile autism: hypertensive diseases during pregnancy (ICD-8 codes 401 and 637 and ICD-9 code 642), uterine atony (weak contractions during labor; ICD-8 codes 657.0 and 657.1 and ICD-9 codes 661A–C), pregestational and gestational diabetes (ICD-8 code 250 and ICD-9 codes 250, 648A, and 648W), bleeding during pregnancy (ICD-8 codes 632 and 651 and ICD-9 code 641), vacuum extraction, and cesarean delivery.

Infant Characteristics

Infant characteristics were gestational age (in completed gestational weeks according to the last menstrual period), birth weight (in grams), birth length (in centimeters), head circumference (in centimeters), small or large size for gestational age (2 standard deviations below or above the mean birth weight for the gestational age according to Swedish birth weight standards¹⁵), twin birth, Apgar scores at 5 minutes, and congenital malformations (ICD-8 and ICD-9 codes 740–759). Season of birth was categorized into the periods January–April and May–December.¹⁶

Statistical Analysis

We expressed associations of maternal and perinatal characteristics with autism as odds ratios (ORs) modeled in conditional logistic regression analyses.¹⁷ The independent variables were treated categorically to allow us to examine the effect of each variable on risk of later developing infantile autism. We calculated univariate and adjusted odds ratios, together with their 95% confidence intervals (CIs), to identify variables independently associated with a subsequent diagnosis of autism. Because delivery and infant characteristics may lie in the causal pathway between maternal characteristics and risk of autism, the multivariate analyses were performed within two main data domains: first, maternal characteristics (confined to 321 cases, because maternal smoking during pregnancy was not included in the Medical Birth Register before 1983), and second, delivery and infant characteristics.¹⁸ Finally, utilizing likelihood ratio tests, we constructed a model allowing for all variables. Because the model assumes independence of observa-

tions, we excluded cases born as twins (three twin pairs with both twins autistic and five cases with a nonaffected twin sibling) and their individually matched controls in the final logistic regression model.

Results

The mean age at first admission with a main diagnosis of autism was 4.4 years for boys and 4.6 years for girls. A secondary diagnosis at discharge from the hospital was reported for 85 (21%) of the cases. The most common secondary diagnoses were moderate intellectual impairment (ICD-9 code 318A; 16 cases), unspecified intellectual impairment (ICD-code 319X; 12 cases), profound intellectual impairment (ICD-9 code 318B; 9 cases), epilepsy partialis complexa (ICD-9 code 345 M; 8 cases), and unspecified epilepsy (ICD-9 code 345X; 7 cases).

Table 1 presents crude odds ratios from the univariate analyses. A high maternal age (≥ 35 years), multiparity (≥ 4), daily smoking in early pregnancy, and maternal birth outside Europe or North America were associated with increased risk for autism in the univariate analyses. Increased risks of autism were also found in pregnancies complicated by hypertensive diseases, bleeding, and a number of delivery and infant characteristics, including cesarean delivery, preterm birth (≤ 36 weeks), low birth weight ($< 2,500$ gm), small or large size for gestational age, low Apgar score (0–6) at 5 minutes, and congenital malformations. The overrepresentation of congenital malformations in autistic children was largely attributable to an excess of heart and circulation malformations (ICD-9 codes 745, 746, and 747; OR = 2.5, CI = 1.1–5.8), palate and lip malformations (ICD-9 code 749; OR = 3.8, CI = 0.94–15.3), and genital malformation (ICD-9 code 752; OR = 2.3, CI = 1.1–4.8).

The multivariate analysis of the association between maternal and pregnancy characteristics and the risk of autism was restricted to 316 cases (77% of the total sample; data available with the electronic version of this article at <http://www.epidem.com>). Maternal birth outside Europe or North America (OR = 2.8; CI = 1.8–4.5) and daily smoking during pregnancy (OR = 1.4; CI = 1.1–1.8) were associated with increased risk for autism. Among maternal pregnancy complications, bleeding was associated with risk for autism (OR = 1.9; CI = 1.1–3.5), and a marginally increased risk for autism was observed among offspring to mothers with pregnancy-induced hypertension (OR = 1.7; CI = 1.0–2.8). Maternal diabetes, a high maternal age, and multiparity were not associated with autism in the multivariate model (data available online).

A multivariate analysis was also undertaken within the domain of delivery and infant characteristics (400 cases; data available with the electronic version of this

article at <http://www.epidem.com>). Risk for autism was increased among infants small for gestational age (OR = 2.3; CI = 1.5–3.7), large for gestational age (OR = 1.6; CI = 1.0–2.6), with a low (0–6) Apgar score at 5 minutes (OR = 2.5; CI = 1.2–5.6), with congenital malformations (OR = 1.5; CI = 0.96–2.4), and delivered by cesarean delivery (OR = 1.6; CI = 1.2–2.1). No association was found for preterm delivery (OR = 1.2; CI = 0.8–1.8), twin birth (OR = 0.7; CI = 0.3–1.6), or winter birth (OR = 1.1; CI = 0.9–1.4). Excluding twins (analysis based on 390 cases) did not change the risk estimates related to delivery and infant characteristics, except to increase slightly the risk estimate for low Apgar score (OR = 3.0; CI = 1.4–6.5).

To investigate the independent influence of maternal, delivery, and infant risk factors, these factors were all analyzed in the same model. Risks associated with maternal, delivery, and infant characteristics remained essentially unchanged (Table 2), indicating that the effects of delivery and infant factors were independent of maternal factors.

When we restricted the analysis of risk of autism related to maternal, delivery, and child characteristics to include only cases without a secondary diagnosis (including 255 cases and 1,316 controls), the estimates remained essentially unchanged (data available on request). Stratifying the study group in Table 2 according to birth time period (1973–1987, 186 cases in the adjusted model with full information on included variables, and in 1988–1993, 123 cases) did not reveal any consistent pattern of change in risk factors by time (data available on request).

Discussion

This case-control study, nested within a national unselected birth cohort, is the largest to address possible associations between perinatal measures and the subsequent development of infantile autism. The sample size allows reliable estimates of risk factors in multivariate analyses. We studied children with a uniform ICD-9 diagnosis identified before age 10 in the Swedish Inpatient Register, which generally is considered to have high validity and reliability.¹²

The register had a nationwide coverage of inpatient treatment facilities during the study period and includes care in child psychiatric clinics, special units for treatment of autistic disorders, and pediatric and other somatic clinics. We were not able to capture cases who were diagnosed and treated only as outpatients. Cases were diagnosed during an 8-year period, and during this time there may have been an increased awareness of autism, recognition of subtler variants, and changes in the criteria for diagnosis.² The selection of cases from inpatient care may have three major implications. First,

TABLE 1. Prenatal and Perinatal Characteristics of Cases and Controls and Univariate Associations with the Risk of Infantile Autism

Characteristic	Cases (N = 408)		Controls (N = 2,040)		Crude Odds Ratios	95% CI
	No.	%	No.	%		
Maternal age at delivery (years)						
≤19	9	2	94	4	0.5	0.3–1.0
20–34*	327	80	1,706	84	1.0	
≥35	72	18	240	12	1.6	1.2–2.1
Parity						
1	146	36	848	42	0.8	0.7–1.0
2–3*	217	53	1,050	51	1.0	
≥4	45	11	142	7	1.5	1.1–2.2
Smoking habits during pregnancy						
Nondaily*	215	53	1,202	59	1.0	
Daily	108	26	472	23	1.2	1.0–1.6
Unknown	85	21	366	18		
Mother's country of birth						
Nordic*	351	86	1,890	93	1.0	
Europe and North America	17	4	58	3	1.6	0.9–2.9
Outside Europe and North America	35	9	72	3	2.9	1.9–4.5
Unknown	5	1	20	1		
Hypertensive diseases						
No*	384	94	1,964	96	1.0	
Yes	24	6	76	4	1.6	1.0–2.6
Diabetes						
No*	404	99	2,029	99	1.0	
Yes	4	1	11	1	1.8	0.6–5.7
Pregnancy bleeding						
No*	391	96	1,993	98	1.0	
Yes	17	4	47	2	1.8	1.0–3.2
Mode of delivery						
Vaginal, noninstrumental*	301	74	1,643	81	1.0	
Vaginal, instrumental	20	5	132	6	0.8	0.5–1.3
Cesarean	87	21	265	13	1.8	1.4–2.4
Season of birth						
January–April	156	38	713	35	1.2	0.9–1.4
May–December*	252	62	1,327	65	1.0	
Twin membership						
Twin	11	3	46	2	1.2	0.6–2.4
Singleton*	397	97	1,993	98	1.0	
Unknown	0		1			
Gestational age (weeks)						
≤36	39	10	125	6	1.6	1.1–2.3
37–41*	328	80	1,745	86	1.0	
≥42	38	9	166	8	1.2	0.8–1.7
Missing	3	1	4			
Birth weight (gm)						
<2,500	37	9	93	5	2.2	1.4–3.2
2,500–4,499*	350	86	1,870	92	1.0	
≥4,500	18	4	66	3	1.5	0.9–2.5
Missing	3	1	11			
Head circumference (cm)						
<31	16	4	49	2	1.7	0.9–3.0
32–33	73	18	349	17	1.0	0.6–1.6
34–35*	187	46	936	46	1.0	
≥36	122	30	672	33	0.9	0.7–1.1
Missing	10	2	34	2		
Birth weight for gestational age						
SGA (<−2 SD)	35	9	71	3	2.8	1.8–4.4
AGA*	343	84	1,876	92	1.0	
LGA (> +2 SD)	24	6	78	4	1.7	1.0–2.7
Missing	6	1	15	1		
Apgar score at 5 minutes						
0–6	12	3	17	1	3.5	1.7–7.4
7–10*	392	96	1,998	98	1.0	
Missing	4	1	25	1		
Congenital malformations						
Yes	28	7	91	4	1.6	1.0–2.5
No*	380	93	1,949	96	1.0	

SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age; SD = standard deviation.

* Reference category.

we likely have an overrepresentation of more severely affected cases that at least temporarily demanded hospital care for a more careful diagnosis or extended treat-

ment. The low frequency of secondary diagnoses does not, however, indicate more severe or atypical autism associated with other medical conditions. Secondly, we

TABLE 2. Adjusted Odds Ratios for Incidence of Autism in Relation to Maternal, Delivery, and Infant Characteristics*

	Odds Ratio	95% CI
Maternal age (years)		
≤19	0.6	0.3–1.4
20–34†	1.0	
≥35	1.3	0.9–1.9
Parity		
1	0.9	0.6–1.1
2–3†	1.0	
≥4	1.3	0.8–2.1
Smoking habits during pregnancy		
Nondaily†	1.0	
Daily	1.4	1.1–1.8
Mothers' country of birth		
Nordic†	1.0	
Europe and North America	1.1	0.5–2.5
Outside Europe and North America	3.0	1.7–5.2
Hypertensive diseases		
No†	1.0	
Yes	1.6	0.9–2.9
Diabetes		
No†	1.0	
Yes	1.2	0.3–5.7
Pregnancy bleeding		
No†	1.0	
Yes	1.6	0.8–3.3
Mode of delivery		
Vaginal†	1.0	
Cesarean	1.6	1.1–2.3
Season of birth		
January–April	1.3	0.96–1.6
May–December†	1.0	
Gestational age (weeks)		
≤36	0.9	0.5–1.6
37–41†	1.0	
≥42	1.0	0.6–1.6
Birth weight for gestational age		
SGA (<–2 SD)	2.1	1.1–3.9
AGA†	1.0	
LGA (> +2 SD)	1.6	0.9–2.8
Apgar score at 5 minutes		
0–6	3.2	1.2–8.2
7–10†	1.0	
Congenital malformations		
Yes	1.8	1.1–3.1
No†	1.0	

* 316 cases and 1,436 controls included in the analyses. Results for each variable are controlled for all other variables in the model. SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age.

† Reference category.

cover only a proportion of cases on a population base. We estimate that we have a coverage of about 50% of expected cases (based on the prevalence figures of Gillberg and Wing² and Fombonne¹⁹) and considering our inclusion years, the coverage of both rural and urban areas, and our narrow definition of autism and age cutoff points. Thirdly, the homogeneity of the risk factors by time period of the study might be questioned. However, stratifying the study group according to time period did not reveal any consistent changes in risk factors by time.

The quality of the exposure variables from the Swedish Medical Birth Register is high,²⁰ and a matching procedure by year and hospital of birth ensures conformity of diagnostic routines and obstetric care between cases and controls. We used exposure data routinely collected at the time of birth and so ascertainment bias

is not likely. Maternal smoking status refers to the first prenatal visit, and some women stop smoking later in pregnancy.²¹ However, this misclassification would only have diluted the results.²²

We found an excess of deviations from normal conditions in the prenatal and perinatal periods among infants who later manifested infantile autism. These results extend previous diverse but inconsistent findings.^{7,11} Specifically, increased risks of autism were obtained for small-for-gestational-age infants and for infants with congenital malformations or a low Apgar score, all of which suggest compromise of the infant. The risk associated with SGA was only slightly attenuated after we adjusted for factors known to influence fetal growth, such as maternal smoking, pregnancy-induced hypertensive diseases, and other maternal factors (maternal age and parity, and mother's country of birth). Information about socioeconomic status (SES) was not available, but SES is closely associated with maternal smoking and other included variables. Thus, we find it unlikely that also adjusting for SES would substantially influence the association between SGA and risk of autism.

Birth weight, birth length, and head circumference, as well as the pattern of intrauterine growth, have frequently been studied in other psychiatric disorders.^{23,24} The evidence on birth size and autism is not consistent,^{11,25} and birth weight for gestational age has been studied only retrospectively in small samples.²⁶ In the present investigation, a two-fold increase in risk was observed among infants born SGA. Such infants represent a heterogeneous group in terms of etiology. This condition is associated with a number of chromosomal and congenital anomalies, adverse asphyxic and metabolic outcomes,²⁷ and a higher incidence of chronic neurological handicaps.²⁸ An interaction between asphyxia and intrauterine growth retardation has been reported previously in studies of neurodevelopmental disorders.²⁹ Our finding of a three-fold increase in risk of autism among children with a low 5-minute Apgar score³⁰ also suggests an association between perinatal asphyxia and risk of autism.

Congenital malformations, well documented among autistic children,³¹ can be caused by genetic factors, chromosomal changes, drugs, chemicals, or infections. SGA infants (especially if premature) have the highest incidence of congenital anomalies of all gestational age and weight groups. Malformations in children with autism, particularly the elevated rate of minor craniofacial anomalies, have been interpreted as the result of an initiating injury around the time of neural tube closure.³² The most specific evidence is found in data regarding thalidomide-induced autism,³³ showing ear anomalies without limb anomalies in cases of autism. This suggests an injury between days 20 and 24, and abnormal devel-

opment very early in gestation. Growth aberrations and congenital malformations could be the result of similar factors, such as variations in levels of specific growth factors at critical embryonic stages, increased susceptibility to injury, or a decrease in the ability of the embryo to recover from an insult.

Daily smoking during pregnancy has not been associated previously with increased risk of autism. Nonetheless, other adverse effects of maternal smoking habits are well documented, especially with regard to fetal growth retardation.^{34,35} The long-term effects of fetal exposure to cigarette smoking on subsequent cognitive and physical development of the child are less clearly understood, but smoking has been associated with several childhood behaviors, including impulsive behavior, conduct disorder, and attention deficit hyperactivity disorder.^{36–38} The proposed underlying mechanisms include fetal hypoxia, changes in dopaminergic systems, and changes in the DNA and RNA synthesis in the brain.³⁷ Unfortunately, we were not able to examine the potential moderating effect of maternal psychopathologic factors and maternal alcohol or other drugs during pregnancy. The three-fold risk for autism among children of mothers born outside Europe or North America is striking and confirms earlier findings.³⁹ Selective migration of persons with a genetic vulnerability of autism or suffering from an autism spectrum disorder have been suggested to account for this finding.³⁹ Another possible explanation is a lack of immunity to certain viral infections during pregnancy, uncommon in the mother's country of origin.⁴⁰

Our observations support the possibility that a subgroup of children developing infantile autism suffer from intrauterine growth restriction and are exposed to adverse prenatal and neonatal asphyxia. Although several of the reported associations could be a function of genetic risk in the fetus,¹⁰ several of the findings are consistent with nongenetic environmental mediation of risks. Future studies should attempt to disentangle the effects of intrauterine environment and genetic factors on subsequent risk of infantile autism.

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