ORIGINAL ARTICLE

Perinatal Factors and the Development of Autism

A Population Study

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Background: Autism is considered to have a genetic basis, although exposure to certain stimuli in the prenatal period has been implicated to be causal in some cases. Some investigations have shown an association with obstetric complications but findings have been inconsistent owing to differences in sampling and methods.

Objective: To examine the association of obstetric factors with autism spectrum disorders for a cohort of children, using obstetric data contained in a statutory database collected at the time of birth.

Design: Subjects born in Western Australia between 1980 and 1995 and diagnosed with an autism spectrum disorder by 1999 were included as cases (n=465). Siblings of the cases (n=481) and a random population-based control group (n=1313) were compared with the cases on obstetric information contained in the Maternal and Child Health Research Database of Western Australia.

Results: Compared with control subjects, cases had significantly older parents and were more likely to be firstborn. Case mothers had greater frequencies of threatened abortion, epidural caudal anesthesia use, labor induction, and a labor duration of less than 1 hour. Cases were more likely to have experienced fetal distress, been delivered by an elective or emergency cesarean section, and had an Apgar score of less than 6 at 1 minute. Cases with a diagnosis of autism had more complications than those with pervasive developmental disorder not otherwise specified or Asperger syndrome. Nonaffected siblings of cases were more similar to cases than control subjects in their profile of complications.

Conclusions: Autism is unlikely to be caused by a single obstetric factor. The increased prevalence of obstetric complications among autism cases is most likely due to the underlying genetic factors or an interaction of these factors with the environment.

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AUTISM IS A DEVELOPMENTAL disorder that is characterized by severe impairment in social interaction and communication and by the presence of stereotypic behavior.[1] It has an estimated prevalence of 10 to 20 per 10 000 individuals.[2-4] Autism is diagnosed by clinical criteria,[1,5] usually around 3 to 4 years of age when social and communication milestones are not achieved. Symptoms are often noticed by 12 months of age,[6] and affected people show large individual differences in their symptomatology.[7] Autism is part of a spectrum of disorders that includes Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS).[1] The latter 2 diagnoses are made when affected individuals have fewer or milder symptoms. The prevalence of all autism spectrum disorders is estimated at approximately 60 per 10 000 people.[8]

The genetic basis of autism spectrum disorders is supported by clustering in families, higher concordance in monozygotic twins than in dizygotic twins, and evidence for the broader phenotype, or variable expressivity, in other family members.[9-13] The precise mechanisms leading to the development of autism or autistic symptoms are unknown, but it is likely that many different genes are involved.[14]

In some cases, neurological differences,[15-17] ear rotation,[18] and the distinct phalanx ratios[19] suggest that a prenatal influence has acted in a direct or contributory manner. Specific prenatal factors have also been observed.[20-30] The development of autistic symptoms may be dependent on the timing of exposure and/or genetic predisposition to certain environmental stimuli before birth.

During the past 30 years, numerous investigations have attempted to identify a pattern or causal pathway from the obstetric experience of people who develop autism. Generally, an increase in the number of obstetric complications has been observed, with the most consistent find-

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ings being advanced maternal age, maternal bleeding during early pregnancy, maternal medication use during pregnancy, and an increased risk of autism among firstborn infants. However, findings are inconsistent and often contradictory because of considerable variation in methods, sample size, variable selection, analyses, data quality, and control groups. Sample size has typically ranged between 53 and 87 cases,[31-35] with the larger samples using retrospectively collected obstetric data from medical records and/or maternal interviews.[36-38]

The largest and most recent study compared 408 children identified for autism in the Swedish Inpatient Register with 2040 matched infants from the Swedish Medical Birth Register.[39] The autism group was characterized by maternal smoking during early pregnancy, a cesarean section delivery, small size for gestational age, low Apgar scores, maternal birth outside Europe and North America, and congenital malformations. While the Hultman et al[39] study is large and rigorous, no comparison was made with siblings, thereby restricting the interpretation of the influence of either genetics or the maternal environment. An increase in obstetric complications has also been observed in some nonautistic sibling groups,[31,40] suggesting that autism is not necessarily caused by the complications but rather may be an epiphenomenon of a strongly genetic disorder.[35]

The population of Western Australia is approximately 1.9 million people, 73% of whom reside in the metropolitan area of Perth.[41] For every birth since 1980, obstetric data, including information on parental demographics, maternal obstetric history, pregnancy, delivery, and neonate data, are recorded in the state Maternal and Child Health Research Database (MCHRDB).[42] Diagnoses and service delivery for people with autism are centralized by the state government, and historically, diagnoses have been made at 5 centers. Diagnoses are made using the criteria specified in the *DSM* for the period.[1,43,44] The Gillberg criteria[45] for Asperger syndrome are sometimes used as a supplement to, or instead of, the *DSM* criteria for Asperger syndrome because of the perceived value of the detailed qualitative descriptions they offer for the diagnostic process.

The aim of the present study was to use the centralized resources contained in Western Australia to improve on the methods used in previous studies that have investigated the correlation between obstetric experience and autism development. Although no single factor from the prenatal environment has been identified to cause autistic symptoms later in life, certain variables, such as advanced maternal age, have sometimes emerged as risk factors. The methods used by each study have varied significantly to the point where it is difficult to compare across samples. It is possible that the methodological differences, such as small sample size, have had an effect on the findings.

The present study used a large population-based sample with high-quality data and rigorous research methods to identify risk factors from prenatal and perinatal experience for developing autism. It included a comparison group of siblings to measure familial differences and compared diagnostic subgroups within the autism spectrum. It is unique for incorporating the largest number of autistic cases born in a geographic region, using obstetric data collected at the time of birth, comparing cases with a large population-based control group and comparing cases with siblings.

METHODS

CASE ASCERTAINMENT

Approval to obtain diagnostic information was received from the ethics committees of the 5 diagnostic centers, as well as the University of Western Australia, Perth. Diagnostic reports of all persons born after 1980 identified as having an autism spectrum disorder or autistic features before 1997 were personally examined by a pediatric registrar (G.C.) involved in autism assessments. Those who had been assessed using the *DSM* criteria for an autism spectrum disorder according to the version used in that period were included in the study.[1,43,44] The collection of data by the pediatric registrar was limited by what was contained in the files, so descriptive information, such as IQ, was not available for every case. Diagnoses made between 1997 and 1999 from the 2 main diagnostic centers that are responsible for at least 90% of all diagnoses and registrations and who were subject to centralized diagnoses during this period were added. Since June 1997, for a child to receive government funding for early intervention services in Western Australia, autism spectrum diagnoses must incorporate assessments by a pediatrician, speech pathologist, and a clinical psychologist who must all agree on the diagnosis. This ensured a comprehensive listing of people born since 1980, diagnosed between 1986 and 1999.

DATA LINKAGE

Cases were electronically linked to the MCHRDB using probabilistic record linkage methods[46] and manual checking to confirm possible matches. Based on the number of cases reviewed by the pediatric registrar, it was predicted prior to case extraction that approximately 350 autism cases would be identified. For such a sample size, to detect a 2.2-fold increase in the risk of bleeding during pregnancy (one of the more consistent findings in previous studies with a prevalence of 3.7% for all births in the MCHRDB) at 80% power and 5% level of significance, 3 control subjects per case would be needed. Five hundred one autism cases were identified and linked to their birth record, and sibling data were also extracted. The control group (n=1503) was matched for sex but otherwise randomly selected across the same range of birth years as the cases (1980-1997). After case ascertainment, it was apparent that cases born in 1996 and 1997 were few in number (n=36) because they were diagnosed at an especially young age (younger than 3 years). The pattern of symptoms that appears in very young children with autism may differ from that seen at the more prototypic age of 4 or 5 years. Including these children may have introduced a bias, particularly because most children born in these birth years who develop autism but were not yet diagnosed would have been omitted. Therefore, these cases were excluded from the study along with any control subject or sibling born in the same 2-year period.

VARIABLE SELECTION

The following variables were selected from the MCHRDB:

- Parental characteristics. Maternal and paternal age at the time of the infant's birth.
- Pregnancy characteristics. Pregnancy complications (threatened abortion at <20 weeks' gestation; urinary tract in-

fection; preeclampsia; antepartum hemorrhage; premature membrane rupture; and "other," as coded by *International Classification of Diseases, Ninth Revision (ICD-9)* classifications[47]).

- Labor and delivery characteristics. Type of anesthesia used, labor onset, labor complications (precipitate delivery, fetal distress, umbilical cord around neck, cephalopelvic disproportion, postpartum hemorrhage >500 mL, and "other," coded by *ICD-9* classifications), hours of labor, type of delivery, and birth presentation.
- Infant characteristics. Birth order, gestational age, head circumference, length, weight, Apgar scores at 1 and 5 minutes, time to spontaneous respiration, and time spent in special care.

STATISTICAL ANALYSES

Analyses were performed using the Statistical Package for the Social Sciences version 10.0 (SPSS Inc, Chicago, Ill). Comparisons were made on each variable using χ^2 tests; odds ratios (ORs) were used for categorical variables and *t* tests for continuous variables. To investigate the possible effect of several variables simultaneously, cases and control subjects were compared using binary logistic regression, and ORs and 95% confidence intervals (CIs) were calculated, with values of $P<.05$ considered significant.

RESULTS

A total of 465 linked cases was identified (314 autism, 67 Asperger syndrome, and 84 PDD-NOS) (**Table 1**). There were 1313 control subjects and 481 siblings of cases.

Table 1. Number of Autism Cases, Their Siblings, and Control Subjects by Sex

	Total	Men, No. (%)	Women, No. (%)
Cases*	**465**	391 (84.1)	74 (15.9)
Case siblings	**481**	251 (52.2)	230 (47.8)
Control subjects	**1313**	1098 (83.6)	215 (16.4)

*Eight siblings of cases had also been diagnosed with an autism spectrum disorder and were included in the case group.

One hundred thirty cases were singletons, 200 had 1 sibling, 97 had 2 siblings, and 30 had 3 or more siblings. Eight cases had a sibling who also had been diagnosed with an autism spectrum disorder, including 1 set of concordant male twins, and these siblings were all included in the case group. Three of the sibling pairs did not have any other siblings, and the remaining 5 pairs had 1 unaffected sibling. The random removal of 1 of each of the sibling pairs from the case group or the removal of all familial cases from the case group did not alter the research findings.

UNIVARIATE ANALYSES

Cases Compared With Control Subjects

Case parents were significantly older than control subject parents. The mean age of case mothers was 28.62 years, and the mean age of control subject mothers was 27.01 years. ($t=5.71$; $P<.001$); the mean age of case fathers was 31.74 years, and the mean age of control subject fathers was 30.31 years ($t=4.19$; $P<.001$) (**Table 2**). Among case pregnancies, 175 mothers (37.6%) had at least 1 pregnancy complication recorded compared with 426 control subject mothers (32.4%). Case mothers were more likely to experience a threatened abortion before 20 weeks' gestation (OR, 2.41; 95% CI, 1.56-3.73) (**Table 3**) and significantly more "other" pregnancy complications than mothers of control subjects (OR, 1.36; 95% CI, 1.04-1.78). Case and control subject mothers experienced 92 different conditions within the "other" pregnancy category and had up to 3 conditions listed each. The most common conditions (hypertension, early labor, and fetal/placental problems) were found in similar proportions in both the case and control subject groups. Case mothers had higher frequencies of anesthesia use during labor (327 [88.6%] of 369 cases with data recorded since 1986 compared with 616 [85.2%] of 723 control subjects with data recorded since 1986), specifically an epidural caudal anesthesia (OR, 1.68; 95% CI,

Table 2. Cases Compared With Control Subjects for Continuous Variables

	No. of Cases	No. of Control Subjects	Cases, Mean (SD)	Control Subjects, Mean (SD)	*t* Test	*P* Value
Delivery variables						
Hours of labor	464	1310	5.42 (4.51)	5.56 (4.32)	−0.59	.56
Neonatal variables						
Apgar score at 1 min*	277	512	7.76 (1.66)	7.89 (1.43)	−1.14	.26
Apgar score at 5 min	464	1309	9.00 (0.88)	9.05 (0.82)	−1.06	.29
Gestational age	464	1305	39.03 (1.84)	39.10 (1.98)	−0.60	.55
Head circumference*	277	515	34.60 (1.64)	34.55 (1.73)	0.45	.65
Length	463	1310	50.30 (2.87)	50.58 (3.05)	−1.67	.10
Days in special care	174	371	1.65 (5.58)	3.25 (12.40)	−2.07	.04†
Minutes to spontaneous respiration	451	1289	1.33 (1.04)	1.25 (1.22)	1.22	.22
Birth weight	465	1312	3378 (555)	3432 (571)	−1.76	.08
Demographic variables						
Maternal age	464	1312	28.62 (4.99)	27.01 (5.30)	5.71	<.001†
Paternal age	444	1224	31.74 (6.12)	30.31 (6.17)	4.19	<.001†
Previous children	464	1308	0.85 (1.04)	1.04 (1.21)	−2.95	.003†

*Only included in the Maternal and Child Health Research Database since 1990.
†Indicates significant difference.

Table 3. Cases Compared With Control Subjects for Dichotomous Variables of Pregnancy, Labor, and Infant Characteristics

	No. of Cases (n = 465)	No. of Control Subjects (n = 1313)	Odds Ratio (95% Confidence Interval)	*P* Value	χ^2 Test
Pregnancy complications					
Threatened abortion at <20 wk	39	48	2.41* (1.56-3.73)	<.001	16.52
Urinary tract infection	17	68	0.70 (0.40-1.20)	.19	1.75
Preeclampsia	33	94	0.99 (0.66-1.50)	.96	0.002
Antepartum hemorrhage	18	47	1.09 (0.62-1.89)	.77	0.08
Premature membrane rupture	14	38	1.04 (0.56-1.94)	.90	0.02
Other	95	209	1.36 (1.04-1.78)	.03	4.93
Anesthesia used†					
Epidural caudal	191	290	1.68* (1.12-2.51)	.01	6.48
General	25	50	1.27 (0.70-2.32)	.43	0.63
Other	159	349	1.16 (0.78-1.74)	.47	0.53
Labor onset					
No labor	83	140	2.04* (1.50-2.76)	<.001	21.26
Induced	131	314	1.43* (1.12-1.83)	.004	8.11
Labor complications					
Precipitate delivery	19	69	0.77 (0.46-1.29)	.32	1.00
Fetal distress	88	168	1.59* (1.20-2.11)	.001	10.47
Umbilical cord around neck	34	89	1.09 (0.72-1.64)	.70	0.15
Cephalopelvic disproportion	33	78	1.21 (0.79-1.84)	.38	0.78
Postpartum hemorrhage >500 mL	13	16	2.33* (1.11-4.89)	.02	5.32
Other	193	413	1.55 (1.24-1.92)	<.001	15.44
Delivery type					
Forceps or vacuum	88	258	1.14 (0.86-1.50)	.38	0.78
Elective cesarean section	77	125	2.05* (1.49-2.82)	<.001	20.55
Emergency cesarean section	57	121	1.57* (1.11-2.22)	.01	6.55
Presentation					
Breech	33	63	1.52 (0.98-2.35)	.06	3.58
Neonatal variables					
Special care needed	48	109	0.92 (0.61-1.37)	.67	0.19
Resuscitation needed	169	468	1.03 (0.83-1.29)	.77	0.08
Time to spontaneous respiration >1 min	72	152	1.42* (1.05-1.93)	.02	5.19
Apgar score at 1 min < 7	54	66	1.64* (1.10-2.43)	.01	6.08
Privately insured patient	239	658	0.94 (0.76-1.17)	.59	0.29

*Indicates significant difference.
†Information on anesthesia has been collected in the Maternal and Child Health Research Database since 1986. Data were available for 369 cases and 723 control subjects.

1.12-2.51).Case mothers were more likely to experience no labor (OR, 2.04; 95% CI, 1.50-2.76), be induced (OR, 1.43; 95% CI, 1.12-1.83), or have a labor duration of less than 1 hour (89 cases [19.1%]; 155 control subjects [11.8%]) (OR, 1.8; 95% CI, 1.3-2.4). More case mothers experienced a labor complication (290 cases [62.4%]; 680 control subjects [51.8%]). Case mothers had greater frequencies of postpartum hemorrhage (OR, 2.33; 95% CI, 1.11-4.89) and "other" labor complications (OR, 1.55; 95% CI, 1.24-1.92). There were 120 differently coded "other" labor complications across case and control subject mothers. Case mothers were more likely to have an elective cesarean section (OR, 2.05; 95% CI, 1.49-2.82) or an emergency cesarean section (OR, 1.57; 95% CI, 1.11-2.22).

Control subject mothers had higher parity than the case mothers ($P=.01$) (**Table 4**). Among the cases, there were 13 twin pairs, 1 of which was concordant (one autism diagnosis and one PDD-NOS diagnosis). Of the 12 discordant pairs, 10 were diagnosed with autism and 2 with PDD-NOS. Seven twin pairs were the same sex, but information on zygosity was not known from the birth records. The rate of twinning in this sample has been previously described[48] and does not implicate twinning as a risk factor for autism.

Table 4. Birth Order Frequencies in Cases and Control Subjects*

	Cases	Control Subjects
Firstborn	215 (46.2)	530 (40.4)
Second born	156 (33.6)	418 (31.8)
Third born	59 (12.7)	237 (18.1)
Fourth or later born	35 (7.5)	127 (9.7)

*Values are expressed as number (percentage) of patients. $\chi^2_3 = 10.8$; $P = .01$.

Cases were more likely to have experienced fetal distress during labor (OR, 1.64; 95% CI, 1.15-2.34). Apgar scores calculated at 1 minute showed that significantly more cases achieved a score of 6 or less (54 [19.5%] of 277 cases with data recorded since 1991; 66 [12.9%] of 512 control subjects with data recorded since 1991)(OR, 1.6; 95% CI, 1.1-2.4), and cases were more likely to have taken more than 1 minute before

Table 5. Cases Compared With Their Siblings for Dichotomous Variables of Pregnancy, Labor, and Infant Characteristics

	Cases (n = 465)	Case Siblings (n = 481)	Odds Ratio (95% Confidence Interval)	*P* Value	χ^2 Test
Pregnancy complications					
Threatened abortion at <20 wk	39	26	1.60 (0.96-2.68)	.07	3.29
Urinary tract infection	17	18	0.98 (0.50-1.92)	.94	0.01
Preeclampsia	33	37	0.92 (0.56-1.49)	.73	0.12
Antepartum hemorrhage	18	17	1.10 (0.56-2.16)	.78	0.08
Premature membrane rupture	14	11	1.33 (0.60-2.95)	.49	0.48
Other	95	98	1.00 (0.73-1.38)	.98	0.00
Anesthesia used*					
Epidural caudal	191	157	1.27 (0.79-2.04)	.31	1.01
General	25	24	1.09 (0.54-2.20)	.81	0.06
Other	159	132	1.26 (0.78-2.04)	.34	0.90
Labor onset					
No labor	83	88	1.08 (0.76-1.52)	.67	0.19
Induced	131	107	1.40† (1.03-1.90)	.03	4.65
Labor complications					
Precipitate delivery	19	24	0.81 (0.44-1.50)	.51	0.45
Fetal distress	88	60	1.64† (1.15-2.34)	.01	7.46
Umbilical cord around neck	34	30	1.19 (0.71-1.97)	.51	0.43
Cephalopelvic disproportion	33	39	0.87 (0.54-1.40)	.56	0.34
Postpartum hemorrhage >500mL	13	8	1.70 (0.70-4.14)	.22	1.40
Other	193	203	0.97 (0.75-1.26)	.83	0.05
Delivery type					
Vacuum or forceps	88	81	1.20 (0.85-1.70)	.31	1.04
Elective cesarean section	77	75	1.13 (0.79-1.63)	.50	0.46
Emergency cesarean section	57	53	1.19 (0.79-1.79)	.42	0.66
Presentation					
Breech	33	25	1.40 (0.82-2.39)	.22	1.50
Neonatal variables					
Special care	48	37	1.09 (0.66-1.80)	.73	0.12
Resuscitation	169	154	1.22 (0.93-1.59)	.15	2.04
Time to spontaneous respiration >1 min	72	45	1.81† (1.21-2.69)	.00	8.69
Apgar score at 1 min <7	54	31	1.64† (1.02-2.65)	.04	4.13
Privately insured patient	239	237	1.08 (0.83-1.40)	.57	0.33

*Information on anesthesia has been collected in the Maternal and Child Health Research Database since 1986. Data were available for 369 cases and 336 siblings.
†Indicates significant difference.

the onset of spontaneous respiration (OR, 1.4; 95% CI, 1.0-1.9). Apgar scores at 5 minutes showed that fewer cases achieved a score of at least 8 (437 cases [94.2%]; 1258 control subjects [96.1%]), but differences were not significant (OR, 0.7; 95% CI, 0.4-1.1). No differences in gestational age (including the proportion of premature infants), weight for gestational age, head circumference, or length were observed between cases and control subjects. Female cases were shorter in length ($t=2.47$; $P=.01$) and had a longer gestational age ($t=-2.73$; $P=.007$) compared with male cases. Female control subjects weighed less ($t=1.98$; $P=.048$) and had a longer gestational age ($t=-2.26$; $P=.02$) than male control subjects.

Comparison of Cases With Their Siblings

Compared with their siblings, cases were more likely to have been induced (OR, 1.40; 95% CI, 1.03-1.90), experienced fetal distress (OR, 1.64; 95% CI, 1.15-2.34), had an Apgar score at 1 minute of 6 or less (OR, 1.64; 95% CI, 1.02-2.65), and needed longer than 1 minute to breathe spontaneously (OR, 1.81; 95% CI, 1.21-2.69) (**Table 5**). The cases had a higher rate of threatened abortion than their siblings, but this was not statistically significant (OR, 1.60; 95% CI, 0.96-2.68). When adjusted for sex, these differences remained. The cases did not differ from their siblings on any of the continuous variables tested.

Comparison by Diagnostic Grouping

When compared with control subjects, the diagnostic groupings differed in their pattern of obstetric experience (**Table 6**). The autism group had the greatest number of complications. The PDD-NOS group had similar types of complications to the autism group, but fewer variables reached statistical significance. The Asperger syndrome group had the fewest obstetric differences and was distinguished by a lack of significantly increased pregnancy and labor complications requiring forceps or vacuum extraction and by having private health insurance. When compared with the autism group on the same variables, the PDD-NOS group only differed by having a greater risk of cephalopelvic disproportion (OR, 3.0; 95% CI, 1.3-6.8). Compared with

Table 6. Each Autism Diagnostic Grouping Compared With Control Subjects for Dichotomous Variables of Pregnancy, Labor, and Infant Characteristics*

	Autism Cases (n = 314)	PDD-NOS Cases (n = 84)	Asperger Cases (n = 67)
Pregnancy complications			
Threatened abortion at <20 wk	2.4 (1.4-3.9)†	3.6 (1.7-7.3)†	1.2 (0.4-4.1)
Urinary tract infection	0.7 (0.4-1.3)	0.9 (0.3-2.6)	0.6 (0.1-2.4)
Preeclampsia	0.9 (0.5-1.4)	1.2 (0.5-2.6)	1.3 (0.6-3.0)
Antepartum hemorrhage	1.0 (0.5-1.9)	0.7 (0.2-2.8)	2.2 (0.8-5.6)
Premature membrane rupture	1.2 (0.6-2.4)	0.8 (0.2-3.4)	0.5 (0.1-3.8)
Other	1.4 (1.0-1.9)†	1.6 (1.0-2.8)	0.8 (0.4-1.7)
Anesthesia used			
Epidural caudal	1.5 (0.9-2.4)	1.5 (0.7-3.0)	5.4 (1.2-22.8)†
General	1.6 (0.8-3.1)	0.4 (0.1-1.8)	1.1 (0.1-12.1)
Other	1.2 (0.8-1.9)	0.8 (0.4-1.7)	2.6 (0.6-11.5)
Labor onset			
No labor	1.9 (1.4-2.8)†	2.6 (1.5-4.6)†	1.8 (0.9-3.7)
Induced	1.4 (1.1-1.9)†	1.2 (0.7-2.1)	1.8 (1.1-3.2)†
Labor complications			
Precipitate delivery	0.8 (0.4-1.4)	1.4 (0.6-3.3)	1.0 (0.9-1.0)
Fetal distress	1.6 (1.2-2.3)†	1.6 (1.0-2.8)	1.4 (0.7-2.6)
Umbilical cord around neck	1.2 (0.8-2.0)	0.3 (0.1-1.4)	1.4 (0.6-3.2)
Cephalopelvic disproportion	0.8 (0.4-1.4)	2.4 (1.2-4.7)†	1.8 (0.8-4.2)
Postpartum hemorrhage >500 mL	2.7 (1.2-5.9)†	2.0 (0.4-8.7)	1.2 (0.2-9.4)
Other	1.6 (1.3-2.1)†	1.4 (0.9-2.2)	1.4 (0.8-2.3)
Delivery type			
Forceps or vacuum	1.0 (0.7-1.4)	0.7 (0.4-1.5)	2.5 (1.4-4.5)†
Elective cesarean section	1.9 (1.3-2.8)†	2.5 (1.4-4.6)†	2.1 (1.0-4.6)†
Emergency cesarean section	1.4 (0.9-2.1)	2.0 (1.0-3.8)†	2.0 (0.9-4.4)†
Presentation			
Breech	1.6 (1.0-2.7)†	1.3 (0.5-3.2)	1.3 (0.4-3.6)
Neonatal variables			
Special care	0.9 (0.6-1.4)	1.0 (0.4-2.4)	1.1 (0.3-3.5)
Resuscitation needed	1.1 (0.8-1.4)	0.8 (0.5-1.4)	1.0 (0.6-1.7)
Time to spontaneous respiration >1 min	1.4 (1.0-2.0)	1.4 (0.8-2.7)	1.6 (0.9-3.1)
Apgar score at 1 min <7	1.7 (1.1-2.6)†	1.3 (0.6-2.8)	2.2 (0.9-5.5)
Privately insured patient	0.8 (0.6-1.0)	1.0 (0.6-1.5)	1.9 (1.1-3.3)†

Abbreviation: PDD-NOS, pervasive development disorder not otherwise specified.
*Values are expressed as odds ratio (95% confidence interval).
†Indicates significant difference.

the autism group, the Asperger cases were more likely to have a vacuum or forceps delivery (OR, 2.5; 95% CI, 1.3-4.7) and have private health insurance (OR, 2.4; 95% CI, 1.3-4.2).

LOGISTIC REGRESSION ANALYSIS

Year of birth and birth order were entered into the regression analysis along with all other variables. Numerous interactions were also included, but none were significant. After the deletion of 3 individuals with missing values, 1775 were available for the analysis (464 cases and 1311 control subjects). **Table 7** shows regression coefficients, Wald statistics, ORs, and 95% CIs for ORs for each of the 6 predictors. The model predictors using autism as an outcome were year of birth (cases were more likely to be recently born), birth order (cases were more likely to be firstborn), maternal age (cases were more likely to have an older mother), threatened abortion (more likely to be present in cases), fetal distress (more likely to be present in cases), and elective cesarean section (more likely to be present in cases).

Table 7. Logistic Regression Model With 6 Explanatory Variables (All Cases Compared With Control Subjects)

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Intercept	0.00	<.001
Year of birth	1.12 (1.09-1.15)	<.001
Birth order (compared with firstborn)		
Second born	0.79 (0.61-1.04)	.09
Third born	0.47 (0.33-0.67)	<.001
Fourth or later born	0.46 (0.29-0.73)	.001
Maternal age, y (compared with 25-29 y)		
<20	0.51 (0.30-0.88)	.02
20-24	0.61 (0.44-0.84)	.002
30-34	1.41 (1.07-1.87)	.02
≥35	1.54 (1.04-2.30)	.03
Threatened abortion (compared with absence)		
At <20 wk	2.09 (1.32-3.32)	.002
Fetal distress (compared with absence)	1.52 (1.12-2.06)	.007
Elective cesarean section (compared with absence)	1.83 (1.32-2.54)	<.001

COMMENT

To our knowledge, this study is the largest reported population-based sample to date of people born and diagnosed with an autism spectrum disorder within a single geographical area, using prospectively collected obstetric data and comparing siblings and autism subgroups in a single research design. The findings indicate that individuals diagnosed within the autism spectrum are more likely to have experienced obstetric difficulties during pregnancy, labor, delivery, and the neonatal period compared with people without an autism diagnosis. This is in agreement with the general interpretations in previous studies.[31,32,34-36,39,49,50]

The study sample is representative of the Western Australian population at a point in time but was restricted to cases who had received a formal diagnosis in the autism spectrum. Therefore, a proportion of cases are likely to have been missed from the case ascertainment process, in particular milder and/or older cases who were not referred for autism services. The study also does not include cases who were born between 1980 and 1995 but subsequently diagnosed after 1999.

Advanced maternal age in case mothers was one of the strongest findings of the study. Increased maternal age has previously been found as a risk factor in autism, regardless of the range of birth years examined.[51-54] The effect in this study was incremental such that younger mothers had the lowest risk and older mothers had the highest risk. In the Croen et al[55] study that compared maternal age of 4356 autism cases born in California with nearly 3.5 million control subject mothers, the risk of mothers 35 years or older having a child with autism was increased 3-fold compared with mothers younger than 20 years.[55] This effect was also found in the present data and in the recent Swedish cohort of 408 cases.[39] Older mothers have an increased risk of complications during labor and delivery,[56,57] possibly attributable to the dysfunction of the uterine muscles and blood supply that occurs with age,[57] which may be compounded by older mothers delivering a larger number of firstborn cases. However, in the present study, increased maternal age emerged as an independent risk factor after adjustment for the other variables.

Paternal age was also greater in fathers of cases compared with fathers of control subjects. Paternal age is not usually addressed or has been found to be unimportant[53] in previous studies. Increased paternal age has been documented in patients with schizophrenia.[58,59] It has a recognized effect in autosomal dominant mutations such as Apert syndrome and achondroplasia,[60,61] in Down syndrome,[62] and also in the inheritance of *MeCP2* mutations in girls with Rett syndrome.[63] Increased paternal age did not emerge as a significant predictor in the regression analysis and was statistically weaker in the univariate analyses, suggesting that its effect is most likely to be related to increased maternal age.

Threatened abortions were significantly more common in the case pregnancies compared with control subjects and attained the highest OR value. Bleeding during pregnancy has previously been reported in case mothers[32,34,36,39,40,64] and also an increased number of prior miscarriages.[65,66] A higher prevalence of previous miscarriages and stillbirths among case mothers was not observed in the present dataset.

Elective cesarean sections were more common among case births and their siblings compared with control subjects and emerged as a risk factor after adjusting for maternal age and year of birth. The prevalence of cesarean sections has increased in recent decades, the reasons for which are both socially and medically complex.[67-69] The most common antecedents for a cesarean section are previous cesarean section, failure to progress in labor, fetal distress, multiple pregnancies, breech presentation, and unstable lie.[70,71] Recently, there has been an increasing trend for women to request a cesarean delivery, and this is becoming the most popular reason for having the procedure.[72,73] Unfortunately, the reasons for performing cesarean section deliveries are not recorded in the MCHRDB, and thus, inferences cannot be made from the available data.

Epidural caudal anesthesia was more commonly administered to case mothers during labor and may have been used for cesarean section or maternal pain relief.[74,75] Physiological responses to pain include increased blood pressure and decreased uterine blood flow and may negatively affect the fetus by altering heart rate and increasing oxygen consumption.[75,76] Epidural anesthesia is considered the most effective method of pain relief during labor,[71,77] but it is a cause of intrapartum fever and may have adverse effects on the fetus if the fetal core temperature becomes elevated above the maternal core temperature.[76] Adverse effects such as low Apgar scores may be observed at birth and may also be associated with administration of epidural caudal anesthesia and the decision to perform an elective caesarean section in some cases.

In laboratory experiments, cesarean section deliveries can produce rats with significantly increased binding of dopamine D1 receptors in the nucleus accumbens compared with rats delivered vaginally.[78] The effect is enhanced by anesthesia and may be related to the presence of hypoxia. The increase in D1-receptor binding is only evident in the rat brain during adulthood, possibly owing to an interaction with events during development. This may be more severe in rats that are genetically susceptible because there are different responses among rat strains.[78] In some individuals with autism, problem behaviors may be managed effectively with dopamine inhibitors.[79] These individuals may represent a subgroup whose etiology involves early damage to the ventral basal ganglia, which may be associated with cerebral changes that are initiated at birth.

The presence of fetal distress, no labor, caesarean section delivery, and poor condition at birth (as measured by a low Apgar score at 1 minute and taking greater than 1 minute to spontaneously respirate) was characteristic of the case group. This suggests an association with anoxia and/or placental deficiency, evidence of which was found in the Hultman et al[39] cohort. Anoxia is often caused by placental abruption that typically results in delivery within 1 hour, meconium staining, abnormal fetal heart patterns, and umbilical cord blood acidity.[80] There are no data on the long-term effects of abnormal placen-

tas, reflecting the lack of knowledge about its role in development. This is an important direction for future research. The simultaneous presence of anoxia and hyperthermia before birth has been shown to produce neurological consequences in animal offspring and could therefore be a potential source of injury to neonates.[81-83]

Although the case group spent less time in special care when compared with the statistical mean, both groups were similar using the median statistic. This indicates that some control subjects spent lengthy periods in special care, and this has affected the comparison of the 2 groups. Unfortunately, the reasons for requiring special care are not available from the MCHRDB, and thus, no judgments can be made on the qualitative differences in the 2 groups' need for care.

Cases were more likely to be firstborn compared with control subjects. The finding is consistent with other reports of first births carrying a risk for autism.[31,36,54] The earlier finding of autism cases more commonly being born fourth or later[31,34,54] was not observed. Those born first or fourth or later naturally have more complications, but the autism group experienced more complications at all birth orders. A possible explanation is that pregnancy complications are part of the phenotypic expression of some of the group of autism genes rather than a contributory cause.

Overall, case siblings had fewer complications than their affected siblings but more than control subjects. They had similar experiences to the cases during the pregnancy period but experienced less fetal distress during labor, were less likely to be induced than the cases, and were more likely to take more than 1 minute for spontaneous respiration. These findings remained after adjusting for sex. Several inferences can be made from this relationship. First, the obstetric complications may represent a compromised maternal environment to which all offspring are exposed but autism develops in only some offspring, either because of certain environmental stimuli or a particular genotype that is vulnerable to develop the disorder. Second, if the development of autism depends on having a certain number of genes, then siblings who share some genes may also show complications in utero and may also have milder autistic traits. Siblings and other close relatives of people with autism often show mild autistic traits on cognitive assessments.[9-12] This is consistent with the hypothesis that shared genes cause similarities in utero and those with the autism genotype will develop the disorder and siblings who share some of the genes show milder symptomatology.

Alternatively, individuals with autism may react differently to the same environmental stimuli and may have less tolerance to the prenatal experience compared with their siblings. Given that siblings had similar obstetric experiences to the cases, some other factor could be influential in late pregnancy for the case births, but not for siblings, to cause autism. It could also be that the measurement of complications is too crude and that a more refined measurement may reveal the subtle differences of the prenatal experience of the child with autism.

When compared with the control group, the profile of obstetric complications differed by autism subgroup, whereby the Asperger syndrome group had fewer complications than the PDD-NOS group, which in turn had fewer, but similar, complications than the autism group. This pattern suggests there is a positive relationship between autism severity and adverse obstetric experience. The Asperger syndrome group had a more favorable experience during the pregnancy and labor periods. Previous investigations of the obstetric experience for people with Asperger syndrome have used small sample sizes, ranging from 10 to 23 cases.[45,84,85] All report an increase in complications in the Asperger groups compared with the control subjects but fewer than the autism groups, which is similar to the present dataset. Fewer complications may be related to the decreased probability of people with Asperger syndrome having comorbid medical conditions.[86] Clinically, people diagnosed with Asperger syndrome generally have better-developed language skills and a higher level of intelligence than those with autism.[2,6,87,88] Autism cases who have a lower IQ have been shown to experience more obstetric complications[33,40,64,89] and also more severe symptoms than those with a high IQ.[90] It is therefore likely that IQ is a factor that is associated with obstetric experience.

CONCLUSIONS

This research has used a population-based cohort of people diagnosed with autism spectrum disorders to investigate whether the etiology or nature of autism can be defined by the presence of particular biological characteristics around the time of birth. For some cases, differences in the environment and/or in their reaction to it occur in utero, as seen by an increased number of risk factors and obstetric complications that differentiate the experience of autism cases from nonautistic control subjects. The strongest findings were increased maternal age and a threatened abortion during pregnancy. It is unlikely that single factors or events cause autistic disorders, although it is possible that early nongenetic influences may act on the causal pathway for some cases. The observed complications are generally nonspecific and cannot predict autism development. This research supports the hypothesis that the development of autism spectrum disorders is dependent on the genotype, and the presence of complications can be explained by a compromised prenatal experience for that genotype.

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Correction

Error in Figure. In the Original Article titled "Effects of Perceived Treatment on Quality of Life and Medical Outcomes in a Double-blind Placebo Surgery Trial" published in the April issue of the ARCHIVES (2004;61:412-420), an incorrect version of **Figure 3** was published. Figure 3 is published correctly here. Online versions of this article on the *Archives of General Psychiatry* Web site were corrected on April 13, 2004. The ARCHIVES regrets the error.

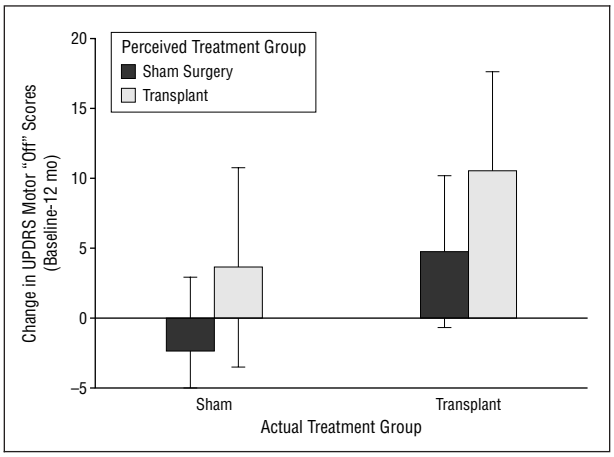

Figure 3. Mean changes in Unified Parkinson's Disease Rating Scale (UPDRS) motor "off" scores (baseline to 12 months) for the total group in the parent study (n=39). Increased scores indicate improvement. Error bars represent SEM.