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ORIGINAL CONTRIBUTIONS

Risk Factors for Autism: Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status

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Research suggests that heredity and early fetal development play a causal role in autism. This case-control study explored the association between perinatal factors, parental psychiatric history, socioeconomic status, and risk of autism. The study was nested within a cohort of all children born in Denmark after 1972 and at risk of being diagnosed with autism until December 1999. Prospectively recorded data were obtained from nationwide registries in Denmark. Cases totaled 698 children with a diagnosis of autism; each case was individually matched by gender, birth year, and age to 25 controls. Analyses by conditional logistic regression produced risk ratios and 95% confidence intervals. Adjusted analyses showed that the risk of autism was associated with breech presentation (risk ratio (RR) = 1.63, 95% confidence interval (CI): 1.18, 2.26), low Apgar score at 5 minutes (RR = 1.89, 95% CI: 1.10, 3.27), gestational age at birth <35 weeks (RR = 2.45, 95% CI: 1.55, 3.86), and parental psychiatric history (schizophrenia-like psychosis: RR = 3.44, 95% CI: 1.48, 7.95; affective disorder: RR = 2.91, 95% CI: 1.65, 5.14). Analyses showed no statistically significant association between risk of autism and weight for gestational age, parity, number of antenatal visits, parental age, or socioeconomic status. Results suggest that prenatal environmental factors and parental psychopathology are associated with the risk of autism. These factors seem to act independently.

autistic disorder; fetal growth retardation; mental disorders; parturition; perinatology; pregnancy outcome

Abbreviations: ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision; IDA, Integrated Database for Longitudinal Labour Market Research; MBR, Medical Birth Register; PCR, Psychiatric Central Register.

Editor's note: *An invited commentary on this article appears on page 926.*

Autism spectrum disorders are a group of pervasive developmental disorders characterized by impaired communication and social interaction as well as restricted and repetitive interests and behaviors. Included are autistic disorder (infantile autism), pervasive developmental disorder–not otherwise specified, and Asperger's disorder. The term "autism" is often used to refer to autistic disorder, which affects approximately one to two children per 1,000

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(1–5). The prevalence of autism spectrum disorders as a whole may range from two to six per 1,000 (2, 3, 5, 6). The etiology of these disorders is not completely understood, but twin and family studies suggest that genetic factors play a substantial causal role; the concordance rate is found to be at least 36 percent for monozygotic twins and is expected to be about 3 percent for dizygotic twins (7). However, a concordance rate for monozygotic twins of less than 100 percent indicates that nongenetic factors also play a causal role. Prenatal exposure to valproic acid, thalidomide, rubella, and alcohol has been associated with an increased risk of autism spectrum disorders (8–11).

Several studies have focused on perinatal risk factors for autism (12–21). However, the sample sizes have been relatively small, studies have used different methodologies, and results among studies are conflicting. Some studies (12–15), but not all (16, 17), found an increased risk of autism associated with the presence of one or more unfavorable obstetric events. Studies focusing on single perinatal risk factors have reported a positive association for low birth weight (<2,500 g) (15, 16), low Apgar score (<6 or <7) at 5 minutes (15, 18), being small for gestational age (18), gestational age at birth of less than 37 weeks (15, 18), cesarean section (18), and congenital malformations (18). A number of studies examined several or all of the factors mentioned without identifying any significant risk factors (19–21). A gender stratification in one study indicated an increased risk of autism among boys, but not girls, of low birth weight (<2,500 g) (21).

Compared with parents of children with other handicaps, parents of autistic children more frequently have schizoid personality traits (22), and women with schizophrenia are at increased risk of an adverse pregnancy outcome (23, 24). A family record of psychiatric history may therefore confound the association between perinatal factors and autism. A familial propensity to disorder has been taken into account somewhat in some studies of perinatal risk and autism by using siblings as controls (14, 21), but no studies are known to have examined whether the association between perinatal factors and autism disappears when adjusting for parental psychiatric history. Most studies on perinatal factors and autism have not been able to adjust for socioeconomic status. Socioeconomic status may be associated with adverse pregnancy outcomes as well as autism (2, 24).

This large, population-based, case-control study used Danish national registry data to explore the associations between autism and perinatal factors, parental psychiatric history, and socioeconomic status. It also considered the effect of parental psychiatric history and socioeconomic status on the association between perinatal factors and autism.

MATERIALS AND METHODS

Register information

Data were obtained from the Danish Psychiatric Central Register (PCR) (25), the Danish Medical Birth Register (MBR) (26), and the Integrated Database for Longitudinal Labour Market Research (IDA) (27). The registries were linked by means of a unique personal registration number assigned to all residents in Denmark. This number is used in all contacts with authorities and by all national registers, which ensures accurate and complete linkage between registers.

The PCR contains data on all admissions to Danish psychiatric inpatient facilities since April 1969. In Denmark, inpatients include both patients who stay at the hospital overnight and patients who come to the hospital daily for evaluation and treatment. Information about outpatient visits to psychiatric departments has been included in the register since January 1, 1995. Until December 31, 1993, diagnostic information was coded according to the World Health Organization's *International Classification of Diseases*, Eighth Revision (ICD-8); since January 1, 1994, the *International Classification of Diseases*, Tenth Revision (ICD-10) has been used. The PCR has a coverage rate of nearly 100 percent, and the data are close to complete because of routine validation (25). There are no private psychiatric treatment facilities in Denmark, and all treatment is free of charge. Children in whom autism is suspected are referred by general practitioners, schools, and psychologists to specialists in child psychiatry. Only specialists in child psychiatry diagnose and code autism, and all registrations enter the PCR. The validity of the autistic disorder diagnosis in the register was assessed by Madsen et al. (28). A consultant in child psychiatry with expertise in autism examined 40 medical records, and 37 met the operational criteria for autistic disorder according to a systematic coding scheme. The scheme was developed by the Centers for Disease Control and Prevention (Atlanta, Georgia) for surveillance of autism and was previously used in a prevalence study in Brick Township, New Jersey (6). The validation concerned only those children diagnosed according to the ICD-10 system.

The MBR was established in 1968 and has been computerized since January 1, 1973. The register comprises data on all livebirths and stillbirths among women who reside in Denmark permanently. The registration includes selected characteristics of the mother and the newborn in addition to variables describing the pregnancy and delivery. Validation of the data in the MBR demonstrated good agreement with both medical records and the National Register of Patients regarding most pregnancy complications (26).

The IDA contains longitudinal information about the entire Danish population from 1980 to the present. It includes demographic variables (e.g., gender, age, marital status, citizenship), family information (e.g., identification of parents and siblings), and socioeconomic data (e.g., employment, education, wealth). The data are updated annually by linking several registers, all based on central administrative registers. Because the IDA data are required to be collected by various government authorities in Denmark, the database holds complete and valid information about all inhabitants of Denmark. The IDA is administrated by Statistics Denmark, the central Danish authority for collecting and managing societal statistical information.

Design and study sample

We conducted a nested case-control study based on children born in Denmark since January 1, 1973, and at risk

of being diagnosed with autism before the end of December 1999. The cases included all children ($N = 698$, 167 girls, 531 boys, born in 1973–1994) discharged from a Danish psychiatric hospital with a diagnosis of infantile or atypical autism (ICD-8 diagnosis codes 299.00–299.01 or ICD-10 diagnosis codes F84.0–F84.1x) before the end of December 1999.

For each case, we identified 25 controls through the IDA by means of incidence density sampling. The controls were individually matched to the cases by gender, birth year, and age in days.

For all children, information about perinatal characteristics was obtained from the MBR. The children's parents were identified through the IDA; by linkage with the PCR, parental psychiatric history was found.

The study was approved by the Danish Data Protection Agency, by the Committee on Human Research of the Bloomberg School of Public Health of the Johns Hopkins University, and by a committee formed in Aarhus, Denmark, for single project assurance under the regulations of the National Institutes of Health (Bethesda, Maryland).

Investigated risk factors

Perinatal risk factors. The perinatal factors investigated were categorized as 1) delivery and newborn characteristics: fetal presentation, mode of delivery, Apgar score at 5 minutes, birth weight, gestational age at birth, and weight for gestational age; 2) pregnancy characteristics: multiple gestation, preeclampsia, and number of antenatal visits; and 3) parental characteristics: number of previous pregnancies, maternal smoking reported at the first antenatal visit, maternal citizenship, and maternal and paternal ages. Birth weight for gestational age was categorized into three groups according to the gender-specific birth-weight distribution at a given gestational age in a sample of children ($N = 97{,}596$) born in Denmark between 1980 and 1994: small for gestational age ($<$10th centile), appropriate for gestational age (10th–90th centile), and large for gestational age ($>$90th centile). Information about Apgar score, gestational age at birth, and birth weight for gestational age was available from 1978 only; information about preeclampsia and maternal smoking was collected for only the years 1978–1990 and 1991–1994, respectively.

Parental psychiatric history. A parent was defined as having a psychiatric history if a psychiatric diagnosis had been recorded before the date that autism was diagnosed in the child. A ranking of psychiatric diagnosis determined how the parents were categorized; the parent with the highest-ranking diagnosis determined the specific category. The diagnoses were ranked as follows (in order of most to least severe): schizophrenia-like psychosis (ICD-8 diagnosis codes 295, 297, 298.39, 301.83 or ICD-10 diagnosis codes F20–F25, F28–F29); affective disorder (ICD-8 diagnosis codes 296, 298.09, 298.19, 300.4 or ICD-10 diagnosis codes F30–F39); substance abuse (ICD-8 diagnosis codes 303, 304 or ICD-10 diagnosis codes F10–F19.9 excluding F1x.0); or other mental disorders (any other mental disorder diagnosis, ICD-8 or ICD-10, in the PCR).

Socioeconomic status. Socioeconomic factors included maternal education and parental wealth. The wealth variable was based on the gross income of each parent assessed at the child's birth (birth after January 1, 1980) or in 1980 (when the IDA was initiated). First, individual income was classified according to the year-, gender-, and age-specific (5-year groups) distribution of gross income based on a 5 percent subsample of the IDA. The distribution quartiles determined the classification: highest, high-middle, low-middle, or lowest income. The wealth variable was defined according to the parent whose income was in the highest quartile.

Data analyses

Data were analyzed by using conditional logistic regression with Stata 7 statistical software (Stata Corporation, College Station, Texas), conditioning on the matching characteristics. In this paper, estimates of odds ratios are interpreted as risk ratios (29), and asymptotic 95 percent confidence intervals are given.

Unadjusted analyses were performed for all risk factors for the time periods covered by the individual variable. For all variables, stratified analyses on gender, age at diagnosis (1–5 years, 6–10 years, $\geq$11 years), and diagnosis group (ICD-8, ICD-10) were examined, and tests for interactions were conducted. An additional analysis of children born full term only explored the association between birth weight and autism, independent of the effects of shortened gestation. In addition, the association between socioeconomic status and autism was explored by stratification on birth year (before 1980, 1980–1994) to find any indication of bias introduced by using information from 1980 in connection with birth years before 1980.

Adjusted analyses were performed after excluding multiple gestations to avoid associations between prematurity, obstetric complications, and birth weight in multiple births. Because of the limited time coverage of the Apgar score and gestational age at birth, the adjusted analyses included the birth years from 1978 only. In the adjusted analyses, we first included all of the perinatal factors previously described except for birth weight, covering the period beginning in 1978. Since weight for gestational age is considered a better measure of intrauterine growth than birth weight alone, we included weight for gestational age and gestational age in the adjusted analyses. Second, we added parental psychiatric history and socioeconomic status variables to the first model separately. Finally, we added variables for both parental psychiatric history and socioeconomic status to the first model.

RESULTS

A summary of the characteristics of the cases (gender, age at diagnosis, diagnosis group) is given in table 1. Of the 698 cases included in this study, 364 (52 percent) were born in 1989–1994, yielding a prevalence proportion among the early birth cohorts of 3.5 per 10,000 and a prevalence proportion among the late birth cohorts of 9.2 per 10,000 (overall, 5.2 per 10,000) by January 1, 2000. Only 18 percent of cases ($n = 129$) were diagnosed according to the ICD-8 system; thus, the majority of cases were diagnosed after 1993 (a few in 1993), according to ICD-10.

TABLE 1. Gender, age at diagnosis, and diagnosis group for infantile or atypical autism cases and associated controls among all children born in Denmark after 1972 and at risk of autism until the end of 1999

	Cases ($n = 698$)	Controls ($n = 17,450$)	%
Gender			
Male	531	13,275	76.1
Female	167	4,175	23.9
Age at diagnosis (years)			
1–5	324	8,100	46.4
6–10	206	5,150	29.5
11–15	98	2,450	14.0
16–20	48	1,200	6.9
21–24	22	550	3.2
Diagnosis group			
ICD-8*	129	3,225†	18.5
ICD-10*	569	14,225†	81.5

* ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision.

† Number of controls matched to cases diagnosed according to the given diagnosis group.

A description of age at diagnosis for different case groups is given in table 2.

Perinatal risk factors

In the unadjusted analyses, breech presentation, low Apgar score ($\leq$7) at 5 minutes, low birth weight ($\leq$2,500 g), gestational age at birth of less than 35 weeks, and being small for gestational age were associated with a statistically significantly increased risk of autism (table 3). Furthermore, high parental age (mother, $\geq$30 years; father, $\geq$35 years) was found to be statistically significantly associated with the risk of autism. No statistically significant associations were found between autism and multiple gestation, preeclampsia, number of previous pregnancies, number of antenatal visits, or smoking reported at the first antenatal visit.

TABLE 2. Age at diagnosis for infantile or atypical autism cases among all children born in Denmark after 1972 and at risk of autism until the end of 1999

	No.	%	Age at diagnosis (years)		
			Mean	Median	Range
All	698	100.0	7.7	6.0	1–24
Males	531	76.1	8.4	6.0	1–24
Females	167	23.9	7.5	6.0	1–24
Diagnosed before 1994	154	22.1	6.2	5.0	1–20
Diagnosed in 1994–1999	544	77.9	8.1	6.0	1–24

We found an increased risk of autism for children whose birth weight was less than 2,501 g in general and less than 2,001 g in particular. When we restricted the analysis to children born at term ($\geq$37 weeks, 619 cases and associated controls), the risk of autism remained higher for children whose birth weight was less than 2,501 g (birth weight $<$2,001 g: risk ratio = 4.35, 95 percent confidence interval: 1.48, 12.77; birth weight 2,001–2,500 g: risk ratio = 2.21, 95 percent confidence interval: 1.45, 3.36) compared with children whose birth weight was 3,001–3,500 g.

Parental psychiatric history and socioeconomic status

The unadjusted analyses showed a statistically increased risk of autism associated with parental history of any psychiatric disease. In addition, low parental wealth was associated with an increased risk of autism, while no statistically significant association was found between autism and maternal education. The analyses stratified on birth year for the socioeconomic variables showed the same trends over the period before 1980 (112 cases) as for 1980–1994 (586 cases). Slightly higher risk estimates were found for the earlier period but, because of the smaller number of cases, also wider 95 percent confidence intervals.

Stratified analyses, as well as tests for interactions, did not reveal any differences in the risk of autism associated with any of the investigated risk factors by gender, age at diagnosis, or diagnosis group.

Adjusted analyses

Because of exclusion of multiple gestations and the limited coverage period for some variables, a total of 595 cases and associated controls were included in the adjusted analyses. The results may be interpreted by comparing them with the unadjusted results just described, because unadjusted analyses on this subset showed the same patterns as on the total sample. On the basis of the results from model 1, which included all perinatal factors, the risk of autism was increased for breech presentation, children whose gestational age at birth was less than 35 weeks, children who were small for gestational age, and children whose Apgar score was 7 or less at 5 minutes (table 4, model 1). We observed an increased risk of autism for children of young mothers (aged $<$20 years) and for children of older fathers (aged $\geq$35 years).

The results for the adjusted analyses were similar when information about parental psychiatric history and socioeconomic status was added, either separately or together, to the first adjusted model (table 4, model 2). However, the associations between autism and being small for gestational age, having a young mother ($<$20 years), and having an older father ($\geq$35 years) became statistically insignificant. The full model revealed a marked increased risk of autism for the children of parents with a psychiatric history of schizophrenia-like psychosis or affective disorder. In the full model, parental wealth was not associated with a significantly increased risk of autism.

TABLE 3. Distributions, unadjusted risk ratios, and 95% confidence intervals for perinatal risk factors, parental psychiatric history, and socioeconomic characteristics among children born in Denmark after 1972 and at risk of autism until the end of 1999

	Cases ($n = 698$)		Controls ($n = 17,450$)		RR*	95% CI*
	No.	%	No.	%		
Fetal presentation						
Cephalic	620	88.8	16,364	93.8	Reference	
Breech	58	8.3	851	4.9	1.80	1.36, 2.38
Other	5	0.7	54	0.3	2.44	0.97, 6.13
Missing	15	2.2	181	1.0		
Apgar score at 5 minutes†						
10	543	88.6	14,119	92.1	Reference	
8–9	34	5.6	858	5.6	1.03	0.72, 1.47
1–7	18	2.9	177	1.2	2.63	1.61, 4.31
Missing	18	2.9	171	1.1		
Birth weight (g)						
≤1,500	16	2.3	106	0.6	3.99	2.31, 6.87
1,501–2,000	25	3.6	153	0.9	4.24	2.73, 6.60
2,001–2,500	43	6.2	632	3.6	1.79	1.28, 2.51
2,501–3,000	112	16.1	2,521	14.5	1.18	0.93, 1.48
3,001–3,500	221	31.7	5,843	33.5	Reference	
3,501–4000	181	25.9	5,607	32.1	0.85	0.70, 1.04
4,001–4,500	78	11.2	2,111	12.1	0.97	0.75, 1.26
>4,500	16	2.3	423	2.4	0.99	0.59, 1.67
Missing	6	0.9	54	0.3		
Gestational age at birth (weeks)†						
<35	38	6.2	299	2.0	3.32	2.35, 4.71
35–36	18	2.9	453	3.0	1.04	0.64, 1.68
37–42	536	87.4	14,011	91.4	Reference	
>42	5	0.8	150	1.0	0.88	0.36, 2.14
Missing	16	2.6	412	2.7		
Birth weight for gestational age†						
Small for gestational age (<10th decile)	82	13.4	1,590	10.4	1.32	1.04, 1.68
Appropriate for gestational age	459	74.9	11,764	76.8	Reference	
Large for gestational age (>90th decile)	52	8.5	1,525	9.9	0.87	0.65, 1.17
Missing	20	3.3	446	2.9		
Multiple gestation						
No	679	97.3	17,021	97.5	Reference	
Yes	19	2.7	429	2.5	1.11	0.70, 1.77
Preeclampsia‡						
No	353	97.0	8,919	98.0	Reference	
Yes	11	3.0	181	2.0	1.54	0.83, 2.86
No. of antenatal visits†						
≥9	485	79.1	12,937	84.4	0.87	0.68, 1.12
6–8	90	14.7	1,786	11.7	Reference	
1–5	25	4.1	366	2.4	0.98	0.59, 1.63
0/missing	13	2.1	236	1.5		

Table continues

TABLE 3. Continued

	Cases ($n = 698$)		Controls ($n = 17,450$)		RR	95% CI
	No.	%	No.	%		
No. of previous pregnancies						
0	244	35.0	6,064	34.8	1.05	0.89, 1.24
1–2	344	49.6	8,948	51.3	Reference	
≥3	109	15.6	2,429	13.9	1.17	0.94, 1.46
Missing	1	0.1	9	0.1		
Smoking (first antenatal visit)§						
Yes	79	31.7	1,857	29.8	1.06	0.80, 1.39
No	159	63.9	3,953	63.5	Reference	
Unknown	11	4.4	415	6.7		
Maternal age (years)						
<20	20	2.9	400	2.3	1.41	0.88, 2.25
20–24	136	19.5	3,818	21.9	1.00	0.81, 1.24
25–29	250	35.8	7,080	40.6	Reference	
30–34	206	29.5	4,507	25.8	1.30	1.08, 1.57
35–39	66	9.5	1,386	7.9	1.36	1.03, 1.79
>39	20	2.9	259	1.5	2.19	1.37, 3.52
Paternal age (years)						
<25	56	8.0	1,933	11.0	0.81	0.60, 1.08
25–29	206	29.5	5,803	33.3	Reference	
30–34	216	30.9	5,688	32.6	1.07	0.88, 1.30
35–39	127	18.2	2,580	14.8	1.40	1.11, 1.75
>39	77	11.0	1,287	7.4	1.69	1.29, 2.22
Missing	16	2.3	159	0.9		
Parental psychiatric history						
No psychiatric history	568	81.4	16,187	92.8	Reference	
Schizophrenia-like psychosis	10	1.4	61	0.4	4.81	2.44, 9.48
Affective disorder	19	2.7	159	0.9	3.44	2.12, 5.58
Substance abuse	14	2.0	200	1.2	2.01	1.16, 3.47
Other	87	12.5	843	4.8	2.96	2.33, 3.74
Maternal education						
Elementary school	254	36.4	5,848	33.5	Reference	
High school/vocational/high school + 3 years	291	41.7	8,026	46.0	0.83	0.70, 0.99
Bachelor's/master's/doctorate degree	102	14.6	2,467	14.1	0.95	0.75, 1.20
Missing	51	7.3	1,109	6.4		
Parental wealth						
Highest	284	40.7	7,749	44.4	Reference	
High middle	173	24.8	5,288	30.3	0.89	0.73, 1.08
Low middle	144	20.6	3,002	17.2	1.31	1.07, 1.61
Lowest	96	13.8	1,370	7.9	1.92	1.51, 2.44
Missing	1	0.1	41	0.2		

* RR, risk ratio; CI, confidence interval.
† Covers birth years 1978–1994 only: 613 cases and 15,325 controls.
‡ Covers birth years 1978–1990 only: 364 cases and 9,100 controls.
§ Covers birth years 1991–1994 only: 249 cases and 6,225 controls.

TABLE 4. Adjusted risk ratios and 95% confidence intervals for perinatal risk factors, parental psychiatric history, and socioeconomic characteristics among children born in Denmark after 1977 and at risk of autism until end of 1999

	Model 1*		Model 2†	
	RR‡	95% CI‡	RR	95% CI
Fetal presentation				
Cephalic	Reference		Reference	
Breech	1.62	1.17, 2.24	1.63	1.18, 2.26
Other	1.86	0.57, 6.12	1.92	0.58, 6.36
Apgar score at 5 minutes				
10	Reference		Reference	
8–9	0.85	0.59, 1.24	0.84	0.58, 1.23
1–7	1.97	1.15, 3.36	1.89	1.10, 3.27
Gestational age at birth (weeks)				
<35	2.57	1.64, 4.03	2.45	1.55, 3.86
35–36	1.05	0.63, 1.75	1.06	0.63, 1.77
37–42	Reference		Reference	
>42	0.93	0.38, 2.29	0.97	0.40, 2.39
Birth weight for gestational age				
Small for gestational age (<10th decile)	1.30	1.01, 1.68	1.28	0.99, 1.65
Appropriate for gestational age	Reference		Reference	
Large for gestational age (>90th decile)	0.87	0.65, 1.17	0.90	0.67, 1.22
No. of antenatal visits				
≥9	0.87	0.68, 1.12	0.91	0.70, 1.17
6–8	Reference		Reference	
1–5	0.98	0.59, 1.63	0.88	0.52, 1.48
0/missing	1.05	0.56, 1.99	1.02	0.54, 1.95
No. of previous pregnancies				
0	1.02	0.84, 1.23	1.06	0.87, 1.29
1–2	Reference		Reference	
≥3	0.92	0.71, 1.18	0.83	0.64, 1.08
Maternal age (years)				
<20	1.82	1.04, 3.18	1.54	0.87, 2.74
20–24	1.12	0.87, 1.44	1.03	0.80, 1.34
25–29	Reference		Reference	
30–34	1.15	0.92, 1.43	1.18	0.95, 1.48
35–39	1.02	0.72, 1.43	1.07	0.76, 1.52
>39	1.48	0.84, 2.61	1.55	0.87, 2.74
Paternal age (years)				
<25	0.62	0.42, 0.90	0.61	0.42, 0.89
25–29	Reference		Reference	
30–34	1.13	0.90, 1.42	1.10	0.88, 1.38
35–39	1.33	1.00, 1.77	1.28	0.96, 1.69
>39	1.58	1.12, 2.23	1.36	0.96, 1.93
Parental psychiatric history				
No psychiatric history			Reference	
Schizophrenia-like psychosis			3.44	1.48, 7.95
Affective disorder			2.91	1.65, 5.14
Substance abuse			1.42	0.73, 2.75
Other			2.85	2.20, 3.69
Maternal education				
Elementary school			Reference	
High school/vocational/high school + 3 years			0.92	0.75, 1.13
Bachelor's/master's/doctorate degree			0.89	0.67, 1.19
No information			1.02	0.72, 1.44
Parental wealth				
Highest			Reference	
High middle			0.83	0.67, 1.02
Low middle			1.09	0.85, 1.38
Lowest			1.30	0.97, 1.75
No information			1.04	0.13, 8.18

* Adjusted model including all perinatal factors; each variable was controlled for all of the other variables in the model.

† Adjusted model including perinatal factors, parental psychiatric history, and socioeconomic characteristics; each variable was controlled for all of the other variables in the model.

‡ RR, risk ratio; CI, confidence interval.

DISCUSSION

The main strengths of this study are its large, population-based sample and the fact that information on both risk factors and autism was collected prospectively, thereby being independent of parental recall. Furthermore, the data we used are relatively complete because of the uniformly organized and comprehensive health care system in Denmark. This system allows access to health care personnel and psychologists at all schools and enables extensive evaluation and diagnosis of autism, led by specialists in child psychiatry. Severe autism is likely to be diagnosed and reported to the PCR at some point. Diagnosis and reporting of less severe or atypical autism cases are probably less complete. Our case sample and estimates of prevalence in the birth cohorts showed an increased prevalence of autism in birth cohorts over time. This trend was also reflected in the incidence over time, as studied by Madsen et al. (30), who also used information from the PCR. They reported trends and rates (about 0.5 per 10,000 until 1990, increasing to about 9 per 10,000 until 1999, for children aged 2–9 years) similar to those in studies conducted in other countries (31, 32). The increase in incidence may reflect a true rise in the true incidence. However, factors such as increased attention to autism spectrum disorders and the change in diagnostic criteria during the last decade may explain part of the increase. In addition, inclusion of outpatients from 1995 onward may have exaggerated the rates in the later years, which may also explain the increase in age in the later years as patients attending child psychiatric treatment before 1995 were recorded for the first time.

We believe that the validity of our data is high concerning the diagnosis of autism. Madsen et al. (28) found a validity of 92.5 percent when they examined the ICD-10 autistic disorder diagnosis. Furthermore, the results from analyses stratified on both diagnosis group and age at diagnosis suggest that neither the change in classification system from ICD-8 to ICD-10 nor the age at diagnosis had a major influence on the overall results. However, differences in the associations between the risk factors and autism by diagnostic subgroups within the autism spectrum were not considered in this study.

The quality of information on risk factors is also considered high. The MBR suffers from changes in coding systems over time, but we found no indication of differences in distributions of the variables over time, and any small differences would be independent of the diagnosis of autism. The IDA is limited because it started in 1980, which might have led to overestimation of the risks of autism associated with socioeconomic status. It could be imagined that having a child with autism is detrimental to income and/or education. However, analyses stratified on birth years before and after 1980 indicated that the risks associated with the different wealth and education groups might have been overestimated, although the evidence was limited because of very few cases and also because only 16 cases were diagnosed with autism before 1980.

The finding of an association between perinatal risk factors and autism corroborates earlier studies showing that autism is related to adverse pregnancy and delivery processes, reflected in breech presentation, low Apgar score, gestational age at birth of less than 35 weeks, and being small for gestational age. Interpretation of these risk factors individually is difficult since the factors may reflect various aspects of the same adverse event during pregnancy. The effect of breech presentation, low Apgar score, and gestational age at birth of less than 35 weeks did not disappear after adjustment for other potential risk factors, which may be due to residual confounding. However, it may also reflect different etiologic aspects of a compromised infant. Intrauterine conditions, maybe in combinations with external environmental exposures or specific genotypes, may lead to developmental or growth disturbances. Another possibility is that autistic persons may react differently to the intrauterine environment, leading to fetal distress during the last part of pregnancy and during delivery.

Our findings show a strong association between birth weight and autism. Birth weight is the net result of at least three factors: genetic growth potential, duration of the pregnancy, and rate of fetal growth. The genetic growth potential is unknown, making it difficult to disentangle the effect of these factors (33). Our findings of an increased risk of autism associated with gestational age at birth of less than 35 weeks, low birth weight among children born at term, and being small for gestational age indicate that both intrauterine growth retardation and preterm birth are associated with an increased risk of autism. These findings are consistent with those of a recent large, register-based study from Sweden (18).

Although our findings indicate associations between intrauterine disturbances and autism, it is unknown whether the disturbances may directly compromise the fetus and result in autism or whether they reflect the effects of a fetus compromised by other factors. Other investigations have suggested that the association may be due to either a genetic vulnerability to both autism and adverse pregnancy outcome or the possibility that the intrauterine environment harbors a condition from which the fetus does not recover (12).

Research has suggested that birth order (especially first or last born) is a risk factor for autism (12, 17, 34) and that differences in the number of unfavorable pre- or perinatal events between autistic children and siblings were attributable to differences in parity (17, 35). Our study contradicts these results; in both unadjusted and adjusted analyses, we found no association between number of previous pregnancies and autism.

Although we observed a strong association between parental psychiatric history and autism, adding parental psychiatric history to the multivariable model had little impact on the association between the perinatal risk factors and autism, suggesting that these factors are independently associated with autism. In our data, the psychiatric diagnosis for the parents originated before the date of case diagnosis but not necessarily before the birth of the child; therefore, the order of precedence in terms of etiology is uncertain. For example, autistic children of parents with a diagnosed psychiatric disorder may more likely to be identified and diagnosed than autistic children of parents without a psychiatric diagnosis. However, genetic links have been found between schizoid personality traits and autism (22, 36), and

children of schizophrenic mothers are at increased genetic risk of schizophrenia and neurodevelopmental impairment (37, 38). The causal direction between autism and parental affective disorder, substance abuse, or other mental illness is less clear. Because genetic inheritance patterns may differ for mothers and fathers, it would be ideal to consider psychiatric history of the mother and the father separately. The number of affected parents was limited in this study, so we were unable to consider parental differences related to the risk of autism in the offspring.

Genetic inheritance might be related to high parental age (39). However, our adjusted results showed no increased risk of autism associated with high parental age.

We did not adjust for preeclampsia and smoking in our adjusted analyses; information on these factors was available for limited time periods only. Both of these factors are associated with reduced fetal growth (40, 41), and smoking may affect the behavioral outcome in childhood (42). The results from the unadjusted analyses showed only weak associations between autism and each of these two factors, which argues against a strong confounding effect.

In contrast to previous studies, we were able to adjust for information about socioeconomic status. In the unadjusted analyses, the risk of autism was higher for those with less parental wealth; however, after we adjusted for other variables, socioeconomic status—measured by either parental wealth or maternal education—did not have a significant effect. Adjustment for socioeconomic status did not have any influence on the associations between perinatal factors and autism. Thus, socioeconomic factors play little or no role in the etiology of autism in Denmark, where access to the health care system is equally available for all and is free of charge.

Of the risk factors investigated in this study, parental psychiatric history was associated with the highest independent risk of autism. Parental psychiatric history was more common among the cases (17 percent) than the presence of one or more of the significant adverse perinatal risk factors: breech presentation, low Apgar score, and gestational age at birth of less than 35 weeks (13 percent). For only 2 percent of the cases, both risk factors were present. The results suggest that prenatal environmental factors and parental psychopathology are associated with the risk of autism and that these factors seem to act independently. Because none of the single significant risk factors found in this study were present in the majority of cases, we still have much to learn about the many different factors that contribute to autism and how they may potentially interact.

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