Recurrence of Autism Spectrum Disorders in Full- and Half-Siblings and Trends Over Time:

A Population-Based Cohort Study

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Abstract

IMPORTANCE—To date, this is the first population-based study to examine the recurrence risk for autism spectrum disorders (ASDs), including time trends, and the first study to consider the ASDs recurrence risk for full- and half-siblings.

OBJECTIVES—To estimate the relative recurrence risk for ASDs in a Danish population, including recurrence in full- and half-siblings, and to examine time trends in ASDs relative to the recurrence risk.

DESIGN, SETTING, AND PARTICIPANTS—Population-based cohort study in Denmark. All children (about 1.5 million) born in Denmark between January 1, 1980, and December 31, 2004, were identified and followed up to December 31, 2010. We identified a maternal sibling subcohort derived from mothers with at least 2 children and a paternal sibling subcohort derived from fathers with at least 2 children.

EXPOSURES—Children having an older sibling with ASDs are compared with children not having an older sibling with ASDs.

MAIN OUTCOMES AND MEASURES—The adjusted hazard ratio for ASDs among children having an older sibling with ASDs compared with children not having an older sibling with ASDs.

RESULTS—The overall relative recurrence risk for ASDs was 6.9 (95% CI, 6.1–7.8), and it did not change significantly over time; similar risks were observed in maternal and paternal full-

siblings. The relative recurrence risks were 2.4 (95%CI, 1.4–4.1) for maternal half-siblings and 1.5 (95%CI, 0.7–3.4) for paternal half-siblings.

CONCLUSIONS AND RELEVANCE—Our population-based recurrence risk estimate is lower than the recently reported estimates from clinical samples. Our results demonstrate no time trend in the ASDs recurrence risk as seen in the ASDs prevalence. The difference in the recurrence risk between full- and half-siblings supports the role of genetics in ASDs, while the significant recurrence risk in maternal half-siblings may support the role of factors associated with pregnancy and the maternal intrauterine environment in ASDs.

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by difficulties in social interaction and communication accompanied by stereotypic, repetitive behavior and narrow interests.[1,2] Childhood autism (CA)[1,2] accounts for approximately 30% of all ASD cases[3] and generally is the most severe form of ASDs. The reported prevalence of ASDs has increased during the last 2 decades. The ASDs prevalence is estimated to be approximately 1%[4–6] but has been reported to be as high as 2.6%.[7] The rise in the reported ASDs prevalence may be rooted in a multitude of factors, such as earlier diagnosis, revised diagnostic criteria, improved case identification, and greater awareness of the disorders, as well as a true increase in the ASDs prevalence.[8] The cause remains unknown for most individuals with ASDs, although it is likely that multiple factors contribute, such as perinatal factors, specific genes, and de novo mutations.

The genetic component in ASDs is believed to be strong. A higher concordance has been reported in monozygotic twins than in dizygotic twins,[9–11] but twin studies are often limited by small study samples and ascertainment bias.[12] The results of a recent twin study[13] suggest a smaller effect of genetic factors and a larger effect of environmental factors than previous studies. An important measure of genetic contribution to ASDs is the risk for recurrence in siblings of a child with ASDs. Siblings of an affected child have been reported to be at much higher risk for ASDs than the background population,[14–16] although studies[14,16–20] are few, with only 2 being recent studies[16,20] (Table 1).

Previous studies[14,16–20] about the ASD recurrence risk estimated the risk as a proportion of affected later-born siblings based on study samples that only consisted of children with ASDs and their siblings. This required the investigators to compare their estimated recurrence risk with an external, potentially outdated, estimated ASDs prevalence from other studies[14,16,18]; therefore, they could not account for changes in the ASDs prevalence over time. A more valid approach is to compare the recurrence risk with the general ASDs risk at the same time in the base population from which sibships were drawn, providing a relative measure of the ASD recurrence risk.

The primary objective of this study was to estimate in a Danish population-based cohort the ASD relative recurrence risk in later-born siblings compared with the ASD risk in the background population at the same time. Another unique feature of the analysis was examination of the relative recurrence risk for both full- and half-siblings. The increasing ASDs prevalence over time also raises the question whether the profile of causative factors contributing to ASDs, including the genetic contribution as seen in the recurrence risk, has

changed over time. Therefore, a secondary study objective was to examine potential time trends in the ASD relative recurrence risk.

Methods

Study Population

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health. The study cohort consisted of all children born between January 1, 1980, and December 31, 2004, identified in the Danish Medical Birth Registry,[21] comprising 1 546 667 children, including multiple births. Excluding multiple births, we identified the following 2 subcohorts: (1) a maternal sibling subcohort derived from mothers with at least 2 children and consisting of their first and second live-born children (comprising 464 057 sibling pairs) and (2) a paternal sibling subcohort derived from fathers with at least 2 children and consisting of their first and second live-born children (comprising 484 189 sibling pairs) (Figure). Because parity is defined with regard to maternal reproductive history and because first and second live-born children of the same father may have different mothers, the paternal sibling pairs may not always be parity 1 and 2, unlike the maternal sibling pairs. Most full-siblings in the maternal sibling subcohort (92.9%) were also included as full-siblings in the paternal sibling subcohort.

All live-born children in Denmark are assigned a personal identification number.[22] This unique number was used to link information from the national registries. Mothers were linked to their children in the Danish Medical Birth Registry, and fathers were linked to their children through the Danish Civil Registration System.[22] Data on death were obtained from the Danish Civil Registration System.

Main Outcome Measures

Diagnoses of ASDs are entered in the Danish Psychiatric Central Register,[23] which includes information on all inpatient admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark since April 1, 1969, and all outpatient contact since January 1, 1995. All registered diagnoses are made by psychiatrists. Children who are suspected of having an ASD are referred by general practitioners or school psychologists to a child psychiatric ward, where they are evaluated by a multidisciplinary team and are assigned a final diagnosis by a child psychiatrist. All cases of ASDs are registered in the Danish Psychiatric Central Register once a formal diagnosis is established and without regard to need for treatment or educational provisions. The *International Classification of Diseases, Eighth Revision* (*ICD-8*)[1] was the diagnostic instrument used by physicians in Denmark from April 1, 1969, through January 1, 1994. In 1994, the *International Statistical Classification of Diseases, 8th Revision* (*ICD-8*) was replaced by the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*),[2] which is still being used. The main study outcome measure was ASDs (*ICD-8* codes 299.00, 299.01, 299.02, and 299.03 and *ICD-10* codes F84.0, F84.1, F84.5, F84.5, and F84.9). A second outcome measure was CA (*ICD-8* code 299.00 and *ICD-10* code F84.0). A follow-up period began for all children from birth and continued until diagnosis of ASDs (or CA) or death or the end

of follow-up period on December 31, 2010, whichever occurred first, providing at least 6 years of follow-up data for each child.

Statistical Analysis

In the population cohort, the ASDs prevalence and recurrence risk were estimated using Kaplan-Meier methods. For the population cohort, siblings were defined as having the same mother. In the recurrence risk estimation, the younger sibling became at risk for an ASDs diagnosis when the older sibling was diagnosed as having ASDs (time-dependent covariate). We only estimated the recurrence risk for the birth year groups with at least 5 recurrent cases. For the relative recurrence risk, the hazard ratio (HR) associated with an ASD in an older sibling was estimated using Cox proportional hazards regression model, with separate diagnostic baseline rates for each birth year to adjust for changes in the ASDs prevalence over time. Multiple births underwent specific analysis. If the older sibling having an ASD diagnosis was a multiple birth, then the undiagnosed multiples were not classified as exposed because only younger siblings were considered exposed. If younger siblings were part of a multiple birth and had an older sibling diagnosed as having an ASDs, each child in the multiple birth counted as a child at risk for a recurrence. We also estimated the recurrence risks with the exclusion of all multiple births.

Because ASDs is a rare disorder (<10% prevalence),we can interpret an HR as a relative risk[24]; hence, we interpret our estimates as the relative recurrence risks. The group having no ASD diagnoses in older siblings is representative of the background population. Similarly, we estimated the prevalence, the recurrence risk, and the relative recurrence risk for CA in cases in which both the index child and the older sibling had a CA diagnosis. The Cox proportional hazards regression assumption was evaluated for all variables by comparing estimated log-minus-log survivor curves over the different categories of variables investigated. Control for the lack of independence of children within the same family was obtained using a robust (Huber-White Sandwich) variance estimator.

In the adjusted analyses, we included parity, sex of the child, parental age at birth, and parental psychiatric history.[25,26] Information about birth date and sex is included with the personal identification number. Maternal and paternal ages were categorized into the following 3 groups: younger than 35 years, 35 to 39 years, and 40 years or older. Parental psychiatric history was obtained from the Danish Psychiatric Central Register. Maternal and paternal psychiatric histories were defined as at least 1 psychiatric diagnosis (*ICD-8* code 290–315 and *ICD-10* codes F00–F99) before the birth of the child. Parity was obtained from the Danish Civil Registration System, which included all siblings for each child, from which the parity was calculated. Parity was grouped as 1, 2, and 3 or more.

We estimated the crude and adjusted relative recurrence risks for the whole cohort. We also estimated the adjusted relative recurrence risks using the definition of parental psychiatric history as a psychiatric diagnosis before the first-born child of the mother.

Based on the 2 subcohorts, we estimated the crude and adjusted relative recurrence risks for ASDs for the following 4 types of siblings: (1) full-siblings in the maternal sibling subcohort (parity 1 and 2), (2) maternal half-siblings, (3) full-siblings in the paternal sibling subcohort

(all parities), and (4) paternal half-siblings. Furthermore, we estimated the crude relative recurrence risks for ASDs in the 4 combinations of sexes of the first-born and second-born children (eAppendix in the Supplement).

Results

The distribution of the variables included in the adjusted analysis is summarized in Table 2 for children having an older sibling with ASDs and for children not having an older sibling with ASDs. A total of 13 164 cohort children were diagnosed as having ASDs, of which 3494 were diagnosed as having CA. Table 3 lists the number of births and the ASDs and CA cases and prevalence, as well as the number of recurrent cases and the recurrence risks for the birth year groups. The overall cohort prevalence of ASDs was 1.2% (95% CI, 1.2%– 1.2%), and there were 276 recurrent ASDs cases. Across the birth year groups, the ASDs recurrence risks ranged from 4.5% to 10.5%. The overall cohort prevalence of CA was 0.3% (95% CI, 0.3%–0.3%), and the CA recurrence risks ranged from 4.1% to 8.8%; for most years, the CA recurrence risk could not be estimated because of fewer than 5 recurrent cases. The relative recurrence risks are summarized in Table 4. Children with an older sibling diagnosed as having ASDs were almost 7 times more likely to be diagnosed as having ASDs compared with children without an older sibling having ASDs (adjusted HR [aHR], 6.9; 95% CI, 6.1–7.8). The relative recurrence risk for CA was almost twice as high as that for ASDs (aHR, 13.0; 95% CI, 9.4–18.0). No significant time trend was observed in the relative recurrence risk for ASDs ($P = .77$) (Table 4); there were too few cases to investigate time trends for CA.

Of 464 057 sibling pairs in the maternal sibling subcohort, 4061 first-born children and 3978 second-born children had an ASD. Of 484 189 sibling pairs in the paternal sibling subcohort, 3987 first-born children and 4000 second-born children had an ASD. We found comparable relative recurrence risk estimates for ASDs in the maternal and paternal sibling subcohorts compared with the whole population cohort (Table 5). In the maternal sibling subcohort, we found a lower but statistically significant relative recurrence risk for ASDs for maternal half-siblings (aHR, 2.4; 95% CI, 1.4–4.1) compared with that for full-siblings (aHR, 7.5; 95% CI, 6.3–9.0) ($P < .001$). Compared with the maternal sibling subcohort estimates, the adjusted relative recurrence risk in the paternal sibling subcohort was comparable in full-siblings (aHR, 7.4; 95% CI, 6.2–8.9; $P < .001$), but the risk in paternal half-siblings was lower (aHR, 1.5; 95% CI, 0.7–3.4). Furthermore, the adjusted relative recurrence risk for ASDs for paternal half-siblings was nonsignificant ($P = .32$).

Changing the definition of parental psychiatric history in any of the adjusted analyses did not markedly change the estimates (data not shown). Similarly, exclusion of all multiple births did not change the results.

Discussion

The recurrence risks for ASDs varied from 4.5% to 10.5% depending on the birth year group, which is a much higher than the ASDs risk of 1.18% (95% CI, 1.16%–1.21%) in the overall Danish population. In adjusted analyses, we found an almost 7-fold increase in ASDs

risk if an older sibling had an ASD diagnosis compared with no ASD diagnoses in older siblings, and no significant time trend was observed in the ASD relative recurrence risk during 25 birth years in the study period. In children with the same mother, the adjusted relative recurrence risk of 7.5 in full-siblings was significantly higher than the risk of 2.4 in half-siblings. In children with the same father, the adjusted relative recurrence risk was 7.4 in full-siblings and significant, but no statistically significant increased risk was observed among paternal half-siblings.

Our absolute recurrence risk estimates (4.5%–10.5%) are lower than the other recent estimates[16,20] based on enrollment of families with at least 1 child having an ASD. Siblings of a child with ASD may have a higher risk for being diagnosed as having ASD than children in a family with no ASD diagnoses in part because of increased parental awareness. This increased awareness might enhance the recurrence risk relative to the general population risk. However, a parental awareness effect may be mitigated somewhat in population-based studies like ours that include all families and void bias from differential participation. Our estimate of the relative recurrence risk is lower than what can be derived from the recurrence risk estimates and the referent ASDs prevalence reported recently.[16]

Twin studies[9–12] investigated the genetic contribution to ASDs using the estimates of heritability. From these twin studies and reports of a high sibling recurrence risk, the genetic component in ASDs is believed to be strong. The results of a recent twin study[13] suggest that the environmental component in ASDs is much stronger than previously believed. However, ASDs twin studies have been limited by small sample sizes and potential ascertainment bias. Our estimates of the absolute and relative recurrence risks support the genetic pathway to ASDs, but they suggest a lower inherited genetic contribution to ASDs recurrence than previous findings. Furthermore, we found no significant trend in the relative recurrence risk over time, despite an overall increase in ASDs prevalence. Therefore, the factors contributing to the risk for ASDs recurrence in siblings (perhaps a combination of genetic and environmental factors) either have not changed over time, or the changes have not affected the risk for recurrence. In our data, the ASDs absolute recurrence risk was about 7 times the ASDs risk in the general population. With an ASDs prevalence of about 1%, our best estimate for a benchmark for parental counseling is 7%.

The relative recurrence risk is a measure of the contribution to ASD origin from genes and environmental factors shared within the family. The genetic contribution includes the genes transmitted from parent to offspring. A fundamental genetic difference between full-siblings and half-siblings is that full-siblings share one-half of their genes (the genetic contributions from both shared parents), whereas half-siblings only share one-quarter of their genes (the genetic contribution from the shared parent). The significantly higher relative recurrence risk for ASDs in full-siblings compared with both maternal and paternal half-siblings supports the genetic pathway to ASDs because full-siblings are genetically more similar than half-siblings. In contrast, familial environmental factors include maternal perinatal factors and intrauterine environment and the family's lifestyle. Maternal half-siblings share genes from their mother, as well as exposures derived from their mother's intrauterine environment and perinatal history that may be common across her different pregnancies; paternal half-siblings share genes from their father but lack shared environmental factors

associated with pregnancy. The significantly elevated relative recurrence risk for ASDs in maternal half-siblings, along with the somewhat lower risk in paternal half-siblings that was not significant, suggests that environmental factors unique to the mother's pregnancy history may contribute to ASDs. An important issue to address in the study of ASD recurrence is the tendency that parents having a child with ASDs may choose to not have any more children. This phenomenon, known as stoppage, may result in an underestimate of the recurrence risk for several reasons,[27] including the possibility that parents who stop reproducing are systematically different from the ones who continue. Those who stop may be parents of children with the most severe ASD cases, and these may be the families with the strongest genetic component. In this example, the liability of recurrence may be higher among the parents who stop, and our recurrence risk estimates become a lower boundary for the recurrence risk. Therefore, it would be relevant to estimate the recurrence risks in families with more than 1 affected individual, but this was impossible in the present study.

Parental psychiatric history is known to be associated with the risk for ASDs[26,28,29] and should be adjusted for in analyses concerning other risks for ASDs. In recurrence risk studies, the definition of parental psychiatric history may be problematic because the parental psychiatric diagnoses could be a consequence of an older sibling's ASD diagnosis. To address this potential source of uncontrolled confounding, we changed the parental psychiatric history definition to only include diagnoses before birth of the first-born child, and we observed no change in the results in the adjusted analyses.

The CA diagnosis in the Danish Psychiatric Central Register has been validated[25]; among 499 evaluated medical records of children diagnosed as having CA, 94% met the criteria for CA. The quality of ASD diagnosis has not been validated but is generally believed to be high.[30] We are potentially missing some ASD diagnoses made before 1995 because children are not registered as having ASDs if they were only seen in the outpatient clinic from January 1, 1980, through December 31, 1994, and had no contact with a psychiatric ward after 1994. However, this potential outcome misclassification is most likely nondifferential for the recurrence risk because we observed no trend in the relative recurrence risk over time. There may be undetected cases, resulting in underestimation of the ASDs prevalence and recurrence risks.

In conclusion, our results based on a large, population-based sample and adjustment for several important confounders indicate a recurrence risk for ASDs of about 7%, which is substantially lower than recent reports from smaller, clinic-based populations. If used as a benchmark for parental counseling, this estimate should be reassuring to parents having a child with an ASD if they are considering having another child.[31,32] Although the results from our comparison of recurrence in full- and half-siblings support the role of genetics in ASDs, the significant recurrence in maternal half-siblings may support the idea of a contributing role of factors associated with pregnancy and the maternal intrauterine environment. Finally, the lack of a time trend in the relative recurrence risk in our data suggests that the likely combination of genetic and environmental factors contributes to the risk for ASD recurrence in siblings or that the risk for recurrence because of such factors has not been affected by the rise in the ASD prevalence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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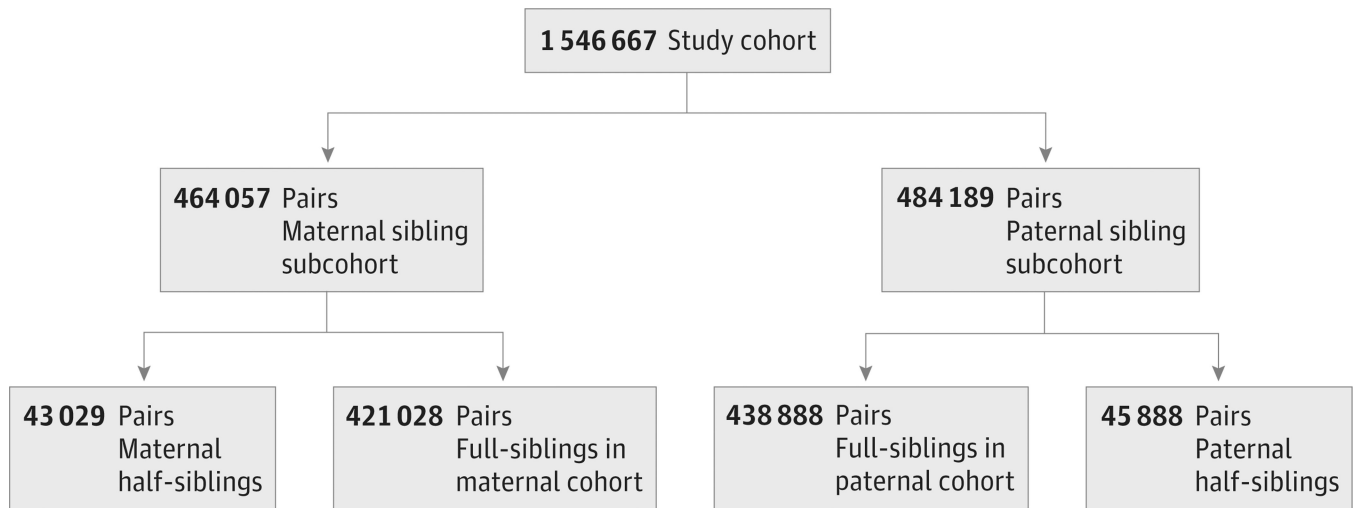
Figure.
The Study Cohort and Maternal and Paternal Sibling Subcohorts

Table 1

Overview of the ASDs Recurrence Risk Studies

Source	Siblings	Birth Years	Sample Size	Recurrence Risk (95% CI), %[a]	Referent ASDs Prevalence[a]	Relative Recurrence Risk
Ritvoetal,[14] 1989	Later born	1960–1984	207 Families having 1 child with ASD	8.6 (5.8–12.2)	4 Per 10 000	215[a]
Boltonetal,[17] 1994	All	NA	99 Families having 1 child with ASD	5.8	NA	NA
Chudley et al,[18] 1998	All	Assessed between January 1991 and August 1996	86 Families having 1 child with ASD	7.1	2 Per 1000	36[b]
Sumi et al,[19] 2006	All	1995–1999	269 Families having 1 child with ASD	10.0 (6.0–18.1)	21 Per 1000	5[b]
Constantino et al,[16] 2010	Later born	1989–2003	1235 Families having 1 child with ASD	14.2	9 Per 1000	16[b]
Ozonoff et al,[20] 2011	Later born	NA	664 Infants having an older sibling with ASD	18.7 (13.3–25.5)	NA	NA

Abbreviations: ASD, autism spectrum disorder; NA, not available.

[a] As reported in the article.

[b] Calculated from the estimates reported in the article.

Table 2

Description of the Study Cohort

Variable	ASDs, No. (%)	
	Yes (n = 7284)	No (n = 1 539 383)
ASDs in an older sibling		
Yes	276 (3.8)	12 888 (0.8)
No	7008 (96.2)	1 526 495 (99.2)
Childhood autism in an older sibling		
Yes	83 (1.1)	3411 (0.2)
No	7201 (98.9)	1 535 972 (99.8)
Sex		
Male	3698 (50.8)	790 241 (51.3)
Female	3586 (49.2)	749 142 (48.7)
Maternal age at birth, y		
<35	5809 (79.8)	1 368 920 (88.9)
35–39	1277 (17.5)	148 585 (9.7)
40	198 (2.7)	21 878 (1.4)
Paternal age at birth, y		
<35	4434 (60.9)	1 148 224 (74.6)
35–39	1848 (25.4)	258 136 (16.8)
40	958 (13.2)	119 595 (7.8)
Missing	44 (0.6)	13 428 (0.9)
Maternal psychiatric history[a]		
Yes	340 (4.7)	31 131 (2.0)
No	6944 (95.3)	1 508 252 (98.0)
Paternal psychiatric history[a]		
Yes	230 (3.2)	28 247 (1.8)
No	7054 (96.8)	1 511 136 (98.2)

Abbreviation: ASDs, autism spectrum disorders.

[a]Parental psychiatric history defined as at least 1 psychiatric diagnosis before the birth of the child.

Table 3

Description of the Study Cohort, With the ASDs and Childhood Autism Prevalence and Recurrence Risk in Danish Families Among Births From 1980 to 2004

Birth Year of the Index Child	No. of Births	No. of Cases	Prevalence (95% CI), %	No. of Recurrent Cases	Recurrence Risk (95% CI), %
ASDs					
1980–1984	265 223	782	0.3 (0.3–0.3)	1	NA
1985–1989	285 047	1765	0.7 (0.6–0.7)	11	5.7 (2.6–12.3)
1990–1991	127 642	1228	1.0 (0.9–1.1)	13	4.5 (2.5–7.8)
1992–1993	135 024	1515	1.2 (1.1–1.2)	24	8.7 (5.4–13.9)
1994–1995	139 393	1864	1.5 (1.4–1.5)	33	7.1 (4.8–10.3)
1996–1997	135 376	1681	1.4 (1.3–1.5)	54	10.5 (7.8–14.0)
1998–1999	132 573	1542	1.3 (1.2–1.4)	48	9.4 (7.0–12.6)
2000–2001	132 625	1386	1.2 (1.1–1.3)	41	7.0 (5.1–9.5)
2002–2004	193 764	1401	1.0 (0.9–1.0)	51	5.8 (4.4–7.7)
Overall	**1 546 667**	**13 164**	1.2 (1.2–1.2)	**276**	6.1 (5.3–7.0)[a]
Childhood Autism					
1980–1984	265 223	114	0.0 (0.0–0.1)	0	NA
1985–1989	285 047	259	0.1 (0.1–0.1)	3	NA
1990–1991	127 642	213	0.2 (0.1–0.2)	0	NA
1992–1993	135 024	317	0.2 (0.2–0.3)	3	NA
1994–1995	139 393	436	0.3 (0.3–0.4)	2	NA
1996–1997	135 376	457	0.4 (0.3–0.5)	8	8.8 (4.1–18.3)
1998–1999	132 573	525	0.4 (0.4–0.5)	8	6.5 (3.2–13.0)
2000–2001	132 625	517	0.4 (0.4–0.5)	6	4.3 (1.9–9.3)
2002–2004	193 764	656	0.4 (0.4–0.4)	12	4.1 (2.3–7.3)
Overall	**1 546 667**	**3494**	0.3 (0.3–0.3)	**42**	3.7 (2.7–5.2)[a]

Abbreviations: ASDs, autism spectrum disorders; NA, not available.

[a] Calculated using all the birth years.

Table 4

Autism Spectrum Disorders (ASDs) and Childhood Autism Relative Recurrence Risk in Danish Families Among Births From 1980 to 2004

Variable	Relative Recurrence Risk (95% CI)	P Value[a]
ASDs		
Study cohort crude	6.1 (5.4–6.9)	<.001
Study cohort adjusted[b]	6.9 (6.1–7.8)	<.001
Birth years		
1980–1984	7.4 (1.0–53.7)	.05
1985–1989	5.9 (3.2–10.6)	<.001
1990–1991	5.5 (3.2–9.6)	<.001
1992–1993	5.6 (3.7–8.4)	<.001
1994–1995	4.8 (3.3–6.8)	<.001
1996–1997	7.2 (5.4–9.4)	<.001
1998–1999	6.7 (5.0–9.0)	<.001
2000–2001	5.5 (4.0–7.6)	<.001
2002–2004	6.8 (5.1–9.1)	<.001
Childhood Autism		
Study cohort crude	12.6 (9.2–17.4)	<.001
Study cohort adjusted[b]	13.0 (9.4–18.0)	<.001

[a] Test for no relative recurrence risk. No significant time trend was observed in the relative recurrence risk for ASDs ($P = .77$, test for no time trend).

[b] Parental psychiatric history defined as at least 1 psychiatric diagnosis before the birth of the child.

Table 5

Autism Spectrum Disorders (ASDs) Relative Recurrence Risk in the Maternal and Paternal Sibling Subcohorts

Variable	Crude Relative Recurrence Risk (95% CI)	P Value[b]	P Value[c]	Adjusted Relative Recurrence Risk (95% CI)[a]	P Value[b]	P Value[c]
Maternal Sibling Subcohort						
All	6.5 (5.5–7.7)	<.001		6.3 (5.3–7.4)	<.001	
Full-siblings	7.5 (6.2–8.9)	<.001	<.001	7.5 (6.3–9.0)	<.001	<.001
Half-siblings	2.4 (1.4–4.2)	.002		2.4 (1.4–4.1)	.002	
Paternal Sibling Subcohort						
All	6.4 (5.4–7.6)	<.001		6.3 (5.3–7.5)	<.001	
Full-siblings	7.5 (6.3–9.0)	<.001	<.001	7.4 (6.2–8.9)	<.001	<.001
Half-siblings	1.4 (0.6–3.2)	.37		1.5 (0.7–3.4)	.32	

[a] Parental psychiatric history defined as at least 1 psychiatric diagnosis before the birth of the child.

[b] Test for no relative recurrence risk.

[c] Test for no difference in the relative recurrence risk for full-siblings and half-siblings.