Original Investigation

The Familial Risk of Autism

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IMPORTANCE Autism spectrum disorder (ASD) aggregates in families, but the individual risk and to what extent this is caused by genetic factors or shared or nonshared environmental factors remains unresolved.

OBJECTIVE To provide estimates of familial aggregation and heritability of ASD.

DESIGN, SETTING, AND PARTICIPANTS A population-based cohort including 2 049 973 Swedish children born 1982 through 2006. We identified 37 570 twin pairs, 2 642 064 full sibling pairs, 432 281 maternal and 445 531 paternal half sibling pairs, and 5 799 875 cousin pairs. Diagnoses of ASD to December 31, 2009 were ascertained.

MAIN OUTCOMES AND MEASURES The relative recurrence risk (RRR) measures familial aggregation of disease. The RRR is the relative risk of autism in a participant with a sibling or cousin who has the diagnosis (exposed) compared with the risk in a participant with no diagnosed family member (unexposed). We calculated RRR for both ASD and autistic disorder adjusting for age, birth year, sex, parental psychiatric history, and parental age. We estimated how much of the probability of developing ASD can be related to genetic (additive and dominant) and environmental (shared and nonshared) factors.

RESULTS In the sample, 14 516 children were diagnosed with ASD, of whom 5689 had autistic disorder. The RRR and rate per 100 000 person-years for ASD among monozygotic twins was estimated to be 153.0 (95% CI, 56.7-412.8; rate, 6274 for exposed vs 27 for unexposed); for dizygotic twins, 8.2 (95% CI, 3.7-18.1; rate, 805 for exposed vs 55 for unexposed); for full siblings, 10.3 (95% CI, 9.4-11.3; rate, 829 for exposed vs 49 for unexposed); for maternal half siblings, 3.3 (95% CI, 2.6-4.2; rate, 492 for exposed vs 94 for unexposed); for paternal half siblings, 2.9 (95% CI, 2.2-3.7; rate, 371 for exposed vs 85 for unexposed); and for cousins, 2.0 (95% CI, 1.8-2.2; rate, 155 for exposed vs 49 for unexposed). The RRR pattern was similar for autistic disorder but of slightly higher magnitude. We found support for a disease etiology including only additive genetic and nonshared environmental effects. The ASD heritability was estimated to be 0.50 (95% CI, 0.45-0.56) and the autistic disorder heritability was estimated to 0.54 (95% CI, 0.44-0.64).

CONCLUSIONS AND RELEVANCE Among children born in Sweden, the individual risk of ASD and autistic disorder increased with increasing genetic relatedness. Heritability of ASD and autistic disorder were estimated to be approximately 50%. These findings may inform the counseling of families with affected children.

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Autism spectrum disorder (ASD) affects almost 1% of all children born in the United States[1] and is defined as impairment in social interaction and communication and the presence of restricted interests and repetitive behaviors. Autistic disorder is the most profound form of ASD.[1]

Family studies found that ASD aggregates in families and early twin studies estimated the proportion of the phenotypic variance due to genetic factors (the heritability) to be about 90%,[2-6] making it the most heritable of all developmental disorders. As a consequence, etiological research in ASD has focused predominantly on genetic factors.[7] Although recent twin studies support high heritability,[5,6] a large twin study[7] indicated a substantial role for shared environmental influences. Results of family studies also raise questions about the relative influence of genetic factors[8] and contribute to uncertainty regarding the etiology of ASD.

Previous studies have limitations. Twin studies often have small samples, limiting the reliability when studying rare diseases such as ASD. None of the previous studies represent a prospective, population-based, random sample, which raises concerns for potential biases introduced by population selection. Restricted follow-up time and possible differences in etiology for different ASD subtypes may also limit reliability.

Although heritability estimates provide a valuable metric for estimating the effects of genetic factors in the population, they do not provide any information on individual risk. Detailed etiological models will require accounting for risk on a population level, as well as providing quantitative information in a given individual, thus allowing for individualized disease prevention and treatment.[9] Recurrence risk expresses the risk of having another affected family member in an already-affected family. The relative recurrence risk (RRR) measures this recurrence in relation to disease in families without any affected members but can be interpreted and compared between groups that may differ in disease prevalence.

Consequently, there is a need for reliable estimates of heritability for ASD, as well as combining these population-based estimates with individual-level risk estimates to provide a more precise and complete picture of the etiology of ASD.

To that goal, we conducted a longitudinal cohort study of all births in Sweden between 1982 and 2006. Using all pairs of monozygotic and dizygotic twins, full siblings, half siblings, and cousins in the population, we determined the family clustering of ASD by estimating RRR within families and assessed the importance of genetic vs environmental factors associated with ASD.

Methods

Study Population

The study was approved by the ethics committee at the Karolinska Institutet, Stockholm, Sweden. Informed consent was waived by the ethics committee. A birth cohort of all children born alive in Sweden between January 1, 1982, and December 31, 2006, was established using data from Swedish national registers including the Swedish Medical Birth Register,[10] the Swedish Multi-generation Register,[11] the National Patient Register,[12-14] the Swedish Twin Registry,[15] and the Statistics Sweden Total Population Register for vital statistics. Single-child families were excluded from the cohort. Twin zygosity was obtained from the Swedish Twin Registry, and was determined by DNA analysis in 86% of same-sex twins. For the remainder, an algorithm based on 5 parent-reported items assessing twin similarity was used. The Swedish Multi-generation Register contains identifiers for the parents of all children born from 1932 onwards. This allowed us to determine family relations (full siblings, maternal and paternal half siblings, and cousins) using the unique identifiers of the parents and grandfathers. Cousins were derived for full siblings only. Further details are provided in eAppendix A in the Supplement. Data are collected routinely by Swedish government agencies and were merged and anonymized by an independent government agency (Statistics Sweden), and the code linking the personal identification numbers to the new case numbers was destroyed immediately after merging.

Ascertainment of Autism and Psychiatric Diagnosis

In Sweden, all infants and preschool children regularly undergo routine medical and developmental examinations. At age 4 years, a mandatory developmental assessment (motor, language, cognitive, and social development) is conducted. Children with suspected developmental disorders are referred for further assessment by a specialized team in a child psychiatry unit or habilitation service. Diagnostic information is reported to the National Patient Register. The register has nearly complete national coverage[12] of psychiatric diagnoses since 1973. With a rare disease, the sensitivity is a smaller problem than the specificity of the diagnostic codes. We relied on previous validation studies of psychiatric codes generally[12,14] and for autism specifically.[16] Prospective follow-up was conducted until December 31, 2009. Autistic disorder was defined by codes from the *International Classification of Diseases, version 9* code 299.A/B/X and *version 10* (*ICD-10*) code F84.0; ASD also included *ICD-10* codes F84.1 (atypical autism), F84.5 (Asperger syndrome), F84.8 (other pervasive developmental disorders), and F84.9 (pervasive developmental disorder, unspecified).

Covariates

We considered several factors that might confound or modify the familial associations. Parental psychiatric history has been associated with autism in the offspring. Parental psychiatric history was classified as present or not present for each parent separately using any psychiatric diagnosis at any time before the birth of the oldest child in a sibling or cousins pair using *ICD 7th-10th revisions* (eTable 1 in the Supplement). We also obtained information on paternal and maternal age at birth of the child, birth year, and sex.

Statistical Methods

Relative Recurrence Risk

The RRR for siblings is the risk of an autism diagnosis in a sibling of a child with autism compared with a sibling of a child without autism. We calculated RRR in families of different genetic relatedness: full siblings, half siblings, and cousins. Cousin

pairs were defined as cohort members having the same grandparents but no parents in common. To allow a direct comparison between cousin RRR and sibling RRR, we did not consider cousins between single-child families.

We estimated the RRR for ASD by a Cox proportional hazards regression model using sibling-attained age as the underlying time scale.[17] Each individual in a sibling or cousin pair was entered into the cohort and followed for a diagnosis of autism starting from the age of 1 year or from January 1, 1987 (when a code for autism was first available), whichever came last. Each sibling or cousin was then followed-up to his/her first autism diagnosis, death, emigration, or death or emigration of the sibling without autism or December 31, 2009, whichever came first. The exposure (sibling with or without autism) was treated as a time-varying covariate in the models. Each sibling in a family typically contributed to the calculations in 2 ways: as an exposed sibling and as a proband per pair. An individual sibling may have contributed to more than 1 pair. Consequently, we used robust standard errors to account for the dependence between (pairs of) individuals in a family.[18] Further details of the RRR calculations is given in eAppendix A in the Supplement.

For descriptive purposes, we calculated the cumulative probability (ie, the prevalence) of ASD up to the age of 20 years using the Cox model. For the calculation of RRR, the Cox model makes an implicit assumption of hazards ratios constant across time (age of the sibling). We verified the validity of this assumption by plotting the Schoenfeld residuals.[19]

A change in RRR for later birth cohorts may be due to truncation of follow-up time or changes in incidence. The children born in 1982 were followed-up for 28 years, whereas the children born in 2006 were only followed-up for 3 years. In the Cox model, this could show up as a violation of the proportional hazards assumption, for which we tested. To address this further, we calculated the RRR by birth cohort using all available follow-up time.

The RRR was calculated separately for monozygotic and dizygotic twins, full siblings, and maternal and paternal half siblings, as well as for cousins. We excluded twins from the sibling analyses. We considered several factors that might confound the RRR, including parental psychiatric history, parental age, birth year, and sex of the exposing sibling. As parental psychiatric history and parental age may be on a causal path between familial risk and adverse developmental outcome, we fitted models adjusting for confounding with and without these covariates. We treated the covariates categorically as sex of the exposed sibling and of the proband, birth cohort (1982-1986, 1987-1991, 1992-1996, 1997-2001, and 2002-2006), maternal age (≤35 years and >35 years) and paternal age (≤40 years and >40 years) of the exposed sibling, and paternal and maternal psychiatric history (yes or no) at birth of the oldest sibling.

Heritability

Autism diagnosis is a dichotomy (yes or no). By assuming that a continuous normally distributed trait underlies the observed autism diagnosis, the correlation of autism diagnosis between family members can be estimated. These are called tetrachoric correlations and are frequently calculated in family and twin studies to obtain approximate estimates of genetic and nongenetic influences. We fitted liability-threshold models using monozygotic and dizygotic twins, full siblings, paternal half siblings, and maternal half siblings to decompose the variance in liability into factors for additive genetic effect (reflecting inherited additive effects of different alleles), nonadditive genetic factors (reflecting interaction effects between alleles at the same gene locus), shared environmental factors (reflecting nongenetic influences that contribute to similarity within pairs of siblings), and nonshared environmental factors (reflecting experiences that make sibling pairs dissimilar). From each family, 1 sibling pair was randomly included in the calculations.

Using likelihood ratio tests, we compared the full model vs different smaller submodels obtained by dropping both or only 1 of the 4 genetic and environmental parameters in order to explain the observed data and pattern of variance, using as few parameters as possible. The proportion of the ASD liability contributed by genetic factors, the heritability, was then calculated as the variance associated with the genetic term(s) divided by the total variance. Details of the models are presented in eAppendix B in the Supplement.

All calculations were done for ASD and autistic disorder separately. All tests of statistical hypothesis were done on the 2-sided 5% level of significance. We used SAS software (SAS Institute), version 9.3, and the R software (for Cox model, Linux 64-bit package; for heritability, OpenMx, version 1.3.1-2179[20]), version 2.15.2.

In addition, we also performed a few sensitivity analyses. We calculated the ASD RRR by adjusting for 1-year birth cohorts using natural splines. To assess whether the ASD RRRs were dependent on family size, stoppage (couples who stopped reproducing following the onset of the disorder in a child), or fertility, we calculated the full siblings RRR in subgroups of family size.

Results

The cohort included a total of 2 049 973 unique siblings or cousins; 2 642 064 full sibling pairs, 432 281 maternal half sibling pairs, 445 531 paternal half sibling pairs and 37 570 twin pairs and 5 799 875 cousin pairs. We found 14 516 children with ASD, of whom 5689 (39%) had a diagnosis of autistic disorder (**Table 1**). The male:female ratio was 2.7 for ASD cases and 2.4 for autistic disorder cases.

For individuals with a full sibling with ASD, the cumulative probability of an ASD diagnosis at age 20 years was estimated to be 12.9% compared with 1.2% for individuals without (**Figure 1**). The cumulative probability of an ASD diagnosis at age 20 years was 59.2% for monozygotic twins, 12.9% for dizygotic twins, 8.6% for maternal half siblings, 6.8% for paternal half siblings, and 2.6% for cousins.

Relative Recurrence Risk

Figure 2 presents adjusted RRR for ASD and associated 2-sided 95% CIs for the different degrees of genetic distance between

Table 1. Confounder and Baseline Characteristics Across Sibling Relations, the Study Participant, and His/Her Exposing Proband[a]

Variable	Siblings			Cousins	Twins	
	Full	Maternal Half	Paternal Half		Dizygotic	Monozygotic
Participants	1 788 009	288 671	286 705	1 241 166	29 032	8338
Participant pairs (discordant)[b]	2 641 822 (34 465)	432 114 (8896)	445 335 (8179)	5 798 842 (73 615)	29 216 (411)	8354 (56)
Boys, %	51.5	51.2	51.1	51.5	51.0	47.2
Cases, No. (%)						
ASD	12 033 (0.67)	2955 (1.02)	2538 (0.89)	8073 (0.65)	215 (0.74)	41 (0.49)
Autistic disorder	4762 (0.27)	1000 (0.35)	877 (0.31)	2996 (0.24)	97 (0.33)	21 (0.25)
Psychiatric history, No. (%)[c]						
Maternal	39 233 (2.2)	18 419 (6.4)	14 475 (5.0)	25 180 (2.0)	908 (3.1)	196 (2.4)
Paternal	38 427 (2.1)	15 666 (5.4)	16 137 (5.6)	23 778 (1.9)	792 (2.7)	200 (2.4)
Age ≥35, No. (%)						
Maternal	209 941 (11.7)	41 019 (14.2)	37 624 (13.1)	132 881 (10.7)	1216 (14.6)	6590 (22.7)
Paternal	149 650 (8.3)	26 685 (9.2)	40 900 (14.3)	79 668 (6.4)	776 (9.3)	4020 (13.8)
Median (5th-95th percentile)						
Birth year	1993 (1984-2005)	1993 (1983-2005)	1993 (1983-2005)	1993 (1984-2004)	1996 (1983-2005)	1994 (1982-2002)
Age at ASD diagnosis	13 (4-22)	13 (4-22)	13 (4-23)	13 (4-22)	11 (4-21)	10 (4-25)
Person-years	14 (4-23)	10 (3-20)	10 (3-20)	15 (4-24)	13 (4-25)	14 (7-26)

Abbreviation: ASD, autism spectrum disorder.

[a] Besides the "sibling pairs," the statistics (count, percent, median, and percentiles) are calculated across unique participants in each group.

[b] Pairs are the pairs of siblings (cousins) who enter the statistical analysis.

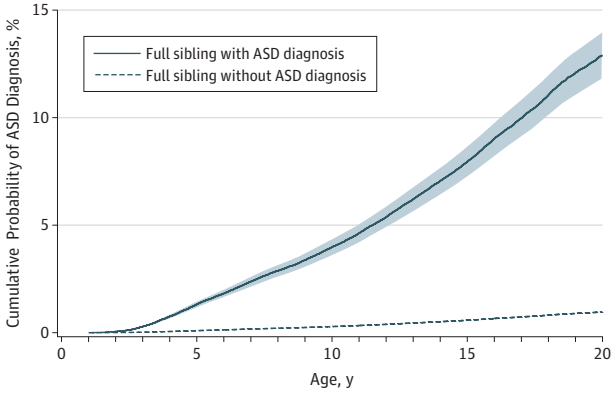
[c] At birth of the proband, that is, at the birth of the oldest sibling in the family.

family relatives (rates in eTable 2 in the Supplement). The RRR remained stable after adjustment for sex, parental psychiatric history, and parental age. There was some support for confounding attributable to birth cohorts (Figure 2). When adjusting for 5-year birth cohorts, sex, parental age, and parental psychiatric history, the RRR and rate per 100 000 person-years for monozygotic twins was 153.0 (95% CI, 56.7-412.8; rate, 6274 for exposed vs 27 for unexposed); for dizygotic twins, 8.2 (95% CI, 3.7-18.1; rate, 805 for exposed vs 55 for unexposed); for full siblings, 10.3 (95% CI, 9.4-11.3; rate, 829 for exposed vs 49 for unexposed); for maternal half siblings, 3.3 (95% CI, 2.6-4.2; rate, 492 for exposed vs 94 for unexposed); for paternal half siblings, 2.9 (95% CI, 2.2-3.7; rate, 371 for exposed vs 85 for unexposed); and for cousins, 2.0 (95% CI, 1.8-2.2; rate, 155 for exposed vs 49 for unexposed). For crude RRR, see eTable 3 in the Supplement.

RRR for autistic disorder are presented in **Figure 3** and rates in eTable 4 in the Supplement. Adjusting for 5-year birth cohorts, sex, parental age, and parental psychiatric history, the RRR and rate per 100 000 person-years for monozygotic twins was 116.8 (95% CI, 16.7-814.2; rate, 4748 for exposed vs 14 for unexposed); for dizygotic twins, 16.9 (95% CI, 5.1-55.7; rate, 776 for exposed vs 25 for unexposed); for full siblings, 14.6 (95% CI, 12.5-17.1; rate, 486 for exposed vs 124 for unexposed); for maternal half siblings, 4.3 (95% CI, 2.5-7.5; rate, 240 for exposed vs 33 for unexposed); for paternal half siblings, 2.9 (95% CI, 1.5-5.9; rate, 124 for exposed vs 31 for unexposed); and for cousins, 2.3 (95% CI, 1.8-2.8; rate, 61 for exposed vs 18 for unexposed).

There was no statistically significant difference in RRR between boys or girls or in RRR in participants with a male or female sibling (Figure 2 and Figure 3). The model goodness of fit supported the assumption of hazards being proportional over the time of follow-up. For the sensitivity analyses of ASD RRR for full siblings, adjusting for 1-year birth cohorts did not change the results (RRR, 9.9 [95% CI, 9.0-10.8]) and the ASD RRR did not change in subgroups of family size (eTable 5 in the Supplement).

Figure 1. Age-Cumulative Probabilities for ASD Diagnosis in Siblings With a Full Sibling With ASD and in Siblings With a Full Sibling Without an ASD Diagnosis



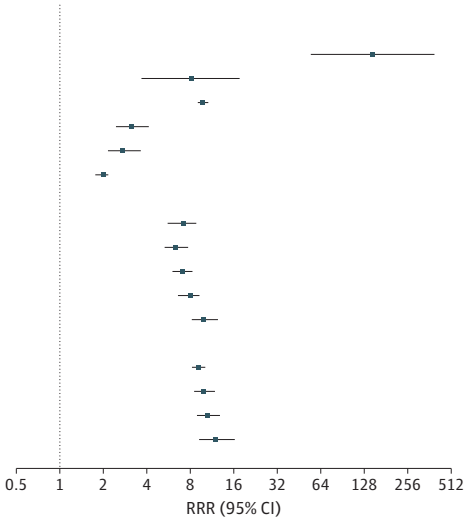
ASD indicates autism spectrum disorder. Shaded areas represent 95% 2-sided point-wise confidence interval bands. The siblings who had a full-sibling with ASD were followed for 76 481 person-years resulting in 634 ASD events. The siblings who had a full sibling without ASD were followed for 35 486 922 person-years resulting in 17 327 ASD events.

Heritability

The unadjusted ASD tetrachoric correlation was estimated to be 0.54 (SD, 0.20) for monozygotic twins; 0.25 (SD, 0.13) for dizygotic twins; 0.25 (SD, 0.02) for full siblings; 0.11 (SD, 0.04) for maternal half siblings; and 0.07 (SD, 0.05) for paternal half siblings (eTable 6). The correlations for autistic disorder are presented in eTable 7. The tetrachoric correlations adjusted for sex and birth cohort were almost identical (eTable 6 and eTable 7 in the Supplement).

Figure 2. Adjusted Relative Recurrence Risks for Autism Spectrum Disorder Among Full and Maternal and Paternal Half Siblings, Cousins, and Monozygotic and Dizygotic Twins

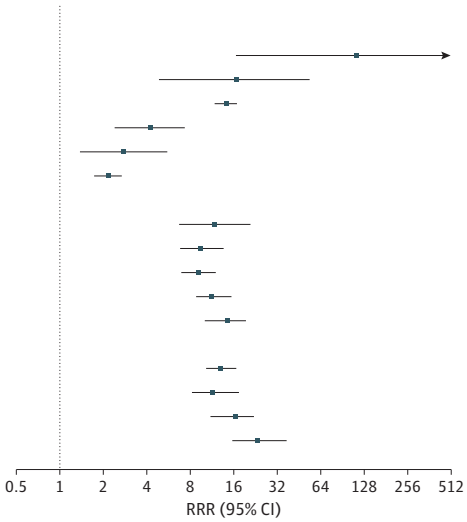
	Rate of ASD per 100 000 Person-Years		Person-Years of Follow-up		
Source	Exposed	Unexposed	Exposed	Unexposed	RRR (95% CI)
Family Types					
Monozygotic twins	6274	27	130 720	96	153.0 (56.7-412.8)
Dizygotic twins	805	55	385 521	869	8.2 (3.7-18.1)
Full siblings	829	49	35 486 922	76 481	10.3 (9.4-11.3)
Maternal half siblings	492	94	4 641 500	16 273	3.3 (2.6-4.2)
Paternal half siblings	371	85	4 651 888	15 638	2.9 (2.2-3.7)
Cousin	155	49	148 053 914	31 373	2.0 (1.8-2.2)
Full Siblings Birth Cohorts					
1982-1986	463	26	8 750 181	14 467	7.3 (5.9-9.1)
1987-1991	728	45	12 268 494	24 580	6.6 (5.6-7.8)
1992-1996	1014	63	8 650 801	21 206	7.3 (6.3-8.4)
1997-2001	962	71	4 116 561	11 743	8.1 (6.9-9.6)
2002-2006	1338	64	1 700 884	4485	10.4 (8.3-13.1)
Full Siblings Gender Risk					
Male exposed to male	1036	67	9 378 760	28 587	9.4 (8.3-10.8)
Female exposed to male	512	28	8 871 116	27 527	10.4 (8.7-12.5)
Male exposed to female	1254	68	8 878 053	10 045	11.1 (9.2-13.4)
Female exposed to female	688	30	8 358 993	10 323	12.5 (9.6-16.3)



ASD indicates autism spectrum disorder; RRR, relative recurrence risk. Point estimates and 2-sided 95% CIs. Rate indicates the number of autism spectrum disorder cases per 100 000 person-years for participants exposed and unexposed for sibling autism spectrum disorder; person-year, the sum of years of follow-up for participants exposed and unexposed for sibling autism spectrum disorder. Model is adjusted for 5-year birth cohorts, sex, parental age, and parental psychiatric history.

Figure 3. Adjusted Relative Recurrence Risks for Autistic Disorder Among Full and Maternal and Paternal Half Siblings, Cousins, and Monozygotic and Dizygotic Twins.

	Rate of Autistic Disorder per 100 000 Person-Years		Person-Years of Follow-up		
Source	Exposed	Unexposed	Exposed	Unexposed	RRR (95% CI)
Family Types					
Monozygotic twins	4748	15	130 855	42	116.8 (16.7-814.2)
Dizygotic twins	776	25	386 501	387	16.9 (5.1-55.7)
Full siblings	486	20	35 574 718	34 138	14.6 (12.5-17.1)
Maternal half siblings	240	33	4 661 940	6250	4.3 (2.5-7.5)
Paternal half siblings	124	31	4 670 597	6436	2.9 (1.5-5.9)
Cousin	61	18	148 418 487	133 335	2.3 (1.8-2.8)
Full Siblings Birth Cohorts					
1982-1986	139	7	8 770 373	5032	12.4 (7.0-22.1)
1987-1991	362	15	12 302 896	9386	10.0 (7.1-14.1)
1992-1996	440	27	8 673 579	10 234	9.5 (7.2-12.7)
1997-2001	662	40	4 124 828	6642	11.9 (9.1-15.6)
2002-2006	1266	46	1 703 041	2844	14.8 (10.6-20.5)
Full Siblings Gender Risk					
Male exposed to male	647	28	9 411 567	12 987	13.6 (10.9-16.9)
Female exposed to male	219	11	8 892 456	12 343	12.2 (8.3-17.9)
Male exposed to female	792	29	8 899 609	4422	16.6 (11.7-23.5)
Female exposed to female	456	11	8 371 086	4386	24.7 (15.7-38.9)



RRR indicates relative recurrence risk. Point estimates and 2-sided 95% CIs. Rate indicates the number of autistic disorder cases per 100 000 person-years for participants exposed and unexposed for sibling autistic disorder; person-year, the sum of years of follow-up for participants exposed and unexposed for sibling autistic disorder. Model is adjusted for 5-year birth cohorts, sex, parental age, and parental psychiatric history.

Table 2. Autism Spectrum Disorder and Autistic Disorder Heritability

Models, Terms Included[b]	Model Comparison Measures				Estimated Variance (95% CI)[a]				
	No. of Parameters in the Model	-2 LL	Diff -2 LL	*P* Value[c]	Additive Genetic[d]	Dominant Genetic	Environment		Total Genetic[e]
							Shared	Nonshared	
Autism spectrum disorder									
Full model[f]	14	143 910	NA	NA	0.33 (0.00-0.55)	0.16 (0.00-0.59)	0.05 (0.00-0.17)	0.46 (0.24-0.65)	0.49 (0.21-0.75)
Excluding the dominant genetic term	13	143 910	0.7	.41	0.42 (0.19-0.55)	NA	0.04 (0.00-0.15)	0.54 (0.45-0.66)	0.42 (0.19-0.55)
Excluding the shared environment term	13	143 911	0.8	.38	0.44 (0.24-0.55)	0.13 (0.00-0.51)	NA	0.43 (0.23-0.55)	0.57 (0.45-0.77)
Excluding the additive genetic term	13	143 913	3.0	.08	NA	0.45 (0.18-0.71)	0.14 (0.07-0.20)	0.41 (0.21-0.62)	0.45 (0.18-0.71)
Additive genetic + nonshared environment	12	143 911	1.2	.55	0.50 (0.45-0.56)	NA	NA	0.50 (0.44-0.55)	0.50 (0.45-0.56)
Dominant genetic + nonshared environment	12	143 934	23.8	<.001	NA	1.00 (1.00-1.00)	NA	0.00 (0.00-0.00)	1.00 (1.00-1.00)
Shared + nonshared environment term	12	143 923	13.3	.001	NA	NA	0.24 (0.21-0.26)	0.76 (0.73-0.79)	NA
Nonshared environment term only	11	144 178	268.8	<.001	NA	NA	NA	1.00 (1.00-1.00)	NA
Autistic disorder									
Full model[f]	14	64 586	NA	NA	0.49 (0.00-0.64)	0.00 (0.00-0.61)	0.02 (0.00-0.24)	0.48 (0.18-0.72)	0.49 (0.04-0.82)
Excluding the dominant genetic term	13	64 586	0.0	.99	0.49 (0.04-0.64)	NA	0.03 (0.00-0.24)	0.48 (0.36-0.72)	0.49 (0.04-0.64)
Excluding the shared environment term	13	64 586	0.1	.81	0.54 (0.25-0.64)	0.00 (0.00-0.54)	NA	0.46 (0.17-0.56)	0.54 (0.44-0.83)
Excluding the additive genetic term	13	64 591	4.5	.03	NA	0.65 (0.00-0.84)	0.11 (0.04-0.30)	0.23 (0.10-0.79)	0.65 (0.00-0.84)
Additive genetic + nonshared environment	12	64 586	0.1	.97	0.54 (0.44-0.64)	NA	NA	0.46 (0.36-0.55)	0.54 (0.44-0.64)
Dominant genetic + nonshared environment	12	64 646	59.4	<.001	NA	1.00 (1.00-1.00)	NA	0.00 (0.00-0.00)	1.00 (1.00-1.00)
Shared + nonshared environment term	12	64 591	4.7	.096	NA	NA	0.26 (0.21-0.31)	0.74 (0.69-0.79)	NA
Nonshared environment term only	11	64 683	96.8	<.001	NA	NA	NA	1.00 (1.00-1.00)	NA

Abbreviations: Diff −2 LL, 2 * difference in log-likelihood between the model and the full model; NA, not applicable; −2 LL, −2 * log-likelihood.

[a] The 95% CIs are 2-sided.

[b] All models adjusted for sex and birth cohort.

[c] *P* value for the testing the hypothesis: the parameters not in the model but in the full model are all equal to zero.

[d] Additive genetic indicates narrow-sense heritability, which only includes the additive genetic component.

[e] Total genetic indicates broad-sense heritability, which includes both the additive and the dominant genetic.

[f] Full model includes terms for additive genetic, dominant genetic, shared environment, and nonshared environment (usually referred to as an ACDE model).

The model including additive genetic, shared and nonshared environmental parameters was chosen as the full model under which nested submodels were tested. The best fitting model was the model including only additive genetic and nonshared environmental parameters (**Table 2**). Using this model the ASD heritability was estimated to be 0.50 (95% CI, 0.45-0.56) and the nonshared environmental influence was 0.50 (95% CI, 0.44-0.55).

In the full model also including the shared environment, the variance associated with the shared environment was estimated to be 0.04 (95% CI, 0.00-0.15); nonshared environment, 0.54 (95% CI, 0.44-0.66); and heritability, 0.42 (95% CI, 0.19-0.55). Using only twins, the heritability was estimated to be 0.52.

For autistic disorder the model including only additive genetic and nonshared environment parameters was the best fitting model as well (Table 2) and the autistic disorder heritability was estimated to be 0.54 (95% CI, 0.44-0.64).

Discussion

Including more than 2 million families, this is, to our knowledge, the largest population-based longitudinal study evaluating familial risk of ASD. The RRR of ASD increased with increasing genetic relatedness. Genetic and nongenetic influences on the risk for ASD and autistic disorder were similarly important. The RRR of ASD was 10.3 for full siblings, 3.3

for maternal half siblings, 2.9 for paternal half siblings, and 2.0 for cousins. There is a well-documented sex bias in autism,[21] and it has been suggested that females may require greater familial etiological load to manifest the autistic phenotype.[22] We did not find support for any sex-specific differences in the RRR.

Heritability of ASD was estimated to be 50%, suggesting that genetic factors explain half of the risk for autism. This is considerably lower than the 90% in earlier twin studies[2-4] and closer to the 38% (95% CI, 14%-67%) reported in a recent California twin study,[7] but estimated with substantially higher precision. In a Swedish twin cohort[23] of 12 000 children, heritability of between 49% and 72% was reported for autisticlike traits (social impairment, communication impairment, and restricted and repetitive behavior and interests).

Earlier twin studies showed only minimal nonshared environmental contribution to the risk of ASD. A California twin study,[7] in contrast, suggested substantial shared environmental influences. The extensive family data in our study indicated that such influences have only a negligible effect on ASD etiology. Despite differences in shared maternal prenatal environment, dizygotic twins and full siblings had comparable risks for ASD and maternal half siblings and paternal half siblings had comparable risks for ASD. In the presence of familial confounding, factors affecting all members of a family, the RRR is expected to be lower for dizygotic twins compared with full siblings and for maternal half siblings compared with paternal half siblings.

The interpretation of the RRR of autism can be put in a wider context by comparing it with the RRR of schizophrenia, another neurodevelopmental disease that affects individuals, although later in life than autism, but with overlap in diagnosis and with shared clinical and etiological features.[24] In a sample overlapping with the parents and grandparents of our study, the RRR for schizophrenia was estimated to be 8.5 for full siblings, 2.5 for half siblings, and 2.3 for cousins.[25]

The differences with earlier research may be attributed to sampling, case ascertainment and analytical approach. Our study used a population-based sample, continuously following participants from birth. Previous twin studies relied on considerably less robust methodologies for case ascertainment, including self-referral, service registers, and parental reports of diagnosis. Even when detailed diagnostic assessment was done, the participation rates were low, and it could not be ruled out that participation was associated with presence of a child with autism in the family,[2] limiting generalizability. We adjusted for birth cohort, addressing biases due to differences in length of follow-up with participants in different birth years.[26] It is unclear how this was addressed in previous studies, but such a bias could inflate the shared environment component. Our low precision in RRR for monozygotic and dizygotic twins illustrates the problem in earlier small twin studies.

A possible factor affecting the variance for nonshared environment is the misclassification of cases, possibly due to differences in etiology across the different forms of ASD. Our data do not support this though, as our results for the liability of ASD and autistic disorder were similar.

The RRR between different pairs of family members reflects genetic influences and offers a quantitative measure of familial risk. Thus, the RRR has an important interpretation that distinguishes it from the more theoretical measures of heritability. For example, although genetic factors account for 50% of individual differences in risk of ASD, a sibling of a proband with ASD who shares 50% of the genes has a 10-fold increase in risk. This can potentially be applied at an individual level for family counseling.

Few earlier studies have been able to calculate RRR.[8,27,28] Two studies used self-selected samples[8,28] and had limited family data. A recent Danish study provided reliable estimates using an epidemiological sample similar to ours. They found lower RRR (7.5) for full siblings, but similar relative relationships between full siblings and maternal and paternal half siblings. Our sample included twice as many cases of ASD and more detailed family data, including monozygotic and dizygotic twins and cousins. Our larger sample also allowed us to investigate the sex of offspring in more detail. Several earlier studies have reported absolute sibling recurrence risk,[28-34] but absolute risk is a cumulative measure that depends on the length of follow-up (higher at age 15 years than at age 5 years) and will differ between populations. As elsewhere in epidemiology, where the relative risk is a preferred measure of disease risk, the RRR circumvents these limitations.

This study has multiple strengths, including the large, full-nation, population-based sample with prospective follow-up and a health system with equal access. In addition to sibling pairs, we were also able to include cousins and twins, including zygosity information, and adjust for parental psychiatric history. To estimate the RRR, we used time-to-event methods to avoid introduction of bias due to differences in follow-up time for different participants. Analyzing risk between siblings and not requiring the risk to act from an older to a younger sibling, which is frequently done, also adjusted for potential bias due to changes in prevalence of autism in later years when later-born siblings may be expected to have a higher risk of being diagnosed.

Our cohort approach with prospective follow-up, following all participants from birth using clinical registers, avoids selection biases due to disease status or factors such as parental education. It also avoids problems associated with self-report and retrospective collection of data.

Limitations include lack of information on parental education or socioeconomic status. In Sweden, there is free and equal access to health services, minimizing the risk of selection biases. Also, we were not able to study monozygotic twins raised together and apart and dizygotic twins raised together and apart, which could have contributed information to the estimation of the shared and nonshared environment.

Conclusions

Among children born in Sweden, the individual risk of ASD and autistic disorder increased with increasing genetic relatedness. Heritability of ASD and autistic disorder were estimated to be approximately 50%. These findings may inform the counseling of families with affected children.

ARTICLE INFORMATION

Author Contributions: Dr Sandin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Sandin, Hultman.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Sandin, Kuja-Halkola.
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Administrative, technical, or material support: Lichtenstein, Hultman.
Study supervision: Lichtenstein, Larsson, Hultman, Reichenberg.

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