Recurrence Risk of Autism in Siblings and Cousins: A Multi-National, Population-Based Study

RH = Familial Recurrence Risk of Autism

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Abstract

Objective: Familial recurrence risk is an important population-level measure of the combined genetic and shared familial liability of autism spectrum disorder (ASD). Objectives were to estimate ASD recurrence risk among siblings and cousins by varying degree of relatedness and by sex.

Method: Population-based cohort study of 1998-2007 livebirths from California, Denmark, Finland, Israel, Sweden and Western Australia followed through 2011-2015. Subjects were monitored for an ASD diagnosis in their older siblings or cousins (exposure) and for their own ASD diagnosis (outcome). The relative recurrence risk was estimated for different sibling- and cousin-pairs, for each site separately and combined, and by sex.

Results: During follow-up, 29,998 cases of ASD were observed among the 2,551,918 births used to estimate recurrence in ASD and 33,769 cases of childhood autism (CA) were observed among the 6,110,942 births used to estimate CA recurrence. Compared to the risk in unaffected families, we observed an 8.4-fold increase in the risk of ASD following an older sibling with ASD and an 17.4-fold increase in the risk of CA following an older sibling with CA. A 2-fold increase in the risk for cousin recurrence was observed for both disorders. We also found a significant difference in sibling ASD recurrence risk by sex.

Conclusion: Our estimates of relative recurrence risks for ASD and CA will assist clinicians and families in understanding autism risk in the context of other families in their population. The observed variation by sex underlines the need to deepen our understanding of factors influencing ASD familial risk.

Keywords: autism, recurrence, familial risk, multi-national, longitudinal

Introduction

Autism spectrum disorder (ASD) affects 1-2% of all children born in Europe, the United States and other developed regions[1,2], and is defined by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities.[3] The etiology of ASD includes a strong genetic component as seen by familial aggregation and variation in familial risk by degree of relatedness.[4] Familial aggregation has typically been measured by the familial recurrence risk [5-15].

Recurrence risk measures familial clustering owing to the combination of genetic factors and non-genetic factors shared within the family. For ASD, it is defined as the risk of ASD in a specific family member given that another family member is already affected by ASD.[16] The relative recurrence risk (RRR) quantifies the impact on ASD risk of having another family member with ASD and is defined as the risk of ASD among individuals with an affected family member compared to the risk of ASD among individuals without an affected family member. The RRR may be compared across populations with different ASD risk profiles and may be used as evidence of a genetic component in ASD by assessing how it varies in magnitude by degree of relatedness. In addition, the RRR may be used to inform families with an ASD child about a potentially elevated risk of ASD in subsequent children. Reliable estimates of the RRR are thus important to understand the familial liability of ASD.

Studies on recurrence risk have historically been based on twins with the concordance rate being of interest. The concordance rate is defined as the proportion of twin pairs where both have ASD among pairs with at least one ASD diagnosis yielding an absolute measure of recurrence risk. Several twin studies [5-7] have reported concordance rates for dizygotic twins well above 30% whereas one Swedish study reported a concordance rate around 15%.[8] Across all twin studies, however, has the concordance rate among monozygotic twins been more than twice as large as that of dizygotic twins – a ratio that aligns with the hypothesis of a strong genetic liability in ASD.[17]

As twin studies are often limited by small samples, there has been a growing interest in recurrence risk among non-twin siblings and cousins. Studies on ASD sibling recurrence have reported RRRs between 8 and 20 among full- and half-siblings, with full-sibling RRRs up to 3-fold that of half-siblings.[11,13-15] Only one study has estimated the RRR in cousins, reporting an RRR of 2.3 for ASD.[11] Additionally, a couple of studies found that the recurrence risk in US families depends on the sex of both the younger and older sibling.[18,19]

A Swedish study did, however, not find this pattern in the relative recurrence risk although this might just reflect the relatively small number of recurrent cases in their sample when stratified by sex.[11] Collectively the current literature suggests that ASD recurrence risk is large among siblings, that its magnitude among extended family members depends greatly on the degree of relatedness and likely also on their sexes. However, small sample sizes have limited reliable recurrence risk estimates among smaller subgroups, such as by sex, by varying degree of relatedness, or for childhood autism (CA) separately.[11,13] Studying these subgroups will enhance understanding of the familial risk across different ASD phenotypes and how it compares to that of CA which is the most severe subtype of ASD.

The aims of this study are to provide the most reliable and precise estimates of sibling and cousin recurrence risk to date for ASD and CA, overall as well as stratified by sex, using the first multi-national, population-based sample pooling data from California, Denmark, Sweden, Finland, Israel and Western Australia. For ASD as a whole, our data comprise over 2.5 million births and 29,998 ASD cases and for CA, our data comprise six million individuals and almost 33,769 CA cases. Our multi-national approach applies carefully harmonized data with a common analytic methodology across different sites thereby enhancing the validity of a combined analysis.

Method

This study is carried out as part of the 'Multigenerational Familial and Environmental Risk for Autism' (MINERvA) network. The purpose of MINERvA is to gain a better understanding of the etiologic roles of family history, prenatal environmental factors, and potential biologic mechanisms using multi-national, population-based data. The structure of MINERvA is based on the 'International Collaboration for Autism Registry Epidemiology' (iCARE) network[20] and uses the same software platform, ViPAR[21], to pool and analyze data across data sites. The study was approved and informed consent waived by the relevant ethical and data authorities at each individual site.

Study population

For analyses of ASD, the study population comprised all livebirths in Denmark, Finland, Sweden, and Western Australia in 1998-2007. The ASD data also included a sample of children from Israel whose parents were Meuhedet healthcare members; Meuhedet is one of four national non-profit health maintenance organizations in Israel and is the largest health care provider to children under age 15. Specifically, the data from Israel consisted of all live births in 1998-2007 who had an ASD diagnosis during follow-up (2015) and their siblings as well as a random sample of 33% of Meuhedet members born 1998-2007 and their siblings. For analyses of CA alone, an additional sample of singletons born 1998-2007 in California was included consisting of all children with at least one sibling born in the same period and a random sample of 10% of the remaining children. For all analyses and across all sites, only children with maternal information were included.

Familial information

Data on two-generational family linkages (parents and their offspring) were available from all sites. Data on three-generational family linkages, allowing the identification of cousins, were available in Denmark, Finland, Sweden and Western Australia. The Californian data used in the CA analyses had both two- and three-generational linkages, although three-generational linkages were available only for the subset of children whose parents were born in California from 1982 and onwards, corresponding to the availability of electronic birth certificate records in California. Information on linkages between offspring and parents were obtained either by birth certificates (California and Western Australia) or by the national birth register in the respective country (Denmark, Finland and Sweden). The use of birth certificates to create parental linkages has been described elsewhere for Western Australia[22] and so have the medical birthregisters in Denmark, Finland and Sweden[23-25]. In Israel, this information were sourced from a health provider, which only holds information on two-generational linkages.

For each child born 1998-2007 ('index child') we identified siblings, full-siblings, maternal- and paternal half-siblings. A sibling to an index child was defined as a child also born in 1998-2007 who shared the same mother. A full-sibling was defined as a child who shared the same mother and father, whereas maternal- and paternal half-siblings shared only one of their parents. For all index children we also identified the set of full- and half-cousins where data allowed. A full-cousin was defined as a child also born in 1998-2007 who shared two or more grandparents and a half-cousin shared only one grandparent. Moreover, we defined a cousin as either a half- or full-cousin.

Outcome and covariate information

Outcome and covariate information were provided by national health registers (Denmark, Finland, Sweden), by government-maintained health and administration registers (California, Western Australia) and by the Meuhedet register (Israel). Different diagnostic systems were used across sites (see Table S1, available online) and the diagnostic codes for ASD and CA harmonized accordingly (Table S2, available online). In particular, CA is seen to be a subtype of ASD and is believed to be the most severe one.

Statistical analyses

As family linkages and outcome availability differed across sites, we worked with four different analysis cohorts: an ASD sibling cohort, an ASD cousin cohort, a CA sibling cohort and a CA cousin cohort. Table 1 shows site contributions to the four cohorts. We used a 'firstborn-older-sibling approach' for estimating the sibling recurrence risk for which an index child was eligible for sibling recurrence if, among his/her older siblings, the oldest sibling born in 1998-2007 had an ASD/CA diagnosis. Specifically, an index child became eligible for recurrence at the time of ASD/CA diagnosis of the firstborn older sibling (time-dependent covariate). This approach has the advantage of being robust against some aspects of stoppage (the phenomenon that parents tend to stop having children after the birth of an affected child)[26,27], since the probability of being eligible for recurrence does not depend on the number of siblings. For cousin recurrence, we adopted a 'firstborn-older-cousin approach' defined similarly.

Index children were followed from birth until ASD/CA diagnosis, emigration, death, or end of follow-up, whichever occurred first, and age was chosen as the underlying time-scale. The end of follow-up varied between 2011 and 2015 across sites (Table S1, available online) but this variation was accounted for using time-to-event methods. We investigated recurrence in both ASD and CA by letting each disorder define eligibility for recurrence and outcome in the index child resulting in four recurrence patterns: ASD-to-ASD, CA-to-CA, ASD-to-CA and CA-to-ASD. For each recurrence pattern, the RRR as well as the absolute recurrence risk (ARR) were estimated for each family type separately.

The RRRs were estimated as hazard ratios by fitting a Cox regression model for each family type. To ensure the proportionality assumption in this model we allowed each site and the two birth sub-cohorts (1998-2002 and 2003-2007) to have their own baseline rate. Both crude and adjusted RRR estimates were obtained with the latter being adjusted for sex, parity and parental age at index birth. Parity and parental age were categorized: 1, 2 and 3+ for parity and <35, 35-39, 40+ years for parental age. The RRRs were estimated for each site individually and combined RRRs were obtained by pooling data across sites. However, we excluded Western Australia in the combined estimate of ASD-to-ASD recurrence risk as 86% of their ASD diagnoses were CA diagnoses in contrast to Denmark, Finland, Israel and Sweden where only 25%-50% of all ASD diagnoses were CA diagnoses indicating a clear site difference in the diagnostic profile of ASD. Finally, we investigated the influence of sex by stratifying on both the sex of the index child and the family member used to define eligibility for recurrence.

For the recurrence risk estimates, we considered all siblings combined, full-siblings, paternal- and maternal half-siblings, and full- and half-cousins. Cousins were further divided according to whether a cousin-pair was related through their mother or father, which resulted in four combinations.

Although the main focus is on the RRR, we also estimated the absolute risk (AR) of ASD and CA within the follow-up period for each site separately as well as the absolute recurrence risks for all family

types across all sites. The procedure for this is described in detail in the online material (Supplement 1, available online).

Sensitivity analyses were performed to address the robustness of the recurrence approach adopted here. Specifically, we compared our approach ('firstborn-older-sibling approach') with two other approaches; a 'lastborn-older-sibling approach' and an 'all-sibling approach' (details available in Supplement 1). We also investigated the impact on cousin recurrence risk of the differences in availability of three-generational family linkages, i.e. the missing grandparental links of a relatively large proportion of the California data and of the entire Israeli sample (see also Supplement 1, available online). All analyses were performed using Stata v. 14.2.

Results

Only 4.9% of the study population had missing paternal information (Table S3, available online) making it possible to determine siblingships reliably for the majority of the study cohort. Denmark, Finland and Sweden had the most reliable cousin relationships with 11-15% having missing information for 1-2 grandparents and up to 9% having missing information on all four grandparents.

The ASD sibling cohort comprised 2,551,918 individuals of whom 29,998 (1.2%) received an ASD diagnosis during the follow-up period and 13,997 (0.5%) had a firstborn older sibling with ASD (Table 2). Of the 2,463,139 individuals in the ASD cousin cohort, 29,037 (1.2%) received an ASD diagnosis and 18,039 (0.7%) had a firstborn older cousin with ASD. The CA sibling cohort comprised 6,110,942 individuals of whom 33,769 (0.6%) received a CA diagnosis and 14,448 (0.2%) had a firstborn older sibling with CA. Of the 6,022,163 individuals in the CA cousin cohort, 33,284 (0.6%) received a CA diagnosis and 6,194 (0.1%) had a firstborn older cousin with CA.

Relative recurrence risk

The RRR for ASD for any sibling type ranged from 5.6(95%-CI: 4.8-6.6) in Denmark, 7.9(7.1-8.8) in Sweden to 8.9(6.9-11.5) in Finland and 9.0(5.9-13.7) in Israel; the latter being identical to the full-sibling RRR as the Israeli sample consists only of full-siblings. We saw a much larger estimate for Western Australia of 15.6 (10.6-22.9) (Table 3). A combined unadjusted estimate of this RRR, using data from Denmark, Finland, Israel and Sweden, was 7.6(7.0-8.3) with the corresponding adjusted estimate being 8.4(7.8-9.2), see also Table 3.

The RRR for ASD was significantly greater for full-siblings compared to half-siblings; 9.3 (8.5-10.1) versus 4.8 (3.7-6.2). The RRR for maternal half-siblings was estimated a little larger compared to paternal half-siblings although not significantly different; 5.8 (4.2-8.1) vs. 3.9 (2.6-5.8). The RRR for cousins was estimated at 1.9 (1.7-2.2) which was similar among both full-cousins and half-cousins; 1.9 (1.7-2.2) and 1.4 (1.0-2.0), respectively. See Figure 1 for a visual presentation of how the combined RRRs depend on the degree of relatedness for ASD.

The adjusted sibling RRR for CA was 17.4 (16.3-18.7) with site-specific estimates ranging from 9.2 (6.7-12.5) in Denmark to 24.8 (13.7-45.0) in Finland. The adjusted RRR for full-siblings was significantly larger than for half-siblings; 18.5 (17.2-19.8) vs. 11.4 (8.9-14.6). The RRR for maternal half-siblings was also significantly larger than that of paternal half-siblings; 13.0 (10.1-16.9) vs. 5.2 (2.3-11.6). The RRR for cousins was estimated at 2.1 (1.6-2.9) similar to that of full-cousins, 2.2 (1.6-3.1), and half-cousins, 1.5 (0.6-3.6). See again Figure 1 for a visual presentation of these results for CA.

Table 4 shows the adjusted combined RRRs for ASD stratified by sex of the family member and index child. For siblings, female-to-female recurrence was largest with an RRR of 10.2 (8.6-12.1) and male-to-male recurrence was smallest with an RRR of 6.6 (5.9-7.4); their difference being statistically significant. This pattern was not observed for cousin recurrence.

RRR estimates stratified by type of cousin-pair showed no significant variation across cousin-pairs (Table S4, available online). RRR estimates for ASD-to-CA recurrence and CA-to-ASD recurrence are given in

Table S5 (available online). For example, the sibling RRR for CA-to-ASD was 9.3 (8.2-10.6) similar to that for ASD-to-ASD recurrence; 8.4 (7.8-9.2).

AR estimates by site are presented in Table S6, available online, and reveals that ASD is most common in Denmark and Sweden with estimates of 2.0% (2.0%-2.1%) and 2.3% (2.2%-2.4%), respectively. The AR estimates for the remaining countries are somewhat smaller; 0.9% (0.9%-1.0%) in Finland, 0.4% (0.4%-0.5%) in Israel and 0.5% (0.5%-0.6%) in Western Australia. A similar pattern was observed for CA across the six sites. ARR estimates for ASD-to-ASD recurrence by site and family type are presented in the Table S7, available online.

Sensitivity analyses

RRR estimates obtained by different recurrence risk estimation approaches were either similar or a little smaller in magnitude compared to the approach used in the main analysis (Table S8, available online). Moreover, the cousin RRR estimates did not change when analyzing only the sample of children with at least one valid grandparental link (for any of the four recurrence patterns) nor when excluding the entire California sample (for the CA-to-CA recurrence pattern). In the latter analysis, we found e.g. a crude RRR of 2.2 (1.6-3.1) for cousins altogether and a crude RRR of 2.3 (1.6-3.2) for full-cousins which was very similar to those presented in Table 3.

Discussion

Based on rigorously harmonized multi-national data, we present estimates of the relative recurrence risk for ASD and CA, which are important, benchmark population-level measures of overall familial liability in autism. These estimates may also assist clinicians and families in understanding autism risk in the context of other families in the population. Our results are in line with previous studies[11,13] and confirm the notion of a strong genetic influence in both ASD and CA as seen by the decline in RRR by degree of relatedness. This observed decline fits well with what one would expect by looking at the percentage of shared genetic material in the various family members. The average percentage of shared genetic material is 50% for full-siblings, 25% for half-siblings, 12.5% for full-cousins and 6.25% for half-cousins. By this reasoning, one could argue that, if the RRR was solely determined by genetics, then we would expect an estimate for full-siblings that was twice as large compared to half-siblings, four times as large compared to full-cousins and eight times as large compared half-cousins. This is roughly the case for the combined ASD estimates of Table 3/ Figure 1: full-siblings; 9.3, half-siblings; 4.8, full-cousins; 1.9, and half-cousins; 1.4. Any deviations from this pattern might be explained by the fact that the RRR, to some extent, also depends on environmental factors shared by the relevant family members. This observed recurrence risk pattern was also very consistent across sites, despite differences in populations, case ascertainment and risk profiles.

Our study is the first to find a larger risk of ASD for children having an older female sibling with ASD compared to having an older male sibling with ASD when measured relatively to the risk in unaffected families. Compared to the male-to-male sibling RRR, the female-to-male and female-to-female sibling RRRs were both 1.5 times larger; the latter being significantly larger. A previous study[11] had concluded no such sex effect in sibling recurrence in a European population-based sample but they also had substantially fewer recurrent cases. Another study[14] from California, also with substantially fewer recurrent cases, reported the opposite pattern in the absolute recurrence risk but this is likely due to the differences in methodology. A third study from the US[19] did observe the same pattern as ours, namely that the recurrence risk are increased for children following an older affected female sibling compared to an older affected male sibling although their results were quantified in terms of absolute recurrence risks (ARRs).

Our observed sex difference suggests that families where the oldest female sibling has ASD have a larger familial liability for ASD compared to families where the oldest male sibling is affected. This pattern may reflect the fact that female ASD diagnoses are often a more severe ASD phenotype (e.g., often with a co-morbidity such as intellectual disability) but whether it also reflects a more deleterious genetic or

otherwise shared familial risk for ASD in these families cannot be addressed with these data and warrants further investigation.

Like previous studies[11,13], we found no evidence for a difference in RRR between maternal- and paternal half-siblings for ASD and neither were there any differences between types of cousin-pairs for any of the four maternal/paternal ASD recurrence patterns (Table S4, available online). For CA-to-CA recurrence, we did however see an RRR for maternal half-siblings that was more than twice as large as for paternal half-siblings. These results suggest that it is difficult to tease out the contributions of the genetic vs. non-genetic shared familial liability in the RRR estimates as greater divergence, especially between maternal- and paternal- siblings, might be expected for ASD.

Despite consistent recurrence risk patterns across sites, the specific magnitudes of the estimated RRRs varied a great deal. This variation is most likely due to the aforementioned site differences; however, we cannot rule out that they may, in part, reflect population differences in risk arising from the combination of factors contributing to shared familial liability separate from genetics, such as familial environmental factors and possibly their interaction with genetic factors.

A major strength of our study is the large population-based sample used, highlighting the importance and value of the MINERvA network in merging data across several sites and addressing scientific questions for which previous studies had limited power. We were uniquely able to assess differences in recurrence risk for combinations of male and female siblings but also in cousins in much greater detail than done previously. In contrast to a meta-analysis, we were able to align the birth years, harmonize variable definitions and use the same statistical methods across all sites. We have chosen to provide site-specific estimates as well as combined estimates obtained by pooling data across sites (to the extent it was feasible) totaling more than 2.5 million subjects for ASD recurrence and more than six million subjects for CA recurrence. This provides a much more nuanced picture in that the reader may choose to focus only on one or a couple of the individual sites or may choose to focus on the combined estimates if they find them useful. Sensitivity analyses showed that our results were fairly robust against the choice of recurrence methodology which increased confidence in our findings.

As sibling and cousin relationships are determined by parent-offspring linkages, we believe that this information is very complete especially since efforts were made to make linkages based on birth certificates as complete as possible[22]. Maternal linkages are considered very valid as they are recorded at the time of birth by the hospital or midwife and subsequently reported to the birth register in Denmark, Finland and Sweden. However, as the father need not be present at the time of birth, this linkage will be missing a lot more. In these cases, we used a second national register to identify the legal father at the time of birth. We acknowledge that this might not be the biological father but in most cases we believe it will be.

Among the study limitations is the variation in data sources, case ascertainment, variable definitions and geographic location across sites requiring a thorough harmonization process to best bring data together in a comparable format. We observed a clear difference in case identification practices across sites as indicated by the large variation in ASD risk estimates (Table S6, available online). Since the diagnostic systems used across sites were very similar (mainly ICD-10 and DSM-IV have been used), these observed differences must be attributed to factors other than the diagnostic system, e.g., differences in referral mechanisms and parental awareness and action. For this reason, we felt it was important to report both site-specific estimates and combined estimates and it led us to exclude Western Australia in the combined ASD recurrence estimates because the ASD diagnostic profile in Western Australia appeared very different from that in the other four sites. Another limitation was the large number of missing grandparental links especially for the California data, however, several sensitivity analyses indicated that this issue was not likely to be a source of bias.

Our novel findings of variation in recurrence risk by sibling sex, as well as the observed variation in the magnitude of recurrence across sites despite a common methodology, underpins the need to deepen our understanding of factors influencing ASD familial risk and to have continued focus on sex differences in the context of familial liability.

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Tables

Table 1. Data Contributions by Site

	Analysis Cohort			
Site	**ASD Sibling**	**ASD Cousin**	**CA Sibling**	**CA Cousin**
California			x	x
Denmark	x	x	x	x
Finland	x	x	x	x
Israel	x		x	
Sweden	x	x	x	x
W. Australia	x	x	x	x
Total no. births	2,551,918	2,463,139	6,110,942	6,022,163
Note: ASD = autism spectrum disorder; CA = childhood autism.				

Table 2. Site-Specific and Overall Distribution of Outcome Variables and Covariates

	Site, No. (%)						
Variable	California	Denmark	Finland	Israel	Sweden	W. Australia	Total
ASD variables							
ASD							
Yes	N/A	9,210 (1.4)	3,945 (0.7)	961 (1.1)	14,665 (1.5)	1,217 (0.5)	29,998 (1.2)
No	N/A	644,370 (98.6)	565,666 (99.3)	87,818 (98.9)	964,833 (98.5)	259,233 (99.5)	2,521,920 (98.8)
ASD in firstborn older sibling							
Yes	N/A	4,279 (0.7)	2,005 (0.4)	459 (0.5)	6,738 (0.7)	516 (0.2)	13,997 (0.5)
No	N/A	649,301 (99.3)	567,606 (99.6)	88,320 (99.5)	972,760 (99.3)	259,934 (99.8)	2,537,921 (99.5)
ASD in firstborn older cousin							
Yes	N/A	4,279 (0.7)	2,005 (0.4)	459 (0.5)	6,738 (0.7)	516 (0.2)	13,997 (0.5)
No	N/A	649,301 (99.3)	567,606 (99.6)	88,320 (99.5)	972,760 (99.3)	259,934 (99.8)	2,537,921 (99.5)
CA Variables							
CA							
Yes	21,137 (0.6)	3,654 (0.6)	977 (0.2)	486 (0.5)	6,468 (0.7)	1,047 (0.4)	33,769 (0.6)
No	3,537,887 (99.4)	649,926 (99.4)	568,634 (99.8)	88,293 (99.5)	973,030 (99.3)	259,403 (99.6)	6,077,173 (99.4)
CA in firstborn older sibling							
Yes	9,495 (0.3)	1,397 (0.2)	394 (0.1)	184 (0.2)	2,545 (0.3)	433 (0.2)	14,448 (0.2)
No	3,549,529 (99.7)	652,183 (99.8)	569,217 (99.9)	88,595 (99.8)	976,953 (99.7)	260,017 (99.8)	6,096,494 (99.8)
CA in firstborn older cousin							
Yes	200 (0.0)	2,004 (0.3)	589 (0.1)	N/A	3,074 (0.3)	327 (0.1)	6,194 (0.1)
No	3,558,824 (100.0)	651,576 (99.7)	569,022 (99.9)	N/A	976,424 (99.7)	260,123 (99.9)	6,015,969 (99.9)
Other covariates							
Sex							
Male participants	1,819,313 (51.1)	335,162 (51.3)	291,442 (51.2)	45,337 (51.1)	503,954 (51.5)	132,885 (51.0)	3,128,093 (51.2)
Female participants	1,739,711 (48.9)	318,418 (48.7)	278,169 (48.8)	43,442 (48.9)	475,544 (48.5)	127,565 (49.0)	2,982,849 (48.8)
Birth sub-cohort							
1998-2002	1,632,452 (45.9)	329,302 (50.4)	280,964 (49.3)	43,479 (49.0)	459,191 (46.9)	125,505 (48.2)	2,870,893 (47.0)
2003-2007	1,926,572 (54.1)	324,278 (49.6)	288,647 (50.7)	45,300 (51.0)	520,307 (53.1)	134,945 (51.8)	3,240,049 (53.0)
Parity							
1	1,240,433 (34.9)	284,658 (43.6)	238,440 (41.9)	34,957 (39.4)	416,795 (42.6)	76,860 (29.5)	2,292,143 (37.5)
2	1,205,044 (33.9)	239,244 (36.6)	187,393 (32.9)	25,224 (28.4)	342,425 (35.0)	46,735 (17.9)	2,046,065 (33.5)
≥3	1,033,670 (29.0)	126,002 (19.3)	143,778 (25.2)	28,598 (32.2)	183,872 (18.8)	22,799 (8.8)	1,538,719 (25.2)
Missing	79,877 (2.2)	3,676 (0.6)	0 (0.0)	0 (0.0)	36,406 (3.7)	114,056 (43.8)	234,015 (3.8)
Maternal age at birth, years							
<35	3,081,506 (86.6)	543,392 (83.1)	462,674 (81.2)	73,251 (82.5)	793,972 (81.1)	212,927 (81.8)	5,167,722 (84.6)
35-39	396,726 (11.1)	94,898 (14.5)	86,986 (15.3)	12,247 (13.8)	155,957 (15.9)	40,058 (15.4)	786,872 (12.9)
≥40	80,792 (2.3)	15,290 (2.3)	19,951 (3.5)	3,281 (3.7)	29,569 (3.0)	7,465 (2.9)	156,348 (2.6)
Paternal age at birth, years							
<35	2,460,197 (69.1)	430,088 (65.8)	381,871 (67.0)	61,002 (68.7)	629,176 (64.2)	165,928 (63.7)	4,128,262 (67.6)
35-39	540,554 (15.2)	140,760 (21.5)	115,744 (20.3)	17,704 (19.9)	217,696 (22.2)	53,910 (20.7)	1,086,368 (17.8)
≥40	558,273 (15.7)	82,732 (12.7)	71,996 (12.6)	10,073 (11.3)	132,626 (13.5)	40,612 (15.6)	896,312 (14.7)

Note: ASD = autism spectrum disorder; CA = childhood autism; N/A = not available

Table 3. Site-Specific and Combined Relative Recurrence Risks for Autism Spectrum Disorder (ASD) and Childhood Autism (CA) Among Siblings and Cousins Stratified by Degree of Relatedness

Type of recurrence			Site, RRR (95% CI)[a]						Combined[b]	
Family member	Index child	Family type	California	Denmark	Finland	Israel	Sweden	West Australia	Crude	Adjusted
ASD	ASD	Siblings	N/A	5.6 (4.8 - 6.6)	8.9 (6.9 - 11.5)	9.0 (5.9 - 13.7)	7.9 (7.1 - 8.8)	15.6 (10.6 - 22.9)	7.6 (7.0 - 8.3)	8.4 (7.8 - 9.2)
		Full	N/A	5.8 (4.9 - 6.9)	9.7 (7.4 - 12.6)	9.0 (5.9 - 13.7)	8.5 (7.6 - 9.5)	16.5 (11.1 - 24.5)	8.0 (7.3 - 8.8)	9.3 (8.5 - 10.1)
		Half	N/A	4.2 (2.7 - 6.6)	4.9 (2.0 - 11.7)	-	4.6 (3.2 - 6.4)	-	5.2 (4.0 - 6.7)	4.8 (3.7 - 6.2)
		Maternal half	N/A	5.3 (3.1 - 9.0)	5.2 (1.7 - 16.0)	-	4.8 (3.1 - 7.4)	-	5.8 (4.2 - 8.0)	5.8 (4.2 - 8.1)
		Paternal half	N/A	2.7 (1.2 - 6.0)	4.1 (1.0 - 16.3)	-	4.7 (2.8 - 7.6)	-	4.5 (3.0 - 6.8)	3.9 (2.6 - 5.8)
		Cousins	N/A	2.0 (1.6 - 2.4)	1.6 (1.0 - 2.7)	N/A	1.8 (1.5 - 2.2)	2.7 (1.0 - 7.3)	1.9 (1.7 - 2.2)	1.9 (1.7 - 2.2)
		Full	N/A	2.0 (1.6 - 2.5)	1.6 (0.9 - 2.8)	N/A	1.8 (1.5 - 2.2)	2.2 (0.7 - 6.9)	1.9 (1.7 - 2.3)	1.9 (1.7 - 2.2)
		Half	N/A	1.4 (0.8 - 2.5)	1.7 (0.4 - 6.8)	N/A	1.4 (1.0 - 2.2)	-	1.5 (1.1 - 2.1)	1.4 (1.0 - 2.0)
CA	CA	Siblings	17.8 (16.5 - 19.2)	9.2 (6.7 - 12.5)	24.8 (13.7 - 45.0)	17.7 (9.2 - 33.9)	13.6 (11.3 - 16.4)	18.5 (12.2 - 28.0)	18.0 (16.8 - 19.3)	17.4 (16.3 - 18.7)
		Full	18.5 (17.1 - 20.1)	10.4 (7.6 - 14.3)	33.2 (18.8 - 58.7)	17.7 (9.2 - 33.9)	14.3 (11.8 - 17.4)	20.6 (13.5 - 31.5)	18.9 (17.6 - 20.3)	18.5 (17.2 - 19.8)
		Half	13.5 (10.2 - 17.8)	4.8 (1.6 - 15.0)	-	-	7.3 (3.8 - 14.0)	-	11.7 (9.1 - 15.0)	11.4 (8.9 - 14.6)
		Maternal half	13.5 (10.2 - 17.8)	8.7 (2.8 - 26.9)	-	-	9.0 (4.0 - 20.0)	-	13.6 (10.5 - 17.6)	13.0 (10.1 - 16.9)
		Paternal half	-	-	-	-	6.3 (2.4 - 16.9)	-	5.1 (2.3 - 11.4)	5.2 (2.3 - 11.6)
		Cousins	-	2.4 (1.4 - 3.9)	5.7 (2.1 - 15.3)	N/A	1.6 (1.0 - 2.6)	1.9 (0.5 - 7.8)	2.0 (1.5 - 2.8)	2.1 (1.6 - 2.9)
		Full	-	2.5 (1.5 - 4.2)	5.1 (1.6 - 15.7)	N/A	1.6 (1.0 - 2.8)	2.1 (0.5 - 8.6)	2.1 (1.5 - 3.0)	2.2 (1.6 - 3.1)
		Half	-	-	-	N/A	1.5 (0.6 - 4.0)	-	1.4 (0.6 - 3.4)	1.5 (0.6 - 3.6)

Note: N/A = not available; RRR = relative recurrence risk.

[a] Dash (-) indicates insufficient recurrent events for estimation.

[b] Using data from Denmark, Finland, Israel and Sweden for ASD and data from all six sites for CA.

[c] Adjusted for sex of child, parity and parental age at birth.

Table 4. Combined Adjusted Relative Recurrence Risks for Autism Spectrum Disorder (ASD) Among Siblings and Cousins Stratified by Degree of Relatedness, and Sex of Family Member and Index Child

			Combined[a] adjusted[b] RRR (95% CI)			
Type of recurrence			Sex (family member - index child)			
Family member	Index	Family type	Male - male	Female - female	Male - female	Female - male
ASD	ASD	Siblings	6.6 (5.9 - 7.4)	10.2 (8.6 - 12.1)	7.5 (6.2 - 9.2)	9.8 (7.1 - 13.5)
		Full	6.8 (6.0 - 7.7)	10.9 (9.1 - 13.0)	8.7 (7.0 - 10.7)	9.3 (6.5 - 13.2)
		Half	5.4 (3.9 - 7.5)	5.2 (2.8 - 9.6)	3.2 (1.6 - 6.5)	11.1 (5.3 - 23.4)
		Maternal half	6.1 (4.0 - 9.1)	4.7 (1.9 - 11.2)	2.8 (1.1 - 7.5)	18.1 (8.1 - 40.5)
		Paternal half	5.1 (3.1 - 8.4)	5.5 (2.3 - 13.1)	3.6 (1.4 - 9.7)	3.2 (0.5 - 22.6)
		Cousins	2.0 (1.8 - 2.4)	2.1 (1.6 - 2.7)	1.7 (1.3 - 2.3)	1.6 (0.9 - 2.8)
		Full	2.1 (1.8 - 2.5)	1.9 (1.3 - 2.6)	1.6 (1.1 - 2.3)	1.6 (0.9 - 3.0)
		Half	1.8 (1.3 - 2.6)	2.8 (1.6 - 4.7)	1.9 (1.0 - 3.5)	1.3 (0.3 - 5.0)
		Maternal-maternal	2.4 (1.9 - 3.1)	2.2 (1.4 - 3.5)	2.0 (1.3 - 3.3)	2.0 (0.8 - 4.8)
		Paternal-paternal	1.9 (1.4 - 2.6)	1.7 (0.9 - 2.9)	0.7 (0.3 - 1.7)	1.5 (0.5 - 4.5)
		Maternal-paternal	2.1 (1.6 - 2.8)	2.2 (1.3 - 3.7)	2.0 (1.2 - 3.4)	1.8 (0.7 - 4.9)
		Paternal-maternal	1.6 (1.2 - 2.2)	1.7 (1.0 - 3.0)	1.9 (1.2 - 3.2)	1.3 (0.4 - 3.9)

Note: RRR = relative recurrence risk.

[a] Using data from Denmark, Finland, Israel and Sweden.

[b] Adjusted for site, parity and parental age at birth.

Figure 1. Combined Relative Recurrence Risks for Autism Spectrum Disorder (ASD) and Childhood Autism (CA) Among Siblings and Cousins Stratified by Degree of Relatedness

Note: RRR = relative recurrence risk