Familial Recurrence of Autism Spectrum Disorder: Evaluating Genetic and Environmental Contributions

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Objective: This study was designed to examine the pattern of familial recurrence of autism spectrum disorder (ASD) in terms of genetic and environmental contributions related to timing of birth.

Method: The authors linked California Department of Developmental Services records with state birth certificates to identify all siblings and half siblings of individuals affected with ASD born between 1990 and 2003. A total of 6,616 full siblings, 644 maternal half siblings, and 299 paternal half siblings born after ASD index cases were used to calculate recurrence risks. Control families, identified through matching to cases, were included for comparison (a total of 29,384 siblings).

Results: The overall sibling recurrence risk was 10.1%, compared with a prevalence of 0.52% in siblings of controls. The recurrence risk in second-born children was higher (11.5%) than in later-born siblings (7.3%); a similar pattern was observed for maternal half siblings (6.5% for second-born compared with 3.0% for later-born siblings; 4.8% overall). The recurrence risk was significantly higher for siblings who immediately followed the index case in birth order compared with those later in birth order. The recurrence risk for paternal half siblings (2.3%) was half the overall recurrence risk for maternal half siblings but was similar to that for later-born maternal half siblings. An exponential effect of short interbirth interval was observed, with the recurrence risk reaching 14.4% for an interbirth interval of 18 months or less, compared with 6.8% for an interval of 4 years or more. An identical phenomenon was observed in maternal half siblings.

Conclusions: The results support genetic susceptibility in the familial recurrence of ASD along with factors related to timing of birth.

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Historically, the genetic epidemiology of autism and autism spectrum disorder (ASD) has been impaired by a lack of large samples and the fact that it is unusual for individuals with ASD to reproduce. Early twin studies based on very small samples led to the conclusion that ASD has high genetic heritability (1–3), primarily as a result of high monozygotic twin concordance and very low dizygotic twin concordance. More recent twin studies have observed a higher dizygotic concordance, leading to a more moderate estimate of genetic heritability (4).

Generally, recurrence in nuclear families has also been the basis of genetic epidemiologic inference. Over the past several decades, only a handful of such studies have appeared. A few have been derived from epidemiologic surveys (5–8), while others have been based on volunteer registries (9, 10), family history studies (11, 12), or longitudinal follow-up of couples with an affected child (13).

Evaluation of recurrence risks in half siblings, both maternal and paternal, can also provide important inferences regarding the genetic epidemiology of ASD. Only a few such studies have appeared, with modest sample sizes (8, 10). While a higher recurrence risk for full siblings compared with maternal half siblings is an indication of genetic effects, comparison of recurrence risks for maternal half siblings and paternal half siblings and evaluation of timing of births in sibships may reveal clues to nongenetic contributions.

Method

Data Sources

Data on ASD in sibships were derived from the records of the California Department of Developmental Services. The Department, which has been described elsewhere (4, 14, 15), manages a system of 21 regional centers that coordinate and provide assessments and services for persons with developmental disabilities (including autism and mental retardation) throughout the state of California. To identify nuclear families including both full and half siblings, the electronic client file was linked by staff of the California Center for Autism and Developmental Disabilities Research and Epidemiology to state of California birth certificate files, as described below.

Study Diagnoses

The autism-related diagnoses from this resource have been described previously (4, 14, 15). For this study, we included as affected with ASD any individual with Department of Developmental Services eligibility for autism or, for children deemed

This article is featured in this month's AJP Audio and is the subject of a CME course (p. 1229)

TABLE 1. Demographic Characteristics of Mothers and Fathers of Case and Control Subjects and California Reference Population in a Study of Familial Recurrence of Autism Spectrum Disorder

Variable	Mothers						Fathers					
	Case Subjects (N=27,033)		Control Subjects (N=54,316)		California Reference (N=5,643,100)		Case Subjects (N=27,033)		Control Subjects (N=54,316)		California Reference (N=5,643,100)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	29.6	6.02	29.5	6.06	27.5	6.19	32.4	7.08	32.0	7.00	30.0	7.02
	N	%	N	%	N	%	N	%	N	%	N	%
Race/ethnicity												
White	11,009	40.8	22,221	40.9	2,219,660	40.3	11,497	43.4	21,776	40.9	2,218,193	40.3
Latino	10,010	37.1	20,128	37.1	2,378,899	43.2	9,462	35.7	20,097	37.8	2,367,264	43.0
Asian	3,997	14.8	8,067	14.9	567,683	10.3	3,454	13.0	6,993	13.1	505,120	9.2
African American	1,999	7.4	3,871	7.1	342,563	6.2	2,060	7.8	4,332	8.1	412,178	7.5
Education												
Less than high school	4,589	17.1	12,137	22.5	1,482,071	26.3	4,217	16.3	11,099	21.3	1,459,374	25.9
High school graduate	7,232	27.0	14,727	27.4	1,688,114	29.9	7,109	27.4	15,049	29.0	1,743,094	30.9
At least some college	14,991	55.9	26,954	50.1	2,472,915	43.8	14,647	56.4	25,776	49.6	2,440,632	43.2

eligible for services based on another condition, a code indicating comorbid ASD or suspected ASD. A twin study derived from the same electronic registry in which individuals were directly assessed with the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule (4) found a high correspondence between the client file diagnoses and ASD as defined using the research instrument score criteria of Risi et al. (16), with a sensitivity of 94.6% and a specificity of 84.6%. Cases for the initial sample cohort were defined as all individuals born in California between 1990 and 2003 who had ASD as defined above in the electronic files. The electronic registry and birth certificate matching took place at the end of 2010, by which time the youngest individuals in the cohort (born in 2003) would be 7 years old, an age by which ASD symptoms have usually been detected (15).

Linkage to State of California Birth Certificates

Full and half siblings of affected individuals were identified through linkage of the case file data to California birth certificates. Affected individuals were matched to birth certificates based on first and last name, birth date, birth place, mother's and father's names, and Social Security number in later years. The birth certificate files were then searched to find other individuals whose maternal or paternal information matched that of the index case. Information available for matching varied by birth year. During the years 1990–1996, last name (or maiden name) and date of birth were available for fathers and mothers, and first names were available for mothers only. In 1997, Social Security numbers of both parents became available. After 1997, first names became available for fathers, and middle names became available for both parents. The birth certificate files were searched for the years 1990–2003 to identify all children who matched an index case for at least one parent.

Matching criteria required an exact match for Social Security numbers and a near-exact match for names. After 1997, matching was highly precise and led to unambiguous matches and nonmatches. Before 1997, some potential matches were ambiguous, so manual inspection was conducted and resolved many of these cases.

Children whose information matched that for both parents were declared full siblings. Children whose information matched that for one parent but not the other were declared half siblings. The information to define maternal and paternal half siblings was also not comparable because before 1997, first names were only available for mothers. This led to a small number of unambiguous paternal half siblings (for whom paternal first names and/or Social Security numbers were available). To expand the number of paternal half siblings, we instituted an additional matching criterion for fathers based on the observed infrequency of the last name in the entire birth certificate database. If the matching paternal last name for two or more children occurred no more than 40 times in the entire database, along with a date of birth match, the two children were declared paternal half siblings. We determined that at this threshold, the chances were extremely small that two unrelated children would have such matching paternal information.

The initial matching identified 29,074 case families (mean sibship size, 1.99). Of these, 48 (0.17%) had impossible relationships and were excluded. An additional 1,649 families (5.7%) in which full sibling versus half sibling ambiguity was not resolved were excluded. At this step, 299 paternal half siblings were identified and retained. Because the analyses of recurrence were calculated by birth order, we required that the oldest child of a couple be born after 1990 (i.e., leading to removal of families in which the oldest identified child was parity >1, indicating that an older child was born before 1990 and thus not captured in our cohort), which excluded 6,486 families (23.7%). We further excluded 925 families (4.4%) with multiple births. Occasionally, when reconstructing families, one of the other birth order offspring was missing. For these sibships, analyses included individuals up to the first missing birth order offspring. Finally, we excluded 6,413 singleton families (32.1%). These procedures led to a total of 13,533 case families. Within these families, there were 6,621 full siblings and 644 maternal half siblings born after the first affected individual in the family (the remainder were born before any affected siblings were born), allowing for calculation of recurrence risk without reproductive stoppage bias.

Selection of Control Families

For the estimation of population prevalence, we identified two index controls for each index case, matched on sex, birth year, birth location, and mother's race/ethnicity and age. Index controls were confirmed not to be clients in the same electronic registry. We used procedures identical to those described above, matching controls to state birth certificates between 1990 and 2003 to identify siblings of these control individuals. Qualifying ASD diagnoses were permitted among the siblings of controls. The initial number of control families was 59,285 (mean sibship

TABLE 2. Risk of Recurrence of Autism Spectrum Disorder for Siblings and Maternal Half Siblings, by Birth Order[a]

			Birth Order of Sibling					
			2			3		
Subgroup	Sex of Index Case	Sex of Sibling	N	Risk	95% CI	N	Risk	95% CI
Full siblings								
One previous affected	All	All	4,323	0.115	0.106, 0.125	1,873	0.074	0.062, 0.086
	All	Male	2,239	0.168	0.153, 0.184	953	0.103	0.084, 0.122
	All	Female	2,084	0.059	0.048, 0.069	920	0.043	0.030, 0.057
	Male	All	3,661	0.111	0.101, 0.121	1,569	0.072	0.059, 0.085
	Female	All	662	0.140	0.114, 0.167	304	0.082	0.054, 0.119
	Male	Male	1,895	0.162	0.145, 0.179	803	0.103	0.082, 0.124
	Female	Male	344	0.203	0.162, 0.250	150	0.100	0.057, 0.160
	Male	Female	1,766	0.056	0.045, 0.067	766	0.039	0.025, 0.053
	Female	Female	318	0.072	0.044, 0.101	154	0.065	0.032, 0.116
First child affected	All	All	4,323	0.115	0.106, 0.125	635	0.044	0.028, 0.060
Second child affected	All	All				1,180	0.080	0.064, 0.095
Third child affected	All	All						
Two previous affected	All	All				83	0.289	0.195, 0.399
Maternal half siblings								
	All	All	338	0.065	0.041, 0.097	244	0.029	0.012, 0.058
	All	Male	185	0.081	0.046, 0.130	118	0.034	0.009, 0.085
	All	Female	153	0.046	0.019, 0.092	126	0.024	0.005, 0.068
	Male	All	284	0.067	0.041, 0.103	201	0.030	0.011, 0.064
	Female	All	54	0.056	0.012, 0.154	43	0.023	0.001, 0.129
	Male	Male	158	0.076	0.040, 0.129	97	0.041	0.011, 0.102
	Female	Male	27	0.111	0.024, 0.292	21	0.000	0.000, 0.161
	Male	Female	126	0.056	0.023, 0.111	104	0.019	0.002, 0.068
	Female	Female	27	0.000	0.000, 0.128	22	0.045	0.001, 0.228

[a] For this analysis, "index" is defined as the first affected child; N is number of individuals at risk.

size, 2.08); after exclusions, the number was 20,981, encompassing 29,384 siblings of index controls (15,160 male, 14,224 female). Control families were slightly larger than case families because of reproductive stoppage in the latter (17).

The study was approved by the state of California's Committee for the Protection of Human Subjects.

Recurrence Risks

Recurrence risk is defined as the probability of a second child being affected given that another is already affected. Because recurrence risk analysis of full sibship data can lead to a downward bias in the presence of reproductive stoppage (17), defined as the curtailment of reproduction after manifestation of ASD in an affected child, we analyzed the sibship (and maternal half sibship) data in a sequential fashion, calculating the recurrence risk (proportion affected) by including only siblings born after an affected individual, stratified by absolute birth order (e.g., birth orders 2, 3, and 4 when the first child is affected; birth orders 3 and 4 when the second child is affected but the first is not). In other words, these counts excluded unaffected individuals born before the first affected child. These recurrence risks were also calculated after stratifying on sex of index case (the oldest affected in this situation) and sex of sibling (or maternal half sibling) and by the number of previously affected siblings (or maternal half siblings). Exact confidence intervals were calculated assuming a binomial distribution.

Because no birth order information was available for paternal half siblings, they were analyzed as a single group. For comparison, population prevalence of ASD was derived from the control sibships by calculating the affected proportion among all siblings of unaffected index subjects. Statistical comparisons of recurrence risks were based on chi-square tests with one degree of freedom.

Interbirth interval has been previously shown to be associated with the risk of ASD in nonfamilial cases, with short intervals increasing the risk (18). Here, we recalculated the sibling recurrence risks stratified by the number of months since the birth of the previous child.

Multivariate Analysis

To determine the influence of a variety of factors (sex, birth order, parental age, birth weight, interbirth interval, number of prior affected siblings) on recurrence risk, we performed a multivariate analysis of the sequential sibling (and maternal half sibling) recurrence risk data using logistic regression. The dependent variable was always the dichotomous affected status of a sibling (or maternal half sibling). The model covariates were related to the sibling and included sex, birth year, maternal race/ethnicity (white, Asian, African American, Latino), birth weight, birth order (2, 3, or ≥4), maternal and paternal age at birth of child, interbirth interval from previous child (in logarithm months), number of prior affected siblings (0, 1, or 2), number of prior affected female siblings (0, 1, or 2), and birth order of prior affected siblings (1, 2, or 3). The estimates provided are relative recurrence risks, defined as the ratio of recurrence risks for those with different values of the covariate of interest (1 or 0 for the dichotomous variables and per unit value for continuous variables).

Birth Order of Sibling					
≥4			All		
N	Risk	95% CI	N	Risk	95% CI
420	0.071	0.049, 0.100	6,616	0.101	0.094, 0.108
231	0.095	0.061, 0.141	3,423	0.145	0.133, 0.157
189	0.042	0.018, 0.082	3,193	0.053	0.045, 0.061
342	0.073	0.048, 0.106	5,572	0.098	0.090, 0.105
78	0.064	0.021, 0.143	1,044	0.118	0.098, 0.137
190	0.095	0.057, 0.146	2,888	0.141	0.129, 0.154
41	0.098	0.027, 0.231	525	0.170	0.137, 0.202
157	0.045	0.018, 0.090	2,689	0.051	0.042, 0.059
37	0.027	0.001, 0.142	509	0.067	0.045, 0.088
81	0.037	0.008, 0.104	5,039	0.105	0.097, 0.114
165	0.079	0.043, 0.131	1,345	0.080	0.065, 0.094
145	0.062	0.029, 0.115	145	0.062	0.029, 0.115
34	0.118	0.033, 0.275	117	0.239	0.165, 0.327
62	0.032	0.004, 0.112	644	0.048	0.031, 0.065
32	0.063	0.008, 0.208	335	0.063	0.039, 0.094
30	0.000	0.000, 0.116	309	0.032	0.016, 0.059
58	0.034	0.004, 0.119	543	0.050	0.031, 0.068
4	0.000	0.000, 0.602	101	0.040	0.011, 0.098
29	0.069	0.008, 0.228	284	0.063	0.038, 0.098
3	0.000	0.000, 0.708	51	0.059	0.012, 0.162
29	0.000	0.000, 0.119	259	0.035	0.016, 0.065
1	0.000	0.000, 0.975	50	0.020	0.001, 0.106

In all analyses, birth year, paternal age, and maternal and paternal race/ethnicity and education were not significant; however, birth year was retained in the final model. Birth interval was characterized in logarithm months because of an apparent exponential relationship between interbirth interval and recurrence risk. A p value of 0.05 was used for statistical significance throughout.

In the first multivariate analysis, we included only second-born offspring. In the next analysis, we focused on third-born offspring and added independent covariates representing the affected status of the first two children in the family (first affected, second affected, both affected). In the final analysis, we included all birth orders ≥2 and included birth order and number of previous affected siblings as independent variables for the analysis. Because of sample size, the multivariate analysis of maternal half siblings included all birth orders ≥2, with the same covariates as used in the analysis of full siblings.

Results

The demographic characteristics of the case and control subjects are summarized in Table 1, along with corresponding values for all California non-ASD births occurring during the same period (14). Case and control subjects were matched for birth year and location and for maternal age and race/ethnicity. The maternal and paternal ages of case and control subjects were elevated, as expected, compared with the reference population, and Asians were relatively overrepresented and Latinos underrepresented among case and control subjects. Case subjects were slightly more educated than control subjects, and both groups had higher education levels compared with the reference population. In a previous multivariate analysis from this resource (15), the race/ethnicity and education differences were attenuated and nonsignificant after adjusting for parental age and other covariates.

Recurrence risks to full siblings and maternal half siblings born after affected index cases, stratified by birth order, are listed in Table 2. A significant birth order effect was observed, where the recurrence risk in second-born siblings was 11.5%, 1.58-fold greater ($p<0.0001$) than later-born siblings, who had a recurrence risk of 7.3%. There was no difference between third-born and later-born siblings. The recurrence risk among brothers was 14.5%, compared with 5.3% among sisters, and 10.1% for the sexes combined. This is 20-fold greater ($p<0.0001$) than the prevalence of 0.52% (153/29,384) observed among the siblings of the control index subjects (0.88% for males [134/15,160] and 0.19% for females [19/14,224]).

For maternal half siblings, the recurrence risk was more than twofold greater ($p<0.05$) for second-born (6.5%) compared with later-born maternal half siblings (2.9%), with no difference between third and later-born half siblings. The overall maternal half sibling recurrence risk across all birth orders was 4.8%, with recurrence risks of 6.3% and 3.2% for the half brothers and half sisters, respectively. Overall, we found a paternal half sibling recurrence risk of 2.3% (7/299; 95% CI=1.2, 6.2), less than half the recurrence risk for maternal half siblings ($p<0.05$).

Recurrence risk was greater when two previous children in the sibship were affected. For these families, the overall recurrence risk was 23.9%, more than double the recurrence risk when a single prior child was affected ($p<0.0001$). The recurrence risk was higher ($p<0.05$) for third-born children (28.9%) compared with later-born children (11.8%), again indicating a birth order effect.

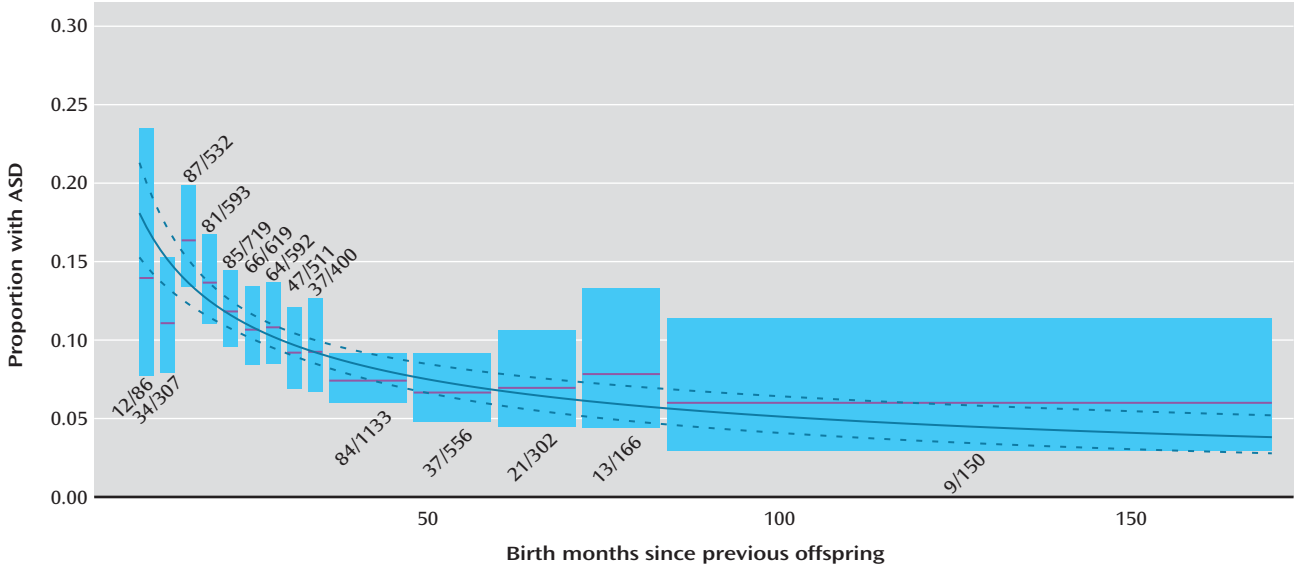
Interbirth Interval

The effect of interbirth interval on ASD recurrence risk is illustrated in Figure 1. There was a significant increase in ASD recurrence risk with decreasing birth interval. A logistic regression model applied to the data in Figure 1, where the independent variable was ln(interbirth months), provided an adequate fit to the data and resulted in a highly significant regression coefficient (-0.588, SE=0.088, $p<10^{-11}$). For children born within 18 months of the previous child, the recurrence risk was twofold greater than for children born 4 or more years afterward (14.4% [133/925] compared with 6.8% [80/1,164]).

Multivariate Analysis

In the multivariate analysis of second-born children, male sex, previous affected female, higher birth weight, and older maternal age all significantly increased the recurrence

FIGURE 1. Autism Spectrum Disorder (ASD) Recurrence Risk, by Interbirth Interval[a]



[a] Intervals in the diagram are 3 months in length from 12 months to 36 months; 12 months in length from 36 months to 84 months; and 84 months in length from 84 months to 168 months. The vertical extent of each bar represents the 95% confidence interval for the proportion affected in that interbirth interval. Numbers adjacent to the bars represent the number affected divided by the number at risk for that interval. The horizontal solid line within each bar represents the sib recurrence risk for that interval. The solid curved line transecting all boxes represents the regression estimated recurrence risk by interbirth interval, and the dashed lines represent the 95% confidence interval for the estimated recurrence risk.

risk, and interbirth interval was inversely associated (Table 3). For third-born children, comparable associations were observed for male sex and interbirth interval but not for birth weight, maternal age, or previous affected female. For this group, having two previous affected siblings significantly increased the recurrence risk. When one previous sibling was affected, the recurrence risk was significantly greater when the previous affected child was second born rather than first born. For all birth orders combined, male sex and maternal age were positively associated and interbirth interval was inversely associated with recurrence risk. Recurrence risk was significantly increased when two or more previous siblings were affected and significantly decreased for siblings of birth orders >2. These results are generally consistent with the univariate analyses of the same variables, with little or no attenuation of effect sizes, so there appeared to be little confounding.

The pattern for maternal half siblings closely mimicked that for full siblings. Recurrence risk increased with male sex, birth weight, maternal age, and female index case, and it decreased with interbirth interval; however, only male sex and interbirth interval were statistically significant. Recurrence risk was significantly increased when two or more previous half siblings were affected, and also decreased for birth orders >2.

Discussion

This study offers a number of strengths. It is population based with high ascertainment of affected individuals; is the largest ever performed in terms of siblings and maternal and paternal half siblings; it incorporates important demographic covariates, such as parental age, race/ethnicity, and education; and it systematically examines recurrence risk while avoiding reproductive stoppage bias. Potential limitations include the lack of structured diagnoses and possible incompleteness in the birth certificate linkage process. In the family linkage, we excluded 53.5% of the originally identified case families. The majority of these exclusions occurred because our study did not capture the oldest children in the sibship (born before 1990) and because of cases that had no siblings or half siblings and hence had no impact on our recurrence risk calculations. Some families were excluded because of ambiguity in relationships. These exclusions were few and were based on quality of matching information from birth certificates; however, such information was unlikely to be differential based on the constellation of affected and unaffected children in the family, as birth certificates (and the information they contain) precede the onset of symptoms. However, as less matching information was available for fathers before 1997, we were not able to produce as large a sample of paternal half siblings as maternal half siblings, so the estimates for paternal half siblings are based on smaller numbers.

As we have noted, the electronic registry diagnoses appear to have high correspondence with conventional research criteria for ASD (16). However, underascertainment is likely because not all affected children will be receiving services, especially the mildest cases. A previous

TABLE 3. Results of Multivariate Logistic Regression Modeling of Familial Recurrence Risks for Autism Spectrum Disorder[a]

	Full Siblings							
	Second-Born Sibling		Third-Born Sibling		All Siblings		Maternal Half Siblings	
Variable	RRR	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Male	3.18	2.56, 3.95***	2.71	1.85, 3.98***	3.02	2.51, 3.62***	2.31	1.03, 5.22*
Birth weight	1.22	1.02, 1.46*	0.99	0.72, 1.37	1.15	0.98, 1.34	1.19	0.63, 2.21
Maternal age	1.02	1.01, 1.04*	1.00	0.96, 1.03	1.02	1.00, 1.03*	1.04	0.96, 1.12
Months to last birth (ln)	0.55	0.44, 0.68***	0.43	0.29, 0.64***	0.53	0.44, 0.63***	0.43	0.23, 0.80*
Birth year (minus 1990)	1.02	0.99, 1.06	1.03	0.96, 1.10	1.03	1.00, 1.05	1.11	0.97, 1.27
Prior affected females	1.31	1.02, 1.68*	0.88	0.55, 1.42	1.18	0.95, 1.45	1.57	0.34, 7.30
Sibling 2 affected, sibling 1 not affected			1.71	1.10, 2.66*				
Siblings 1 and 2 affected			8.81	4.67, 16.61*				
Previous number affected					4.07	2.56, 6.47***	10.93	1.64, 72.73*
Birth order 3					0.59	0.48, 0.72***	0.22	0.06, 0.82*
Birth order ≥4					0.41	0.27, 0.61***	0.16	0.02, 1.09

[a] RRR=relative recurrence risk; ln=natural logarithm. "Prior affected females" means number of affected females earlier in the birth order. "Sibling 2 affected, sibling 1 not affected" means sibling of birth order 1 is affected and sibling of birth order 2 is unaffected. "Siblings 1 and 2 affected" means sibling of birth order 1 and sibling of birth order 2 are both affected. For birth order 3 and birth order ≥4, birth order 2 is the reference.
* $p<0.05$. *** $p<0.001$.

TABLE 4. Reported Prevalence in Controls and Recurrence Risk of Autism Spectrum Disorder in Siblings and Half Siblings From the Literature

Author	Description of Sample	Prevalence in Controls (%)	Recurrence Risk (%)
Full siblings			
Ritvo et al. (5)	Utah epidemiologic cohort	0.04	8.6
Lauritsen et al. (6)	Denmark population and psychiatric registry linkage	0.15	3.4
Sumi et al. (7)	Nagoya, Japan, epidemiologic survey	2.1	17.8
Constantino et al. (9)	U.S. national volunteer registry	Not given	9.5
Bolton et al. (11)	U.K. family history	0	5.8
Chudley et al. (12)	Canada family history	Not given	7.1
Liu et al. (19)	California registry and birth certificate linkage	0.40	9.7
Ozonoff et al. (13)	Prospective neonatal follow-up	Not given	18.7
Grønborg et al. (8)	Denmark population and psychiatric registry linkage	0.85	6.1
This study	California registry and birth certificate linkage	0.52	10.1
Maternal half siblings			
Cheslack-Postava et al. (18)	California registry and birth certificate linkage	0.40	3.4
Constantino et al. (10)	U.S. national volunteer registry	Not given	5.2
Constantino et al. (10)	Autism Centers of Excellence registry	Not given	7.3
Grønborg et al. (8)	Denmark population and psychiatric registry linkage	0.85	2.0
This study	California registry and birth certificate linkage	0.52	4.8
Paternal half siblings			
Constantino et al. (10)	U.S. national volunteer registry	Not given	0
Grønborg et al. (8)	Denmark population and psychiatric registry linkage	0.85	1.2
This study	California registry and birth certificate linkage	0.52	2.3

study estimated that approximately 75% of prevalent ASD cases are found in this registry (15). Also, there is some concern that follow-up may be less complete for the younger (ages 7–10) compared with the older (ages 11–20) siblings. However, there was no trend toward decreased recurrence risk with birth year, which would have been the hallmark of reduced follow-up. Furthermore, it is also likely that a parent who already had an affected child who was receiving services at a regional center would bring any other affected children to the same center, leading to their ascertainment.

A variety of studies (5–13, 18, 19) with different designs have examined recurrence risks for full siblings and maternal and paternal half siblings (Table 4), and some of these have included reference population prevalences for comparison while others have not. Our result for full siblings is close to the median of previous studies (range, 3.4%–18.7%), as is our population prevalence estimate (0.52%) compared with previous studies (range, 0.04%–2.1%).

Similarly, our recurrence risk for maternal half siblings (4.8%) is close to the median of previous studies (range,

2.0%−7.3%). All studies show a maternal half sibling recurrence risk lower than the corresponding full sibling risk, with a risk ratio ranging from about 0.35 to 0.75 and a median around 0.50, close to our risk ratio of 0.48, strongly supporting a genetic contribution for ASD. By comparison, recurrence risks for paternal half siblings were consistently lower than for maternal half siblings in this study and two previous studies (8, 10), but still considerably above the population prevalence in this study and one previous study (8), again supporting genetic heritability.

While the lower recurrence risk for paternal compared with maternal half siblings also provides evidence suggestive of a maternal environmental effect, the variation in recurrence risk by birth order and interbirth interval provides additional support. The recurrence risk for second-born siblings was 1.6-fold higher than for later-born siblings. These results are consistent with a previous study of highly ascertained ASD family collections (20). Similarly, studies of multiplex ASD sibships suggest that the second affected child is on average more severely affected than the first (21–24). Also, our finding that children born within 18 months of the previous child had a twofold greater recurrence risk than siblings born 4 or more years afterward is consistent with two previous independent studies of nonfamilial ASD cases (18, 25). Notably, the same phenomena regarding interbirth interval and birth order were seen for maternal half siblings, strengthening support for a maternal environment effect. Furthermore, birth order proximity to a previous affected child also matters, as the recurrence risk is greater for a child born right after an affected child compared with children born after an intervening unaffected child.

It is of interest to consider various explanations for these timing-of-birth observations. First, the results could represent a noncausal relationship due to residual confounding (26). Children with late birth order and long interbirth intervals will tend to be younger and with older parents. Older parents will tend to have a greater risk. On the other hand, younger affected children may not be ascertained if a family migrated out of state. In our regression analysis, the birth order and interbirth interval effects were undiminished after including birth year, maternal age, maternal race/ethnicity, maternal education, sex of child, and family history; the interbirth interval effect was observed for all birth orders, making the timing-of-birth observations less likely to be artifactual. Second, mothers with higher genetic susceptibility may have shorter interbirth intervals. However, this would not explain the observed birth order phenomenon and increased risk to a third-born sibling when the immediately preceding child is affected rather than a child earlier in the birth order. If the birth order and birth-interval effects were paternal in origin, we would have seen an attenuation of the effect sizes in the maternal half siblings compared with the full siblings even in the presence of assortative mating, which we did not.

While likely correlated with maternal environment, the specific factor(s) could be postnatal (such as sibling competition or suboptimal infant breastfeeding) or prenatal (such as maternal nutrition depletion, folate depletion, cervical insufficiency, or vertical transmission of infections) (27). Short interbirth interval has been associated with other adverse neonatal outcomes, including low birth weight and preterm birth (28), cerebral palsy (29), and congenital malformations (30), as well as with schizophrenia (31, 32), albeit with more modest impact.

In conclusion, our results support a complex model of familial aggregation involving genetic inheritance that is influenced by maternal effects operating most prominently on second-born offspring and those with short interbirth intervals.

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