Familial Recurrence of Autism: Updates From the Baby Siblings Research Consortium

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abstract

OBJECTIVES: Autism spectrum disorder (ASD) is estimated to be ~10 times higher in children with versus without an autistic sibling in population-based studies. Prospective studies of infant siblings have revealed even higher familial recurrence rates. In the current prospective longitudinal study, we provide updated estimates of familial ASD recurrence using a multinational database of infants with older autistic siblings.

METHODS: Data were collated across 18 sites of the Baby Siblings Research Consortium, an international network studying the earliest manifestations of ASD. A total of 1605 infants with an older autistic sibling were followed from early in life to 3 years, when they were classified as ASD or non-ASD. Hierarchical generalized linear modeling, with site as a random effect, was used to examine predictors of recurrence in families and calculate likelihood ratios.

RESULTS: A total of 20.2% of siblings developed ASD, which is not significantly higher than the previously reported rate of 18.7%. Male infant sex and >1 older affected sibling were significant predictors of familial recurrence. Proband sex also influenced recurrence rates, with siblings of female probands significantly more likely to develop ASD than siblings of male probands. Race and maternal education were also associated with recurrence in families.

CONCLUSIONS: The familial recurrence rate of ASD, as measured in infant sibling studies, has not changed appreciably since previous estimates were made in 2011. Younger siblings of autistic children, particularly those who are male, have an affected female sibling, multiple affected siblings, or are impacted by social inequities, should be closely monitored and promptly referred for diagnostic evaluation.

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Dr Ozonoff conceptualized and designed the study, acquired funding, contributed data, assisted in the interpretation of data, and drafted the initial manuscript; Dr Young conceptualized and designed the study, had full access to all data, conducted data analyses, had responsibility for the integrity of the data and the accuracy of the analyses, and drafted the initial manuscript; (Continued)

WHAT'S KNOWN ON THIS SUBJECT: In 2011, the familial recurrence rate of ASD was estimated at 18.7% by using a prospective longitudinal familial history design. Temporal changes in ASD prevalence, referral patterns, and diagnostic criteria necessitate updated estimates of the recurrence rate.

WHAT THIS STUDY ADDS: We found a 20.2% familial recurrence rate in an independent, larger, more diverse sample, which is not significantly different from 2011 estimates. Given the elevated likelihood that a younger sibling will develop ASD, close developmental surveillance and prompt referrals are warranted.

To cite: Ozonoff S, Young GS, Bradshaw J, et al. Familial Recurrence of Autism: Updates From the Baby Siblings Research Consortium. *Pediatrics*. 2024;154(2):e2023065297

Families with an autistic child want to know the likelihood that subsequent children will also be affected so that they can better prepare for and support that child.[1] A 2011 study on the recurrence rates of autism spectrum disorder (ASD) in families who have had 1 child diagnosed revealed that 18.7% of later-born siblings were themselves diagnosed with ASD.[2] The authors of that study used an infant sibling design, in which babies born into families who already have 1 or more autistic children are followed from shortly after birth through the window when ASD typically emerges.

Population-based studies using large databases from health care systems and insurance networks around the world (eg, Australia, Denmark, Israel, Sweden, the United States)[3–7] have observed likelihood ratios for ASD 7 to 14 times higher in children with an autistic sibling relative to those without an autistic sibling. Prospective longitudinal family history designs, such as the 2011 recurrence study,[2] have an insufficient sample without a family history of ASD to calculate a likelihood ratio. However, a comparison of the 2011 study's estimated familial recurrence rate with the concurrent ASD prevalence rate (1 in 110) at the time of data collection[8] suggested a 20-fold increase relative to the general population. The higher familial recurrence rates found in prospective studies are likely due to methodologic differences. The authors of population-based studies use community diagnoses from national health care databases, with differing diagnostic procedures and levels of expertise across practitioners and time. In contrast, infant sibling designs use serial assessments by autism experts, which may lead to higher sensitivity of identification and reduce biases related to disparities in health care access.

Several factors indicate the need to update estimates of the likelihood of autism recurrence within a family. In the past decade, autism prevalence has increased to 1 in 36,[9] which may reflect changes in referral patterns and diagnosis. In particular, there is greater awareness and identification of autistic females[10] and cognitively able, verbal children. New diagnostic criteria have been published, with different thresholds for diagnosis, which may also affect recurrence rates. Given these temporal changes, it is not clear whether previous estimates of familial recurrence still apply. Updated recurrence rates can inform early developmental monitoring and family counseling by clinical providers. In the current study, we used a multisite infant sibling design and employed the same methods and statistical analyses as the 2011 study[2] on an independent sample, facilitating a direct comparison with 2011 familial recurrence rates. We also examined the potential effects of attrition because the selective retention of more affected participants could artificially inflate estimates of recurrence likelihood within a family.

METHOD

The Baby Siblings Research Consortium (BSRC) is an international network that pools data from individually funded research sites to study the developmental origins and earliest signs of ASD. The present analyses were conducted on data collected between 2010 and 2019 by 18 international BSRC sites with sufficiently similar procedures and common measures to permit data pooling and harmonization. Institutional review board approval to collect and analyze deidentified data was obtained from all sites. Because current data were derived from the same database used in the 2011 article,[2] data used in the previous article were excluded from the current data set. Unless otherwise noted, all procedures and variables were identical to the 2011 article.[2]

Participants were later-born biological siblings of autistic children. Sites recruited from service agencies, community events, registries, websites relevant to ASD, word of mouth, community fliers, and social media. The inclusion criteria included a documented *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis in the affected sibling (hereafter, proband) and no neurologic or genetic condition in the infant or proband that could account for an ASD diagnosis (eg, fragile X syndrome). To minimize biases, including preexisting parental concerns, that might inflate familial recurrence estimates, the inclusion criteria required enrollment at no later than 18 months of age (mean = 5.61 months, SD = 4.53). More than 80% of participants were enrolled by 9 months, before the mean age of first concerns in parents with an already diagnosed child,[11] and 96% were enrolled in the first year of life. Additional inclusion criteria were an outcome assessment age of 35 to 60 months and diagnostic determination by January 2020, before the coronavirus disease (COVID) 2019 pandemic. Finally, all sites included in this analysis used the *Autism Diagnostic Observation Schedule, 2nd Edition* (ADOS-2)[12] and DSM-based outcome criteria to determine ASD diagnosis, preventing biases in outcomes based on access to diagnostic resources that could impact recurrence estimates. For families with multiple enrolled infants, only 1 participant per family, the infant closest in age to the proband, was included. This resulted in a total sample size of 1605 participants.

Measures

The ADOS-2 and Mullen Scales of Early Learning (MSEL) were administered at 36 months of age. The ADOS-2 is a standardized protocol with high reliability that measures autism characteristics and yields an empirically derived cutoff for ASD.[12] A severity score ranging from 1 to 10 is calculated, with scores of 4 and above indicative of ASD. The MSEL is a standardized developmental test with good internal consistency and test–retest reliability; it measures nonverbal cognitive, language, and motor skills from birth to 68 months.[13]

Demographic information was collected from parents using site-specific forms. Race and ethnicity are social constructs (not genetic or biological categories) that, as important social determinants of health, were included because they may reflect inequities underlying ASD-related health disparities.[14] Race was analyzed dichotomously (white vs Other Race) because of different definitions across countries and a high number of participants reported as "more than one race." Other race included US census categories of Asian, Black or African-American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and >1 race, as well as additional races reported by non-US sites. Maternal and paternal education were measured on a 4-point scale indicating high school, some college, college degree, or graduate degree. Maternal and paternal age at the participant's birth were measured as continuous variables. The birth order of the infant was recorded as a 3-level variable (second-, third-, or fourth- or later-born). A variable indicating whether the infant had 1 older autistic sibling (simplex) or >1 older affected sibling (multiplex) was available from a subset of sites.

Procedure

Infants were seen for serial evaluations, starting as early as 6 months of age, for up to 7 visits. On the basis of the final 36-month assessment, participants were classified into 1 of 2 of the following outcome groups: ASD (obtained a DSM diagnosis of ASD from an expert clinician and a comparison score of 4 or above on the ADOS-2) and non-ASD (all other participants).

Statistical Approach

Hierarchical generalized linear modeling was employed to model ASD outcome as a binomial distribution using a logit-link function. There were significant differences in recurrence rates by site, but site did not interact with or moderate the effect of any variables in predicting ASD recurrence in families. Consequently, the site variable was included as a random effect in all models. Potential associations of demographic variables (race, ethnicity, parental education, parental age) with outcome were examined first. Child-specific variables (infant sex, age at enrollment, multiplex family status, birth order) were examined in subsequent models. Main and interaction effects were tested by using χ-square tests of differences between the goodness of fit values (2 log-likelihood values) for nested models with and without the effect of interest by using the difference in model parameters as the degrees of freedom. Odds ratios were transformed into relative risk (RR) ratios,[15] which define the likelihood of recurrence in families of one group (eg, females) relative to another group (eg, males). All analyses were conducted with R version 4.1.2[16] using the lme4 package.[17]

RESULTS

Table 1 contains descriptive statistics for the main variables of interest. It also contains sample descriptives reported in the 2011 paper[2] and simple statistical comparisons between the samples. Eleven of the 18 sites contributing data to the current sample also contributed data to the 2011 sample,[2] but there was no overlap of participants. There were significant differences between the samples for mean age at enrollment (current sample is younger), race (current sample is more diverse), birth order (current participants born later in sibships), and maternal and paternal education (lower in current sample).

Overall Familial Recurrence Rates

For analyses on the current sample, the initial statistical model was an unconditional random effects model. The intercept logit of the model was −1.38 (SE = 0.12), which translates to an overall familial recurrence rate of 20.2% (95% confidence interval [CI] = 16.6% to 24.3%). Combining the current and 2011 data and testing for sample effects, a small difference in recurrence rates between samples was observed but did not reach statistical significance ($P = .06$). See Table 2 for detailed comparisons across samples.

Familial Recurrence Rates as a Function of Demographic Variables

Race was a significant predictor of recurrence ($P < .01$). In white infant siblings, the recurrence rate was 17.8% (95% CI = 13.9% to 22.6%); in other race participants, it was 25.0% (95% CI = 19.9% to 32.0%), RR = 1.54 (95% CI = 1.12 to 2.21). The examination of Hispanic versus non-Hispanic ethnicity was not significant ($P = .24$). In the 2011 article, race and ethnicity were collapsed into a single variable (non-Hispanic white or not). For purposes of comparison with 2011 rates, we also analyzed this dichotomous variable within the current sample, finding a significant effect ($P < .01$). For non-Hispanic white families, the recurrence rate was 17.4% (95% CI = 13.5% to 22.2%), whereas it was 24.3% (95% CI = 19.1% to 30.3%) for Other Race and Hispanic families.

The inclusion of parental education revealed a significant effect only for mothers ($P < .01$); paternal education was not significant ($P = .09$). The familial recurrence rate in infants whose mothers attained high school or less education was 32.6% (95% CI = 23.6% to 43.2%); some college was 25.5% (95% CI = 17.5% to 35.6%); college degree was 19.7% (95% CI = 13.4% to 28.0%); and graduate degree was 16.9% (95% CI = 11.0% to 25.0%). Simple comparisons using high school or less as the referent category revealed that recurrence rates were significantly lower in both the college degree (RR = 0.61, 95% CI = 0.41 to 0.86) and graduate degree (RR = 0.51, 95% CI = 0.34 to 0.77) groups.

There were no significant effects for maternal or paternal age at the time of the participant's birth ($P = .69$ and

TABLE 1 Characteristics of the Current and 2011 Samples

	Current Sample		2011 Sample	
Variable	**Statistic**	***n***	**Statistic**	***n***
Mean age at enrollment, mo (SD)*	5.6 (4.5)	1605	8.4 (4.4)	664
Infant sex, % male	57.8	1604	55.6	663
Race, % other race*	25.0	1181	13.2	562
Asian[a]	7.0	1181	—	—
Black or African American[a]	2.8	1181	—	—
American Indian or Alaska Native[a]	0.4	1181	—	—
Native Hawaiian or Pacific Islander[a]	0.3	1181	—	—
>1 race[a]	14.1	1181	—	—
Another race[a,b]	0.7	1181	—	—
Ethnicity, % Hispanic*	16.6	909	24.2	165
Birth order, % third-born or later*	48.4	477	39.7	458
Sex of proband, % male	84.9	662	84.2	658
Multiplex status, % with >1 affected older sibling	8.7	677	6.0	619
Maternal education, % college degree or higher*	67.5	1398	77.1	365
Paternal education, % college degree or higher*	64.5	1369	74.3	338
Mean maternal age, y (SD)	34.9 (4.6)	443	34.5 (4.4)	566
Mean paternal age, y (SD)	37.6 (6.0)	486	36.9 (5.2)	563

n indicates total sample size available for calculation of the variable.
* Indicates samples significantly differ on respective statistic at $P < .05$.
[a] Individual race categories not available for 2011 sample.
[b] Another race includes races reported by non-US sites, such as Sikh, Ashkenazi Jewish, Kurdish, etc.

0.43, respectively), nor for birth order ($P = .10$) or age at enrollment ($P = .07$).

Familial Recurrence Rates as a Function of Child Sex and Multiplex Status

As found in 2011,[2] there was a significant effect for infant sex ($P < .001$), with the recurrence rate in female infants (13.1%, 95% CI = 10.0% to 16.9%) being significantly lower than that in male infants (25.3%, 95% CI = 20.0% to 31.4%). The RR for male infants versus female infants was 1.93 (95% CI = 1.58 to 2.35).

Retaining infant sex in the model, we found that the main effect for multiplex status significantly predicted familial recurrence above and beyond infant sex ($P < .01$), with a recurrence rate of 21.2% (95% CI = 13.2% to 32.3%) in simplex families versus 36.9% (95% CI = 24.8% to 50.9%) in multiplex families (RR = 1.74 [95% CI = 1.17 to 2.40]).

TABLE 2 Recurrence Rates in Current Sample and Comparison With 2011 Sample

	Current Sample			2011 Sample		
Effect	**Recurrence Probability**	**RR**	***n***	**Recurrence Probability**	**RR**	***n***
Overall recurrence rate	20.2%		1605	18.7%		664
Other race[a] or Hispanic versus white	24.3% vs 17.4%	1.39*	1181	24.9% vs 17.8%	1.40	657
Maternal education (graduate degree versus high school)	16.9% vs 32.6%	0.51*	1398	15.6% vs 17.3%	0.90	410
Maternal age (40 vs 35 y)[b]	27.8% vs 26.9%	1.01	443	15.5% vs 17.1%	0.98	566
Paternal age (44 vs 38 y)[b]	26.7% vs 25.1%	1.01	486	13.7% vs 16.6%	0.97	563
Birth order (second- versus third-born)	24.8% vs 21.3%	1.16	477	23.9% vs 17.2%	1.39	458
Age at enrollment (1 vs 6 mo)[c]	25.4% vs 21.2%	1.03	592	18.0% vs 19.9%	0.98	664
Infant sex (male versus female)	25.3% vs 13.1%	1.93*	1604	26.2% vs 9.1%	2.8*	663
Multiplex (multiplex versus simplex)	36.9% vs 21.2%	1.74*	677	32.2% vs 13.5%	2.2*	619
Infant sex by multiplex (multiplex male versus multiplex female)	36.5% vs 39.5%	0.92	677	47.1% vs 19.7%	2.4	619
Infant sex by multiplex (simplex male versus simplex female)	29.2% vs 12.6%	2.32*	677	22.9% vs 7.6%	3.0	619
Proband sex (female versus male)[d]	34.7% vs 22.5%	1.82*	418	19.6% vs 14.6%	1.43	616

* Significant difference, $P < .05$.
[a] Other race includes standard US census categories of Asian, Black or African-American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and >1 race. It also includes races reported by non-US sites, such as Sikh, Ashkenazi Jewish, Kurdish, etc.
[b] Comparison based on mean and mean + 1 SD from current sample.
[c] Comparison made to reflect canonical recruitment ages.
[d] Main effect in the presence of infant sex and multiplex main effects.

There was a significant interaction between infant sex and multiplex status ($P < .05$), see Fig 1. This effect was driven primarily by female infant siblings. Female infants from a simplex family had a recurrence rate of 12.6% (95% CI = 8.3% to 18.6%), whereas female infants from a multiplex family had a recurrence rate of 39.5% (95% CI = 21.3% to 61.1%), which was a significant difference (RR = 3.14, 95% CI = 1.67 to 4.90, $P < .001$). In contrast, for male infants, the recurrence rate in simplex families (29.2%, 95% CI = 22.3% to 37.2%) was not significantly different from that in multiplex families (36.5%, 95% CI = 21.4% to 54.8%). Recurrence rates between male infants and female infants were significantly different in simplex families, with male infants significantly more likely to develop ASD than female infants (RR = 2.32, 95% CI = 1.50 to 3.36), which is consistent with general sex ratios in ASD and our 2011 results.[2] In contrast, recurrence rates in male infants and female infants did not differ significantly in multiplex families (36.5% and 39.5% respectively, RR = 0.92).

We next added proband sex to the model containing main effects for both infant sex and multiplex status. In this main-effects model, proband sex was significant ($P < .05$). For families with a male proband, the recurrence rate was 22.5% (95% CI = 18.3% to 27.4%), whereas for those with a female proband, the familial recurrence rate was 34.7% (95% CI = 24.5% to 46.6%; RR for those with female versus male probands = 1.82, 95% CI = 1.05 to 3.20).

Attrition Analyses

Finally, to explore possible attrition biases, we compared the current sample to 509 participants who dropped out of the study before the 36-month outcome determination (an inclusion criterion for the current analyses). The mean age at the last visit of those who were lost to attrition was 17.36 months (SD = 7.69). To examine whether there were sociodemographic or functioning differences between the analyzed sample and those who did not complete the study that could affect familial recurrence rate estimates, we compared MSEL standard scores and ADOS-2 severity scores at the last visit (36 months for the analyzed sample and age of final visit for those not retained), as well as infant sex, race, ethnicity, and maternal education. Group comparisons between dropped and retained groups are shown in Table 3. There were significant differences in all MSEL standard scores, with the retained group having significantly higher scores than the dropped group except for fine motor functioning. There was no significant difference in ADOS-2 severity scores. There were no differences in infant sex, race, or ethnicity, but mothers of those retained had significantly higher levels of educational attainment than those not retained. Attrition effects did not change when controlling for age at the last visit.

TABLE 3 Comparison of Developmental and Sociodemographic Variables in Retained and Not Retained Subsamples (Estimated Marginal Means [SE])

Variable	Not Retained	Retained
MSEL early learning composite*	96.10 (1.39)	101.27 (1.41)
MSEL expressive language T score*	45.71 (1.17)	50.88 (1.12)
MSEL receptive language T score*	45.54 (1.16)	49.29 (1.12)
MSEL fine motor T score*	50.66 (1.23)	47.40 (1.03)
MSEL visual reception T score*	50.48 (0.84)	55.84 (0.92)
ADOS-2 severity score	2.99 (0.30)	3.05 (0.25)
Infant sex (% male)	56.9 (2.3%)	58.1 (1.2%)
Maternal education (% college or higher)*	59.6 (2.6%)	72.9 (1.2%)
Race (% other race[a])	22.8 (2.3%)	17.7 (1.1%)

SE, standard error.
* $P < .01$.
[a] Other race includes standard US census categories of Asian, Black or African-American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and >1 race. It also includes races reported by non-US sites, such as Sikh, Ashkenazi Jewish, Kurdish, etc.

DISCUSSION

In this article, we report updated recurrence rates of ASD in families already raising 1 or more autistic children. Using a familial history design, an independent sample, and parallel data collection and analysis methods to our initial report,[2] we directly compared familial recurrence rates in 2011 to current rates. The current sample is more than twice as large and significantly more diverse than the 2011 sample. We found both similarities to and differences from the initial publication in familial recurrence estimates and associated factors. The overall familial recurrence estimate of 20.2% in the current sample was statistically similar to the 2011 estimate of 18.7%. This small increase in recurrence rates contrasts with the large increase in population prevalence rates over the same period (from 0.9% to 2.8%).[8,9] Temporal trends in referral and diagnosis over the past decade, such as increasing recognition of ASD in females,[10] more cognitively able children, and those with more subtle manifestations, as well as changes in diagnostic criteria and thresholds, spurred us to update estimates of recurrence. They do not, however, appear to have had a significant impact on familial recurrence rates in this infant sibling study design.

We replicated previous studies revealing that the 2 most prominent predictors of recurrence in families were infant male sex[2,5–7,18] (male versus female recurrence rates: 25.3% vs 13.1%) and multiplex status[2,19] (children with 2 or more affected siblings versus 1 affected sibling: 36.9% vs 21.2%). In our previous article,[2] we did not find an interaction between infant sex and multiplex family status, whereas this effect was significant in the present sample. There was no difference in familial recurrence rates between simplex and multiplex male infants, whereas there was more than a threefold difference between simplex and

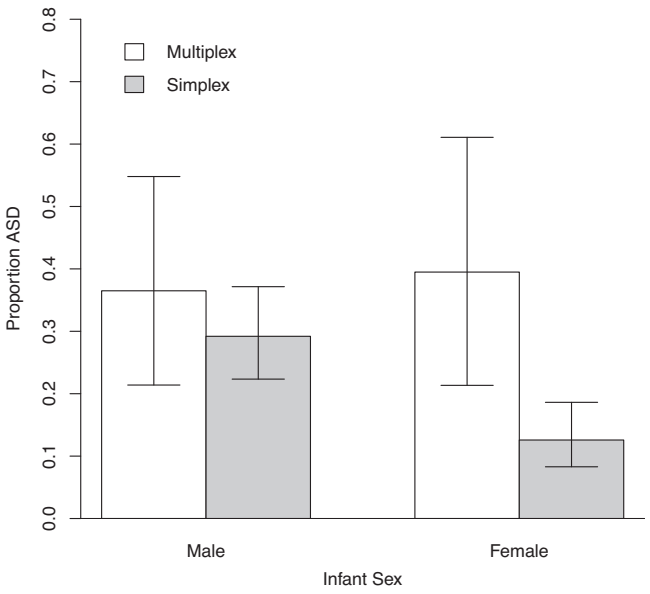

FIGURE 1
ASD recurrence rates as a function of infant sex and family multiplex status.

multiplex female infants. This pattern of differences from the 2011 article was driven by the substantially higher recurrence rate in multiplex female infants in the current sample (39.5%) than in the 2011 sample (19.7%).

A polygenic threshold model of ASD, in which females must accumulate more genetic factors than males to develop ASD, has been proposed for many years to account for the unbalanced sex ratio. Supportive evidence of a female protective effect (FPE)[20] includes higher recurrence rates in families with female probands than male probands,[5–7] and the current sample replicated this finding. The strength of the evidence for FPE is complicated, however, by the lower sex ratio in the current sample; although a male-to-female ratio of 3.8:1 was reported in the United States[9] and a ratio of 2.8:1 was reported in our previous work,[2] it was only 1.9:1 in the full sample and 1:1 within multiplex families, which suggests an attenuated FPE. This may reflect the recent focus on potential differences in autism characteristics and their measurement in females,[10,21,22] which may have led to better identification of autistic girls in the current sample.

Another apparent difference between the current and previous findings is a significant effect of race on recurrence, with families of white infants having significantly lower recurrence rates than families of participants of other races (17.4% vs 24.3%). As evident in Table 2, however, the RR of 1.39 in the current sample is almost identical to that of the 2011 sample (1.40), suggesting that the larger current sample size enabled the detection of a significant effect. We also found significantly lower recurrence in families of mothers with higher educational attainment. As with ASD prevalence, recurrence rates may be affected by disparities in access to timely and accurate identification, as well as biases in diagnostic tools and clinical impressions.[10,23,24] The factors underlying the race and maternal education effects we found on familial recurrence are likely complex and our ability to interpret them is limited by the narrow range of sociodemographic variables available for analysis. Recent Centers for Disease Control and Prevention estimates[9] also revealed reduced prevalence among white children compared with Black and Hispanic children, as well as associations between lower socioeconomic status and higher prevalence rates. Collectively, these findings indicate the need for further research examining social, economic, and environmental contributions to health care disparities generally and increased recurrence in more vulnerable families specifically.[23,24]

Examining the effects of attrition is critical to determining the soundness of a study's conclusions and broader generalizability. Of relevance to the current study, the selective retention of more affected participants could have artificially inflated familial recurrence estimates. We found, however, that retained participants did not show more autistic behaviors than those who dropped out. Retained participants did have higher developmental scores and maternal education than participants who left the study, but because both variables are associated with lower odds of familial recurrence, this presents a conservative bias that could reduce (but would not inflate) recurrence estimates.

The current results have several clinical implications. They emphasize the need for close developmental surveillance of infant siblings during well-child visits to ensure timely referral for diagnostic evaluations or early intervention services. Heightened surveillance (eg, more frequent developmental screening, specific questions addressing social and communication development during well-child visits, lower thresholds for referral)[25] should be considered for infants in families with an elevated likelihood of recurrence (eg, infants who are male, have >1 autistic sibling, or are from families facing potential social inequities in access to services). More than a decade has passed since the last prospective study on familial recurrence, and during that time, population prevalence estimates have markedly increased, leading to ambiguity about whether previous recurrence estimates would still apply. Having the results of 2 large, independent studies report familial recurrence rates in the same range may reassure providers about the reliability of the information they offer when counseling families in clinical practice. Although familial recurrence estimates are based on group averages and are not generally informative regarding individual likelihoods,[1] this information may be useful to families in planning for and supporting future children.

CONCLUSIONS

The current study reinforces the importance of developmental surveillance and screening[25] for younger siblings

of autistic children, particularly those who are male, have an affected female sibling, or have multiple affected siblings. This study also highlights the increased likelihood of recurrence in families who may experience social disparities because of race, education, or other sociodemographic factors. Such infants merit additional monitoring and prompt referral for intervention so as not to delay diagnosis in potentially disadvantaged groups.

ACKNOWLEDGMENTS

We are grateful to the families for their generous participation in these studies. We acknowledge the following individuals who led data-contributing sites and obtained funding for this project: Mirella Dapretto, PhD, University of California Los Angeles; Ami Klin, PhD, Marcus Autism Center and Emory University School of Medicine; Charles A. Nelson III, PhD, Harvard University; Joseph Piven, MD, University of North Carolina; Jane E. Roberts, PhD, University of South Carolina; Wendy L. Stone, PhD, University of Washington; Helen Tager-Flusberg, PhD, Boston University; Sara Jane Webb, PhD, University of Washington. The following individuals were additional members of the BSRC recurrence workgroup: Jessica A. Brian, PhD, Holland Bloorview Kids Rehab, University of Toronto; Sarah Shultz, PhD, Emory University School of Medicine; Beth A. Smith, PhD, Keck School of Medicine, University of Southern California. We thank Alycia Halladay, PhD, Autism Science Foundation, for her long-term support of this project and for organizing, providing infrastructure for, and participating in BSRC meetings and the recurrence workgroup.

ABBREVIATIONS

ADOS-2: *Autism Diagnostic Observation Schedule, 2nd Edition*
ASD: autism spectrum disorder
BSRC: Baby Siblings Research Consortium
CI: confidence interval
DSM: *Diagnostic and Statistical Manual of Mental Disorders*
FPE: female protective effect
MSEL: Mullen Scales of Early Learning
RR: relative risk

Drs Charman, Chawarska, Iverson, Landa, Messinger, Schmidt, and Zwaigenbaum acquired funding, contributed data, and participated in study conceptualization and data interpretation; Drs Bradshaw, Klaiman, McDonald, and Wilkinson assisted in study conceptualization, design, and interpretation and contributed data; and all authors critically reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Deidentified individual participant data will not be made available.

DOI: https://doi.org/10.1542/peds.2023-065297

Accepted for publication May 15, 2024

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FUNDING: Funded by the National Institutes of Health (NIH; R01 MH068398, PI: Ozonoff; R01 MH099046, PI: Ozonoff; P50 HD103526, PI: Abbeduto; P50 MH100029, PI: Klin; R01 MH059630, PI: Landa; R01 R01MH059630, PI: Nelson/Tager-Flusberg; R01 MH090194, PI: Roberts; R01 MH107573, PI: Roberts; K23 MH120476, PI: Bradshaw; P50 HD055784, PI: Jeste/Dapretto; K23 HD096046, PI: McDonald;R01 HD054979, PI: Iverson; R01 HD073255, PI: Iverson; P50 HD055782, PI: King. P50 MH115716, PI: Chawarska; R01 MH087554, PI: Chawarska; R01 MH100182, PI: Chawarska; R01 MH124892, PI: Chawarska; U24 ES028533, PI: Schmidt, Chambers; R01ES028089, PI: Hertz-Picciotto); R01 HD057284, PI: Stone/Messinger; R01 HD047417, PI: Messinger; R01 HD055741, PI: Piven; K23 DC07983, PI: Wilkinson; the Autism Science Foundation (BSRC 17-001, PI: Young; BSRC 21-001, PI: Young; BSRC 22-001, PI: Lasso Informatics; BSRC 23-001, PI: Young;); Autism Speaks (AS8370, PI: Ozonoff; AS6020, PI: Piven); the Canadian Institutes of Health Research (PI Zwaigenbaum); the UK Medical Research Council (MR/R011427/1, G0701484, MR/K021389/1, MR/T003057/1, CI: Charman); the Simons Foundation for Autism Research (SFARI-863967, PI: Schmidt; SFARI-140209, PI: Piven); the Marcus Foundation (PI: Jones/Klin); the Joseph B. Whitehead Foundation (PI: Jones/Klin); and the Georgia Research Alliance (PI: Jones/Klin/Lewis). The funders had no role in the design and conduct of the study and did not require reporting of race or ethnicity.

CONFLICT OF INTEREST DISCLOSURES: Dr Ozonoff reports travel reimbursements and honoraria from Autism Speaks and the Autism Science Foundation and book royalties from Guilford Press. Dr Charman has served as a paid consultant to F. Hoffmann-La Roche Ltd and Servier and has received royalties from Sage Publications and Guilford Publications. Dr Zwaigenbaum is supported by the Stollery Children's Hospital Foundation Chair in Autism. Dr Klaiman reports a consulting agreement with EarliTec Diagnostics Inc. and book royalties from Wiley. Dr Schmidt has received funding from the Simons Foundation and consults for the Beasley Law Firm and Linus Technology, Inc. The remaining authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

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