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**Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study**

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**Recurrence Risk for Autism Spectrum Disorders:****A Baby Siblings Research Consortium Study**

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**Abbreviations:**

ADOS: Autism Diagnostic Observation Schedule

ASD: Autism Spectrum Disorders

BSRC: Baby Siblings Research Consortium

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition, Text  
Revision

PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified

**Keywords:** autism, recurrence, sibling risk

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**Short Title:** Sibling recurrence risk for ASD

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## Contributors' Statement

Author Contributions: Drs. Ozonoff and Young had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Ozonoff, Young, Carter, Messinger, Yirmiya, Zwaigenbaum, Bryson, Carver, Constantino, Iverson, Rogers, Sigman

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*Analysis and interpretation of data:* Ozonoff, Young, Carter, Yirmiya, Zwaigenbaum, Bryson, Carver, Constantino, Hutman, Stone

*Drafting of the manuscript:* Ozonoff, Young

*Critical revision of the manuscript for important intellectual content:* Ozonoff, Young, Carter, Messinger, Yirmiya, Zwaigenbaum, Bryson, Carver, Constantino, Dobkins, Hutman, Iverson, Landa, Rogers, Sigman, Stone

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**What's Known on this Subject:**

The sibling recurrence risk of autism has been estimated between 3 and 10%. Most previous research was conducted prior to DSM-IV and affected by small samples, selection, stoppage, or reporting limitations. Updated estimates of recurrence risk are needed.

**What this Study Adds:**

Studying a large sample and using a prospective longitudinal design, this study demonstrated that the sibling recurrence risk of ASD is substantially higher than previous estimates. This elevated risk has important implications for infant screening and genetic counseling.

## Abstract

**Objective:** The recurrence risk of autism spectrum disorders (ASD) is estimated between 3 and 10%, but previous research was limited by small sample sizes and biases related to ascertainment, reporting, and stoppage factors. This study used prospective methods to obtain an updated estimate of sibling recurrence risk for ASD.

**Methods:** A prospective longitudinal study of infants at risk for ASD was conducted by a multi-site international network, the Baby Siblings Research Consortium. Infants (n=664) with an older biological sibling with ASD were followed from early in life to 36 months, when they were classified as ASD or Non-ASD. An ASD classification required surpassing the cutoff of the Autism Diagnostic Observation Schedule and receiving a clinical diagnosis from an expert clinician.

**Results:** 18.7% of infants developed an ASD. Infant sex and the presence of more than one older affected sibling were significant predictors of ASD outcome, with an almost three-fold increase in risk for males and an additional two-fold increase in risk if there was more than one older affected sibling. In contrast, the age of the infant at study enrollment, the sex and functioning level of the infant's older sibling, and other demographic factors did not predict ASD outcome.

**Conclusions:** The sibling recurrence rate of ASD is higher than suggested by previous estimates. The size of the current sample and the prospective nature of the data collection minimized many limitations of previous studies of sibling recurrence, including ascertainment bias, stoppage, and over-reporting. Clinical implications, including genetic counseling, are discussed.

## Introduction

Autism spectrum disorders (ASD) are among the most common neurodevelopmental disorders, with recent surveillance efforts indicating that 1 in 110 American children meet criteria for an ASD.<sup>1</sup> The sex ratio is highly skewed, with approximately 80% of affected individuals being male. There is strong evidence that genetic factors play a critical role in vulnerability to ASD,<sup>2</sup> with heritability estimates from twin studies as high as 90%.<sup>3</sup> Moreover, there have been recent advances in identifying specific genetic causes of ASD, such as genomic copy number variants (CNVs) in genes involved in synaptic cell adhesion and related pathways, which have been identified in as many as 7-10% of people with ASD.<sup>4,5</sup> However, there are still many individuals with ASD for whom etiology is not yet known.

An important measure of genetic contribution is the risk of recurrence in siblings. Previous studies have examined the rate of ASD in families who already have one affected child, with recurrence estimates ranging from 3 to 10%.<sup>6-8</sup> However, only a few studies have taken into account the effects of stoppage<sup>9</sup> (the tendency for families to halt reproduction after the diagnosis of an affected child) by studying families in which there are later-born siblings. A large epidemiological survey of autism in Utah in the 1980's reported a recurrence risk of 8.6% in siblings born after an affected child.<sup>10</sup> An even higher risk to later-born siblings of 14.2% was recently reported in a large U.S. registry of children with ASD.<sup>11</sup> The Utah study found that the risk to later-born children was approximately twice as high if the first affected child was a female, consistent with a multifactorial threshold model of transmission, in which risk is elevated for relatives of a

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3 proband in which the condition is less common.<sup>10, 12</sup> More recent studies, however, have  
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5 provided mixed evidence for this threshold model.<sup>13,14</sup>  
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8 While reproductive stoppage leads to under-estimates of sibling recurrence risk,  
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10 ascertainment biases and over-reporting can lead to inflation of sibling recurrence  
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12 risk.<sup>15,16</sup> Parents who already have an affected child may focus more attention on the new  
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14 infant's development,<sup>17</sup> which may increase the probability of both true positive and false  
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16 positive identification. Samples may be more or less biased by strictness of inclusion  
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18 criteria, age of participant enrollment, and diagnostic methods. Optimal estimates require  
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20 both population-based epidemiological methods to assure that the sample is maximally  
21  
22 representative of all families who have a child with ASD and expert direct assessment to  
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24 supplement parent report methods.<sup>15</sup>  
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29 The present study reports on data from a large cohort of infants collected as part  
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31 of an international collaboration to study the earliest signs of ASD in infants with an  
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33 older affected sibling. Infants were followed prospectively through the window of risk for  
34  
35 symptom emergence. Diagnostic assessments were performed at 36 months of age by  
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37 expert examiners. The prospective design, direct assessment methods, gold standard  
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39 diagnostic procedures, young age of enrollment, geographic diversity of recruitment, and  
40  
41 large sample size minimize many methodological limitations of previous research and  
42  
43 provide updated estimates of recurrence risk.  
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#### 48 Patients and Method

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50 The Baby Siblings Research Consortium (BSRC) is an international network  
51  
52 supported by Autism Speaks that pools data from individually funded research sites to  
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54 study the development of high-risk infants. The present analyses were carried out on data  
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3 contributed from 12 sites (University of Alberta, Dalhousie University, Kennedy Krieger  
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5 Institute, McMaster University, University of California – Davis, University of California  
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7 – Los Angeles, University of California – San Diego, University of Miami, University of  
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9 Pittsburgh, University of Toronto, Vanderbilt University, and Washington University-St.  
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11 Louis) that had sufficiently similar procedures and common measures to permit data  
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13 pooling. IRB approval to collect and analyze de-identified data from all sites was  
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15 obtained.  
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20 Infant participants were later-born biological siblings of a child with ASD<sup>a</sup>.  
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22 Diverse community recruitment strategies were employed. All sites recruited participants  
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24 from clinics and agencies serving individuals with ASD, community events (lectures,  
25  
26 health fairs, local autism society meetings) targeted at families affected by ASD, and  
27  
28 other studies of ASD at their respective universities. Most sites also recruited participants  
29  
30 through websites targeted to ASD, word of mouth (parents referring other parents), and  
31  
32 fliers posted in the community. A few sites also used mailings and media announcements  
33  
34 to recruit participants. Inclusion criteria included a documented diagnosis<sup>b</sup> of DSM-IV  
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36 Autistic Disorder, Asperger Disorder, or Pervasive Developmental Disorder Not  
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38 Otherwise Specified (PDD-NOS) in the affected sibling (hereafter called the proband)  
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40 and no identified neurological or genetic condition in the infant or proband that could  
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42 account for an ASD diagnosis (e.g., fragile X syndrome). Additional inclusion criteria  
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44 were maximum enrollment age of 18 months, minimum outcome assessment age of 36  
45  
46 months (see Figure 1), and availability of both a clinical diagnosis and an Autism  
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48 Diagnostic Observation Schedule (ADOS).<sup>18</sup> For families with multiple enrolled infants,  
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3 only one participant per family, the infant recruited at the youngest age, was included.  
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6 This resulted in a total sample size of 664 participants.  
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8 The ADOS and the Mullen Scales of Early Learning were administered at 36  
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10 months of age. The ADOS is a standardized protocol that measures symptoms of ASD  
11  
12 and yields an empirically derived cutoff for ASD.<sup>18</sup> Psychometric studies report high  
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14 inter-rater reliability and agreement in diagnostic classification for individuals aged 24  
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16 months and older.<sup>18</sup> The Mullen Scales of Early Learning is a standardized  
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18 developmental test for children birth to 68 months that measures nonverbal cognitive,  
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20 language, and motor skills.<sup>19</sup> The Mullen subscales have excellent internal consistency,  
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22 and test-retest reliability. Demographic information was also collected at each site. Race  
23  
24 and ethnicity of the infant were reported by parents using categories specified by the  
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26 National Institutes of Health, which were then collapsed for analysis into a dichotomous  
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28 variable (Non-Hispanic White v. Other Race/Ethnicity). Maternal and paternal education  
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30 were measured on a 4-point scale indicating high-school, some college, college degree, or  
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32 graduate degree. Maternal and paternal ages at the birth of the child were measured as  
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34 continuous variables. Birth order of the infant was recorded as a 3-level variable (2<sup>nd</sup>  
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36 born, 3<sup>rd</sup> born, 4<sup>th</sup> born or later). A dichotomous variable was created indicating whether  
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38 the infant's family was simplex (one older sibling with ASD, n=582) or multiplex (more  
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40 than one older sibling with ASD, n=37).  
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48 Based on the 36-month assessment, participants were classified into one of two  
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50 outcome groups. The ASD outcome group included participants who scored above the  
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52 ASD cutoff of the ADOS and received a clinical diagnosis of DSM-IV-TR Autistic  
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3 Disorder or PDD-NOS according to an expert clinician at each site. The Non-ASD  
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5 outcome group included all other participants.  
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8 Statistical approach. Hierarchical Generalized Linear Modeling was employed to  
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10 model outcome as a binomial distribution using a logit-link function. Although  
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12 preliminary analyses revealed site heterogeneity in recurrence risk, site did not interact  
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14 with or moderate the effect of any variables in predicting prevalence estimates of ASD  
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16 outcome. Therefore, only the main effect of site was included as a random effect to  
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18 account for site heterogeneity in all models. Potential associations of demographic  
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20 variables (race/ethnicity, parental education, parental age) with outcome were examined  
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22 first. Child-specific variables (infant sex, multiplex family status, proband severity) were  
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24 examined in subsequent models. Variables that were significant predictors of outcome  
25  
26 were retained in the model such that all subsequent analyses controlled for the retained  
27  
28 variables. Main and interaction effects were tested using Chi-square tests of differences  
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30 between goodness of fit values (-2log-likelihood values) for nested models with and  
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32 without the effect of interest, using the difference in model parameters as the degrees of  
33  
34 freedom. Relative risk and respective confidence intervals were estimated using a Poisson  
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36 quasi-likelihood method using SAS PROC GENMOD. All other analyses were  
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38 conducted using R version 2.9.1, employing the lme4 package for multi-level modeling.  
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#### 46 Results

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48 There were 132 infants (29 female) who met criteria for ASD at outcome,  
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50 yielding an estimated recurrence rate of 18.7% (95% CI=13.34% to 25.5%). Of these 132  
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52 participants, 54 (40.9%) received a clinical diagnosis of Autistic Disorder and 78 (59.1%)  
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54 received a clinical diagnosis of PDD-NOS.  
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Table 1 includes demographic characteristics of the sample. Analyses of demographic variables as predictors of outcome revealed no significant main effects for race/ethnicity ( $X^2=2.6$ ,  $df=1$ ,  $p=.10$ ), maternal education ( $X^2=2.3$ ,  $df=3$ ,  $p=.52$ ), paternal education ( $X^2=4.7$ ,  $df=3$ ,  $p=.20$ ), or maternal age at birth of the child ( $X^2=0.8$ ,  $df=1$ ,  $p=.38$ ). There was a non-significant trend ( $X^2=2.9$ ,  $df=1$ ,  $p=.09$ ) for group differences in paternal age, with fathers of participants with ASD outcomes being slightly younger than fathers of children with non-ASD outcomes. Birth order was not a significant predictor of outcome ( $X^2=3.1$ ,  $df=2$ ,  $p=.21$ ), nor was age of study enrollment ( $X^2=1.1$ ,  $df=1$ ,  $p=.30$ ).

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Sex of the infant significantly predicted outcome ( $X^2=34.9$ ,  $df=1$ ,  $p < .001$ ), with 26.2% (CI=19.2% to 34.6%) of males receiving an ASD diagnosis versus 9.1% (CI=5.7% to 14.2%) of females. The estimated relative risk for sex was 2.8 (CI=1.9 to 4.0), indicating an almost 3-fold increase in the risk of an ASD outcome in male relative to female siblings.

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Analysis of ASD diagnosis at outcome as a function of family multiplex status revealed a significant main effect, above and beyond infant sex ( $X^2=8.0$ ,  $df=1$ ,  $p < .01$ ). The estimated relative risk of 2.2 (CI=1.4 to 3.3) indicated a 2-fold increase in the probability of an ASD diagnosis at outcome for infant siblings who had multiple older affected siblings (32.2%, CI=21.8% to 44.7%) relative to those who had only one older affected sibling (13.5%, CI=8.4% to 20.9%).<sup>c</sup> There was no interaction between multiplex status and sex ( $p=.28$ ). Figure 2 displays the estimated proportions of ASD outcomes as a function of infant sex and family multiplex status.

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Sex of the older sibling was considered next, building on the previous model, which included infant sex and multiplex status as predictors. There was no main effect of

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proband sex in predicting ASD outcome ( $p=.20$ ), and no 2-way or 3-way interactions between proband sex and infant sex or multiplex status (all  $p$ 's  $> .50$ ). The lack of effect for proband sex persisted even when considering models without infant sex or multiplex status ( $p=.52$ ).

Finally, we examined proband functioning levels, as measured by full-scale IQ and ADOS scores, as predictors of ASD outcome, above and beyond infant gender and multiplex status. Full-scale IQ was available for 210 probands (30.6%), using a number of different IQ tests. All scores were converted to standard scores, with a mean of 100 and standard deviation of 15. Results revealed no significant effect of proband intellectual functioning on ASD outcome, above and beyond gender and multiplex status ( $X^2=0.01$ ,  $df=1$ ,  $p=.92$ ; ASD outcome  $M = 71.9$ , Non-ASD outcome  $M = 80.7$ ).

Removing multiplex status from the model, the effect remained non-significant. ADOS scores were available for 54.5% of the probands ( $n=374$ ). Proband symptom severity, as measured by the social-communication algorithm score of the ADOS, was also not predictive of outcome, above and beyond gender and multiplex status ( $X^2=2.5$ ,  $df=1$ ,  $p=0.11$ ; ASD outcome  $M = 15.6$ , Non-ASD outcome  $M = 14.4$ ). Without multiplex status included in the model, the effect for proband symptom severity remained non-significant.

## Discussion

The current study is the largest prospective investigation of ASD sibling recurrence yet conducted. The primary finding was a substantially higher rate of ASD in infant siblings of children with ASD than previously documented. Earlier investigations reported recurrence estimates ranging from 3 to 14%,<sup>6-8,10-12,14</sup> while in this study, 18.7%

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3 of infants with at least one older sibling with ASD developed the disorder. The two  
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5 strongest predictors of an ASD diagnosis were sex of the infant and number of affected  
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7 older siblings. Male sex and multiplex family status were independent and significant  
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9 predictors of ASD outcome, with a 2.8-fold increase in risk for ASD for male infants  
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11 (25.9% of high-risk males v. 9.6% of high-risk females) and an additional 2-fold increase  
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13 in risk if there was more than one older affected sibling (13.5% of simplex v. 32.2% of  
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15 multiplex). The increased risk for male infants replicates previous research.<sup>10,11</sup> The  
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17 recurrence rate for multiplex families reported here (32.2%) is similar to that found in an  
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19 earlier population-based study conducted in Utah (35.3%).<sup>10</sup> Previous investigations also  
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21 suggested that the sex of the proband was associated with recurrence rates,<sup>10,14</sup> with ASD  
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23 outcomes more likely if the older affected child was female. The current data did not  
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25 support such a threshold polygenic model of inheritance, in that similar rates of  
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27 recurrence were found in families with male and female probands, as previously reported  
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29 by others.<sup>13</sup> Additional proband, demographic, and family factors, such as proband IQ  
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31 and autism severity, infant race, ethnicity and birth order, and parental education and age,  
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33 also did not predict outcome. There was variability across sites in ASD outcome rates,  
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35 which may reflect geographic diversity, regional variation, and/or method differences.  
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37 Site heterogeneity was accounted for as a random variable in all statistical models and did  
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39 not interact with any predictors of outcome.  
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48 The design of the current investigation minimized many of the limitations of  
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50 earlier research, such as stoppage, over-reporting, and ascertainment bias.<sup>15,16</sup> Stoppage,  
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52 or the tendency of couples with an affected child to stop reproducing, leads to an  
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54 underestimate of recurrence rate if uncorrected.<sup>9</sup> Earlier studies of large unrestricted  
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Sibling recurrence risk for ASD

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3 samples reported that between 4 and 10% of families had more than one affected child,<sup>6-8,</sup>  
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6 <sup>11</sup> while studies that restricted the sample to families with later-born siblings reported  
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8 higher sibling recurrence rates, between 9 and 14%.<sup>10,11</sup> Stoppage was addressed in the  
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10 current investigation, by design, through studying only families with later-born siblings.

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12 Over-reporting is a second threat to the estimation of sibling recurrence risk. Due  
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14 to limitations in time and resources, the affected status of children in previous studies was  
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16 often determined by parent report or record review,<sup>11,13</sup> which has been demonstrated to  
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18 inflate recurrence rate estimates.<sup>15</sup> The present study addressed over-reporting biases  
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20 through prospective data collection and diagnostic methods that combined structured,  
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22 reliable assessment tools with expert clinical diagnosis. Diagnostic outcome was  
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24 determined at 36 months, an age at which multiple studies have documented excellent  
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26 diagnostic stability, with over 85% of children retaining a diagnosis several years  
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28 later.<sup>20,21</sup> Since outcome was determined prior to the age that milder forms of ASD, such  
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30 as Asperger Disorder, are accurately diagnosed,<sup>22</sup> the true recurrence rate may in fact be  
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32 higher than that reported here.  
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39 There are several types of ascertainment bias that may affect recurrence rate  
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41 estimates, particularly in samples such as this one which were not epidemiologically  
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43 ascertained. Of primary interest for the present study is the over-inclusion of families  
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45 who have developmental concerns about their later-born infant. Over-selection of infants  
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47 with pre-existing developmental delays was minimized in the present investigation by the  
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49 early age of enrollment, with two-thirds of the sample recruited before 6 months, when  
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51 behavioral signs and parent concerns of ASD are rare.<sup>17, 23-26</sup> That there were no effects of  
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3 age at enrollment on rates of ASD outcomes suggests that over-selection was not a  
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5 significant bias in the present study.  
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8 Comparing the current sample to population-based studies of children with ASD  
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10 is also relevant to evaluating ascertainment bias. The sex ratios of both the probands and  
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12 the infants with ASD outcomes in this study were similar to those reported in the general  
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14 ASD population.<sup>27,28</sup> If multiplex families were over-represented in the current sample,  
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16 this could elevate recurrence rates, but this was not the case. The current sample was 6%  
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18 multiplex (prior to the birth of the infant), while other studies report multiplex rates  
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20 around 10%.<sup>10,11,14</sup> Together, this information suggests that the recurrence rates provided  
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22 by this study were not overly biased, despite the fact that the sample was not  
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24 epidemiologically ascertained. However, the true rate of sibling recurrence in the general  
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26 population of families affected by ASD will ideally be estimated in the future through  
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28 large population-based studies.  
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34 These results have significant family planning and genetic counseling  
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36 implications.<sup>29,30</sup> At the present time, genetic counseling for ASD is constrained by the  
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38 fact that currently cited risk estimates are largely based on data from the 1980's and  
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40 1990's, when earlier, less inclusive versions of the DSM were in use. The updated  
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42 information provided in this report will give families risk estimates that more accurately  
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44 reflect recurrence as defined by current diagnostic practice (i.e., DSM-IV-TR). Many  
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46 families actually believe that the risk to later-born siblings is higher than either the  
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48 current investigation or previous studies suggest it to be.<sup>31,32</sup> If families base reproductive  
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50 decisions on perceived risk of recurrence, it is important that they receive updated  
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52 information about these risks. Genetic counseling is most often provided for Mendelian  
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3 disorders and is a complex undertaking for disorders of multifactorial inheritance that are  
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5 influenced by multiple unknown susceptibility genes and other factors. Therefore, it is  
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7 critical that these data are provided to families in a sensitive manner, with extensive  
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9 counseling that helps them evaluate risk as we understand it at this time.<sup>33</sup> It is important  
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11 to convey that recurrence estimates are based on group averages and, in most cases, it is  
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13 not yet possible to counsel parents regarding individual levels of risk. A thorough genetic  
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15 work-up is essential as part of the etiologic investigation for all individuals with ASD and  
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17 may have important implications for risk counseling.<sup>34</sup> DNA collection for genotyping  
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19 the current high risk sample is underway and may, in the future, yield critical information  
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21 about genetic etiologies of ASD.  
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27 Finally, this study highlights the importance of routine surveillance and rapid  
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29 referral for infant siblings of children with ASD. Given the higher than expected  
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31 recurrence rates, particularly for male infants and multiplex families, it is critical that  
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33 primary care professionals monitor closely the development of infants who have older  
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35 siblings with ASD, screening them routinely at well-child visits using a tool appropriate  
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37 for infants.<sup>35-38</sup> Red flags identified should be followed by immediate referral for infant  
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39 intervention, rather than adopting a “wait and see” attitude, since early specialized  
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41 intervention is considered best practice for ASD<sup>39,40</sup> and may represent the best hope for  
42  
43 reducing symptoms and overall disability in high-risk infants who are developing ASD.<sup>41</sup>  
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#### 48 Conclusion

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50 The sibling recurrence rate of ASD is substantially higher than suggested by  
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52 previous estimates. The size of the current sample and the prospective nature of the data  
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54 collection minimized many limitations of previous studies of sibling recurrence,  
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including ascertainment bias, stoppage, and over-reporting. The elevated risk has important implications for infant screening and genetic counseling.

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## Footnotes

<sup>a</sup> Less than 1% of participants were half-siblings (6 of 664). Exclusion of these participants did not change the results, so they were retained in the analyses.

<sup>b</sup> All sites verified clinical diagnosis of the proband. Most sites collected standardized diagnostic assessments (e.g., ADOS) and/or parent diagnostic interviews (e.g., Autism Diagnostic Interview-Revised [ADI-R] or Social Communication Questionnaire [SCQ]) as part of the proband diagnostic verification process. N=99 probands had both ADOS and ADI-R or SCQ. N=273 probands had ADOS alone. N=149 probands had ADI or SCQ alone.

<sup>c</sup> In supplementary analyses, simplex families were also defined more stringently as those who have at least one unaffected older sibling, in addition to the affected proband and the infant. When analysis was restricted to only families with 3 or more children (total n=380, simplex n=343, multiplex n=37), the recurrence rate of 32.2% in multiplex families continues to be significantly higher than the simplex rate of 20.1%,  $X^2 = 9.54$ ,  $df=1$ ,  $p=.002$ .

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Figure Legends

Figure 1: Frequencies of age at first visit and age at outcome.

Figure 2: Proportion of ASD outcome by infant sex and family multiplex status.

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Sibling recurrence risk for ASD

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Table 1: Descriptive Characteristics of the Sample.

	N	Descriptor
Mean age at enrollment in months (SD)	664	8.4 (4.4)
Sex (% male)	663	55.6%
Race/Ethnicity (% Other)	657	16.0%
Birth order (% 3 <sup>rd</sup> born or later)	458	39.7%
Sex of proband (% male)	658	84.2%
Multiplex status (% with > 1 affected older sibling)	619	6.0%
Maternal education (% college degree or higher)	365	77.1%
Paternal education (% college degree or higher)	338	74.3%
Mean maternal age in years (SD)	566	34.5 (4.4)
Mean paternal age in years (SD)	563	36.9 (5.2)

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Figure 1

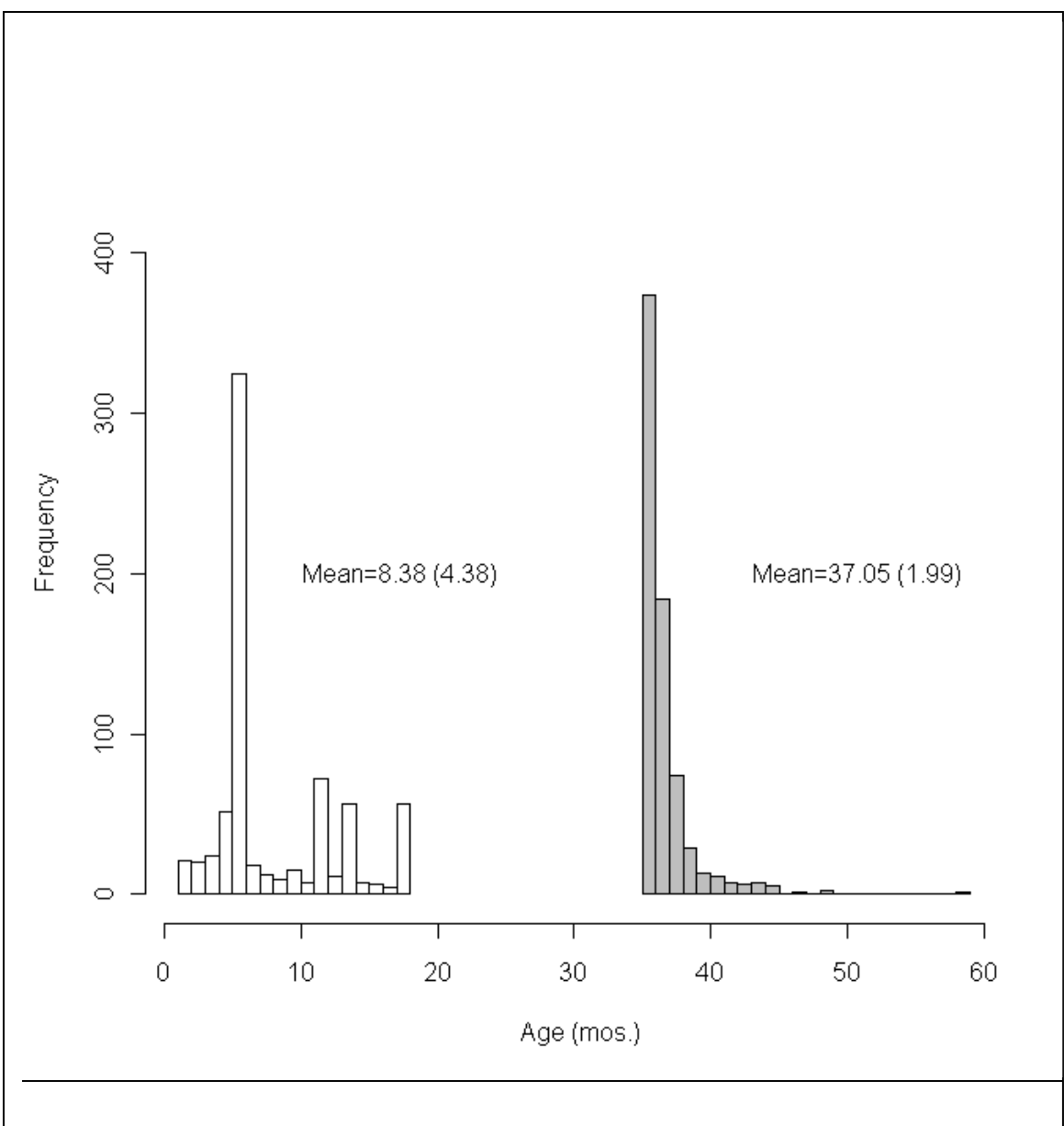


Figure 2

