



Early Head Growth in Infants at Risk of Autism: A Baby Siblings Research Consortium Study

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Disclosures: Drs. Brian, Bryson, Carver, Dobkins, Hutman, Iverson, Messinger, Landa, Stone, Ozonoff, and Young report no biomedical financial interests or potential conflicts of interest.

Abstract

Objective: While early brain overgrowth is frequently reported in autism spectrum disorder (ASD), the relationship between ASD and head circumference (HC) is less clear, with inconsistent findings from longitudinal studies that include community controls. Our aim was to examine whether head growth in the first 3 years differed between children with ASD from a high-risk (HR) sample of infant siblings of children with ASD (by definition, multiplex), HR siblings not diagnosed with ASD, and low-risk (LR) controls.

Method: Participants included 442 HR and 253 LR infants from 12 sites of the international Baby Siblings Research Consortium. Longitudinal HC data were obtained prospectively, supplemented by growth records. Random effects non-linear growth models were used to compare HC in HR infants and LR infants. Additional comparisons were conducted with the HR group stratified by diagnostic status at age 3: ASD (n=77), developmental delay (DD; n=32), and typical development (TD; n=333). Nonlinear growth models were also developed for height to assess general overgrowth associated with ASD.

Results: There was no overall difference in head circumference growth over the first 3 years between HR and LR infants, although secondary analyses suggested possible increased total growth in HR infants, reflected by the model asymptote. Analyses stratifying the HR group by 3-year outcomes did not detect differences in head growth or height between HR infants who developed ASD and those who did not, nor between infants with ASD and LR controls.

Conclusion: Head growth was uninformative as an ASD risk marker within this HR cohort.

Keywords

Autism spectrum disorder; head circumference; high risk design; longitudinal study; early detection

INTRODUCTION

Autism spectrum disorders (ASD) are among the most common neurodevelopmental disorders, with recent US prevalence estimates at over 1 in 100 children.¹ Current early detection strategies focus on behavioral signs that can be reliably detected in the second year of life.² However, the identification of biomarkers for ASD could improve the predictive accuracy of behavioral signs alone and help shift surveillance to the first year.^{3, 4} Several lines of evidence including results from neuroimaging⁵⁻⁸ and postmortem studies⁹ have identified early brain overgrowth as a distinguishing feature of ASD. Indeed, increased head size has been described in children with autism since Kanner's original case series.¹⁰ Head circumference (HC), available from physician growth records, is correlated with brain volume¹¹ and thus represents a potential biomarker for ASD. In fact, macrocephaly (HC > 97th percentile) has been reported in many cross-sectional studies of children with ASD with rates averaging about 20%.¹²⁻²² Some longitudinal studies have suggested a unique trajectory of head growth in ASD, with a normal or slightly reduced HC at birth,^{18, 23-26} followed by accelerated growth and macrocephaly by around the first birthday,^{7, 23, 27, 28} in some cases coinciding with symptom onset²⁸ and/or correlating with parent-reported developmental regression.^{29, 30} Elder et al.³¹ reported that infants from a

high-risk sample (younger siblings of children with ASD) were more likely to be diagnosed with ASD if they had increased HC at 12 months and decelerating HC growth rate from 12 to 24 months.

Recent studies, however, suggest the need to re-examine the evidence for head overgrowth in ASD, which is based largely on comparisons with published population norms. A systematic review by Raznahan et al.³² identified five independent longitudinal cohorts of typically developing children that demonstrate trajectories in HC *z*-scores that deviate from Centers for Disease Control (CDC) norms³³ in ways similar to those reported in children with ASD, suggesting general norm biases rather than disease-specific biomarkers. The few longitudinal studies of head growth in children with ASD that have incorporated community controls rather than relying on population norms identify only modest differences. Hazlett et al.⁷ used a non-linear (exponential) mixed model to compare head growth trajectories from birth to 35 months in 51 children with ASD, 11 with developmentally delay (DD) and 14 typically developing (TD) controls, finding increased growth in the group with ASD relative to the other two groups combined. Dissanayake et al.³⁴ reported increased head growth in 28 children with ASD and IQ>70 compared to 19 TD children of similar mental age, although this only reached statistical significance using a one-tailed test. In both studies, divergence in head size between groups with and without ASD was not apparent until after the first year.^{7, 34} Similarly, a recent birth cohort study from Norway³⁵ (n=106,082) that compared children with ASD (n=376) to others in the population in the first year using mixed effects models found no overall group differences in head growth, although rates of macrocephaly were elevated among boys with ASD (8.7%) compared to other boys (3.3%), presumably due to increased variability in the group with ASD. A US birth cohort study that included 100 children with ASD found no overall ASD-related differences in head growth based on measurement of HC at 9, 24, and 36 months, based on cross-sectional comparisons at each time point.³⁶ There is also uncertainty as to whether increased head growth in ASD, when detected, is a component of generalized somatic overgrowth,^{34, 37, 38} or is independent of group differences in height and/or weight.^{7, 28, 39; 57} As well, two recent studies also reported similar head growth in children with ASD compared to children other developmental or mental health diagnoses^{23, 25}; notably, in one of these studies, both groups would have been regarded as having accelerated head growth in the first 18 months if assessed relative to CDC norms.²⁵ Thus, evidence for increased HC as an ASD-specific risk marker remains inconsistent.

Another key question is whether increased head growth is specific to ASD, or rather, is also expressed in relatives without ASD who share genetic vulnerability. Macrocephaly has been reported in 19-31% of parents of probands with ASD^{16, 20} and 12-16% of siblings.^{16, 41} Indeed, a recent analysis of HC from the California Autism Twin Study indicates that rates of macrocephaly are 20-27%, with no differences among probands with ASD, concordant and discordant co-twins.⁵³ Studies reporting HC in relatives have generally not included data regarding other relevant phenotypes (e.g., subthreshold symptoms), so it is difficult to know whether increased rates of macrocephaly are due to non-specific familial correlations in HC⁴² or represent co-segregation of macrocephaly and behavioral symptoms of the 'broader autism phenotype,'^{43, 44} presumably due to the expression of genes involved in susceptibility to ASD.

The objective of this study was to examine whether head growth in the first 3 years differed between high-risk infants who developed ASD versus high-risk infants who did not and low-risk controls. Our longitudinal design allowed prospective as well as retrospective measurement of HC in one of the largest samples of children with ASD and non-diagnosed siblings studied to date.

METHOD

Participants

The Baby Siblings Research Consortium (BSRC) is an international network dedicated to studying early development in infants at increased risk of ASD. The present analyses included data from 12 BSRC sites (University of Alberta, Dalhousie University, Kennedy Krieger Institute, McMaster University, University of California – Davis, University of California – Los Angeles, University of California – San Diego, University of Miami, University of Pittsburgh, University of Toronto, Vanderbilt University, and Washington University-St. Louis). IRB approval to collect and analyze de-identified data from all sites was obtained. Data were compiled in a central database at UC Davis, where analyses were conducted.

Participants comprised two groups: later-born biological siblings of a child with ASD ('high-risk'; HR) and infants with no known family history of ASD ('low-risk'; LR). HR infants were recruited from clinics and agencies serving individuals with ASD. LR infants were recruited by mailings, media announcements, and word-of-mouth. Inclusion criteria for HR infants included a documented diagnosis of *DSM-IV-TR* autistic disorder, Asperger syndrome, or pervasive developmental disorder not otherwise specified (PDD-NOS; the *DSM-IV-TR* refers to these conditions collectively as the 'pervasive developmental disorders'; in this paper, we use the term autism spectrum disorder (ASD), but recognize that this is not equivalent to ASD as defined in the *DSM-5*) in the affected sibling (the 'proband') and no identified neurological or genetic condition in the infant or proband accounting for the ASD diagnosis (e.g., fragile X syndrome). Additional inclusion criteria were maximum enrollment age of 18 months, minimum outcome assessment age of 35 months, and availability of a clinical best estimate diagnosis (based on the *DSM-IV-TR*) and the Autism Diagnostic Observation Schedule (ADOS) to assess ASD outcomes. For families with multiple enrolled infants, only the infant recruited at the youngest age was included. Exclusion criteria for both HR and LR infants included prematurity (<37 weeks gestation) and low birth weight (<2,500 g).

Measures

Demographics—Demographic variables included the sex, race, and ethnicity of participating infants, which were reported by parents using categories specified by the National Institutes of Health.

Head growth—Head growth data were obtained prospectively (measurement of HC during study visits between 6 and 36 months) and retrospectively (review of growth records from the child's community physician). Although our focus was on prospective data, the earliest

age of the initial study visit was generally 6 months of age or older; thus, including retrospective data allowed us to assess head growth earlier in the first year. Height/length data (hereafter, height; as per usual methods of assessing growth in young children, length was measured in children <24 months, and height in children 24 months and older) were obtained by the same means. Only HC data with concurrent height measurements were used.

Outcome Assessment and Classification—Outcomes were assessed at 36 months of age by clinical best estimate (CBE), based on DSM-IV-TR, and informed by review of developmental history and administration of the ADOS. The ADOS is a semi-structured, standardized protocol that measures symptoms of ASD and yields an empirically derived cutoff for ASD.⁴⁵ Participants were also assessed at 36 months using the Mullen Scales of Early Learning (MSEL), a standardized developmental test for children, from birth to 68 months, that measures nonverbal cognitive, language, and motor skills.⁴⁶

The sample was divided into outcome groups based on the 36-month assessments. Participants who scored above the ASD cutoff on the ADOS and received a CBE diagnosis of *DSM-IV-TR* autistic disorder or PDD-NOS were classified as ‘ASD’. Those who did not meet criteria for ASD but had the MSEL composite score and at least one subscale – Fine Motor, Visual Reception, Receptive Language, Expressive Language – more than 1.5 SDs below the mean were classified as Developmental Delay (DD). Children not meeting criteria for ASD or DD were classified as typically developing (TD).

Data Analysis

We used a random effects⁴⁷ nonlinear growth model (i.e., negative exponential model), estimating asymptote, intercept, and the natural log of the rate of HC growth. This approach has effectively modeled biological growth in previous studies,^{48, 49} and provides not only a very good fit to the data (see Figure 1), but also a clearly appropriate theoretical model to examining asymptotic biological growth such as head-circumference. Although linear or quadratic growth models are sometimes used for examining growth in head circumference,^{27, 29} neither offers a model that is a plausible model of biological growth for head circumference. Linear models presume infinitely increasing growth, and quadratic models often result in eventual decreases in head circumference, both of which are implausible models at best. In contrast, the asymptotic curves afforded by a negative exponential model are an obvious and significant, if still imperfect, improvement, both empirically and theoretically. The formula $HC = \alpha + (\beta - \alpha) * e^{(-\gamma * x)}$ describes a nonlinear function where α represents the asymptote (a maximum size for growth within the time-frame considered), β represents the intercept at age (x) = 0 (the HC at birth), and γ represents the anti-log of the rate of change (how rapidly or slowly growth occurs from birth toward the asymptote at 36 months). The three growth parameters of asymptote, intercept, and rate of change were estimated for each participant. Then, as each covariate was introduced (e.g., height, sex, outcome), its effect with respect to each growth parameter (asymptote, intercept, and rate of change) was tested for significance just as would be done for a traditional linear model testing for intercept and slope effects. Models were fit using the first-order method of Beal and Sheiner.⁵⁰

The analyses proceeded as follows: after fitting the basic growth model, height was added as a time-varying covariate, followed by a dummy-coded variable indicating prospective versus retrospective data collection, and sex. Although we had initially hoped to use site as an additional statistical control in the overall baseline model, the addition of site resulted in 33 additional parameters being estimated (3 growth parameters x 11 (k-1) sites), which resulted in model convergence problems. However, to assess for site differences, a generalized linear model was run using only prospective measures in high-risk subjects with site explicitly tested after controlling for height and sex. Results revealed no significant site differences for either intercept at 36 months or linear growth over time (all $p > .10$). Building upon this baseline model, we then compared HR and LR infants (regardless of outcome) on each modeled growth parameter (intercept at birth, rate of growth, and asymptote). Then, the HR group was stratified by 3-year outcomes (i.e., HR-ASD, HR-DD and HR-TD), with LR as the reference comparison group. This approach allowed us to first compare HR (collapsed across 3-year outcome) to LR infants and then to follow up with an examination of differences among HR-ASD, HR-DD, HR-TD, and LR groups. Next, we assessed potential sex by group interactions using product vectors of each outcome group (coded by dummy variables) multiplied by sex. Each model in this sequence was tested against the prior, simpler model by assessing the difference between -2 Log Likelihood values as a Chi-square value with degrees of freedom equal to the difference in model parameters. Finally, we assessed whether HC growth varied across the continuum of ASD symptoms (indexed by ADOS algorithm scores) and developmental level (indexed by the MSEL) at 3 years in the HR group, adjusting for height, method, and sex, as in the previous models.

RESULTS

The final dataset consisted of 695 participants, including 442 HR infants (77 HR-ASD, 32 HR-DD, and 333 HR-TD) and 253 LR infants. LR children with ASD ($n=7$) or DD ($n=15$) were excluded as the numbers were too small for formal group comparisons. Sex ratio varied by group ($X^2=31.4$, $df=3$, $p<.001$); pair-wise comparisons indicated that a higher proportion of boys were found in the HR-ASD (72.7%) and HR-DD (84.4%) groups compared to HR-TD (45.9%) and LR (53.8%) groups. There were no group differences by race or ethnicity. Participants of non-Caucasian ancestry comprised 26 of 167 (15.6%) of the LR group and 67 of 343 (19.5%) of the HR group for whom data were available, with no differences by outcome within the HR group (see Table 1).

A total of 2,597 HC measurements were available (mean = 4.09 per participant; $SD=2.52$), of which 67% ($n=1750$) were collected prospectively by study sites. A negative binomial regression analysis of the counts of measurements for each outcome group showed no significant differences between any of the groups (Wald $X^2=2.59$, $df=3$, $p=.46$). As expected, there were differences in the number of measurements by site (Wald $X^2=64.69$, $df=6$, $p<.001$), ranging from an average of 1.94 ($SD=1.03$) to 6.36 ($SD=3.08$) per site. There were also significant differences in the number of measurements by prospective (3.06, $SD=1.37$) versus retrospective methods (6.71, $SD=2.84$; Wald $X^2=72.65$, $df=1$, $p<.001$). As anticipated, the age points represented by retrospective growth records data were significantly younger on average ($M=8.26$ mos., $SD=8.03$) than age points represented by

prospective data ($M=19.72$ mos., $SD=9.78$; $t_{(2596)}=25.98$, $p<.001$). A scatterplot of HC by age for each data collection method is shown in Figure 1.

Basic Growth Model

Random effects models were tested for random asymptote only versus random asymptote and rate. Test of model improvement was significant ($X^2=196.1$, $df=2$, $p<.001$). Adding random intercept improved model fit ($X^2=402.0$, $df=3$, $p<.001$). A test of models with independent random effects versus correlated random effects suggested that the model with correlated random effects (i.e., intercept, rate, and asymptote) provided the best fit to the data. This growth model fit the observed raw data well, with no discernable structure to the residual error distribution. The unconditional growth model had an average overall intercept at age 0 of 36.82 cm (95% CI = 36.49 to 37.15), an average overall asymptote of 50.05 cm (95% CI = 49.91 to 50.19) and an average overall log(rate) of growth of -2.16 (95% CI = -2.20 to -2.12).

Covariates: Height, Method, and Sex

After fitting the basic growth model, height was added as a time-varying covariate. The overall effect for height was significant ($X^2=480.4$, $df=3$, $p<.001$), meaning that height accounted for a significant portion of HC variability. The main effect of height was significant for asymptote (0.08 cm, 95% CI = 0.06 to 0.09, $t_{(693)}=9.53$, $p<.001$), intercept (0.22 cm, 95% CI = 0.19 to 0.25, $t_{(693)}=13.76$, $p<.001$) and log-rate (-0.01 cm, 95% CI = -0.014 to -0.006 , $t_{(693)}=-5.07$, $p<.001$).

Next, we tested for the effects of obtaining data either prospectively or retrospectively on the model, controlling for height. The overall effect for method was significant ($X^2=29.1$, $df=3$, $p<.001$). Relative to retrospective data, prospective data had significantly larger intercepts (37.18 cm, 95% CI = 36.55 to 37.82 versus 35.84 cm, 95% CI = 35.57 to 36.10; $t_{(693)}=3.84$, $p<.001$), slower rate of growth (-2.19 , 95% CI = -2.37 to -2.02 versus -2.03 , 95% CI = -2.16 to -1.91 ; $t_{(693)}=2.21$, $p<.05$), and a marginally significant larger asymptote (47.66 cm, 95% CI = 46.83 to 48.50 versus 47.39 cm, 95% CI = 46.55 to 48.22; $t_{(693)}=1.83$, $p=.07$). The main effect of method was retained in all subsequent models. Method did not interact with any subsequent variables in the model.

Finally, we found a main effect for sex, controlling for height and method ($X^2=117.5$, $df=3$, $p<.001$). There was no significant effect of sex for intercept. Compared to females, males showed a faster rate of growth (-1.99 , 95% CI = -2.12 to -1.86 versus -2.10 , 95% CI = -2.24 to -1.96 ; $t_{(693)}=2.48$, $p<.05$), and a higher asymptote (48.05 cm, 95% CI = 47.17 to 48.92 versus 47.83 cm, 95% CI = 46.21 to 47.96, $t_{(693)}=7.47$, $p<.001$).

Comparison of High-Risk (\pm Stratification by 3-Year Outcomes) and Low-Risk Groups

The HR group was compared to the LR group, shown in Figure 2, first as a whole, and then stratified by 36-month outcome (i.e., pair-wise comparisons between the HR-ASD, HR-DD, HR-TD, and LR groups). The overall model effect for group was not significant ($X^2=11.5$, $df=9$, $p=.24$), although risk group comparisons on individual parameters revealed that the HR group showed a significantly higher asymptote (47.77 cm, 95% CI = 46.92 to 48.62)

compared to the LR group (47.47 cm, 95% CI = 46.60 to 48.33, $t_{(693)}=2.34, p<.05$). In simple comparisons that stratified the HR group by ASD, DD, and TD outcomes, the HR-TD group showed higher asymptotes (47.82 cm, 95% CI = 46.96 to 48.68) when compared to the LR group (47.47 cm, 95% CI = 46.60 to 48.33, $t_{(693)}=2.52, p<.05$). All other comparisons between outcome groups for asymptote, intercept, and rate of change were not significant.

The final model included the interaction between group and sex, to assess whether group differences were specific to boys or girls. The overall effect for the group by sex interaction term in the model was marginally significant ($X^2=15.5, df=9, p=.08$). Overall, the HR males (regardless of outcome; 48.33 cm, 95% CI = 47.47 to 49.18) had significantly higher asymptotes than the LR males (47.77 cm, 95% CI = 46.92 to 48.63, $t_{(370)}=-3.15, p<.01$). Stratifying the HR group by outcome revealed a non-significant trend towards asymptotes of HR-ASD males (48.28 cm, 95% CI = 47.33 to 49.22) being higher than those of LR males (47.77 cm, 95% CI = 46.92 to 48.63; $t_{(190)}=1.89, p=.06$). The asymptotes of HR-TD males (48.35 cm, 95% CI = 47.48 to 49.23) were significantly higher than those of LR males ($t_{(287)}=3.02, p<.01$). There were no risk group differences for females on any of the growth parameters, although inspection of model parameter estimates for each outcome group separately indicated a non-significant trend towards a lower asymptote in HR-ASD females (46.46 cm, 95% CI = 45.39 to 47.54) compared to LR females (47.17 cm, 95% CI = 46.27 to 48.07; $t_{(136)}=1.88, p=.06$), and a significantly lower asymptote than HR-TD females (47.24 cm, 95% CI = 46.39 to 48.10; $t_{(199)}=-2.14, p<.05$). Figure 3 shows the asymptotes for HR-ASD males compared to LR males, and Figure 4 shows the asymptotes of ASD females compared to LR females.

We also assessed whether standard scores on the MSEL subscales or ADOS algorithm scores at 3 years were related to HC growth in the HR group, adjusting for height, method and sex as in the previous models. Results revealed that none of these variables were related to HC growth parameters.

Analyses of Height

Although height was included in the HC growth models as a time-varying covariate, we conducted a similar set of analyses for height over time as a dependent variable to investigate group differences (i.e., among HR-ASD, HR-DD, HR-TD and LR infants) in a parameter indexing general growth. As was done for the HC analyses, data collection method and sex were entered as covariates, and both showed a significant effect in terms of model fit. Critically, the main effect for group was not significant ($X^2=13.00, df=9, p=.16$). The gender by group interaction was also not significant ($X^2=13.00, df=9, p=.16$). However, inspection of specific model parameters revealed a non-significant trend towards lower height asymptotes in HR-ASD males (102.06 cm, 95% CI = 98.22 to 105.91) compared to LR males (106.63 cm, 95% CI = 103.41 to 109.85, $t_{(190)}=1.89, p=.06$), and showed a higher rate of growth -2.95 , 95% CI = -3.09 to -2.81) compared to the LR males (-3.11 , 95% CI = -3.22 to -3.01 , $t_{(190)}=-1.99, p<.05$); that is, the male ASD outcome group initially grew faster in height but ended up shorter. No effects were observed for HR-ASD females compared to LR females, nor to HR-DD, nor HR-TD females.

Analyses of Head Circumference Without Height as Covariate

Given the lack of group differences for growth models of height, and in order to provide a comparison to studies that have examined HC without controlling for overall growth, we next analyzed growth in HC without including height as a covariate. The same modeling strategy was used as in the previous analyses for HC. Results revealed very little change in any of the findings regarding risk status, outcome diagnosis, or outcome by sex interactions. The HR group (50.05 cm, 95% CI = 49.86 to 50.24) continued to show larger asymptotes than the LR group (49.75 cm, 95% CI = 49.50 to 50.01, $t_{(693)}=-1.94$, $p=.05$), with comparisons by outcome showing that only the HR-TD group (50.07 cm, 95% CI = 49.85 to 50.28) had significantly higher asymptotes than the LR group ($t_{(584)}=-1.97$, $p<.05$). Overall, the HC growth models without height as a covariate showed less substantial effects, suggesting that the inclusion of height in the previously described growth models served to increase the sensitivity of the models to group differences (i.e., height may act as a suppressor variable).

DISCUSSION

This study examined early head growth in ASD using a prospective design (complemented by retrospective growth records to increase the density of measurement in the first year), and is the first to compare high-risk children with ASD to non-diagnosed high-risk children and community controls using longitudinal growth models. There are several intriguing findings. First, there are no significant differences in the overall model comparing head growth between HR infants (regardless of outcome) and LR controls in the first 3 years of life. The HR group had a higher asymptote in the non-linear model relative to the LR group, suggesting that even trends towards risk group differences were due to differences in maximum growth rather than differences in growth rate. Second, there were no differences in any aspect of head growth related to clinical outcome within the HR group (that is, no differences between HR-ASD, HR-DD, and HR-TD subgroups, nor any relationship with MSEL nor ADOS scores), suggesting that the modest risk group difference in asymptote was not specific to participants with ASD. Third, although the overall group by sex interaction did not reach statistical significance, there were interesting trends towards higher asymptotes in HR males (regardless of ASD outcome) compared to LR males, and towards lower asymptotes in HR females with ASD compared to other HR and LR infants. Overall, head growth was largely uninformative as an ASD risk marker within this HR cohort. Finally, contrary to some recent studies,^{37, 38} we did not find evidence of general somatic overgrowth in children with ASD, either relative to other HR infants or LR controls.

Our findings are broadly consistent with a recent systematic review that identified eleven published longitudinal studies that compared HC in young children in ASD to population (CDC) norms or community controls.³² All four studies comparing HC growth in ASD to CDC norms reported substantial differences in the first year,^{23, 24, 28, 30} whereas only four of seven studies comparing children with ASD to community controls^{7, 27, 29, 34} identified periods of accelerated head growth. Moreover, effect sizes in studies with community controls varied by analytic approach.³² The two studies^{27, 29} that modeled linear growth trajectories within selected age bands reported robust evidence of accelerated HC growth in

ASD in the first year, similar to studies that include multiple cross sectional group comparisons (e.g.,³⁸). In contrast, studies using nonlinear approaches (arguably better suited to modeling biological growth processes⁴⁸) reported either small differences emerging in the second year^{7,34} or no differences.^{25,51}

Only one previous study³¹ has examined head growth during infancy in ASD in a HR cohort (n=77), reporting accelerated growth as indexed by z-scores relative to CDC norms and using separate linear models in the first and second years. Growth data were from retrospective growth records and diagnostic outcomes were not reported. Although there was a modest relationship between 12-month z-scores and social-communication symptoms, positive z-scores and inclining slopes were observed at all symptom levels, emphasizing the limitations of relying on population norms to characterize head growth differences in ASD.

It is worth emphasizing that although we did not identify differences in HC growth that were specific to ASD, there was a modest difference between the HR group as a whole and community controls in final growth level, indexed by the model asymptote. Thus, increases in head growth may be an endophenotype for ASD⁵² related to genetic vulnerability, but not specifically associated with ASD symptoms or diagnosis within this HR cohort. Indeed, previous studies have reported elevated rates of macrocephaly in first-degree relatives of children with ASD.^{16,20,41} Moreover, recent analyses from the California Autism Twin Study indicated similar rates of macrocephaly in affected (n=53) and unaffected (n=149) co-twins, with similar familial correlation in HC in concordant and discordant twin pairs.⁵³

Our study has a number of strengths, including the large sample size and relative density of longitudinal data, much of which was collected prospectively. Comparison of children with ASD to other HR and LR participants, examination of the relationship between head growth and ASD based on both categorical outcomes and a quantitative measure of symptom severity, and distinguishing head growth from general somatic (i.e., height) growth are other unique features that lend further weight to the overall findings. However, there are several potential limitations. First, findings from HR infants who developed ASD (by definition, multiplex cases) do not necessarily generalize to other children with ASD. There may be etiologic differences (e.g., higher rates of rare genomic variants⁵⁴) that index processes involved in early brain development and somatic growth in HR individuals with ASD. Further comparison of longitudinal head growth as a potential biomarker of ASD in single and multiple incidence families is warranted, as different sets of genetic and environmental factors may contribute etiologically. Second, although head growth in our HR sample was not associated with ASD outcomes, this does not imply that accelerated brain growth during infancy would be uninformative. Hazlett et al.⁵⁵ did not detect differences in brain volume at 6 months related to ASD outcomes in 98 HR infants, but comparisons at subsequent time points involving that cohort are still forthcoming. Finally, despite our large sample, ASD is characterized by marked etiologic and phenotypic heterogeneity, and we cannot exclude the possibility that early acceleration in head growth is associated with ASD in a subgroup of HR infants. Indeed there are examples of specific genetic subtypes of ASD (e.g., PTEN mutation) that are associated with marked head and brain overgrowth.⁵⁶ However, head growth was not predictive of ASD within our HR cohort as a whole, nor was there evidence that children with ASD were overrepresented among outliers in the first year (i.e., >90th

percentile; >97th percentile; data available on request). We also acknowledge that the HR-DD group is relatively small for group comparisons, although analyses treating MSEL subscales as continuous variables also failed to find association with head growth trajectories.

Thus, although reports of macrocephaly in ASD date back to Kanner's original case study,¹⁰ further data are still needed on the relationship between early head and brain growth and risk of ASD within familial HR samples. The current study suggests that while there are modest differences in early head growth between HR and LR groups, these differences are not specifically predictive of ASD.

Acknowledgments

Autism Speaks funds the Baby Siblings Research Consortium (BSRC) database, used for the study analyses. Sites contributing data were supported by grants from the National Institutes of Health (NIH: HD54979, J.I.; MH059630, R.L.; HD052804, K.D., L.C.; HD043292, W.S.; HD047417, D.M.; HD0057284, D.M, W.S; MH068398, S.O.; HD055784 and MH096961, T.H.), the Canadian Institutes of Health Research (62924 and 102665, S.E.B., J.B., L.Z.), Autism Speaks (J.I., W.S.), Autism Speaks Canada (S.E.B., J.B., L.Z.), and NeuroDevNet (S.E.B., J.B., L.Z.). Dr. Gregory S. Young served as the statistical expert for this research.

The authors thank Alycia Halliday, PhD, of Autism Speaks for organizational support, and members of the BSRC for their input and guidance. The authors also thank the children and families who participated in this research.

Dr. Zwaigenbaum is the site PI of a study sponsored by SynapDx (receives operating funds but no honoraria).

REFERENCES

1. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators, Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2008. *MMWR Surveill Summ.* 2012; 61(3):1–1.
2. Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected ASD: Insights from studies of high-risk infants. *Pediatrics.* 2009; 123:1383–91. [PubMed: 19403506]
3. Newschaffer CJ, Croen LA, Fallin MD, et al. Infant siblings and the investigation of autism risk factors. *J Neurodev Disord.* 2012; 4(1):7. [PubMed: 22958474]
4. Walsh P, Elsabbagh M, Bolton P, Singh I. In search of biomarkers for autism: Scientific, social and ethical challenges. *Nat Rev Neurosci.* 2011; 12:603–12. [PubMed: 21931335]
5. Courchesne E, Karns C, Davis H, et al. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology.* 2001; 57:245–54. [PubMed: 11468308]
6. Sparks BF, Friedman SD, Shaw DW, et al. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology.* 2002; 59:184–92. [PubMed: 12136055]
7. Hazlett HC, Poe M, Gerig G, et al. Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. *Arch Gen Psychiatry.* 2005; 62(12):1366–1366. [PubMed: 16330725]
8. Schumann CM, Bloss CS, Barnes CC, et al. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci.* 2010; 30:4419–27. [PubMed: 20335478]
9. Courchesne E, Mouton PR, Calhoun ME, et al. Neuron number and size in prefrontal cortex of children with autism. *JAMA.* 2011; 306:2001–10. [PubMed: 22068992]
10. Kanner L. Autistic disturbances of affective contact. *Nervous Child.* 1943; 2:217–50.
11. Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. *Neuropediatrics.* 2002; 33:239–41. [PubMed: 12536365]

12. Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002; 59(2):175–175. [PubMed: 12136053]
13. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychol Med*. 1995; 25(1):63–63. [PubMed: 7792363]
14. Bolton PF, Roobol M, Allsopp L, Pickles A. Association between idiopathic infantile macrocephaly and autism spectrum disorders. *Lancet*. 2001; 358:726–7. [PubMed: 11551582]
15. Davidovitch M, Patterson B, Gartside P. Head circumference measurements in children with autism. *J Child Neurol*. 1996; 11:389–93. [PubMed: 8877607]
16. Fidler DJ, Bailey JN, Smalley SL. Macrocephaly in autism and other pervasive developmental disorders. *Dev Med Child Neurol*. 2000; 42:737–40. [PubMed: 11104344]
17. Fombonne E, Roge B, Claverie J, Courty S, Fremolle J. Microcephaly and macrocephaly in autism. *J Autism Dev Disord*. 1999; 29(2):113–113. [PubMed: 10382131]
18. Lainhart JE, Piven J, Wzorek M, et al. Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry*. 1997; 36:282–90. [PubMed: 9031582]
19. Miles JH, Hadden LL, Takahashi TN, Hillman RE. Head circumference is an independent clinical finding associated with autism. *Am J Med Genet*. 2000; 95(4):339–339. [PubMed: 11186888]
20. Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ. Autism and macrocephaly. *Lancet*. 1997; 349:1744–5. [PubMed: 9193390]
21. Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, Le Couteur A. Head circumference in autism and other pervasive developmental disorders. *J Child Psychol Psychiatry*. 1996; 37:665–71. [PubMed: 8894947]
22. Courchesne E, Pierce K. Brain overgrowth in autism during a critical time in development: Implications for frontal pyramidal neuron and interneuron development and connectivity. *Int J Dev Neurosci*. 2005; 23:153–70. [PubMed: 15749242]
23. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. *JAMA*. 2003; 290:337–44. [PubMed: 12865374]
24. Dementieva YA, Vance DD, Donnelly SL, et al. Accelerated head growth in early development of individuals with autism. *Pediatr Neurol*. 2005; 32:102–8. [PubMed: 15664769]
25. Gray KM, Taffe J, Sweeney DJ, Forster S, Tonge BJ. Could head circumference be used to screen for autism in young males with developmental delay? *J Paediatr Child Health*. 2012; 48:329–34. [PubMed: 22077913]
26. Mason-Brothers A, Ritvo ER, Pingree C, et al. The UCLA-University of Utah epidemiologic survey of autism: Prenatal, perinatal, and postnatal factors. *Pediatrics*. 1990; 86:514–9. [PubMed: 2216614]
27. Constantino JN, Majmudar P, Bottini A, et al. Infant head growth in male siblings of children with and without autism spectrum disorders. *J Neurodev Disord*. 2010; 2:39–46. [PubMed: 20651949]
28. Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biol Psychiatry*. 2007; 61:458–64. [PubMed: 17137564]
29. Nordahl CW, Lange N, Li DD, et al. Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. *Proc Natl Acad Sci USA*. 2011; 108:20195–200. [PubMed: 22123952]
30. Webb SJ, Nalty T, Munson J, Brock C, Abbott R, Dawson G. Rate of head circumference growth as a function of autism diagnosis and history of autistic regression. *J Child Neurol*. 2007; 22:1182–90. [PubMed: 17940244]
31. Elder LM, Dawson G, Toth K, Fein D, Munson J. Head circumference as an early predictor of autism symptoms in younger siblings of children with autism spectrum disorder. *J Autism Dev Disord*. 2008; 38:1104–11. [PubMed: 18058011]
32. Raznahan A, Wallace GL, Antezana L, et al. Compared to what? Early brain overgrowth in autism and the perils of population norms. *Biol Psychiatry*. 2013; 74(8):563–75. [PubMed: 23706681]
33. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the united states: Methods and development. *Vital Health Stat 11*. 2002; (246):1–190. [PubMed: 12043359]

34. Dissanayake C, Bui QM, Huggins R, Loesch DZ. Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life. *Dev Psychopathol.* 2006; 18:381–93. [PubMed: 16600060]
35. Surén P, Stoltenberg C, Bresnahan M, et al. Early growth patterns in children with autism. *Epidemiology.* 2013; 24:660–70. [PubMed: 23867813]
36. Barnard-Brak L, Sulak T, Hatz JK. Macrocephaly in children with autism spectrum disorders. *Pediatr Neurol.* 2011; 44:97–100. [PubMed: 21215908]
37. Chawarska K, Campbell D, Chen L, Shic F, Klin A, Chang J. Early generalized overgrowth in boys with autism. *Arch Gen Psychiatry.* 2011; 68:1021–31. [PubMed: 21969460]
38. Mraz KD, Green J, Dumont-Mathieu T, Makin S, Fein D. Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders. *J Child Neurol.* 2007; 22:700–13. [PubMed: 17641255]
39. Fukumoto A, Hashimoto T, Mori K, Tsuda Y, Arisawa K, Kagami S. Head circumference and body growth in autism spectrum disorders. *Brain Dev.* 2011; 33:569–75. [PubMed: 20934821]
40. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: A magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry.* 1996; 35(4):530–530. [PubMed: 8919716]
41. Campbell M, Geller B, Small AM, Petti TA, Ferris SH. Minor physical anomalies in young psychotic children. *Am J Psychiatry.* 1978; 135:573–5. [PubMed: 645950]
42. Livshits G, Peter I, Vainder M, Hauspie R. Genetic analysis of growth curve parameters of body weight, height and head circumference. *Ann Hum Biol.* 2000; 27:299–312. [PubMed: 10834294]
43. Bailey A, Luthert P, Dean A, et al. A clinicopathological study of autism. *Brain.* 1998; 121:889–905. Pt 5. [PubMed: 9619192]
44. Piven J, Palmer P, Jacobi D, Childress D, Arndt S. Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. *Am J Psychiatry.* 1997; 154(2):185–185. [PubMed: 9016266]
45. Lord C, Risi S, Lambrecht L, et al. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* 2000; 30(3):205–205. [PubMed: 11055457]
46. Mullen, E. Mullen Scales of Early Learning. American Guidance Service, Inc.; Circle Pines, MN: 1995.
47. von Bertalanffy L. Untersuchungen über die gesetzlichkeit des wachstums. I. allgemeine grundlagen der theorie; mathematische und physiologische gesetzlichkeiten des wachstums bei wassertieren. *Arch Entwicklungsmech.* 1934; 131:613–52.
48. He JX, Stewart DJ. A stage-explicit expression of the von bertalanffy growth model for understanding age at first reproduction of great lakes fishes. *Can J Fish Aquat Sci.* 2002; 59:250–61.
49. Ratkowsky DA. Statistical properties of alternative parameterizations of the von Bertalanffy growth curve. *Can J Fish Aquat Sci.* 1986; 43:742–747.
50. Beal SL, Sheiner LB. Heteroscedastic nonlinear regression. *Technometrics.* 1988; 30:327–38.
51. Rommelse NN, Peters CT, Oosterling IJ, et al. A pilot study of abnormal growth in autism spectrum disorders and other childhood psychiatric disorders. *J Autism Dev Disord.* 2011; 41:44–54. [PubMed: 20428954]
52. Szatmari P, Maziade M, Zwaigenbaum L, et al. Informative phenotypes for genetic studies of psychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet.* 2007; 144B(5):581–8. [PubMed: 17219386]
53. Froehlich W, Cleveland S, Torres A, et al. Head circumferences in twins with and without autism spectrum disorders. *J Autism Dev Disord.* 2013; 43:2026–37. [PubMed: 23321801]
54. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. *Science.* 2007; 316(5823):445–445. [PubMed: 17363630]
55. Hazlett HC, Gu H, McKinsty RC, et al. Brain volume findings in 6-month-old infants at high familial risk for autism. *Am J Psychiat.* 2012; 169:601–8. [PubMed: 22684595]

56. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet.* 2005; 42:318–21. [PubMed: 15805158]
57. Chaste P, Klei L, Sanders SJ, et al. Adjusting head circumference for covariates in autism: clinical correlates of a highly heritable continuous trait. *Biol Psychiatry.* 2013; 74:576–84. [PubMed: 23746936]

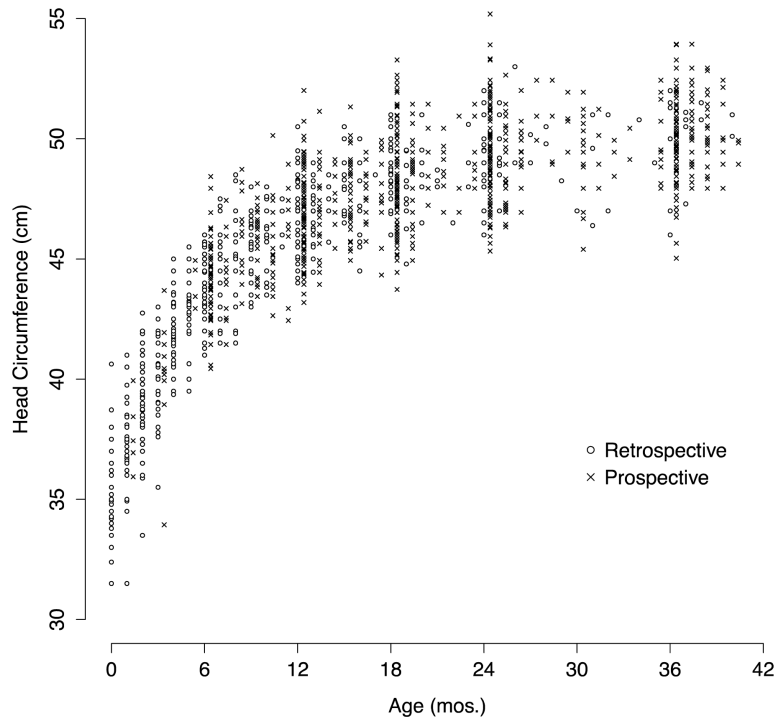


Figure 1. Head circumference data over time using retrospective and prospective methods.

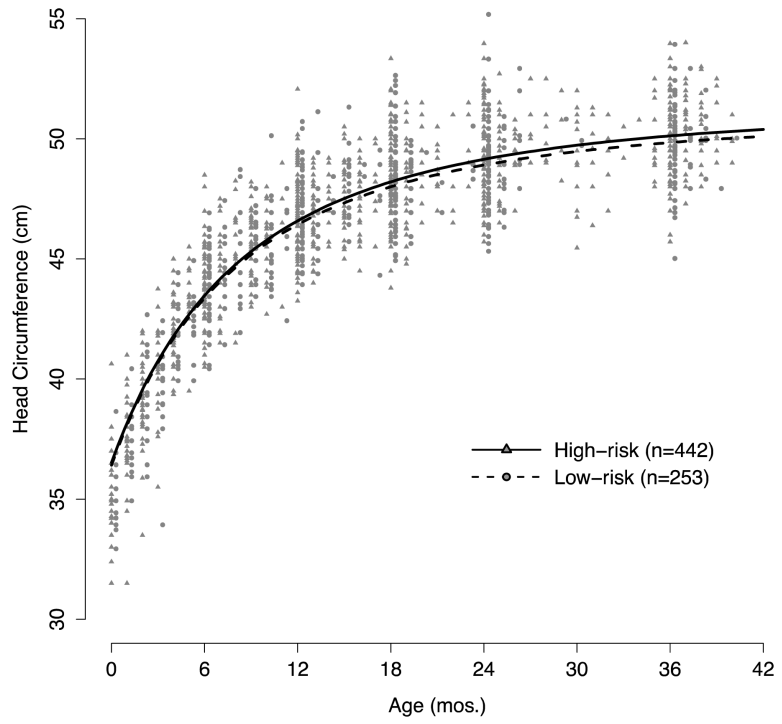


Figure 2. Head circumference growth trajectories in high-risk versus low-risk participants.

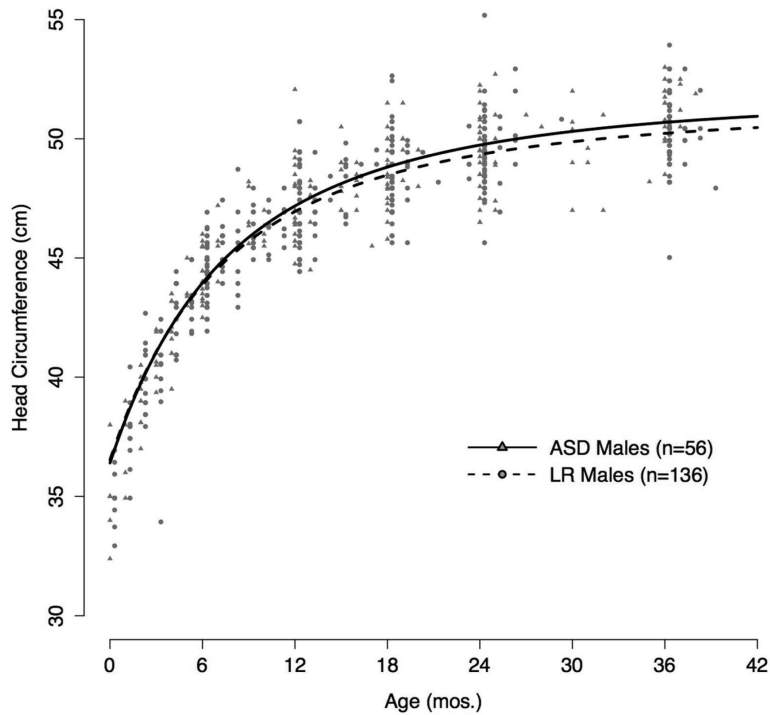


Figure 3.

Head circumference growth trajectories in high-risk males with autism spectrum disorder (ASD), compared to low-risk (LR) males. Note: Although linear or quadratic growth models are sometimes used for examining growth in head circumference,^{27, 29} neither offers a model that is a plausible model of biological growth for head circumference. Linear models presume infinitely increasing growth, and quadratic models often result in eventual decreases in head circumference, both of which are implausible models at best. In contrast, the asymptotic curves afforded by a negative exponential model are an obvious and significant, if still imperfect, improvement, both empirically and theoretically.

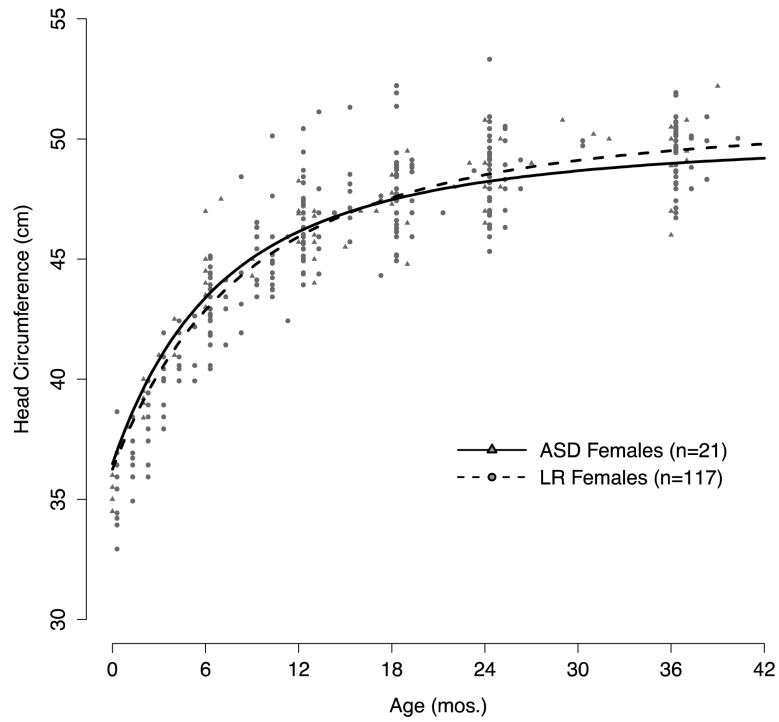


Figure 4. Head circumference growth trajectories in high-risk (HR) females with autism spectrum disorder (ASD) compared to low-risk (LR) females. Note: For ease of comparison between HR-ASD and LR groups, HR-developmental delay (DD) and HR-typically developing (TD) data are not depicted in Figures 3a and 3b due to overlapping trajectories with the HR-ASD group; graphs with these subgroups are available on request.

Table 1

Sample Characteristics

	LR-TD (n=253)	HR-TD (n=333)	HR-DD (n=32)	HR-ASD (n=77)
Sex (% Male)	53.8 (n=136/253)	45.9 (n=153/333)	84.4 (n=27/32)	72.7 (n=56/77)
Race (% Minority)	15.6 (n=26/167)	20.1 (n=51/254)	27.6 (n=8/29)	13.3 (n=8/60)
Ethnicity (% Hispanic)	10.2 (n=9/88)	17.0 (n=18/106)	16.7 (n=2/12)	37.5 (n=6/16)
Household Income (%)				
under \$25k	4.7 (n=4/86)	2.8 (n=3/109)	30.0 (n=3/10)	12.5 (n=2/16)
\$25k to \$49k	14.0 (n=12/86)	17.4 (n=19/109)	20.0 (n=2/10)	25.0 (n=4/16)
\$50k to \$74k	17.4 (n=15/86)	15.6 (n=17/109)	10.0 (n=1/10)	12.5 (n=2/16)
\$75k to \$99k	10.5 (n=9/86)	19.3 (n=21/109)	0.0 (n=0/10)	12.5 (n=2/16)
\$100k to \$124k	14.0 (n=12/86)	18.3 (n=20/109)	10.0 (n=1/10)	12.5 (n=2/16)
\$125k and above	39.5 (n=34/86)	26.6 (n=29/109)	30.0 (n=3/10)	25.0 (n=4/16)
Maternal Education (%)				
High school	2.9 (n=5/173)	8.3 (n=22/265)	21.4 (n=6/28)	13.1 (n=8/61)
Some college	10.4 (n=18/173)	11.7 (n=31/265)	21.4 (n=6/28)	13.1 (n=8/61)
College degree	46.8 (n=81/173)	52.5 (n=139/265)	50.0 (n=14/28)	49.2 (n=30/61)
Graduate degree	39.9 (n=69/173)	27.5 (n=73/265)	7.1 (n=2/28)	24.6 (n=15/61)
Paternal Education (%)				
High school	9.7 (n=17/175)	9.0 (n=24/267)	32.1 (n=9/28)	18.5 (n=12/65)
Some college	13.7 (n=24/175)	12.4 (n=33/267)	21.4 (n=6/28)	13.8 (n=9/65)
College degree	40.6 (n=71/175)	45.7 (n=122/267)	25.0 (n=7/28)	40.0 (n=26/65)
Graduate degree	36.0 (n=63/175)	33.0 (n=88/267)	21.4 (n=6/28)	27.7 (n=18/65)

Note: HR-ASD = high risk autism spectrum disorder; HR-DD = high risk developmental delay; HR-TD = high risk typically developing; LR-TD = low risk typically developing.