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Early Generalized Overgrowth in Autism Spectrum Disorder: Prevalence Rates, Gender Effects, and Clinical Outcomes

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Abstract

Objective—Although early head and body overgrowth have been well-documented in autism spectrum disorder (ASD), their prevalence and significance remain unclear. It is also unclear whether overgrowth affects males and females differentially, and whether it is associated with clinical outcomes later in life.

Method—To evaluate prevalence of somatic overgrowth, gender effects, and associations with clinical outcomes, head circumference, height, and weight measurements were collected retrospectively between birth and 2 years of age in toddlers with ASD (n=200) and typically developing (TD; n=147) community controls. Symptom severity, verbal, and nonverbal functioning were assessed at 4 years.

Results—Abnormalities in somatic growth in infants with ASD were consistent with early generalized overgrowth (EGO). Boys but not girls with ASD were larger and exhibited an increased rate of extreme EGO compared to community controls (18.0% versus 3.4%). Presence of a larger body at birth and postnatal overgrowth were associated independently with poorer social, verbal, and nonverbal skills at 4 years.

Conclusion—Although early growth abnormalities in ASD are less common than previously thought, their presence is predictive of lower social, verbal, and nonverbal skills at 4 years, suggesting that they may constitute a biomarker for identifying toddlers with ASD at risk for less-optimal outcomes. The results highlight that the search for mechanisms underlying atypical brain

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development in ASD should consider factors responsible for both neural and non-neural tissue development during prenatal and early postnatal periods, and can be informed by the finding that early overgrowth may be more readily observed in males than females with ASD.

Keywords

autism; infancy; head circumference; overgrowth; gender

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by severe impairments in social communication and interaction and a range of restricted, repetitive patterns of behaviors, interests, or activities[1]. Although as a group children later diagnosed with ASD are normocephalic at birth, their head circumference (HC) growth rate subsequently accelerates, leading to an enlarged HC in early preschool age[2–9]. Because of the high correlation between HC and total brain volume (TBV), HC growth rate in ASD has been considered an index for abnormal brain development in infancy[10]. Recent work suggests that early HC enlargement is accompanied by increased extra-axial fluid volume by 6–9 months and increased total cerebral volume by 12–15 months in infants later diagnosed with ASD[11]. By preschool age, children with ASD exhibit increased cortical surface area[12] and enlargements of the frontal, temporal, and parietal lobes[12–15] involving both gray and white matter[12, 5]. Initial reports suggested that HC overgrowth is independent of growth rates in other morphological features[2, 3]; however, more recent work indicates that atypical growth patterns in ASD are also observed in height and weight[4, 5, 7, 7, 16–18]. Despite high heritability of physical body parameters, the increase in HC in affected children does not appear to be accounted for entirely by parental head size or height[22,29, 66]. Simultaneous analysis of individual growth curves along all three dimensions suggests that infants with rapid HC growth rates also experience increased growth in height and weight, suggesting an early generalized overgrowth (EGO)[7]. A comparison with other disabled groups suggests that EGO may be specific to infants with ASD[7].

Not surprisingly considering the 4:1 male-to-female ratio in ASD[19], relatively few studies have examined gender effects on early growth in ASD. Those studies suggest that somatic overgrowth in the first year of life is more common in boys than in girls with ASD, although specific patterns differ across studies. In a study of Japanese infants with ASD, boys showed overgrowth in HC, height, and weight compared to community controls throughout the first year, but girls were larger only shortly after birth[8]. A population-based Norwegian study suggested that boys but not girls were larger and heavier than the community controls in the first year of life[18]. The two studies have the advantage of including community-based comparison samples, which is particularly important given the reported secular and ancestral biases in population norms (e.g., Centers for Disease Control) [7, 20–22]. However, growth data in these studies were only available for a limited age range (birth to 12 months), and, given markedly smaller sample sizes in girls than in boys, it was not clear whether the null results in girls were due to limited power to detect the gender effects. Moreover, neither of the studies attempted to directly examine the relationship between HC, height, and weight growth trajectories on an individual level. Although gender effects on the prevalence of macrocephaly or megalencephaly have been more frequently investigated, the results also remain inconclusive. Macrocephaly rates have been reported to be higher in boys than in

girls with ASD[23] or comparable between the two sexes[22, 24–26]. Evidence for enlargement in total brain volume (TBV) in young females with ASD is also mixed, with some reporting presence of TBV enlargement[15, 27, 28] and others reporting none[9]. Thus, sex effects on head and somatic growth patterns in early development remain to be further examined.

ASD is a highly heterogeneous disorder with regard to its behavioral expression as well as increased variability in head size[29] and somatic growth patterns[7, 18]. Estimates of prevalence of HC overgrowth in infants later diagnosed with ASD have ranged from 35% to 59%[2, 3], which inspired a discussion of whether HC overgrowth might constitute an early marker of risk for ASD[30, 31]. However, considering recent reports that the previously reported macrocephaly rates in older individuals with ASD (11%–27%) may be inflated due to ancestral or secular biases in the normative samples employed in these studies[21, 22, 32], there is a pressing need to re-examine the rates of early HC and somatic overgrowth amongst infants later diagnosed with ASD using community-based comparison samples[7, 20, 21]. Otherwise, reliance on questionable norms may lead to over-identification of outliers and thus may thwart the discovery of more homogenous and meaningful subgroups of children with ASD based on their growth patterns.

Although early overgrowth may signal a pathological process leading to disproportions in brain architecture in older individuals with ASD, its associations with clinical outcomes are unclear. While some studies report that early HC overgrowth is more pronounced in children with a more severe form of ASD (autism versus pervasive developmental disorder-not otherwise specified [PDD-NOS]) [2,7,17], language impairment[7], and regression[9], others link overgrowth with higher adaptive and verbal skills[3]. Thus, verification and elaboration of any predictive relationships with clinical outcomes are needed. Considering the progressive nature of atypical brain development in ASD, the effects of early overgrowth on behavior might depend on the amount of time elapsing between the period of growth acceleration and the time when its putative effects on the phenotype are examined. Consequently, measurement of outcomes within a relatively narrow age range should help to clarify predictive links between growth patterns and later levels of functioning.

The aims of this paper are to examine: (1) EGO patterns in ASD within gender; (2) prevalence of EGO in the first 2 years of life; and (3) predictive associations between features of EGO in infancy and clinical outcomes at 4 years.

Method

This study was approved by the Human Investigations Committee of the Yale University School of Medicine, and informed written consent was obtained from all parents prior to testing.

Participants

Participants (n=347) consisted of children enrolled consecutively in studies of social cognition or referred for a differential diagnosis of ASD to a university-based clinic. They included 200 children with ASD (161 boys, 39 girls) and 147 typically developing (TD) community controls (98 boys, 49 girls). The participants were born between 1997 and 2010

primarily in the Northeastern US. Children with ASD and those TD were evaluated for the first time around their second birthday; those with ASD underwent a second comprehensive evaluation at the age of 4 years. Children with ASD were assessed with standard measures including the Mullen Scales of Early Learning[33] (MSEL) and the Autism Diagnostic Observation Scale – Generic[34] (ADOS-G). Clinical best estimate (CBE) diagnosis of ASD was based on all available assessments and a review of medical and developmental history[37] collected at the age of 4 in 83% of cases. In the remaining 17% of cases, which were lost to follow-up, the diagnoses were based on assessments at the age of 2 years. Such early CBE diagnoses were considered sufficiently reliable in view of their established 90% to 100% stability in clinic-referred samples such as ours [44, 64, 65]. Developmental status in TD children was confirmed using the MSEL. Exclusion criteria were seizure disorder, visual or auditory abnormalities, known genetic disorders (e.g., fragile X syndrome, phosphatase and tensin homolog [PTEN] mutation), encephalitis and hydrocephalus, and gestational age (GA) below 32 weeks. TD children with familial history of ASD were not included. The groups did not differ with regard to race, parental age, or education. However, children with ASD had lower GA compared to TD controls ($p<.001$); thus, GA was included as a covariate in the growth curve modeling. Verbal, nonverbal, adaptive, and social impairment scores are presented in Table 1.

Procedures

HC, height, and weight measurements were obtained retrospectively from pediatric medical records at birth, 2 weeks, and 2, 4, 6, 9, 12, 15, 18, and 24 months, corresponding to the standard pediatric health surveillance points[38]. To ensure the compatibility of HC, height, and weight measures in the combined analyses, only visits containing all of the three measures were kept (4,403 visits or 62.2%). The mean (SD) number of morphological measurements per child was 7.27 (2.17), with no significant differences between groups ($p=.10$) or genders ($p=.30$).

Statistical Analysis

As in the previous study[7], effects contributing to growth curves for HC, height, and weight were modeled as spline functions[39] in a multilevel model incorporating overall, group-level, and individual-level effects with gender and GA included as covariates. The models were fit via Markov chain Monte Carlo methods in JAGS[40], and results were summarized and analyzed in R[41]. Estimated differences between group-level (ASD and TD) curves were separately evaluated at 100 age points from birth to 24 months, separately for boys and girls. Cohen's *d* effect size curves for these ASD versus TD comparisons were calculated using the set of fitted individual-level curves. To assess joint patterns of HC, height, and weight growth, principal components analysis (PCA) was applied to age-corrected individual-level curves. Scores for each principal component were computed for each subject at each age point, and the first two components were analyzed with the same spline models as described above, with curves for each principal component compared across groups. See Supplement 1, available online, for additional details on growth modeling and analysis. To determine how components of growth are related to clinical outcome captured by Verbal and Nonverbal developmental quotients (VDQ and NVDQ) and ADOS-G comparison scores[42], multiple linear regression models were fit using the ASD sample. These three outcome

variables were chosen to capture levels of functioning in the areas highly associated with long-term outcomes in ASD. Baseline values (principal component [PC] scores at birth) and changes over time (differences in PC score between birth and 18 months) for each individual were scaled to have variance 1 and were included as predictors in regression models, along with gender and gender-growth interaction.

Results

Age and Gender Effects on HC, Height, and Weight

Head circumference—There was no statistically significant difference between boys with ASD and TD controls in HC at birth. Between 10.7 and 22.8 months of age, boys with ASD had significantly larger HC than TD boys, and by 24 months, the magnitude of the difference reached about .64 cm (Figure 1A). No statistically significant differences in HC were observed in girls with ASD compared to TD girls at any age, and the difference by 24 months was −.17 cm (Figure 1A).

Height—There were no differences among groups in length at birth. Boys with ASD grew significantly longer than TD boys by 3.6 months, with the difference reaching 2.51 cm by 24 months (Figure 1B). Although girls with ASD showed a slight increasing trend, becoming on average 0.77 cm taller than TD girls by 24 months, these effects were not statistically significant (Figure 1B).

Weight—There were no differences among groups in weight at birth. Boys with ASD were significantly heavier than TD boys by 8.7 months (Figure 1C), with the difference by 24 months reaching .81 kg. Girls with autism and PDD-NOS showed a similar albeit non-significant trend, becoming heavier than TD girls by .70 kg by 24 months (Figure 1C).

The results of the PCA performed on the full sample were consistent with previous work[7]. The first component (PC1, explaining 69% of the variance), with coefficients .54, .58, and .61 for HC, height, and weight, reflected overall body size. The second component (PC2, explaining 20% of the variance), with coefficients .81, −.56, and −.18, reflected head size relative to height and weight.

Boys with ASD were larger overall (PC1) than TD boys beginning at 5.8 months (Figure 2). There were no significant differences in relative head size (PC2) between ASD and TD groups. An analogous analysis on females revealed no statistically significant departure from the curves derived from TD controls in either overall body size or relative head size (Figure 2). To evaluate whether the absence of statistical significance in girls was solely due to the smaller sample size, we compared PC1 effect size curves for boys and girls in Figure 3. The magnitude of the group differences for girls was approximately half of that for boys. Notably, the patterns of between-group differences remained the same when the growth curve modeling and PCA analysis were conducted only on full-term children (GA > 38 weeks).

Effects of EGO on Clinical Outcomes

To test the hypotheses that early atypical growth patterns are associated with less optimal outcomes in ASD, we conducted multiple linear regression analyses on three response variables: ADOS-G comparison scores, VDQ, and NVDQ collected at the age of 4 years. Physical parameters at birth, change in growth parameters from birth to 24 months, and gender were tested as predictors in the regression models (Table 2). The analyses indicated that a larger overall body size at birth ("PC1 at birth") was associated with decreased VDQ (p=.02), NVDQ (p=.007), and increased ADOS comparison scores (p=.03) at 4 years. A more rapid increase in body size ("PC1 change") was associated with decreased VDQ (p=.004) and NVDQ (p=.01) at 4 years. Relative head size at birth ("PC2 at birth") was associated with decreased ADOS comparison scores (p=.04) at 4 years only; all other effects of relative head size were not statistically significant. There was no significant gender by growth interaction for any outcome measure, suggesting that the effects of EGO on clinical phenotype were similar across genders. However, girls generally had higher ADOS-G comparison scores (p=.046) than boys. These p-values were not corrected for multiple comparisons, but less than one p-value would be expected to be < 0.05 by random chance, and seven p-values were observed below this threshold.

The effects of size at birth and the rate of postnatal growth on clinical outcome were additive. For instance, a child with an overall size (PC1) at birth 1 SD above the mean for the ASD group would have lower expected VDQ by 6.7 points 4 years later; if the same child's rate of growth in PC1 also exceeded the mean by 1 SD, the expected VDQ would drop by an additional 8.4 points, 15.1 points in total, which represents a highly clinically significant effect. By the same token, a child whose size at birth and rate of growth are both 1 SD below the means for ASD would be expected to have VDQ 15.1 points above the mean for ASD. Intermediate cases arise when size at birth and rate of growth deviate from the mean in opposite directions, with smaller size at birth mitigating the negative effects of postnatal overgrowth.

Prevalence Rates of Extreme Size and Growth

Subsequently, we evaluated the proportion of toddlers who exhibited extreme EGO between birth and 24 months, defined as the PC1 score at 24 months minus the PC1 score at birth exceeding 2 SD above the mean of such differences for the TD group. Extreme EGO was evident in 18% of boys with ASD and 4.1% of TD control boys (p<.001). In comparison, 7.7% of girls with ASD exhibited extreme EGO, which was not significantly higher than the 2.1% observed in TD girls (p=.206). A direct comparison of boys and girls with ASD revealed no significant difference (p=.115).

To facilitate comparisons with other studies that report rates of atypical growth on samples collapsed across gender, we computed rates of extreme growth patterns for the boys and girls combined. Extreme EGO was observed in 16.0% of ASD cases compared to 3.4% of TD cases (p < .001). We also computed the proportion of toddlers with ASD who exhibited body size in the extreme range, defined as PC1 score 2 SD above (macrosomy) or below (microsomy) the mean of the TD controls at birth and 24 months. After controlling for gestational age, at birth 9.5% of infants with ASD had microsomy as compared with 3.4% of

the TD group (p = .03). Rates of macrosomy were also increased in ASD (2.7%) compared to TD group (0%; p=.03). At 24 months 8.5% of children with ASD were macrosomic compared to 2.0% of TD participants (p = .01), but there was no longer a significant difference in microsomy (1.0% versus 1.4% in ASD and TD groups, respectively).

A similar comparison for HC indicated that extreme HC overgrowth was present in 15.0% of toddlers with ASD but only 3.4% of TD controls (p < .001). At birth, 7.0% of toddlers with ASD were microcephalic (HC 2 SD below the mean of the TD group), compared to 1.4% of TD cases (p = .02), but there was no difference in rates of macrocephaly (HC 2 SD above the mean of the TD group) in ASD and TD groups (1.0% versus 2.0%, p=.65). At 24 months, rates of both micro and macrocephaly were comparable in the two groups, as macrocephaly was observed in 6.0% of toddlers with ASD compared with 4.1% of TD controls (p = .47) and microcephaly was seen in 1.5% and 1.4% in participants with ASD and TD (p=1).

Discussion

This study extends previous results regarding EGO in boys with ASD[7]. Consistent with earlier reports[7, 18], overgrowth in boys becomes apparent first with regard to length/height around 4 months of age, followed by HC and weight overgrowth by 8–10 months. When these dimensions are considered jointly, they reveal a pattern of generalized overgrowth occurring around 6 months of age. This timetable suggests that although early overgrowth precedes the onset of overt behavioral signs of ASD typically manifesting in the second year of life[44, 45], it coincides with the emergence of prodromal attentional[46–48], neurophysiological[49], and neuroanatomical[11, 50] abnormalities observed in infants later diagnosed with ASD. Future studies will be necessary to elucidate the relationships among these processes and their roles in the pathogenesis of ASD. There was no evidence suggestive of abnormalities in head relative to height and weight growth (PC2). That rapid head enlargement in infants with ASD is accompanied by overgrowth in other morphological features by no means undermines the importance of the impact that accelerated brain growth in infancy may have on the development of neural architecture and behavior of toddlers with ASD. However, the discovery of a strong association between atypical HC and skeletal growth in infancy may help constrain the search for its underlying mechanisms.

The pattern of results reflecting gender differences in our sample were more complex. Consistent with previous reports[8, 18], girls with ASD did not differ in overall body size from TD controls in the first year of life, and our work extends these findings into the second year. Similarly, compared to community controls, the rates of extreme EGO were not significantly increased in girls with ASD. The magnitude of the overall overgrowth effect was approximately half of that observed in boys, suggesting that the non-significant results in girls may not be due solely to the small sample size. At the same time, although girls with ASD were less likely to exhibit extreme EGO than boys with ASD, these rates were not statistically different. Moreover, a lack of interaction effects in the regression analysis suggests that atypical physical growth in ASD affects early social and cognitive development similarly in both genders. At present, it is not clear whether the pattern of

results observed in girls is due to lower penetrance of pathogenic factors associated with growth abnormalities or the presence of protective factors mitigating risk effects (e.g., estrogens or sex chromosome gene dosage)[51]. These findings suggest that early generalized somatic overgrowth may represent one of the aspects of sexual dimorphism in ASD, though replication with a larger sample of girls will be necessary to confirm this hypothesis.

The data shed light on the prevalence of atypical growth features in ASD. Although consistent with other work [7,8,18,53] on the group level, newborns later diagnosed with ASD did not deviate from typical controls with regard to body or head size, at the individual level, significantly more newborns exhibited both microsomy and microcephaly. These results were present after the effects of gestational age were accounted for and highlight the presence of an increased variability in prenatal somatic growth amongst newborns later diagnosed with ASD[52]. Regardless of the starting point at birth, 16% of participants with ASD exhibited extreme EGO over the course of the first two years of life, which represents a significant increase over TD controls. HC overgrowth was seen in 15% of ASD cases. These overgrowth rates are lower than reported in earlier studies[2, 3], which likely reflects the advantage of employing the contemporaneous community-based control sample[20, 21]. By 24 months, rates of macrosomy but not macrocephaly exceeded the rates observed in TD controls. Thus, due to lower somatic size at birth, not all instances of postnatal EGO resulted in macrosomy or macrocephaly by the age of 2 years, which underscores the need to consider not only individual growth rate, but also size at birth. Considering that somatic growth extends into adolescence and that total brain volume reaches 95% of adult size by the age of 6 years,[55] these proportions are likely to continue to change over time and should be monitored in longitudinal samples such as ours.

This study also suggests that EGO in infancy predicts later behavioral and cognitive development. Amongst toddlers with ASD, a steeper postnatal increase in body size was associated with lower verbal and nonverbal skills at 4 years. Moreover, a larger body size at birth predicted lower verbal and nonverbal skills as well as more severe autism symptoms beyond the postnatal effects, highlighting the role of prenatal factors in the emergence of ASD[52]. The magnitudes of these effects were statistically and clinically significant. Interestingly, a smaller body size at birth may provide protection against deleterious effects of steeper postnatal growth. These findings suggest that factors underlying subtle deviations in pre- and postnatal somatic development reflect underlying atypical brain development and motivate further investigation into the role of such factors in the etiology of ASD. Considering the predictive links with clinical features, EGO may represent a biomarker or an endophenotype[58, 59] useful for identifying toddlers with ASD in the second year of life who are at risk for less optimal outcomes. Early identification of such ASD cases would create an important window of opportunity for intervening at a more specialized level to optimize outcome in this group, which is sometimes referred to as ‘difficult-to-treat’.

The study has several potential limitations. A replication study will be needed to evaluate EGO in more diverse, epidemiologically ascertained ASD samples. Morphological measurements were obtained retrospectively from pediatric records, which may present measurement variability, although error associated with this measurement is likely to be random. The study design did not include more extensive biological measures, including

genotyping[22] or measurement of brain structure[12], connectivity[50], and chemistry[54]. Inclusion of such measures will be helpful to further our understanding of the etiological factors associated with early overgrowth in autism. Parental physical parameters were not available in this study. Controlling for parental physical parameters in analysis of growth patterns in infancy may offer additional insights into genetic and epigenetic factors associated with growth abnormalities in the affected individuals. Although our results are suggestive of gender effects on growth patterns, given the small sample size, these data should be considered preliminary.

The study is based on a large prospective sample that was assembled at the time of the first diagnosis, which resulted in the inclusion of children with rapid and slow improvement rates and with a range of severity of symptoms and cognitive impairments, thus enhancing the generalizability of the results to the broader population of toddlers with ASD. Inclusion of a contemporaneous community control sample represents an important advantage over studies employing population norms[21, 22]. In light of the observed heterogeneity in growth patterns with regard to gender (present study), diagnostic subcategories,[7] and onset patterns[9], the idea that growth patterns in infancy may constitute a universal diagnostic marker of ASD does not appear to be viable[7, 21, 56, 57]. However, EGO may represent a biomarker for a subgroup of individuals with ASD at risk for greater cognitive, language, and social impairment. Future studies will be necessary to determine whether EGO plays a role in the etiology of the disorder and to ascertain its underlying mechanisms, which may lead to the identification of novel treatment targets during early stages of the disorder. Furthermore, considering that different biological factors contribute to brain and body growth in infancy, toddlerhood, school age, and adolescence, understanding extended growth trajectories in children with ASD will inform the search for underlying pathology in autism throughout the lifespan. Our results highlight that the search for genetic[22, 60], neuroanatomical[11, 50], endocrine[61, 62], and immunological[63] mechanisms underlying early atypical brain development should consider factors responsible for both neural and non-neural tissue development during the prenatal and postnatal periods, and can be informed by the finding that atypical growth patterns in infancy may be more pronounced in males than females with ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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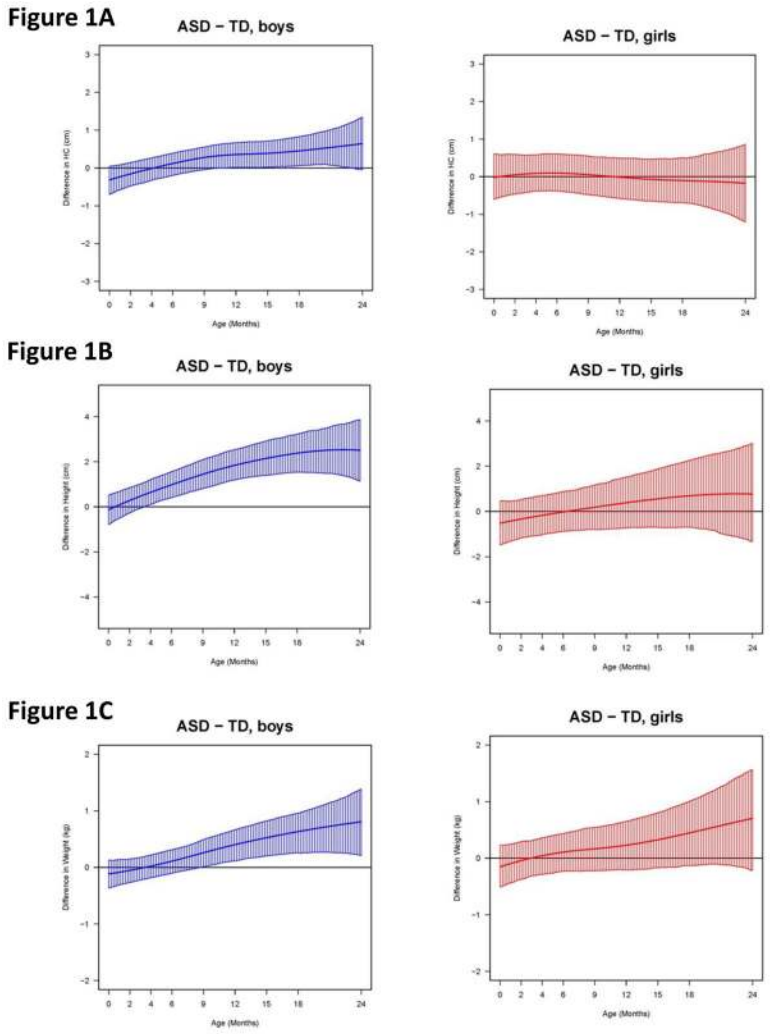

Figure 1.

A–C: Group differences in morphological measures: comparisons among groups with autism spectrum disorder (ASD) and typically developing (TD) groups in (A) head circumference, (B) height, and (C) weight, from birth to 24 months. Note: graphs display mean difference curves and 95% credible bands for ASD-TD differences in boys (left) and in girls (right). Separation of the 95% credible bands from 0 represents a statistically significant difference between means at the 0.05 level (two-sided).

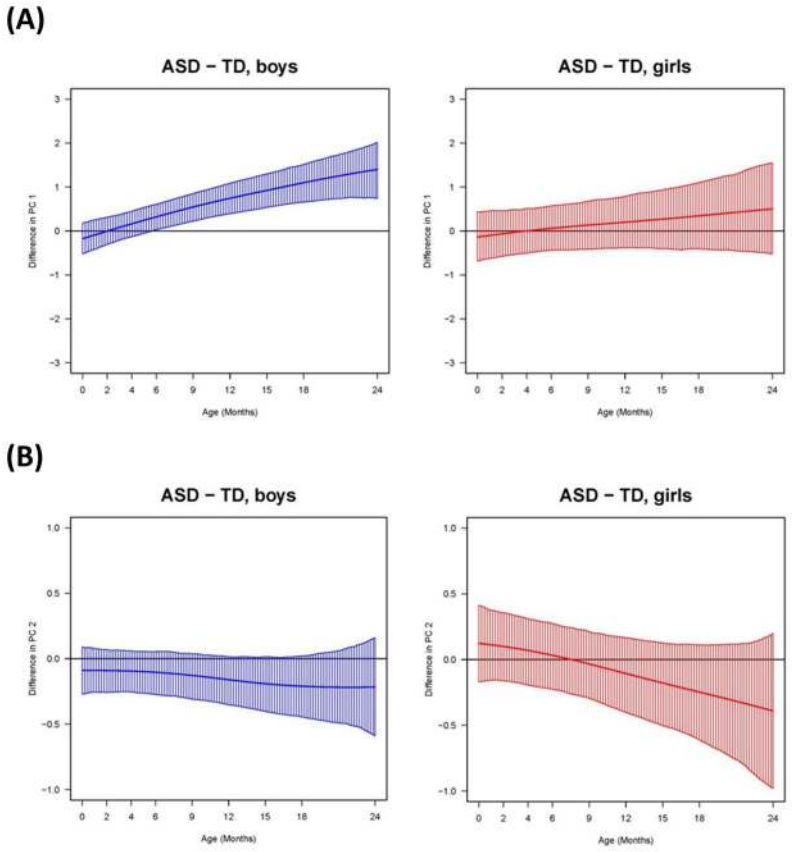

Figure 2.

A–B: Group differences in overall body size and relative head size: comparisons between groups with autism spectrum disorder (ASD) and typically developing groups (TD) in (A) overall body size (PC1) and (B) relative head size (PC2), from birth to 24 months. Note: graphs display mean difference curves and 95% credible bands for ASD-TD differences in boys (left) and in girls (right). Separation of the 95% credible bands from 0 represents a statistically significant difference between means at the 0.05 level (two-sided).

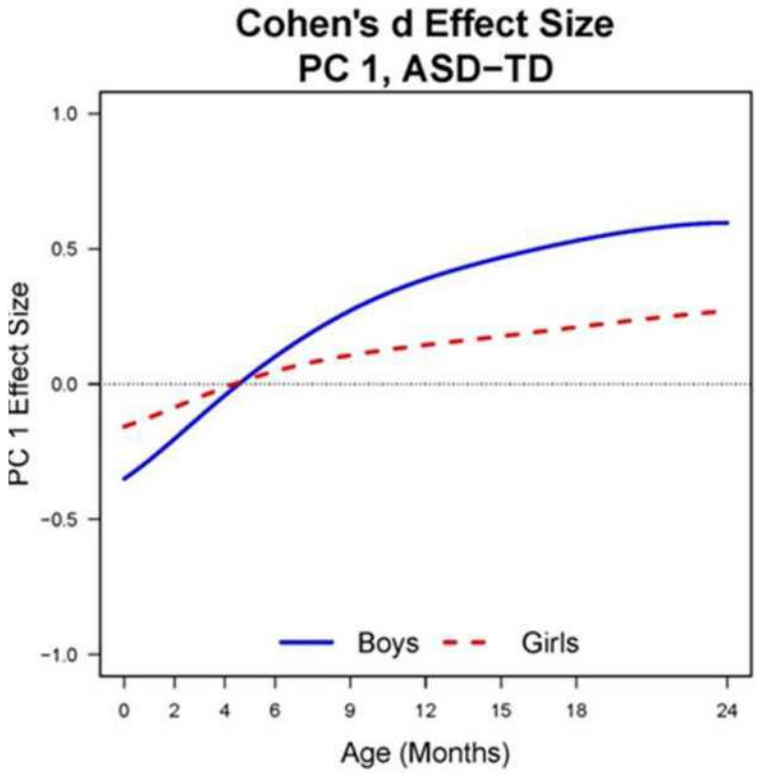

Figure 3.

Group difference effect sizes. Note: Cohen's *d* effect sizes for group differences as a function of time for overall body size (PC1); ASD = autism spectrum disorder; TD = typically developing.

Table 1

Sample Characterization

Group	ASD (n=200)	TD (n=147)	*p*-Value
% Male	80.5	66.7	.005
GA, weeks	38.9 (1.9)	39.8 (1.4)	<.001
% Caucasian	78.0	82.3	.39
Maternal age, years	35.2 (5.2)	34.7 (4.9)	.40
Paternal age, years	37.3 (5.6)	36.6 (6.0)	.30
% Mothers with college degree	76.5	80.1	.54
% Fathers with college degree	72.2	74.1	.83
Visit 1			
Age, months	24.3 (5.5)	21.3 (6.9)	<.001
MSEL Verbal DQ	51.2 (27.4)	100.4 (22)	<.001
MSEL Nonverbal DQ	79.8 (18.4)	106.0 (16)	<.001
ADOS comparison score	7.1 (2.0)	--	
Visit 2			
Age, months	41.4 (8.4)	--	
MSEL Verbal DQ	73.3 (33.2)	--	
MSEL Nonverbal DQ	79.5 (22.0)	--	
ADOS comparison score	7.6 (2.1)	--	

Note: ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; DQ = developmental quotient; GA = gestational age; MSEL = Mullen Scales of Early Learning; TD = typically developing.

Table 2

Four-Year Outcome Regression Results

Response Variable at 4 Years	Regression Results	Explanatory Variables	β	p-Value
MSEL Verbal DQ (n=158)	R^2: 0.085 $F(5,152)=2.83$ $p=.02$	**PC1 at birth**	**−6.68**	**.02**
		PC1 change	**−8.41**	**.004**
		PC2 at birth	4.70	.08
		PC2 change	0.96	.71
		Gender (Female)	−7.34	.24
MSEL Nonverbal DQ (n=157)	R^2: 0.076 $F(5,151)=2.49$ $p=.03$	**PC1 at birth**	**−5.18**	**.007**
		PC1 change	**−4.83**	**.01**
		PC2 at birth	3.08	.09
		PC2 change	−0.73	.67
		Gender (Female)	−3.45	.41
ADOS Comparison Score (n=156)	R^2: 0.067 $F(5,150)=2.15$ $p=.06$	**PC1 at birth**	**0.43**	**.03**
		PC1 change	0.09	.67
		PC2 at birth	**−0.37**	**.04**
		PC2 change	0.11	.53
		Gender (Female)	**0.85**	**.046**

Note: Bolding denotes significant effects. ADOS = Autism Diagnostic Observation Schedule; DQ = developmental quotient; MSEL = Mullen Scales of Early Learning; PC1 = overall size; PC2 = head size.