

Accelerated Head and Body Growth in Infants Later Diagnosed With Autism Spectrum Disorders: A Comparative Study of Optimal Outcome Children

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Previous research has demonstrated accelerated head and body growth during infancy in children with autism spectrum disorders. No study has yet examined head growth in children who lose their autism spectrum disorder diagnoses. Head circumference, length, and weight growth during infancy for 24 children who maintained their diagnoses were compared with 15 children who lost their diagnoses, and to 37 typically developing controls. Results showed that head circumference and weight growth were significantly greater in both autism spectrum disorder groups compared with controls, with no significant

differences between autism spectrum disorder groups. However, when length and weight were controlled for, accelerated head growth remained significant in the children who lost their diagnoses. Findings suggest that children who lose their autism spectrum disorder diagnoses and children who maintain their diagnoses show similar head circumference, length, and weight growth trajectories during infancy, although subtle differences in body growth between groups may exist.

Keywords: autism; head circumference; recovery; growth

Autism is a neurological disorder, whose clinical symptoms often do not become apparent until the second or, sometimes, the third year of life, with diagnosis typically occurring between 2 and 4 years of age.¹⁻³ However, it is presumed that some neurological abnormality underlies the behavioral manifestations of the disorder and therefore might precede these first clinical signs. By using longitudinal studies during infancy, autism researchers have compared the developing autistic brain with the typically developing brain in hopes of determining when during development the autistic brain begins to deviate from normal. Such a neurological indicator could serve as a warning signal that a child is at risk for

developing autism and could be used in combination with behavioral markers during infancy to aid in the early detection of autism.

Macrocephaly (head circumference > 97th percentile) is the most consistent biological finding associated with autism spectrum disorder⁴⁻¹⁸ and occurs in approximately 20% of cases. However, several studies in the autism literature have narrowed this period of accelerated brain growth to early childhood and infancy.^{4,12,19,20} Such studies have used both head circumference measurement, which has been shown to be a valid indicator of whole-brain weight and volume,²¹⁻²³ and magnetic resonance imaging, to assess changes in brain volume over the course of early development.

Courchesne et al found that mean head circumference measurement at birth in infants later diagnosed with an autism spectrum disorder was significantly smaller than Centers for Disease Control and Prevention averages,²⁴ and subsequent growth was characterized by a sudden increase in head circumference beginning after 1 to 2 months and continuing through 6 to 14 months.²⁰ A follow-up study with this sample found that 95.8% of children with an autism spectrum disorder and 92.3% of controls were correctly classified based on a discriminant function analysis of magnetic resonance imaging brain

Received September 23, 2008. Received revised November 25, 2008. Accepted for publication November 26, 2008.

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The authors have no conflicts of interest to disclose with regard to this article.

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Mraz KD, Dixon J, Dumont-Mathieu T, Fein D. Accelerated head and body growth in infants later diagnosed with autism spectrum disorders: a comparative study of optimal outcome children. *J Child Neurol.* 2009;24:833-845.

measurements, with the autism spectrum disorder group showing significantly greater whole brain volumes and cerebellar white matter volumes than controls.²⁵

Based on their findings, Courchesne et al hypothesized that brain growth during the first year of life is accelerated in autism, with overgrowth followed by a period of slowed or arrested growth, such that the autistic brain reaches its maximum size by 4 to 5 years of age, approximately 8 years earlier than the typically developing brain. They argue that because this growth is compressed into a small window of time, this does not allow for the creation, reinforcement, and elimination of synapses guided by experience. The end result is an overabundance of neuronal connections that are not particularly adaptive.

Cellular and growth abnormalities in autism spectrum disorder have been shown to be most pronounced in frontal, cerebellar, and temporal structures,^{26,27} those structures that mediate higher order functions including the development of social, language, emotional, attentional, and cognitive processes. Findings from a diffusion tensor imaging study also demonstrate reduced density of white matter tracts adjacent to dorsal and mesial prefrontal cortices in older children with an autism spectrum disorder.²⁸ In addition, a postmortem study of individuals with an autism spectrum disorder, ages 5 to 44 years, presents microscopic evidence of an ongoing inflammatory response in the gray and white matter of the frontal lobe and cerebellum, as indicated by the presence of activated astroglia and associated degeneration in nearby neuronal structures.²⁹ Courchesne et al hypothesize that cellular abnormalities in the frontal cortex, specifically defects in minicolumn microcircuitry,³⁰⁻³² might result from early neuroinflammation in response to some aberrant prenatal or postnatal genetic or environmental influence. They further propose that these processes result in increased local frontal cortical connectivity but reduced long distance connectivity between the frontal cortex and other brain regions, impairing the integration of information from multiple systems in autism spectrum disorder.

Several attempts to replicate these brain growth findings have provided further evidence for acceleration of head circumference growth during the first year of life in autism spectrum disorder^{8,33-37}; however, clinical correlates of this acceleration have been inconsistent. Some studies have found accelerated growth, rapid deceleration, or larger absolute head size to be correlated with better skills in an autism spectrum disorder sample,⁸ whereas others have found these indices correlated with more severe delays and symptoms.^{20,38,39}

In contrast to the findings of Courchesne et al,²⁰ several studies have shown that children later diagnosed with an autism spectrum disorder are significantly longer and/or heavier during infancy compared with controls.^{7,12,15,35,37,40-43} In our prior study,³⁵ infants later diagnosed with an autism spectrum disorder were significantly

longer and heavier than typically developing infants beginning at 1 to 2 months, such that differences in head circumference were no longer significant after controlling for length and weight. Torrey et al⁴¹ were unable to replicate Courchesne's findings of accelerated head growth in an autism sample; however, results showed significantly greater weights and lengths at birth and 4 months compared with controls. Torrey et al hypothesize that abnormal metabolism, growth factors, or developmental processes in individuals with autism contribute to diffuse overgrowth as opposed to specific brain overgrowth. In support of this hypothesis, a recent study by Mills et al showed elevated levels of growth-related hormones, specifically insulin-like growth factor (IGF-1, IGF-2), insulin-like growth factor binding protein (IGFBP-3), and growth hormone binding protein (GHBP), in addition to greater weights, body mass indices, and head circumferences in an autism spectrum disorder sample, ages 4 to 8 years.⁴⁴ Thus, the majority of studies have amply replicated the accelerated head and brain growth in early development in autism spectrum disorder, but patterns of relationship with clinical outcome variables are inconsistent, as are patterns of length and weight development.

In the aforementioned study by Mraz et al,³⁵ it was observed that 5 of the 35 infants comprising the autism spectrum disorder sample who met criteria for autism spectrum disorder at their first diagnostic evaluation (mean age of 26.6 months) did not meet criteria for a diagnosis of autism spectrum disorder at their second evaluation (mean age of 51.8 months). This led us to question whether these 5 children who ultimately "lost" their autism spectrum disorder diagnosis might demonstrate a unique pattern of brain and/or body growth during infancy compared with children who maintained their autism spectrum disorder diagnosis over time.

The notion of "recovery" from autism first received widespread attention when Lovaas et al reported that 47% of children who received intensive behavioral-based treatment achieved normal intellectual and educational functioning by first grade.⁴⁵ A follow-up evaluation of these children at a mean age of 13 years showed that they preserved their excellent outcomes.⁴⁶ Although by no means universally accepted as a possible outcome for autism spectrum disorder, and with generally lower proportions of excellent outcome, other behavioral and longitudinal studies have also reported some cases of virtual recovery.⁴⁷⁻⁴⁹ A recent study by Fein and colleagues showed significant residual attention deficits in a sample of 11 children who lost their diagnosis of autism spectrum disorder, but met criteria for attention-deficit hyperactivity disorder by a mean age of 7 years.⁵⁰ A related study by the same group also provided evidence for residual language deficits in a sample of 14 children who had lost their autism spectrum disorder diagnoses over

time, noting subtle residual impairments on more complex language tasks, despite average performance on overall language testing.⁵¹ Sutter et al also reported that a significant minority of children followed prospectively after an early autism spectrum disorder diagnosis lost the diagnosis 2 years later, with motor skills being the best early predictor of good outcome.⁵² Most, but not all, of the children in these 3 studies received intensive early intervention, usually behavioral.

At present, the relationship between successful behavioral intervention and neurobiological development is unclear. It is unknown whether treatment is capable of producing long-lasting neurological changes, altering a child's developmental trajectory, thus leading to "recovery" in autism, or whether a certain neurological pattern of growth during infancy, before intervention typically begins, might make a child more receptive to the effects of later intervention. It also seems to be the case that although early intervention is a major contributing factor, and probably necessary for achieving optimal outcome, it is not sufficient. Prognosis appears to be dependent upon the relationship between child characteristics, such as initial language, motor, and social skills, and the amount of intervention.⁵³ Based on the findings of a previous study,³⁵ together with those findings of Courchesne et al,²⁰ we hypothesized that children with autism spectrum disorders who achieved an optimal outcome might show a more normal rate of head and/or body growth during infancy, compared with those children who maintain their autism spectrum disorder diagnoses at age 4. Such a normal growth pattern could potentially reflect an adaptability or propensity to respond more positively to the effects of intervention. It is important to note that such changes would probably not be reflected in a change in head circumference growth after the age of 2 due to the fact that the cranium fuses at approximately 2 years of age.⁵⁴

The current study, therefore, examined head circumference, length, and weight measurements taken during the first 2 years of life in a sample of optimal outcome children with a history of autism spectrum disorder, and these measurements were compared with those of typically developing children as well as to those of children who maintained their autism spectrum disorder diagnoses over time. The purpose of this study is to further elucidate the neurodevelopmental trajectory of children who appear to recover from autism and may also enable researchers to determine whether there is a subset of children whose early head and body growth patterns make them more responsive to the positive effects of intervention. This study was approved by the institutional review board of the University of Connecticut. Informed consent was obtained from each participant in the study.

Method

Participants

Autism spectrum disorder–stable group. As part of an earlier head circumference study, head circumference, length, and weight data were collected from 24 children with an autism spectrum disorder, ages 4 years 10 months to 9 years 8 months, who received an autism spectrum disorder diagnosis at both their initial (mean age = 26.6 months; standard deviation [SD] = 4.2 months) and their second evaluation (mean age = 49.9 months; SD = 4.4 months). These 24 children were selected from a sample of 35 children who participated in an earlier head circumference study by the same author,³⁵ based on the stability of their autism spectrum disorder diagnoses over time. The children were evaluated as part of the Early Detection study at the University of Connecticut, after screening positive on the Modified Checklist for Autism in Toddlers. All children met criteria for a diagnosis of autistic disorder or pervasive developmental disorder–not otherwise specified based on the clinical best estimate judgment per the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.⁵⁵ Children and parents were administered the Autism Diagnostic Interview–Revised,⁵⁶ the Autism Diagnostic Observation Schedule,⁵⁷ the Childhood Autism Rating Scale,⁵⁸ the Vineland Adaptive Behavior Scales,⁵⁹ and the Mullen Early Learning Scales.⁶⁰ Results of the Autism Diagnostic Interview–Revised,⁵⁶ the Autism Diagnostic Observation Schedule,⁵⁷ and the Childhood Autism Rating Scale⁵⁸ were used in making the clinical best estimate diagnosis. Of these 24 children, 13 were diagnosed with autistic disorder and 11 were diagnosed with pervasive developmental disorder–not otherwise specified at their first evaluation. At their second evaluation, 16 of 24 children received a diagnosis of autistic disorder, whereas 8 received a diagnosis of pervasive developmental disorder–not otherwise specified. Five children who were diagnosed with pervasive developmental disorder–not otherwise specified at their first evaluation later received a diagnosis of autistic disorder at their second evaluation, whereas 2 children who were diagnosed with autistic disorder at their first evaluation later received a diagnosis of pervasive developmental disorder–not otherwise specified at their second evaluation. The autism spectrum disorder–stable (ASD-S) sample consisted of 3 females (12.5%) and 21 males (87.5%), and the ethnic composition of the sample was 92% Caucasian, 4% Hispanic, and 4% Asian. Individuals with comorbid known genetic disorders or other medical conditions or with a history of seizures were excluded. In addition, all children who were premature at birth (earlier than 37 weeks) were excluded.

Autism spectrum disorder–optimal outcome group. The group was comprised of 15 children, ages 36 months to 14 years 2 months, who were diagnosed with an autism spectrum disorder at their initial evaluation (mean age = 29.8 months; SD = 11.1 months) and then no longer met criteria for any autism spectrum disorder diagnosis at their second evaluation (mean age = 57.1 months; SD = 15.6 months). Of the 15 children, 4 received a diagnosis of autistic disorder at their initial evaluation, whereas

11 children received a diagnosis of pervasive developmental disorder—not otherwise specified. Of these 15 children, 11 participated in the Early Detection study and therefore initial and final diagnoses were based on the aforementioned criteria. Of these 11 children, 7 received a diagnosis of pervasive developmental disorder—not otherwise specified at their initial evaluation, whereas 3 children received an initial diagnosis of autistic disorder. Of these 11 children, 9 children were administered the Childhood Autism Rating Scale⁵⁸ at their second evaluations, all of whom obtained total scores which were less than or equal to 23, falling within the nonautistic range. Although none of the 11 children met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,⁵⁵ criteria for an autism spectrum disorder diagnosis at their second evaluation, 1 child received a final diagnosis of mental retardation, whereas 1 child received a final diagnosis of mild expressive language delay. The child with mental retardation had expressive and receptive language scores on the Mullen Early Learning Scales⁶⁰ approximately 2 SD below the mean, and although no visuospatial score was able to be calculated due to noncompliance, a visuospatial score obtained 2 years prior was 2 SD below the mean. The child diagnosed with mild expressive language delay received visuospatial and receptive language scores on the Mullen Early Learning Scales⁶⁰ within the average range, and an expressive language score approximately 2 SD below the mean.

Of the 15 autism spectrum disorder-optimal outcome, (ASD-OO) children, 2 were participants in an Optimal Outcome study at the University of Connecticut. Children in the Optimal Outcome study were evaluated by a clinical neuropsychologist with expertise evaluating children with autism spectrum disorders (fourth author of this article), who also evaluates children through the Early Detection study. These 2 children were administered the Autism Diagnostic Observation Schedule,⁵⁷ the Vineland Adaptive Behavior Scales,⁵⁹ and either the Wechsler Pre-School Scale of Intelligence Scale⁶¹ or the Wechsler Intelligence Scale for Children—Third Edition⁶² depending on the age of the child at the time of the evaluation. These results were used in making the clinical best estimate diagnosis. Both children were diagnosed with pervasive developmental disorder—not otherwise specified at their first evaluation and then no longer met criteria for an autism spectrum disorder diagnosis at their second evaluation. One child received a final diagnosis of a mild expressive language delay. Visuospatial and receptive language scores on the Mullen Early Learning Scales⁶⁰ fell within the Average range, whereas the child's expressive language score was greater than 1.5 SD below the mean. The other child did not meet criteria for any disorder.

The remaining 2 of the 15 ASD-OO children were evaluated through University of Connecticut's Psychological Services Clinic by a psychologist who also evaluates children through the Early Detection study, and by the aforementioned neuropsychologist and author in her private practice. One child was administered the Autism Diagnostic Observation Schedule,⁵⁷ the Differential Abilities Scales,⁶³ and the Vineland Adaptive Behavior Scales,⁵⁹ whereas the other child was administered the Vineland Adaptive Behavior Scales⁵⁹ and the Mullen Early Learning Scales.⁶⁰ Both received an initial diagnosis of pervasive developmental disorder—not otherwise specified based on the clinical best estimate diagnosis and then did not meet criteria for any autism spectrum disorder diagnosis at their second evaluation.

However, 1 of these children was diagnosed with a mild expressive/receptive language delay at their second evaluation. This child's nonverbal reasoning and general conceptual ability scores on the Differential Ability Scales⁶³ were within the average range, whereas the child's verbal reasoning score was greater than 1 SD below the mean. The second child did not meet criteria for any disorder.

In addition, Vineland Adaptive Behavior Scale's total scores for 14 of the 15 children who were administered this measure at their second evaluations were greater than or equal to 77 (approximately 1.5 SD below the mean). Of these 14 children, 13 scored within 1.5 SD below the mean on the Vineland Adaptive Behavior Scales Communication subdomain, and all 14 scored within 1.5 SD below the mean on the Vineland Adaptive Behavior Scales Socialization subdomain.

The ASD-OO group consisted of 2 females (13%) and 13 males (87%), and the ethnic composition of the sample was 87% Caucasian, 6.5% Hispanic, and 6.5% Asian. Data were obtained for 5 of these children as part of an earlier head circumference study; the remaining 10 families were contacted via phone and written consent was obtained. Medical records were accessed to obtain head circumference, length, and weight measurements taken during the first 2 years of life.

Control group. Head circumference, length, and weight data were also collected from an independent control group of 37 typically developing children, ages 34 months to 11 years 3 months. The control sample consisted of 16 females (43%) and 21 males (57%), and the ethnic composition of the sample was 88% Caucasian, 6% Asian, and 6% African American. These children were recruited through 2 local pediatrician's offices and several community groups. Children who were diagnosed with any learning, psychological, or developmental disorder, or who were referred to Birth to Three Services due to a language or motor delay were excluded from the sample. In addition, children who were premature at birth (earlier than 37 weeks) or whose mothers experienced serious problems during pregnancy or childbirth were excluded.

Statistical Analyses

Mean raw measurements for head circumference, length, and weight were calculated by averaging raw scores across the following age intervals: birth to 2 weeks, 1 to 2 months, 3 to 5 months, 6 to 9 months, 10 to 14 months, and 15 to 25 months. Raw measurements were used in correlations related to sample characteristics as well as in growth curve modeling. In addition, raw scores were normalized for sex and age (based on the 0.5-month increments) by converting to *z* scores based on the Centers for Disease Control and Prevention normative data.²⁴ The *z* scores were also averaged across the aforementioned age intervals to examine mean differences between groups.

Results

The ASD-S group and the ASD-OO group differed significantly from the control group, but not from each other,

Table 1. Mean Head Circumference z Scores for ASD-S, ASD-OO, and Control Groups

	ASD-S Group	ASD-OO Group	Control Group
Birth to 2 weeks	-0.23	-0.38	-0.49
1 to 2 months	-0.01	0.17	0.09
3 to 5 months	0.32	0.34	0.16
6 to 9 months	0.79	0.85	0.26
10 to 14 months	0.98	1.52	0.45
15 to 25 months	0.64	1.03 (t)	0.31

Note: Measurements that differed significantly from the local controls are shown in boldface. (t) represents a trend toward significance. ASD-S, autism spectrum disorder-stable; ASD-OO, autism spectrum disorder-optimal outcome.

with respect to gender. Both autism spectrum disorder groups were predominantly male (7 to 1 for ASD-S; 6.5 to 1 for ASD-OO), whereas the control group was comprised of an approximately equal number of males and females (1.3 to 1). This gender difference between the autism spectrum disorder groups and control group to some extent affects the interpretation of observed differences in mean raw head circumference, length, and weight measurements, which will be addressed in the discussion section. However, head circumference, length, and weight means were also normalized for gender and age and analyses of variances (ANOVAs) were performed based on the normalized mean data. There were no significant differences between groups with respect to ethnicity or mean annual family income.

Bivariate Correlations

Bivariate correlations were computed between raw head circumference, length, and weight measurements at each age interval for each group separately. In the ASD-S group, raw head circumference was highly correlated with raw length at 1 to 2 months ($r = .55, P < .01$) and 3 to 5 months ($r = .44, P < .05$), and with raw weight at 1 to 2 months ($r = .70, P < .001$) and 3 to 5 months ($r = .55, P < .01$). Raw length and raw weight were significantly correlated at birth to 2 weeks ($r = .51, P < .05$), 1 to 2 months ($r = .69, P < .001$), 3 to 5 months ($r = .48, P < .05$), and 15 to 25 months ($r = .54, P < .01$).

In the ASD-OO group, head circumference was highly correlated with raw length at birth to 2 weeks ($r = .81, P < .05$) and with raw weight at birth to 2 weeks ($r = .86, P < .005$), 1 to 2 months ($r = .55, P = .05$), and 6 to 9 months ($r = .57, P < .05$). Raw length and raw weight were highly correlated at every age interval: birth to 2 weeks ($r = .92, P < .001$), 1 to 2 months ($r = .95, P < .001$), 3 to 5 months ($r = .83, P < .001$), 6 to 9 months ($r = .73, P < .005$), 10 to 14 months ($r = .71, P = .005$), and 15 to 25 months ($r = .78, P = .001$).

In the control group, head circumference was highly correlated with raw length at every age interval: birth to 2 weeks ($r = .49, P < .05$), 1 to 2 months ($r = .59,$

Table 2. Mean Length z Scores for ASD-S, ASD-OO, and Control Groups

	ASD-S Group	ASD-OO Group	Control Group
Birth to 2 weeks	0.48	0.23	0.26
1 to 2 months	0.57	0.62	0.52
3 to 5 months	0.97	0.68	0.62
6 to 9 months	1.1	0.89	0.58
10 to 14 months	1.06	0.76	0.22
15 to 25 months	0.89 (t)	0.81	0.36

Note: Measurements that differed significantly from the local controls are shown in boldface. (t) represents a trend toward significance. ASD-S, autism spectrum disorder-stable; ASD-OO, autism spectrum disorder-optimal outcome.

Table 3. Mean Weight z Scores for ASD-S, ASD-OO, and Control Groups

	ASD-S Group	ASD-OO Group	Control Group
Birth to 2 weeks	-0.08	-0.29	-0.08
1 to 2 months	0.51	0.16	0.53
3 to 5 months	0.66	0.21	0.44
6 to 9 months	0.55	0.08	0.16
10 to 14 months	0.3	0.15	-0.12
15 to 25 months	0.45	0.32	-0.02

Note: ASD-S, autism spectrum disorder-stable; ASD-OO, autism spectrum disorder-optimal outcome.

$P < .001$), 3 to 5 months ($r = .60, P < .001$), 6 to 9 months ($r = .61, P < .001$), 10 to 14 months ($r = .62, P < .001$), and 15 to 25 months ($r = .50, P < .005$). Head circumference was also highly correlated with raw weight at every age interval: birth to 2 weeks ($r = .53, P < .01$), 1 to 2 months ($r = .67, P < .001$), 3 to 5 months ($r = .66, P < .001$), 6 to 9 months ($r = .60, P < .001$), 10 to 14 months ($r = .70, P < .001$), and 15 to 25 months ($r = .60, P < .001$). Last, raw length and raw weight were highly correlated at every age interval: birth to 2 weeks ($r = .81, P < .001$), 1 to 2 months ($r = .74, P < .001$), 3 to 5 months ($r = .67, P < .001$), 6 to 9 months ($r = .65, P < .001$), 10 to 14 months ($r = .78, P < .001$), and 15 to 25 months ($r = .68, P < .001$). There was no relationship between ethnicity or annual family income and raw head circumference, length, or weight measurements for any of the groups.

Mean Differences Between ASD-S, ASD-OO, and Local Controls

Mean head circumference, length, and weight z scores at each age interval were calculated for the ASD-S group, ASD-OO group, and control group (Tables 1-3, Figures 1-3). Analyses of variances were performed at each age interval to examine whether there were mean differences in head circumference, length, or weight z scores between groups. Results from ANOVAs showed mean

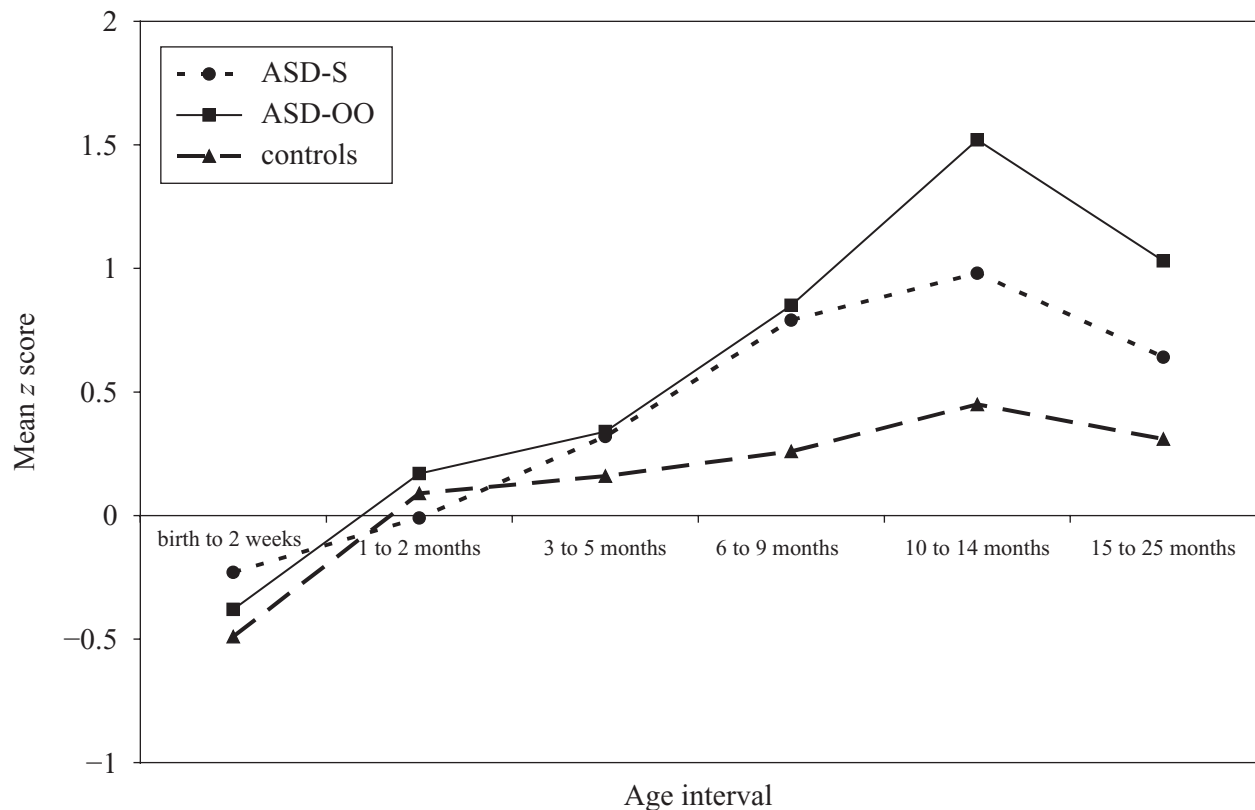


Figure 1. Mean head circumference z scores for autism spectrum disorder-stable (ASD-S), autism spectrum disorder-optimal outcome (ASD-OO), and control groups.

head circumference z score differences between groups at 6 to 9 months, 10 to 14 months, and with a trend toward significance at 15 to 25 months ($P < .05$, $.01$, $.07$, respectively). Contrasts using a Bonferroni correction were performed and results showed that the ASD-OO group head circumference was significantly larger than controls at 10 to 14 months, with a trend toward significance at 15 to 25 months ($P = .01$, $.07$, respectively). Mean head circumference in the ASD-S group did not differ significantly from controls nor from the ASD-OO group at any age interval and was intermediate between the 2 other groups (Figure 1). Results from ANOVAs showed that mean length differed significantly between groups at 10 to 14 months, with a trend toward significance at 15 to 25 months ($P = .01$, $.06$, respectively). Contrasts using a Bonferroni correction showed that mean lengths in the ASD-S group were significantly larger than controls at 10 to 14 months, with a trend toward significance at 15 to 25 months ($P = .01$, $P = .08$, respectively). Mean length in the ASD-OO group did not differ significantly from controls nor from the ASD-S group at any age interval. Groups did not differ with respect to mean weight at any of the age intervals.

Mean Differences Between ASD-S, ASD-OO, and Centers for Disease Control and Prevention Normative Data

Mean head circumference, length, and weight differences between autism spectrum disorder groups and Centers for Disease Control and Prevention normative data were more pronounced than those differences obtained between autism spectrum disorder groups and the local control group. The ASD-S group had significantly larger mean head circumference z scores beginning at 6 to 9 months ($P = .002$, $.003$, $.02$, respectively), significantly larger mean length z scores at every age interval ($P = .02$, $.03$, $.001$, $<.001$, $<.001$, $<.001$, respectively), and significantly larger mean weight z scores from birth through 6 to 9 months ($P = .03$, $.02$, $.02$, respectively) compared with Centers for Disease Control and Prevention norms. The ASD-OO group also showed significantly larger mean head circumference z scores than Centers for Disease Control and Prevention normative data beginning at 6 to 9 months ($P = .005$, $<.001$, $.001$), significantly larger mean length z scores at every age interval ($P = .01$, $.08$, $.008$, $.05$, $.003$), and did not differ significantly from Centers for

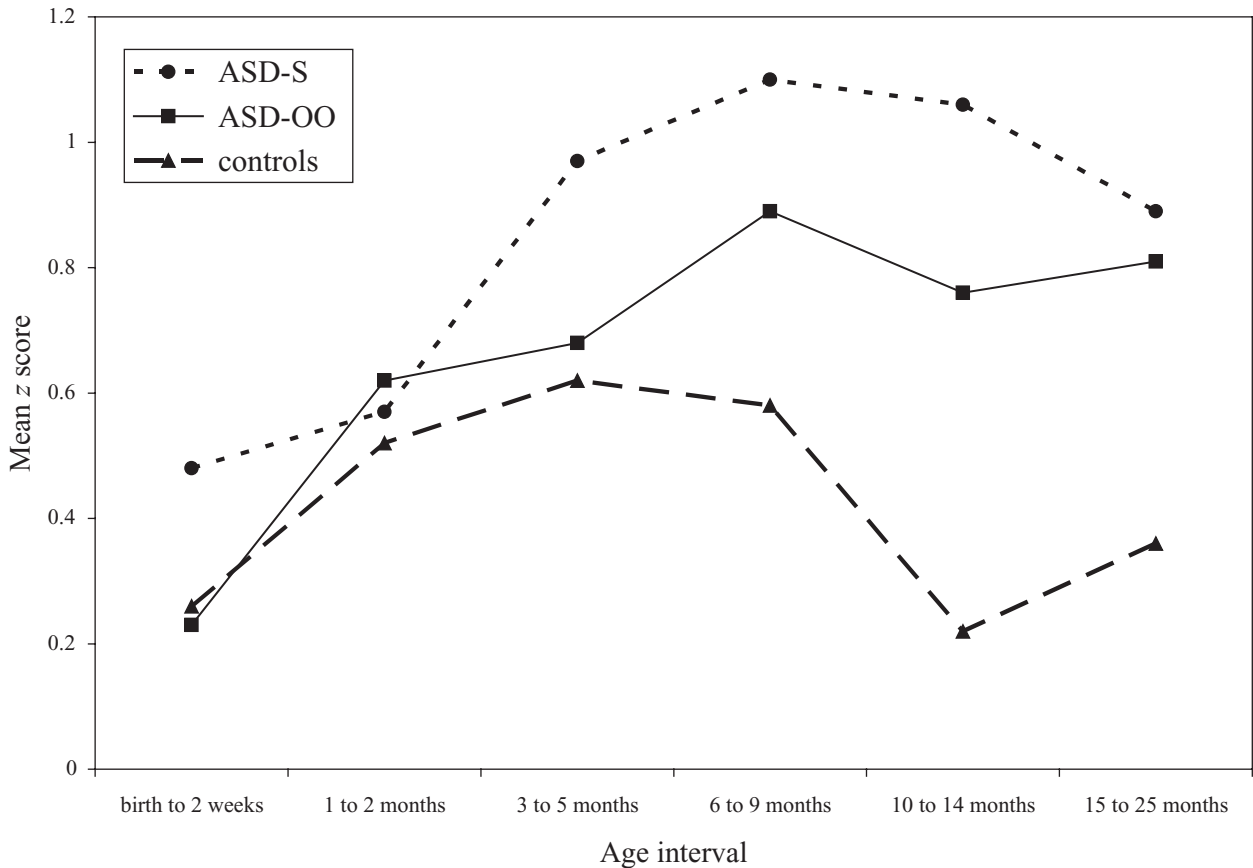


Figure 2. Mean length z scores for autism spectrum disorder-stable (ASD-S), autism spectrum disorder-optimal outcome (ASD-OO), and control groups.

Disease Control and Prevention norms with respect to mean weight z scores at any age interval.

Mean Differences Between Local Controls and Centers for Disease Control and Prevention Normative Data

With respect to mean differences between the local control group and Centers for Disease Control and Prevention norms, 1 sample *t* tests showed that the local control group showed a significantly smaller mean head circumference at birth to 2 weeks ($P = .01$) and a significantly larger head circumference beginning at 10 to 14 months ($P = .01, .05$, respectively). Mean length z scores were significantly greater than Centers for Disease Control and Prevention norms from 1 to 2 months through 6 to 9 months ($P = .003, .002, .001$, respectively), and again at 15 to 25 months ($P = .02$). Mean weight z scores for the control group were significantly larger than Centers for Disease Control and Prevention norms from 1 to 2 months through 3 to 5 months ($P = .002, .02$, respectively).

Growth Curve Modeling

Longitudinal growth curve modeling was used to construct a best fit growth curve for individuals in the ASD-S, ASD-OO, and control groups based on the raw head circumference, length, and weight measurements. This allowed for comparison among groups of (a) head and body measurements at birth (intercept), (b) the rate of head and body growth during the first 2 years of life (slope), and (c) the rate at which head and body growth slowed over time (quadratic).

Results showed that there were no significant differences in birth head circumference between the 3 groups. However, the rate of head circumference growth was greater in both the ASD-S and ASD-OO groups compared with local controls (coefficient [*B*] = .08, SE = .03, $t = 2.41$, $P = .02$; $B = .13$, SE = .04, $t = 3.26$, $P = .001$, respectively), whereas the rate of head circumference growth was not significantly different between the ASD-S and the ASD-OO groups. In addition, the rate of head circumference growth in both the ASD-S group and the ASD-OO group decelerated more rapidly over time

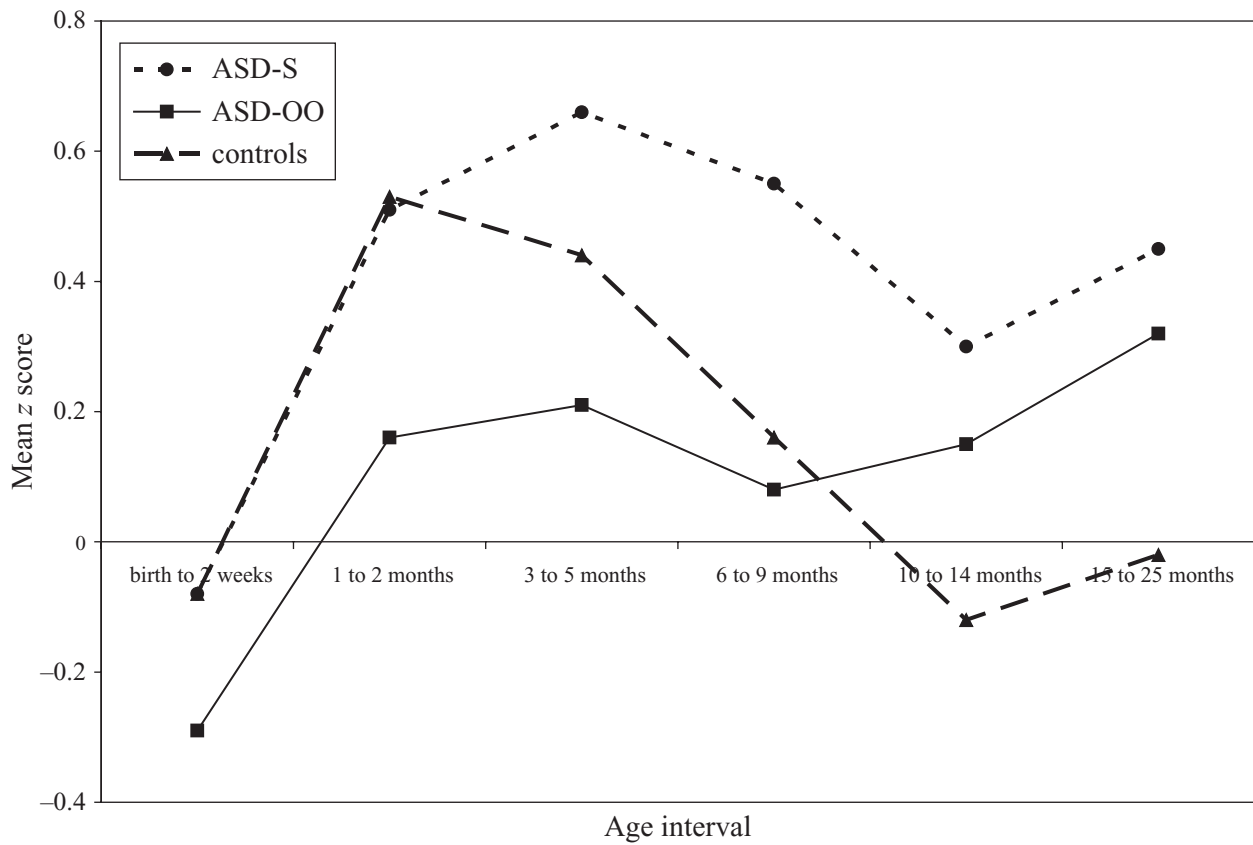


Figure 3. Mean weight z scores for autism spectrum disorder-stable (ASD-S), autism spectrum disorder-optimal outcome (ASD-OO), and control groups.

compared with local controls ($B = -.002$, $SE = .001$, $t = -2.05$, $P = .04$; $B = -.003$, $SE = .001$, $t = -2.48$, $P = .01$, respectively). This decrease in the rate of head growth over time was not significantly different between the ASD-S and the ASD-OO groups.

With respect to length, there were no significant differences in birth length between groups. The rate of length growth in the ASD-S group was significantly greater than local controls ($B = .31$, $SE = .09$, $t = 3.61$, $P = .0003$); the ASD-OO group showed intermediate values and did not differ significantly from either of the other groups. In addition, results showed that the rate of length increase in the ASD-S group slowed more rapidly than controls ($B = -.009$, $SE = .003$, $t = -2.96$, $P = .003$), whereas there were no significant differences with respect to slowing of length increase between the ASD-S and the ASD-OO groups nor between the ASD-OO group and controls.

With respect to weight, there were no significant differences in birth weight between groups. The rate of weight increase was significantly greater in both the ASD-S and ASD-OO groups compared with controls ($B = .08$, $SE = .03$, $t = 2.41$, $P = .02$; $B = .13$, $SE = .04$, $t = 3.26$,

$P = .001$, respectively), whereas the autism spectrum disorder groups did not differ significantly from each other. Last, the rate of weight increase slowed more rapidly in both the ASD-S group and the ASD-OO group compared with controls ($B = -.002$, $SE = .001$, $t = -2.05$, $P = .04$; $B = -.003$, $SE = .001$, $t = -2.48$, $P = .01$, respectively), whereas autism spectrum disorder groups did not differ significantly from each other.

Due to the fact that body size has been shown to have a confounding effect on head circumference,⁶⁴ such that individuals with larger bodies tend to have larger heads,⁶⁵ length and weight, both separately and together, were controlled for to determine the resulting effect on head circumference growth parameters for the ASD-S, ASD-OO, and control groups. Results for controlling length alone, weight alone, and length and weight together were identical, and therefore only those controlling for length and weight together will be reported below. After controlling for both length and weight, birth head circumference between groups was not significantly different. In addition, change in head circumference growth continued to be significantly greater in the ASD-OO group compared with both the control group ($B = -.10$, $SE = .04$,

$t = -2.66, P = .008$) and the ASD-S group ($B = -.09, SE = .04, t = -2.20, P = .03$). However, the rate of head circumference growth in the ASD-S group was no longer significantly different from the control group after length and weight were accounted for. With respect to the rate at which head circumference growth decelerated, the rate of head circumference growth in the ASD-OO group slowed more rapidly over time compared with both the ASD-S group ($B = .003, SE = .001, t = 1.96, P = .05$) and controls ($B = .003, SE = .001, t = 2.57, P = .01$). The rate at which head circumference growth slowed did not differ significantly between the ASD-S group and controls.

Growth curve modeling was also used to make comparisons between the autism spectrum disorder subtypes (autistic disorder versus pervasive developmental disorder—not otherwise specified) with respect to the aforementioned growth curve parameters. These comparisons were made in the ASD-S group only, and the child's second evaluation diagnosis was used because it has been shown to be more stable as compared with diagnosis at age 2.⁶⁶ Results showed that there were no differences between autistic disorder, pervasive developmental disorder—not otherwise specified, and control groups with respect to birth head circumference, rate of head circumference growth, or rate of growth slowing. For length, both the autistic disorder and pervasive developmental disorder—not otherwise specified groups showed a greater rate of length increase compared with controls ($B = .26, SE = .09, t = 2.89, P = .005$; $B = .28, SE = .14, t = 2.0, P = .04$, respectively), and the autistic disorder group had a rate of length increase which slowed more rapidly over time ($B = -.007, SE = .003, t = -2.33, P = .02$), whereas the pervasive developmental disorder—not otherwise specified group showed a trend for the same slowing of length increase ($B = -.009, SE = .005, t = -1.8, P = .06$). However, the autistic disorder and pervasive developmental disorder—not otherwise specified groups were not significantly different from one another based on birth length, rate of length increase, or rate of slowing of length increase. For weight, the autistic disorder group showed a greater rate of weight increase compared with controls ($B = .11, SE = .03, t = 3.67, P = .0001$) and a trend for a greater rate of increase compared with the pervasive developmental disorder—not otherwise specified group ($B = .07, SE = .05, t = 1.4, P = .11$). The rate of weight increase in the autistic disorder group also slowed more rapidly compared with both controls and the pervasive developmental disorder—not otherwise specified group ($B = -.003, SE = .0008, t = -3.75, P < .0001$; $B = -.003, SE = .001, t = -3.0, P = .05$, respectively). However, there were no weight differences between the pervasive developmental disorder—not otherwise specified group and controls for birth weight, rate of weight increase, and rate of slowing of weight increase.

Discussion

Findings for the ASD-S Group

The current study replicated previous findings demonstrating accelerated head growth during infancy in autism spectrum disorder^{8,20,33,34,36,37} in a sample of children who maintained their autism spectrum disorder diagnoses over time compared with a control group of typically developing children. The ASD-S group showed an accelerated rate of head circumference growth from birth to 2 years, which decelerated over time, compared with local controls. The ASD-S group also showed an increased rate of both length and weight growth, whose acceleration also slowed at an increasing rate over time compared with local controls. Mean length z scores were significantly larger than controls at 10 to 14 months, with a trend toward significance at 15 to 25 months. Mean weight z scores did not differ significantly from controls at any age interval.

Because body size has a confounding effect on head size,⁶⁴ differences in length and weight were controlled for to determine whether differences in head circumference still persisted between the ASD-S and control groups. Findings demonstrate that when length and weight differences are accounted for in children who maintain their autism spectrum disorder diagnoses over time, their rate of head growth during infancy is not significantly different from that of controls.

Findings for the ASD-OO Group

Results from the current study do not support the prediction that children who lose their autism spectrum disorder diagnoses would show less acceleration of head and/or body growth over time or in other words, more normal growth parameters, compared with children who maintain their diagnoses. The ASD-OO group showed accelerated head circumference and weight growth compared with local controls, which slowed at an increasing rate over time, and these rates were not significantly different from those of the ASD-S group. Mean head circumference z scores in the ASD-OO group were also significantly greater than controls. In addition, length growth in the ASD-OO group was not significantly different from that of the ASD-S group. Mean head circumference, length, and weight z scores were not significantly different between ASD-S and ASD-OO groups at any of the age intervals.

The most striking difference, however, between the ASD-S and ASD-OO groups was the fact that after length and weight differences were controlled for using growth curve modeling, the ASD-OO group continued to show accelerated head circumference growth compared with both controls and the ASD-S group. Thus, there may be

subtle differences in length and weight growth between children who maintain their autism spectrum disorder diagnoses and those who lose their diagnoses, although the small sample size of the ASD-OO group necessitates replication with a larger sample. In addition, results from bivariate correlations show that the ASD-OO and control group's raw length and weight measurements were highly correlated with each other at every age interval, whereas the ASD-S group's raw length and weight measurements were moderately correlated from birth to 5 months and then from 15 to 25 months, only. In addition, with respect to the subtypes of autism spectrum disorder, children diagnosed with autistic disorder at their second evaluations showed a trend for a greater rate of weight increase, with this rate of weight increase slowing more rapidly, but not a greater rate of head circumference or length increase, compared with both children diagnosed with pervasive developmental disorder—not otherwise specified and controls. There were no other significant differences between autism spectrum disorder subtypes.

It seems that general body growth might be more aberrant in children who maintain their autism spectrum disorder diagnoses, and that head overgrowth might be a byproduct of this general body overgrowth. It might also be that length and weight growth during infancy in children later diagnosed with an autism spectrum disorder, and possibly more so with autistic disorder, is more variable and sporadic, whereas length and weight growth in typical children and children who lose their autism spectrum disorder diagnoses over time might be more coordinated. It also may be the case that children who lose their autism spectrum disorder diagnosis show accelerated head growth in excess of length and weight growth, and that this growth might be adaptive as opposed to detrimental, serving as a compensatory or protective mechanism in response to some abnormality during gestation or early infancy. Previous findings that show a positive correlation between head circumference acceleration and adaptive functioning lend support to the notion that head circumference acceleration during infancy in autism spectrum disorder might sometimes serve a compensatory function.⁸ Clearly, given the relatively small sample size in the current study, these findings need to be replicated with a larger sample.

Limitations and Future Directions

One limitation of the current study was the fact that our local Connecticut control group had mean head circumferences, lengths, and weights, which were significantly different from national normative data at several age intervals. The control group showed a smaller mean head circumference at birth to 2 weeks and then a larger mean head circumference beginning at 10 to 14 months. Mean lengths were greater than national normative data for

almost every age interval, whereas mean weights were greater from 1 to 2 months through 3 to 5 months. Some researchers have questioned the accuracy of Centers for Disease Control and Prevention Data normative data, suggesting that there is a trend for infants to be larger today compared with 7 years ago when national norms were collected.⁶⁷ In addition, our control group was composed of only 37 children. Therefore, it is possible that some of these differences obtained between control group data and normative data would have disappeared, given a larger control group sample size or updated Centers for Disease Control and Prevention norms. Another limitation of the current study is the fact that nutritional factors, such as whether an infant was breastfed, were not taken into account in any of the groups. Breastfed babies have been shown to follow a different growth trajectory, particularly with respect to head circumference and weight growth.⁶⁸ Thus, it is possible that the groups were differentially breastfed due to factors such as fussiness and so on and that this affected head circumference, length, and weight growth differences between groups.

A further limitation of this study was the difference in gender composition between the local control group and both autism spectrum disorder groups. Because autism spectrum disorder is more prevalent in males (approximately a 4:1 ratio), our autism spectrum disorder samples were predominately male, whereas our control sample had an approximately equal number of males and females. This difference confounded the interpretation of raw measurement mean differences between groups due to the fact that one would expect males to demonstrate larger head circumferences, lengths, and weights at every age interval during infancy, as evidenced by Centers for Disease Control and Prevention normative data. Raw measurement differences would therefore be expected to be an overestimate of true differences. Due to this fact, raw means were normalized across age and gender by converting to z scores based on the Centers for Disease Control and Prevention norms, and these z scores were then used in the ANOVAs. Future studies would benefit from matching the control sample and autism spectrum disorder samples for gender composition, which would eliminate the need to use Centers for Disease Control and Prevention normative data for autism spectrum disorder and control group comparisons. Longitudinal growth curve analyses also used raw measurements. However, one would expect gender composition differences between groups to have an effect only on the intercept value and not on the rate of change due to the fact that although birth measurements are larger in males, the rate of growth is similar for both genders. This did not appear to be an issue due to the fact that there were no significant intercept or birth measurement differences between groups.

An additional limitation of this study was the small size of the ASD-OO sample, mainly due to the fact that only a

very small percentage of children lose their autism spectrum disorder diagnoses over time. A larger ASD-OO sample would have allowed for further analyses with respect to head circumference, length, and weight differences between the children who received an initial diagnosis of autistic disorder and those who received an initial diagnosis of pervasive developmental disorder—not otherwise specified. Future studies would benefit from comparing subtype differences with respect to head circumference, length, and weight growth between children who maintain their autism spectrum disorder diagnoses and those who are initially diagnosed with autistic disorder or pervasive developmental disorder—not otherwise specified and then lose this diagnosis.

A final limitation of this study was the fact that the parental head circumference was not measured and controlled for in the analyses. It has been shown that up to 50% of the normal variation in head size is familial,⁶⁹ and that one of the best predictors of head circumference in individuals with an autism spectrum disorder is average parental head circumference.⁴⁰ Future studies would also benefit from controlling for autism spectrum disorder prevalence among siblings due to the fact that genetic loading for head circumference, length, and weight in multiplex cases (in which multiple individuals are affected within a family) would be expected to be greater compared with sporadic cases (in which 1 individual is affected within a family and there is no family history of an autism spectrum disorder).

Findings from this study support the notion that accelerated length and weight growth during infancy could be used as a physical risk marker for autism spectrum disorder in addition to accelerated head growth.²⁰ However, this necessitates that physicians be knowledgeable about a variety of disorders that may present as head and/or body overgrowth (eg, Sotos syndrome, Simpson-Golabi-Behmel, hydrocephaly, Canavan disease, neurofibromatosis, Cowden syndrome), but which are capable of being distinguished from autism spectrum disorder based on the clinical characteristics. It will be important for future studies to replicate our findings of accelerated head growth in the absence of concurrent body growth in children who “recover” from autism spectrum disorder, with the goal of elucidating whether there are 2 different mechanisms by which head and/or body overgrowth occurs in children who lose their autism spectrum disorder diagnoses compared with children who maintain their autism spectrum disorder diagnoses. It will also be important to determine at what age during infancy slowing of head circumference begins to take place in autism spectrum disorder, and whether there might exist some underlying cause or clinical manifestations associated with this decelerating rate of head growth. In addition, we question whether the timing of the deceleration of head growth might be important with respect to intervention. For

example, it may be the case that children, who receive some type of intervention prior to this point when head circumference growth appears to decelerate, are more responsive to the effects of intervention. If head circumference acceleration is in fact adaptive or compensatory,⁸ and children with an autism spectrum disorder do experience a compressed timetable for creating or eliminating synapses,²⁰ it is possible that providing intervention during this abbreviated window of time, before deceleration begins, might alter a child’s growth trajectory and potentially delay head growth deceleration.

Results from the current study do not provide clear evidence for a specific head circumference, length, and/or weight growth trajectory that would make a child more likely to lose an autism spectrum disorder diagnosis or potentially more responsive to the effects of early intervention. Further investigation of differences in head and body growth, specifically as they relate to improvements in functioning, would aid in the earlier detection of autism spectrum disorder, a better understanding of its etiology and developmental course, and most importantly might enable us to maximize the effects of early intervention.

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