Skeletal Growth Dysregulation in Australian Male Infants and
Toddlers with Autism Spectrum Disorder

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Abstract

Recent findings suggest that children with Autism Spectrum Disorder (ASD) are larger in size for head circumference (HC), height, and weight compared to typically developing (TD) children; however, little is known about their rate of growth, especially in height and weight. The current study aimed to: 1. confirm and extend upon previous findings of early generalized overgrowth in ASD; and 2. determine if there were any differences in the rate of growth between infants and toddlers with ASD compared to their TD peers. Measurements of HC, height, and weight were available for 135 boys with ASD and 74 TD boys, from birth through 3 years of age. Size and growth rate in HC, height, and weight were analyzed using a linear mixed-effects model. Infants with ASD were significantly smaller in size at birth for HC, body length, and weight compared to TD infants (all $p < 0.05$); however, they grew at a significantly faster rate in HC and height in comparison to the TD children ($p < 0.001$); there was no significant difference between the groups in growth rate for weight ($p > 0.05$). The results confirmed that male infants and toddlers with ASD exhibit skeletal growth dysregulation early in life.

Keywords:

Autism Spectrum Disorder
Body size
Growth
Infant
Child
Head circumference
Body height

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Lay Summary

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Recent findings suggest that infants with Autism Spectrum Disorder (ASD) are smaller in size at birth compared to typically developing infants, but grow larger than their peers during the first year. Little is known about their rate of growth, especially for height and weight. Our findings confirmed that infants with ASD are smaller in size at birth for head circumference (HC), height, and weight, but grow at a faster rate in HC and height than their peers from birth to 3 years.

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Introduction

Autism Spectrum Disorder (ASD) manifests in infancy and early childhood, with deficits in social communication and a repertoire of restricted interests and repetitive behaviors becoming more prevalent with age (American Psychiatric Association, 2013). While the underlying causes remain unclear, there is little doubt that ASD is biological in origin with a strong genetic component (Chapman et al., 2015; Jeste & Geschwind, 2014; Robinson et al., 2016) and increasing evidence suggests the presence of biological subtypes within the spectrum (Chawarska et al., 2011). ASD occurs in 1 in 68 children, and affects more boys (1 in 42) than girls (Centers for Disease Control and Prevention, 2016). These odds increase with a family history of an ASD (The Autism Genome Project Consortium, 2007), and traits of ASD are increased amongst first degree family members of multiplex families (more than one family member diagnosed with ASD) compared to simplex (one family member diagnosed with ASD) families (Gerds et al., 2013).

To further understand the biological underpinnings of ASD, researchers have studied the physical growth trajectories of children with ASD. A meta-analysis of studies of head circumference and brain size in ASD provided evidence of brain overgrowth in ASD in early childhood (Sacco et al., 2015), which has since been corroborated by more recent studies (Albores-Gallo et al., 2017; Hazlett et al., 2017; Libero et al., 2016). Similarly, a review of overall growth in ASD by Green et al. (2015) found that the majority of studies provide converging evidence of an increase in brain size, head size, body length, and weight in children with ASD compared to typically developing (TD) children. Although this increase in growth is evident at a young age, there are conflicting results regarding the exact point in development at which these differences become apparent, and very little is known about the rate of growth in height and weight (Green et al., 2015).

Compared to TD infants, head and brain size in infants with ASD is either similar (Chawarska et al., 2011; Fukumoto et al., 2008; Gillberg, 2002; Webb et al., 2007; Whitehouse et al., 2011) or slightly smaller (Courchesne et al., 2003; Dissanayake et al., 2006; Mraz et al., 2007b) at birth. Head and brain growth in infants with ASD accelerates abnormally within the first year of life (Chawarska et al., 2011; Courchesne et al., 2003; Dawson et al., 2006; Dissanayake et al., 2006; Fukumoto et al., 2008; Gillberg, 2002; Hazlett et al., 2017; Lainhart et al., 2006; Mills et al., 2007; Mraz et al., 2007b; Rommelse et al., 2011; Webb et al., 2007), and then begins to decelerate sometime between 1-5 years of age (Courchesne et al., 2001; Dawson et al., 2006; Lainhart et al., 2006; Redcay & Courchesne, 2005; Rommelse et al., 2011). Fewer studies have been conducted on height; however, it appears that for children with ASD, growth in height follows a similar trajectory to that of HC. Several studies have found increased height in infants with ASD compared to TD infants, although the exact age at which a difference becomes apparent is unclear, and varies anywhere from 1-2 months of age to 4-7 months of age (Chawarska et al., 2011; Fukumoto et al., 2008; Idring et al., 2014; Mraz et al., 2009; Mraz et al., 2007b; Surén et al., 2013; Torrey et al., 2004; van Daalen et al., 2007; Webb et al., 2007). This finding is consistent both in individuals who retain a diagnosis of an ASD, and those who move off the spectrum (Mraz et al., 2009). The rate of growth in height appears to be accelerated as well, especially between 2-3 years of age (Dissanayake et al., 2006).

Although most studies have reported increased HC and height in infants and toddlers with ASD compared to those who are TD, several studies have found no difference in growth in HC or height between the two groups (Barnard-Brak et al., 2011; Dinstein et al., 2017; Mraz et al., 2009; Riikonen et al., 2006; van Daalen et al., 2007; Vanhala et al., 2001; Zwaigenbaum et al., 2014). A large longitudinal study of growth in infants and toddlers aged 1-3 years examined measurements of HC and height in high-risk siblings (i.e., children with a

sibling with ASD) as well as TD infants from the community, and infants with a developmental delay (Zwaigenbaum et al., 2014). They found no differences in growth in HC or height between high-risk siblings who later received a diagnosis of ASD compared to those who did not. Although they found no overall differences in growth in HC or height between the high-risk and low-risk groups, head growth was moderately increased in the high-risk groups compared to the low-risk groups in secondary analyses.

A study of pre-natal measurements of head and body growth found no difference between the high-risk and low-risk groups (Unwin et al., 2016). While HC or height did not serve as a potential biomarker in this sample, the authors discussed the importance of viewing the findings within the context of potentially different etiologies in multiplex compared to simplex families. With the exception of studies that aim to explore differences in high-risk or multiplex groups compared to low-risk or simplex groups, authors rarely report the percentage of participants in their ASD groups that come from multiplex families, and it is assumed that these ASD groups comprise a mixture of both multiplex and simplex cases of ASD. Direct comparison is therefore difficult, as the results from multiplex families are not necessarily generalizable to the entire spectrum of ASD.

In van Daalen et al.'s (2007) sample, while no differences in HC were found between infants with ASD compared to normative data, or between their TD group and normative data, they did find increases in height and weight in their ASD group compared to normative data. Mraz et al. (2009) found increased size and rate of head growth in infants with ASD; however, the difference in rate of growth was no longer significant after controlling for height and weight.

A recent study of 66 toddlers who were later diagnosed with ASD compared to matched controls found that while toddlers with ASD were significantly smaller in size for HC and weight at birth (height was not measured at birth), there were no significant

differences in size for HC, height, or weight from three months through three years of age (Dinstein et al., 2017). The authors pointed to methodological differences between their study and many previous studies which have found differences in size between toddlers with ASD compared to controls, namely the use of a local control group, and the potential confounds of including children with genetic syndromes and the changing diagnostic criteria.

Indeed, methodological differences between studies reporting no differences in growth in HC or height, compared to those that did, make direct comparisons difficult. For example, there were a limited number of participants with ASD in both Riikonen et al. (2006) and Vanhala et al.'s (2001) studies (25 and 11 children respectively), which included both males and females who were diagnosed, and both use outdated standards of diagnoses. In Barnard-Brak's (2011) sample, ASD diagnoses were confirmed by parent report only. Additionally, Vanhala et al. did not recruit TD participants, but instead reported that the HC of their ASD participants were within the normal limits. The use of control groups not representative of the general population is problematic in this field of research (Dinstein et al., 2017; Green et al., 2015). Local control groups of TD children often differ quite dramatically from normative data. Thus Raznahan et al. (2013) conducted a systematic review of HC growth in infants and toddlers with ASD, and found that early overgrowth of HC in ASD may be more subtle than previously thought, and concluded that growth dysregulation, rather than enlargement of HC, may be more relevant in ASD. However, given the heterogeneity of the autism spectrum, the issue of non-representative samples is unlikely to only be restricted to TD samples, but likely applies to ASD samples as well.

Perhaps the most obvious methodological issue to consider when summarising the findings of HC in infants and toddlers is measurement error. Unlike height and weight, HC measurements are arguably more prone to human error, especially in infants and toddlers, as

they involve the use of a soft, flexible measuring tape. Despite this, the majority of studies have reported similar findings for HC in infants and toddlers with ASD compared to TD.

Along with the possible increase in HC and stature, infants and toddlers with ASD may also have increased weight and body mass index (BMI) (Green et al., 2015). Again, it is unclear exactly when weight increases in infants with ASD compared to TD, with studies reporting differences emerging anywhere from 1-2 months of age to 11 months of age (Chawarska et al., 2011; Dissanayake et al., 2006; Fukumoto et al., 2008; Gillberg, 2002; Mills et al., 2007; Mraz et al., 2007b; Surén et al., 2013; Torrey et al., 2004; van Daalen et al., 2007; Xiong et al., 2009). It is important to note, however, that compared to HC and height, weight is not a measure of skeletal growth and is subject to external factors such as lifestyle and eating habits, and findings regarding weight should be considered within an environmental context.

Together, the findings suggest that physical overgrowth in ASD is not limited to brain and head growth, but also manifests in height and perhaps in weight, indicating a skeletal, and possible overall growth dysregulation. To date, very few studies have measured all of these growth parameters, and the majority of research has focused on small groups of children within a narrow range of the autism spectrum. Only one other study (Surén et al., 2013) has collected these measurements in a large sample of infants (n=310 boys and 66 girls) across the autism spectrum. Although there is increasing evidence that the heads and brains of infants and toddlers with ASD grow at a faster rate compared to TD infants and toddlers, very little is known about their rate of growth in height and weight. When investigating different types of growth measures, it is important to consider the growth mechanisms of each. To date, the term ‘generalized growth’ has been used to refer to one type of growth in particular: skeletal growth. To more accurately understand ‘growth’ in ASD, it is important to differentiate skeletal measures of growth, such as head circumference

measurements, from other types of growth such as weight or brain growth. An understanding of various growth patterns of infants with ASD will highlight the biological differences between children with ASD and their TD peers. These differences may provide insight into underlying biological mechanisms implicated in the development of ASD, and possible subgroups that may be characterized by different growth profiles.

In the current study, three growth parameters (HC, height, and weight) were available in a large sample of children across the entire autism spectrum. Our aim was to determine both differences in physical size as well as differences in the rate of physical growth between infants and toddlers with ASD compared to their TD peers. While studies have reported findings of “accelerated” growth in ASD, this term has been used to reflect a trend to increase in physical measures in individual age groups, and is almost always used in reference to head and brain measures, rather than height and weight. In addition to Dissanayake et al. (2006) and Dinstein et al. (2017), the current study is the only other study to date to examine the rate of growth across all three physical parameters of HC, height, and weight from birth to three years of age; it is also the only study to examine these growth parameters in a large representative group of participants with ASD during these early years.

Methods

Participants

Measurements of growth from birth through to 3 years of age were available for 209 boys (135 ASD, 74 TD) across two samples (Barbaro & Dissanayake, 2010; Green, 2012). Participants were recruited via advertisements, as well as from the Child Development Unit registry and the Olga Tennison Autism Research Centre (OTARC) registry as part of a longitudinal study (sample 1; Green, 2012) conducted at OTARC. Growth data for additional participants with ASD (n = 66) and TD (n = 52) were also available from a previous study (sample 2; Barbaro & Dissanayake, 2010). Ethics approval was obtained from the La Trobe

University Human Ethics Committee [Project Number (PN) 09-015], the Department of Education and Early Childhood Development (PN 2010_000635), and the Catholic Education Office: Archdiocese of Melbourne (PN GE11/0009;1721).

As participants were recruited before the release of either the Autism Diagnostic Observation Schedule - second edition (ADOS-2; Lord et al., 2012) and the Diagnostic and Statistical Manual for Mental Disorders - fifth edition (DSM-5; American Psychiatric Association, 2013), the Autism Diagnostic Observation Schedule - Generic (ADOS-G; Lord et al., 1999) and the Diagnostic and Statistical Manual for Mental Disorders - fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) guidelines and diagnostic criteria were used to assess ASD. Participants with ASD were administered the ADOS to confirm clinic-based diagnoses of ASD, and TD participants were required to have no known language, developmental, or cognitive delay. Typically developing siblings of children with ASD were excluded, as were any participants with medical conditions which could potentially affect growth, children who were born prematurely, and children who had a significant illness documented in their medical records ($n = 1$ TD and 7 ASD). To account for differences in growth due to ethnic origin, only Caucasian participants were included in the final analyses.

All participants resided within Victoria, Australia, mostly within the Melbourne metropolitan region. Participants with ASD across the samples ($n = 66$ in sample 1 and 69 in sample 2) and TD ($n = 22$ and 52) were similar in regards to education and socio-economic status. There were no differences according to ADOS classification of Autistic Disorder (AD) compared to ASD between the ASD groups in the two samples (Barbaro & Dissanayake, 2010; Green, 2012). Of the 135 boys with ASD, 71(53%) met the ASD cut-off on the ADOS and 64 (47%) met the AD cut-off. Estimates of cognitive functioning were

available for 130 boys with ASD; 74 (57%) boys (39 with AD and 35 with ASD) had IQ $\geq$ 70, and 56 (43%) boys (32 with AD and 24 with ASD) had IQ < 70 .

Materials and Procedure

Physical measures. Head circumference, body length/height, and weight were available from each participant's Child Health Record. These measurements are made and recorded for every Victorian child during regular visits to their local Maternal and Child Health (MCH) Centres from birth through approximately three and a half years of age. The measurements are obtained in a uniform fashion across MCH Centres by trained MCH nurses. Body length/height (crown-heel length) is measured using a reclining measuring board until two years of age, after which a free-standing anthropometer is used. Head (occipitofrontal) circumference is measured by wrapping a paper measuring tape around the widest part of the head, from the most prominent part of the forehead to the widest part of the back of the head. Weight is measured using standard scales.

Behavioral assessment. All participants with ASD were administered the ADOS (Lord et al., 1999) which is a semi-structured standardized assessment designed to highlight deficits in the specific areas associated with ASD: social interactions, communication, and stereotyped and restricted interests and behaviors. The activities vary across modules which are both development and age specific: Module 1 assesses the abilities of pre-verbal children; Module 2 assesses the abilities of children with phrase speech; Module 3 assesses the abilities of children and adolescents with fluent speech; and Module 4 assesses older adolescents and adults with fluent speech. Each module provides a diagnostic algorithm to allow individuals to be classified as having either AD or ASD (including PDD-NOS). The administrators of the ADOS were all research reliable ($> 80\%$) in administration and coding.

Statistical procedure. Size at birth and growth rate in HC, height, and weight were analysed using a linear mixed-effects model (LMEM; Laird & Ware, 1982), employing the same

method as Dissanayake et al. (2006). Typically, for longitudinal data a repeated measures ANOVA or ANCOVA is used; however, with retrospective growth data, data points are rarely spaced at fixed intervals in time, and each participant is likely to have a different number of data points available. This was the case in the current study, where multiple measurements from infants and toddlers were not always taken at regular intervals. To account for irregularly spaced data points, a LMEM is best suited, and was therefore used in the current study.

A LMEM (Laird & Ware, 1982) is flexible and can accommodate unbalanced longitudinal data by approximating the mean function of longitudinal data using linear or nonlinear functions. This model consists of a random effects component and an overall fixed effects component. The random effects component takes into account how each individual participant deviates from the average, while the fixed effects component contains details about the overall sample. It also takes into account the correlation between observations within individuals. Infants and toddlers initially grow at a rapid rate before 3 years of age, at which time the rate of growth steadily decreases. Applying a transformation of age simplifies the relationship between each growth variable and age, resulting in a linear relationship. For example, in Fig 1, height (cm) versus age (weeks) was plotted for children under 3 years of age (TD group in red, ASD group in green). Fig 1 (A) shows that the rate of growth is nonlinear in relation to age for the first year of life and then almost linear thereafter. When age was transformed using a square root function and plotted against height in Fig 1 (B), this relationship becomes linear across all ages. Formally, the model takes the form: $Y = \alpha + \beta_{age}Age^{\lambda} + \beta_{ASD}ASD + \beta_{int}Age^{\lambda} \times ASD$, where Y represents height, weight or head circumference; variable ASD has a value of 1 for ASD boys and 0 for TD boys. That is, for TD the model is $Y = \alpha + \beta_{age}Age^{\lambda}$, while for ASD the model is $Y = (\alpha + \beta_{ASD}) + (\beta_{age} + \beta_{int})Age^{\lambda}$, and thus the difference in average growth rate between TD and ASD is the

interaction parameter β_{int} . A value between 0 and 1 was selected for parameter λ for each outcome variable using both Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) to find best fitted model. In our application, the minimum value of AIC and BIC was found when $\lambda = 0.5$ (square root function) for height and weight and $\lambda = 0.2$ for head circumference. The models were fitted using the nlme package (Pinheiro et al., 2011) within the publicly available R software (R Development Core Team, 2011).

[Insert Figure 1]

Figure 1 Title: Rate of Growth in Height.

Figure 1 Caption: Scatter plot of height against A) untransformed age (in weeks), showing that the rate of growth is nonlinear for the first year of life and then almost linear thereafter; B) the square root of age, which show a linear relationship. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

Size at birth and overall growth rate were compared between the boys with ASD and those with TD. Comparisons of size at specific ages (i.e., 6 months, 12 months, etc.) was not possible because each child was measured at slightly varying points in time and many children did not attend their 3 year check-up, which limited the amount of data available at this age.

Results

Preliminary Analyses

The size at birth and overall growth rates of the TD children between sample 1 (Green, 2012) and sample 2 (Barbaro & Dissanayake, 2010) were compared using a LMEM. There were no significant differences between these TD samples in height ($p = .805$), weight

($p = .248$), or HC ($p = .390$) at birth. Likewise, as there were no significant differences in rate of growth from birth through 3 years of age for height ($p = 0.120$), weight ($p = 0.660$), or HC ($p = 0.548$), the TD groups were combined for further analyses.

Before comparing the ASD groups between sample 1 (Green, 2012) and sample 2 (Barbaro & Dissanayake, 2010), the participants with ASD were divided into AD and ASD groups according to ADOS cut-offs, and sizes and growth rates were compared to firstly ascertain if there were any differences between them. There were no significant differences in size or rate of growth between participants characterised as AD or ASD.

The participants with ASD from sample 1 and 2 were also compared for height, weight, and HC. No significant differences were found in size at birth for height ($p = .121$) or weight ($p = .151$) between boys with ASD from sample 1 and sample 2; however, boys with ASD from sample 2 had a significantly larger HC at birth ($p = .005$) compared to boys with ASD from sample 1. As there were no significant differences in rate of growth between the two ASD groups for height ($p = .403$), weight ($p = .277$) or HC ($p = .086$), these groups were combined for comparison with the TD participants.

Main Analyses

For the combined data, comparisons between boys with ASD and TD for size at birth and overall rate of growth from birth through to 3 years of age for HC, height, and weight are presented in Table 1. Scatter plots with fitted lines for the TD and ASD groups are shown for height in Fig 1 (A), HC in Fig 2, and weight in Fig 3. Participants with ASD were significantly smaller in size at birth for HC ($\alpha = -1.87, p < 0.0001$), height ($\alpha = -1.67, p < 0.0001$), and weight ($\alpha = -247, p = 0.032$) compared to TD participants. Significant differences were also found in growth rate across the whole age range for HC ($\beta = 0.659, p < 0.0001$) and height ($\beta = 0.216, p < 0.0001$), with the boys with ASD growing faster than the TD boys. However, there was no significant difference between the groups in growth rate for

336 weight ($\beta = 0.009, p = 0.726$). The results remained the same for growth rate for weight and
337 HC when adjusted for height. The distribution of growth parameters for the two groups of
338 boys was plotted in Fig 4, where the Kernel density estimation was plotted for each group
339 separately.

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Running head: GROWTH DYSREGULATION IN ASD

[Insert Table 1]

Table 1 Title: Comparison of Head Circumference, Height, and Weight between TD and ASD Boys using a Linear Mixed-Effects Model.

[Insert Figure 2]

Figure 2 Title: Rate of Growth in Head Circumference.

Figure 2 Caption: Scatter plot of HC against age in weeks. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

[Insert Figure 3]

Figure 3 Title: Rate of Growth in Weight.

Figure 3 Caption: Scatter plot of weight against age in weeks. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

[Insert Figure 4]

Figure 4 Title: Comparison of Growth Rate for Head Circumference, Height, and Weight between TD and ASD Boys using Kernel Density Estimation.

Figure 4 Caption: Distribution of growth rate, using Kernel density estimation, for head circumference (HC), weight and height (left panel), and adjusted for height (right panel). The TD group is depicted by a solid blue line, and the ASD group by a dashed red line.

Discussion

The current study confirmed past findings indicating that male infants and toddlers with ASD grow at a faster rate than their TD peers, from birth through to 3 years of age, and explored the extent to which this occurs across three measures of growth: HC, height and weight. Based on measurements collected on 135 boys with ASD compared to 74 TD boys, infants with ASD were smaller at birth in HC, height, and weight compared to TD infants. However, the infants and toddlers with ASD had increased rates of growth in HC and height compared to the TD infants and toddlers from birth to 3 years of age. In contrast, the groups had similar rates of growth in weight. Thus, differences in growth rate between the groups were only found for measures of skeletal growth; despite being smaller at birth, male infants with ASD proceeded to grow at a faster rate throughout infancy and toddlerhood compared to TD infants and toddlers.

Similar to previous studies (Courchesne et al., 2003; Dissanayake et al., 2006; Mraz et al., 2007b), the current study found that head size at birth was smaller in infants with ASD compared to TD infants. Our findings of increased growth rates in stature and HC in infants and toddlers with ASD corroborate with those from ASD populations from the United States (Chawarska et al., 2011; Courchesne et al., 2003; Dawson et al., 2006; Hazlett et al., 2017; Lainhart et al., 2006; Libero et al., 2016; Mills et al., 2007; Mraz et al., 2009; Mraz et al., 2007a; Webb et al., 2007), Italy (Sacco et al., 2015), Japan (Fukumoto et al., 2008), Mexico (Albores-Gallo et al., 2017), Sweden (Gillberg, 2002), Norway (Surén et al., 2013), and the Netherlands (Rommelse et al., 2011; van Daalen et al., 2007), as well as from a previous Australian cohort (Dissanayake et al., 2006), and support the hypothesis of growth dysregulation in ASD during the first three years of life. However, there are limitations that should be considered when interpreting these findings.

Firstly, although growth in stature is highly heritable, it may also be susceptible to a range of confounding factors (Chaste et al., 2013). Although we excluded participants who were born prematurely as well as those who had known medical conditions (e.g., fragile X syndrome) or were taking medications that may have affected growth, it is possible that children with undetected genetic syndromes that have an impact on growth may have been included in our sample. Single-gene mutations, resulting in “syndromic” ASD, are often associated with dysmorphic features (Persico & Bourgeron, 2006). A subset of these single-gene mutations have been associated with increases in head size, height, and/or weight, such as mutations in *PTEN* (Butler et al., 2005). Other single-gene mutations have been associated with decreases in growth, as seen in a *de novo* mutation *DYRK1A* which was associated with microcephaly and ID in individuals with ASD (van Bon et al., 2016). However, a recent study of the impact of *de novo* protein-truncating variants in ASD suggests that the percentage of ASD cases with *de novo* mutations that contribute to the ASD phenotype may be smaller than previously thought, at approximately 6.55% of ASD cases (Kosmicki et al., 2017). While these genetic variants are important to consider, given the small proportion of ASD cases they account for, they cannot account entirely for the overgrowth effects observed in ASD samples in this and previous studies. Likewise, we were not able to account for heritable variation. While it was difficult to collect the family data in our study that utilized growth measurements obtained from medical records, future studies should attempt to collect this information as well as a detailed developmental and medical history, to adjust for both heritable and non-heritable effects.

Secondly, there is evidence of potentially different genetic and environmental vulnerabilities in multiplex families compared to simplex families (Gerds et al., 2013); it is unknown what impact on physical development and growth these factors may have. As this

information was not available for all the participants in the study, we were unable to compare differences in growth between these two categories.

Lastly, our sample included only male infants and toddlers, where ASD is 3-4 times more prevalent than in females. To date, only one study (Surén et al., 2013) has comprehensively examined growth in infant girls with ASD (n=66). Girls with ASD had reduced head circumference and weight during the first year of life compared to their TD peers; however, these differences appeared to be driven by individuals with ID, genetic disorders, and epilepsy, and after adjusting for covariates, the differences between the groups largely disappeared. These findings need to be confirmed in future studies of ASD without comorbidities in order to hypothesize that the factors leading to growth dysregulation are sex-limited.

While the evidence for dysregulation of early growth in height and head and brain size in boys with ASD is strong and consistent between the present and the majority of earlier studies, the data on weight have been controversial. Some studies found increased weight in infants with ASD from as early as 1-3 months (Fukumoto et al., 2008; Mraz et al., 2007a; van Daalen et al., 2007), other studies have reported no differences in weight until 4- (Torrey et al., 2004), 6- (Surén et al., 2013), or 11 months of age (Chawarska et al., 2011), or not at all (Mraz et al., 2009), when compared to TD infants. Similar to Dinstein et al. (2017) the current study found that infants with ASD were lighter in weight at birth compared to TD infants; however, contrary to the earlier finding of Dissanayake et al. (2006), infants and toddlers with ASD in our study did not display an increased acceleration in weight from birth through 3 years of age relative to the TD infants.

One possible explanation for the inconsistent findings is the high variability in weight during these early years, which may be determined by factors not necessarily similar to those affecting stature or HC in both normal and abnormal conditions. Infants and young children

often become sick, have difficulties with sleeping, and sometimes have trouble feeding early on, all of which can easily disturb weight. Children whose records noted any substantial sickness, or any sickness or difficulty that could potentially affect their weight were removed from the current analyses ($n = 1$ TD and 7 ASD). However, it is possible that not all such instances had been covered accounted for in the analyses. Moreover, common weight fluctuations in infancy and toddlerhood might have contributed to a discrepancy between the present results and most of the earlier results, and also indicates that this measure is not a reliable indicator of overall growth during these periods.

A second explanation for inconsistent results across studies is the heterogeneity of the autism spectrum, as mentioned earlier. While TD samples are not necessarily representative of the population, it is just as likely, if not more, that ASD samples are not representative of the ASD population. This was evident in the current study, where the ASD groups from samples 1 and 2 had significantly different HC measures at birth, despite that they were from the same metropolitan region and were similar regarding diagnostic classification, socioeconomic status, and parental education.

Despite its limitations, the current study represents one of the largest longitudinal studies of growth in infants and toddlers with ASD conducted to date, with over 200 male participants and covering major growth parameters. Moreover, we recruited a local sample of TD participants, rather than using normative data from the Centers for Disease Control and Prevention (CDC). The fact that the current study found differences in the rate of growth in head size and height between contemporaneous samples provides further evidence for a legitimate growth dysregulation in ASD.

Another strength of the current study was that it included participants from across the autism spectrum, whereas many previous studies have relied on high-functioning individuals (Dissanayake et al., 2006). Although our findings as well as evidence from previous studies

suggest that there are no differences in growth between the separate diagnostic categories within ASD (Chawarska et al., 2011; Davis et al., 2013; Dissanayake et al., 2006; Surén et al., 2013; Webb et al., 2007), it is nevertheless important to not restrict samples more than necessary. It is possible that there may be more subtle differences in growth that vary across the spectrum, rather than by diagnostic cut-offs.

Future Directions

The findings from this study provide evidence that growth dysregulation may not be limited to head and brain growth in ASD, but affects stature as well. A potential mechanism of this growth dysregulation may include a dysregulation of the hypo-thalamo-pituitary (HPA) axis, which regulates the secretion of neuroendocrines, including growth hormones; therefore, a dysregulation of the HPA axis could potentially impact growth regulation.

Future studies should therefore explore mechanisms of growth regulation, including the HPA axis, to understand the underlying mechanisms of the overall growth dysregulation that is apparent in infancy and toddlerhood in ASD and extending into adolescence. Very few studies have investigated growth throughout older childhood and adolescence, a period where the effects of pubertal growth hormones in ASD, and thus any HPA axis dysregulation, should be most apparent. It is unclear whether the proposed growth dysregulation that occurs throughout infancy and toddlerhood persists into these later years. There is some evidence to suggest that a growth dysregulation may exist in older childhood and adolescence (Courchesne et al., 2011; Green, 2012; Mills et al., 2007; Redcay & Courchesne, 2005; Whitely et al., 2004).

It is also important to investigate the possibility of biologically distinct subgroups within ASD. Although previous findings indicate that there are no differences between the DSM-IV diagnostic categories within ASD (Chawarska et al., 2011; Davis et al., 2013; Dissanayake et al., 2006; Surén et al., 2013; Webb et al., 2007), there is recent evidence to

suggest that extreme overgrowth across multiple parameters is associated with increased ASD severity (Chawarska et al., 2011) and that overgrowth of the brain and head that is disproportionate to body size (megalencephaly) is also associated with increased ASD severity and disability (Amaral et al., 2017). Identifying phenotypes that are associated with specific biological, cognitive, or behavioural parameters is the first step to identifying distinct subgroups, or endophenotypes, within the autism spectrum.

Conclusion

There is increasing evidence from around the world that there is a general growth dysregulation in (male) infants and toddlers with ASD. An increased rate of growth in head and brain size has already been established as a consistent biomarker of ASD, and it is possible that an increased rate of growth in height may also serve as an additional biomarker of ASD in infants and toddlers. Further investigations of the rate of growth in ASD, particularly for height and weight, are needed to validate the current results and to provide more detailed knowledge of the physical growth trajectory of infants and toddlers across the autism spectrum. Future studies are also needed on growth in older childhood and adolescence which will assist in understanding the possible mechanisms of generalized growth dysregulation in ASD.

505

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 674

Table 1. Comparison of Head Circumference, Height, and Weight between TD and ASD Boys using a Linear Mixed-Effects Model.

		Size at Birth			Growth Rate Not Controlling for Height			Growth Rate Controlling for Height		
		<i>Coefficient (α)</i>			<i>Coefficient (β)</i>			<i>Coefficient (β)</i>		
		<i>S.E.</i>	<i>p</i>		<i>S.E.</i>	<i>p</i>		<i>S.E.</i>	<i>p</i>	
HC (cm)	TD	26.64	0.261	< 0.0001	9.163	0.123	< 0.0001	7.587	0.218	< 0.0001
	ASD	-1.867	0.328	< 0.0001	0.659	0.155	2.3 x 10 ⁻⁵	0.586	0.154	0.0001
Weight (kg)	TD	2.568	0.092	< 0.0001	1.069	0.020	< 0.0001	0.668	0.028	< 0.0001
	ASD	-0.247	0.115	0.0321	0.009	0.025	0.7256	0.007	0.021	0.7399
Height (cm)	TD	47.57	0.280	< 0.0001	4.058	0.043	< 0.0001	-	-	-
	ASD	-1.674	0.347	< 0.0001	0.216	0.053	5.0 x 10 ⁻⁵	-	-	-

Note. Coefficients for ASD for size at birth and growth rate were the difference between ASD and TD. The *p*-values for the TD group were for testing whether the size at birth and growth rate were significantly different from zero, whereas the *p*-values for ASD were testing the difference between ASD and TD.

Scatter plot of height against A) untransformed age (in weeks), showing that the rate of growth is nonlinear for the first year of life and then almost linear thereafter; B) the square root of age, which show a linear relationship. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

209x297mm (200 x 200 DPI)

Scatter plot of HC against age in weeks. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

209x297mm (200 x 200 DPI)

Scatter plot of weight against age in weeks. Each data point in the TD group is depicted by a red 'x', while the ASD group's data points are depicted by a green '+', with a fitted line for each group.

209x297mm (200 x 200 DPI)

Distribution of growth rate, using Kernel density estimation, for head circumference (HC), weight and height (left panel), and adjusted for height (right panel). The TD group is depicted by a solid blue line, and the ASD group by a dashed red line.

209x297mm (300 x 300 DPI)

Plot of velocity versus age – For Reviewer #1's first question (not for the paper).

Figure: Plot of height velocity versus age for ASD and TD boys.

Figure: Plot of height velocity versus age for ASD and TD boys up to 5 week.

Figure: Plot of height velocity versus age for ASD and TD boys between 5 and 52 weeks.

Figure: Plot of height velocity versus age for ASD and TD boys between 52 and 156 weeks.

Figure [for reviewer]: Lines plot of the height versus age for ASD boys.

Figure [for reviewer]: Lines plot of the head circumference versus age for ASD boys.

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