Early Growth Patterns in Children with Autism

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Background: Case-control studies have found increased head growth during the first year of life in children with autism spectrum disorder. Length and weight have not been as extensively studied, and there are few studies of population-based samples.

Methods: The study was conducted in a sample of 106,082 children from the population-based Norwegian Mother and Child Cohort. The children were born in 1999–2009; by the end of follow-up on 31 December 2012, the age range was 3.6 through 13.1 years (mean 7.4 years). Measures were obtained prospectively until age 12 months for head circumference and 36 months for length and weight. We compared growth trajectories in autism spectrum disorder cases and noncases using Reed first-order models.

Results: Subjects included 376 children (310 boys and 66 girls) with specialist-confirmed autism spectrum disorder. In boys with autism spectrum disorder, mean head growth was similar to that of other boys, but variability was greater, and 8.7% had macrocephaly (head circumference >97th cohort percentile) by 12 months of age. Autism spectrum disorder boys also had slightly increased body growth, with mean length 1.1 cm above and mean weight 300 g above the cohort mean for boys at age 12 months. Throughout the first year, the head circumference of girls with autism spectrum disorder was reduced—by 0.3 cm at birth and 0.5 cm at 12 months. Their mean length was similar to that of other girls, but their mean weight was 150–350 g below at all ages from birth to 3 years. The reductions in mean head circumference and weight in girls with autism spectrum disorder appear to be driven by those with intellectual disability, genetic disorders, and epilepsy.

Discussion: Growth trajectories in children with autism spectrum disorder diverge from those of other children and the differences are sex specific. Previous findings of increased mean head growth were not replicated.

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Longitudinal case-control studies have reported increased head growth during the first year of life in children with autism spectrum disorders.[1–7] As head growth in early childhood is tightly correlated with brain growth,[8] these anomalies have been attributed to brain overgrowth. Magnetic resonance imaging studies have demonstrated increased brain size, with larger volumes of both grey and white matter, in autism spectrum disorder children.[9–15] There appears to be a rostral-to-caudal gradient, with frontal lobes more affected than temporal lobes, which in turn are more affected than the parietal and occipital lobes.[15] It has been hypothesized that overgrowth results from excess neurogenesis in the frontal and temporal cortical regions.[1] This was supported by a recent postmortem study of brain tissue from seven children with autism spectrum disorders,[16] which found an increased number of neurons in the dorsolateral and mesial subdivisions of the prefrontal cortex compared with controls, as well as increased overall brain weight in the autism spectrum disorder cases. Larger head size might also result from incomplete or improper timing of processes required to refine brain circuitry in the postnatal period, such as synaptic pruning and programmed cell death.[17]

Although increased head growth is commonly postulated to be a general feature of autism spectrum disorders, it has never been demonstrated in a population-based study sample. On the contrary, the only study conducted in a population-based child cohort did not find any significant deviance in mean head circumference in autism spectrum disorder children.[18] Furthermore, it is unclear whether there are any sex-specific differences in head growth in autism spectrum disorder children, as previous studies have included very few girls, or excluded girls altogether. It is also unknown whether

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deviations in head growth are accompanied by deviations in body growth. Length and weight development in autism spectrum disorder has not been as extensively studied, and findings are inconsistent.[5–7,18–20]

We used longitudinal data from the population-based Norwegian Mother and Child Cohort Study (MoBa)[21] to investigate growth patterns of head circumference, length, and weight in children with autism spectrum disorders. Our specific objectives were to establish whether growth trajectories for autism spectrum disorder children differed from the cohort mean and to identify the ages at which differences in growth first appeared and when they were maximal.

METHODS

Study Population

The MoBa cohort is nationwide and includes 109,000 children born from 1999 to 2009. Mothers were recruited at ultrasound examinations around week 18 of pregnancy, and 38.5% of invited women consented to participation. Cases of autism spectrum disorder (autistic disorder, Asperger syndrome, and pervasive developmental disorder–not otherwise specified) in the cohort are identified by a substudy of autism, the Autism Birth Cohort Study.[22] The analyses in this study reflect data collected and processed by 31 December 2012. Participation in MoBa and the Autism Birth Cohort Study is based on written informed consent from the mother. Both studies are approved by the regional committee of medical research ethics for Southeastern Norway.

Measures of Autism Spectrum Disorder

Cases of autism spectrum disorder were identified through (1) questionnaire screening of mothers at offspring ages 3, 5, and 7 years; (2) professional and parental referrals of participants suspected of having autism spectrum disorder; and (3) linkages to the Norwegian Patient Registry. Referrals were elicited through annual newsletters to MoBa participants and information on the website of the Norwegian Institute of Public Health. The Norwegian Patient Registry collects data on diagnoses from all hospitals and outpatient clinics in Norway beginning in the year 2008, thereby capturing data for all children diagnosed with autism spectrum disorders by Norwegian health services, irrespective of year of birth.[23]

When a child with autism spectrum disorder or potential autism spectrum disorder was detected through any of the mechanisms described above, he or she was invited to participate in a clinical assessment that included standardized diagnostic, cognitive, and behavioral instruments. The primary diagnostic tools were the research standard instruments for diagnosis of autism spectrum disorders, the Autism Diagnostic Interview–Revised (ADI-R)[24] and the Autism Diagnostic Observation Schedule,[25] which have shown high reliability and validity in making diagnoses of autism spectrum disorder in children. Diagnostic conclusions were best estimate clinical diagnoses derived from test and interview results and from information collected from parents and teachers. The diagnoses were based on Diagnostic and Statistical Manual of mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) criteria, and the case definition included codes 299.00 (Autistic Disorder), 299.80 (Asperger Syndrome), and 299.80 (Pervasive Development Disorder, Not Otherwise Specified).

The registry contains International Classification of Diseases, 10th Revision, codes determined by Norwegian specialist health services, and the autism spectrum disorder case definition of the autism study includes codes F84.0 (Childhood Autism), F84.1 (Atypical Autism), F84.5 (Asperger Syndrome), F84.8 (Other Pervasive Developmental Disorder), and F84.9 (Pervasive Developmental Disorder, Unspecified). In this article, we have used the terms autistic disorder for code F84.0 and pervasive development disorder–not otherwise specified for codes F84.1, F84.8, and F84.9.

Size Measures

Measures of head circumference, length, and weight at birth were obtained from the Medical Birth Registry of Norway. Postnatal measures were recorded in questionnaires in which mothers were asked to copy data from their children's health report cards. These measures had been taken and recorded by public health nurses according to guidelines from the Norwegian Directorate of Health.[26] All measures were routinely obtained at age 6 weeks and 3, 6, 8, and 12 months. Length and weight were also measured at 15–18 months, and 2 and 3 years. Child body mass index (BMI) was calculated by dividing weight (in kilograms) by length (in meters) squared. The extremes of the head size distribution in autism spectrum disorder cases were examined by calculating the proportions of autism spectrum disorder children with macrocephaly (head circumference >97th cohort percentile) and microcephaly (head circumference <3rd cohort percentile).

Growth Models

Early childhood growth starts out rapidly during infancy. The growth rate then decreases gradually to become relatively (although not perfectly) constant during the late preschool years.[27] In time periods wherein size increases monotonically while the slope of the growth curve decreases monotonically, fractional polynomial functions represent a flexible and effective way to model growth.[28,29] We compared several established models for child growth: the childhood component of the Karlberg model,[30] the Count model,[28] and the Reed first- and second-order models,[27] for boys and girls separately. These models are special cases of fractional polynomial models in age (t) with terms t, t^2, 1/t, and ln(t).

Growth trajectories were modeled using mixed-effects models to take into account the within-subject correlation of head and body sizes.[31] Sex-specific models were fitted for the whole cohort and separately for autism spectrum disorder children. Age was measured in days. As per convention for the Count and Reed models, 30 days were added to the logarithmic and inverse terms to ensure that they were defined

for age = 0 (birth).[27] Model choice was based on criteria of fit indices, that is, the −2 log likelihood and the Bayesian Information Criterion.[32] For all three size measures, the mixed-effects Reed first-order models provided the best fit and were chosen for the main analyses:

$$Y_{ij}(t) = \beta_{0j} + \beta_{1j} \cdot t_{ij} + \beta_{2j} \cdot \ln\left(t_{ij} + 30\right) + \beta_{3j} / \left(t_{ij} + 30\right) + e_{ij} \quad (1)$$

where $Y_{ij}(t)$ is the size measure (head circumference/length/weight) for child j at occasion i (i = 1, 2,…n_j; j = 1, 2,…n_j), t_{ij} is the age in days, e_{ij} is the occasion-specific random error term, and β_{0j}, β_{1j}, β_{2j}, and β_{3j} are the subject-specific parameters. To examine how autism spectrum disorder children differ from other children, we added fixed effects (v_0, v_1, v_2, and v_3) for the interactions between autism spectrum disorder status and the age terms:

$$\begin{aligned} Y_{ij}(t) = {} & \beta_{0j} + \beta_{1j} \cdot t_{ij} + \beta_{2j} \cdot \ln\left(t_{ij} + 30\right) + \beta_{3j} / \left(t_{ij} + 30\right) \\ & + \mathrm{ASD}_j \left(v_0 + v_1 \cdot t_{ij} + v_2 \cdot \ln\left(t_{ij} + 30\right) + v_3 / \left(t_{ij} + 30\right)\right) + e_{ij} \end{aligned} \quad (2)$$

The interaction term represents the difference in mean between autism spectrum disorder cases and noncases. We first fitted models (1) and (2), and model (2) was then adjusted for potential confounding factors: parental education, maternal smoking during pregnancy, parity, gestational age at birth, breastfeeding, and parental height (for the analysis of head circumference and length) and BMI (for the analysis of weight). Information on covariates was obtained from the birth registry and from questionnaires completed by the parents.

Some children had incomplete records of growth measures, either because the measurement schedule had not been completed exactly as recommended or because the mothers did not respond to all the questionnaires. We adjusted for missing data by refitting the growth models with inverse probability weights (IPWs).[33] The IPWs were derived from covariates that were predictive of response at child's age 3 years (this questionnaire included growth measures from ages 2 and 3 years). The covariates examined for IPW calculations were the potential confounders listed above.

Approximately 15% of the study subjects were younger siblings of other children in the study sample. To examine the effects of correlation within sibships, we repeated our analyses using three-level models in which measurements (level 1) were clustered within children (level 2) and then within sibships (ie, the same mother, level 3). The mean trajectories estimated from three-level models did not differ substantially from those obtained from two-level models; hence, we only present results from two-level models here.

Mixed-effects models were fitted in MLwiN (University of Bristol, Bristol, UK). Other analyses were conducted in SPSS version 19.0 (SPSS Inc., Chicago, IL).

Subgroup Analyses

In order to explore whether deviances in growth were associated with specific phenotypic characteristics, we made comparisons between autism spectrum disorder subtypes (autistic disorder, Asperger syndrome, and pervasive development disorder–not otherwise specified) and between autism spectrum disorder cases with and without genetic disorders, epilepsy, and intellectual disability (intelligence quotient [IQ]<70 or IQ≥70), respectively. We explored potential ascertainment bias by comparing the older children born in 1999–2003, for whom the majority of cases have presumably been identified, to the younger children born in 2004–2009. We also compared the autism spectrum disorder cases who were clinically assessed through the autism study with the autism spectrum disorder cases detected through the registry.

RESULTS

The children eligible for the analyses were study subjects recorded to be alive and living in Norway by 3 years of age (n = 106,954). We excluded children with gestational age <32 weeks at birth (n = 872) because their growth patterns deviated substantially from those of other children in early life. The final study sample included 106,082 children (54,336 boys and 51,746 girls). On average, there were 4.1 head circumference measures, 5.7 length measures, and 5.9 weight measures per child available. A total of 376 children in the study sample had been diagnosed with autism spectrum disorder (310 boys and 66 girls). Of the autism spectrum disorder cases, 199 (53%) had been clinically assessed through the autism study, whereas the remaining 177 (47%) had specialist-confirmed diagnoses recorded in the Norwegian Patient Registry. Table 1 shows the distribution of cases by sex and clinical subtype. Registry diagnoses of autism spectrum disorders had a high validity for the diagnosis as a whole; of 60 children with registry diagnoses validated through the autism study, 58 were found to meet the DSM-IV criteria for autism spectrum disorders, generating a positive predictive value (PPV) of 97% (95% confidence interval [CI] = 88%–100%). The estimate of PPV was also high for a specific diagnosis of autistic disorder 17/20 (85%; [95% CI = 62%–97%]) but lower for the other autism spectrum disorder subtypes 8/22 (36%; [17%–59%]) for Asperger syndrome and 10/18 (56%; [31%–78%]) for pervasive development disorder–not otherwise specified. PPV estimates for the subtype diagnoses should be interpreted with caution, as the number of cases in each group was low.

Head Growth

At birth, mean head circumference for boys with autism spectrum disorder was 35.50 cm (95% CI = 35.30–35.70), which was close to the mean of 35.57 cm (35.56–35.59) for boys without autism spectrum disorder (Table 2). As shown in Figure 1A, the subsequent mean head growth trajectory for autism spectrum disorder boys was similar to the general

TABLE 1. Autism Spectrum Disorder Cases by Year of Birth

		Total Cases	Autistic Disorder	Asperger Syndrome	Pervasive Developmental Disorder–Not Otherwise Specified
Year of Birth	Total N	No. (%)	No. (%)	No. (%)	No. (%)
1999–2000	2,184	12 (0.55)	1 (0.05)	8 (0.37)	3 (0.14)
2001	4,176	22 (0.53)	7 (0.17)	6 (0.14)	9 (0.22)
2002	8,620	63 (0.73)	22 (0.26)	20 (0.23)	21 (0.24)
2003	12,485	84 (0.67)	35 (0.29)	22 (0.18)	27 (0.22)
2004	13,448	52 (0.39)	20 (0.15)	10 (0.07)	22 (0.16)
2005	15,414	51 (0.33)	23 (0.15)	6 (0.04)	22 (0.14)
2006	17,179	45 (0.26)	20 (0.12)	4 (0.02)	21 (0.12)
2007	15,925	23 (0.14)	13 (0.08)	1 (0.01)	9 (0.06)
2008	13,306	22 (0.17)	17 (0.13)	0 (0.00)	5 (0.04)
2009	3,345	2 (0.06)	2 (0.06)	0 (0.00)	0 (0.00)
Total	106,082	376 (0.35)	160 (0.15)	77 (0.07)	139 (0.13)

Includes cases identified by December 31, 2012, among children with gestational age ≥32 weeks at birth (n = 106,082).

trajectory for boys throughout the first year of life. The difference in mean head circumference between cases and noncases was never more than 0.1 cm (Table 2). Adjustment for parental height, parental education, maternal smoking during pregnancy, parity, gestational age at birth, and breastfeeding did not change the difference substantially (Figure 1B). Although mean head circumference was similar in cases and noncases, the variability was greater in cases (Table 2), and there was an increase in the proportion with macrocephaly in autism spectrum disorder boys by age 12 months, to 8.7% (4.7%–14.4%) (Table 3).

Autism spectrum disorder girls had a mean head circumference of 34.67 cm (34.26–35.08) at birth, which was 0.28 cm lower than the mean of 34.95 cm (34.94–34.97) for girls without autism spectrum disorders (Table 2). Mean head size in girls with autism spectrum disorder continued to be lower than the cohort mean for girls throughout the first year of life, as shown in Figure 1A. The difference between cases and noncases in girls reached 0.5 cm at 12 months of age (Table 2). Adjustment for covariates attenuated the difference to 0.2 cm at 12 months (Figure 1B). The number of girls with

TABLE 2. Mean Head Circumference by Age

	Autism Spectrum Disorder						
	Yes			No			
Age[a]	No.	Mean (95% CI)	SD	No.	Mean (95% CI)	SD	*P* Value[b]
Boys	n = 310			n = 54,026			
Birth	304	35.50 (35.30–35.70)	1.76	53,000	35.57 (35.56–35.59)	1.55	0.49
6 weeks	168	39.04 (38.82–39.25)	1.43	33,251	38.94 (38.92–38.95)	1.30	0.38
3 months	202	41.47 (41.29–41.66)	1.34	39,181	41.36 (41.35–41.37)	1.19	0.25
6 months	193	44.38 (44.17–44.59)	1.48	39,079	44.40 (44.39–44.41)	1.21	0.83
8 months	147	45.72 (45.46–45.97)	1.59	25,882	45.72 (45.71–45.74)	1.27	0.95
12 months	150	47.39 (47.12–47.65)	1.64	28,860	47.41 (47.40–47.43)	1.29	0.85
Girls	n = 66			n = 51,680			
Birth	65	34.69 (34.26–35.10)	1.63	50,741	34.95 (34.94–34.97)	1.49	0.20
6 weeks	28	37.79 (37.24–38.34)	1.42	31,762	38.03 (38.01–38.04)	1.22	0.38
3 months	42	40.07 (39.64–40.50)	1.38	37,576	40.23 (40.22–40.24)	1.15	0.46
6 months	42	43.00 (42.57–43.43)	1.38	37,354	43.16 (43.15–43.17)	1.17	0.45
8 months	30	44.01 (43.38–44.63)	1.66	24,943	44.45 (44.44–44.47)	1.21	0.15
12 months	33	45.63 (45.09–46.16)	1.51	27,834	46.12 (46.10–46.13)	1.23	0.07

[a]Head circumference measures were centered to the exact ages at which the measures were supposed to be obtained. The centering was done using parameters obtained from the Reed first-order models.
[b]Independent samples *t* test, two-sided *P* value assuming unequal variances.
SD indicates standard deviation.

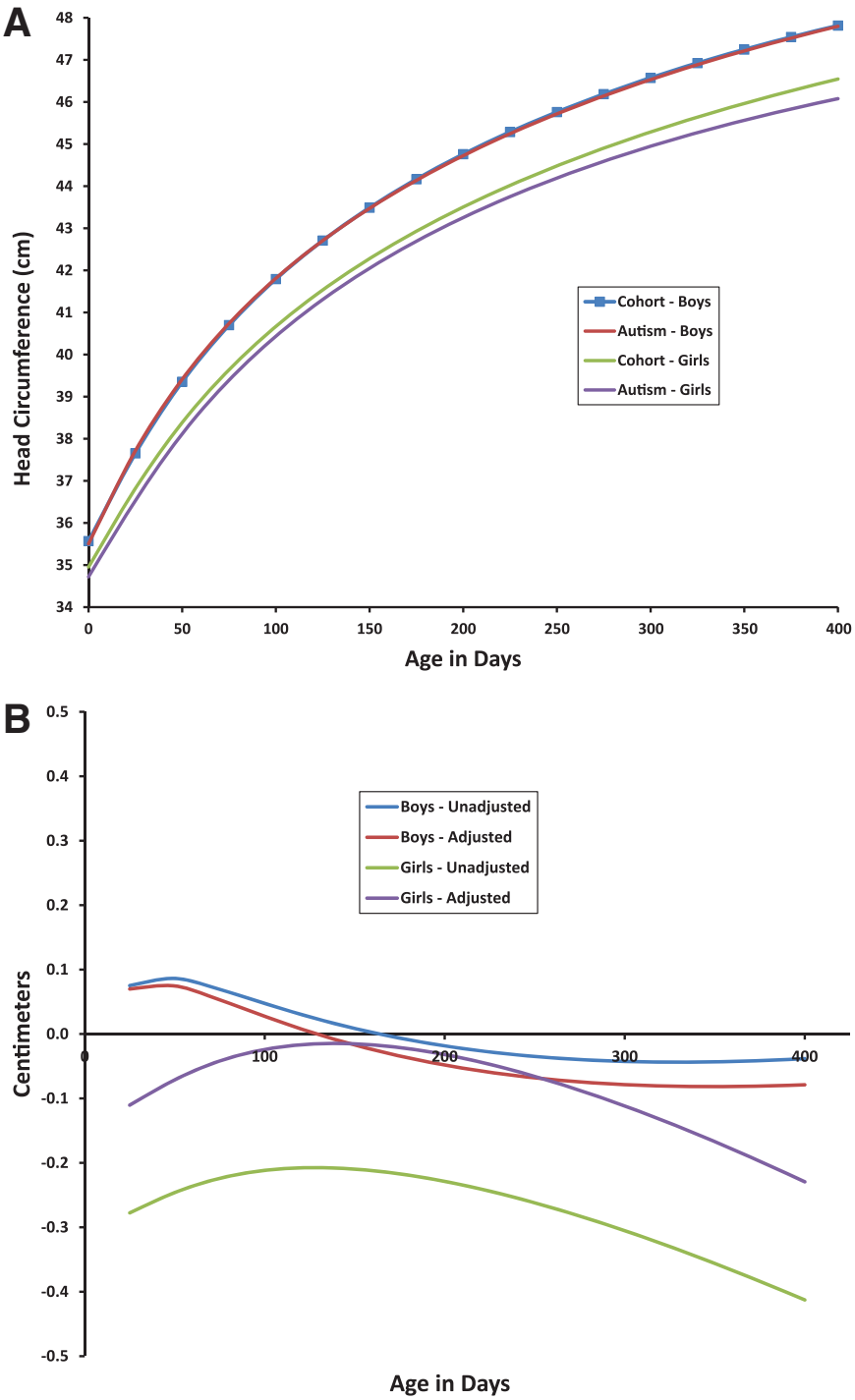

FIGURE 1. A, Mean growth trajectories for head circumference. Estimated from unadjusted mixed-effects Reed first-order models. B, Difference in mean head circumference (cm) between autism spectrum disorder cases and noncases. Estimated from mixed-effects Reed first-order models. Adjusted models include adjustment for parental height, parental education, maternal smoking, parity, gestational age at birth, and breastfeeding.

autism spectrum disorders was too low to reliably determine the proportions of macrocephaly and microcephaly.

Length Growth

Mean birth length for autism spectrum disorder boys was 50.68 cm (95% CI = 50.40–50.97), that is, almost identical to the mean of 50.73 cm (50.71–50.75) for boys without autism spectrum disorders (Table 4). Autism spectrum disorder boys grew faster after birth and were taller by 0.5 cm at 6 months and 1.1 cm at 12 months, but the mean difference reverted to 0.6 cm by age 3 years (Figure 2A and Table 4). The difference in mean length between autism spectrum disorder boys and other boys increased slightly after adjustment for covariates (Figure 2B). For autism spectrum disorder girls, the mean birth length of 49.29 cm (48.61–49.98) was 0.64 cm lower than the mean of 49.93 cm (49.91–49.95) for girls without autism spectrum disorders (Table 4). However,

TABLE 3. Prevalence of Macrocephaly and Microcephaly in Boys with Autism Spectrum Disorder

		Macrocephaly[a]			Microcephaly[a]		
Age[b]	n	No.	%	(95% CI)	No.	%	(95% CI)
Birth	304	13	4.3	(2.2–7.2)	16	5.3	(3.0–8.4)
6 weeks	168	9	5.4	(2.5–9.9)	6	3.6	(1.3–7.6)
3 months	202	10	5.0	(2.4–8.9)	7	3.5	(1.4–7.0)
6 months	193	9	4.7	(2.2–8.7)	9	4.7	(2.2–8.7)
8 months	147	7	4.8	(1.9–9.6)	5	3.4	(1.1–7.8)
12 months	150	13	8.7	(4.7–14.4)	5	3.3	(1.1–7.6)

[a]Macrocephaly was defined as being above the sex-specific 97th percentile for the cohort, and microcephaly was defined as being below the sex-specific 3rd percentile.
[b]Head circumference measures were centered to the exact ages at which the measures were supposed to be obtained. The centering was done using parameters obtained from the Reed first-order models.

the differences in means were smaller at other ages (Figure 2A and Table 4), and adjustment for covariates eliminated the difference altogether (Figure 2B).

Weight Growth

Similar to the findings for birth length, there was no difference in mean birth weight between boys with autism spectrum disorder and other boys. Mean birth weight for autism spectrum disorder boys was 3613 g (95% CI = 3,543–3,683), whereas the mean for other boys was 3647 g (3,642–3,652) (Table 5). After birth, autism spectrum disorder boys had a more rapid increase in mean weight and were on average about 300 g heavier than other boys from age 12 months (Figure 3A and Table 5). Adjustment for the selected covariates did not affect the difference (Figure 3B). In autism spectrum disorder girls, mean birth weight was 3357 g (3,198–3,516), which was 162 g lower than the mean of 3519 g (3,515–3,524) for other girls (Table 5). As shown in Figure 3A and Table 5, mean weight in autism spectrum disorder girls continued to be 150–350 g lower up to age 3 years, but the 95% CIs for cases and noncases were mostly overlapping. The difference in means largely disappeared after adjustment for covariates (Figure 3B).

BMI Trajectories

Boys with autism spectrum disorder had similar mean BMIs to other boys at all ages, indicating that the observed increase in body growth (length and weight) was symmetrical. Girls with autism spectrum disorder had somewhat lower mean BMIs throughout, as a result of their lower mean weight, although the 95% CIs were always overlapping with those of noncases.

Adjustment for Missing Data

The likelihood of responding to the questionnaire at age 3 years was positively associated with higher levels of parental education, parental height, and breastfeeding and negatively associated with maternal smoking during pregnancy. For autism spectrum disorder boys, the analyses with IPWs generated similar results as the analyses without such adjustment, indicating that the findings were not biased by nonresponse. For autism spectrum disorder girls, the number of cases was too low to allow for reliable modeling with IPWs.

Subgroup Analyses

Of the 310 boys with autism spectrum disorders, 137 had autistic disorder, 65 had Asperger syndrome, and 108 had pervasive development disorder–not otherwise specified. The trajectories for mean growth were similar across the three subtypes. Genetic disorders were recorded in 16 (5%), and epilepsy was recorded in 29 (9%). Excluding boys with genetic disorders and epilepsy did not affect the overall growth trajectories for autism spectrum disorder boys. Data on IQ were available for 155 autism spectrum disorder boys, of whom 43 (28%) had intellectual disability (IQ<70). Growth trajectories were similar in autism spectrum disorder boys with and without intellectual disability.

Of the 66 girls with autism spectrum disorders, there were 23 with autistic disorder, 12 with Asperger syndrome, and 31 with pervasive development disorder–not otherwise specified. Like for autism spectrum disorder boys, the growth trajectories for girls were similar across the subtypes. Genetic disorders were recorded in 10 (15%), and epilepsy was recorded in 9 (14%). When these girls were excluded, the difference in mean head circumference between cases and noncases became smaller. There were 33 autism spectrum disorder girls with IQ data, of whom 15 (45%) had intellectual disability. Autism spectrum disorder girls with intellectual disability had lower mean head circumference and lower mean weight than girls without, but no such deviations were found in autism spectrum disorder girls without intellectual disability.

The growth trajectories for autism spectrum disorder children were similar for the older children (born 1999–2003) and the younger children (born 2004–2009). There were also no differences between autism spectrum disorder cases ascertained by the autism study and autism spectrum disorder cases detected through the Norwegian Patient Registry.

DISCUSSION

This population-based cohort study did not replicate the findings of increased mean head growth from previous case-control studies of autism spectrum disorders. Boys in our study with autism spectrum disorders had increased variability

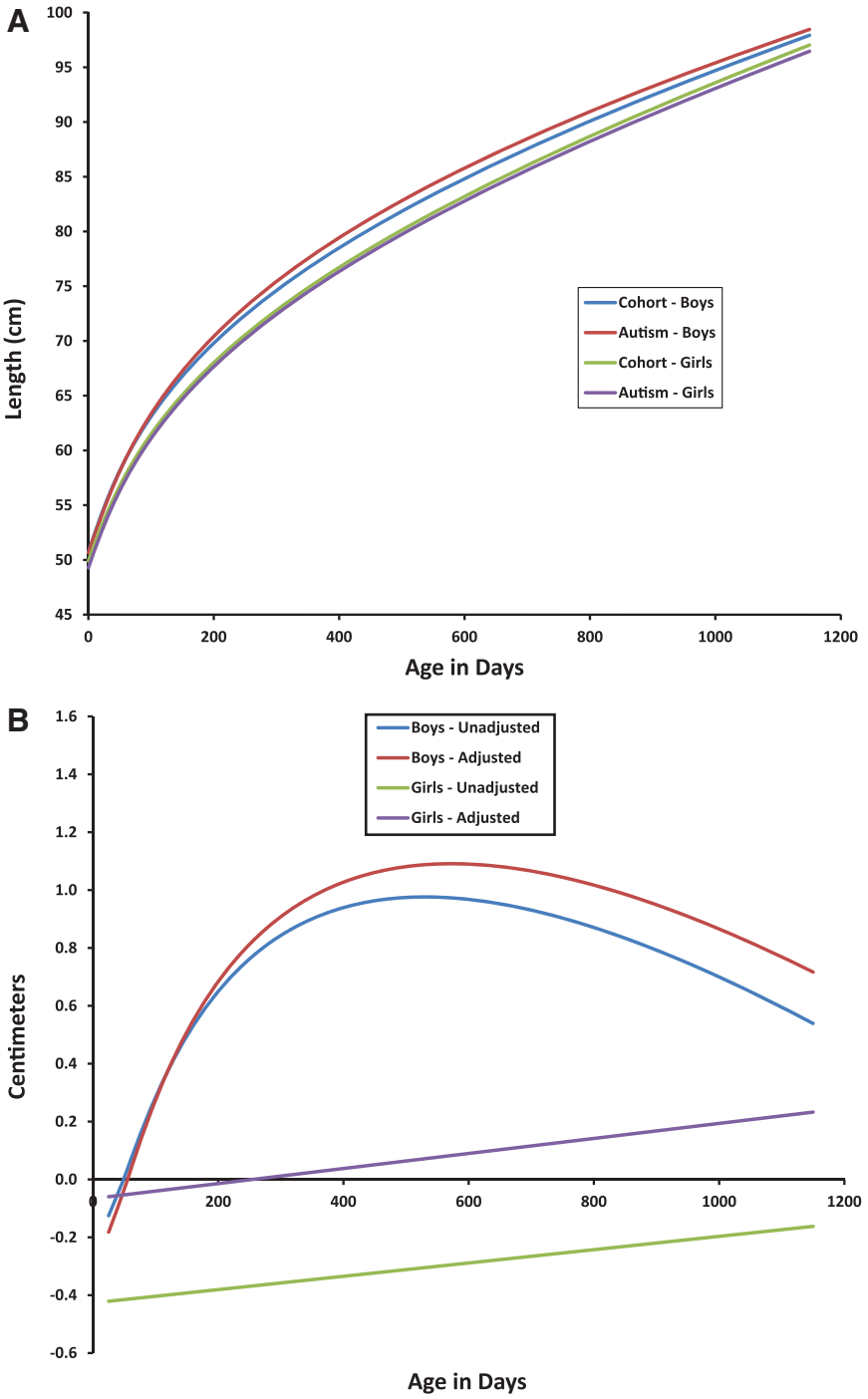

FIGURE 2. A, Mean growth trajectories for length. Estimated from unadjusted mixed-effects Reed first-order models. B, Difference in mean length (cm) between autism spectrum disorder cases and noncases. Estimated from mixed-effects Reed first-order models. Adjusted models include adjustment for parental height, parental education, maternal smoking, parity, gestational age at birth, and breastfeeding.

in head circumference, as well as an increase in macrocephaly at age 12 months, but mean head circumference was similar to that of other boys at all ages. Girls with autism spectrum disorders had lower mean head circumference than other girls at all ages, and that difference appeared to be largely driven by autism spectrum disorder girls with genetic disorders, epilepsy, or intellectual disability. The finding of sex-specific differences in head growth in autism spectrum disorder children is previously unreported, but most previous studies either included too few girls to be able to draw inferences or excluded girls altogether.

The discrepancy with previous studies of head growth may be explained by differences in recruitment and inclusion criteria. Most previous studies have used clinic samples of autism spectrum disorder cases and applied strict inclusion criteria, excluding all children with genetic disorders and medical comorbidities associated with reduced head growth. Exclusion of autism spectrum disorder cases with genetic

TABLE 4. Mean Length by Age

	Autism Spectrum Disorder						
	Yes			No			
Age[a]	No.	Mean (95% CI)	SD	No.	Mean (95% CI)	SD	*P* Value[b]
Boys	n = 310			n = 54,026			
Birth	300	50.70 (50.41–50.98)	2.52	52,082	50.73 (50.71–50.75)	2.28	0.80
6 weeks	161	57.12 (56.75–57.48)	2.32	30,702	57.00 (56.97–57.03)	2.45	0.54
3 months	226	62.60 (62.25–62.94)	2.61	42,724	62.41 (62.39–62.43)	2.35	0.29
6 months	227	69.54 (69.19–69.89)	2.68	43,478	69.05 (69.02–69.07)	2.31	0.006
8 months	164	72.68 (72.28–73.08)	2.60	29,699	72.04 (72.01–72.06)	2.38	0.002
12 months	187	78.19 (77.79–78.60)	2.84	34,248	77.08 (77.05–77.11)	2.55	<0.001
16.5 months[c]	217	82.85 (82.44–83.26)	3.05	36,213	81.88 (81.85–81.91)	2.77	<0.001
24 months	90	88.71 (87.93–89.50)	3.75	16,160	88.19 (88.14–88.25)	3.27	0.20
36 months	127	97.57 (96.72–98.42)	4.84	23,023	96.96 (96.91–97.01)	3.80	0.16
Girls	n = 66			n = 51,680			
Birth	59	49.32 (48.65–50.00)	2.59	49,549	49.93 (49.91–49.95)	2.17	0.08
6 weeks	28	55.37 (54.44–56.30)	2.41	28,878	55.84 (55.82–55.87)	2.31	0.31
3 months	49	60.57 (59.84–61.29)	2.43	40,539	60.80 (60.78–60.82)	2.26	0.51
6 months	49	66.80 (66.04–67.56)	2.64	41,423	67.17 (67.14–67.19)	2.25	0.34
8 months	34	69.97 (68.81–71.13)	3.32	28,545	70.18 (70.15–70.21)	2.34	0.72
12 months	39	74.96 (73.94–75.99)	3.17	32,892	75.33 (75.30–75.36)	2.53	0.48
16.5 months[c]	41	79.88 (78.75–81.00)	3.58	34,651	80.30 (80.27–80.33)	2.78	0.45
24 months	27	86.83 (85.49–88.16)	3.37	15,337	86.76 (86.71–86.81)	3.28	0.92
36 months	30	96.33 (94.91–97.75)	3.80	22,117	95.87 (95.82–95.92)	3.85	0.52

[a]Length measures were centered to the exact ages at which the measures were supposed to be obtained. The centering was done using parameters obtained from the Reed first-order models.
[b]Independent samples *t* test, two-sided *P* value assuming unequal variances.
[c]Measures were obtained between 15 and 18 months of age.
SD indicates standard deviation.

disorders and epilepsy did not have any noticeable effect on the mean head growth trajectory for boys with autism spectrum disorder in our study sample, but for girls it made a substantial difference. Population-based recruitment—as opposed to clinic-based recruitment—is likely to bring in a wider range of autism spectrum disorder children that may display greater diversity in head growth patterns. This is supported by the increased variability in head growth observed in children with autism spectrum disorders in our study sample.

Our study also found evidence of accelerated body growth in boys with autism spectrum disorders. Increases in mean length and weight became apparent around 6 months of age, and the differences in means between autism spectrum disorder boys and other boys widened until 12 months of age. The biological relevance of these findings is uncertain, and further investigation would be required to determine whether the increase in growth has biological underpinnings or any relation to the core neurological deficits associated with autism spectrum disorders. The symmetric increase in growth suggests that there may be differences in growth regulation in autism spectrum disorder boys, but the fact that the difference in mean length decreased after 18 months indicates that accelerated growth, if present, may be a transient phenomenon of early childhood and not a persistent feature of autism spectrum disorders. The mean BMIs of autism spectrum disorder boys were similar to those of other boys at all ages, and there was no indication of an increase in early childhood obesity in boys with autism spectrum disorder.

Adjustment for the selected covariates (parental height and weight, parental education, maternal smoking during pregnancy, parity, gestational age at birth, and breastfeeding) did not have any substantial effects on the growth models for autism spectrum disorder boys. For girls with autism spectrum disorder, the reductions in length, weight, and head circumference were attenuated by adjustment for covariates, which suggests that growth deviations in autism spectrum disorder girls may also be influenced by other characteristics of these girls and their parents.

We chose to use a relatively simple growth model in which the growth curve is modeled by one equation throughout the entire age interval under study. There are other ways to model growth that are more mathematically sophisticated, for example, by spline models that allow parameters to vary from one age interval to the other. However, spline models provided no advantage in this analysis, as the Reed first-order models fit well with the crude means at all ages under study.

TABLE 5. Mean Weight by Age

	Autism Spectrum Disorder						
	Yes			No			
Age[a]	No.	Mean (95% CI)	SD	No.	Mean (95% CI)	SD	*P* Value[b]
Boys	n = 310			n = 54,026			
Birth	309	3,613 (3,543–3,683)	624	53,986	3,647 (3,642–3,652)	562	0.34
6 weeks	201	5,136 (5,035–5,236)	721	38,553	5,118 (5,111–5,125)	701	0.72
3 months	227	6,639 (6,531–6,747)	828	43,384	6,562 (6,555–6,570)	792	0.16
6 months	227	8,416 (8,277–8,554)	1,062	43,698	8,313 (8,305–8,322)	913	0.15
8 months	164	9,297 (9,112–9,482)	1,201	29,786	9,102 (9,091–9,113)	988	0.04
12 months	188	10,542 (10,346–10,739)	1,364	34,201	10,228 (10,217–10,240)	1,078	0.002
16.5 months[c]	216	11,630 (11,437–11,822)	1,433	36,525	11,350 (11,338–11,362)	1,186	0.005
24 months	92	13,186 (12,865–13,507)	1,548	16,125	12,955 (12,933–12,978)	1,466	0.16
36 months	138	15,579 (15,217–15,941)	2,148	23,596	15,273 (15,250–15,295)	1,769	0.10
Girls	n = 66			n = 51,680			
Birth	66	3,364 (3,207–3,522)	640	51,638	3,519 (3,515–3,524)	540	0.05
6 weeks	39	4,416 (4,215–4,617)	620	36,966	4,750 (4,744–4,757)	621	0.002
3 months	51	5,813 (5,563–6,064)	890	41,543	6,004 (5,997–6,011)	719	0.13
6 months	49	7,486 (7,171–7,802)	1,097	41,749	7,678 (7,670–7,687)	863	0.23
8 months	34	8,226 (7,809–8,643)	1,195	28,698	8,440 (8,429–8,451)	951	0.30
12 months	40	9,307 (8,913–9,701)	1,232	32,914	9,527 (9,515–9,538)	1,039	0.27
16.5 months[c]	41	10,652 (10,177–11,126)	1,503	34,964	10,650 (10,638–10,662)	1,150	0.99
24 months	27	12,089 (11,425–12,754)	1,680	15,227	12,342 (12,319–12,365)	1,459	0.44
36 months	33	14,375 (13,595–15,155)	2,200	22,719	14,734 (14,711–14,757)	1,785	0.36

[a]Weight measures were centered to the exact ages at which the measures were supposed to be obtained. The centering was done using parameters obtained from the Reed first-order models.
[b]Independent samples *t* test, two-sided *P* value assuming unequal variances.
[c]Measures were obtained between 15 and 18 months of age.
SD indicates standard deviation.

The main limitation of the study was the lack of head circumference data after 12 months of age, which prevented us from detecting any potential head growth increase occurring after that age. However, all but one of the longitudinal studies that have demonstrated increased head growth in autism spectrum disorder found the increase to occur during the first year of life.[2–7] The only exception was a small study of 28 boys with high-functioning autistic disorder and Asperger syndrome, which found head growth to be increased in the second year of life.[20] Another limitation of our data was that growth measures were obtained from a secondary source (health report cards). We have not done any independent validation of these measures, and we are not aware of any studies in Norway that have validated anthropometric data obtained by public health nurses.

Incompleteness of growth data because of nonresponse may also have represented a limitation in this study. The analyses with adjustment for missing data (using IPWs) did not indicate that our results for autism spectrum disorder boys were biased by nonresponse, but the IPW method rests upon the assumption that data are missing at random. This assumption may have been violated if the likelihood of responding to questionnaires was associated with child growth and the IPWs did not appropriately capture the factors influencing response rates.

The ascertainment of autism spectrum disorder cases is still incomplete, particularly among the younger children. The prevalence of diagnosed autism spectrum disorders was lower than the most recent figures from the United Kingdom and the United States,[34,35] although that discrepancy is not merely attributable to underascertainment because the nationwide autism spectrum disorder prevalence is also lower in Norway.[23] For the country as a whole, the prevalence is estimated to be 0.8% in 12-year-olds, which is not very different from the 0.7% prevalence in children born in 1999–2003 in our study sample (who were 9–13 years old at the end of follow-up). The similarity of our findings across birth year categories indicates that the analyses were not substantially affected by ascertainment bias.

The strengths of the study were the population-based recruitment, prospective data collection, and the combination of screening, referrals, and registry linkage for detection of cases. Our study is the first investigation of growth in autism spectrum disorder done entirely within the framework of a cohort of children. This was a particular advantage because we did not have to depend on external reference norms. If

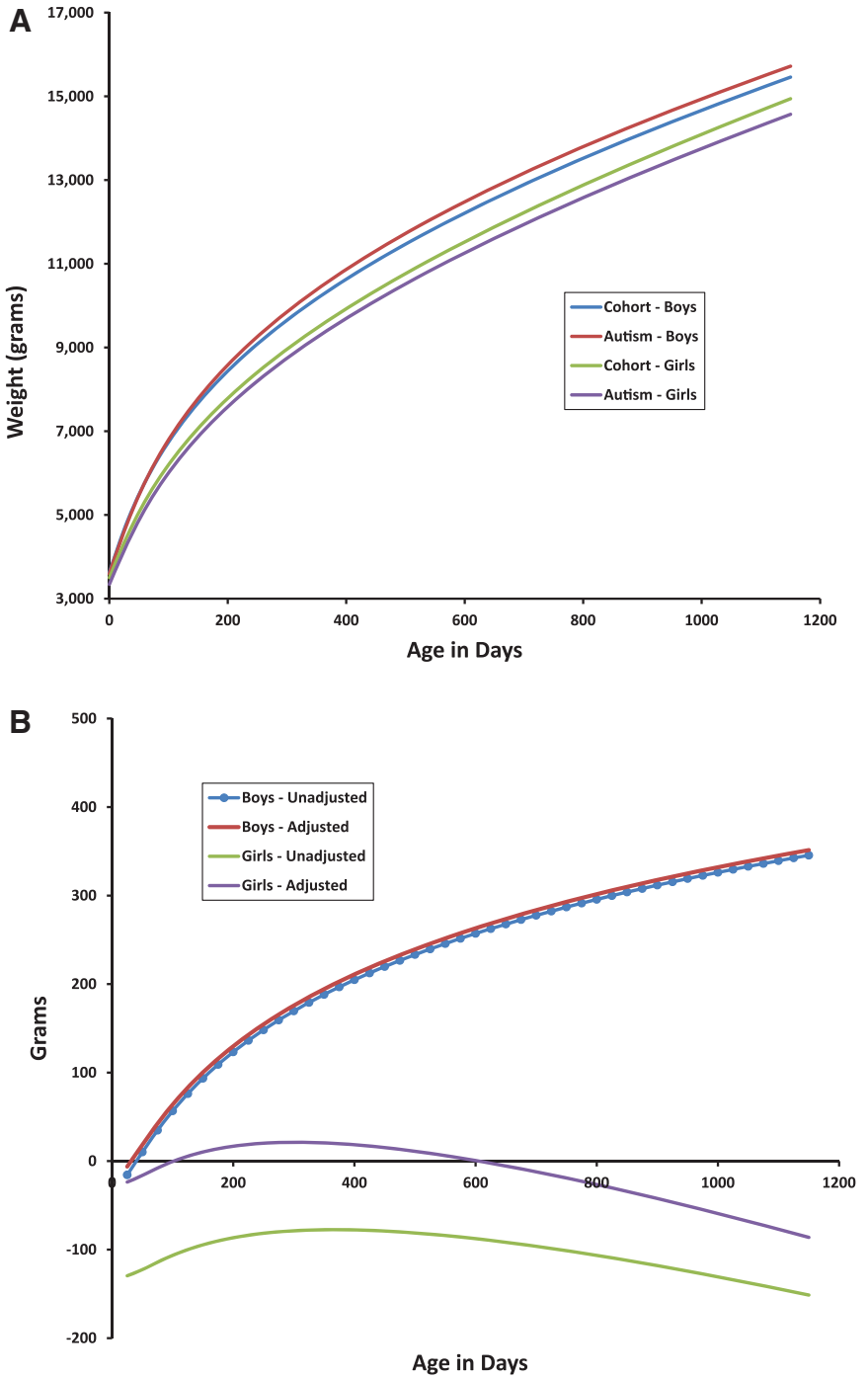

FIGURE 3. A, Mean growth trajectories for weight. Estimated from unadjusted mixed-effects Reed first-order models. B, Difference in mean weight (g) between autism spectrum disorder cases and noncases. Estimated from mixed-effects Reed first-order models. Adjusted models include adjustment for parental BMI, parental education, maternal smoking, parity, gestational age at birth, and breastfeeding.

the source population of the cases deviates from an external reference population, observed differences between cases and controls may be falsely attributed to case status when it actually only reflects underlying population differences. That would indeed have been the case here; when we compared the growth curves from the Norwegian birth cohort to those of the Norwegian subsample used to construct the World Health Organization growth standards,[36] we found that the children in the Norwegian birth cohort were somewhat larger on average for all three measures. By using the cohort itself as the basis for comparison, we eliminated the bias that such an external reference sample would have introduced.

Previous findings of accelerated head growth, excess neurogenesis, and disturbances in synaptic pruning and apoptosis (programmed cell death) in autism spectrum disorder are not negated by this study. The emerging increase in macrocephaly in autism spectrum disorder boys by age 12 months in our study indicates that accelerated head growth does occur,

but it does not appear to be a general feature of the autism spectrum. It is worth noting that the only other longitudinal population-based study of growth in autism spectrum disorder also failed to demonstrate any increase in mean head circumference.[18] Future studies of growth in autism spectrum disorder would benefit from using population-based study samples that are representative of the full autism spectrum.

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