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Body stature growth trajectories during childhood and the development of myopia

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Abstract

Purpose—Stature at a particular age can be considered the cumulative result of growth during a number of preceding growth trajectory periods. We investigated whether height and weight growth trajectories from birth to age 10 years were related to refractive error at ages 11 and 15 years, and eye size at age 15 years.

Design—Prospective analysis in a birth cohort.

Participants—Children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC) United Kingdom birth cohort (minimum N=2,676).

Methods—Growth trajectories between birth and 10 years were modeled from a series of height and weight measurements (N=6,815). Refractive error was assessed by non-cycloplegic autorefraction at ages 11 and 15 years (minimum N=4,737). Axial length and radius of corneal curvature were measured with an IOLmaster at age 15 years (minimum N=2,676). Growth trajectories, and an allelic score for 180 genetic variants associated with adult height, were tested for association with refractive error and eye size.

Main outcome measures—Non-cycloplegic autorefraction at ages 11 and 15 years, and axial length and corneal curvature at age 15 years.

Results—Height growth trajectory during the linear phase between 2.5-10 years was negatively associated with refractive error at 11 and 15 years ($P<0.001$), but explained <0.5% of inter-subject variation. Height and weight growth trajectories, especially shortly after birth, were positively associated with axial length and corneal curvature ($P<0.001$), predicting 1-5% of trait variation. Height growth after 2.5 years was not associated with corneal curvature, whilst the association with axial length continued up to 10 years. The height allelic score was associated with corneal curvature ($P=0.03$) but not with refractive error or axial length.

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Conclusions—Up to the age of 10 years, shared growth mechanisms contribute to scaling of eye and body size but minimally to the development of myopia.

Keywords

ALSPAC; myopia; growth trajectories; longitudinal; refractive error

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Introduction

In Western countries, myopia is rare in infancy, but then increases in prevalence to reach a level of 25-50% by adulthood[1-5]. Other countries show a similar trend of refractive error shifting towards more negative values during childhood, albeit with widely differing proportions of the population becoming myopic[5-7]. The major structural cause of myopia is an excessive axial elongation of the eye: On average, each diopter (D) of myopia in young adults is associated with an axial length increase of approximately 0.3-0.5 mm[8,9]. In a longitudinal study, Jones et al.[10] observed that the childhood growth trajectory of eyes destined to become myopic differed from that of eyes destined to remain emmetropic. At the age of 6 years, both sets of children had similarly sized eyes (axial length ~22.5 mm). However, while the eyes of would-be-emmetropes elongated at a rate of ~1 mm per $\log_e$ yearly increase in age, those of would-be-myopes grew at a rate of ~2.4 mm per unit $\log_e$ (age).

The growth of the eye at a time when body stature is also increasing suggests the potential for a shared mechanism of action. Indeed, studies in newborns, children and adults have demonstrated associations between body stature and axial eye length, providing indirect evidence for co-ordinated growth of the eye and body (after adjusting for the typically observed difference in axial length between the sexes)[11-21]. Direct support for a causal association comes from studies of individuals who fail to produce insulin-like growth factor 1 (IGF-1) due to growth hormone (GH) deficiency. Children with GH deficiency have shorter than usual axial lengths as well as short stature[22]. Furthermore, GH supplementation in these patients, and IGF-1 supplementation in patients with Laron syndrome (dysfunction of the GH receptor), at least partially brings axial length back within the normal range, as also occurs for height[23,24]. Furthermore, in both humans[25] and chickens[26], a common set of genetic variants has been shown to regulate the growth of the body and the eye, although none of the variants themselves have yet been identified. However, a recent meta-analysis of genome-wide association study (GWAS) results for 183,727 individuals identified 180 single nucleotide polymorphisms (SNPs) associated with height in adulthood[27]. Together, these SNPs explain about 10% of variation in adult height.

In contrast to the consensus of reports describing significant associations between body stature and axial length, the literature on the relationship between body stature and refractive error is contradictory[5,28-36]. In emmetropic eyes, a long axial length is generally offset by a flatter cornea[9,37]. In humans and animal models there is evidence that these two major determinants of refractive error are co-ordinately regulated by genetic means[26,38,39]. Thus, in order for an increase in body stature to be associated with a change in refraction, the

growth mechanism concerned might well operate differently or separately to the system that ensures co-ordination between the ocular components.

Whereas a person's weight or height at any instant during their life represents the cumulative result of their growth up to that point, growth trajectories allow the study of factors affecting growth at given ages[40]. A recent "lifecourse analysis" of longitudinally-collected data on body stature in the National Child Development Study (NCDS) 1958 British birth cohort, coupled with refractive error measurement carried out in adulthood, highlighted associations between myopia and intrauterine growth restraint, as well as childhood growth trajectories[5]. To explore the relationship between growth trajectories for body stature and their relationship to myopia in more detail, we carried out a comprehensive analysis of these variables in a contemporary British birth cohort – the Avon Longitudinal Study of Parents and Children (ALSPAC). Furthermore, as a recent study has shown that the 180 SNPs currently known to be associated with adult height explain 5-6% of the variation in height growth trajectories of children in the ALSPAC cohort[41], we also explored the extent to which these SNPs could explain variation in refractive error.

Methods

Sample

ALSPAC is an ongoing longitudinal birth cohort study designed to investigate the determinants of development, health, and disease during childhood and beyond[42]. Pregnant women with an expected date of delivery between 1st April 1991 and 31st December 1992, resident in the former Avon health authority area in Southwest England, were eligible to participate in the study. A cohort of 14,541 pregnant women was established resulting in 13,988 children who were alive at 12 months of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases that failed to join the study originally, resulting in an additional 548 children. Data collection has been by various methods including self-completion questionnaires sent to the mother, to her partner and after age 5 to the child; direct assessments and interviews in research clinics held when the participants reached particular ages; biological samples and linkage to school and hospital records. Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and the three local research-ethics committees.

Outcomes

Subjects were invited to research clinics when they were aged approximately 11 and 15 years old. At both clinics, refractive error was measured using non-cycloplegic autorefraction (Canon R50 instrument, Canon USA Inc., Lake Success, NY). Approximately midway during the period when the 15 year clinic was running, equipment was obtained to assess axial length (AXL) and radius of corneal curvature (RCC) so these were also measured in a subset of participants (Zeiss IOLmaster, Carl Zeiss Meditec, Welwyn Garden City, UK). The mean spherical equivalent (MSE) refractive error was calculated as the sphere power plus half of the cylinder power. Outlier MSE measurements were set as missing values. The average of the MSE in the right and left eyes was used in the

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analyses[43,44], and likewise for AXL and RCC. The primary outcome measure was MSE at age 15. Secondary outcomes of interest were MSE at age 11, and AXL and RCC at age 15.

Growth measures and modelling

Birth weight was extracted from medical records, and birth length was measured by ALSPAC staff who visited newborns soon after birth (median 1 day, range 1-14 days), using a Harpenden neonatometer. Height and weight data were extracted from health visitor records, parental questionnaires, and measurements from research clinic attendances. During clinic attendance, height was measured to the last complete mm using a Harpenden Stadiometer and weight was measured using a Tanita Body Fat Analyser (Model TBF 305; Tanita Europe Ltd, Amsterdam, The Netherlands).

The number of measures per child was very variable, as were the ages at which each measurement was taken for example, the median number of height measures per child was 8, inter quartile range 6-11. Thus a methodology was required to estimate a full and comparable growth trajectory for each child regardless of when and how many times they were measured. Multi-level modelling is one way of doing this[45]. All available measures for each child are included in the analysis, under a missing at random assumption, and a full trajectory from birth to age 10 years is estimated for each child as long as they have two or more growth measures in that time. Such multi-level models were used to derive trajectories of height and weight from birth to age 10.

The full methodology has been described previously[45,46]. Briefly, measurements >4 SD from the mean for each sex and age-specific group were re-coded as missing values (101 measurements from 96 subjects). Individual trajectories were estimated using linear spline mixed-effects models (two levels: measurement occasion and individual), with the software package MLWiN version 2.10 (www.cmm.bristol.ac.uk/MLwiN/index.shtml; last accessed 29th February 2012). We identified three spline points that demarcated four intervals during the period from birth to age 10 during which the rates of height and weight change were approximately linear[46,47]. All models were constructed separately for boys and girls and separate spline points were identified for height and weight trajectories. For height in boys, the four periods of linear growth were: 0-3 months, 3-10 months, 10-29 months and 29-120 months. For girls, the height periods were between: 0-2 months, 2-11 months, 11-32 months and 32-120 months. For weight in boys, the four periods of linear growth were: 0-4 months, 4-11 months, 11-80 months and 80-120 months. For girls, the weight periods were between: 0-4 months, 4-10 months, 10-80 months and 80-120 months. The positions of spline points were optimized by comparing the log-likelihood values of models using spline points around the estimated ages, to the nearest one month. The source of measurement was included in the models as both fixed and random effects (to allow for parental under- and over-estimation and for the different measurement errors of each of the sources)[45,46].

We avoided modelling growth trajectories beyond the age of 10 for two reasons. Firstly, the onset of puberty would have necessitated individual child-specific spline points due to variation in the age of puberty onset. Secondly, the upper limit of 10 years provided a clear separation between the exposure (growth trajectories) and the main outcome measure (MSE at age 15) of this prospective study, thus making reverse causality extremely unlikely.

Individual level residuals describing each individual's deviation from the average in terms of: intercept (birth length or birth weight) and rate of growth in each of the four periods of height/weight change were estimated by the multi-level model. These were standardized (i.e., subtract the mean and divide by the standard deviation, by gender) to have a mean of zero and variance of one. These standardized individual level residuals are used as the exposure in our analyses.

Additional covariates

Information about parental self-reported myopia, parental social class, maternal age, gestational age, breastfeeding, maternal smoking, time spent reading for pleasure, time spent outdoors and parity were collected as described elsewhere[48,49] Fat mass (as an indicator of obesity) was estimated by whole-body dual-energy X-ray absorptiometry (DXA)-scanning, with a Lunar Prodigy narrow fan-beam densitometer (GE Healthcare, Bedford, UK).

Allelic score derived from 180 SNPs associated with adult height

Genome-wide single nucleotide polymorphism (SNP) genotyping of the majority of the ALSPAC cohort was carried out using Illumina HumanHap550 quad arrays, as described[41]. After quality control steps to remove subjects with unreliable data or SNPs with rare minor allele frequencies, poor call rate or departure from Hardy-Weinberg equilibrium, genotypes at nongenotyped common SNP sites were imputed using MACH[41]. An allelic score for each child was calculated by summing the dose (on the scale 0-2) of "tall" alleles at each of the 180 SNP loci associated with adult height[27]. Together, these 180 SNPs explain approximately 10% of the variance in adult height and approximately 5% of the variance in height by age 10 amongst the ALSPAC cohort. Further details allelic score calculation method have been reported elsewhere[27,41].

Statistical methods—For each of the four outcome measures (MSE, AXL and RCC at age 15, and MSE at age 11) we assessed the association with each of the growth trajectory measures (individual-level residuals, i.e., deviation from the average in terms of birth weight/length, and each of the four growth rates). We carried out the analysis using the height trajectories, weight trajectories, and the weight trajectories adjusted for the height trajectories. The resulting regression coefficients can be interpreted as the change in outcome associated with a one standard deviation increase in birth weight/length or the rate of growth.

The basic model ("Model 1") was adjusted for gender, "Model 2" was adjusted for gender and all preceding growth periods, and "Model 3" was adjusting also for fat mass (measured contemporaneously to the outcome measure), number of myopic parents, better social class of parents, maternal age, gestational age, breastfeeding (never, up to 4 months, > 4 months), maternal smoking during first trimester of pregnancy (Yes/No), time spent reading for pleasure (High/Low), time spent outdoors (High/Low) and parity (first, second, third, fourth-or-above) using SPSS v.18 (SPSS Inc., Chicago, USA). Several of the covariates included in Model 3 were measured *after* one or more of the growth intervals: For example, time spent reading for pleasure and time spent outdoors were assessed when children were aged 8-9 years old – close to the end our the growth trajectory modelling period. Strictly, these

variables were not potential confounders. However, we made the assumption that children's behaviour would track backwards in time, such that a child who spent little time outdoors relative to their peers at age 8-9 years, for example, would also have spent a relatively short time outdoors at earlier ages.

The allelic score variable (mean = 180.6, standard deviation = 8.4) was standardized, and then tested for association with each of the four outcome measures (MSE, AXL and RCC at age 15, and MSE at age 11) using linear regression. The regression coefficients from these analyses can be interpreted as the change in refractive error (or AXL or RCC) associated with a one standard deviation increase in the allelic score.

Results

The demographics of the study sample are presented in Table 1. Of the baseline group of 14536 ALSAPC children alive at 1 year (13988 core cohort and 548 'new' cases); 193 multiple births were excluded. Complete growth data were available for 13509. Of these, 11510 and 10747 children were invited to attend the 11 and 15 year clinics respectively (i.e., had not been lost to the study due to death, loss of contact details or explicit withdrawal). 7153 and 5515 children attended the 11 year and 15 year clinics, respectively, with a total of 6815 having growth trajectory data and at least one outcome measure. Table 1 demonstrates that children included in the study were more likely to come from higher social class families, have mothers who did not smoke and have lower parity and were more likely to be breastfed for longer. A summary of the raw, unadjusted body stature and outcome measures are given in Table 2.

Refractive error and growth trajectory

The rate at which a child grew in height during the long, roughly linear growth interval between months 32-120 months (~2½-10 years) was related – albeit with low magnitude – to their MSE at age 15 years (Table 3). Specifically, children whose rate of height increase was one standard deviation above the average over this period had a more negative refractive error by −0.06 D (95% CI: −0.09, −0.03; P<0.0001) such that they were less hyperopic/more myopic than the average for the cohort (which was −0.04 D). This relationship was not reduced after adjusting for height at birth, for the rates of height increase during the preceding 2½ years, and for a range of covariates potentially related to refractive development (difference in MSE for a one standard deviation above-average increase in height velocity, after adjustment: −0.08 D; 95% CI: −0.13, −0.03; P=0.001). A child's rate of height increase during this 2½-10 years interval was also (i.e., already) associated with their MSE at age 11 years (Table 4): The magnitude of the association being very similar to that observed at age 15. Changes in a child's height growth trajectory before 2½ years of age exhibited weaker (or negligible) associations with MSE at ages 15 and 11 years. Furthermore, although there was a tendency for babies with above average birth lengths to have a slightly more negative (myopic) MSE by the time they reached 11 years of age, this association was no longer evident when they reached age 15 (Tables 3 and 4). Overall, the results indicated that children with above-average rates of height growth between the ages of 2½-10 years became more myopic/less hyperopic, on average, than their

peers during this period. Moreover, the shift in MSE was maintained for the next 4 years. Nevertheless, the magnitude of the association was low (e.g., in our model, a one standard deviation increase in height velocity predicted between 0.3% and 0.6% of the variation in refractive error of the cohort).

Children's rates of weight gain over the period from birth to 10 years of age showed a different general growth trajectory pattern to that of their height. Thus, whereas height "velocity" was approximately linear from the age of 2½ years right up until the age of 10, weight "velocity" was roughly linear between ~1-7 years (10-80 months of age) and then continued at a lower linear rate during the period from 7 to 10 years. Interestingly, there was little evidence of an association between the rate of weight gain and MSE at age 15, especially after adjustment for preceding growth periods (Table 3). Similarly, the magnitude of associations between weight growth trajectory and MSE at age 11 were very small, although there was some evidence of a negative association between weight change between 1-7 and 7-10 years and MSE at 11 years in the unadjusted models (not seen for MSE at 15 years) (Table 4).

Because of the difference in the results for the height velocity and weight velocity, we examined whether the growth trajectory of "weight-for-height" was associated with refractive error. For MSE at both ages 11 and 15 (Table 3 and 4), the strongest association was with weight-for-height at birth (difference in MSE at 15 years for a one standard deviation above-average increase: +0.10 D, 95% CI: 0.04, 0.15). Again, however, the effect size was low (in our model, weight-for-height at birth predicted <0.3% of the variation in MSE at age 15 years), and postnatal weight for height changes had negligible associations with MSE.

Axial length, radius of corneal curvature and growth trajectory

The growth trajectory for height over the full 10 year period was strongly positively associated with AXL at age 15 (Table 5). The magnitude of the association was greatest very early in life: For instance, length at birth predicted ~2.5% of the normal variation in axial length at age 15 years, and, after adjustment for preceding growth periods, subjects with a one standard deviation above-average increase in the rate of height growth during the periods 0-2 months, 2-11 months, and 11-32 months had an AXL that was longer than average by 0.09 (95% CI: 0.04, 0.14; P<0.0001), 0.08 (95% CI: 0.04, 0.13; P=0.07) and 0.06 (95% CI: 0.03, 0.09; P<0.0001) mm. Prior to adjustment for preceding growth intervals, the growth trajectory for height over the 2½-10 years (32-120 months) interval was also associated with AXL (0.10 mm; 95% CI: 0.07, 0.13; P<0.0001) but this association was much reduced after adjustment for preceding growth periods (0.04 mm; 95% CI: 0.01, 0.08; P<0.0001). Overall, the results suggested that above-average increases in the rate of height growth trajectory were associated with above average increases in AXL throughout the birth-to-10 years growth period, with the associations being stronger prior to the age of 2½ years. The pattern of results for weight growth trajectory was very similar to that for height, while weight for height showed little or no association with AXL (Table 5). Adjustment for risk factors potentially related to refractive development had little impact on the magnitude of the associations between height or weight gain and AXL at age 15 (Model 3, Table 5).

The modelling results for RCC (Table 6) were similar to those for AXL except that growth trajectory close to the time of birth was even more strongly predictive of RCC at age 15 than was the case for AXL. Birth length and height growth trajectory during the 2 months following birth each predicted ~4% of the normal variation in RCC, with a one standard deviation above-average increase being associated with a ~0.06 mm (95% CI: 0.05, 0.07; P<0.0001) flattening of RCC in each case. After adjustment for birth length, the effect size of the 0-2 months association was reduced by about 50%: being associated with an RCC ~0.03 mm (95% CI: 0.02, 0.05; P<0.0001) flatter than average, and predicting less than 0.7% of the variation in RCC. However, further adjustment for risk factors potentially related to refractive development did not affect the magnitude of the association appreciably. Between 2½-10 years the magnitude of the association between height trajectory and RCC at age 15 was effectively zero (95% CI: −0.01, 0.01) after adjusting for preceding growth periods. As with AXL, the growth trajectory for weight showed a similar pattern of association with RCC as that seen with height. Again, the weight for height growth trajectory showed little or no association with RCC (Table 6).

Adult height genetic variants (allelic score), refractive error and eye size

There was no evidence that the group of 180 SNPs associated with height in adulthood was associated with refractive error (MSE at age 11, P=0.46; MSE at age 15, P=0.60; Table 7). Similarly, the allelic score for these height SNPs was not associated with AXL (P=0.22). However, for RCC at age 15 years, there was suggestive evidence of an association: individuals with a one standard deviation above-average increase in the height allelic score had an RCC that was 0.01 mm (95% CI: 0.001, 0.024; P=0.03) flatter than average. The height allelic score explained ~0.2% of the variation in RCC (Table 7).

Discussion

The height of many human populations has increased over recent decades[50] as has the prevalence of myopia[51,52], which raises the question as to whether these changes may be causally related. Unfortunately, the literature describing the association between body stature and refractive error paints a complex picture. Nearly all prior studies have been cross-sectional in design, with measurements of stature and refraction obtained at a single, co-incident point in time. Because changes in stature and eye size are cumulative, such comparisons become complicated by growth during preceding time intervals. The level of complication increases further still if the subject cohort is not of a uniform age, since refractive error and height can continue to vary through adulthood[5,53]. In the study with perhaps the greatest statistical power to disclose a relationship between stature and refractive error at a single time-point, Rosner et al.[30] found no association between myopia and either height or weight, in a large sample (N=106,926) of male military conscripts with a narrow age range (17-19 years). However, the possibility remains that a change in growth velocity during a specific time period is associated with refractive error, even though the population's stature at any given instant in time is not. Here we found that an above-average rate of height increase during the roughly linear growth velocity interval between ~2½-10 years had a statistically significant, but low magnitude association with refractive error. Thus, even dramatic differences in growth trajectory during this interval would have led to

differences in refractive error of less than 0.50 D by the time children reached the age of 15. To our knowledge, the only prior study to have investigated growth trajectories and myopia is that of Rahi et al.[5] In a sample of 2,487 subjects from a national birth cohort, they observed that the growth trajectories for height and body mass index were related to refractive error in adulthood (specifically, age 44 years). However, the study of Rahi et al.[5] was a full lifecourse analysis that encompassed a broad range of prenatal and early-life influences, and hence the authors provided only a limited account of the role of growth trajectories.

The average height of human populations is strongly influenced by environmental factors relating to diet and socioeconomic status[46]. On the other hand, within affluent populations, variation in height is largely controlled by additive polygenes, i.e., a very large number of genetic variants each exerting a small, independent, “push” or “pull” away from or towards the mean[54]. By comparing growth trajectories in children with the stature of their parents, Botton et al.[40] have shown that this relatively straightforward scenario hides a complex interplay of maternal and paternal genetic, epigenetic or shared environment effects, alternating in their impact at different stages of childhood. Our findings regarding the growth trajectories of height (and weight) and ocular component dimensions at age 15, were in accordance with the consensus from previous work[13-19,25], namely, that tall individuals tend to have larger eyes (a longer axial length and a flatter cornea). Again, however, the magnitude of these associations in the ALSPAC cohort was modest – explaining at most a few percent of the natural variation in AXL and RCC at age 15 years. Interestingly, different relationships were seen for AXL and RCC in regard to the timing of their respective associations with body growth trajectory. For instance, an above-average rate of increase in height up until the age of 10 was associated with a longer AXL at age 15, whereas only growth velocities during the first few years of life were predictive of RCC at age 15. This suggests that early growth is more important in determining RCC in young adulthood than is the case for AXL, which is consistent with the virtual cessation in RCC growth seen in both cross-sectional and longitudinal studies after the first few years of life, compared to the continued elongation of the globe[10,14,55,56]. The association between stature and eye size has led to the suggestion that genetic variants known to influence height might also influence axial length[25,56,57]. However, we found no evidence that a group of common SNPs that explain ~10% of the variation in adult height[27] and 5-6% of the variation in height by age 10 years[41] was predictive of AXL. Nevertheless, there was suggestive evidence that this group of SNPs was predictive of RCC, but together the SNPs explained only ~0.2% of the variation in this trait. Our results appear to contradict previous findings that suggest inter-subject variation in axial length, corneal curvature and height are controlled in part by a common set of genetic variants[26,57]. A lack of statistical power is one potential reason for the lack of association observed here. Other possible explanations are (i) that the modelling assumptions we used in constructing the allelic score variable (for example, that all SNPs had an equal effect size) were overly simplistic, (ii) that the SNPs which co-regulate eye and body growth tend to have lower minor allele frequencies (MAFs) than SNPs controlling height alone (as such low-MAF SNPs would be under-represented in the group of 180 currently known SNPs we tested), and (iii) that the previously observed genetic co-regulation of eye and body growth is driven more by gene-gene or gene-

environment interactions, or transgenerational epigenetic effects, than by the additive genetic effects that seem to largely control the inheritance of height in adults[54].

At the population level[59], even a small negative shift in the mean of the refractive error distribution, produced by a shared effect of increasing height and eye size, might be sufficient to raise the prevalence of myopia considerably. However, despite the appeal of this line of reasoning, and the attraction of axial length as an endophenotype for refractive error[60], recent results in an animal model of myopia suggest that the genetic variants that influence overall body size and eye size might be distinct from those that confer susceptibility to myopia[26,61]. Moreover, cross-sectional studies in both children and adults demonstrate that the relationship between axial length and refractive error is not "one-to-one" in nature, as exemplified by the large range of axial lengths observed in emmetropes, and the observed correlations between refractive error and both crystalline lens and corneal growth trajectories[10, 37, 61-63]. The findings here also suggest that – at the level of the individual – the genetic variants found to influence height in adulthood might not be predictive of myopia development to any useful extent.

As well as the strengths of a large sample size, a unique approach to modelling growth trajectories, and a large number of repeat measurements of body stature, this study had a number of limitations. Firstly, refractive error was measured using non-cycloplegic autorefraction. Independent evaluation[64] of the readings obtained at age 15 suggested that lack of cycloplegia resulted in only a small systematic bias of approximately −0.25 D (Supplementary Material online). However, the variation about this mean error value will have reduced our statistical power to detect associations with growth trajectories. The measurement error of non-cycloplegic autorefraction would have been greater for the readings obtained at age 11. Secondly, AXL and RCC were measured on only a single occasion. It would have been interesting to monitor changes in these parameters concurrently with height and weight throughout childhood, since this would have helped to narrow down the interval most closely associated with myopia development. Thirdly, we did not investigate the influence of puberty, which is known to have a profound impact on growth. According to a previous report[45], most of the ALSPAC subjects were considered prepubertal at the age we terminated our growth trajectory modelling (10 years). Hence, puberty may have introduced only a limited degree of additional variation into our model parameters. Finally, there was a bias towards better familial status in those children included in the study. This may have led to an under-estimate of the associations we have shown here, due to the social inequalities in childhood growth[46].

In conclusion, the height growth trajectory of children between the ages of 2½-10 years was weakly predictive of their refractive error at age 15 years, explaining ≤0.5% of the inter-subject variation in MSE. Over the same period, the growth trajectories for height and weight were slightly more predictive of ocular dimensions at age 15, with growth trajectory predicting 1-5% of the inter-subject variation in AXL and RCC. We found no association between participants' refractive error and their summed genotypes ("tall" vs "short" alleles) at a set of 180 SNPs known to be associated with adult height. This implies that, as a group, these variants do not strongly influence myopia development up to age 15 and thus that the aberrant axial eye growth that characterizes myopia arises in large part through mechanisms

distinct from those controlling the growth of organs contributing to body stature. The subtle association between growth trajectory and refractive error at 15 in our data could be the result of direct effects of as yet unidentified genetic variants or indirect mechanisms involving known variants, such as gene-environment interaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics in subjects used for growth trajectory modelling.

Variable	Included[a] (n=6,815)	Excluded[a] (n=7,528)	P-value
Gender			P<0.0001
Boy	49.6%	54.1%	
Girl	51.4%	46.9%	
Family social class[b]			P<0.0001
I	13.9%	7.9%	
II	39.1%	28.7%	
III NM	11.6%	10.2%	
III M	26.1%	37.0%	
IV	7.6%	12.1%	
V	11.7%	4.1%	
Parity			P<0.0001
0	47.0%	42.5%	
1	34.3%	35.6%	
2+	18.7%	21.9%	
Breastfeeding duration			P<0.0001
Never	23.0%	33.7%	
1-4 months	37.5%	34.6%	
4+ months	39.5%	31.7%	
Maternal smoking			P<0.0001
No	86.2%	73.8%	
Yes	13.8%	26.2%	
Maternal age (years)			P<0.0001
Mean (SD)	29.0 (4.6)	26.9 (5.1)	

[a]The combined sample of those included and excluded comprised of ALSPAC participants who were alive at 1 year and were singletons or the first born of multiple births.

[b]Family Social class defined as the highest reported by the mother and her partner based on occupation - ranges from I (professional) through II, III (subdivided into Manual and Non-Manual), IV and V

Abbreviations: SD - Standard Deviation; ALSPAC - Avon Longitudinal Study of Parents and Children

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Table 2

Summary statistics for mean growth rate and ophthalmic outcome variables, by gender. Values are presented as Mean (Standard Deviation).

Variable	Boys	Girls
Mean growth rate		
Height		
At birth (cm)	50.65 (1.78)	49.65 (1.58)
Period 1 (cm/month)	3.83 (0.20)	3.86 (0.16)
Period 2 (cm/month)	1.69 (0.20)	1.84 (0.16)
Period 3 (cm/month)	0.96 (0.09)	0.90 (0.09)
Period 4 (cm/month)	0.53 (0.04)	0.53 (0.04)
Weight		
At birth (kg)	3.59 (0.52)	3.46 (0.46)
Period 1 (kg/month)	0.96 (0.15)	0.82 (0.13)
Period 2 (kg/month)	0.43 (0.11)	0.44 (0.10)
Period 3 (kg/month)	0.19 (0.03)	0.20 (0.03)
Period 4 (kg/month)	0.27 (0.09)	0.28 (0.10)
Ophthalmic outcome		
MSE at 15 years (D)	−0.001 (1.16)	−0.076 (1.10)
MSE at 11 years (D)	−0.383 (1.29)	−0.415 (1.26)
AXL at 15 years (mm)	23.67 (0.87)	23.18 (0.85)
RCC at 15 years (mm)	7.87 (0.27)	7.77 (0.251)

Abbreviations: MSE – Mean Spherical Equivalent; AXL – Axial Length; RCC – Radius of Corneal Curvature; D-Diopters

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Table 3

Associations between various growth periods and mean spherical equivalent at 15 years (minimum n=4,737)

	Model 1[a]		Model 2[b]		Model 3[c]	
	Effect size (95% CI)	**p-value**	**Effect size (95% CI)**	**p-value**	**Effect size (95% CI)**	**p-value**
Height: Birth	−0.026 (−0.064, 0.011)	0.174			−0.022 (−0.061, 0.017)	0.273
Height: 0-2 months	−0.036 (−0.074, 0.003)	0.061	−0.033 (−0.086, 0.020)	0.224	−0.032 (−0.096, 0.031)	0.319
Height: 2-11 months	−0.016 (−0.054, 0.021)	0.396	−0.021 (−0.071, 0.029)	0.403	0.017 (−0.043, 0.077)	0.582
Height: 11-32 months	−0.003 (−0.039, 0.034)	0.881	0.009 (−0.029, 0.048)	0.640	0.034 (0.011, 0.080)	0.138
Height 32-120 months	−0.059 (−0.092, −0.027)	<0.0001	−0.071 (−0.111, −0.032)	<0.0001	−0.081 (−0.129, 0.034)	0.001
Weight: Birth	0.022 (−0.015, 0.059)	0.254			0.024 (−0.018, 0.066)	0.257
Weight: 0-4 months	−0.015 (−0.052, 0.022)	0.422	−0.018 (−0.055, 0.019)	0.355	−0.034 (−0.077, 0.010)	0.13
Weight: 4-10 months	−0.032 (−0.068, 0.004)	0.280	0.030 (−0.008, 0.068)	0.125	0.039 (−0.005, 0.082)	0.081
Weight: 10-80 months	−0.030 (−0.062, 0.002)	0.080	−0.047 (−0.085, −0.009)	0.016	−0.006 (−0.055, 0.043)	0.819
Weight 80-120 months	−0.018 (−0.055, 0.019)	0.066	0.002 (−0.053, 0.057)	0.952	0.011 (−0.057, 0.080)	0.740
Weight for height: Birth	0.095 (0.039, 0.152)	0.001			0.079 (0.023, 0.135)	0.006
Weight for height: 0-4 months	0.001 (−0.041, 0.042)	0.983	0.003 (−0.040, 0.045)	0.898	−0.020 (−0.069, 0.030)	0.405
Weight for height: 4-10 months	0.034 (−0.007, 0.075)	0.184	0.061 (0.018, 0.133)	0.005	0.066 (0.012, 0.109)	0.015
Weight for height: 10-80 months	−0.044 (−0.088, −0.001)	0.047	−0.049 (−0.095, −0.003)	0.038	−0.014 (−0.073, 0.046)	0.654
Weight for height: 80-120 months	0.009 (−0.032, 0.049)	0.674	0.031 (−0.026, 0.089)	0.285	0.065 (−0.007, 0.138)	0.078

[a] Adjusted for gender (boy, girl);

[b] Adjusted for gender (boy, girl) and all preceding growth periods;

[c] Adjusted for gender (boy, girl), all preceding growth periods and fat mass (kg) at time of outcome, family social class (I, II, III NM, III M, IV, V), gestation (in weeks), maternal age, breastfeeding duration (Never, 1-4 months, 4+ months), parity (0, 1, 2+), maternal smoking in pregnancy (Yes, No), number of myopic parents (0, 1, 2), time spent reading for pleasure (High, Low), time spent outdoors (High, Low), and ethnicity (white European, other).

Abbreviations: CI – Confidence Interval

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Table 4

Associations between various growth periods and mean spherical equivalent at 11 years (min n=6,355)

	Model 1[a]		Model 2[b]		Model 3[c]	
	Effect size (95% CI)	**p-value**	**Effect size (95% CI)**	**p-value**	**Effect size (95% CI)**	**p-value**
Height: Birth	−0.043 (−0.071, −0.014)	0.003			−0.041 (−0.075, −0.007)	0.017
Height: 0-2 months	−0.051 (−0.079, −0.021)	0.001	−0.040 (−0.080, 0.001)	0.050	−0.036 (−0.084, 0.013)	0.147
Height: 2-11 months	−0.020 (−0.047, 0.009)	0.176	−0.032 (−0.070, 0.010)	0.096	−0.009 (−0.054, 0.036)	0.692
Height: 11-32 months	−0.031 (−0.059, −0.003)	0.027	−0.018 (−0.048, 0.011)	0.229	0.001 (−0.033, 0.036)	0.941
Height 32-120 months	−0.079 (−0.104, −0.054)	<0.0001	−0.079 (−0.011, −0.049)	<0.0001	−0.075 (−0.112, −0.039)	<0.0001
Weight: Birth	−0.007 (−0.035, 0.022)	0.642			−0.008 (−0.044, 0.029)	0.680
Weight: 0-4 months	−0.013 (−0.042, 0.051)	0.360	−0.013 (−0.041, 0.016)	0.385	−0.014 (−0.049, 0.020)	0.403
Weight: 4-10 months	0.009 (−0.018, 0.038)	0.50	0.010 (−0.019, 0.040)	0.484	0.011 (−0.023, 0.045)	0.536
Weight: 10-80 months	−0.036 (−0.063, −0.009)	0.010	−0.040 (−0.068, −0.011)	0.007	−0.026 (−0.065, 0.015)	0.214
Weight 80-120 months	−0.036 (−0.061, −0.012)	0.004	−0.021 (−0.064, 0.022)	0.333	−0.031 (−0.087, 0.026)	0.286
Weight for height: Birth	0.060 (−0.016, 0.103)	0.007			−0.005 (−0.036, 0.026)	0.761
Weight for height: 0-4 months	0.011 (−0.021, 0.042)	0.499	0.010(−0.022, 0.041)	0.541	0.004 (−0.033, 0.042)	0.816
Weight for height: 4-10 months	0.023 (−0.010, 0.054)	0.155	0.042 (−0.054, 0.014)	0.071	0.033 (−0.006, 0.071)	0.095
Weight for height: 10-80 months	−0.027 (−0.060, 0.005)	0.102	−0.020 (−0.054, 0.014)	0.246	−0.010 (−0.060, 0.040)	0.680
Weight for height: 80-120 months	0.014 (−0.016, 0.045)	0.352	0.007 (−0.057, 0.0582)	0.745	0.026 (−0.035, 0.088)	0.395

[a] Adjusted for gender (boy, girl);

[b] Adjusted for gender (boy, girl) and all preceding growth periods;

[c] Adjusted for gender (boy, girl), all preceding growth periods and fat mass (kg) at time of outcome, family social class (I, II, III NM, III M, IV, V), gestation (in weeks), maternal age, breastfeeding duration (Never, 1-4 months, 4+ months), parity (0, 1, 2+), maternal smoking in pregnancy (Yes, No), number of myopic parents (0, 1, 2), time spent reading for pleasure (High, Low), time spent outdoors (High, Low), and ethnicity (white European, other).

Abbreviations: CI – Confidence Interval

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Table 5

Associations between various growth periods and axial length at 15 years (minimum n=2,623)

	Model 1[a]		Model 2[b]		Model 3[c]	
	Effect size (95% CI)	**p-value**	**Effect size (95% CI)**	**p-value**	**Effect size (95% CI)**	**p-value**
Height: Birth	0.147 (0.114, 0.181)	<0.0001			0.169 (0.118, 0.220)	<0.0001
Height: 0-2 months	0.150 (0.116, 0.185)	<0.0001	0.087 (0.039, 0.135)	<0.0001	0.077 (0.020, 0.135)	0.009
Height: 2-11 months	0.031 (−0.002, 0.005)	0.066	0.083 (0.039, 0.126)	0.066	0.094 (0.041, 0.146)	<0.0001
Height: 11-32 months	0.088 (0.056, 0.120)	<0.0001	0.060 (0.027, 0.094)	<0.0001	0.051 (0.012, 0.090)	0.011
Height 32-120 months	0.099 (0.070, 0.128)	<0.0001	0.044 (0.011, 0.078)	<0.0001	0.037 (−0.003, 0.078)	0.072
Weight: Birth	0.114 (0.081, 0.147)	<0.0001			0.128 (0.075, 0.182)	<0.0001
Weight: 0-4 months	0.075 (0.042, 0.109)	<0.0001	0.063 (0.029, 0.096)	<0.0001	0.070 (0.031, 0.110)	<0.0001
Weight: 4-10 months	0.029 (−0.003, 0.062)	0.074	0.054 (0.021, 0.088)	0.001	0.056 (0.017, 0.095)	0.005
Weight: 10-80 months	0.098 (0.068, 0.130)	<0.0001	0.065 (0.033, 0.098)	<0.0001	0.065 (0.021, 0.108)	0.003
Weight 80-120 months	0.055 (0.027, 0.083)	<0.0001	−0.041 (−0.088, 0.006)	0.091	−0.038 (−0.098, 0.021)	0.206
Weight for height: Birth	0.008 (−0.043, 0.060)	0.753			0.014 (−0.058, 0.089)	0.698
Weight for height: 0-4 months	0.010 (−0.027, 0.048)	0.581	0.020 (−0.017, 0.058)	0.288	0.034 (−0.010, 0.078)	0.125
Weight for height: 4-10 months	0.019 (−0.016, 0.056)	0.281	0.009 (−0.029, 0.046)	0.645	0.011 (−0.033, 0.054)	0.633
Weight for height: 10-80 months	0.073 (0.035, 0.111)	<0.0001	0.027 (−0.012, 0.066)	0.176	0.024 (−0.029, 0.077)	0.374
Weight for height: 80-120 months	−0.002 (−0.037, 0.032)	0.882	−0.050 (−0.108, −0.006)	0.027	−0.074 (−0.138, −0.010)	0.023

[a] Adjusted for gender (boy, girl);

[b] Adjusted for gender (boy, girl) and all preceding growth periods;

[c] Adjusted for gender (boy, girl), all preceding growth periods and fat mass (kg) at time of outcome, family social class (I, II, III NM, III M, IV, V), gestation (in weeks), maternal age, breastfeeding duration (Never, 1-4 months, 4+ months), parity (0, 1, 2+), maternal smoking in pregnancy (Yes, No), number of myopic parents (0, 1, 2), time spent reading for pleasure (High, Low), time spent outdoors (High, Low), and ethnicity (white European, other).

Abbreviations: CI – Confidence Interval

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Table 6

Associations between various growth periods and corneal curvature at 15 years (minimum n=2,549)

	Model 1[a]		Model 2[b]		Model 3[c]	
	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value
Height: Birth	0.060 (0.050, 0.070)	<0.0001			0.054 (0.049, 0.072)	<0.0001
Height: 0-2 months	0.059(,0.048, 0.069)	<0.0001	0.031 (0.016, 0.045)	<0.0001	0.030 (0.013, 0.047)	0.001
Height: 2-11 months	0.005(−0.005, 0.015)	0.338	0.023 (0.010, 0.036)	<0.0001	0.021 (0.005, 0.037)	0.009
Height: 11-32 months	0.026 (0.016, 0.036)	<0.0001	0.015 (0.005, 0.025)	0.003	0.016 (0.004, 0.028)	0.009
Height 32-120 months	0.025 (0.016, 0.033)	<0.0001	0.001 (−0.009, 0.012)	0.791	−0.002 (−0.014, 0.010)	0.749
Weight: Birth	0.054 (0.044, 0.063)	<0.0001			0.046 (0.032, 0.058)	<0.0001
Weight: 0-4 months	0.029 (0.019, 0.039)	<0.0001	0.023 (0.013, 0.033)	<0.0001	0.025 (0.013, 0.036)	<0.0001
Weight: 4-10 months	0.019 (0.009, 0.029)	<0.0001	0.031 (0.021, 0.041)	<0.0001	0.027 (0.015, 0.039)	<0.0001
Weight: 10-80 months	0.025 (0.015, 0.034)	<0.0001	0.006 (−0.004, 0.006)	0.242	0.017 (0.004, 0.030)	0.011
Weight 80-120 months	0.009 (0.001, 0.018)	0.031	−0.018 (−0.032, −0.004)	0.012	−0.004 (−0.022, 0.014)	0.647
Weight for height: Birth	0.021 (0.006, 0.036)	0.007			0.019 (0.007, 0.031)	<0.0001
Weight for height: 0-4 months	0.004 (−0.007, 0.015)	0.486	0.008 (−0.003, 0.020)	0.139	0.011 (−0.002, 0.024)	0.105
Weight for height: 4-10 months	0.020 (0.010, 0.032)	<0.0001	0.021 (0.009, 0.032)	<0.0001	0.017 (0.004, 0.030)	0.012
Weight for height: 10-80 months	0.015 (0.004, 0.027)	0.01	−0.007 (−0.019, 0.005)	0.227	0.004 (−0.012, 0.020)	0.606
Weight for height: 80-120 months	−0.007 (−0.018, 0.003)	0.167	−0.020 (−0.035, −0.055)	0.008	−0.005 (−0.024, 0.014)	0.572

[a] Adjusted for gender (boy, girl);

[b] Adjusted for gender (boy, girl) and all preceding growth periods;

[c] Adjusted for gender (boy, girl), all preceding growth periods and fat mass (kg) at time of outcome, family social class (I, II, III NM, III M, IV, V), gestation (in weeks), maternal age, breastfeeding duration (Never, 1-4 months, 4+ months), parity (0, 1, 2+), maternal smoking in pregnancy (Yes, No), number of myopic parents (0, 1, 2), time spent reading for pleasure (High, Low), time spent outdoors (High, Low), and ethnicity (white European, other).

Abbreviations: CI – Confidence Interval

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Table 7

Associations between an allelic score derived from 180 genetic variants associated with height in adults and ophthalmic outcome variables.

Trait	N	Association with a one standard deviation increase in the allelic score (95% CI)		R^2
MSE at 15 years	3,887	−0.011 (−0.053, 0.031)	P=0.60	0.0001
MSE at 11 years	5,154	−0.095 (−0.356, 0.156)	P=0.46	0.0001
AXL at 15 years	2,122	0.024 (−0.014, 0.062)	P=0.22	0.0007
RCC at 15 years	2,092	0.013 (0.001, 0.024)	P=0.03	0.0022

Abbreviations: MSE – Mean Spherical Equivalent; AXL – Axial Length; RCC – Radius of Corneal Curvature; CI – Confidence Interval