Longitudinal Changes of Axial Length and Height Are Associated and Concomitant in Children

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PURPOSE. To examine the association between the longitudinal changes of axial length (AL) and height in Chinese children.

METHODS. The study participants were recruited from the Guangzhou Twin Registry. AL and height were measured every year from 2006 to 2008. AL was measured using partial coherence laser interferometry. Height was measured with the participants standing without shoes. Bivariate correlation coefficients and a multivariate generalized regression model were used to calculate the association between the changes of AL and height. Data from the first-born twins were selected to present the results. The right eye was arbitrarily selected to represent AL of the specific individual.

RESULTS. Mean annual increases of AL and height were 0.22 (SD, 0.17) mm and 3.93 (SD, 3.02) cm, respectively. Correlations between AL and height were 0.47 (95% CI, 0.40–0.52) in 2006. The correlation between AL at 2006 and height at 2008 was 0.44 (95% CI, 0.37–0.51); the correlation between AL at 2008 and height at 2006 was 0.38 (95% CI, 0.32–0.45). These cross-trait cross-time correlation coefficients remained statistically significant after adjusting for age and sex. Plotting the changes of AL and height suggested that the changes of AL and height with age were concomitant; greater changes were observed in younger children.

CONCLUSIONS. The association between AL and height in cross-sectional analysis and longitudinal changes may suggest common pathways for the development of eye size and body size in children. (Invest Ophthalmol Vis Sci. 2011;52:7949–7953) DOI: 10.1167/iovs.11-7684

Myopia is a leading cause of visual impairment in many regions of the world and its prevalence is on the rise. The refractive state depends on many biometric components, such as the corneal curvature, anterior chamber depth, vitreous cavity length, lens thickness and axial length (AL), as well as the refractive power of cornea and lens. Among them, AL is the most important biometric component for myopia, particularly in children. Furthermore, longitudinal studies demonstrate that myopia development is characterized by an increased axial length as well as an elongation of vitreous cavity. Therefore, AL could be used as a surrogate for the research on myopia development.

Cross-sectional studies consistently suggest that AL is positively correlated to height. Taller persons are more likely to have longer ALs (+0.23 mm longer AL, for every 0.10 m difference in height in adults, and +0.29 mm longer AL in boys, +0.32 mm in girls). The changes in eye size in early life or during childhood are concomitant with overall growth and physical development, whereas the cessation ages for AL progression were about the same as the cessation ages for increases in height. Our previous work confirms the shared genetic mechanism between height and AL based on cross-sectional measurement. This suggests potential common pathways for the development of eye size and stature. However, the association between AL and height comes solely from cross-sectional studies. The detailed pattern of development and relationship between AL and height throughout children’s physical development is unknown. This requires a longitudinal observation on a cohort of children over time and, to our best knowledge, reports on the association of longitudinal changes of AL and height are not available.

In the present study, we sought to evaluate the associations between AL and height development in 7- to 15-year-old children by analyzing data from a prospective cohort study. Our primary hypotheses were that changes in AL would be positively associated with changes in height and the patterns of the AL and height changes with age are concomitant during the physical development.

MATERIALS AND METHODS

Participants

The study participants were recruited from the Guangzhou Twin Registry, which has been described in depth elsewhere. In brief, this registry was established in Guangzhou City, China in 2005–2006. All twins born between 1987 and 2000 were identified using an official Household Registry of Guangzhou and followed with door-to-door verification. In July and August 2006, we invited the twins ranging in age from 7 to 15 years (defined at the date of July 1, 2006) living in two districts for the baseline data collection and subsequent annual examinations. For all invited participants, written informed consent was obtained either from parents or legal guardians of the twins after an in-depth explanation of the study. Ethical approval was obtained from the Zhongshan University Ethical Review Board and Ethical Committee of Zhongshan Ophthalmic Center and this study was conducted in accordance with the Tenets of the World Medical Association’s Declaration of Helsinki.

Examinations and Measurements

All participants were examined annually from 2006 to 2008. Age at baseline was defined as the year difference between the birthday and July 1, 2006. Height and AL were measured according to a standardized protocol. Height was measured to the nearest 0.1 cm, with children standing without shoes; AL was measured by noncontact partial-
coherence laser interferometry (IOL Master; Carl Zeiss Meditec, Oberkochen, Germany) in a dark room (~5 lux illumination) before pharmacologic dilation of the pupils. The mean result of 10 continuous measurements was used. Poor measurements with signal-to-noise ratio (SNR) \( < 2.0 \) (displayed as “Borderline SNR,” or “Error”) or measurements with one result differing by >0.1 mm from the others (displayed as “Evaluation!”) were deleted and remeasured. If a participant’s height score was 5 cm less than it was recorded in the last year or the AL score was 2 mm less than it was recorded in the last year, the participant was abandoned. We arbitrarily chose the right eye of each twin in data analysis.

### Statistical Analysis

Analyses were performed by using a statistical analysis system (Release 9.0; SAS Institute, Cary, NC). Descriptive statistics of changes in AL and height were calculated. Changes were defined as differences between the examinations in 2008 and 2006. Results of changes in AL and height were presented as the mean and SE.

Bivariate correlations between AL and height were calculated as the linear correlation between these two traits measured in the same year and cross-trait cross-time correlations were estimated between AL observed in 2006 versus height observed in 2008, as well as AL observed in 2008 versus height observed in 2006. The correlation coefficients were presented as \( R \) (95% confidence interval [CI]) after adjusting for sex and age. A multivariate generalized linear regression model was also used to analyze the multivariate longitudinal data. Child’s sex and age were entered as dependent variables because previous research has suggested that these factors may partly explain variation in AL and height.

### RESULTS

A total of 553 twin pairs ranging in age from 7 to 15 years in 2006 were available for data analysis after excluding 10 pairs with missing data. Given that the first-born and second-born twin data were similar, the first-born twins were arbitrarily selected for analysis. Table 1 describes the changes in AL and height by age and sex categories. All participants were divided into three age groups: 7 to 9 years, 10 to 12 years, and 13 to 15 years. Mean annual increases of AL and height were 0.22 ± 0.17 mm and 3.93 ± 3.02 cm, respectively. Changes of AL in girls were slightly greater than those in boys (\( t \)-test, \( P < 0.001 \)), but greater height changes were observed in boys (\( t \)-test, \( P < 0.001 \)).

Figure 1 and Figure 2 show the distribution of AL and height with age at baseline. Figure 3 describes the 2-year changes of AL and height with age at baseline.
AL and height with age. The tendencies of these two traits with age are somewhat similar. In general, the degree of growth decreases with age for both AL and height. The greatest growth was recorded at 8 years old for AL and at 10 years old for height.

Bivariate correlations between AL and height are given in Table 2. Cross-time correlations between AL and height were statistically significant for 2006 ($r = 0.47$, $P < 0.001$), 2007 ($r = 0.39$, $P < 0.001$), and 2008 ($r = 0.38$, $P < 0.001$). After adjusting for age and sex, the correlation coefficients decreased but remained significant for 2006 ($r = 0.18$, $P < 0.001$), 2007 ($r = 0.12$, $P < 0.001$), and 2008 ($r = 0.16$, $P < 0.001$). Significant longitudinal correlations were also found between AL and height across 2006 to 2008 ($P < 0.05$). Table 3 presents partial correlation coefficients between AL and height calculated by a multivariate linear regression model, and the results were consistent with the results of linear bivariate correlations.

Table 4 shows that AL changes increased across the quartiles of height change, indicating that the trend of changes in AL and height was consistent over time.

**DISCUSSION**

This analysis of longitudinal data from a prospective cohort study of 7- to 15-year-old children revealed that AL is positively associated with height in both cross-sectional analysis and longitudinal analysis. These correlations were statistically significant even after adjusting for age and sex. To the best of our knowledge, this study is the first to prospectively evaluate the relationship between longitudinal changes of AL and height in a large cohort of children.

The results of the present study showed that AL elongated over the 2-year time period in 7- to 15-year-old children, and AL increased more in the younger children (greatest in those aged 8 years old). This association has previously been reported in a Correction of Myopia Evaluation Trial study.19

Greater AL elongation was observed in female participants during follow-up, which is in accordance with the data from Singapore.3 However, greater changes in stature were found in boys. If one assumes the sex differences on AL and stature were determined by sex hormone, the findings appear to suggest different hormonal patterns in eye size and stature. Interestingly, our study found that height development is greater in young children instead of those at pubertal age, which is consistent with other studies, in which puberty was found to have less effect on growth than gender.20–22

Our results are largely in agreement with the previous cross-sectional studies, reporting significant positive relationships between AL and height.6,8 The Reykjavik Eye Study of adults and the Sydney Myopia Study of Australian children reported a positive correlation between height and AL.12,13 Similarly, recent Singaporean studies in children and adults also found a strong positive correlation between height and AL.5,14 Importantly, our study confirms the longitudinal changes of AL and height are correlated even after adjusting for age and sex. It is notable that the changes in AL and height are concomitant, both traits develop more in younger ages, and the rate of development slows after the age of 12 years.

The significant cross-sectional and longitudinal association between height and AL indicated that height and AL may share some common biological pathways. It is well known that the final height of an individual is mainly determined by longitudinal bone growth, which is regulated by a multitude of genetic and hormonal factors, growth factors, environment, and nutrition.23–25 The major systemic hormones that regulate longitudinal bone growth during childhood are growth hormone and insulin-like growth factor 1 (IGF-1), thyroid hormone (T3 and T4), and glucocorticoids (GCs), whereas during puberty, the sex steroids (androgens and estrogens) contribute a great deal

**TABLE 2. Bivariate Correlations between AL and Height**

<table>
<thead>
<tr>
<th>Factor/Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>555</td>
<td>0.47 (0.40–0.52)</td>
<td>0.18 (0.09–0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>469</td>
<td>0.39 (0.31–0.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>471</td>
<td>0.33 (0.25–0.41)</td>
</tr>
<tr>
<td>2007</td>
<td>468</td>
<td>0.44 (0.36–0.51)</td>
<td>0.12 (0.03–0.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>474</td>
<td>0.39 (0.31–0.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>441</td>
<td>0.32 (0.25–0.40)</td>
</tr>
<tr>
<td>2008</td>
<td>466</td>
<td>0.44 (0.37–0.51)</td>
<td>0.13 (0.04–0.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>438</td>
<td>0.38 (0.30–0.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>664</td>
<td>0.38 (0.32–0.45)</td>
</tr>
</tbody>
</table>

* Correlation coefficients adjusted for age and sex.

**TABLE 3. Partial Correlation Coefficients between AL and Height in Multivariate Generalized Linear Model**

<table>
<thead>
<tr>
<th>Factor/Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>0.13</td>
<td>0.0062</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0091</td>
<td>0.0169</td>
</tr>
<tr>
<td>2007</td>
<td>0.11</td>
<td>0.0261</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0289</td>
<td>0.0507</td>
</tr>
<tr>
<td>2008</td>
<td>0.11</td>
<td>0.0191</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0130</td>
<td>0.0187</td>
</tr>
</tbody>
</table>

$R$, partial correlation coefficient, cross-trait cross-time correlations are included; $P$, $P$ values of correlation coefficient.
to this process. Our previous study confirmed a shared genetic mechanism between height and AL in children.\textsuperscript{17} This shared genetic mechanism was proved by some experiments that showed some of the hormones that regulate longitudinal bone growth during childhood were also found to play roles in experimental myopia, such as thymic hormone, IGFs, and growth factors.\textsuperscript{27–29} Previous studies have proved that genetic mechanism was proved by some experiments that showed some of the hormones that regulate longitudinal bone growth and eye development. Indian hedgehog was recognized as a regulator of the pace of chondrocyte differentiation and thus influenced the bone growth.\textsuperscript{50–52} Zebrafish strains known to have mutations in hh signaling pathways exhibit microphthalmic eyes and retardation of photoreceptor differentiation,\textsuperscript{53,54} and an increased expression of Sonic hedgehog in chick retinas was discovered to induce experimental myopia.\textsuperscript{55} A recent publication in Nature demonstrated that hundreds of single-nucleotide polymorphism variants are associated with human height and most of these variants are not randomly distributed but instead are enriched for genes that are connected to biological pathways.\textsuperscript{56} The common pathways between height and AL may shed new insight on the etiology of myopia and the efforts on identifying genetic variants associated with myopia.

The results of the study must be taken within the context of limitations. First, the study participants are children ranging in age from 7 to 15 years. The eye globe and body stature are in a phase of physical development. Therefore, the measurements taken in the study do not necessarily represent the final parameters in adulthood when the development is completed. However, a study in younger children would allow us to observe the association during the development. Second, the children were enrolled from a twin study. One may argue that the twins may not be the same as the sporadic siblings. However, our recent analysis suggests that our twin cohort appears to have very similar features in comparison with population-based siblings, at least with respect to refractive error.\textsuperscript{57}

In conclusion, this study identifies an association of AL and height based on both cross-sectional and longitudinal data. More interestingly, the development of AL and height appears to be concomitant in children. This work may suggest common pathways for the development of the eye and height. One may consider the role of stature in the investigation of genetic and environmental effects of myopia.

References


