Original Article

Longitudinal Relationship between Axial Length and Height in Chinese Children：Guangzhou Twin Eye Study

Decai Wang[1]，Chen Zhao[2]，Shengsong Huang[1]，Wenyong Huang[1]，Mingguang He[1,*]
1 State Key Laboratory of Ophthalmology，Zhongshan Ophthalmic Center，Sun Yat-sen University，Guangzhou 510060，China
2 State Key Laboratory of Reproductive Medicine，Department of Ophthalmology，the First Affiliated Hospital of Nanjing Medical University，Nanjing 210029，China

Abstract

Purpose：To understand the growth model of axial length （AL） and height，and to explore the relationship between the two with the passage of time.

Methods：We followed twins in the Guangzhou Twin Eye Study for five years. The AL of both eyes was measured by partial coherence interferometry，and height was measured by a standard scale during each visit. A multivariate multilevel mixed model was adopted for data analysis.

Results：A total of 1217 children were included in the study. Both AL and height increased， but the rate of growth slowed down with age. The mitigation rate of height growth was –0.34 cm/year；while that of AL growth was –0.01 mm/year. AL was positively related to height，with a relevant coefficient of R=0.22 （Cov［height intercept，AL intercept］=1.56，95% CI=1.14 to 1.99）. The growth rates of AL and height were also positively related， with a relevant coefficient of R=0.18 （Cov［height slope，AL slope］=0.03，95%CI=0.01 to 0.05）. However，taller children had slower rates of height increases，with a relevant coefficient of R=–0.12 （Cov［height intercept，height slope］=–1.33，95%CI=–2.25 to –0.42）； but had faster AL growth，with a relevant coefficient of R=（Cov［height intercept，AL slope］=0.02，95%CI=–0.05 to 0.08，R=0.02）. AL and its growth rate were positively related to each other，with a relevant coefficient of R=（Cov［AL intercept, AL slope］=0.04，95%CI=0.03 to 0.05，R=0.3）；while the growth rates of AL and height were negatively related to each other， with a relevant coefficient of R=（Cov［AL intercept，height slope］=––0.03 95%CI=–0.16 to 0.1，R=–0.02）.

Conclusion：The increase in children's AL is relevant to their height increases. The faster their height increases，the faster their AL increases. （***Eye Science 2015；30：1–6***）

Keywords：axial length；height；longitudinal relationship

Chinese children's axial length （AL） is a decisive factor determining refractive error[1]. Apart from the biological eyeball parameters，previous studies have discovered that anthropometry parameters，including body height，weight，and body mass index （BMI），were related to the refractive status and the biological eyeball parameters[2–4]. However，most research indicates that instead of being directly related to refractive status，body measurements indirectly influence the refractive status of the eyes through AL growth[2，5–10]. Previous studies have also discovered that a taller height was associated with a longer AL. If the height of adults increases by 10 cm，their AL will increase by 0.23 mm，whereas in children，an increase of 10 cm in their height will lead to an increase of 0.29 mm in the boys' AL and 0.32 mm in the girls' AL. Children's AL growth and height increases occur almost simultaneously. The age when AL stops growing generally coincides with the age when height stops increasing[6，11–13].

However，previous studies were based on cross-sectional data. Determination of the growth model between children's AL and their height，as well as their relationship in the growth pattern，requires longitudinal studies. The Guangzhou Twin Eye Study was a population-based study[9]. This research utilizes the data obtained by the Guangzhou Twin Eye Study over five years to explore the change in pattern of children's AL and height along with age，and the

---

DOI：10.3969/j.issn.1000–4432.2015.01.001

Funding：Natural Science Foundation of China （No. 81271037）

＊**Corresponding author：** Mingguang He，E–mail：mingguanghe@gmail.com

relationship between the change patterns.

Materials and methods

Source of samples

Research subjects were derived from the population in the Guangzhou Twin Eye Study program[14]. The program commenced in 2006 and followed the children with annual ocular examinations and body measurements. Twins aged 7 to 18 were enrolled at baseline. This research adhered to the tenets of the Declaration of Helsinki. All the inspection programs were approved by the Medical Ethical Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University. Twins were not included in this research, if one or both of the twins had:

1. Congenital or acquired diseases which might influence their physical development;
2. Refractive media opacity;
3. Strabismus or amblyopia;
4. Pathologic changes in eyes, such as retinopathy of prematurity, congenital cataract, *etc.*;
5. Recent vision correction through corneal contact lenses.

Clinical examination

The IOL Master (IOL Master; Carl Zeiss Meditec, Oberkochen, Germany) was adopted for AL measurements. The measurements were conducted in a dark room with children not wearing their glasses. Children were asked to rest their chins and foreheads on the device and fixate on the red spot light source in front of them. The focus was concentrated on the green cross in the center by adjusting the joystick. One measurement was completed by pressing the button once and each child was measured five times consecutively. The device then automatically worked out an average value for the measured parameters. If the error between the maximum value and the minimum value was greater than 0.2 mm after the five measurements, the error was indicated as an out-of-range fluctuation and the average value was not generated. In these circumstances, measurements were repeated until an average value was generated. If the difference between the two measurements was greater than 0.1 mm or if the signal-to-noise ratio (SNR) was less than 2, the measurement was also repeated. The measurement result was the average value of ten measurements. Height was measured from the top of the head to the bottom of the feet after removal of shoes. Body weights were measured after removal of coats and shoes. Heights and weights were measured to the closest 0.1 cm and 0.1 kg, respectively.

Statistical analysis

The measurement results within the same individual were not independent and missing data occurred when a subject failed to take part in every measurement. Consequently, linear regression analysis was not always appropriate for exploring the relation between AL and height with time. Given this condition, we referred to a multivariate multilevel mixed model proposed by Hoffman et al[15,16]. In the analysis, time at baseline was defined as "0" and the follow-up visits were as "1, 2, 3, and 4". The intercept of the analysis model would be explained as the initial value of the spherical equivalent refraction (SER), height, or AL, while the slope of the analysis model would be explained as the rate of change in SER, height, or AL with time. The fixed effects estimated by the model suggested an impact of the predictive factors, such as age and gender, and the interaction of the predicative factors on AL and height. The random effects suggested the relation between AL and height with time. Age and gender were adopted as predicative factors in the equation and age was standardized to the age of 6. The statistical analysis was conducted with the SAS (Version 9.2, SAS Institute; Cary, NC) software package.

Since the biological parameters between the right and the left eye were not independent and were highly correlated (the relevant coefficient of the right and the left eye was 0.91 in the first measurement of SER; 0.95 in AL; 0.92 in anterior chamber depth [ACD]; and 0.96 in corneal curvature [CC]), only the results for the right eyes were listed and used in the analysis. Since the measurements within the twin pair were not independent, only the older twins were included in the analysis.

Results

After excluding the subjects with either cataract, maculae corneal, retinopathy, strabismus, or other defects, a total of 1217 older twins were involved in the baseline visit. The mean age was 10.8±0.1 years old. Among them 593 were boys, accounting for 44.29% of the population and the average age was 10.7 ±0.1 years old; the other 624 were girls, accounting for 55.71% of the population and whose average age was 1.9±0.1 years old. All together, 987 older twins underwent a second visit, of which 477 were boys, accounting for 48.33% of the population. The third visit consisted of 657 older twins, of which 328 were boys, accounting for 49.92% of the population. The fourth visit involved 457 older twins, of which 224 were boys, accounting for 49.2% of the population. The fifth visit involved 208 boys, accounting for 48.37% of the population. The average values and the standard deviation of AL and height for each visit were shown in Table 1.

A multivariate multilevel mixed model was used to analyze the changing relation between AL and height with time. The fixed effects of the model suggested the changes of AL and height with time. The growth pattern of the two variables was consistent with the secondary growth curve (Table 2). After adjusting for age and gender, the model estimated that the mean AL of the 6-year-old boys was 23.45 mm and their average height was 126.13 cm. Both height and AL increased with age, but the growth speed slowed down gradually. The mitigation speed of height growth was -0.34 cm/year; while that of AL was -0.01 mm/year. When time and age were not taken into consideration, boys were taller than girls by 2.81 cm at age 6. However, the difference in height between boys and girls decreased with time (-1.20 cm/year, *P*<0.001). The AL of the boys was also longer than that of the girls by 0.47mm. The AL difference between boys and girls also reduced as age increased (-0.003 mm/year, *P* =0.72). Older children were taller, on average, by 4.53 cm/year. However, this growth speed decreased gradually at a rate of -0.75 cm/year as age increased. Older children also had a longer AL, on average, of 0.17 mm per year. This growth speed also decreased with age, at a rate of -0.03 mm/year.

Table 1 List of boys' and girls' axial length and height in each measurement

Parameters	Boy			Girl			Total		
	BoyNumber(%)	Mean	SD	Number(%)	Mean	SD	Number	Mean	SD
AL(mm)									
Visit 1	593(44.29)	23.75	1.12	624(55.71)	23.33	1.11	1217	23.53	1.13
Visit 2	477(48.33)	24.02	1.18	510(51.67)	23.6	1.12	987	23.8	1.17
Visit 3	330(50.08)	24.26	1.17	329(49.92)	23.78	1.16	659	24.02	1.19
Visit 4	223(48.90)	24.42	1.15	233(51.10)	24.04	1.17	456	24.22	1.17
Visit 5	208(48.48)	24.62	1.09	221(51.52)	24.17	1.18	429	24.39	1.16
Height(cm)									
Visit 1	593(48.67)	144.18	15.5	624(51.33)	142.46	13.68	1217	143.3	14.61
Visit 2	477(48.33)	150.28	14.91	510(51.67)	147.34	11.4	987	148.76	13.29
Visit 3	328(50.00)	155.65	14.01	328(50.00)	151.39	9.52	656	153.52	12.16
Visit 4	224(49.02)	159.32	12.3	233(50.98)	154.49	7.63	457	156.86	10.46
Visit 5	208(48.37)	163.77	9.81	222(51.63)	156.34	6.23	430	159.93	8.96

The random effects revealed by the model indicated a relationship between AL and height with time (Table 3). AL and height were positively correlated, with a relevant coefficient of R=0.22 (Cov [height intercept, AL intercept]=1.56, 95%CI=1.14 to 1.99). The growth speeds of AL and height were also positively correlated, with a relevant coefficient of R= 0.18 (Cov [height slope, AL slope] =0.03, 95%CI= 0.01 to 0.05). However, taller children at baseline had slower height increases, with a relevant coefficient of R=-0.12(Cov[height intercept, height slope] =-1.33, 95%CI=-2.25 to -0.42); but faster growth of their AL, with a relevant coefficient of R =(Cov [height intercept, AL slope] =0.02, 95%CI=-0.05 to 0.08, R=0.02).

Discussion

Analysis of the five-year longitudinal data of AL and height in a population-based sample in this study revealed the relationship between the growth pattern of AL and height in children aged 7 to 15 years old.

Table 2 The fixed effects of the multivariate multilevel mixed model for changes in axial length and height

Fixed Effects	Estimate	SE(10–2)	*t* value	*P*>|t|	95%CI
Height					
Height intercept	126.13	73.51	171.57	*P*<0.001	(124.68, 127.57)
Height gender	–2.81	41.41	–6.78	*P*<0.001	(–3.62, –2.00)
Height gender * time	–1.20	12.80	–9.37	*P*<0.001	(–1.45, –0.95)
Height age	4.53	7.29	62.15	*P*<0.001	(4.39, 4.67)
Height age * time	–0.75	2.39	–31.40	*P*<0.001	(–0.80, –0.70)
Height time	10.95	24.18	45.29	*P*<0.001	(10.48, 11.43)
Height time * time	–0.34	2.38	–14.41	*P*<0.001	(–0.39, –0.30)
AL					
AL intercept	23.45	10.32	227.23	*P*<0.001	(23.24, 23.65)
AL gender	–0.47	5.82	–8.15	*P*<0.001	(–0.59, –0.36)
AL gender * time	–0.003	0.91	–0.35	0.72	(–0.02, 0.01)
AL age	0.17	1.02	16.81	*P*<0.001	(0.15, 0.19)
AL age * time	–0.03	0.16	–17.49	*P*<0.001	(–0.032, –0.026)
AL time	0.42	1.69	24.88	*P*<0.001	(0.39, 0.45)
AL time * time	–0.01	0.14	–10.19	*P*<0.001	(–0.02, 0.01)

Table 3 The random effects of the multivariate multilevel model of AL and height

	Variances, Covariances, and Intercorrelations of Random Intercept and Slopes			
	Height intercept	AL intercept	Height slope	AL slope
Height intercept	49.88(21.32)	1.56(0.22)	–1.33(0.47)	0.02(0.03)
AL intercept	0.22**	1.04(0.04)	–0.03(0.06)	0.04(0.00)
Height slope	–0.12*	–0.02	2.34(0.19)	0.03(0.01)
AL slope	0.02	0.30**	0.18**	0.01(0.00)
Residual variance:		Estimates	95%CI	
Height residual variance		4.00(0.15)	(3.73, 4.3)	
AL residual variance		0.01(0.00)	(0.01, 0.01)	
Height AL residual covariance		0.05(0.01)	(0.04, 0.06)	

Note: ***P*<0.001 **P*<0.01

The concomitant variables estimated by the multivariate multilevel model are shown in the upper right corner. The values within the brackets are the standard errors. The relevant coefficients of various variables are shown in the lower left corner.

To the best of our knowledge, this is the first cohort study that conducted retrospective analysis of the changing relationship between AL and height with the time.

The refractive status of the eye is mainly determined by the interaction and relation between the ocular biometric parameters, including CC, ACD, vitreous chamber depth (VCD), crystalline lens depth, AL, and the refractive power of the crystalline lens. Among these parameters, AL is the predominant variable of the refractive status, especially during childhood and the adolescent period. Therefore, AL can serve as the intermediate phenotype for studying the progression of myopia[1,17-19]. In a recent study, Mutti et al. found that a longer AL was a risk factor for myopia progression[20]. In the current research, we found that a longer AL in children was associated with faster AL growth. This was one potential explanation for the vulnerability to myopia in children with long AL.

Previous studies have suggested that AL is positively related to height[5,6–8,9,11,12,21-23], such that a taller body height is associated with a longer AL. An average increase of 0.23 mm in AL corresponded to an increase in height of 10 cm in adults. In children, an increase in height of 10 cm was also related to an increase in AL: of 0.32 mm in girls and 0.29 mm in boys[11,17]. The increases in AL and height in children also occur at almost the same time. The age when AL stops increasing generally coincides with the age when height stops increasing[12,13]. The outcome of this study therefore agrees with those of the previous studies. Other researchers also found that girls were more likely to develop myopia and with faster progression[3,18,24,25]. In this research, we found that boys were taller, with longer ALs. However, these gender difference in height and AL decline as age increases. This indicates that during the follow-up visit, girls' AL increases faster, which may explain their higher vulnerability to the development and progression of myopia. In comparison, height increases faster in boys than in girls, while AL increases faster in girls than in boys. This phenomenon may be explained by the different modes action of the sex hormones on height and AL in boys and girls.

The significant correlation observed between AL and height suggests that a shared biological pathway may influence children's myopia development and height increases. The height of a person is clearly determined by skeletal development, while the skeletal development is decided by a series of different factors, including genetic factors, hormonal levels, growth factors, environmental factors, and nutri tion[26-29]. The hormones that might influence children's skeletal development include the growth factors (GH), the insulin-like growth factors (IGF-1), thyroid hormone (T3 and T4), glucocorticoids (GC) and androgen and estrogen, which play important roles during adolescence. The changes in levels of some hormones, such as thymin, T3 and T4, and IGF-1, which influence children's physical development, can be detected in induced animal models of myopia[30-32].

Several important biochemical pathways are closely related to body height. All these pathways also influence the development of children's eyeballs. For example, the skeletal development signaling pathway contains three genes that are thought to be closely related to height, including Indian hedgehog (IHH), patched 1 (PTCH1), and hedgehog-interaction protein (HHIP). These genes all belong to the hedgehog signaling pathway and are related to the vertebral column. However, the sonic hedgehog signaling pathway is differentially expressed in chicken eyes with experimentally-induced myopia[33,34]. Other important genes of the skeletal development signaling pathway include bone morphogenic proteins (BMPs), such as BMP2, BMP6, and GDF5, and the adjustment factor, Noggin. Genes of this kind can trigger the formation and induction of bone and cartilage. BMPs are expressed in the cornea and the retina of eyes, which could influence the development of myopia in experimentally-induced animals[35-37].

The shared biological pathways between myopia and height have provided new insight into the pathogenesis of myopia. The increases in AL and height are mainly determined by genetic factors[38-41]. The significant correlation between AL and height indicates that common environmental and genetic factors may exist that may influence both myopia development and height.

Conclusion

A positive relationship exists in children between the increase in AL and increases in height, which indicates that the growth rates for AL and height may be determined by the same environmental and genetic factors.

References

1 Wang D, Liu B, Huang S, et al. Relationship between refractive error and ocular biometrics in twin children: Guangzhou Twin Eye Study.eye science, 2014, 29:129–133.

2 Teikari JM. Myopia and stature.Acta ophthalmologica, 1987;65:673–676.

3 Khandekar R, Harby SA, Mohammed AJ. Determinants of myopia among Omani school children: a case-control study.Ophthalmic epidemiology, 2005;12:207–213.

4 Kinge B, Midelfart A. Refractive errors among engineering students in Norway. Ophthalmic epidemiology, 1994; 1:5–13.

5 Saw SM, Carkeet A, Chia KS, et al. Component dependent rwask factors for ocular parameters in Singapore Chinese children. Ophthalmology, 2002, 109:2065–2071.

6 Saw SM, Chua WH, Hong CY, et al. Height and its relationship to refraction and biometry parameters in Singapore Chinese children.Investigative Ophthalmology & Visual Science, 2002, 43:1408–1413.

7 Rasooly R, Zauberman H. Correlations between ocular optical components, height and head circumference.Ophthalmic and Physiological Optics, 1988, 8:351–352.

8 Ojaimi E, Morgan IG, Robaei D, et al. Effect of stature and other anthropometric parameters on eye size and refraction in a population-based study of Australian children. Investigative Ophthalmology & Visual Science,

2005;46:4424–4429.

9 Wu HM, Gupta A, Newland HS, et al. Association between stature, ocular biometry and refraction in an adult population in rural Myanmar: the Meiktila eye study. Clinical & Experimental Ophthalmology 2007,35:834 – 839.

10 Nangia V, Jonas JB, Sinha A, et al. Axial length and its associations in an adult population of central rural India: the Central India Eye and Medical Study.Ophthalmology, 2010,117:1360–1366.

11 Wong TY, Foster PJ, Johnson GJ, et al. The relationship between ocular dimensions and refraction with adult stature: the Tanjong Pagar Survey.Investigative Ophthalmology & VIsual Science,2001;42:1237–1242.

12 Goss DA, Cox VD, Herrin-lawson GA, et al. Refractive error, axial length,and height as a function of age in young myopes.Optometry & Vision Science,1990,67: 332–338.

13 Larsen JS. The sagittal growth of the eye. Acta Ophthalmologica,1971,49:239–262.

14 He M, Ge J, Zheng Y, et al. The Guangzhou twin project.Twin Research and Human Genetics,2006,9:753 – 757.

15 MacCallum RC, Kim C, Malarkey WB, et al. Studying multivariate change using multilevel models and latent curve models.Multivariate Behavioral Research,1997,32: 215–253.

16 Hoffman L, Rovine MJ. Multilevel models for the experimental psychologwast: Foundations and illustrative examples.Behavior Research Methods,2007,39:101–117.

17 Lam CSY, Edwards M, Millodot M, Goh WSH. A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. Optometry & Vision Science,1999,76:370–380.

18 Saw S, Chua W, Gazzard G, Koh D, et al. Eye growth changes in myopic children in Singapore.Britwash Journal of Ophthalmology,2005,89:1489–1494.

19 Zadnik K, Mutti DO, Friedman NE, et al. Ocular predictors of the onset of juvenile myopia.Investigative Ophthalmology & Visual Science,1999,40:1936–1943.

20 Mutti DO, Hayes JR, Mitchell GL, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Investigative Ophthalmology & Visual Science,2007,48:2510–2519.

21 Johnson G, Matthews A, Perkins E. Survey of ophthalmic conditions in a Labrador community. I. Refractive errors. Britwash Journal of Ophthalmology,1979,63:440–448.

22 Lee KE, Klein BE, Klein R, et al. Association of age, stature,and education with ocular dimensions in an older white population.Archives of Ophthalmology,2009,127: 88–93.

23 Šelović A,Juresa V,Ivankovic D,et al.Relationship between axial length of the emmetropic eye and the age, height, and body weight of schoolchildren.American Journal of Human Biology,2005,17:173–177.

24 Zadnik K, Manny RE, Yu JA, et al. Ocular component data in schoolchildren as a function of age and gender. Optometry & Vision Science,2003,80:226–236.

25 Carr JK. Refractive error study in children: results from Shunyi Dwastrict,China. Evidence–Based Ophthalmology,2001;2:48–49.

26 Chen L, Li C, Qiao W, et al. A Ser365→ Cys mutation of fibroblast growth factor receptor 3 in mouse downregulates Ihh/PTHrP signals and causes severe achondroplasia. Human Molecular Genetics, 2001, 10:457–465.

27 Chryswas D, Ritzen E, Savendahl L. Growth retardation induced by dexamethasone was associated with increased apoptoswas of the growth plate chondrocytes.Journal of Endocrinology,2003,176:331–337.

28 Chubinskaya S, Kuettner KE. Regulation of osteogenic proteins by chondrocytes. The International Journal of Biochemwastry & Cell Biology, 2003,35:1323–1340.

29 Chusho H, Tamura N, Ogawa Y, et al. Dwarfwasm and early death in mice lacking C-type natriuretic peptide.Proceedings of the National Academy of Science,2001;98: 4016–4021.

30 Seko Y, Tanaka Y, Tokoro T. Influence of bFGF as a potent growth stimulator and TGF-β as a growth regulator on scleral chondrocytes and scleral fibroblasts in vitro. Ophthalmic Research,1995,27:144–152.

31 Rada JAS, Wiechmann AF. Ocular expression of avian thymic hormone:changes during the recovery from induced myopia.Molecular Vision,2009,15:778.

32 Kusakari T, Sato T, Tokoro T. Vwasual deprivation stimulates the exchange of the fibrous sclera into the cartilaginous sclera in chicks.Experimental Eye Research, 2001,73:533–546.

33 Bwasmuth K,Relaix F. Genetic regulation of skeletal muscle development. Experimental Cell Research,2010, 316:3081–3086.

34 Escaño MF,Fujii S,Sekiya Y,et al.Expression of< i > Sonic Hedgehog</i> and Retinal Opsin Genes in Experimentally–induced Myopic Chick Eyes.Experimental Eye Research,2000,71:459–467.

35 Wang Q,Zhao G,Xing S,et al.Role of bone morphogenetic proteins in form –deprivation myopia sclera. Molecular Vision,2011,17:647.

36 Wallman J.Retinal influences on sclera underlie vwasual deprivation myopia. Ciba Foundation Symposium 155–Myopia and the Control of Eye Growth:Wiley Online Library; 1990:126–148.

37 Chen D,Zhao M,Mundy GR.Bone (conti to page 12)