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Longitudinal changes in crystalline lens thickness and power in children aged 6-12 years old

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Abstract

Objectives: To determine the three-year changes in crystalline lens power (LP) and thickness (LT) in children and their associated factors.

Methods: Schoolchildren aged 6-12 years living in Shahroud, northeast Iran were examined in 2015 and 2018. The Bennett formula was used to calculate LP. Multiple generalized estimating equations (GEE) analysis was used for data analysis.

Results: Among the 8089 examined eyes, the mean LP in Phase 1 and 2, and the three-year change were 21.61 ± 1.47D, 21.00 ± 1.42D, and -0.61 ± 0.52D, respectively. The GEE model showed that negative shifts in LP were less pronounced with increasing age ($\beta = 0.176$; $p < 0.001$), and were also less noticeable in hyperopes compared to emmetropes ($\beta = 0.120$; $p < 0.001$). The changes in LP decreased when outdoor activity increased among urban residents ($\beta = 0.013$; $p = 0.039$), while it increased in rural area ($\beta = -0.020$; $p = 0.047$). Mean three-year change in LT was 0.002 ± 0.13 mm. Female sex and aging by one year increased the LT by 0.022 mm ($P < 0.001$). However, LT decreased in 6-8-year-olds, while it increased in 10-12-year-old children, both in a linear fashion. The change in LT was less in myopes than in emmetropes ($\beta = -0.018$, P-value = 0.010).

Conclusion: LP decreases after three years in 6 to 12-year-old children. LT increases slightly after three years in 6 to 12-year-old children. The changes in LP and LT were associated with the refractive errors, place of residence, age and gender and outdoor activity time.

Key words: Lens Power; Lens thickness; Children; Cohort; Iran

Introduction

The spherical equivalent of new-born infants typically has a normal distribution with a mean value of +2 to -3 dioptre.1, 2 During emmetropization until 6 years of life, the axial length (AL) increases by about 5 mm.3 Simultaneously, the corneal power decreases from 48D to 43.2D, and the crystalline lens power reduces from 49D to 24.5D.4 These changes shift the refractive status of the infant eye towards a leptokurtic distribution with a peak at 1 D at the first or second year of life.5-7 During childhood and adolescence, the eyes grow and refractions remain stable while the lens power decreases at a rate of 0.2-0.5 D per year.8,9, 10 The crystalline lens plays an important role in determining the refractive status of the eye.2 In schoolchildren, the balance between AL elongation and lens power reduction contributes to the emmetropization process, and myopia may develop if this balance is disturbed. In other words, if AL growth exceed the crystalline lens power reduction, possibly because the crystalline lens may have reached some limit beyond which it can no longer compensate for increased rate of axial elongation, myopia develops. 11-14

Crystalline lens power changes result from changes in the lens thickness, curvature, and internal structure. Evidence suggests that the lens thickness reduces by about 0.2 mm between 6 – 10 years of age,14 but no significant changes were found in adolescents.9, 12 The anterior and posterior lens surfaces also become flatter during childhood and adolescence, with their radii of curvature increasing by about 1.0 mm and 0.2-0.4 mm respectively, corresponding with a reduction of about 2 D in the crystalline lens power.9, 15 The anterior surface of lens becomes flatter until about 12-15 years and steeper thereafter. The posterior side just seems to slowly get flatter.4

Although several cross-sectional studies have investigated crystalline lens thickness and power changes, there are only a few longitudinal studies with limited sample sizes. Moreover, there was no similar research in this WHO region (MENA), characterized by a low prevalence of myopia. The associated factors with changes in LP and LT especially indoor and outdoor activity times have not been fully investigated. A better understanding of the role of environmental factors in crystalline lenses development and its association with AL growth in children is necessary. Therefore, we conducted a cohort study with children with low prevalence and incidence of myopia.

Considering the importance of the crystalline lens in determining the refractive status, the present study evaluated the three-year changes in the crystalline lens and its associated factors in a large sample of schoolchildren aged 6-12 years. This study also investigated LP and LT according to the age, sex, axial length and refractive groups, which can be considered as another novelty of present study.

Methods

The Shahroud Schoolchildren Eye Cohort Study (SSCECS) was performed on schoolchildren aged 6-12 years living in rural and urban areas of Shahroud. The first Phase was conducted in 2015. The methodological, sampling, and examination details of the first Phase have been already published.[16] In brief, considering the limited number of rural students, census sampling was done in rural areas while multi-stage cluster sampling was applied to select the students in urban areas. Of 473 classrooms in the urban areas, 200 were selected as clusters proportional to the number of classrooms in each school using systematic randomization. After selecting the students and informing their parents, they were invited for examinations. The students whose parents consented to participation were transferred to the examination site free of charge on a predetermined day. The study was conducted in accordance with the Helsinki Declaration. All procedures involving children were approved by the Ethics Committee of Shahroud University of Medical Sciences. Written informed consent was obtained from the students' parents/legal guardians and oral consent was obtained from all students before testing began.

Demographic data were collected during face-to-face interviews, followed by optometric examinations. These included the measurement of uncorrected visual acuity using the Nidek CP-770 chart projector at three meters. Next, non-cycloplegic refraction was measured using the Nidek ARK-510A auto refractometer and the results were refined using the Heine Beta 200 retinoscope (HEINE Optotechnic, Hersching, Germany). The students whose visual acuity was not 20/20 underwent subjective refraction. The Pentacam HR (Oculus, Inc., Lynnwood, WA) was used for corneal imaging and the Allegro Biograph (WaveLight AG, Erlangen, Germany) was used for biometric measurements. Finally, all students underwent cycloplegic refraction using cyclopentolate 1% drop 2 times and refraction was measured 30 minutes later. A SE between -0.5 to -5 D was considered as myopia and a SE ≥ +2D was considered as hyperopia. High myopia was defined as SE≤-5 D.

In the second Phase, conducted three years later, all participants were invited. The examination site, sequence and settings were the same to Phase one, and the same protocol was implemented. Students with a history of ocular surgery, amblyopia, best corrected visual acuity worse than 20/25, missing data, and erroneous data were excluded.

Lens power calculation

Bennett's formula[17] was applied for lens power calculation, using cycloplegic spherical equivalent (SE), corneal power, AL, anterior chamber depth (ACD), and lens thickness (LT) data. The Olsen method[18] was used to correct the keratometry.

Statistical analysis

Mean, standard deviation (SD), and 95% confidence interval (95% CI) of crystalline lens power and thickness in the first and second phases and its three-year changes were reported according to age, sex, place of residence, and refractive error. The design effect of cluster sampling was considered for standard error calculation and the sampling weight was applied. The results of the fellow eyes were analysed. Considering the correlation between fellow eyes, the relationship between lens power and thickness change and other variables was assessed using simple and multiple generalized estimating equations (GEE) models to control the effect of this correlation. All independent variables that were significant in the simple models with a P-value of <0.2, were entered in the multiple models. Non-significant (P>0.05) variables and those with collinearity (Variance Inflation Factor (VIF) > 10) were removed to have a parsimonious multiple model. In multiple GEE model, due to the correlation of AL with refractive errors, only refractive errors were included in the model. Moreover, among anterior chamber indices, only ACD was used in the model.

Ethical consideration

All procedures involving children were approved by the Ethics Committee of Shahroud University of Medical Sciences and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all parents or students' legal guardians and also oral consent from all the students.

Results

Of 5620 students who participated in first Phase of SSCECS, 5292 (94.2%) joined in second Phase. After applying the exclusion criteria, 8089 eyes of 4280 students were analysed in the present study, of whom 1989 (46.5%) were female. The mean age of the students was 9.13 ± 1.71 years (range: 6 - 12 years) in Phase one and 12.29 ± 1.73 years (range: 9-15 years) in Phase two.

The mean crystalline lens power was 21.61 ± 1.47 Dioptre (D) (95%CI: 21.5, 21.72) in Phase one and 21.00 ± 1.42 D (95%CI: 20.91, 21.09D) in Phase two. The skewness and kurtosis of the lens power distribution was 0.07 and 0.09 in Phase one and 0.06 and 0.10 in Phase two, indicating a normal distribution of the lens power. Table 1 presents the mean, standard deviation, and 95% confidence intervals of the lens power and thickness in Phases 1 and 2, along with the three-year changes of these outcomes by independent variables such as age, gender, place of residence and refractive error.

Figure 1 shows the histogram of the three-year changes in crystalline lens power and thickness. The mean three-year power change was -0.61 ± 0.52 D (95% CI: -0.65, -0.57), which was statistically significant ($p < 0.001$). The skewness and kurtosis of the three-year crystalline lens power change were -0.28 and 0.12, respectively.

Figure 2 is very interesting and shows that children with myopia progression have less lens power loss while at the same time having much faster axial growth. This pattern is more prominent in those with axial length greater than 25 mm, confirming axial growth with a reduced lens power loss in those with more myopic progression.

Supplementary figure 3 compares the mean changes of lens power by different spherical equivalent groups at baseline. Unlike other groups, high myopes ($SE<-5$ D) had a positive lens power change in boys, although the sample size in this group was small and only 6 eyes in boys and 1 eye in girls were categorized as high myopia. Lens power loss was highest in pre-myopes ($SE > -0.50$ to 0.75 D), compared to emmetropes and hyperopes in boys and emmetropes and myopes in girls. In girls, myopes had less changes in lens power, compared to other groups.

Supplementary figure 4 shows the lens power changes according to AL at baseline. The smallest crystalline lens power change over three years was seen in participants with a longer AL. However, the correlation is not strong (Pearson correlation coefficient = 0.16, P value <0.001). The changes of lens power and lens thickness over three years by and age and gender groups and the influence of place of residence are presented in Supplementary figures 5 and 6 respectively. Supplementary figure 7 shows that there is a minor interaction between place of residence, outdoor activity time and lens power changes.

The relationship between the three-year lens power changes and the study variables at baseline was analysed using simple and multiple GEE models (Table 2). The results of the multiple GEE model showed that lens power loss was less pronounced in older children ($\beta = 0.176$; $p < 0.001$), and compared to emmetropes were less noticeable in hyperopes ($\beta = 0.120$; $p < 0.001$) and high myopes ($\beta = 0.721$; $p < 0.001$). Lens power loss was more pronounced in children with myopia and pre-myopia. In the GEE model also, there was an interaction between residence place and outdoor activity time. Lens power loss may be slowed with an increase in outdoor activity among urban residents ($\beta = 0.013$; $p = 0.039$), while it increased in rural areas ($\beta = -0.020$; $p = 0.047$) (Supplementary figure 7). The mean outdoor activity time was higher among rural students (1.98 (95% CI: 1.79 – 2.18) hour/day) compared to urban students (1.53 (95% CI: 1.45 – 1.61) hour/day) and correspondingly, the three-year lens power loss was also greater in rural areas (-0.73D (95% CI: -0.80 to -0.65) vs -0.60D (95% CI: -0.64 to -0.56)). Place of residence was not associated with LP in the multiple GEE model ($p=0.342$). Near work activity ($\beta = -0.007$; $p=0.069$) also was not associated with increase in LP changes (Table 2).

The mean three-year change in crystalline lens thickness was +0.002 ± 0.13 mm (-0.004 to 0.008 mm) and the skewness and kurtosis of its distribution were 0.07 and 3.25, respectively. In the GEE model (Table 3), lens thickness increased 0.022 mm ($p<0.001$), per year of age. However, LT decreased in 6-8-year-olds and increased in 10-12-year-olds children with a linear trend (Supplementary figure 6). The changes in LT were higher in female sex ($\beta = 0.022$; $p < 0.001$). The three-year changes in LT were smaller in myopes compared to emmetropes ($\beta = -0.018$, p-value = 0.010).

Discussion

This work investigated the three-year changes in crystalline lens power and thickness in school-age children. On average, the lens power reduced by 0.61 D, ranging from 1.24 D in 6-year-olds to 0.26 D in 12-year-olds. This is in accordance with previous studies that reported a similar reduction in lens power with age. In the SCORM study that followed children aged 6-9 years for 5 years, the lens power decreased after the age of 10 years,[11, 19] while the Orinda study found a reduction in Gullstrand lens power in 6 and 14 years of age.[20, 21] The longitudinal CLEERE study also showed a reduction in the crystalline lens power in children aged 6-14 years before the onset of myopia.[13, 22] In children, the protein fibres of the crystalline lens become more compact in the nucleus with age and fewer new fibres are made up in the lens cortex, resulting in lens thinning and flattening of the anterior and posterior lens surfaces. This is accompanied with decrease in the lens equivalent refractive index from 1.45 in early infancy to 1.42 by 10 years of age. [5, 20, 21] Moreover, there is influence of increased stretching by the ciliary body until 10-12 years which has an influence on the lens flattening.[4] This reduces the crystalline lens power, especially during the first 10 years of life.[20, 21]

In the present study, the crystalline lens thickness increased on average by 0.002 mm during three years in all participants, whereas; previous studies found a reduction in the lens thickness.[12, 14, 23] Subgroup analysis showed a decreasing trend of lens thickness from 6 to 8 years and an increasing trend thereafter; this finding is accordance with previous studies as well as the lens paradox.[20, 24, 25] Lens thickness does not always reduce with age and the lens becomes thicker and steeper after 10 years with a simultaneous decrease in the lens index and accordingly lens power, which is known as the lens paradox. It is therefore important to consider the age of the participants when comparing the lens thickness changes between studies.

We observed that a longer baseline AL leads to less reduction in crystalline lens power and that in children with myopic progression lens power change stops for an ALs longer than 25 mm (Figure 2). This suggests that there must be a minimum value for the lens power, somewhere between 15-18D. The AL increases by about 3 mm between 9 months and 9 years of age, which results in the development and maintenance of emmetropization along with crystalline lens changes.[5, 22] However, at the onset of myopia, and at least one year afterwards, changes in lens parameters including power reduction, lens thinning and flattening, and the close relationship between AL and crystalline lens power are halted.[13, 22] On the other hand, considering that eyes with longer AL are generally more myopic, the lens must lose less power to maintain emmetropia.

Before myopia onset, the lens power reduces to compensate for the increased AL to maintain emmetropia. After myopia onset, since there is a limit to crystalline lens shape change, due to the higher thickness and longer length of the ciliary muscle attached to the lens, its changes become limited or even stop.[26] Thus, emmetropization may result from lens power loss, a planned passive process that is compensated and neutralized due to the regular and active rate of AL growth resulting from retinal defocus. However, in growing eyes, there might be a slow active feedback mechanism that regulates power lens loss relative to AL growth to protect the eye from environmental factors causing AL overgrowth.

At both Phases of study, the highest and lowest crystalline lens power was observed in hyperopic and myopic participants respectively, a trend that was similar after three years and was in accordance with the results of previous studies.[11, 20] However, crystalline lens power reduction was higher in myopes and pre-myopes compared to emmetropes and was inversely higher in high-myopes and hyperopes. This finding was in accordance to previous studies in which myopic children [27] or children who recently became myopic [11] showed more crystalline lens power loss compared to the other groups. In the longitudinal SCORM study, participants that were emmetropic in the first Phase of study and had SE less than -0.50 D in subsequent Phases (considered as early myopia) showed higher reduction in lens power and thickness at the end of the study.[11] In the Orinda longitudinal study, myopic children had more AL changes compared to emmetropic ones in a 10-year follow-up and the lens power reduced by about 3.5 D during this time in myopic children.[28]

In the present study, lens thickness decreased less in myopes compared to emmetropes over three years. The available evidence suggests that the lens is thinner in myopes,[14, 23] probably because the maximum lens thickness reduction along with crystalline lens power loss have already occurred to compensate for the rapid axial elongation before myopia onset. Therefore, lens structure changes is optimum and there is no room for more change at the onset of myopia,[14] while the mechanism of thickness reduction has a normal trend in hyperopia.

The reason for thinner lenses in myopic participants may be a slow growth rate in the lens epithelial layer controlled by hormonal factors of the retina. Fibroblast growth factor is present in the retina and surrounding vitreous and is the main factor affecting epithelial growth.[29, 30] With the production of new fibers with a lower refractive index, older fibers move to the lens center and become compact resulting in the formation of the gradient refractive index of the lens (responsible for half of the total lens power).[7] However, the growth reduces slowly over time and density remains unchanged.[7] This is why the gradient profile of the lens gradually loses its steep gradient and becomes flat due to reduced growth rate of lens epithelial cells resulting in reduced lens power while relaxed.[7] We believe a relative decrease in the lens growth rate contributes to a thinner lens and lower lens power in myopes compared to emmetropes.

We observed a significant association and interaction between the crystalline lens power changes and the outdoor activity time. Outdoor activity in urban area was positively associated with lens power changes while negative association between these variables observed in the rural area. (Supplementary figure 7). It is difficult to justify this weak interaction, and it shows that although environmental factors play a role in the development of the eye and its biometric components, this role is different in urban and rural areas. It is clear that light intensity is different in urban and rural areas. Recent work has shown that one of the non-canonical opsins (OPN3) found in the skin related to solar pigmentation,[31] is responsible for refractive development in the mouse model, with influence in lens thickness and anterior segment growth.[32] Thus, there is a possible biochemical relationship between light environment and anterior segment dimensions and lens growth, which could in term affect lens power. On the same data we previously shown that higher outdoor time decrease the odds of axial length progression.[33] These findings indicate the role of environmental factors on myopia progression, which is emphasized in other studies.[34-37]

As shown in GEE models, crystalline lens power changes did not differ in urban and rural areas; whereas, its thickness changed negatively in rural compared to urban students. To the best of our knowledge, no other study has evaluated lens power and thickness changes according to place of residence. However, a previous study found that after matching participants for refractive error, AL was longer and the cornea was flatter in the urban group compared to the rural group.[38] Furthermore, crystalline lens power has been reported to be higher in children living in rural areas versus their urban-dwelling counterparts.[39]

Although the results of the present study found no relationship between crystalline lens power changes and sex, lens became significantly thicker in girls over three years. Studies so far have demonstrated higher crystalline lens power in girls than in boys.[26, 39] However, both groups showed rather similar changes in lens power loss between 6 and 12 years of age.[39] Findings related to the lens thickness changes are inconsistent between studies with some studies indicating no significant differences in lens thickness between girls and boys;[21, 40] whereas, others showed a thicker lens in girls.[26] To the best of our knowledge, no studies so far have investigated the lens thickness changes according to the sex. Mutti et al.[22] however found that lens thickness difference between became-myopic and emmetrope children was higher in girls than boys. It might indicate a more prominent role of refractive errors especially myopia in thickness changes than the sex itself.[22]

Conclusions

Crystalline lens power decreased by 0.61 D during three years in schoolchildren aged 6-12 years old and the lens thickness followed the lens paradox. The pattern of changes in lens power was different between different refractive groups and axial length where the maximum lens power loss was observed in pre-myopes and myopes. Environmental factors such as outdoor activity and place of residence can also affect the lens power and thickness.

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Figures

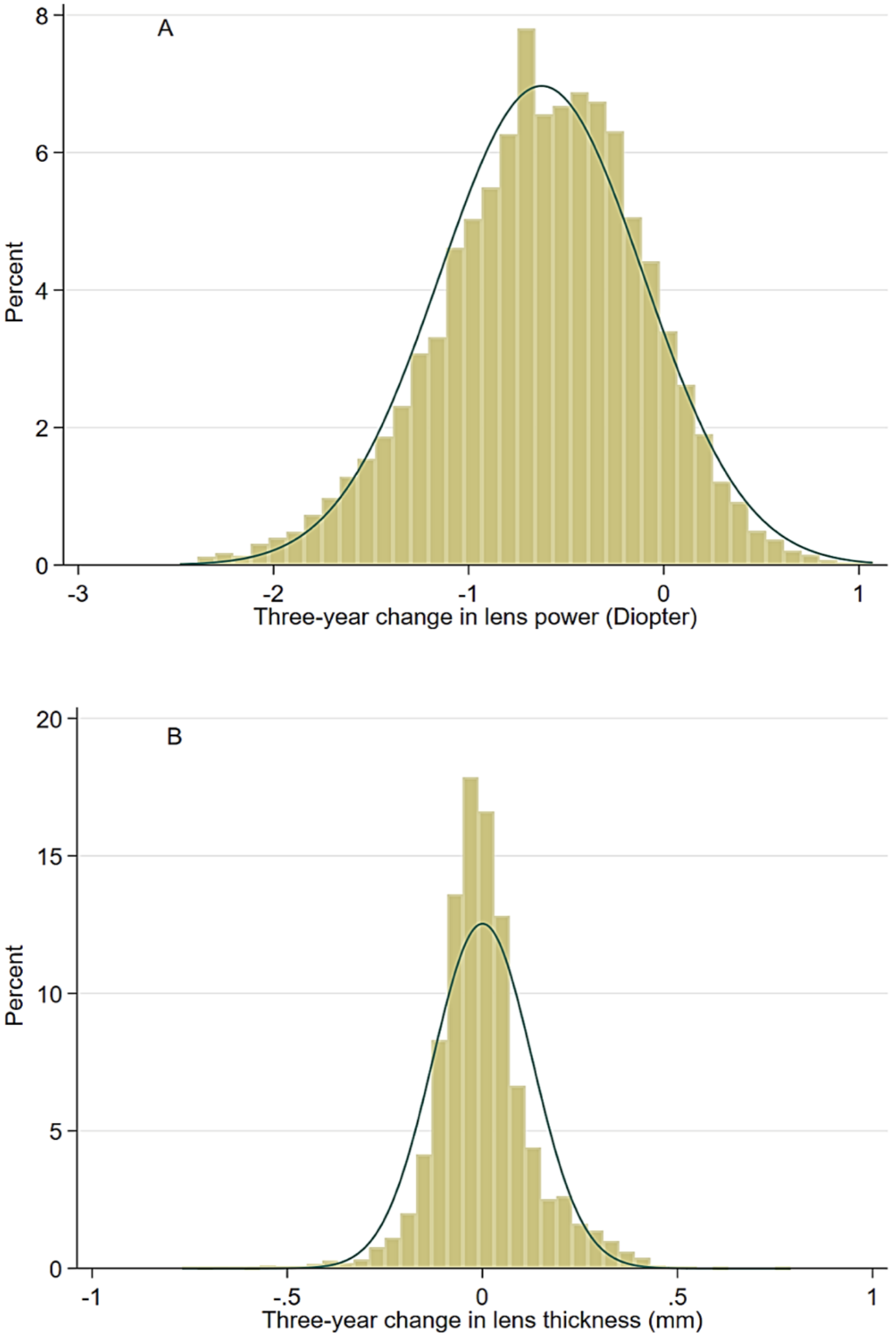


Figure 1: *The distribution of the three-year change in crystalline lens power (A) and thickness (B).*

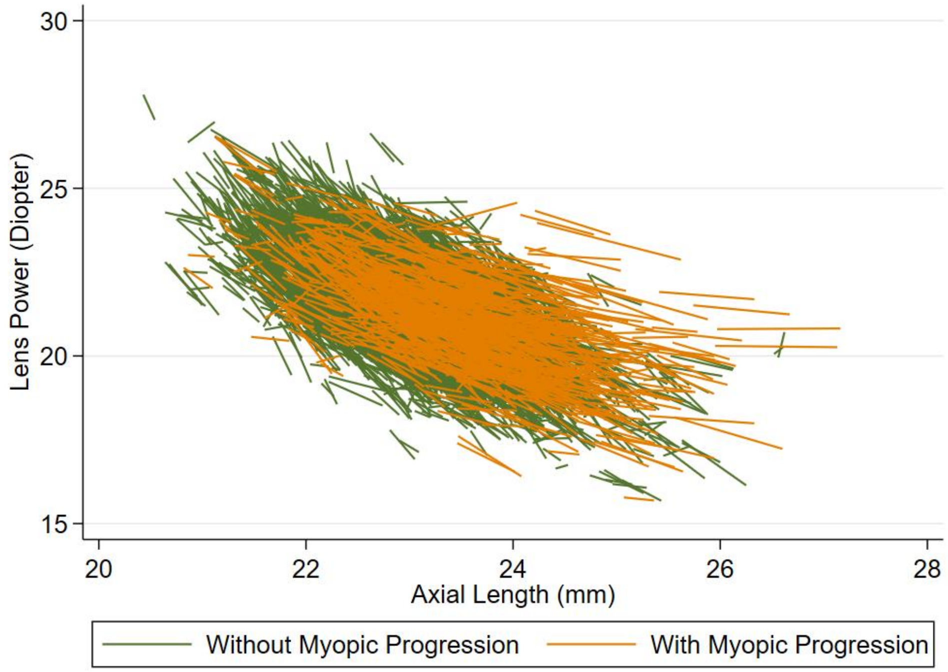
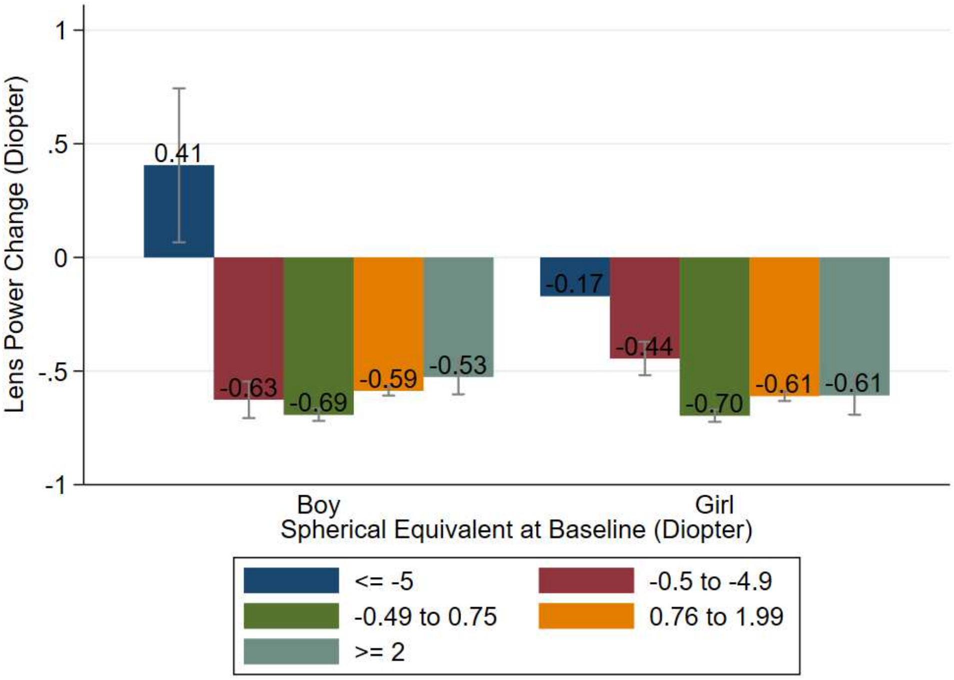
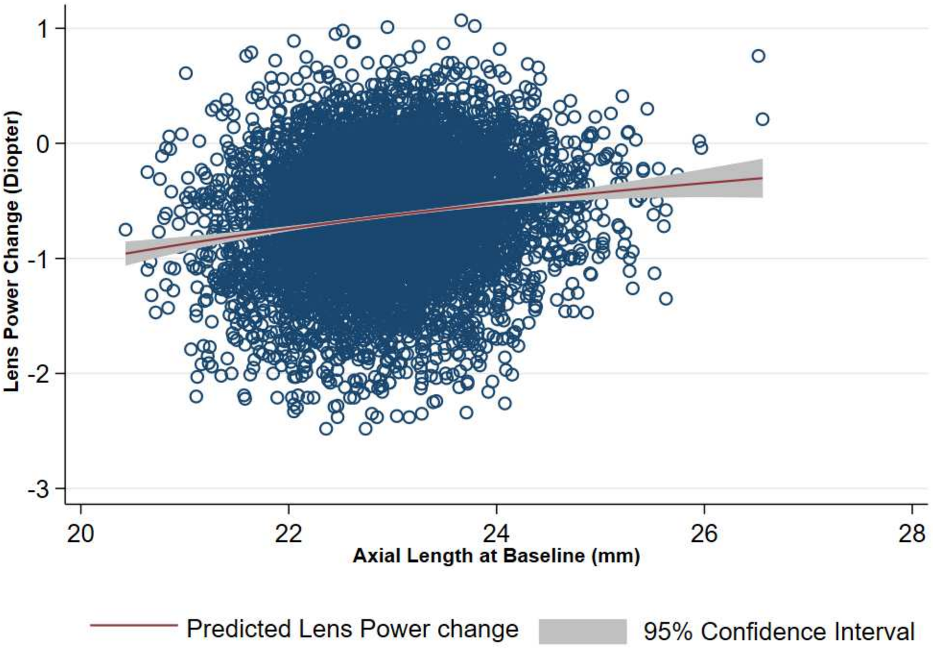


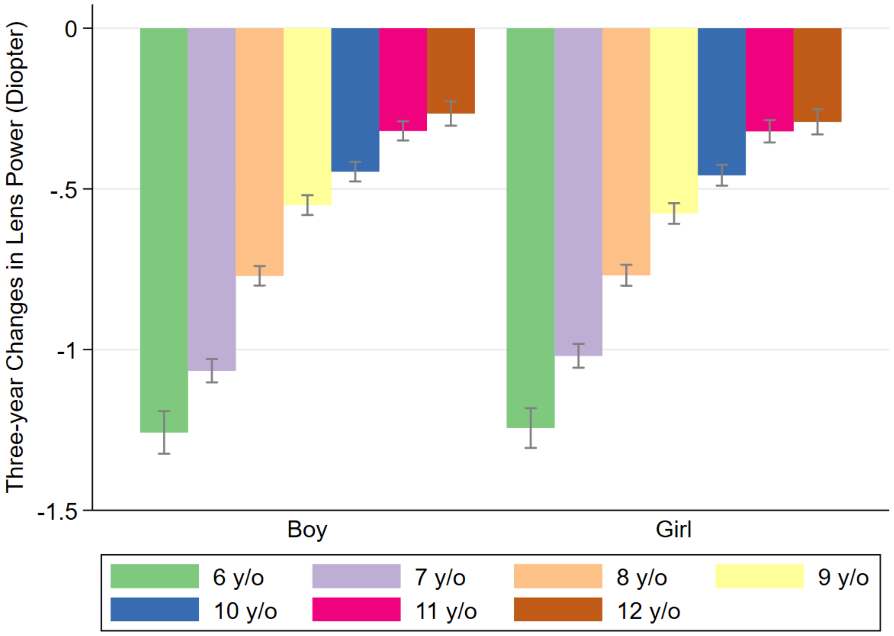
Figure 2: *Three-year changes of lens power by axial length at baseline according to the myopic progression (Spherical Equivalent progression <-0.5 dioptre). Each line represents individual changes from the baseline to follow-up Phases.*



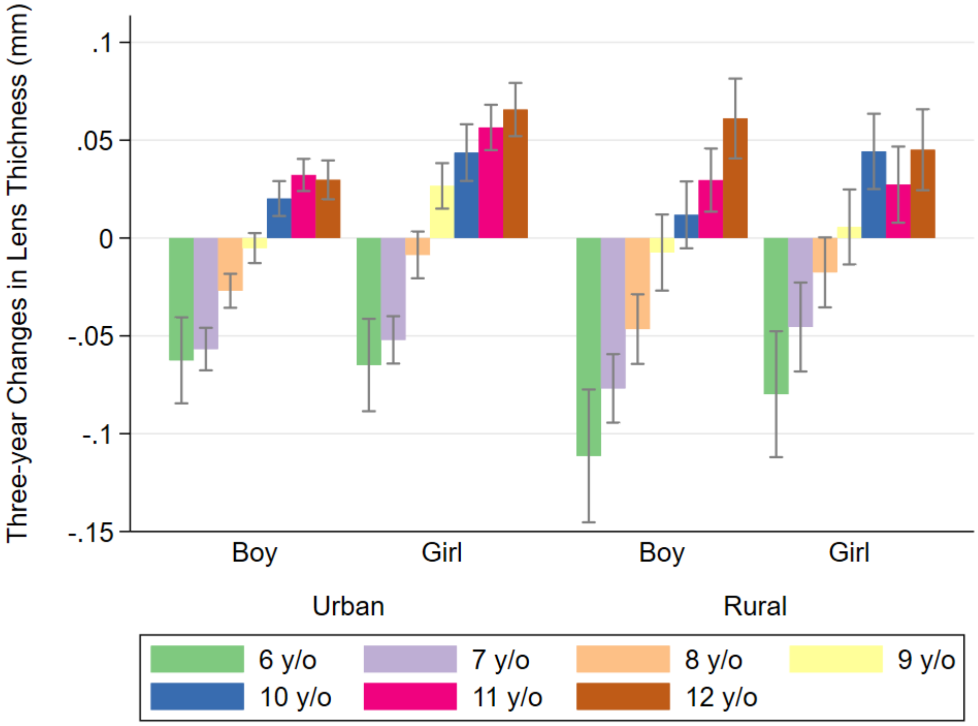
Supplementary figure 3: *Three-year changes in lens power by spherical equivalent groups at baseline. Error bars indicate 95% confidence intervals for mean changes.*



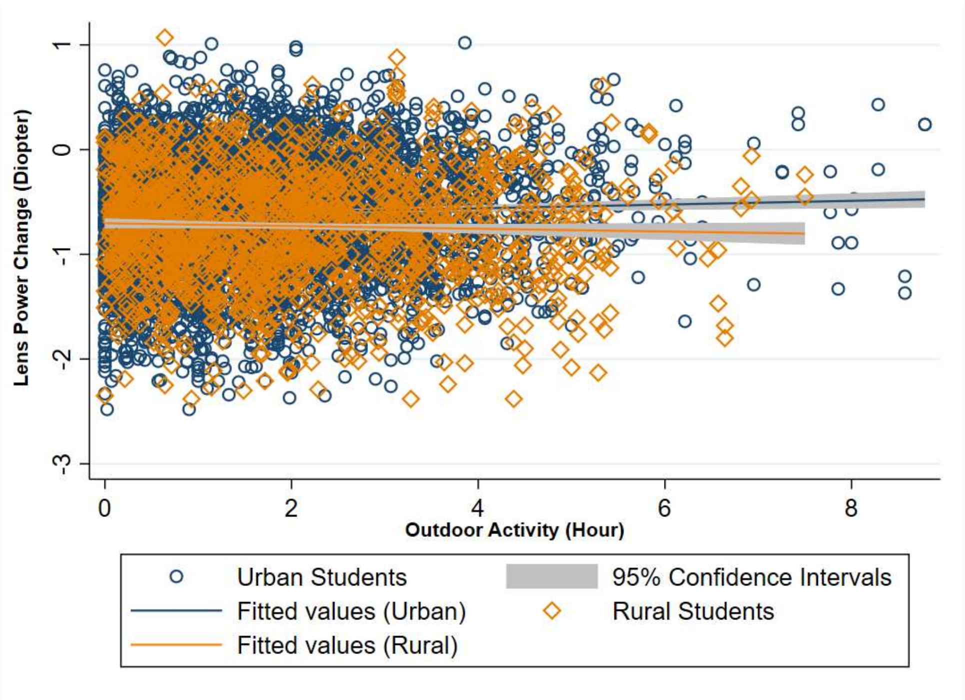
Supplementary figure 4: *The association between axial length at baseline and three-year crystalline lens power changes. CI: Confidence Intervals.*



Supplementary figure 5: *Three-year changes in lens power by age and sex groups. Error bars indicate 95% confidence intervals for mean changes.*



Supplementary figure 6: *Three-year changes in lens thickness by age, sex and place of residence groups. Error bars indicate 95% confidence intervals for mean changes.*



Supplementary figure 7: *The association of outdoor activity at baseline and three-year changes of lens power by residence place.*

Tables

Table 1: The mean, standard deviation (SD) and 95% confidence interval (CI) of crystalline lens power and thickness in phases 1 and 2 and their 3 years changes aby sex, residence place age groups and refractive errors.

Independent Variables		Number of Eyes	Lens power			Lens thickness		
			Phase 1	Phase 2	Three years changes	Phase 1	Phase 2	Three years changes
			mean ± SD (95%CI)	mean ± SD (95%CI)	mean ± SD (95%CI)	mean ± SD (95%CI)	mean ± SD (95%CI)	mean ± SD (95%CI)
Total Participants		8089	21.61 ± 1.47 (21.50, 21.72)	21.00 ± 1.42 (20.91, 21.09)	-0.61 ± 0.52 (-0.65, -0.57)	3.49 ± 0.18 (3.48, 3.50)	3.49 ± 0.20 (3.48, 3.50)	0.002 ± 0.13(-0.004, 0.008)
Gender	Male	4347	21.12 ± 1.35 (21.02, 21.22)	20.52 ± 1.31 (20.45, 20.58)	-0.60 ± 0.52(-0.66, -0.55)	3.47 ± 0.18 (3.46, 3.48)	3.46 ± 0.19 (3.45, 3.47)	-0.01 ± 0.11(-0.01, 0.00)
	Female	3742	22.21 ± 1.38 (22.09, 22.32)	21.58 ± 1.32 (21.51, 21.66)	-0.62 ± 0.52 (-0.68, -0.57)	3.52 ± 0.19 (3.51, 3.53)	3.53 ± 0.21 (3.52, 3.54)	0.01 ± 0.14 (0.00, 0.02)
Residence Place	Urban	6363	21.57 ± 1.37 (21.45, 21.69)	20.97 ± 1.32 (20.88, 21.07)	-0.60 ± 0.48 (-0.64, -0.56)	3.49 ± 0.17 (3.48, 3.50)	3.49 ± 0.19 (3.48, 3.50)	0.003 ± 0.12 (-0.00, 0.01)
	Rural	1726	21.97 ± 2.10 (21.79, 22.15)	21.24 ± 2.06 (21.10, 21.38)	-0.73 ± 0.76 (-0.80, -0.65)	3.51 ± 0.27 (3.49, 3.53)	3.50 ± 0.28 (3.48, 3.52)	-0.01 ± 0.18 (-0.03, 0.00)
Refractive errors	Emmetropia (0.75<SE<2)	4572	21.67 ± 1.42 (21.56, 21.78)	21.09 ± 1.37 (20.99, 21.18)	-0.58 ± 0.51 (-0.63, -0.54)	3.52 ± 0.18 (3.51, 3.53)	3.52 ± 0.19 (3.51, 3.53)	0.002 ± 0.133 (-0.006, 0.009)
	High myopia (SE≤ -5)	7	21.59 ± 1.44 (20.16, 23.02)	21.91 ± 1.48 (20.38, 23.45)	0.32 ± 0.38 (-0.05, 0.70)	3.41 ± 0.19 (3.22, 3.61)	3.45 ± 0.24 (3.20, 3.70)	0.040 ± 0.064 (-0.018, 0.098)
	Myopia (-0.5 ≤SE> -5)	312	21.26 ± 1.41 (21.03, 21.49)	20.73 ± 1.42 (20.50, 20.96)	-0.53 ± 0.48 (-0.60, -0.45)	3.36 ± 0.16 (3.34, 3.39)	3.37 ± 0.18 (3.34, 3.40)	0.007 ± 0.099 (-0.011, 0.024)
	Pre-myopia (-0.5 <SE≤0.75)	2807	21.51 ± 1.54 (21.38, 21.63)	20.82 ± 1.37 (20.72, 20.93)	-0.68 ± 0.52 (-0.73, -0.64)	3.44 ± 0.18 (3.43, 3.46)	3.45 ± 0.20 (3.44, 3.46)	0.003 ± 0.122 (-0.005, 0.018)
	Hyperopia (SE≥ 2)	391	21.98 ± 1.39 (21.78, 22.18)	21.44 ± 1.34 (21.27, 21.61)	-0.55 ± 0.57 (-0.64, -0.45)	3.59 ± 0.18 (3.56, 3.61)	3.58 ± 0.19 (3.56, 3.61)	-0.004 ± 0.125 (-0.021, 0.013)
Age (Year)	6	377	22.56 ± 1.43 (22.32, 22.81)	21.32 ± 1.42 (21.08, 21.56)	-1.24 ± 0.48 (-1.31, -1.17)	3.57 ± 0.20 (3.55, 3.60)	3.50 ± 0.20 (3.48, 3.53)	-0.07 ± 0.14 (-0.09, -0.05)
	7	1291	22.40 ± 1.32 (22.23, 22.57)	21.37 ± 1.39 (21.19, 21.55)	-1.03 ± 0.48 (-1.07, -0.99)	3.56 ± 0.18 (3.54, 3.57)	3.50 ± 0.19 (3.48, 3.52)	-0.06 ± 0.13 (-0.07, -0.05)
	8	1507	21.88 ± 1.37 (21.72, 22.04)	21.12 ± 1.39 (20.96, 21.28)	-0.76 ± 0.44 (-0.80, -0.72)	3.50 ± 0.18 (3.49, 3.52)	3.48 ± 0.19 (3.47, 3.50)	-0.02 ± 0.13 (-0.03, -0.012)
	9	1597	21.55 ± 1.38 (21.40, 21.71)	21.00 ± 1.40 (20.85, 21.15)	-0.56 ± 0.45 (-0.59, -0.52)	3.48 ± 0.18 (3.47, 3.50)	3.49 ± 0.20 (3.48, 3.51)	0.01 ± 0.12 (-0.00, 0.02)
	10	1233	21.28 ± 1.43 (21.09, 21.48)	20.83 ± 1.44 (20.64, 21.02)	-0.45 ± 0.40 (-0.48, -0.42)	3.46 ± 0.19 (3.45, 3.48)	3.49 ± 0.21 (3.47, 3.51)	0.03 ± 0.12 (0.02, 0.04)
	11	1273	21.07 ± 1.35 (20.90, 21.24)	20.77 ± 1.37 (20.60, 20.95)	-0.30 ± 0.40 (-0.33, -0.27)	3.45 ± 0.18 (3.43, 3.47)	3.49 ± 0.20 (3.47, 3.51)	0.04 ± 0.11 (0.03, 0.05)
	12	811	20.95 ± 1.41 (20.72, 21.19)	20.69 ± 1.40 (20.47, 20.91)	-0.26 ± 0.39 (-0.30, -0.23)	3.45 ± 0.18 (3.43, 3.47)	3.49 ± 0.20 (3.47, 3.52)	0.05 ± 0.11 (0.04, 0.06)

Table 2: Association of three-year changes of crystalline lens power with ocular biometrics and other independent variables in simple and multiple generalized estimating equations (GEE).

Independent Variables	**Simple GEE**		**Multiple GEE**	
	Coefficient (95%CI)	**P-value**	**Coefficient (95%CI)**	**P-value**
Age at baseline	0.163 (0.156, 0.170)	<0.001	0.176 (0.169, 0.184)	<0.001
Female Sex	-0.015 (-0.044, 0.014)	0.306	0.016 (-0.012, 0.043)	0.266
Rural Residence	-0.126 (-0.162, -0.091)	<0.001	-0.025 (-0.077, 0.027)	0.342
Height (Cm)	0.021 (0.020, 0.022)	<0.001	NR	
Lens power at baseline (Dioptre)	-0.126 (-0.135, -0.117)	<0.001	NR	
Axial length at baseline (mm)	0.115 (0.096, 0.134)	<0.001	NR	
Anterior chamber depth at baseline (mm)	0.080 (0.022, 0.138)	0.007	NR	
Lens thickness at baseline (mm)	-0.162 (-0.236, -0.089)	<0.001	NR	
Mean keratometry at baseline	-0.017 (-0.027, -0.008)	<0.001	NR	
Central corneal thickness at baseline (Micron)	0.0005(0.0001, 0.0009)	0.009	NR	
Corneal diameter at baseline (mm)	0.024 (0.004, 0.052)	0.096	NR	
Spherical Equivalent (SE) at baseline (D)				
Emmetropia (0.75<SE<2)	Reference group	-	Reference group	-
High myopia (SE≤ -5)	0.648 (0.097, 1.199)	0.021	0.721 (0.670, 0.771)	<0.001
Myopia (-0.5 ≤SE> -5)	-0.016 (-0.084, 0.052)	0.650	-0.141 (-0.205, -0.076)	<0.001
Pre-myopia (-0.5 <SE≤0.75)	-0.137 (-0.163, -0.111)	<0.001	-0.197 (-0.221, -0.172)	<0.001
Hyperopia (SE≥ 2)	0.061 (-0.001, 0.123)	0.054	0.120 (0.063, 0.178)	<0.001
Near work time (hours)	0.012 (0.002, 0.022)	0.014	-0.007 (-0.015, 0.001)	0.069
Outdoor activity time (hours)	0.004 (-0.008, 0.016)	0.515	0.013 (0.001, 0.024)	0.039
Rural Residence *Outdoor activity			-0.032 (-0.055, -0.010)	0.005

CI: Confidence intervals; NR: Not retained in final multiple model due to collinearity with other variables.

Table 3: Association of three- years changes in crystalline lens thickness with ocular biometrics and other independent variables in simple and multiple generalized estimating equations (GEE) models.

Independent Variables	**Simple GEE**		**Multiple GEE**	
	Coefficient (95%CI)	**P-value**	**Coefficient (95%CI)**	**P-value**
Age at baseline	0.022 (0.020, 0.024)	<0.001	0.022 (0.020, 0.024)	<0.001
Female sex	0.019 (0.012, 0.026)	<0.001	0.022 (0.014, 0.029)	<0.001
Rural residence	-0.014 (-0.023, -0.005)	<0.001	-0.011 (-0.019, -0.003)	0.008
Lens thickness at baseline (mm)	-0.268 (-0.286, -0.251)	<0.001	NR	
Axial length at baseline (mm)	0.010 (0.005, 0.014)	<0.001	NR	
Anterior chamber depth at baseline (mm)	0.108 (0.094, 0.123)	<0.001	NR	
Lens power at baseline (Diopter)	-0.005 (-0.007, -0.003)	<0.001	NR	
Mean keratometry at baseline (Diopter)	-0.003 (-0.005, -0.001)	0.009	NR	
Central corneal thickness at baseline (Micron)	-0.00004 (-0.00014, 0.00006)	0.480	NR	
Corneal diameter at baseline (mm)	0.0064 (-0.0004, 0.0132)	0.064	NR	
Spherical Equivalent (SE) at baseline (D)				
Emmetropia (0.75<SE<2)	Reference group	-	Reference group	-
High myopia (SE≤ -5)	0.030 (-0.013, 0.073)	0.166	0.019 (-0.018, 0.055)	0.315
Myopia (-0.5 ≤SE> -5)	0.003 (-0.012, 0.017)	0.701	-0.018 (-0.032, -0.004)	0.010
Pre-myopia (-0.5 <SE≤0.75)	0.003 (-0.003, 0.010)	0.285	-0.006 (-0.012, 0.0002)	0.057
Hyperopia (SE≥ 2)	-0.004 (-0.018, 0.011)	0.605	0.0009 (-0.013, 0.015)	0.905
Near work time (hours)	0.0021 (-0.0002, 0.0045)	0.078	NR	
Outdoor activity time (hours)	-0.005 (-0.007, -0.002)	0.002	NR	

CI: Confidence intervals; NR: Not retained in final multiple model due to collinearity with other variables.