Long-Term Changes in Refractive Error in Children With Myopic Tilted Optic Disc Compared to Children Without Tilted Optic Disc

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Purpose. To compare changes in the spherical equivalent (SE) refractive error between children with and without myopic tilted optic disc.

Methods. Changes in SE refractive error were compared between a group of 88 children with −1.5 diopters or more of myopia with myopic tilted disc and a group of 108 age- and initial SE refractive error–matched children without tilted disc. Factors that significantly influenced changes in SE refractive error were analyzed using mixed models.

Results. Patients in the myopic tilted disc group were followed for 5.3 ± 3.1 years, on average, and patients in the nontilted disc group were followed for an average of 5.3 ± 2.3 years. An overall tendency toward myopic progression during the follow-up period was noted in both groups. According to univariate analysis, patients with a poorer baseline best-corrected visual acuity (BCVA) and tilted discs tended to have greater myopia over time ($P < 0.001$ and $P = 0.009$, respectively). Myopic progression in the tilted disc group was significantly greater than that in the nontilted disc group ($P < 0.001$) after adjusting for sex and initial BCVA.

Conclusions. Patients with myopic disc tilt showed greater myopic progression over time. These data suggest that myopic disc tilt represents a prognostic factor for further myopic progression, but it is unclear whether the disc tilt directly affects the progression rate of myopia or is a noncontributory consequence of other underlying mechanisms. The temporal relationship between the onset of the disc tilt and the myopic progression should be further studied using a prospective design.

Keywords: tilted disc, myopia, children

A tilted appearance of the optic nerve head is a relatively common finding during the course of a routine ophthalmic examination. "Tilted optic discs" can be divided into two broad categories based on their etiology. Firstly, tilted optic discs can be the result of congenital tilted disc syndrome, which manifests as inferonasal tilting of the optic disc, usually with an associated inferonasal crescent, thinning of the retinal pigment epithelium, thinning of the choroid in the inferonasal fundus, posterior staphyloma of the affected inferonasal region of the fundus, and situs inversus of the retinal vessels, occurring in eyes without high myopia.[1,2] Secondly, tilted optic discs can be noncongenital. Tilted optic discs often arise due to acquired changes related to the progression of myopia, known as myopic tilted disc.[1] Because tilted disc syndrome arises from a congenital anomaly, the signs are considered nonprogressive.[1] However, as an acquired condition, myopic tilted disc is often progressive.

With regard to the possible progressive nature of myopic tilted disc, there has been some recent supportive evidence. Previous studies revealed that a high proportion of people with myopic tilted disc have more severe myopia,[3–6] suggesting that the tilted disc is a consequence of myopic progression. Both Nakazawa et al.[6] and Kim et al.[7] nicely illustrated the acquired development of optic disc tilt and temporal crescent formation over time, with disc tilting developing in the relatively early stages of mild myopia in some of the patients.[6,7] Samarawickrama et al.[8] also suggested a temporal pattern of the development of pathologic changes in myopia. They reported the initial development of optic disc tilt and peripapillary atrophy, which was followed by staphyloma and lacquer crack development, and finally observed the onset of chorioretinal atrophy.

Although there is an established association between myopia and tilted disc, not every high myopic patient develops tilted disc, and it is unclear which factors precipitate myopic disc tilt development. One histopathologic study showed that 37.7% of enucleated pathologic myopic eyes had tilted discs, with the retina falling short of the optic disc on one side and the retinal pigment epithelium and choroid extending over a portion of the optic disc on the other side.[9] Also, eyes with tilted optic discs often have greater levels of myopia and astigmatic error.[8,10,11] However, there are no known studies investigating patients with myopia and how the disc tilt could affect further myopic progression.

Because optic disc tilt is relatively common and easily detectable, if there is an association between optic disc tilt and myopic progression, optic disc tilt could be a useful indicator in predicting a patient's prognosis. Our purpose was to determine whether optic disc tilt is only a coincidental finding during

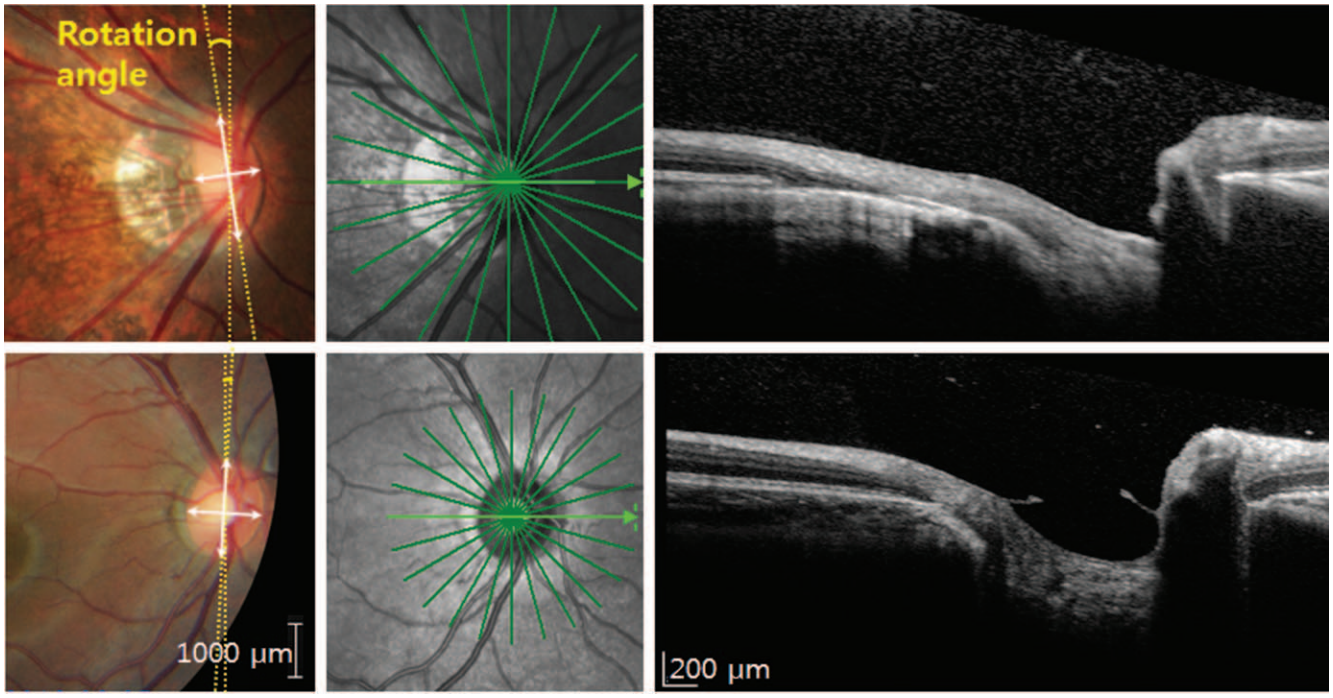

FIGURE 1. Disc photographs and optical coherence tomography images of an 8-year-old girl with severely tilted disc and a horizontal-to-vertical disc diameter ratio of 0.44 (*upper left*), and a 7-year-old boy who had a mildly tilted disc with a horizontal-to-vertical disc diameter ratio of 0.75 (*lower left*). Cross-sectional spectral domain optical coherence tomography images of the optic discs of each patient show absent retinal layers, other than the nerve fiber layer bundle, in the peripapillary atrophy region (*middle and right columns*).

myopic progression or if it serves as an independent risk factor for further myopic progression.

METHODS

This retrospective study was performed at a single center according to the tenets of the Declaration of Helsinki. This study was approved by the institutional review board of Samsung Medical Center (Seoul, Republic of Korea). We retrospectively reviewed the medical records of children with myopia upon initial presentation. Among patients who were examined at the pediatric ophthalmology department at Samsung Medical Center between August 1994 and July 2012, a computerized search was performed to identify patients with myopia according to the International Classification of Diseases, Eleventh Revision H52.1. In patients who first visited the general ophthalmology department and were referred to the pediatric ophthalmology department, we designated the pediatric clinic visit as the first or initial visit for our study purposes. At the initial visit, patients underwent a full ophthalmologic assessment, including visual acuity testing, cycloplegic refraction, slit-lamp biomicroscopy, fundus examination, and fundus photography. The best-corrected visual acuity (BCVA) was measured using the Han Chun Suk visual acuity chart after experienced examiners performed manifest refraction. The corrected visual acuities were transformed to a logarithmic scale (logMAR) for statistical analysis. A single examiner (SYO) performed the cycloplegic refractions using retinoscopy after applying 1% cyclopentolate and 0.5% tropicamide. The spherical equivalent (SE) was calculated as the sphere plus half a cylinder. During the follow-up period, cycloplegic refractions were generally performed every 6 to 12 months. At the initial examination, fundus photographs were acquired using a TRC-50IX digital camera (Topcon, Tokyo, Japan) in all patients who were willing. The patients were seated and properly positioned, with the chin and forehead firmly anchored to the device to minimize head movement during the examination.

For fundus photograph analysis, all photographs were assessed on a graphics tablet monitor (Wacom Technology, Ltd., Saitama, Japan) by two independent observers (K-AP and S-EP) who were blind to patients' clinical information. Using ImageJ software 1.45 (National Institutes of Health, Bethesda, MD), the optic disc margins, defined as the inner border of the peripapillary scleral ring, were lined. Also, the vertical and horizontal diameter and the degree of optic disc rotation, defined as the angle between the imaginary vertical meridian and the long axis of the optic disc, were assessed (Fig. 1). The observers classified each eye into one of two categories based on the presence or absence of a tilted disc. Patients met the criteria for tilted disc if they had an optic disc with a ratio of minimal to maximal disc diameter of 0.75 or less, as described in previous studies,[12,13] and if they had a white semilunar patch of sclera adjacent to the optic disc. In cases of disagreement, a third observer (SYO) served as adjudicator.

Two groups of myopic children were included in the study: those with myopic tilted discs and those without tilted discs upon initial examination. The inclusion criteria for the myopic tilted disc group were as follows: −1.0 diopters (D) or more of myopia; tilted optic disc as described above upon the initial fundus examination, and age between 3 and 17 years. In order to avoid including tilted discs with a congenital etiology, only temporally tilted discs were considered to be myopic tilted discs; discs tilted in another direction, including nasally, superiorly, or inferiorly, were excluded. Tilted discs with axes beyond 45° of the vertical meridian were also excluded. Patients with other ocular pathology or a follow-up interval of less than 1 year were not included in the study. Patients with developmental delay, previous ocular surgery, any form of neurologic impairment, or other diseases of the visual pathways were also excluded from participation.

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TABLE. Baseline Characteristics of Tilted Disc Group and Nontilted Disc Group

Variable	Tilted Disc, $n = 88$	Nontilted Disc, $n = 108$	*P* Value
Age, y, mean ± SD	7.8 ± 3.92	8.3 ± 3.7	
Sex, male/female	41/47	57/51	0.933*
SE refractive error, diopters, Rt, mean ± SD	−4.65 ± 3.41	−4.25 ± 3.19	
Astigmatism, diopters, Rt, mean ± SD	1.13 ± 1.16	1.08 ± 1.12	0.715†

Rt, right eyes.
* Generalized estimating equation.
† Mixed model (initial astigmatism was transformed using natural log due to skewed distribution during analysis).

Subjects whose age and initial refractive error matched those of the children in the tilted disc group were consecutively recruited, and an independent statistician performed the subject-matching procedure. Patients with and without tilted discs were aligned and grouped according to age and refractive error upon their initial presentation to the pediatric ophthalmology department. All subjects and their matched controls had a difference in SE refractive error less than or equal to 2 D and an age difference less than or equal to 1 year. In the event that no matched control subjects were available, the data from recruited subjects were excluded from the study.

Refractive data were collected from the medical records for the follow-up periods. Only right eye data were used in the analyses of results.

An independent statistician performed the statistical analyses, and data were analyzed using Statistical Analysis System version 9.2 (SAS, Inc., Cary, NC). A generalized estimating equation was used to compare sex between the tilted disc group and nontilted disc group. A mixed model was used to compare initial levels of astigmatism between the two groups. During the analysis, the initial astigmatism level was transformed using natural logs due to skewed distribution. Correlations between SE refractive error and multiple factors including age, sex, initial SE refractive error, BCVA, and the presence of myopic tilted disc were analyzed using a mixed model. The compound symmetry covariance structure was used. Comparisons of longitudinal changes in SE refractive error between the tilted disc group and nontilted disc group were performed using a mixed model adjusting for sex and BCVA. The compound symmetry covariance structure was used. A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

The database included a total of 7368 patients. Among these, initial fundus photographs were available for analysis in 6681 patients. The 6681 patients with available fundus photographs and the 687 patients without initial fundus photographs (due to lack of consent from patients or guardians or due to poor image quality) had a similar mean age at the initial visit (age 8.0 ± 4.7 vs. 8.3 ± 4.2 years, $P = 0.070$, *t*-test) and refractive error (−2.2 ± 2.1 vs. −2.1 ± 1.5 D, $P = 0.166$, *t*-test). Of the 6681 patients, we found 135 to be between 3 and 17 years of age, to have −1.5 D or less of initial SE refractive error, and to have a temporally tilted disc. Of these patients, 44 met the exclusion criteria as described above. Three additional patients were excluded due to the inability to appropriately match them with control patients. Among the patients with −1.5 D or less of myopia without temporally tilted discs, 287 patients had tilted discs with axes beyond 45° of the vertical. Patients with −1.5 D or less myopia without tilted discs were lined up and grouped according to their SE refractive error and age at the initial examination. Of these patients, 108 without tilted discs whose refractive error and age matched a patient in the tilted disc group were consecutively selected as controls.

The baseline characteristics are displayed in the Table, and no significant differences between the two groups were identified. The mean length of follow-up was 5.3 ± 3.1 years (range, 1.5–14.8 years) in the tilted disc group and 5.3 ± 2.3 years (range, 1.5–11.9 years) in the nontilted disc group.

According to univariate analysis, BCVA and the presence of a tilted disc significantly affected the final SE refractive error. Patients with a poorer baseline BCVA and a tilted disc tended to have an increasing severity of myopia over time ($P < 0.001$ and $P = 0.009$, respectively). Sex was not a significant factor affecting SE refractive error in this analysis. Age and SE refractive error were not included in the analysis because they were already matched in the recruitment procedure. When the subjects were divided into two groups according to the presence of a tilted optic disc, the mean SE refractive error at the initial examination was −4.65 ± 3.41 D (range, −16.50 to −0.50 D) in the tilted disc group and −4.25 ± 3.19 D (range, −18.50 to −0.50 D) in the nontilted disc group. Figure 2 depicts changes in SE refractive error for the two groups. An overall tendency toward myopia progression during the follow-up period was noted in both groups. The change in SE refractive error was significantly different between the two groups when sex and initial BCVA were adjusted ($P < 0.001$); the reduction in SE refractive error in the tilted disc group was significantly greater than that in the nontilted disc group ($P < 0.001$).

DISCUSSION

In this study, an overall tendency toward myopia progression during the follow-up period was noted in both the tilted and nontilted disc groups, which was not unexpected since myopic progression in children due to axial length growth with aging is well established.[14] For example, the Correction of Myopia Evaluation Trial reported children with mean age of 9.3 ± 1.3 years to have an average myopic progression of 1.34 D in 3 years.[15] When the rate at which myopia progresses is considered, the initial magnitude of SE refractive error is also known to be a strong factor affecting refractive error changes. Mantyjarvi[16] followed 46 hyperopic and 133 myopic children (aged 7–15 years) over 5 to 8 years and found that the mean myopic progression rate was "faster" in the myopic children, who progressed at a rate of −0.55 D/y compared to the hyperopic children, who progressed at a rate of −0.12 D/y. Furthermore, Goldblum et al.[17] illustrated the likelihood of myopic progression for each initial refraction in different age and different refractive error groups. Their study showed that a child (birth to 9 years) initially at −1 D had a 25% probability of increasing his/her myopia by another −1.25 to −3 D, and an even higher likelihood (over 35%) of increasing myopia over −3.25 D within the subsequent 5 years of life. In contrast, a child (birth to 9 years) initially at −6 D had a probability less than 10% of increasing myopia over −3.25 D within the subsequent 5 years of life. A child (10–19 years) initially at −1

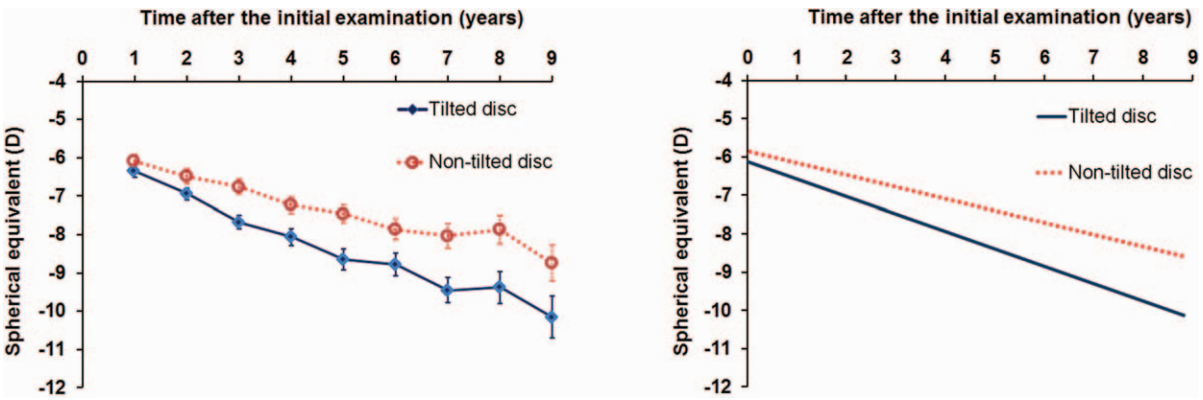

FIGURE 2. Changes in the right SE refractive error for the tilted and nontilted disc groups over time (*left*). An overall tendency toward myopic progression during the follow-up period was noted in both groups. *Central dots* represent mean values, and the *upper and lower bars* represent mean ± standard deviations. The decrease in SE refractive error in the tilted disc group was greater than in the nontilted disc group over time. A regression model of the two groups is also presented (*right*).

D had only a 10% probability of increasing myopia over −3.25 D within the subsequent 5 years of life. Although results from studies investigating myopia progression have been variable and somewhat inconclusive, younger age,[16,18–23] severity of initial myopia,[19,21–24] female sex,[16,19,23–25] and a family history of myopia[26] have been consistently reported to be associated with myopic progression.

Among the various factors associated with myopic progression, acquired myopic tilted disc has been considered to be a noncontributory by-product of axial elongation of the eyeball that occurs with myopic progression, rather than an independent risk factor for further progression.[9] It is postulated that optic disc tilting occurs as a result of the optic nerve being pulled in the temporal direction as the eyeball grows axially and the temporal sclera moves back and becomes flattened.[7] This process usually occurs temporally with concomitant nasal override of the optic disc by the retina, retinal pigment epithelium, and choroid.[9] Although the mechanism of myopic disc tilt is generally accepted, not every patient with myopia develops tilted disc as myopia progresses, and it is unclear which factors affect susceptibility to myopic disc tilt. Kim et al.[7] recently illustrated optic nerve head change in children with incipient myopia. In their study, optic nerve head change was associated with myopic shift according to logistic regression analysis, although the magnitude of disc tilt was not proportional to the degree of myopic shift.

While myopic disc tilting can unarguably occur as a consequence of myopic progression, our current study suggests that the presence of a myopic tilted disc could also serve to predict future progression of myopia. However, it is unclear whether the disc tilt itself directly facilitates myopic progression, or whether other factors are the underlying myopic mechanism and happen to also result in disc tilt. For example, we know that the myopic disc change is caused by axial elongation and scleral thinning around the disc, but this thinning might involve larger areas including the posterior pole. Thinned sclera could be more vulnerable to myopic change due to eyeball elongation. However, correlations between disc tilt and the amount of scleral thinning were not analyzed in this study, and there might also be other hidden factors that affect both the development of disc tilt and the myopic progression. We believe that further studies will clarify the mechanism underlying myopic progression and explain the observed differences between children with myopic tilted discs and those without tilted discs.

As already mentioned, we suggest in this study that the presence of a myopic tilted disc could be considered a risk factor for faster myopic progression, besides being a reflection of previous myopic change. Previously, a number of environmental risk factors have been studied to ascertain their role in myopic development and progression. Near work,[27] accommodation, accommodative lag,[28,29] ambient light,[30,31] and even intelligence[32,33] have all been implicated as possible factors contributing to myopic change. Various treatment strategies (including single vision, bifocal, and multifocal lenses to remove accommodative demands,[34,35] orthokeratologic lenses,[36–38] and various pharmacologic agents[39–41]) have been extensively studied. Although the results of these studies are somewhat controversial, especially those focusing on environmental control, the use of various lenses, and pharmacologic agents, some of them showed statistically significant benefits.[35–40,42,43] Despite this controversy, extensive research is ongoing in this field. We suggest that the families of children with myopic tilted discs be educated about the possibility of further myopic progression, and we recommend environmental control strategies to make every effort to prevent myopic progression in these children, especially those in countries with a high prevalence of myopia. With regard to these preventive strategies, orthokeratologic lenses could be a viable supplemental option.[36–38]

Our study had several limitations. Firstly, the study was retrospective in design, which resulted in several constraints. For example, different patients had different follow-up intervals. Also, we could not account for the onset of the disc tilt. Further prospective research studying the relationship between the onset of disc tilt and the pattern of refractive error change would help us to better understand the association between myopic progression and disc tilt. In addition, we could not analyze the effect of environmental factors or genetic factors such as family history of myopia, near work, or outdoor activity on the progression of myopia because of the retrospective design. Secondly, we did not classify patients according to the grade of disc tilting. Thirdly, we used cases from a single center and the same ethnic group to collect our data, and some of the results may not be valid in other ethnic groups. Fourthly, we did not measure axial elongation. Although it is reported that myopic shift occurring in children is mostly attributable to axial elongation,[15] we cannot definitively rule out the possibility that other biometric changes contribute to the change in refractive error. The fifth limitation is that there is a possibility that we might not completely be ruling out congenital tilted disc. We did limit our recruitment to children with temporally tilted discs, but there is a possibility that congenital tilted discs can present with a

temporally tilted disc. Including congenital tilted discs might have affected our results, making the true between-group differences smaller in magnitude. Further prospective studies that discriminate clearly between the acquired form and the congenital form of tilted disc are needed to avoid this selection error. As mentioned previously, we analyzed only temporally tilted discs, and it should be noted that the results of our study might not be valid when nontemporally tilted discs are considered. In conclusion, the results of this study elucidate a correlation between disc tilt and myopic progression. These data suggest that myopic disc tilt could be used as one of the prognostic factors for further myopic progression. However, it is unclear whether disc tilt affects the myopic progression rate directly or is an inconsequential sequela of other underlying factors. Therefore the temporal aspect of the association between the onset of the disc tilt and the myopic progression should be further studied.

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References

1. Apple DJ, Rabb MF, Walsh PM. Congenital anomalies of the optic disc. *Surv Ophthalmol*. 1982;27:3–41.
2. You QS, Xu L, Jonas JB. Tilted optic discs: the Beijing Eye Study. *Eye (Lond)*. 2008;22:728–729.
3. Hwang YH, Yoo C, Kim YY. Characteristics of peripapillary retinal nerve fiber layer thickness in eyes with myopic optic disc tilt and rotation. *J Glaucoma*. 2012;21:394–400.
4. Hwang YH, Yoo C, Kim YY. Myopic optic disc tilt and the characteristics of peripapillary retinal nerve fiber layer thickness measured by spectral-domain optical coherence tomography. *J Glaucoma*. 2012;21:260–265.
5. Lim L, Gazzard G, Chan YH, et al. Corneal biomechanics, thickness and optic disc morphology in children with optic disc tilt. *Br J Ophthalmol*. 2008;92:1461–1466.
6. Nakazawa M, Kurotaki J, Ruike H. Longterm findings in peripapillary crescent formation in eyes with mild or moderate myopia. *Acta Ophthalmol*. 2008;86:626–629.
7. Kim TW, Kim M, Weinreb RN, Woo SJ, Park KH, Hwang JM. Optic disc change with incipient myopia of childhood. *Ophthalmology*. 2012;119:21–26, e21-e23.
8. Samarawickrama C, Mitchell P, Tong L, et al. Myopia-related optic disc and retinal changes in adolescent children from Singapore. *Ophthalmology*. 2011;118:2050–2057.
9. Grossniklaus HE, Green WR. Pathologic findings in pathologic myopia. *Retina*. 1992;12:127–133.
10. Brazitikos PD, Safran AB, Simona F, Zulauf M. Threshold perimetry in tilted disc syndrome. *Arch Ophthalmol*. 1990; 108:1698–1700.
11. Graham MV, Wakefield GJ. Bitemporal visual field defects associated with anomalies of the optic discs. *Br J Ophthalmol*. 1973;57:307–314.
12. How AC, Tan GS, Chan YH, et al. Population prevalence of tilted and torted optic discs among an adult Chinese population in Singapore: the Tanjong Pagar Study. *Arch Ophthalmol*. 2009;127:894–899.
13. Jonas JB, Kling F, Grundler AE. Optic disc shape, corneal astigmatism, and amblyopia. *Ophthalmology*. 1997;104:1934–1937.
14. Mantyjarvi MI. Changes of refraction in schoolchildren. *Arch Ophthalmol*. 1985;103:790–792.
15. Hyman L, Gwiazda J, Hussein M, et al. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol*. 2005;123:977–987.
16. Mantyjarvi MI. Predicting of myopia progression in school children. *J Pediatr Ophthalmol Strabismus*. 1985;22:71–75.
17. Goldblum D, Brugger A, Haselhoff A, Schmickler S. Longitudinal change of refraction over at least 5 years in 15,000 patients. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:1431–1436.
18. Lam CS, Edwards M, Millodot M, Goh WSA. 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. *Optom Vis Sci*. 1999;76: 370–380.
19. Parssinen O, Hemminki E, Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. *Br J Ophthalmol*. 1989;73:547–551.
20. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. Factors related to the progression of myopia in Singaporean children. *Optom Vis Sci*. 2000;77:549–554.
21. Fan DS, Lam DS, Lam RF, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci*. 2004;45:1071–1075.
22. Braun CI, Freidlin V, Sperduto RD, Milton RC, Strahlman ER. The progression of myopia in school age children: data from the Columbia Medical Plan. *Ophthalmic Epidemiol*. 1996;3: 13–21.
23. Goss DA. Variables related to the rate of childhood myopia progression. *Optom Vis Sci*. 1990;67:631–636.
24. Zhao J, Mao J, Luo R, Li F, Munoz SR, Ellwein LB. The progression of refractive error in school-age children: Shunyi district, China. *Am J Ophthalmol*. 2002;134:735–743.
25. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. *Surv Ophthalmol*. 1999;44(suppl 1):S109–S115.
26. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. Familial clustering and myopia progression in Singapore school children. *Ophthalmic Epidemiol*. 2001;8:227–236.
27. Ip JM, Saw SM, Rose KA, et al. Role of near work in myopia: findings in a sample of Australian school children. *Invest Ophthalmol Vis Sci*. 2008;49:2903–2910.
28. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci*. 2006;47:837–846.
29. Weizhong L, Zhikuan Y, Wen L, Xiang C, Jian G. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic Physiol Opt*. 2008;28:57–61.
30. Guggenheim JA, Hill C, Yam TF. Myopia, genetics, and ambient lighting at night in a UK sample. *Br J Ophthalmol*. 2003;87: 580–582.
31. Quinn GE, Shin CH, Maguire MG, Stone RA. Myopia and ambient lighting at night. *Nature*. 1999;399:113–114.
32. Saw SM, Tan SB, Fung D, et al. IQ and the association with myopia in children. *Invest Ophthalmol Vis Sci*. 2004;45:2943–2948.
33. Williams C, Miller LL, Gazzard G, Saw SM. A comparison of measures of reading and intelligence as risk factors for the development of myopia in a UK cohort of children. *Br J Ophthalmol*. 2008;92:1117–1121.
34. Gwiazda J, Hyman L, Hussein M, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses

on the progression of myopia in children. *Invest Ophthalmol Vis Sci*. 2003;44:1492–1500.

35. Hasebe S, Ohtsuki H, Nonaka T, et al. Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. *Invest Ophthalmol Vis Sci*. 2008;49:2781–2789.
36. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci*. 2012;53:7077–7085.
37. Hiraoka T, Kakita T, Okamoto F, Takahashi H, Oshika T. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. *Invest Ophthalmol Vis Sci*. 2012;53:3913–3919.
38. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R. Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. *Invest Ophthalmol Vis Sci*. 2012;53:5060–5065.
39. Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD, Zadnik K. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J AAPOS*. 2008;12:332–339.
40. Tan DT, Lam DS, Chua WH, Shu-Ping DF, Crockett RS. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology*. 2005;112:84–91.
41. Tong L, Huang XL, Koh AL, Zhang X, Tan DT, Chua WH. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology*. 2009;116:572–579.
42. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology*. 2008;115:1279–1285.
43. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol*. 2009;93:1181–1185.

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