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Lead Guest Editor: Malgorzata Mrugacz

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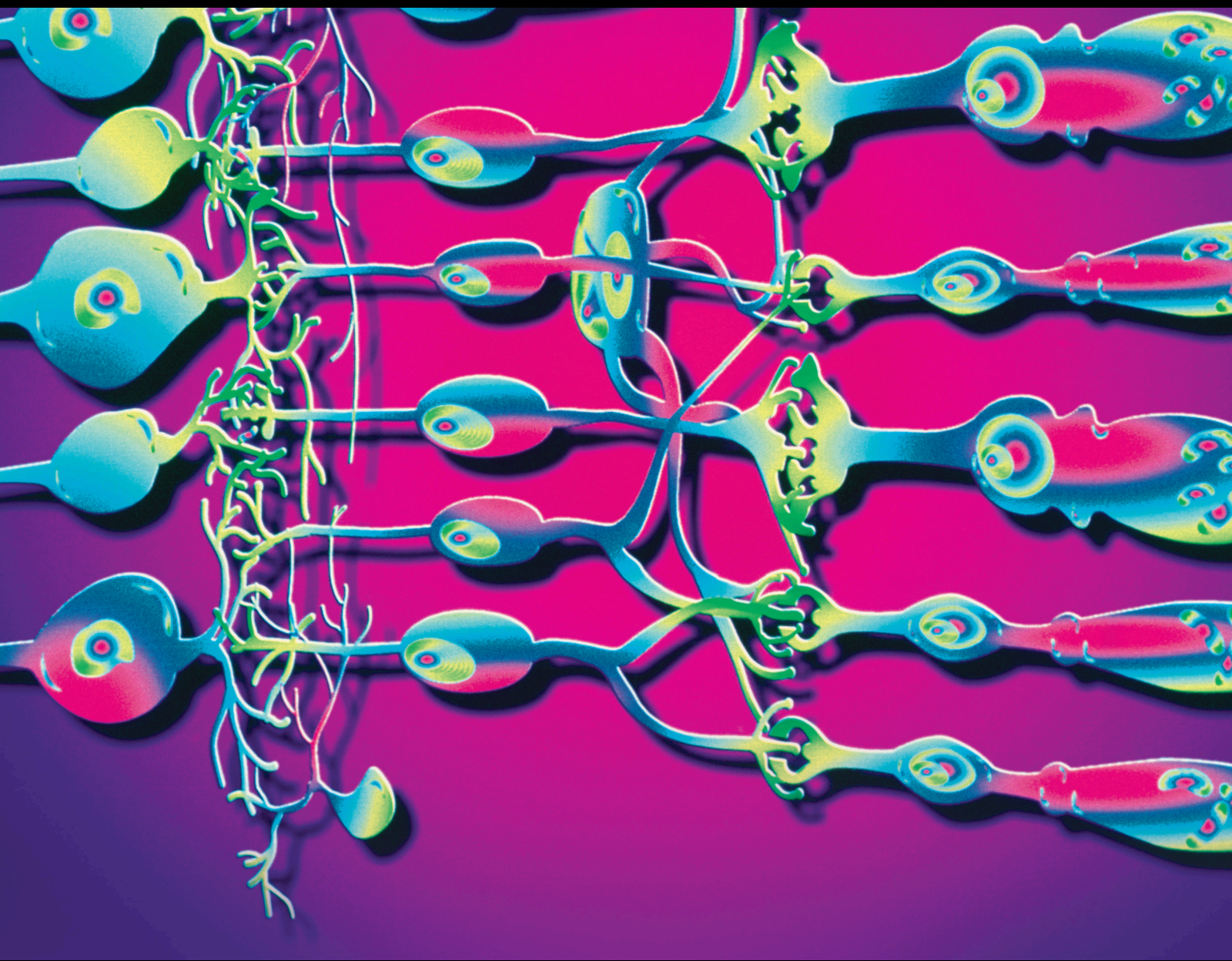

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Contents

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Editorial

Myopia: Risk Factors, Disease Mechanisms, Diagnostic Modalities, and Therapeutic Options 2019

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Myopia is a global problem, being particularly prevalent in the urban areas of east and southeast Asia. It is estimated that 2.5 billion people will be affected by myopia within the next decade. In addition to the economic and social burdens, associated ocular complications may lead to visual impairment. Myopia has a diverse etiology, with both environmental and genetic factors believed to be involved in the myopia's development and progression. Genetic linkage studies have mapped the dozen loci, while association studies have found more than 70 different genes. Many of these genes are involved in common biological pathways known to mediate extracellular matrix composition and regulate connective tissue remodelling. Other associated genomic regions suggest novel mechanisms in the etiology of high myopia, such as mitochondrial-mediated cell death and photoreceptor-mediated visual signal transmission. The environmental factors implicated in myopia include near work, light exposure, lack of physical activity, diet, a higher level of education, and urbanization. The interactions between genes and environmental factors may be significant in determining individual risks of high myopia and may help explain the pathogenetic mechanisms of myopia in human population [1, 2].

The first paper of this special issue addresses the review the current evidence for its complex genetics and evaluates the known or candidate genes and loci. In addition, the authors discuss recent investigations regarding the role of environmental factors and current research aimed at elucidating the signaling pathways involved in the pathogenesis of myopia. The second paper presents the study on the outcomes of femtosecond laser-assisted implantation of a 355-degree intracorneal ring (ICR) (Keraring) in patients with keratoconus. The mean sphere, cylinder, and spherical equivalent have been changed dramatically from preoperative to 3 months postoperative, which is statistically significant ($P \leq 0.001$), and the changes between 1 and 2 years and 2 and 3 years are also considerable and statistically significant. Implantation of a 355-degree intracorneal keraring using femtosecond laser improved the visual, refractive, and topographic parameters in keratoconus patients, with a high rate of ICR extrusion and instability. The authors of the third paper have observed that low-dose atropine does inhibit the short-term effect of hyperopic blur on choroidal thickness and, when used alone, does cause a slight thickening of the choroid in young healthy myopic adults. The three subsequent papers present the prevalence and related factors for myopia in school-aged children. The fourth paper of this special issue presents the analysis of the prevalence of myopia among a sample of more than 6,000 children in Spain. The prevalence of myopia in Spain has increased from 17% in 2016 to 20% in 2017. Likewise, the number of children with high myopia has also increased, from 1.7% in 2016 to 3.6% in 2017. 43.3% of the participants spent more than 3 hours a day doing near activities, and 48.9% of this group spent more than 50% of this time using electronic devices. In addition, only 9.7% spent more than 2.5 hours

outdoors each day. The incidence of myopia among schoolchildren in the experimental classes of the Air Force in China at the 3-year follow-up is 27.01%. A more hyperopic baseline refraction, more time spent outdoors, and longer writing/reading distance were protected against myopia onset, while more near-work time was a risk factor. Gender is associated with the prevalence of myopia among Polish schoolchildren ranging from 9 to 16 years of age. The prevalence of astigmatism decreased slightly over the two-year study period. Longer ALs and higher AL/CRC (axial length (AL) and corneal radius of curvature (CRC)) ratios were independent risk factors for developing CSA. Increased astigmatism was associated with AL growth, AL/CRC (axial length (AL) and corneal radius of curvature (CRC)) ratio increases, and the development of myopia. The eighth article presents the novel method of remotely monitoring and controlling the face device distance and illuminance that can potentially open new paths for myopia prevention and myopia control. The ninth paper evaluates the changes in retinal vessel density and thickness after small incision lenticule extraction (SMILE) with optical coherence tomography angiography (OCTA) in myopic patients. The vessel density at the parafoveal and perifoveal regions decreased at 1 day after SMILE with no effect on the visual acuity and relieved within 2 weeks. Decreased ocular blood flow in response to the spike in IOP may account for such changes. The tenth article addresses myopic anisometropia of more than 2D can that causes a significant impairment of binocular vision. Stereoacuity at distance is more sensitive to myopic anisometropia than stereoacuity at near. Myopic anisometropia involving "against the rule" astigmatism potentially affects binocularity more than anisometropia with regular astigmatism. A prompt correction of anisometropia of more than 2D is needed in children to prevent the development of amblyopia. The final paper describes the natural progression in Chinese patients with pathological myopia. Fundus degenerations in children with pathological myopia may lead its way since the age of 10 years. Besides, children with bilateral pathological myopia can have parallel development in visual acuity.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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References

[1] K. Ohno-Matsui, Y. Ikuno, T. Y. Y. Lai, and C. M. Gemmy Cheung, "Diagnosis and treatment guideline for myopic choroidal neovascularization due to pathologic myopia," *Progress in Retinal and Eye Research*, vol. 63, pp. 92–106, 2018.

[2] E. Dolgin, "The myopia boom," *Nature*, vol. 519, no. 7543, pp. 276–278, 2015.

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Review Article

Update on Myopia Risk Factors and Microenvironmental Changes

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The focus of this update is to emphasize the recent advances in the pathogenesis and various molecular key approaches associated with myopia in order to reveal new potential therapeutic targets. We review the current evidence for its complex genetics and evaluate the known or candidate genes and loci. In addition, we discuss recent investigations regarding the role of environmental factors. This paper also covers current research aimed at elucidating the signaling pathways involved in the pathogenesis of myopia.

1. Introduction

Myopia, also known as nearsightedness, is a common ocular disorder, which is considered a global problem because of the economic and social costs [1]. It affects typically school-age children and seems to progress the most between ages 8 and 15 due to the continuous growth of the eye during childhood [2–4].

The pathophysiology of myopia is multifactorial and is not yet completely understood. There are proofs that multiple genetic variations and environmental and lifestyle factors play an important role in the etiology of this disease [5]. Family linkage analysis, genome-wide association studies, and next-generation sequencing studies as well as a high correlation among monozygotic twins compared to dizygotic twins show that myopia has a genetic component [6–9].

On the contrary, studies have already shown the relationship between myopia and environmental factors such as near work, light exposure, lack of physical activity, and higher level of education revealing their major involvement in myopia development [10–12]. Although the genetic component has been widely studied, human population studies have revealed widely divergent prevalences of myopia among genetically similar populations in different environments, suggesting that development of myopia is controlled by both environmental and genetic factors [13–15].

New hypotheses suggest that the ethiopathogeny of myopia might also have an inflammatory component. Researchers revealed an increased prevalence of this refraction error in children with inflammatory diseases such as diabetes mellitus, juvenile chronic arthritis, uveitis, and systemic lupus erythematosus [16–19].

However, this is not without some controversy because many physiological and biochemical processes, not merely inflammation, are disturbed in these diseases; thus, the relationship between myopia and ocular and systemic inflammatory diseases is still debated in the recent literature. It is hypothesized that chronic hyperglycaemia and hyperinsulinaemia in a carbohydrate-rich diet could lead to overexpression of free insulin-like growth factor (IGF) level

on one hand and underexpression of IGF-binding protein 3 level on the other hand that may result in scleral growth and implicit to juvenile-onset myopia [20].

Concerning the connection between diabetes mellitus and refractive error, there are variable results among studies that provided evidence of a myopic shift among young patients under 10 years with poor glycaemic control. However, in the older patients group there was no statistically significant difference in refraction [16, 21].

As for another autoimmune systemic disease, the association between myopia and juvenile chronic arthritis (JCA) has its limitations due to other biomechanical and biochemical factors that coexist with the inflammatory pathway. Thus, there is a higher incidence of myopic patients with JCA compared with a control group. These data could be explained by the effect of chronic inflammation on the sclera resulting in poor biomechanical properties of the connective tissue that could lead to myopization [22].

Lens-related myopization was found in inflammatory ocular conditions such as uveitis and Vogt–Koyanagi–Harada disease following corticosteroid therapy, respectively, through relaxation of zonular fibers and an increase of the lens' convexity caused by supraciliary exudation [17].

2. Inflammatory Profile in Myopia

It is postulated in the literature that myopia is usually a consequence of abnormal eye elongation, which is associated with scleral remodelation [23, 24]. It also has been shown that ocular size and refraction were regulated by extracellular matrix composition and its biomechanical properties [25].

Sclera is a fibrous connective tissue that consists of fibroblasts which play a key role in maintaining the extracellular matrix [25, 26]. In addition to fibroblasts, sclera comprises an extracellular matrix which consists of collagen fibrils (mainly type 1 collagen) and small amounts of fibril-associated collagens [27]. In myopic eyes, the scleral tissue undergoes constant thinning due to the reduced connective tissue synthesis and increased collagen 1 (COL1) degradation [28, 29].

Various morphological changes in the scleral extracellular matrix have been involved in myopia progression, besides the scleral thinning. All these changes are the result of biochemical and biomechanical signaling pathways showing a decreased amount of biomarkers for collagen and glycosaminoglycans [30].

Scleral fibroblasts are responsible for the expression of some proteins such as matrix metaloproteinase (MMP) and tissue inhibitor of matrix metalloproteinase (TIMP).

Taking into account that an animal model suggested an important role for MMPs in the development of experimental myopia, Hall et al. investigated the relation between myopia and variations in three genes coding for metalloproteinases. Their results suggested an overexpression of MMP 1, MMP 3, and MMP 9 that may contribute to the development of simple myopia [31]. MMPs are a type of enzymes that are responsible for the degradation of extracellular matrix proteins [32], tissue reconstruction [33, 34], and tissue vascularization during the inflammatory response [35] as well as for modulating scleral extensibility. More recent studies have provided evidence that MMPs are regulated by many cytokines and growth factors, including hs-CRP, tumor necrosis factor, and complement components [36–38]. In addition, MMPs are inhibited by tissue inhibitor of metalloproteinases (TIMPs) [32]. This complex (MMP-TIMP) is responsible for the integrity of the connective tissue and a normal wound healing after injuries [39].

Lin et al. demonstrated the presence of CC genotype in (TGF)-β codon 10 in patients with high myopia [40]. Other studies stated the involvement of TGF-β in scleral remodeling [28, 41]. It regulates the production of extracellular matrix, its turnover being the basic mechanism involved in axial length changes [42]. Researchers have reported that TGF-β modulates the level of MMP 2 throughout the activation of nuclear factor (NF)-κB, which determines the production of inflammatory cytokines in fibroblasts such as TNF-α and IL-6 [43]. More than that, overexpression of TGF-β continues to activate expression of MMP2, which cleaves COL1 and becomes downregulated in a myopic eye [44, 45]. Li and colleagues revealed that a reduced expression of TGF-beta isoforms in the sclera is associated with a decreased synthesis of collagen and could be associated to an increased predisposition to pathological axial elongation [46].

TNF-α (tumor necrosis factor-alpha) is a transmembrane protein involved in systemic and local inflammation. It is produced by macrophages, lymphoid cells, and fibroblasts in response to bacterial products, IL-1, or IL-6. Recent evidence suggests that the inflammatory activity of the tumor necrosis factor family is more important than their role in apoptosis [47].

Such interactions between cells within the scleral extracellular matrix demonstrate changes in scleral biomechanical properties and scleral biochemistry, which subsequently lead to ocular elongation and thus a possible development of myopia [30].

In order to study the role of inflammation in myopia progression, Lin et al. investigated the expression of some proteins involved in inflammatory responses such as c-Fos, NFκB, IL-6 (interleukin 6), and tumor necrosis factor-α (TNF-α). The study showed increased levels of these proteins in hamsters with myopia. They also found an increased expression of these proteins in eyes treated with lipopolysaccharide and peptidoglycan and a corresponding increase in myopia progression in hamsters. On the other side, there was a decrease in inflammatory protein expression and a corresponding decrease in myopia progression in hamsters treated with cyclosporine, an anti-inflammatory medication [48].

Wei et al. reported the theory that allergic inflammation of the eye would mediate the development of myopia. The study revealed that children with allergic conjunctivitis have a higher incidence and subsequent risk of myopia (2.35 times higher) compared to those without allergic conjunctivitis.

Moreover, they established an allergic conjunctivitis animal model to demonstrate the possible mechanisms underlying allergic inflammation as a risk factor of myopia. They found that the rats with allergic conjunctivitis have developed myopia (change in refractive error (RE) = -1.68 ± 2.52 D),

whereas the rats in the control group did not (change in refractive error 1.07 ± 1.56 D).

In addition, the axial lengths of allergic conjunctivitis eyes were significantly longer (change in axial length = 0.27 ± 0.12 mm) than those of the control eyes (0.14 ± 0.09 mm).

In normal subjects, activation of the complement system is well regulated in the human body in order to avoid overstimulation and damage resulting from inflammation [45].

Long et al. discovered in 2013 in patients with pathologic myopia the overexpression of C3 and CH50 levels that suggest complement activation-induced inflammation may play an important role in the pathogenesis of myopia [49].

To confirm the relationship between inflammation and myopia, an animal model was established. Gao et al. published statistically significant increased levels of C1q, C3, and C5b-9 in the sclera of guinea pigs with myopia showing that activation of the complement system may induce extracellular matrix remodeling and development of myopia subsequently [50].

Recent studies evidence the correlation between the development and progression of myopia and activation of the complement system. In a meta-analysis of eight transcriptome databases for lens-induced or form-deprivation myopia, Riddell and Crewther found that the complement system is strongly activated in chick models of myopia [51].

3. Contribution of Oxidative Stress to the Development of Myopia

Oxidative stress begins to gain importance in the pathogenesis of glaucoma, age-related macular degeneration, dry eye syndrome, keratoconus, and myopia [52–56]. Oxidative stress results from the imbalance between free radical production on one hand and antioxidant defense mechanisms on the other [57]. It determines oxidative damage by altering cellular functions in addition to causing inflammation and cell death [58, 59].

Numerous studies have shown that elements such as zinc (Zn), copper (Cu), selenium (Se), manganese (Mn), α-tocopherol (vitamin E), ascorbic acid (vitamin C), glutathione (GSH), and β-carotene play an important role in the antioxidative processes [60–62] and in biochemical rebuilding of the sclera [63, 64].

A key role of the retina is to maintain an adequate oxygen supply. Under normal physiological conditions, metabolism of oxygen produces reactive oxygen species, one of the major contributors of oxidative stress [65].

Retinal tissue has the highest oxygen consumption in the body, thus determining the overexpression of ROS [57]. As ROS elevates, it may impair blood flow to the retina, which in consequence could lead to an increased level of oxidative stress [66]. Also, the continuous light exposure of the retina generates high amounts of ROS. These facts, the massive oxygen consumption and the light exposure, could be important conditions to argument the correlation between oxidative stress and myopia [57].

In order to predict the oxidative stress status in myopic patients, Kim et al. measured aqueous humor levels of 8-OHdG in 15 highly myopic eyes and 23 control eyes, taking into consideration that 8-OHdG is one of the most widely analyzed biomarkers regarding cellular oxidative stress [67]. They reported that 8-OHdG level was lower in the highly myopic group compared to the control group, a result that could indicate a reduced metabolic activity in myopic eyes which might bring on a decrease in oxidative stress level [68].

Taking into consideration that Zn insufficiency leads to oxidative damage [69], Fedor and coworkers investigated serum zinc and copper concentration as well as Cu/Zn ratio in the serum of children and adolescents with moderate and high myopia in order to assess the relationship between myopia and oxidative stress. They observed significantly lower serum concentration of Zn as well as significantly higher Cu/Zn ratio in myopic patients in comparison to the control group. Hence, these results may imply an association between insufficiency of these antioxidant microelements and the development of the myopia. Also, the higher ratio Cu/Zn in the study group indicates the disturbances of antioxidative mechanisms in patients with myopia [70].

Genetic studies have demonstrated that myopia is related with various growth factors, such as HGF (hepatocyte growth factor), which is capable of protecting the antioxidant system [71] by activating antioxidant genes such as catalase [72]. Based on the recent literature, it plays a key role in preventing oxidative damage; hence, it could become an important concern in myopia treatment in the future [57].

4. Recent Advances in Genetics of Myopia

It is known that myopia is a complex disease resulting from the interplay between multiple environmental and genetic risk factors. The studies mentioned below will highlight the most relevant conclusions concerning the topic of genetics in myopia.

The wide variability of the prevalence of myopia in different ethnic groups is an important aspect that supports its genetic component [73]. The prevalence of myopia is higher in Asians −70–90% compared with 30–40% in Americans and Europeans [74, 75]. Even if ethnicity has a major contribution to the prevalence of myopia, the literature shows widely divergent prevalences of myopia among genetically similar populations in different environments. For example, Rose and colleagues compared the prevalence and risk factors for myopia in children of Chinese ethnicity in Sydney and Singapore. They found a lower prevalence of myopia in Sydney, 3.3% versus 29.1% in Singapore ($p < 0.001$) which was associated with increased hours of outdoor activities (13.75 versus 3.5 hours per week; $p < 0.001$) [76].

So, whether myopia is due to interethnic differences in the genetic predisposition or cultural influences is still questionable.

In order to better understand the genetic background of myopia, several studies comparing monozygotic and dizygotic twins have been conducted, taking into consideration that monozygotic twins are identical in genetic material, while dizygotic twins share 50% of their genetic

material. In this regard, Karlsson et al. found that the heritability of myopia was greater in monozygotic twins (95%) compared with 29% in dizygotic twins [77]. This finding was confirmed by other studies, in which the heritability in monozygotic twins varied from 55% to 94% [6, 7, 78, 79].

Also, monozygotic twins, who are much similar, phenotypically, than dizygotic twins, have a higher chance to have the same activities and hobbies, so the environmental changes could also have a high impact in myopia development and progression.

Besides the twin studies which underline the important role of genetic factors in the development of myopia, familial aggregation has also provided strong evidence to support the involvement of genetic factors in the pathogenesis of myopia [80–83].

It is considered that while common myopia is generally transmitted as a complex trait, high myopia can be transmitted either as a complex trait or a Mendelian trait, including autosomal dominant (AD), autosomal recessive (AR), and X-linked recessive (XL) inheritance [84].

Mutti et al. evaluated the interaction between near work and parental myopia to test the hypothesis of inherited susceptibility. They reported that myopia appears to be more frequent in children whose both parents are myopic (32.9% versus 6.3% in children whose both parents are emmetropic), with no evidence being found to support the hypothesis that children with myopic parents can inherit a susceptibility to the environment [85].

In supporting this finding, the study conducted by Ip et al. in 2007 reported that the proportions of myopia were 7.6% in children with no myopic parents, 14.9% in children with one myopic parent, and 43.6% in children whose both parents are myopic [81].

Additional evidence supporting the role of genetics in the development of myopia includes the wide variability of the myopia-associated genes. Recent genome-wide association studies (GWAS) have identified more than 20 myopia-associated loci that involved in neurotransmission (e.g., GRIA4), ion transport (e.g., KCNQ5, CD55, and CHNRG), retinoic acid metabolism (e.g., RDH5, RORB, and CYP26A1), extracellular matrix remodeling (e.g., LAMA2 and BMP2), and eye development (e.g., SIX4, PRSS56, and CHD7) [86, 87].

On the other hand, family-based linkage studies have revealed at least 12 myopia-associated loci, with MYP loci numbered according to their time of discovery. These loci were mapped in fewer than 5% of persons with high myopia. Thus, taking into account the high prevalence of high myopia in the general population, it is supposed that more loci and genes will be discovered [46].

To date, candidate gene association studies identified high myopia-associated genes such as collagen, type I, alpha 1 (COL1A1), transforming growth factor beta 1 (TGFB1), transforming growth beta-induced factor (TGIF), lumican (LUM), hepatocyte growth factor (HGF), myocilin (MYOC), paired box 6 (PAX6), and uromodulin-like 1 (UMODL1). However, further studies need to establish the causative mutations [88–95].

Tang et al. focused on PAX6 gene, that is, a gene involved in oculogenesis and has a role in the change of refractive power as well as in the change of axial length, and thus in myopia development or progression [96, 97]. The researchers investigated the association of the paired box gene 6 (PAX6) with different stages of severity of myopia to confirm whether the PAX6 gene is a genetic determinant only for higher grade myopia, or it has an impact also on a low-grade stage of myopia. They found that PAX6 is a genetic determinant for extreme myopia rather than lower grade myopia, suggesting that PAX6 could be involved in the development or progression into severe myopia, but could not impact the myopia onset [98].

Interestingly, the fact that some potential myopia-associated genes may be limited only to certain subtypes of myopia has been of great concern and research interest.

Recent genetic studies suggested that IGF-1 should be evaluated with caution as a candidate gene for myopia. Even if IGF-1 is involved in cellular growth and differentiation as well as in the apoptosis [99, 100], IGF-1 gene may not determine the susceptibility to high or very high myopia in Caucasians and Chinese [101]. This fact suggests that different single-nucleotide polymorphisms (SNPs) of the same gene may have different results in terms of their associations with myopia [30]. For example, HGF gene polymorphisms investigations reported that rs3735520 is associated with mild and moderate myopia, but not with high myopia, while rs2286194 could be related to high myopia. Also, TGFB 1 gene which encodes TGF-β presents similar phenomenon [102].

Another approach for the candidate gene screening relies on the investigation of the genes associated with myopic syndromes [46]. Sun et al. analyzed data from 298 patients with early-onset high myopia and verified mutations in all the genes responsible for systemic diseases accompanied by high myopia, in order to identify another candidate gene associated with myopia. The authors evidence the idea that early-onset high myopia, occurring before school age, is an ideal model for monogenic studies of high myopia because of the minimum influence of environment. Besides the already known genes associated with high myopia (SCO2, ZNF644, LRPAP1, SLC39A5, LEPREL1, and CTSH), they identified another candidate gene. For example, mutations in genes COL2A1 and COL11A1 associated with Stickler syndrome, CACNA1F associated with congenital stable night blindness, and RPGR associated with retinitis pigmentosa were predominantly discovered [103, 104].

In addition, Flitcroft et al. investigated polymorphisms located in and around genes known to cause rare genetic syndromes featuring myopia and found them to be overrepresented in GWAS studies of refractive error and myopia. They identified 21 novel genes (ADAMTS18, ADAMTS2, ADAMTSL4, AGK, ALDH18A1, ASXL1, COL4A1, COL9A2, ERBB3, FBN1, GJA1, GNPTG, IFIH1, KIF11, LTBP2, OCA2, POLR3B, POMT1, PTPN11, TFAP2A, and ZNF469) and several novel pathways (mannosylation, glycosylation, lens development, gliogenesis, and Schwann cell differentiation) potentially involved in myopia [105].

5. Environmental Background

While genetic factors play important roles in ocular refraction, it has been convincingly established that environmental factors have an essential impact on myopia development.

Up to now, lifestyle factors such as near work, light exposure, lack of physical activity, and higher level of education and urbanization have been shown to be involved in the etiopathogenesis of myopia [81, 85,106].

Near-work activities, such as reading, writing, computer use, and playing video games, are supposedly responsible for the high prevalences and progression rates of myopia [81, 107].

The Sydney Myopia Study reported that near work such as close reading distance (<30 cm) and continuous reading (>30 minutes) independently increased the odds of having myopia (odds ratio 2.5; 95% CI 1.7–4; $p < 0.0001$, respectively; odds ratio 1.5; 95% CI 1.05–2.1; $p = 0.02$) [108].

In 2013, French et al. reported on children in the Sydney Adolescent Vascular and Eye Study and noted that children who became myopic performed significantly more near work (19.4 vs. 17.6 hours; $p = 0.02$) compared with children who remained nonmyopic [109].

Huang et al. highlighted, in a recent systematic review and meta-analysis, that near-work activities were related with higher odds of myopia (odds ratio 1.14; 95% CI 1.08–1.20) and that the odds of myopia increased by 2% (OR: 1.02; 95% CI 1.01–1.03) for every one diopter-hour more of weekly near work [110].

In contrast, there are studies reporting that near work is not associated with faster rates of myopia progression [85, 111–113].

Therefore the relationship between near work and myopia is complex and needs to be investigated.

On the other hand, several recent epidemiological studies suggest that greater time spent outdoors might have a protective effect against myopia development and progression [114–116].

The mechanism of this association is still poorly understood, but in the literature there are two theories proposed: One of them is the "light-dopamine theory" which highlights that increased light intensity during time spent outdoor protects against myopia by the increased release of dopamine [114, 117–119].

As for the second one, "vitamin D theory" hypotheses that the increased ultraviolet light triggers the stimulation of vitamin D production, with a direct protection against myopia development [120–123].

The recently published meta-analysis by Tang et al. reported that lower 25-hydroxyvitamin D (25(OH)D) concentration is associated with increased risk of myopia (AOR: 0.92; 95% CI 0.88–0.96; $p < 0.0001$) [124].

Also, the recent Guangzhou randomized trial reported a significant opposed relationship between outdoor activities and incidence of myopia showing that the increase of time spent outdoor determines a relative reduction of 23% of the incidence of myopia [115].

6. Conclusions

Nowadays, myopia is considered a major public health concern. The pathogenesis of myopia is not yet completely understood. We can state that myopia is a complex disease with a multitude of factors including genetic, environmental (external), and microenvironmental components.

We now know that myopia has a genetic component and a number of genes and candidate loci being identified as related to the disease, but environmental factors such as high level of education, prolonged near work, light exposure, and lack of outdoor activities seem to have a very important role. Many studies have shown the role of the inflammatory process in myopia and the expression of some proteins related to changes in collagen fibers, scleral thinning, and axial length elongation.

After reviewing the most relevant and recently published results, we emphasize that the complete mechanism underlying the abnormal physiological changes in the development and progression of myopia would be better understood if the investigation is conducted at the cellular and molecular level. Thus, further studies are required.

A number of genes and candidate loci have been revealed, and as we elucidate, understanding the underlying cause of myopia could help identify potential targets for therapeutic intervention and slow or prevent progression and myopic complications.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

All authors contributed equally to this work.

References

[1] J. Cooper and A. V. Tkatchenko, "A review of current concepts of the etiology and treatment of myopia," *Eye & Contact Lens: Science & Clinical Practice*, vol. 44, no. 4, pp. 231–247, 2018.

[2] N. W. H. Tan, S.-M. Saw, D. S. C. Lam, H.-M. Cheng, U. Rajan, and S.-J. Chew, "Temporal variations in myopia progression in Singaporean children within an academic year," *Optometry and Vision Science*, vol. 77, no. 9, pp. 465–472, 2000.

[3] D. S. P. Fan, D. S. C. Lam, R. F. Lam et al., "Prevalence, incidence, and progression of myopia of school children in Hong Kong," *Investigative Opthalmology & Visual Science*, vol. 45, no. 4, pp. 1071–1075, 2004.

[4] L. Donovan, P. Sankaridurg, A. Ho, T. Naduvilath, E. L. Smith, and B. A. Holden, "Myopia progression rates in urban children wearing single-vision spectacles," *Optometry and Vision Science*, vol. 89, no. 1, pp. 27–32, 2012.

[5] N. Warner, "Update on myopia," *Current Opinion in Ophthalmology*, vol. 27, no. 5, pp. 402–406, 2016.

[6] C. J. Hammond, H. Snieder, C. E. Gilbert, and T. D. Spector, "Genes and environment in refractive error: the twin eye

study," *Investigative Ophthalmology and Visual Science*, vol. 42, no. 6, pp. 1232–1236, 2001.

[7] N. Lyhne, A. K. Sjolie, K. O. Kyvik et al., "The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins," *British Journal of Ophthalmology*, vol. 85, no. 12, pp. 1470–1476, 2001.

[8] M. Dirani, S. N. Shekar, and P. N. Baird, "Adult-onset myopia: the genes in myopia (GEM) twin study," *Investigative Opthalmology & Visual Science*, vol. 49, no. 8, pp. 3324–3327, 2008.

[9] M.-Y. Tsai, L. L.-K. Lin, V. Lee, C.-J. Chen, and Y.-F. Shih, "Estimation of heritability in myopic twin studies," *Japanese Journal of Ophthalmology*, vol. 53, no. 6, pp. 615–622, 2009.

[10] A. Morgan, R. Young, B. Narankhand, S. Chen, C. Cottriall, and S. Hosking, "Prevalence rate of myopia in schoolchildren in rural Mongolia," *Optometry and Vision Science*, vol. 83, no. 1, pp. 53–56, 2006.

[11] T. Y. Wong, P. J. Foster, J. Hee et al., "Prevalence and risk factors for refractive errors in adult Chinese in Singapore," *Investigative Opthalmology & Visual Science*, vol. 41, no. 9, pp. 2486–2494, 2000.

[12] T. Y. Wong, P. J. Foster, G. J. Johnson, B. E. Klein, and S. K. Seah, "The relationship between ocular dimensions and refraction with adult stature: the Tanjong Pagar Survey," *Investigative Opthalmology & Visual Science*, vol. 42, no. 6, pp. 1237–1242, 2001.

[13] I. G. Morgan, "The biological basis of myopic refractive error," *Clinical and Experimental Optometry*, vol. 86, no. 5, pp. 276–288, 2003.

[14] P. N. Baird, M. Schäche, and M. Dirani, "The GEnes in Myopia (GEM) study in understanding the aetiology of refractive errors," *Progress in Retinal and Eye Research*, vol. 29, no. 6, pp. 520–542, 2010.

[15] R. Wojciechowski, "Nature and nurture: the complex genetics of myopia and refractive error," *Clinical Genetics*, vol. 79, no. 4, pp. 301–320, 2011.

[16] N. Jacobsen, H. Jensen, H. Lund-Andersen, and E. Goldschmidt, "Is poor glycaemic control in diabetic patients a risk factor of myopia?," *Acta Ophthalmologica*, vol. 86, no. 5, pp. 510–514, 2008.

[17] C. P. Herbort, M. Papadia, and P. Neri, "Myopia and inflammation," *Journal of Ophthalmic and Vision Research*, vol. 6, no. 4, pp. 270–283, 2011.

[18] N. V. Palejwala, H. S. Walia, and S. Yeh, "Ocular manifestations of systemic lupus erythematosus: a review of the literature," *Autoimmune Diseases*, vol. 2012, Article ID 290898, 9 pages, 2012.

[19] Y. Kamath, A. Singh, S. Bhat, and H. Sripathi, "Acute onset myopia as a presenting feature of systemic lupus erythematosus," *Journal of Postgraduate Medicine*, vol. 59, no. 3, pp. 245-246, 2013.

[20] L. Cordain, S. B. Eaton, J. Brand Miller, S. Lindeberg, and C. Jensen, "An evolutionary analysis of the aethiology and pathogenesis of juvenile-onset myopia," *Acta Ophthalmologica Scandinavica*, vol. 80, no. 2, pp. 125–135, 2002.

[21] S. Handa, A. Chia, H. Htoon, P. Lam, F. Yap, and Y. Ling, "Myopia in young patients with type 1 diabetes mellitus," *Singapore Medical Journal*, vol. 56, no. 8, pp. 450–454, 2015.

[22] H. Fledelius, M. Zak, and F. K. Pedersen, "Refraction in juvenile chronic arthritis: a long-term follow-up study, with emphasis on myopia," *Acta Ophthalmologica Scandinavica*, vol. 79, no. 3, pp. 237–239, 2001.

[23] B. J. Curtin and C. C. Teng, "Scleral changes in pathological myopia," *Transactions—American Academy of Ophthalmology and Otolaryngology*, vol. 62, no. 6, pp. 777–788, 1958.

[24] D. Marzani and J. Wallman, "Growth of the two layers of the chick sclera is modulated reciprocally by visual conditions," *Investigative Ophthalmology and Visual Science*, vol. 38, no. 9, pp. 1726–1739, 1997.

[25] J. A. Rada, S. Shelton, and T. T. Norton, "The sclera and myopia," *Experimental Eye Research*, vol. 82, no. 2, pp. 185–200, 2006.

[26] A. R. Harper and J. A. Summers, "The dynamic sclera: extracellular matrix remodeling in normal ocular growth and myopia development," *Experimental Eye Research*, vol. 133, pp. 100–111, 2015.

[27] B. Rohrer and W. K. Stell, "Basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-β) act as stop and go signals to modulate postnatal ocular growth in the chick," *Experimental Eye Research*, vol. 58, no. 5, pp. 553–561, 1994.

[28] N. A. McBrien, P. Lawlor, and A. Gentle, "Scleral remodeling during the development of and recovery from axial myopia in the tree shrew," *Investigative Ophthalmology and Visual Science*, vol. 41, no. 12, pp. 3713–3719, 2000.

[29] J. A. Rada, J. M. Johnson, V. R. Achen, and K. G. Rada, "Inhibition of scleral proteoglycan synthesis blocks deprivation-induced axial elongation in chicks," *Experimental Eye Research*, vol. 74, no. 2, pp. 205–215, 2002.

[30] P. Kwan, "Myopia: current cellular concepts on the pathology and mechanisms," in *Eye Diseases and Disorders—A Complete Guide*, iConcept Press Ltd., Hong Kong, China, 2014.

[31] N. F. Hall, C. R. Gale, S. Ye, and C. N. Martyn, "Myopia and polymorphisms in genes for matrix metalloproteinases," *Investigative Opthalmology & Visual Science*, vol. 50, no. 6, pp. 2632–2636, 2009.

[32] R. P. Verma and C. Hansch, "Matrix metalloproteinases (MMPs): chemical-biological functions and (Q)SARs," *Bioorganic & Medicinal Chemistry*, vol. 15, no. 6, pp. 2223–2268, 2007.

[33] R. Wojciechowski, J. E. Bailey-Wilson, and D. Stambolian, "Association of matrix metalloproteinase gene polymorphisms with refractive error in Amish and Ashkenazi families," *Investigative Opthalmology & Visual Science*, vol. 51, no. 10, pp. 4989–4995, 2010.

[34] R. Wojciechowski, S. S. Yee, C. L. Simpson, J. E. Bailey-Wilson, and D. Stambolian, "Matrix metalloproteinases and educational attainment in refractive error," *Ophthalmology*, vol. 120, no. 2, pp. 298–305, 2013.

[35] N. A. McBrien, W. K. Stell, and B. Carr, "How does atropine exert its anti-myopia effects?," *Ophthalmic and Physiological Optics*, vol. 33, no. 3, pp. 373–378, 2013.

[36] G. Doronzo, I. Russo, L. Mattiello, M. Trovati, and G. Anfossi, "C-reactive protein increases matrix metalloproteinase-2 expression and activity in cultured human vascular smooth muscle cells," *Journal of Laboratory and Clinical Medicine*, vol. 146, no. 5, pp. 287–298, 2005.

[37] J. M. Gonzalez, C.-W. Franzke, F. Yang, R. Romero, and G. Girardi, "Complement activation triggers metalloproteinases release inducing cervical remodeling and preterm birth in mice," *The American Journal of Pathology*, vol. 179, no. 2, pp. 838–849, 2011.

[38] W. Eichler, U. Friedrichs, A. Thies, C Tratz, and P Wiedemann, "Modulation of matrix metalloproteinase and TIMP-1 expression by cytokines in human RPE cells,"

Investigative Ophthalmology and Visual Science, vol. 43, no. 8, pp. 2767–2773, 2002.

[39] K. Brew, D. Dinakarpandian, and H. Nagase, "Tissue inhibitors of metalloproteinases: evolution, structure and function," *Biochimica et Biophysica Acta (BBA)—Protein Structure and Molecular Enzymology*, vol. 1477, no. 1-2, pp. 267–283, 2000.

[40] H. J. Lin, L. Wan, Y. Tsai et al., "The TGFβ1 gene codon 10 polymorphism contributes to the genetic predisposition to high myopia," *Molecular Vision*, vol. 12, no. 78-79, pp. 698–703, 2006.

[41] J. A. Guggenheim and N. A. McBrien, "Form-deprivation myopia induces activation of scleral matrix metalloproteinase-2 in tree shrew," *Investigative Ophthalmology and Visual Science*, vol. 37, no. 7, pp. 1380–1395, 1996.

[42] J. A. Rada, R. A. Thoft, and J. R. Hassell, "Increased aggrecan (cartilage proteoglycan) production in the sclera of myopic chicks," *Developmental Biology*, vol. 147, no. 2, pp. 303–312, 1991.

[43] Y. Wang, Z. Tang, R. Xue et al., "TGF-β1 promoted MMP-2 mediated wound healing of anterior cruciate ligament fibroblasts through NF-κB," *Connective Tissue Research*, vol. 52, no. 3, pp. 218–225, 2011.

[44] Y. Inamori, M. Ota, H. Inoko et al., "The COL1A1 gene and high myopia susceptibility in Japanese," *Human Genetics*, vol. 122, no. 2, pp. 151–157, 2007.

[45] C.-C. Wei, Y.-J. Kung, C. S. Chen et al., "Allergic conjunctivitis-induced retinal inflammation promotes myopia progression," *EBioMedicine*, vol. 28, pp. 274–286, 2018.

[46] J. Li and Q. Zhang, "Insight into the molecular genetics of myopia," *Molecular Vision*, vol. 23, pp. 1048–1080, 2017.

[47] H. Wajant, K. Pfizenmaier, and P. Scheurich, "Tumor necrosis factor signaling," *Cell Death & Differentiation*, vol. 10, no. 1, pp. 45–65, 2003.

[48] H.-J. Lin, C.-C. Wei, C.-Y. Chang et al., "Role of chronic inflammation in myopia progression: clinical evidence and experimental validation," *EBioMedicine*, vol. 10, pp. 269–281, 2016.

[49] Q. Long, J. Ye, Y. Li, S. Wang, and Y. Jiang, "C-reactive protein and complement components in patients with pathological myopia," *Optometry and Vision Science*, vol. 90, no. 5, pp. 501–506, 2013.

[50] T. T. Gao, Q. Long, and X. Yang, "Complement factors C1q, C3 and C5b-9 in the posterior sclera of Guinea pigs with negative lens-defocused myopia," *International Journal of Ophthalmology*, vol. 8, no. 4, pp. 675–680, 2015.

[51] N. Riddell and S. G. Crewther, "Novel evidence for complement system activation in chick myopia and hyperopia models: a meta-analysis of transcriptome datasets," *Scientific Reports*, vol. 7, no. 1, p. 9719, 2017.

[52] T. H. Wakamatsu, M. Dogru, Y. Matsumoto et al., "Evaluation of lipid oxidative stress status in sjögren syndrome patients," *Investigative Opthalmology & Visual Science*, vol. 54, no. 1, pp. 201–210, 2013.

[53] Y. Chen, G. Mehta, and V. Vasiliou, "Antioxidant defenses in the ocular surface," *The Ocular Surface*, vol. 7, no. 4, pp. 176–185, 2009.

[54] S. M. Ferreira, S. F. Lerner, R. Brunzini, P. A. Evelson, and S. F. Llesuy, "Oxidative stress markers in aqueous humor of glaucoma patients," *American Journal of Ophthalmology*, vol. 137, no. 1, pp. 62–69, 2004.

[55] E. Arnal, C. Peris-Martínez, J. L. Menezo, S. Johnsen-Soriano, and F. J. Romero, "Oxidative stress in keratoconus?," *Investigative Opthalmology & Visual Science*, vol. 52, no. 12, pp. 8592–8597, 2011.

[56] H. Izuta, N. Matsunaga, M. Shimazawa, T. Sugiyama, and T. Ikeda, "Proliferative diabetic retinopathy and relations among antioxidant activity, oxidative stress, and VEGF in the vitreous body," *Molecular Vision*, vol. 16, pp. 130–136, 2010.

[57] B. M. Francisco, M. Salvador, and N. Amparo, "Oxidative stress in myopia," *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 750637, 12 pages, 2015.

[58] K. Ito and T. Suda, "Metabolic requirements for the maintenance of self-renewing stem cells," *Nature Reviews Molecular Cell Biology*, vol. 15, no. 4, pp. 243–256, 2014.

[59] W. R. Markesbery and M. A. Lovell, "Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment," *Archives of Neurology*, vol. 64, no. 7, pp. 954–956, 2007.

[60] X. Huibi, H. Kaixun, G. Qiuhua, Z. Yushan, and H. Xiuxian, "Prevention of axial elongation in myopia by the trace element zinc," *Biological Trace Element Research*, vol. 79, no. 1, pp. 39–47, 2001.

[61] K. A. Sukalski, T. P. LaBerge, and W. T. Johnson, "In vivo oxidative modification of erythrocyte membrane proteins in copper deficiency," *Free Radical Biology and Medicine*, vol. 22, no. 5, pp. 835–842, 1997.

[62] M. A. Rahman, B. Rahman, and N. Ahmed, "High blood manganese in iron-deficient children in Karachi," *Public Health Nutrition*, vol. 16, no. 9, pp. 1677–1683, 2013.

[63] R. B. Rucker, T. Kosonen, M. S. Clegg et al., "Copper, lysyl oxidase, and extracellular matrix protein cross-linking," *The American Journal of Clinical Nutrition*, vol. 67, no. 5, pp. 996S–1002S, 1998.

[64] M. E. Shils, J. A. Olson, M. Shike, and A. C. Ross, *Modern Nutrition in Health and Disease*, Lippincott Williams & Wilkins, Philadelphia, PA, USA, 2nd edition, 1998.

[65] M. Mozzafarieh, M. C. Grieshaber, and J. Flammer, "Oxygen and blood flow: players in the pathogenesis of glaucoma," *Molecular Vision*, vol. 14, pp. 224–233, 2008.

[66] D. M. Kumar and N. Agarwal, "Oxidative stress in glaucoma: a burden of evidence," *Journal of Glaucoma*, vol. 16, no. 3, pp. 334–343, 2007.

[67] L. L. Wu, C.-C. Chiou, P.-Y. Chang, and J. T. Wu, "Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics," *Clinica Chimica Acta*, vol. 339, no. 1-2, pp. 1–9, 2004.

[68] E. B. Kim, H. K. Kim, J. Y. Hyon, W. R. Wee, and Y. J. Shin, "Oxidative stress levels in aqueous humor from high myopic patients," *Korean Journal of Ophthalmology*, vol. 30, no. 3, pp. 172–179, 2016.

[69] S. R. Powell, "The antioxidant properties of zinc," *The Journal of Nutrition*, vol. 130, no. 5, pp. 1447S–1454S, 2000.

[70] M. Fedor, K. Socha, B. Urban et al., "Serum concentration of zinc, copper, selenium, Manganese,and Cu/Zn ratio in children and adolescents with myopia," *Biological Trace Element Research*, vol. 176, no. 1, pp. 1–9, 2017.

[71] S. Tsuboi, "Elevation of glutathione level in rat hepatocytes by hepatocyte growth factor via induction of gammaglutamylcysteine," *Journal of Biochemistry*, vol. 126, no. 5, pp. 815–820, 1999.

[72] R. Kannan, M. Jin, M.-A. Gamulescu, and D. Hinton, "Ceramide-induced apoptosis: role of catalase and hepatocyte growth factor," *Free Radical Biology and Medicine*, vol. 37, no. 2, pp. 166–175, 2004.

[73] S.-M. Saw, J. Katz, O. D. Schein, S.-J. Chew, and T.-K. Chan, "Epidemiology of myopia," *Epidemiologic Reviews*, vol. 18, no. 2, pp. 175–187, 1996.

[74] Y. C. Chow, B. Dhillon, P. T. Chew, and S. J. Chew, "Refractive errors in Singapore medical students," *Singapore Medical Journal*, vol. 31, no. 5, pp. 472-473, 1990.

[75] D. R. Fredrick, "Myopia," *BMJ*, vol. 324, no. 7347, pp. 1195–1199, 2002.

[76] K. A. Rose, I. Morgan, W. Smith, G. Burlutsky, P. Mitchell, and S. M. Saw, "Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney," *Archives of Ophthalmology*, vol. 126, no. 4, pp. 527–530, 2008.

[77] J. I. Karlsson, "Concordance rates for myopia in twins," *Clinical Genetics*, vol. 6, no. 2, pp. 142–146, 2008.

[78] M. Dirani, M. Chamberlain, S. N. Shekar et al., "Heritability of refractive error and ocular biometrics: the genes in Myopia (GEM) twin study," *Investigative Ophthalmology and Visual Science*, vol. 47, no. 11, pp. 4756–4761, 2006.

[79] D. Wang, B. Liu, S. Huang, W. Huang, and M. He, "Relationship between refractive error and ocular biometrics in twin children: the Guangzhou Twin Eye Study," *Eye Science*, vol. 29, no. 3, pp. 129–133, 2014.

[80] M. Yap, M. Wu, Z. M. Liu, F. L. Lee, and S. H. Wang, "Role of heredity in the genesis of myopia," *Ophthalmic and Physiological Optics*, vol. 13, no. 3, pp. 316–319, 1993.

[81] J. M. Ip, S. C. Huynh, D. Robaei et al., "Ethnic differences in the impact of parental myopia: findings from a population-based study of 12-year-old Australian children," *Investigative Opthalmology & Visual Science*, vol. 48, no. 6, pp. 2520–2528, 2007.

[82] J. E. Farbrother, G. Kirov, M. J. Owen, and J. A. Guggenheim, "Family aggregation of high myopia: estimation of the sibling recurrence risk ratio," *Investigative Opthalmology & Visual Science*, vol. 45, no. 9, pp. 2873–2878, 2004.

[83] R. Wojciechowski, N. Congdon, H. Bowie, B. Munoz, D. Gilbert, and S. K. West, "Heritability of refractive error and familial aggregation of myopia in an elderly American population," *Investigative Opthalmology & Visual Science*, vol. 46, no. 5, pp. 1588–1592, 2005.

[84] A. Vagge, L. Ferro Desideri, P. Nucci, M. Serafino, G. Giannaccare, and C. Traverso, "Prevention of progression in myopia: a systematic review," *Diseases*, vol. 6, no. 4, p. 92, 2018.

[85] D. O. Mutti, G. L. Mitchell, M. L. Moeschberger, L. A. Jones, and K. Zadnik, "Parental myopia, near work, school achievement, and children's refractive error," *Investigative Ophthalmology and Visual Science*, vol. 43, no. 12, pp. 3633–3640, 2002.

[86] J. N. Cooke Bailey, L. Sobrin, M. A. Pericak-Vance, J. L. Haines, C. J. Hammond, and J. L. Wiggs, "Advances in the genomics of common eye diseases," *Human Molecular Genetics*, vol. 22, no. R1, pp. R59–R65, 2013.

[87] X. Liao, M. K. H. Yap, K. H. Leung, P. Y. P. Kao, L. Q. Liu, and S. P. Yip, "Genetic association study of KCNQ5 polymorphisms with high myopia," *BioMed Research International*, vol. 2017, Article ID 3024156, 7 pages, 2017.

[88] C.-L. Liang, E. Hsi, K.-C. Chen, Y.-R. Pan, Y.-S. Wang, and S.-H. H. Juo, "A functional polymorphism at 3′UTR of the PAX6 gene may confer risk for extreme myopia in the Chinese," *Investigative Opthalmology & Visual Science*, vol. 52, no. 6, pp. 3500–3505, 2011.

[89] T. Zayats, J. A. Guggenheim, C. J. Hammond, and T. L. Young, "Comment on 'a PAX6 gene polymorphism is associated with genetic predisposition to extreme myopia'," *Eye*, vol. 22, no. 4, pp. 598-599, 2008.

[90] U. Ratnamala, R. Lyle, R. Rawal et al., "Refinement of the X-linked nonsyndromic high-grade myopia LocusMYP1 on Xq28 and exclusion of 13 known positional candidate genes by direct sequencing," *Investigative Opthalmology & Visual Science*, vol. 52, no. 9, pp. 6814–6819, 2011.

[91] J. E. Farbrother, G. Kirov, M. J. Owen, R. Pong-Wong, C. S. Haley, and J. A. Guggenheim, "Linkage analysis of the genetic loci for high myopia on 18p, 12q, and 17q in 51 U.K. Families," *Investigative Opthalmology & Visual Science*, vol. 45, no. 9, pp. 2879–2885, 2004.

[92] T. L. Young, "Dissecting the genetics of human high myopia: a molecular biologic approach," *Transactions of the American Ophthalmological Society*, vol. 102, pp. 423–445, 2004.

[93] L. Bartholin, S. E. Powers, T. A. Melhuish, S. Lasse, M. Weinstein, and D. Wotton, "TGIF inhibits retinoid signaling," *Molecular and Cellular Biology*, vol. 26, no. 3, pp. 990–1001, 2006.

[94] Y. Seko, H. Shimokawa, and T. Tokoro, "Expression of bFGF and TGF-beta 2 in experimental myopia in chicks," *Investigative Ophthalmology and Visual Science*, vol. 36, no. 6, pp. 1183–1187, 1995.

[95] Y. Hasumi, H. Inoko, S. Mano et al., "Analysis of single nucleotide polymorphisms at 13 loci within the transforming growth factor-induced factor gene shows no association with high myopia in Japanese subjects," *Immunogenetics*, vol. 58, no. 12, pp. 947–953, 2006.

[96] T. I. Simpson and D. J. Price, "Pax6; a pleiotropic player in development," *BioEssays*, vol. 24, no. 11, pp. 1041–1051, 2002.

[97] A. Schedl, A. Ross, M. Lee et al., "Influence of Pax6 gene dosage on development: overexpression causes severe eye abnormalities," *Cell*, vol. 86, no. 1, pp. 71–82, 1996.

[98] S. M. Tang, L. Ma, S. Y. Lu et al., "Association of the PAX6 gene with extreme myopia rather than lower grade myopias," *British Journal of Ophthalmology*, vol. 102, no. 4, pp. 570–574, 2018.

[99] H. Werner and D. Le Roith, "New concepts in regulation and function of the insulin-like growth factors: implications for understanding normal growth and neoplasia," *Cellular and Molecular Life Sciences*, vol. 57, no. 6, pp. 932–942, 2000.

[100] A. Bartke, "The somatotropic axis and aging: mechanisms and persistent questions about practical implications," *Experimental Gerontology*, vol. 44, no. 6-7, pp. 372–374, 2009.

[101] M. Miyake, K. Yamashiro, H. Nakanishi et al., "Insulin-like growth factor 1 is not associated with high myopia in a large Japanese cohort," *Molecular Vision*, vol. 19, pp. 1074–1081, 2013.

[102] C.-C. Khor, "TIGR, TGFB1, cMET, HGF, collagen genes, and myopia," in *Myopia: Animal Models To Clinical Trials*, World Scientific Publishing Company, Singapore, 2010.

[103] W. Sun, L. Huang, Y. Xu et al., "Exome sequencing on 298 probands with early-onset high myopia: approximately one-fourth show potential pathogenic mutations in RetNet genes," *Investigative Opthalmology & Visual Science*, vol. 56, no. 13, pp. 8365–8372, 2015.

[104] L. Zhou, X. Xiao, S. Li, X. Jia, P. Wang, and W. Sun, "Phenotypic characterization of patients with early-onset high myopia due to mutations in COL2A1 or COL11A1: why not Stickler syndrome?," *Molecular Vision*, vol. 24, pp. 560–573, 2018.

[105] D. I. Flitcroft, J. Loughman, C. F. Wildsoet, C. Williams, and J. A. Guggenheim, "Novel myopia genes and pathways identified from syndromic forms of myopia," *Investigative Opthalmology & Visual Science*, vol. 59, no. 1, pp. 338–348, 2018.

[106] L. A. Jones, L. T. Sinnott, D. O. Mutti, G. L. Mitchell, M. L. Moeschberger, and K. Zadnik, "Parental history of

myopia, sports and outdoor activities, and future myopia," *Investigative Opthalmology & Visual Science*, vol. 48, no. 8, pp. 3524–3532, 2007.

[107] B. Siemensen and L. O. Thorud, "Adult-onset myopia and occupation," *Acta Ophthalmologica*, vol. 72, no. 4, pp. 469–471, 1994.

[108] J. M. Ip, S.-M. Saw, K. A. Rose et al., "Role of near work in myopia: findings in a sample of Australian school children," *Investigative Opthalmology & Visual Science*, vol. 49, no. 7, pp. 2903–2910, 2008.

[109] A. N. French, I. G. Morgan, P. Mitchell, and K. A. Rose, "Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study," *Ophthalmology*, vol. 120, no. 10, pp. 2100–2108, 2013.

[110] H.-M. Huang, D. S. Chang, and P. C. Wu, "The association between near work activities and myopia in children—a systematic review and meta-analysis," *PLoS One*, vol. 10, no. 10, Article ID e0140419, 2015.

[111] S.-M. Saw, F. J. Nieto, J. Katz, O. D. Schein, B. Levy, and S.-J. Chew, "Factors related to the progression of myopia in Singaporean children," *Optometry and Vision Science*, vol. 77, no. 10, pp. 549–554, 2000.

[112] S. M. Saw, W. H. Chua, C. Y. Hong et al., "Nearwork in early-onset myopia," *Investigative Ophthalmology and Visual Science*, vol. 43, no. 2, pp. 332–339, 2002.

[113] W. Low, M. Dirani, G. Gazzard et al., "Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children," *British Journal of Ophthalmology*, vol. 94, no. 8, pp. 1012–1016, 2010.

[114] K. A. Rose, I. G. Morgan, J. Ip et al., "Outdoor activity reduces the prevalence of myopia in children," *Ophthalmology*, vol. 115, no. 8, pp. 1279–1285, 2008.

[115] M. He, F. Xiang, Y. Zeng et al., "Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial," *JAMA*, vol. 314, no. 11, pp. 1142–1148, 2015.

[116] J. C. Sherwin, M. H. Reacher, R. H. Keogh, A. P. Khawaja, D. A. Mackey, and P. J. Foster, "The association between time spent outdoors and myopia in children and adolescents: a systematic review and metaanalysis," *Ophthalmology*, vol. 119, no. 10, pp. 2141–2151, 2012.

[117] P. L. Megaw, M. G. Boelen, I. G. Morgan, and M. K. Boelen, "Diurnal patterns of dopamine release in chicken retina," *Neurochemistry International*, vol. 48, no. 1, pp. 17–23, 2006.

[118] D. McCarthy, P. Lueras, and P. G. Bhide, "Elevated dopamine levels during gestation produce region-specific decreases in neurogenesis and subtle deficits in neuronal numbers," *Brain Research*, vol. 1182, pp. 11–25, 2007.

[119] W. Li, W. Lan, S. Yang et al., "The effect of spectral property and intensity of light on natural refractive development and compensation to negative lenses in guinea pigs," *Investigative Opthalmology & Visual Science*, vol. 55, no. 10, pp. 6324–6332, 2014.

[120] J. A. Choi, K. Han, Y.-M. Park, and T. Y. La, "Low serum 25-hydroxyvitamin D is associated with myopia in Korean adolescents," *Investigative Opthalmology & Visual Science*, vol. 55, no. 4, pp. 2041–2047, 2014.

[121] J. A. Guggenheim, C. Williams, K. Northstone et al., "Does vitamin D mediate the protective effects of time outdoors on myopia? Findings from a prospective birth cohort," *Investigative Ophthalmology & Visual Science*, vol. 55, no. 12, pp. 8550–8558, 2014.

[122] D. O. Mutti and A. R. Marks, "Blood levels of vitamin D in teens and young adults with myopia," *Optometry and Vision Science*, vol. 88, no. 3, pp. 377–382, 2011.

[123] J. W. L. Tideman, J. R. Polling, T. Voortman et al., "Low serum vitamin D is associated with axial length and risk of myopia in young children," *European Journal of Epidemiology*, vol. 31, no. 5, pp. 491–499, 2016.

[124] S. M. Tang, T. Lau, S. S. Rong et al., "Vitamin D and its pathway genes in myopia: systematic review and meta-analysis," *British Journal of Ophthalmology*, vol. 103, no. 1, pp. 8–17, 2019.

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Clinical Study

Femtosecond Laser Implantation of a 355-Degree Intrastromal Corneal Ring Segment in Keratoconus: A Three-Year Follow-Up

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Purpose. To evaluate the outcomes of femtosecond laser-assisted implantation of a 355-degree intracorneal ring (ICR) (Keraring) in patients with keratoconus in the three-year follow-up. *Setting*. Future Femtolaser Center, Sohag, Egypt. *Design*. Prospective interventional case series. *Patients and Methods*. A prospective case series of 38 eyes of 26 patients with keratoconus had implantation of the 355-degree ICR keraring after tunnel creation with a femtosecond laser. The uncorrected visual acuities (UCVA) and best-corrected visual acuities (BCVA), sphere, cylinder, and manifest refraction spherical equivalent (SE), and mean keratometry (*K*), *K* max, and *K* min were evaluated preoperatively and 3, 6, 12, 24, and 36 months postoperatively, and all complications were reported. *Results*. 38 eyes of 26 patients with mean age 25.92 ± 5.44 years were enrolled in the study, 11 were males (**42.3%**). The mean UCVA improved from 0.93 ± 0.21 to 0.63 ± 0.21 logMAR ($P \leq 0.001$) and the mean BCVA from 0.67 ± 0.22 to 0.43 ± 0.26 logMAR ($P < 0.001$). The mean sphere, cylinder, and spherical equivalent have been changed dramatically from preoperative to 3 month postoperative, which is statistically significant ($P \leq 0.001$), and the changes between 1 and 2 years and 2 and 3 years are also considerable and statistically significant; the *K* max and *K* min and *K mean* improved and the changes were statistically significant ($P \leq 0.001$), and the changes between one, two, and three years were also statistically significant. The safety and efficacy indices were changed through the three-year follow-up. The complications were corneal neovascularization (36.84%), corneal melting (26.3%), and ring extrusion (31.5%) at the end of the study. *Conclusions*. Implantation of a 355-degree intracorneal keraring using femtosecond laser improved the visual, refractive, and topographic parameters in keratoconus patients, with a high rate of ICR extrusion and instability. The study has been registered for the Pan African Clinical Trial Registry (http://www.pactr.org) database within No: PACTR201810796878908 on 29 October 2018.

1. Introduction

Keratoconus is a disease characterized by stromal weakening followed by corneal protrusion leading to irregular astigmatism, which impairs the vision a lot, and its exact etiology cannot be determined; actually, many factors are accused for keratoconus occurrence [1].

In previous studies, the prevalence of keratoconus in different countries ranged from 0.3 per 100,000 in Russia to 23 per 1000 in central India (0.0003%–2.3%) [2, 3], and in recent studies about incidence in upper Egypt, the prevalence was as high as17.5% among the populations who are seeking refractive surgery [4].

So, many techniques are introduced as therapeutic choices for the management keratoconus to give more stability and better optical improvement. The procedures are different, ranging from crosslinking, intracorneal ring segment, and lamellar keratoplasty.

ICRS, small synthetic devices, are designed to be implanted within the corneal stroma aiming to induce a change in the geometry and refractive power of the tissue [5]. The first idea of corneal rings was introduced by Blevatskaya in 1966 [6]. Twenty years ago, the design of ring segments was introduced to correct the myopic refractive error [5]. Then, the rings were shown that they were effective in keratoconus management.

Many types are introduced in the market, and the main types are Keraring (Mediphacos) and Intacs (Addition technologies). In recent years, kerarings are polymethyl methacrylate (PMMA) characterized by triangular cross-sectional design and ultraviolet blocking effect, and they are available in variable thickness and arc length. Mediphacos developed a new *n* interrupted ring of 355°, which is available in a diameter of 5.7 mm and a thickness ranging from 200 to 300 μm [5], designed mainly for nipple keratoconus [5].

There are few studies published in the literature reporting the success of these rings in visual and refractive improvement in patients with central keratoconus [7, 8]; however, long follow-up studies to show its safety and efficacy within years are not available.

The normal orthogonal arrangement of the stromal fibers is distorted in the keratoconus patients so the course of intrastromal rings within these fibers is unpredictable [9]; hence further follow-up studies are needed especially as safety and efficacy are changed within time.

2. Materials and Methods

This prospective, consecutive, interventional study included 38 eyes from 26 patients with central keratoconus (15 females and 11 males), with a mean age of 25.92 ± 5.44 years (range 18–38 years).

The study was approved by the Ethical Committee of Faculty of Medicine, Sohag University, and followed the tenets of the Declaration of Helsinki. After full explanation about the purpose and procedures of the study, an informed written consent was obtained from the patients. The inclusion criteria were age greater than 20 years, central type keratoconus, which is diagnosed by equal or more than 50% of the cone is within the 3.0 mm zone on the posterior elevation map of the Pentacam rotating Scheimpflug device (OCULUS Optikgerate GmbH, Wetzlar, Germany) [10], moderate keratoconus and severe keratoconus cases according to the steepest keratometric reading [11], clear central cornea, pachymetry of above 400 microns, and no visual dysfunctions other than keratoconus. Contact lens wear was discontinued two weeks prior to the examination. Exclusion criteria were active allergic conjunctivitis, a history of keratorefractive surgery on the operative eye, dry eye, pregnancy, lactation, corneal stromal disorders, corneal erosion syndrome, corneal scars, previous herpes keratitis, autoimmune or immunodeficiency diseases, eccentric cone, presence of cataract, and glaucoma or retinal diseases.

A full detailed ophthalmic examination was performed preoperatively and postoperatively, including uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), manifest refraction, spherical equivalent (SE), keratometry (*K*) readings (max *K*, min *K*, and mean *K*), and ultrasound pachymetry. Anterior and posterior corneal surface topography were examined by Scheimpflug imaging using Pentacam; visual acuity was measured using decimal values and then converted to logMAR for statistical analysis.

The safety of implantation of Keraring 355° in patients with keratoconus was assessed using a refractive surgery safety index (safety index = postoperative best-corrected visual acuity ÷ preoperative best-corrected visual acuity in decimal values) [12].

Efficacy was calculated using a refractive surgery efficacy index, which is the mean postoperative UCVA/mean preoperative BCVA [12].

2.1. Surgical Technique. The procedure was performed under topical anesthesia using benoxinate hydrochloride followed by sterilization using Betadine (5% povidine iodine), and a sterile plastic sterile was applied to draw away the lashes, and then the speculum was used to open the eye.

Procedures started by marking the corneal center when the patient was fixating at the fixating light, then followed by application of the suction ring onto the cornea with great care of corneal centralization within the suction ring. The corneal tunnel was created using the femtosecond laser (*iFS Advanced Femtosecond Laser*, *Abbott*, *USA*), with a power of 5 mJ. Passing a spatula was performed through the limbs of the tunnel to check its patency. The 355-degree Keraring (Mediphacos Inc., Belo Horizonte, Brazil) segments were implanted carefully (Figure 1).

The tunnel depth was set at 300 microns subsequently; a silicone-hydrogel bandage contact lens (Bausch and Lomb) was placed on the cornea. Postoperatively, patients were given combined dexamethasone and tobramycin drops (TobraDex; Alcon Laboratories, Novartis, Inc., Fort Worth, Texas, USA) 4 times a day, moxifloxacin 0.5% drops (Vigamox, Alcon Laboratories, Novartis, Inc., Fort Worth, Texas, USA) 6 times a day, and nonpreserved artificial tears (Systane, Alcon Laboratories, Inc., Fort Worth, Texas, USA) 5 times a day. Moxifloxacin drops was discontinued one week postoperatively and dexamethasone drops tapered off during 3 weeks. Bandage contact lenses were removed one day postoperative. Patients were scheduled for postoperative clinical examination at 1st day and after 1 month, 3 months, 6 months, 12 months, 24 months, and 36 months. Intraoperative and postoperative complications were recorded. All the cases were operated by the same surgeon.

2.2. Statistical Analysis. Data were analyzed using SPSS computer program version 22.0.

Quantitative data were expressed as means ± standard deviation, median, and range. Qualitative data were expressed as number and percentage. The data were tested for normality using the Shapiro–Wilk test. The nonparametric Wilcoxon signed-rank test was used because the data were not normally distributed. A 5% level was chosen as a level of significance in all statistical tests used in the study.

2.3. Results. Thirty eight eyes of twenty six patients were enrolled in the study; sixteen eyes (42.1%) were diagnosed as moderate keratoconus with *K* max ≤ 52 D, while twenty-two eyes (57.9%) were diagnosed as severe keratoconus with *K* max >52 D using the steepest *K* reading. The mean age was 25.92 ± 5.44 years. Table 1 shows the patient demographics. The mean UDVA improved from 0.93 ± 0.21 logMAR to 0.63 ± 0.21 ($P \leq 0.001$), and after 36 months, the mean BCVA

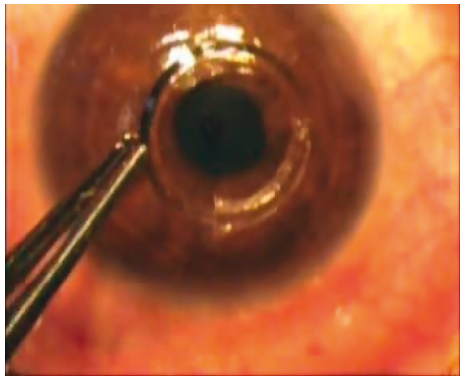


Figure 1: The insertion of the 355-degree keraring in the cornea after femtosecond tunnel formation.

Table 1: Patient demographics.

Number of patients	26
Age	
Mean ± SD	25.92 ± 5.44
Median (range)	24.5 (18–38)
Gender	
Male, n (%)	11 (42.3)
Female, n (%)	15 (57.69)

from 0.67 ± 0.22 logMAR to 0.43 ± 0.26 logMAR ($P < 0.001$), as shown in Table 2. The mean sphere, cylinder, and spherical equivalent have been changed dramatically from preoperative to 3 months postoperative, which are statistically significant, and the changes between 1 and 2 years and 2 and 3 years were also considered due to the high rate of ring extrusion, shown in detail in Table 3; the *K* max and *K* min and *K* mean changed a lot, and the changes between preoperative and postoperative were statistically significant ($P \leq 0.001$); the changes between one, two, and three years were statistically significant, Table 4. The safety and efficacy indices were changed through the three-year follow-up (Table 5). The complications, which were reported, ranged from corneal neovascularization (Figure 2), corneal melting, and ring extrusion (Figure 3), which ended by ring explantation (Figure 4) in about the third of cases at the end of the three-year follow-up, Table 6.

3. Discussion

The aim of ICRS surgery is to induce a geometric change in the central corneal curvature, thus, reducing the refractive error and the mean keratometry and improving the visual acuity. Additionally, corneal remodeling results in an improvement in the optical quality of the cornea, and a reduction in optical aberrations can also be expected [13–15]. So, the aim of this study was to report the efficacy and safety of femtosecond laser implantation of 355-° intrastromal corneal rings in the management of keratoconus; actually, few reports discussed the efficacy and safety of this procedure within a short time of follow-up.

According to the results obtained from this study, the femtosecond laser implantation of a 355-degree intrastromal corneal ring segment was successful according to the definition of success defined by Jorge [15], who defined successful surgery as one of the following characteristics at six months postoperatively: either an improvement in one or more lines of uncorrected visual acuity (UCVA) or BCVA or a decrease in two or more D of spherical equivalent. "Stable cases" were defined as cases without significant changes in corneal topography (<1 D in the mean keratometry mean) over 12 months preoperatively [15].

The ICRS surgery acts by regularizing the anterior corneal surface, thus, decreasing myopia and regular and irregular astigmatism. The introduction of the femtosecond laser in this procedure gave more advantages such as more safety, more accuracy, and easily accessible by the surgeon [16–18], which is advantageous over the study performed by Jadidi et al. [7].

Regarding the results, the UCVA changed dramatically after the procedure, which is statistically significant. This agreed with Jadidi study who implanted 355-degree kerarings via a mechanical technique using keratome: the UCVA improved from preoperative to postoperative at 1 and 3 months and the change between 3 and 6 months showed an improvement which was statistically significant [7], while in this study the change between the 12 and 24 months and between 24 months and 36 months were worse and statistically significant, which is explained by the high rate of ICRS extrusion which affects the final UCVA mean.

The *K* readings including the *K* max, *K* min, and *K* mean changed a lot postoperative and the change was statistically significant ($P \leq 0.001$), which implied the ability of the rings to change the convexity and geometry of the cornea; however, the mean K readings were increased in the subsequent follow-ups due to high incidence of the ring extrusion followed keratoconus progression after ring explantation.

We observed statistically significant reductions in myopia and cylinder. The changes were of a large magnitude, with a mean change in the sphere of 3.36 D and a mean change in the refractive cylinder of 2.01 D after the first year ($P = 0.001$). These levels of refractive change were consistent with those previously reported after MyoRing implantation with mechanical dissection [18–20] and with Femtolaser-assisted implantation of MyoRing implantation carried out by Saeed [21]; in this study, there was an increase in the myopia and the astigmatism values, which was statistically significant ($P = 0.004$ and $P = 0.003$, respectively); between 12-month follow-up and 24-month follow-up correlated to the increased number of cases complicated by ring extrusion, follow-up studies regarding the MyoRing implantation are opposite.

Regarding the complications of this type of rings, it was found there was a high rate of corneal melting at the site of insertion and ring extrusion; most of corneal melting cases began after 6 months postoperative; in this study, there was a high incidence of six ring extrusion cases (15.78%) after 12 months and twelve cases (31.5%) at 36 months; it was observed that the cases of corneal melting and ring extrusion preceded by a corneal neovascularization at the site of the ring insertion, which may imply a state of silent

Table 2: Comparison between preoperative and postoperative UCVA and BCVA measures.

	Preoperative	3 months postoperative	6 months postoperative	12 months postoperative	24 months postoperative	36 months postoperative	*P* value	*P*1	*P*2
UCVA (logMAR)									
Mean ± S.D.	0.93 ± 0.21	0.46 ± 0.18	0.47 ± 0.18	0.49 ± 0.18	0.54 ± 0.18	0.63 ± 0.21	<0.001	<0.001	0.001
Median (range)	0.9 (0.5–1.3)	0.4 (0.2–0.8)	0.45 (0.2–0.8)	0.45 (0.2–0.8)	0.6 (0.2–0.8)	0.6 (0.3–1.1)			
BCVA (logMAR)									
Mean ± S.D.	0.67 ± 0.22	0.29 ± 0.16	0.29 ± 0.15	0.37 ± 0.23	0.39 ± 0.24	0.43 ± 0.26	<0.001	0.248	0.052
Median (range)	0.6 (0.3–1.1)	0.25 (0.1–0.8)	0.3 (0.1–0.8)	0.3 (0.1–0.9)	0.3 (0.1–0.9)	0.3 (0.1–1)			

P value compared the six repeated measures and was calculated by Friedman's two-way ANOVA test. *P*1 compared 12 months postoperative and 24 months postoperative measures and was calculated by using Wilcoxon signed-rank test. *P*1 compared 24 months postoperative and 36 months postoperative measures and was calculated by Wilcoxon signed-rank test. *P* value <0.05 is statistically significant Notes: UCVA: uncorrected visual acuity; BCVA: best-corrected visual acuity; D: diopters; logMAR, logarithm of the minimum angle of resolution; SD: standard deviation.

Table 3: Comparison between preoperative and postoperative sphere, cylinder, and spherical equivalent (SE) measurements.

	Preoperative	12 months postoperative	24 months postoperative	36 months postoperative	*P* value	*P*1	*P*2
Sphere							
Mean ± S.D.	−9.68 ± 3.08	−6.32 ± 2.37	−7.13 ± 3.09	−7.45 ± 3.2	<0.001	0.004	0.129
Median (range)	−8.75 (−4.25–−16)	−5.75 (−3.5–−12.5)	−7.25 (−3.5–15)	−7.75 (−3.75–−15.5)			
Cylinder							
Mean ± S.D.	−5.82 ± 1.55	−3.81 ± 0.81	−4.21 ± 1.24	−4.32 ± 1.24	<0.001	0.003	0.198*
Median (range)	−6.25 (−3.25–−8.5)	−3.88 (−2–5.5)	−4 (−2–7)	−4 (−2–6.75)			
Spherical equivalent SE							
Mean ± S.D.	−12.55 ± 3.64	−8.25 ± 2.62	−8.72 ± 3.39	−9.62 ± 3.73	<0.001	0.173	0.009
Median (range)	−12 (−6.12–−19.75)	−7.75 (5–−14.75)	−7.75 (−5–−19.5)	−9.94 (−5–−18.75)			

P value compared the six repeated measures and was calculated by Friedman's two-way ANOVA test. *P*1 compared 12 months postoperative and 24 months postoperative measures and was calculated by Wilcoxon signed-rank test. *P*1 compared 24 months postoperative and 36 months postoperative measures and was calculated by Wilcoxon signed-rank test. * *P* value was calculated by paired samples *t* test. *P* value <0.05 is statistically significant. SE: spherical equivalent.

Table 4: Comparison between preoperative and postoperative *K* max, *K* min, and *K* mean measures.

	Preoperative	3 months postoperative	6 months postoperative	12 months postoperative	24 months postoperative	36 months postoperative	*P* value	*P*1	*P*2
K max									
Mean ± SD	53.82 ± 4.1	47.48 ± 2.16	47.44 ± 2.11	48.04 ± 2.39	49.51 ± 3.73	50.47 ± 4.08	<0.001	<0.001	0.001
Median (range)	54.6 (47.6–61.2)	48 (43–52)	47.3 (44–51.3)	47.75 (44.2–56.1)	48.95 (44.1–61.5)	49.5 (44.5–62)			
K min									
Mean ± SD	48.83 ± 2.84	45.23 ± 1.99	45.41 ± 1.82	45.8 ± 2.13	46.53 ± 2.46	47.01 ± 2.4	<0.001	<0.001	0.001
Median (range)	49.5 (45–53.2)	45.05 (42–48)	45.75 (41.9–48)	45.6 (42–50)	46 (42.7–55)	46 (43–55)			
K mean									
Mean ± SD	51.29 ± 3.49	46.29 ± 1.48	46.17 ± 1.67	46.57 ± 1.62	47.12 ± 1.62	47.51 ± 1.95	<0.001	0.001	0.055*
Median (range)	52.95 (46–56)	46.6 (43.8–48.4)	46.6 (43–48)	46.55 (43.8–49)	47.35 (44–50)	47.6 (44–52)			

P value compared the six repeated measures and was calculated by Friedman's two–way ANOVA test.*P*1 compared 12 months postoperative and 24 months postoperative measures and was calculated by the Wilcoxon signed-rank test.*P*1 compared 24 months postoperative and 36 months postoperative measures.

Table 5: The efficacy index and safety index of the procedure.

	3 months	6 months	12 months	24 months	36 months
Safety index	2.27	2.27	1.95	1.81	1.70
Efficacy index	1.59	1.59	1.45	1.32	1.09

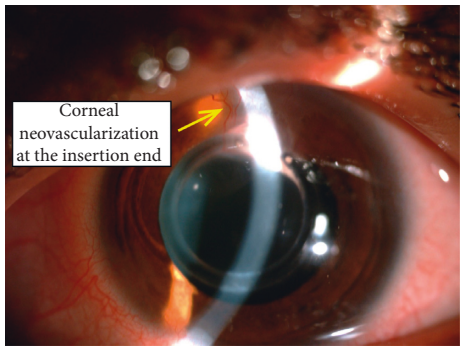


Figure 2: Neovascularization of the cornea at the insertion end of the 355-degree ring.

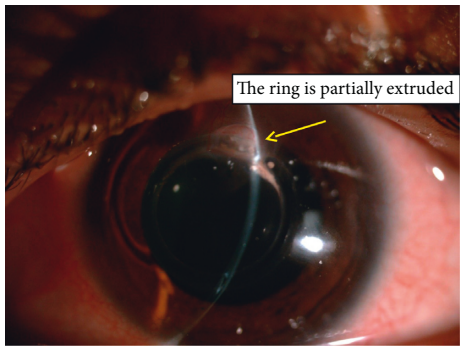
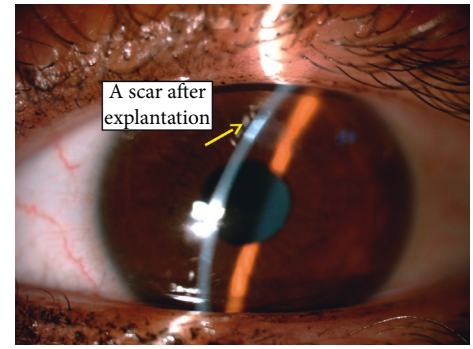
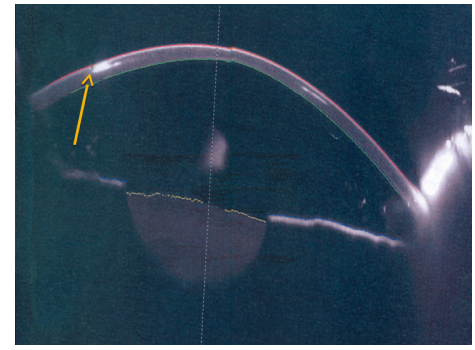


Figure 3: The ring partially extruded.

inflammation with these rings; the ring extrusion is previously mentioned by Jadidi in a small cases series using this 355-kerarings [8]. This high rate of corneal neovascularization and corneal melting which ended by ring explantation was not mentioned in this high percentage before; corneal neovascularization was 0.2% in a previous study of 850 eyes [22]. This claims a lot about the design of these rings. In our explanation; the circular design of the ring is to be about a complete circle which inserted through a tight tunnel, making the ring perform a persistent pressure on the upper corneal stromal fibers causing its melting; otherwise, in two separate segments design, there is a space to relieve pressure transmitted to the stromal fibers through the segment-free tissues. It is worth to mention this high rate of ring extrusion was quite the same in both moderate and severe stages of keratoconus cases; so the high rate of ring extrusion mostly related to the design of rings rather than the stage of keratoconus Although the MyoRing, which is a circular complete 360-degree ring, but it is inserted through a pocket, not a tunnel, making the pressure transmitted to a large area of stroma with less effect on stromal fibers. This



(a)



(b)

Figure 4: (a) Slit lamp photo of the cornea showing a scar after ring explantation and (b) Scheimpflug imaging of the cornea showing the scar.

agreed with previous results of long-term studies regarding the MyoRing as no cases of ring extrusion were reported. [8, 21–23]. However, comparing with a new incomplete 320 intracorneal stomal ring, it was found that the reduction in myopia and astigmatism values and corneal flattening effect are comparable with the 355 rings in this study; however, no cases of ring extrusion were reported in six-month follow-up [24], but there were few reported cases of ring migration [25]; other models of keraring such as 210 ring showed a success in improving the BSCVA; no cases of ring extrusion were reported with them [26]. It was supposed earlier that long-term stability of ICRS implantation depended on the progression pattern of keratoconus at the time of surgery. Thus, stable keratoconus with less progression gave more stable results and more success [27], and Alio suggested that insertion of intrastromal rings should be performed after confirmation of stability in keratoconus patients [28], but this cannot be applied in all cases.

To our knowledge, it is first study which studied the three-year follow-up of this model of ICSR (355-keraring), which highlights the high rate of ring extrusion accompanied with this ring model, agreeing with few previous reports. However, some limitation with this study which should be included in further studies is higher order aberrations analysis, to be compared with other type of ICSR; further studies are needed to study the effect of corneal cross-linking as a compound procedure with 355-keraring to improve its stability and efficacy.

Table 6: The postoperative complications.

	12 months			24 months			36 months		
	Total no.	Moderate keratoconus	Severe keratoconus	Total no.	Moderate keratoconus	Severe keratoconus	Total no.	Moderate keratoconus	Severe keratoconus
Infectious keratitis	0	0	0	0	0	0	0	0	0
Corneal neovascularization	7 (18.4%)	3 (18.75%)	4 (18.18%)	11 (28.9%)	5 (31.16%)	6 (27.27%)	14 (36.84%)	6 (37.5%)	8 (36.36%)
Corneal melting	5 (13.15%)	2 (12.5%)	3 (13.63%)	8 (21%)	3 (18.75%)	7 (22.73%)	10 (26.3%)	4 (25%)	6 (27.27%)
Ring extrusion	6 (15.78%)	2 (12.5%)	4 (18.18%)	10 (26.3%)	4 (25%)	6 (27.27%)	12 (31.5%)	5 (31.25%)	7 (31.82%)

4. Conclusion

Implantation of a 355-degree intracorneal keraring using femtosecond laser improved the visual, refractive, and topographic parameters in keratoconus patients, with a high rate of ICR extrusion and instability in the three-year follow-up.

Data Availability

Data are available on request (videos, Pentcams, and photos) to the corresponding author.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethical Committee of Faculty of Medicine, Sohag University) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Informed written consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

An edited video shows femtosecond tunnel creation and 355-degree keraring insertion. (*Supplementary Materials*)

References

[1] E. Shneor, M. Millodot, S. Blumberg, I. Ortenberg, S. Behrman, and A. Gordon-Shaag, "Characteristics of 244 patients with keratoconus seen in an optometric contact lens practice," *Clinical and Experimental Optometry*, vol. 96, no. 2, pp. 219–224, 2013.

[2] E. N. Gorskova and E. N. Sevost'ianov, "Epidemiology of keratoconus in the urals," *Vestnik Oftalmologii*, vol. 114, no. 4, pp. 38–40, 1998.

[3] J. B. Jonas, V. Nangia, A. Matin, M. Kulkarni, and K. Bhojwani, "Prevalence and associations of keratoconus in rural Maharashtra in central India: the central India eye and medical study," *American Journal of Ophthalmology*, vol. 148, no. 5, pp. 760–765, 2009.

[4] A. Saro, S. AdhamS, R. GamalA, and M. UsamaA, "Screening for keratoconus in a refractive surgery population of upper Egypt," *Delta Journal of Ophthalmology*, vol. 19, no. 1, pp. 19–23, 2018.

[5] A. Vega-Estrada and J. L. Alio, "The use of intracorneal ring segments in keratoconus," *Eye and Vision*, vol. 3, no. 1, p. 8, 2016.

[6] E. D. Blavatskaya, "Intralamellar homoplasty for the purpose of relaxation of refraction of the eye," *Archieve of the American Scoiety of Ophthalmology and Optemetry*, vol. 6, pp. 311–325, 1968.

[7] K. Jadidi, A. M. Seyed, N. Farhad, N. Mostafa, J. Leila, and S. Sara, "Intrastromal corneal ring segment implantation (keraring 355°) in patients with central keratoconus: 6-month follow-up," *Journal of Ophthalmology*, vol. 2015, Article ID 916385, 8 pages, 2015.

[8] J. Khosrow, S. Aliasghar Mosavi, F. Nejat, and A. Alishiri, "Complications of intrastromal corneal ring implantation (keraring 355°) using a femtosecond laser for channel creation," *International Journal of Keratoconus and Ectatic Corneal Diseases*, vol. 3, no. 2, pp. 53–56, 2014.

[9] A. Daxer and P. Fratzl, "Collagen fibril orientation in the human corneal stroma and its implication in keratoconus," *Investigative Ophthalmology & Visual Science*, vol. 38, no. 1, pp. 121–129, 1997.

[10] L. Torquetti, R. F. Berbel, and P. Ferrara, "Long-term follow-up of intrastromal corneal ring segments in keratoconus," *Journal of Cataract & Refractive Surgery*, vol. 35, no. 10, pp. 1768–1773, 2009.

[11] K. Zadnik, J. T. Barr, T. B. Edrington et al., "The collaborative longitudinal evaluation of keratoconus (CLEK) study group. Baseline findings in the collaborative longitudinal evaluation of keratoconus (CLEK) study," *Investigative Ophthalmology & Visual Science*, vol. 39, no. 13, pp. 2537–2546, 1998.

[12] R. Shetty, M. Kurian, D. Anand, P. Mhaske, K. M. Narayana, and B. K. Shetty, "Intacs in advanced keratoconus," *Cornea*, vol. 27, no. 9, pp. 1022–1029, 2008.

[13] M. A. Zare, H. Hashemi, and M. R. Salari, "Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy," *Journal of Cataract & Refractive Surgery*, vol. 33, no. 11, pp. 1886–1891, 2007.

[14] A. Ertan and J. Colin, "Intracorneal rings for keratoconus and keratectasia," *Journal of Cataract & Refractive Surgery*, vol. 33, no. 7, pp. 1303–1314, 2007.

[15] J. Alio, R. Barraquer, S. Esperanza, J. Murta, M. Teus, and A. Vega-Estrada, "Intrastromal corneal ring segments: how

successful is the surgical treatment of keratoconus?," *Middle East African Journal of Ophthalmology*, vol. 21, no. 1, pp. 3–9, 2014.

[16] J. L. Alio, D. P. Pinero, and A. Daxer, "Clinical outcomes after complete ring implantation in corneal ectasia using the femtosecond technology: a pilot study," *Ophthalmology*, vol. 118, no. 7, pp. 1282–1290, 2011.

[17] D. Albert, "Corneal intrastromal implantation surgery for the treatment of moderate and high myopia," *Journal of Cataract & Refractive Surgery*, vol. 34, no. 2, pp. 194–198, 2008.

[18] H. Mahmood, R. S. Venkateswaran, and A. Daxer, "Implantation of a complete corneal ring in an intrastromal pocket for keratoconus," *Journal of Refractive Surgery*, vol. 27, no. 1, pp. 63–68, 2011.

[19] A. Daxer, H. Mahmoud, and R. S. Venkateswaran, "Intracorneal continuous ring implantation for keratoconus: one-year follow-up," *Journal of Cataract & Refractive Surgery*, vol. 36, no. 8, pp. 1296–1302, 2010.

[20] M. Jabbarvand, A. SalamatRad, H. Hashemian, and M. Khodaparast, "Continuous corneal intrastromal ring implantation for treatment of keratoconus in an Iranian population," *American Journal of Ophthalmology*, vol. 155, no. 5, pp. 837–842, 2013.

[21] A. Saeed, "Corneal intrastromal MyoRing implantation in keratoconus treatment," *Journal of the Egyptian Ophthalmological Society*, vol. 107, no. 2, pp. 106–112, 2014.

[22] E. Coskunseven, G. D. Kymionis, N. S. Tsiklis et al., "Complications of intrastromal corneal ring segment implantation using a femtosecond laser for channel creation: a survey of 850 eyes with keratoconus," *Acta Ophthalmologica*, vol. 89, no. 1, pp. 54–57, 2011.

[23] A. Daxer, A. Ettl, and R. Hörantner, "Long-term results of MyoRing treatment of keratoconus," *Journal of Optometry*, vol. 10, no. 2, pp. 123–129, 2017.

[24] M. O. Yousif and A. M. A. Said, "Comparative study of 3 intracorneal implant types to manage central keratoconus," *Journal of Cataract & Refractive Surgery*, vol. 44, no. 3, pp. 295–305, 2018.

[25] L. Torquetti, P. Cunha, L. Allan et al., "Clinical outcomes after implantation of 320°-arc length intrastromal corneal ring segments in keratoconus," *Cornea*, vol. 37, no. 10, pp. 1299–1305, 2018.

[26] A. Kubaloglu, E. S. Sari, Y. Cinar et al., "A single 210-degree arc length intrastromal cornealring implantation for the management of pellucidmarginal corneal degeneration," *American Journal of Ophthalmology*, vol. 150, no. 2, pp. 185–192, 2010.

[27] A. Vega-Estrada, J. L. Alió, L. F. Brenner, and N. Burguera, "Outcomes of intrastromal corneal ring segments for treatment of keratoconus: five-year follow-up analysis," *Journal of Cataract & Refractive Surgery*, vol. 39, no. 8, pp. 1234–1240, 2013.

[28] A. Vega-Estrada, J. L. Alió, and A. B. Plaza-Puche, "Keratoconus progression after intrastromal corneal ring segment implantation in young patients: five-year follow-up," *Journal of Cataract & Refractive Surgery*, vol. 41, no. 6, pp. 1145–1152, 2015.

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Clinical Study

Short-Term Effect of Low-Dose Atropine and Hyperopic Defocus on Choroidal Thickness and Axial Length in Young Myopic Adults

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Purpose. To examine the interaction between a short period of hyperopic defocus and low-dose atropine upon the choroidal thickness and ocular biometrics of healthy myopic subjects. *Methods*. Twenty young adult myopic subjects had subfoveal choroidal thickness (ChT) and ocular biometry measurements taken before and 30 and 60 min following the introduction of optical blur (0.00 D and −3.00 D) combined with administration of 0.01% atropine or placebo. Each combination of optical blur and drug was tested on different days in a fixed order. *Results*. The choroid exhibited significant thinning after imposing hyperopic defocus combined with placebo (mean change of $-11 \pm 2\,\mu$m, $p < 0.001$). The combination of hyperopic blur and 0.01% atropine led to a significantly smaller magnitude of subfoveal choroidal thinning ($-4 \pm 8\,\mu$m), compared to placebo and hyperopic defocus ($p < 0.01$). Eyes treated with 0.01% atropine with no defocus exhibited a significant increase in ChT ($+6 \pm 2\,\mu$m, $p < 0.01$). Axial length also underwent small but significant changes after treatment with hyperopic blur and placebo and 0.01% atropine alone (both $p < 0.01$), but of opposite direction to the changes in choroidal thickness. However, the 0.01% atropine/hyperopic blur condition did not lead to a significant change in axial length compared to baseline ($p > 0.05$). *Conclusion*. Low-dose atropine does inhibit the short-term effect of hyperopic blur on choroidal thickness and, when used alone, does cause a slight thickening of the choroid in young healthy myopic adults.

1. Introduction

Myopia is one of the most common types of refractive error and a leading cause of functional visual loss [1]. Despite extensive attempts to develop effective strategies to combat myopia, there is no fully effective treatment that will prevent its development and progression. Clinical trials examining various myopia control interventions indicate that muscarinic blockers (atropine and pirenzepine) appear to have the strongest preventative effect on myopia progression [2–5]. However, at higher concentrations (above 0.02%), atropine produces ocular side effects such as pupillary dilation, photophobia, and difficulty with near focus (cycloplegia) that limit its practical application [6–10].

As early as mid of 19th century, atropine was proposed as a treatment for myopia control [11], with numerous clinical studies assessing it effectiveness over the past three decades [6, 12, 13]. But it was not until the publication of findings from randomized controlled clinical trials in mainly East Asian children that atropine was recognized as an effective treatment for myopia [7, 8, 10, 14–16]. An important observation from the ATOM 2 study showed that low-dose (0.01%) atropine is almost as effective as higher concentrations (0.5%, 0.25%, and 0.1%) of atropine in slowing the progression of the spherical equivalent refraction (SEQ) of myopia while causing less visual side effects [8]. However, it is worth noting that there was a discrepancy between the refractive error and axial length data for low-dose atropine in this study, with the axial elongation observed in the 0.01% atropine group appearing comparable to that observed in the placebo control group [15]. Although it takes initially longer to produce a therapeutic effect (more than three months),

0.01% atropine yielded a similar reduction in SEQ myopia progression to higher doses in a five-year follow-up study, with a marked reduction in the "rebound effect" that was observed during washout after higher doses [16]. The exact mechanism underlying the "rebound effect" is unclear, but the phenomenon leads to a rapid increase in myopia (0.5 D/year) in children originally treated with higher concentrations of atropine (0.1%, 0.25%, and 0.5%, 1.0%) upon cessation of treatment.

Although much work on the potential of low-dose atropine against myopia has been carried out, there is still considerable ambiguity with regard to its optimal low concentration that is most effective to prevent myopia and its mechanism of action. The current clinical trial (LAMP) has shown the ability of different concentrations of low-dose atropine (0.05%, 0.025%, and 0.01%) to slow myopia progression in myopic children, with 0.05% atropine being the most effective in controlling axial length and SEQ progression [17]. Further, it is generally accepted that atropine inhibition of myopia does not rely on paralysis of accommodation [18] but that atropine may act (directly via a muscarinic mechanism or indirectly through a nonmuscarinic mechanism) on posterior segment tissues such as the retina, retinal pigment epithelium (RPE), choroid, or sclera in order to influence eye growth [19–22]. However, a consistent finding in atropine clinical studies is a reduction in refractive error SEQ progression which is not matched by a reduction in axial length progression, suggesting a possible role for the ciliary muscle in the refractive error changes [7, 8, 10, 14, 16, 17].

Choroidal thickness shows short-term sensitivity to a range of antimuscarinics (atropine, homatropine, and cyclopentolate) that have generally been shown to significantly increase subfoveal choroidal thickness in humans [23–25]. Further, a range of different muscarinic antagonists have also been identified as being able to slow eye growth and trigger a transient thickening of the choroid in animals treated with hyperopic defocus that would typically be expected to lead to choroidal thinning [26, 27]. Recently, two studies have shown that high-dose antimuscarinic agents (atropine 0.5% and homatropine 2%) can inhibit the effect of hyperopic defocus (typically leading to thinning) on subfoveal choroidal thickness [28, 29]. However, the practical question remains whether low-dose atropine (0.01%) can also inhibit short-term changes in choroidal thickness and axial length in response to hyperopic defocus.

In this context, we examined the interaction between short periods of hyperopic retinal defocus and 0.01% atropine upon the choroidal thickness and axial length of young healthy myopes. By investigating ocular changes after combined interventions, we hoped to improve our understanding of the myopigenic mechanisms influencing the thickness of the choroid in humans and provide insights into the possible mechanism underlying the myopia control effects of low-dose atropine.

2. Materials and Methods

2.1. Subjects. Twenty myopic subjects (spherical equivalent refraction of ≥−0.75 DS) with a mean age (±SD) of 27.3 ± 5 years were recruited primarily from the students and staff of the Queensland University of Technology to participate in this randomized, single-masked, placebo-controlled study. The investigation conformed to the principles outlined in the Declaration of Helsinki. Approval was obtained from the university human research ethics committee, and participants gave their informed consent before the experiment. The sample size used in the study provided 80% power to detect a choroidal thickness change of $11 \pm 3\,\mu$m, based upon the findings from our previous work [29]. Of the study population, 70% ($n = 14$) were female and 45% were Caucasian (Caucasian $n = 9$, East Asian $n = 8$, Indian $n = 2$, and Middle Eastern $n = 1$).

Ahead of the study, each participant had a full eye examination, and those with serious eye or systemic problems, history of eye trauma or surgery, or any record of previous myopia interventions were excluded from the experiment. All enrolled participants demonstrated good visual acuity of logMAR 0.00 or better and had a range of refractive errors (spherical equivalent from −0.75 to −6.00 DS). The mean spherical equivalent refractive error was -2.87 ± 1.64 DS. During the experiment, care was taken to test each subject at approximately the same time of day between 9 am and 2 pm, to minimize the potential confounding effect of ocular circadian fluctuations in choroidal thickness and axial length upon the results [30]. The experiment trials consisting of a combination of blur (either monocular hyperopic blur (−3 D) or optimal focus) and atropine (one drop of 0.01% atropine) or placebo (0.3% hydroxypropyl methylcellulose) were tested on separate days, in a fixed order. A hyperopic defocus/placebo trial was tested first and was followed by a no defocus/placebo eye drops trial, a hyperopic defocus/0.01% atropine trial, and finally a no defocus/0.01% atropine trial. We decided to use a fixed order design to minimize the possible contamination of subsequent trials due to the residual action of the previously administered atropine. The sessions were spaced at least two days apart with an average time of 49.03 ± 0.6 hr between sessions. This two-day interval was based on a washout period of five to ten times the terminal elimination half-life of the drug [31], and atropine's terminal half-life is 2.5 ± 0.8 hours [32].

2.2. Pharmacological Agents. One drop (~33 μL) of 0.01% atropine (consisting of 0.0005 g of atropine sulphate, 1.405 g of 0.9% sodium chloride, 0.245 g of 0.001% benzalkonium chloride, and 2.8 g of water) or placebo (0.3% hydroxypropyl methylcellulose) was instilled into the right eye, combined with a different blur condition at each visit. The atropine dose of 0.01% was chosen based on the effective dosage and low rate of adverse effects reported in previous randomized, controlled clinical trials [8, 16]. Since 0.01% concentration is thought to be efficacious in myopia control and to have less disruptive effect on the patient daily activities compared with higher doses of atropine, we decided to use it in our study. The 0.01% dose is also predicted to exceed the published ID50 values (concentration that binds 50% of the possible maximum to the target receptor) of atropine [33]. We attempted to mask participants to the pharmacological agent; however, true masking cannot be achieved due to the

nature of the drug (e.g., some burning sensation after the atropine administration).

2.3. Procedures. All subjects had a set of retinal and choroidal scans as well as ocular biometry collected before and then 30 and 60 min following the start of the trials. To control the potential confounding effect of accommodation on choroidal thickness and axial length results, participants were asked to maintain distance fixation at six meters (watching TV) with their optimal refractive correction for 20 minutes prior to and between measurements. Further, to limit proximal accommodation during biometric measurements, a periscope system was attached to a noncontact biometer (Lenstar LS 900; Haag-Streit AG, Koeniz, Switzerland), as per Sander et al. [23].

The Copernicus SOCT-HR (Optopol Technology S.A., Zawiercie, Poland) was utilized to obtain multiple orthogonal (90- and 180-degree cross pattern), 6 mm length, foveal-centered, chorioretinal B-scans, with each set of scans collected consisting of 30 horizontal and 30 vertical B-scans [29]. Three sets of OCT B-scans were captured from the right eye at baseline (preintervention) and then at 30 and 60 minutes after the introduction of the blur/drug condition and were later averaged.

Ocular biometric data were also measured at the same times using the Lenstar LS 900 biometer [23]. Five separate ocular biometric measurements were acquired for each measurement session, and the data were later averaged.

2.4. Data Analysis. Following data acquisition, the individual B-scan images collected at each session were averaged, and the horizontal and vertical OCT images of the retina and choroid were manually segmented by a masked observer, using customized software [34]. The average foveal retinal thickness was calculated as the axial distance between the ILM and the RPE on each scan, while the average subfoveal choroidal thickness was defined as the distance between the outer boundary of the RPE and the inner boundary of the chorioscleral interface at the fovea. The average biometric data from the Lenstar LS900 (axial length, central corneal thickness, anterior chamber depth, and lens thickness) were also analysed for each testing condition.

As data from all variables were normally distributed at each time point, as assessed by the Kolmogorov–Smirnov test of normality ($p > 0.05$), a repeated-measures analysis of variance (ANOVA) that examined the effect of defocus, drug, and time on ocular parameters was then conducted. Each of the measured variables was used to determine the significance of changes in each of the ocular parameters as a result of the interaction between the different blur conditions and pharmacological agents. The Bonferroni-adjusted post hoc analyses were employed to examine the difference in ocular parameters with significant within-subject effects and interactions.

3. Results

3.1. Within-Session Repeatability. The within-session SD of the ocular biometrics was axial length (11 μm), central corneal thickness (2 μm), anterior chamber depth (12 μm), lens thickness (19 μm), retinal thickness (2 μm), and 3 μm subfoveal choroidal thickness. ICC analysis suggested "excellent" reliability for all variables (ICC > 0.90 for all variables). Table 1 illustrates the repeatability and reliability data for each of the ocular parameters across all measurement sessions.

3.2. Subfoveal Choroidal Thickness. Repeated-measures ANOVA showed a statistically significant increase in subfoveal choroidal thickness from baseline as a result of low-dose atropine, a significant interaction between the effect of low-dose atropine and time, as well as a significant interaction between low-dose atropine, blur condition, and time (all $p < 0.05$). Table 2 shows the change in subfoveal choroidal thickness for all four conditions tested, in comparison with baseline thickness over 30 and 60 minutes.

The combination of hyperopic blur and low-dose atropine led to a relatively small amount of subfoveal choroidal thinning (mean change: -2 ± 4 μm and -4 ± 8 μm after 30 and 60 minutes, respectively) that was not significantly different to baseline (both $p > 0.05$). However, hyperopic blur and placebo led to a small and statistically significant decrease in subfoveal choroidal thickness (mean change: -6 ± 1 μm, $p = 0.008$, and -11 ± 2 μm, $p = 0.0001$, compared to baseline after 30 and 60 minutes, respectively), and this magnitude of choroidal thickness change was significantly different to that observed for the low-dose atropine and hyperopic blur condition ($p = 0.019$ at 60 minutes). The low-dose atropine with no defocus condition caused a small increase in subfoveal choroidal thickness that was statistically significant at 60 minutes (mean change: $+2 \pm 1$ μm, $p = 0.234$, and $+6 \pm 2$ μm, $p = 0.011$, at 30 and 60 minutes compared to baseline).

No significant change in the subfoveal choroidal thickness was found with the placebo and no defocus (mean change: 0 ± 2 μm and 0 ± 1 μm for 30 and 60 minutes, respectively; $p > 0.05$) (Figure 1). There was also no significant difference between the baseline subfoveal choroidal thickness measurements (prior to drug instillation) for any of the four conditions tested on different days.

3.3. Retinal Thickness. All four interventions did not elicit statistically significant changes in retinal thickness at the fovea (Table 2), with the average retinal thickness change being less than 1 μm ($p > 0.05$).

3.4. Axial Length. The average ocular biometric changes following the introduction of the four different interventions are illustrated in Table 2 and Figure 1. There was significantly less change from baseline in axial length observed for the low-dose atropine/hyperopic blur condition ($+4 \pm 8$ μm, $p = 0.756$, and $+3 \pm 8$ μm, $p = 0.87$) compared to the placebo/hyperopic blur (mean change: $+6 \pm 9$ μm, $p = 0.119$, and $+12 \pm 10$ μm, $p = 0.006$) at 30 and 60 minutes, respectively. Eyes treated with low-dose atropine/no defocus

Table 1: Outline of within-session repeatability and reliability for each of the variables measured at each measurement session.

	Mean within-session standard deviation	Mean coefficient of variation (%)	ICC
AL (μm)	11	0.05	0.998
CCT (μm)	2	0.42	0.998
ACD (μm)	12	0.37	0.997
LT (μm)	19	0.53	0.995
Subfoveal ChT (μm)	3	1.14	0.995
RT (μm)	2	0.92	0.998

AL: axial length; CCT: central corneal thickness; ACD: anterior chamber depth; LT: lens thickness; ChT: subfoveal choroidal thickness; RT: retinal thickness; AA: amplitude of accommodation.

Table 2: Effects of 0.01% atropine and placebo with or without hyperopic defocus on the average change in ocular variables at 30 and 60 minutes from baseline.

	ANOVA						
	Average (SD) difference in ocular parameters data from baseline				p value		
	0.01% atropine + hyperopic defocus (μm)	Placebo + hyperopic defocus (μm)	Placebo (μm)	0.01% atropine (μm)	Drug	Drug by time	Drug by time by defocus
AL							
30 min	$+4 \pm 8$	$+6 \pm 9$	0 ± 7	-3 ± 7	**0.015**	**0.007**	**0.046**
60 min	$+3 \pm 8$	$+12 \pm 10^*$	$+1 \pm 6^*$	$-6 \pm 5^*$			
CCT							
30 min	$+1 \pm 1$	0 ± 1	0 ± 1	0 ± 1	0.686	0.427	0.731
60 min	-1 ± 1	-1 ± 1	-1 ± 1	0 ± 1			
ACD							
30 min	$+19 \pm 35$	$+5 \pm 34$	$+7 \pm 4$	$+21 \pm 39$	**0.042**	0.058	0.892
60 min	$+39 \pm 36^*$	$+7 \pm 36$	$+4 \pm 4$	$+40 \pm 34^*$			
LT							
30 min	-10 ± 34	-6 ± 32	-3 ± 33	-11 ± 33	**0.025**	**0.049**	0.678
60 min	-21 ± 35	-4 ± 30	-5 ± 34	$-29 \pm 31^*$			
RT							
30 min	0 ± 1	0 ± 1	0 ± 1	0 ± 1	0.265	0.766	0.364
60 min	$+1 \pm 1$	$+1 \pm 1$	$+1 \pm 1$	$+1 \pm 1$			
Subfoveal ChT							
30 min	-2 ± 5	-6 ± 2	0 ± 2	$+2 \pm 1$	**0.014**	**0.001**	**0.0001**
60 min	-4 ± 8	$-11 \pm 2^*$	0 ± 1	$+6 \pm 2^*$			

Statistically significant ANOVA changes ($p < 0.05$) are highlighted in bold. Asterisks imply significant differences in variables compared to baseline, using post hoc analysis with Bonferroni adjustment ($p < 0.05$). Positive values represent an increase in the ocular parameter, while the negative values correspond to a decrease in the ocular parameter. AL: axial length; CCT: central corneal thickness; ACD: anterior chamber depth; LT: lens thickness; RT: retinal thickness; ChT: subfoveal choroidal thickness.

exhibited shortening of the axial length, and this was statistically significant at 60 minutes (mean change: $-3 \pm 7\,\mu$m, $p = 0.356$, and $-6 \pm 5\,\mu$m, $p = 0.036$, at 30 and 60 minutes).

3.5. Anterior Eye Biometry. Low-dose atropine alone elicited changes in anterior segment components, with anterior chamber depth significantly increasing from baseline (average mean change $+38 \pm 14\,\mu$m, $p = 0.023$) and crystalline lens thickness significantly decreasing from baseline (average mean change $-24 \pm 13\,\mu$m, $p = 0.044$) (Table 2). However, both the placebo/hyperopic blur and the low-dose atropine/hyperopic blur conditions did not cause significant changes in anterior chamber depth or lens thickness (both $p > 0.05$). Central corneal thickness showed no significant changes for any of the tested conditions (all $p > 0.05$).

4. Discussion

The current study has demonstrated that 0.01% atropine produces a small increase in subfoveal choroidal thickness. The magnitude of subfoveal choroidal thickness increase with 0.01% atropine ($6\,\mu$m) was lower than that reported with 1% atropine ($15\,\mu$m) [25], 2% homatropine ($14\,\mu$m) [23], and 1% cyclopentolate ($21\,\mu$m) [24], suggesting a possible dose-dependent response. The inhibition of choroidal thinning with hyperopic defocus by 0.01% atropine is also consistent with earlier studies where muscarinic blockers (0.5% atropine [28] and 2% homatropine [29]) prevented the reduction in choroidal thickness produced by hyperopic blur.

Atropine is a potent muscarinic blocker; however, the exact mechanisms and pathways involved in atropine's antimyopigenic effects as well as site of action for atropine-

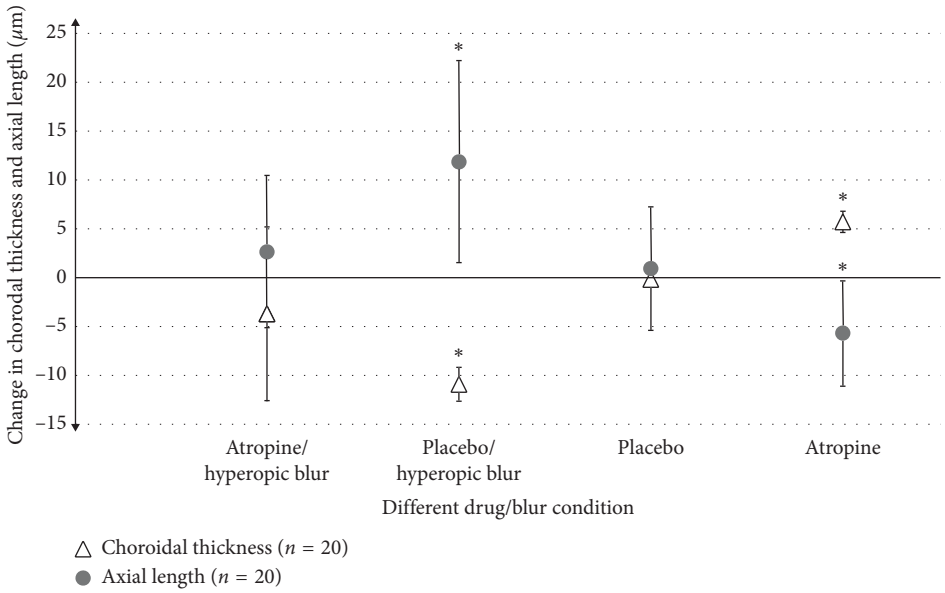

Figure 1: Mean difference in subfoveal choroidal thickness and axial length at 60 minutes after the introduction of the four drug and blur conditions for 20 subjects. Asterisks imply significant differences in choroidal thickness and axial length compared to baseline ($p < 0.01$). Error bars represent ±SD.

meditated myopia inhibition are not clear. Drug absorption following topical application to the eye is a complex process that tends to be influenced by drug kinetics in the cul-de-sac of the conjunctiva and corneal permeability. The atropine eye drops used in this study were combined with benzalkonium chloride (BAK) 0.1 mg/mL, which improves penetration through the cornea [35]. Further, once inside the eye, atropine reaches the intraocular concentration of 659 nM, which is significantly higher than IC50 value for atropine (20 nM) for the human iris and ciliary muscle receptor when using carbachol as the agonist [33] and its affinity at human M4 receptor (0.125–0.25 nM) [36]. Therefore, the concentrations of atropine in the eye after a single topical application in this study are likely to be within a range capable of reaching the choroid within 60 minutes.

Muscarinic receptors including M_1, M_2, and M_4 receptors have been implicated in the development and/or progression of myopia in animal models [20, 21, 26, 37]. Therefore, giving atropine's ability to block muscarinic receptors in the posterior segment, it may interfere in the biochemical cascade involved in the transient response to hyperopic blur and thus prevent myopia. It is important to notice, however, that none of the experimental studies has revealed a presence of a direct correlation between muscarinic receptors in the posterior segment and the antimuscarinic properties of atropine for inhibition of myopia. Further, emerging evidence seems to substantiate nonmuscarinic mechanism in antimyopia effects of atropine. Major arguments that contradict cholinergic mechanism are lack of effectiveness of majority of muscarinic antagonists against myopia progression in experimental studies [20], the high tissue concentrations of muscarinic antagonists (above muscarinic receptor affinity constants) required to inhibit myopia in experimental studies [38], and in vitro data supporting nonmuscarinic targets for atropine including nitric oxide, dopamine, or α2-adrenoreceptors [36, 39].

Previous experimental studies have shown that atropine may trigger the production and depletion of nitric oxide (NO) and this, in turn, impacts choroidal thickness changes [27, 39]. A suppression of prejunctional M_2/M_4 muscarinic receptors on cholinergic-nitrergic nerve terminals in the choroid by atropine modulates a vasodilation response in ocular blood vessels through the neural nitric oxide pathway and this, in turn, influences choroidal thickness changes and ocular growth [40, 41]. Similarly, data of ATOM 2 clinical trial [16] have supported, although indirectly, a nonmuscarinic mechanism. Outcomes of the trial have revealed the development of a "rebound phenomenon" in children who were originally treated with higher concentrations of atropine for 24 months and showed an enhanced myopia progression 12 months after cessation of the therapy. Although the exact mechanism underlying the "rebound effect" is unclear, prior cardiovascular research showed that nitrates, widely used to promote vasodilation via release of nitric oxide, generate a rebound phenomenon. This phenomenon develops when the medication is stopped after continuous use and is probably related to desensitization of the NO-dependent soluble guanylyl cyclase (sGC)/cyclic guanosine monophosphate (cGMP) signalling pathway [42, 43].

Further, some evidence suggests that the ability of atropine to prevent myopia development and/or progression may involve a release of dopamine in the retina, resulting in a transient choroidal thickening and inhibition of ocular growth. Zhong et al. [44] proposed that the eye's response to optical blur is driven by the activity of the amacrine cells. While it has not yet been fully established whether amacrine cells regulate eye growth, previous work has demonstrated

that dopaminergic amacrine cells could play an important role in the detection of ocular defocus [45]. Their function is controlled by suppressive muscarinic cholinergic amacrine cells [46] and GABAergic amacrine cells [47]. Therefore, it is possible that atropine interferes with dopaminergic signalling in the retina by influencing the muscarinic cholinergic amacrine cell responses leading to myopia prevention. Previous research showed that muscarinic blockers may stimulate the synthesis and release of dopamine from dopaminergic amacrine cells that eventually cause expansion of the choroid and retardation of ocular growth [26, 48, 49]. Recent work by Khanal et al. [50] provides further evidence that topical atropine may modify inner retinal cell responses, since multifocal ERG changes evident in the presence of myopic defocus were found to increase in magnitude in the inner peripheral retina, following the instillation of topical atropine. The mechanism of how atropine influences inner retinal dopaminergic signalling, however, has not yet been sufficiently clarified. Recently, Carr and colleagues [36] have demonstrated that atropine, like other muscarinic antagonists, binds to α2-adrenoreceptors at concentrations similar to those used to suppress experimental myopia in chicks. As adrenoreceptors are known to control the activity of tyrosine hydroxylase, the key enzyme in dopamine synthesis, it is possible that atropine acting on α2-adrenoreceptors affects the dopamine level in the retina.

Relatively large magnitude changes were observed in the anterior chamber depth (40 microns deeper) and lens thickness (29 microns thinner) following atropine instillation consistent with a reduction in accommodative tone (Table 2). This supports the possibility that the choroidal thickness changes observed may at least partially be related to the biomechanical forces generated through the relaxation of the ciliary muscle with 0.01% atropine. Previous work shows that changes in accommodation [51] can result in small magnitude choroidal thickness changes.

Similar to previous clinical trials [16, 17], 0.01% atropine, probably due to the minimal magnitude of choroidal thickness changes, did not produce significant changes in axial length. It would be of significant clinical interest to determine if continued treatment with 0.01% atropine leads to a long-term increase in choroidal thickness and thus to a reduction in axial elongation. This, in turn, would decrease the likelihood of developing pathological myopia. The administration of 0.01% atropine also produced an increase in the anterior chamber depth (backward lens movement) and decreased lens thickness, which are both related to the change in ciliary muscle tone and alter the biomechanical forces on the globe.

The study has a number of limitations that need to be considered. The relatively small sample size of 20 subjects is a limitation, along with the 60-minute test duration and the mixed ethnicity of the subjects. Testing over longer durations is difficult because of the need to continuously control the type of visual tasks (accommodation demand) and account for the natural diurnal cycle in choroidal thickness [30, 51]. Testing groups of different ethnicities including East Asians would be useful, since the highest prevalence of myopia occurs in East Asia [52, 53]. Results of a recent systematic review suggested atropine has been more effective in controlling myopia progression in East Asian children compared with Caucasian children [54]. Another shortfall of this study is the relatively small changes in choroidal thickness compared to the measurement accuracy of the OCT. Longer wavelength OCTs and automated segmentation of the choroid should provide more reliable choroidal thickness measurements in the future and will allow better discrimination of small thickness changes. Finally, the use of a single dose of 0.01% atropine (rather than a range of various low concentrations) to assess the short-term ocular changes is another limitation of the study. Recently, Yam et al. [17] have suggested that the higher concentration of low-dose atropine (0.05%) is more effective than 0.01% in controlling SEQ myopic progression and eye growth. However, higher concentrations above 0.02% tend to produce clinically significant pharmacological effects on the iris and ciliary body function. Thus, further work evaluating the effect various concentrations of low-dose atropine on the choroid and eye growth without producing clinically significant side effects is warranted to find the dose that will provide the best balance between benefits and side effects for myopia control.

Low-dose atropine can inhibit the short-term effect of hyperopic blur on choroidal thickness and axial length, similar to higher dose of atropine and homatropine [28, 29]. When administered without blur, low-dose atropine also causes a small magnitude thickening of the choroid in young healthy adult subjects. These findings may improve knowledge about the antimyopia effect of atropine treatments, as well as the possible mechanism underlying eye elongation, and may serve as a base for future studies on the development of new myopia prevention strategies and/or treatment options.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors have no financial or conflicts of interest to disclose.

References

[1] D. Pascolini and S. P. Mariotti, "Global estimates of visual impairment: 2010," *British Journal of Ophthalmology*, vol. 96, no. 5, pp. 614–618, 2012.

[2] J. J. Walline, K. Lindsley, S. S. Vedula, S. A. Cotter, D. O. Mutti, and J. D. Twelker, "Interventions to slow progression of myopia in children," *Cochrane Database of Systematic Reviews*, vol. 12, 2011.

[3] J. Huang, D. Wen, Q. Wang et al., "Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis," *Ophthalmology*, vol. 123, no. 4, pp. 697–708, 2016.

[4] Q. Gong, M. Janowski, M. Luo et al., "Efficacy and adverse effects of atropine in childhood myopia: a meta-analysis," *JAMA Ophthalmology*, vol. 135, no. 6, pp. 624–630, 2017.

[5] P.-C. Wu, M.-N. Chuang, J. Choi et al., "Update in myopia and treatment strategy of atropine use in myopia control," *Eye*, vol. 33, no. 1, pp. 3–13, 2019.

[6] Y.-F. Shih, C.-H. Chen, A.-C. Chou, T.-C. Ho, L. L.-K. Lin, and P.-T. Hung, "Effects of different concentrations of atropine on controlling myopia in myopic children," *Journal of Ocular Pharmacology and Therapeutics*, vol. 15, no. 1, pp. 85–90, 1999.

[7] W.-H. Chua, V. Balakrishnan, Y.-H. Chan et al., "Atropine for the treatment of childhood myopia," *Ophthalmology*, vol. 113, no. 12, pp. 2285–2291, 2006.

[8] A. Chia, W. H. Chua, Y. B. Cheung et al., "Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (atropine for the treatment of myopia 2)," *Ophthalmology*, vol. 119, no. 2, pp. 347–354, 2012.

[9] J. Cooper, N. Eisenberg, E. Schulman, and F. M. Wang, "Maximum atropine dose without clinical signs or symptoms," *Optometry and Vision Science*, vol. 90, no. 12, pp. 1467–1472, 2013.

[10] J. R. Polling, R. G. W. Kok, J. W. L. Tideman, B. Meskat, and C. C. W. Klaver, "Effectiveness study of atropine for progressive myopia in Europeans," *Eye*, vol. 30, no. 7, pp. 998–1004, 2016.

[11] H. Cohn, "Zunahme der myopischen Schüler von Classe zu Classe in 24 deutschen Gymnasien und Realschulen," in *Lehrbuch der Hygiene des Auges*, pp. 232-233, Urban & Schwarzenegger, Wien Leipzig, Austria, 1892.

[12] R. S. Brodstein, D. E. Brodstein, R. J. Olson, S. C. Hunt, and R. R. Williams, "The treatment of myopia with atropine and bifocals: a long-term prospective study," *Ophthalmology*, vol. 91, no. 11, pp. 1373–1378, 1984.

[13] A. C. Chou, Y. F. Shih, T. C. Ho, and L. L.-K. Lin, "The effectiveness of 0.5% atropine in controlling high myopia in children," *Journal of Ocular Pharmacology and Therapeutics*, vol. 13, no. 1, pp. 61–67, 1997.

[14] D. S. P. Fan, D. S. C. Lam, C. K. M. Chan, A. H. Fan, E. Y. Y. Cheung, and S. K. Rao, "Topical atropine in retarding myopic progression and axial length growth in children with moderate to severe myopia: a pilot study," *Japanese Journal of Ophthalmology*, vol. 51, no. 1, pp. 27–33, 2007.

[15] M. A. Bullimore and D. A. Berntsen, "Low-dose atropine for myopia control: considering all the data," *JAMA Ophthalmology*, vol. 136, no. 3, p. 303, 2018.

[16] A. Chia, Q. S. Lu, and D. Tan, "Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops," *Ophthalmology*, vol. 123, no. 2, pp. 391–399, 2016.

[17] J. C. Yam, Y. Jiang, S. M. Tang et al., "Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control," *Ophthalmology*, vol. 126, no. 1, pp. 113–124, 2019.

[18] N. A. McBrien, H. O. Moghaddam, and A. P. Reeder, "Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism," *Investigative Ophthalmology & Visual Science*, vol. 34, no. 1, pp. 205–215, 1993.

[19] G. J. Lind, S. J. Chew, D. Marzani, and J. Wallman, "Muscarinic acetylcholine receptor antagonists inhibit chick scleral chondrocytes," *Investigative Ophthalmology & Visual Science*, vol. 39, no. 12, pp. 2217–2231, 1998.

[20] W. A. Luft, Y. Ming, and W. K. Stell, "Variable effects of previously untested muscarinic receptor antagonists on experimental myopia," *Investigative Opthalmology & Visual Science*, vol. 44, no. 3, pp. 1330–1338, 2003.

[21] D. L. Nickla and J. Wallman, "The multifunctional choroid," *Progress in Retinal and Eye Research*, vol. 29, no. 2, pp. 144–168, 2010.

[22] N. A. McBrien, "Regulation of scleral metabolism in myopia and the role of transforming growth factor-beta," *Experimental Eye Research*, vol. 114, pp. 128–140, 2013.

[23] B. P. Sander, M. J. Collins, and S. A. Read, "The effect of topical adrenergic and anticholinergic agents on the choroidal thickness of young healthy adults," *Experimental Eye Research*, vol. 128, pp. 181–189, 2014.

[24] V. Öner, A. Bulut, and K. Öter, "The effect of topical antimuscarinic agents on subfoveal choroidal thickness in healthy adults," *Eye*, vol. 30, no. 7, pp. 925–928, 2016.

[25] Z. Zhang, Y. Zhou, Z. Xie et al., "The effect of topical atropine on the choroidal thickness of healthy children," *Scientific Reports*, vol. 6, no. 1, 2016.

[26] B. Arumugam and N. A. McBrien, "Muscarinic antagonist control of myopia: evidence for M_4 and M_1 receptor-based pathways in the inhibition of experimentally-induced axial myopia in the tree shrew," *Investigative Opthalmology & Visual Science*, vol. 53, no. 9, pp. 5827–5837, 2012.

[27] D. L. Nickla, L. Lee, and K. Totonelly, "Nitric oxide synthase inhibitors prevent the growth-inhibiting effects of quinpirole," *Optometry and Vision Science*, vol. 90, no. 11, pp. 1167–1175, 2013.

[28] S. T. H. Chiang and J. R. Phillips, "Effect of atropine eye drops on choroidal thinning induced by hyperopic retinal defocus," *Journal of Ophthalmology*, vol. 2018, Article ID 8528315, 6 pages, 2018.

[29] B. P. Sander, M. J. Collins, and S. A. Read, "The interaction between homatropine and optical blur on choroidal thickness," *Ophthalmic and Physiological Optics*, vol. 38, no. 3, pp. 257–265, 2018.

[30] R. Chakraborty, S. A. Read, and M. J. Collins, "Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics," *Investigative Opthalmology & Visual Science*, vol. 52, no. 8, pp. 5121–5129, 2011.

[31] D. Barends, J. Dressman, J. Hubbard et al., *Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability Draft Revision*, WHO, Geneva, Switzerland, 2005.

[32] T. Kaila, J. M. Korte, and K. M. Saari, "Systemic bioavailability of ocularly applied 1% atropine eyedrops," *Acta Ophthalmologica Scandinavica*, vol. 77, no. 2, pp. 193–196, 1999.

[33] P. N. Patil, "Parameters of drug antagonism: re-examination of two modes of functional competitive drug antagonism on intraocular muscles," *Journal of Pharmacy and Pharmacology*, vol. 56, no. 8, pp. 1045–1053, 2004.

[34] D. Alonso-Caneiro, S. A. Read, and M. J. Collins, "Speckle reduction in optical coherence tomography imaging by affine-motion image registration," *Journal of Biomedical Optics*, vol. 16, no. 11, article 116027, 2011.

[35] H. Sasaki, T. Nagano, K. Yamamura, K. Nishida, and J. Nakamura, "Ophthalmic preservatives as absorption promoters for ocular drug delivery," *Journal of Pharmacy and Pharmacology*, vol. 47, no. 9, pp. 703–707, 1995.

[36] B. J. Carr, K. Mihara, R. Ramachandran et al., "Myopia-inhibiting concentrations of muscarinic receptor antagonists block activation of alpha$_{2A}$-adrenoceptors in vitro," *Investigative Opthalmology & Visual Science*, vol. 59, no. 7, pp. 2778–2791, 2018.

[37] N. A. McBrien, B. Arumugam, A. Gentle, A. Chow, and S. Sahebjada, "The M4 muscarinic antagonist MT-3 inhibits

myopia in chick: evidence for site of action," *Ophthalmic and Physiological Optics*, vol. 31, no. 5, pp. 529–539, 2011.

[38] N. A. McBrien, W. K. Stell, and B. Carr, "How does atropine exert its anti-myopia effects?," *Ophthalmic and Physiological Optics*, vol. 33, no. 3, pp. 373–378, 2013.

[39] B. J. Carr and W. K. Stell, "Nitric oxide (NO) mediates the inhibition of form-deprivation myopia by atropine in chicks," *Scientific Reports*, vol. 6, no. 1, p. 9, 2016.

[40] K. Ayajiki, T. Tanaka, T. Okamura, and N. Toda, "Evidence for nitroxidergic innervation in monkey ophthalmic arteries in vivo and in vitro," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 279, no. 4, pp. H2006–H2012, 2000.

[41] N. Toda and M. Nakanishitoda, "Nitric oxide: ocular blood flow, glaucoma, and diabetic retinopathy," *Progress in Retinal and Eye Research*, vol. 26, no. 3, pp. 205–238, 2007.

[42] D. Hébert and J. Y. T. Lam, "Nitroglycerin rebound associated with vascular, rather than platelet, hypersensitivity," *Journal of the American College of Cardiology*, vol. 36, no. 7, pp. 2311–2316, 2000.

[43] T. Münzel, A. Daiber, and A. Mülsch, "Explaining the phenomenon of nitrate tolerance," *Circulation Research*, vol. 97, no. 7, pp. 618–628, 2005.

[44] X. Zhong, J. Ge, E. L. Smith, and W. K. Stell, "Image defocus modulates activity of bipolar and amacrine cells in macaque retina," *Investigative Opthalmology & Visual Science*, vol. 45, no. 7, pp. 2065–2074, 2004.

[45] F. Schaeffel, M. Bartmann, G. Hagel, and E. Zrenner, "Studies on the role of the retinal dopamine/melatonin system in experimental refractive errors in chickens," *Vision Research*, vol. 35, no. 9, pp. 1247–1264, 1995.

[46] N. A. McBrien, L. M. Cornell, and A. Gentle, "Structural and ultrastructural changes to the sclera in a mammalian model of high myopia," *Investigative Ophthalmology & Visual Science*, vol. 42, no. 10, pp. 2179–2187, 2001.

[47] R. A. Stone, J. Liu, R. Sugimoto, C. Capehart, X. Zhu, and K. Pendrak, "GABA, experimental myopia, and ocular growth in chick," *Investigative Opthalmology & Visual Science*, vol. 44, no. 9, pp. 3933–3946, 2003.

[48] H. N. Schwahn, H. Kaymak, and F. Schaeffel, "Effects of atropine on refractive development, dopamine release, and slow retinal potentials in the chick," *Visual Neuroscience*, vol. 17, no. 2, pp. 165–176, 2000.

[49] D. L. Nickla, K. Totonelly, and B. Dhillon, "Dopaminergic agonists that result in ocular growth inhibition also elicit transient increases in choroidal thickness in chicks," *Experimental Eye Research*, vol. 91, no. 5, pp. 715–720, 2010.

[50] S. Khanal, P. R. K. Turnbull, N. Lee, and J. R. Phillips, "The effect of atropine on human global flash mfERG responses to retinal defocus," *Investigative Opthalmology & Visual Science*, vol. 60, no. 1, pp. 218–225, 2019.

[51] E. C. Woodman-Pieterse, S. A. Read, M. J. Collins, and D. Alonso-Caneiro, "Regional changes in choroidal thickness associated with accommodation," *Investigative Opthalmology & Visual Science*, vol. 56, no. 11, pp. 6414–6422, 2015.

[52] Y. C. Chow, B. Dhillon, P. T. Chew, and S. J. Chew, "Refractive errors in Singapore medical students," *Singapore Medical Journal*, vol. 31, no. 5, pp. 472-473, 1990.

[53] S.-M. Saw, "A synopsis of the prevalence rates and environmental risk factors for myopia," *Clinical and Experimental Optometry*, vol. 86, no. 5, pp. 289–294, 2003.

[54] S.-M. Li, S.-S. Wu, M.-T. Kang et al., "Atropine slows myopia progression more in Asian than white children by meta-analysis," *Optometry and Vision Science*, vol. 91, no. 3, pp. 342–350, 2014.

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Research Article

Prevalence and Risk Factors of Myopia in Spain

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Objective. To analyse the prevalence of myopia among a sample of more than 6000 children in Spain as well as to determine the impact of risk factors in its progression. *Methodology*. A total of 6,152 children aged from 5 to 7 were examined. The participants underwent an eye examination that included visual acuity, refraction without cycloplegia, and tests of accommodative and binocular function. In addition, a questionnaire regarding their lifestyle, family history, and geographical data was carried out. Finally, data were analysed using the SPSS version 25 program. *Results*. The prevalence of myopia in the sample of children studied has increased from 17% in 2016 to 20% in 2017. Likewise, the number of children with high myopia has also increased, from 1.7% in 2016 to 3.6% in 2017. 43.3% of the participants spent more than 3 hours a day doing near activities, and 48.9% of this group spent more than 50% of this time using electronic devices. In addition, only 9.7% spent more than 2.5 hours outdoors each day. *Conclusion*. Myopia prevalence appears to be increasing in Spain. Lifestyle factors appear to be increasing the risk of myopia.

1. Introduction

Uncorrected refractive errors are one of the main public health problems throughout the world, regardless of age, sex, and race [1]. As a result, it is expected that by 2060, there will have been a 26% increase in the number of children with visual disability, which will have a negative effect on their educational and psychosocial development [2, 3].

In recent years, there has been a significant increase in the number of cases of myopia globally, and it has become an epidemiological problem [4]. Between 1993 and 2016, the prevalence rate increased from 10.4% to 34.2%, respectively [5]. Short-term estimates indicate that in 2050, 49.8% of all people will be myopic [6].

The prevalence of myopia varies on a geographical basis; it is more prevalent in Asia (70–90%) [7], whereas the figures appear to be lower than in Europe, Australia, and USA [8]. Regarding this, recent studies have determined a higher myopia rate among the children examined in Singapore (62%) and China (49.7%) in comparison with those examined in the USA (20%) and Australia (11.9%) [6, 9]. Additionally, high myopia could be associated with multiple pathologies including retinal detachment, macular degeneration, cataracts, or glaucoma [10]. However, there are no current data about the myopia prevalence in Spain since 2000, when myopia incidence in children from 3 to 8 years old was 2.5% [11].

Nowadays, there is enough evidence on the influence of near activities (reading, writing, watching TV, etc.), in the development of myopia. The hypermetropic peripheral blur in the retina leads to an increase in the axial length of the eye, therefore accelerating its progression [12].

Genetics also plays an important role, so the risk of suffering myopia increases depending on the number of parents with myopia [13].

Recent studies suggest that time outdoors has a protective effect on the appearance of myopia, but it does not stop its progression [14].

An important point when we look at prevalence figures is to know the procedure to measure myopia. The recent report published by the IMI group of experts—*Defining and Classifying Myopia Report*—defines myopia by refraction "when ocular accommodation is relaxed. These definitions avoid the requirement for objective refraction so as to be

independent of technique, but by making reference to relaxation of accommodation are compatible with both cycloplegic and standard clinical subjective techniques" [15]. Although cycloplegic refraction is the gold standard, limitations in the use of some drugs in some countries make important having other alternatives to measure myopia, like objective refraction by noncycloplegic retinoscopy.

If we assess the economic impact which is associated with myopia, a study carried out in 2013 estimated a total cost in the whole population of Singapore of 755 million US dollars per year [16].

Therefore, due to the lack of studies of myopia prevalence in Spain and the need to know which associate factors can help to prevent this epidemiologic problem, the authors carried out this study. We analysed myopia prevalence among children from 5 to 7 years old and the influence of lifestyle and genetics in the figures.

2. Methods

2.1. Data Collection and Inclusion Criteria. A cross-sectional study to estimate myopia prevalence in a sample of children in Spain has been carried out.

Data were collected by convenience sampling from the 2016 and 2017 "School campaign in favor of children's visual health" that is taken every year in Spain. The school campaign is targeted to all schools, so all participants between 5 and 7 years of age that participated were included in the study. The school campaign supplies a free spectacle to those who need them, funded by the Fundación Alain Afflelou.

2.2. Examination. Parents of all of the children that participate in this research signed the informed consent form and underwent an optometric test, which consisted of a questionnaire and an assessment of the refractive and binocular conditions:

(i) Questionnaire: it was divided into several sections and included questions about their *demographic data* (city of residence, age, sex, and nationality), their *lifestyle and family ocular history* (extracurricular activities and number of hours/weeks spent doing these activities, time spent using electronic devices, and genetics), and *anamnesis* (symptoms, main complaint, diagnosis or previous ocular treatment, medication and systemic diseases, and date of last checkup).

(ii) Optometric test: the standard procedure was as follows:

(1) Best-corrected and uncorrected visual acuity.
(2) Objective refraction: non cycloplegic retinoscopy. The authors have estimated differences of $\pm 0.5D$ in the SE when comparing noncycloplegic retinoscopy versus cycloplegic refraction [17].
(3) Subjective refraction.
(4) Binocular vision and accommodative tests: cover-uncover, alternating cover test, ocular motility, Hirschberg test, Worth test, near point of convergence, accommodation range, stereopsis, and colour vision.
(5) Finally, the anterior segment was checked (eyelid, eyelashes, palpebral margin, corneal, conjunctive, and crystalline) using a slit lamp.

2.3. Variable Description. In order to determine the refractive status of the children, and in accordance with other research, the criteria for the spherical equivalent (SE) were as follows: hyperopia (S.E. > +0.50), myopia (S.E. < −0.50), or emmetropia (−0.50 < S.E. > +0.50) [2, 15]. SE was defined as *sphere* + *cylinder*/2.

Within the myopic group, a subdivision of myopia was carried out, based on the *American Academy of Optometry*'s classifications [18] as low (−0.50 < S.E. > −3), medium (−3 < S.E. > −6), and high (S.E. > −6).

To calculate the number of hours that children spend in near activities, using electronic devices and outdoors, and to get the genetic risks, several variables were taken based on the *Clinical Myopia Profile* [19]. Therefore, according to this study, we estimated the risk of suffering myopia in high, medium, or low, taking into consideration the criteria shown in Table 1.

2.4. Statistical Analysis. The data analysis was carried out using the SPSS 25.0 program (SPSS Inc., Chicago, Illinois). To establish the parametric distribution of the variables, the Kolmogorov–Smirnov test was used, resulting in a nonparametric distribution. Therefore, the variables were analysed using the Kruskal–Wallis test. The prevalence was calculated with 95% confidence interval. To assess the statistical significance, we considered a cutoff point $p \geq 0.05$.

3. Results

The checkouts were carried out in September 2016 and September 2017. A total of 6152 children were examined (4159 in 2016 and 1993 in 2017). A total of 711 children were excluded: 210 participants did not fulfill the inclusion criteria (younger than 5 or older than 7 years old) and 501 forms were incomplete as the optometrist didn't follow method properly. The average age was 6.17 ± 0.77 years (2016: 6.16 ± 0.77 years old; 2017: 6.19 ± 0.78 years old). In terms of gender, 55% were male and 45% were female (2016: 56.3% male; 43.7% female; 2017: 52.5% male; 47.5% female). Table 2 shows the percentage of participants from the different autonomous communities across Spain by age and sex.

Figures of myopia prevalence in children aged between 5 and 7 years increased from 16.8% in 2016 to 19.1% in 2017 (OR: 1.19; IC: 1.16–1.22; $p \leq 0.001$). Likewise, the percentage of cases of myopia in female increased by 1.6% (16.5% in 2016, $p = 0.127$; 18.1% in 2017, $p = 0.294$; average: $17.25 \pm 1.2\%$) and 3% in male (17% in 2016, $p = 0.216$; 20% in 2017, $p = 1$; average = $18.55 \pm 2.05\%$). Therefore, no statistically significant differences were found between the risk of suffering from myopia and gender ($p = 0.134$). With regards to age, Figure 1

Table 1: Factors that affect the risk of suffering from myopia.

	High risk	Medium risk	Low risk
Time spent outdoors (with sun light)	Short time (between 0 and 1.6 hours)	Moderate time (between 1.6 and 2.7 hours)	Long time (>2.7 hours)
Time spent doing near activities (excluding school time)	Long time (>3 hours)	Moderate time (between 2 and 3 hours)	Short time (between 0 and 2 hours)
Family history	Both parents suffer from myopia	One of the parents suffer from myopia	Any of parents suffer from myopia

Source: [19].

Table 2: Participants from the different autonomous community by age and gender.

	Male				Female			
	5 years *N* (%)	6 years *N* (%)	7 years *N* (%)	Total *N* (%)	5 years *N* (%)	6 years *N* (%)	7 AÑOS *N* (%)	Total *N* (%)
Basque country	32 (4.5%)	59 (5.4%)	50 (4.2%)	141 (4.7%)	33 (6.2%)	50 (5.4%)	38 (3.8%)	121 (4.9%)
Andalusia	92 (12.9%)	151 (13.9%)	189 (15.9%)	432 (14.5%)	68 (12.8%)	104 (11.2%)	119 (12%)	291 (11.9%)
Valencian Community	36 (5.1%)	68 (6.2%)	91 (7.7%)	195 (6.5%)	23 (4.3%)	6 (6.8%)	59 (6%)	145 (5.9%)
Asturias	0 (0%)	0 (0%)	1 (0.1%)	1 (0%)	—	—	—	—
Catalonia	65 (9.1%)	116 (10.7%)	116 (9.8%)	297 (9.9%)	62 (11.6%)	106 (11.4%)	110 (11.1%)	278 (11.3%)
Castile and Leon	113 (15.9%)	203 (18.6%)	202 (17%)	518 (17.3%)	86 (16.1%)	171 (18.4%)	168 (17%)	425 (17.3%)
Galicia	43 (6%)	52 (4.8%)	58 (4.9%)	153 (5.1%)	30 (5.6%)	37 (4%)	58 (5.9%)	125 (5.1%)
Community of Madrid	164 (23%)	218 (19.9%)	219 (18.5%)	601 (20.1%)	104 (19.5%)	167 (18%)	163 (16.4%)	434 (17.7%)
Aragon	53 (7.4%)	61 (5.6%)	79 (6.7%)	193 (6.5%)	36 (6.8%)	63 (6.8%)	67 (6.8%)	166 (6.8%)
Cantabria	18 (2.5%)	28 (2.6%)	23 (1.9%)	69 (2.3%)	11 (2.1%)	21 (2.3%)	18 (1.8%)	50 (2%)
Navarra	23 (3.2%)	28 (2.6%)	28 (2.4%)	79 (2.6%)	14 (2.6%)	28 (3%)	37 (3.7%)	79 (3.2%)
Extremadura	32 (4.5%)	46 (4.2%)	46 (3.9%)	124 (4.1%)	32 (6%)	56 (6%)	65 (6.5%)	153 (6.2%)
Murcia	0 (0%)	2 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.2%)	0 (0%)	2 (0.2%)	3 (0.1%)
Castile-la Mancha	24 (3.4%)	42 (3.8%)	55 (4.6%)	121 (4%)	17 (3.2%)	39 (4.2%)	52 (5.3%)	108 (4.4%)
Balearic Islands	9 (1.3%)	7 (0.6%)	7 (0.6%)	23 (0.8%)	7 (1.3%)	16 (1.7%)	18 (1.8%)	41 (1.7%)
Melilla	2 (0.3%)	5 (0.5%)	0 (0%)	7 (0.2%)	3 (0.6%)	2 (0.2%)	0 (0%)	5 (0.2%)
La Rioja	6 (0.8%)	6 (0.5%)	21 (1.8%)	33 (1.1%)	6 (1.1%)	4 (0.4%)	17 (1.7%)	27 (1.1%)
Total	712 (100%)	1093 (100%)	1186 (100%)	2991 (100%)	533 (100%)	926 (100%)	990 (100%)	2450 (100%)

shows how the prevalence of myopia increases progressively with age ($p \leq 0.001$).

Table 3 shows myopia prevalence by gender and place in 2016 and 2017.

Out of all of the participants with myopia, in 2016, 90.1% had low myopia, 8.2% had medium myopia, and 1.7% had high myopia. On the other hand, in 2017, the percentage of children with low myopia was 89.1%, with a slight increase in the moderate myopia rates (9%) and the high myopia rates (1.9%). Likewise, there was an increase in the number of individuals who used glasses, from 70.6% in 2016 to 81.5% in 2017. In relation to this and with regards to the prevalence of myopia in the different autonomous communities, statistically significant differences have been found ($p \leq 0.001$).

The spheric myopic equivalence values according to age, sex, and autonomous community in 2016 and 2017 can be observed in Table 4.

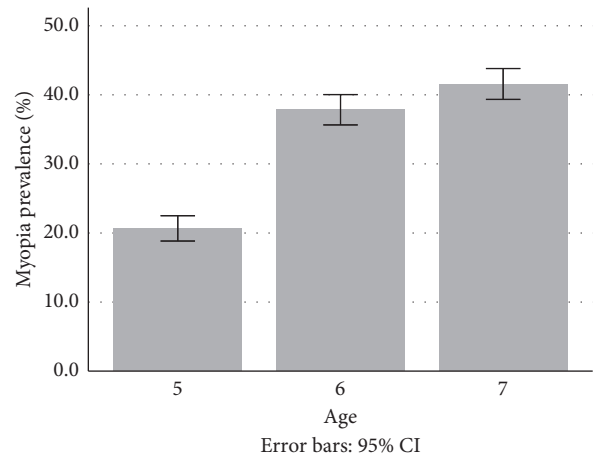

Figure 1: Myopia prevalence according to age.

3.1. Risk Factors. To assess the number of hours in which participants perform near activities, three groups were established: low (between 0 and 2 hours), moderate (between 2 and 3 hours), and high (more than 3 hours). To determine the time spent using electronic devices, three subgroups were established, according to whether they spend <25%, between 25% and 50%, or more than 50% of the time in near activities.

In both 2016 and 2017, 45.5% and 39.7% of the children, respectively, spent a lot of time carrying out near activities. However, 36.1% (35.9% in 2016 and 36.3% in 2017) spent few hours and 21.2% (19.3% in 2016 and 24.1% in 2017) spent a moderate amount of time.

Table 3: Myopia prevalence by gender and place in 2016 and 2017.

	Gender/autonomous community	2016				2017			
		5 years (%)	6 years (%)	7 years (%)	Total (%)	5 years (%)	6 years (%)	7 years (%)	Total (%)
Medium age	Female	46.4	42.1	41.7	42.7	46.5	47.8	42.2	44.8
	Male	53.4	57.9	58.3	57.3	53.5	52.2	57.8	55.2
6.09 ± 0.76 years	Basque country	4.8	5.5	4.6	5	—	8.2	4	4.7
6.29 ± 0.79 years	Andalusia	16.8	20.5	18.7	19	6.3	6.5	13.3	9.8
6.27 ± 0.74 years	Valencian community	8.2	6	6.1	6.4	3.9	4.5	5.7	5
6.17 ± 0.76 years	Catalonia	12	7.6	9.4	9.3	17.3	14.7	8.2	12
6.18 ± 0.76 years	Castile and Leon	14.9	20.5	18.5	18.6	16.5	19.2	21.8	20
6.15 ± 0.81 years	Galicia	2.9	4.3	2	2.9	3.1	5.3	5.9	5.2
6.11 ± 0.79 years	Community of Madrid	17.8	17.6	18.4	18	31.5	23.7	23.2	24.8
6.16 ± 0.79 years	Aragon	3.4	2.1	2.9	2.7	9.4	9	10.8	9.9
6.10 ± 0.76 years	Cantabria	2.9	0.2	1.2	1.2	3.1	1.2	—	1
6.18 ± 0.86 years	Navarra	1	0.5	0.7	0.7	6.3	3.3	4.2	4.3
6.17 ± 0.78 years	Extremadura	3.8	6.2	5.5	5.5	1.6	2.9	1.4	1.9
6.29 ± 0.75 years	Castile-la Mancha	7.2	6.9	7	7	0.8	1.6	1.4	1.4

Table 4: Myopic spherical equivalence according to age, sex, and autonomous community.

		2016			2017		
		5 years	6 years	7 years	5 years	6 years	7 years
Sex	Female	−1.55 ± 0.97	−1.55 ± 1.12	−1.66 ± 1.21	−1.55 ± 0.99	−1.27 ± 0.80	−1.55 ± 1.09
	Male	−1.55 ± 1.65	−1.59 ± 1.34	−1.66 ± 1.58	−2.51 ± 3.27	−1.68 ± 1.84	−1.73 ± 1.41
Autonomous community	Basque Country	−1.38 ± 1.11	−1.23 ± 0.81	−1.38 ± 0.95	—	−1.36 ± 0.48	−1.84 ± 2.20
	Andalusia	−1.86 ± 2.11	−1.82 ± 1.63	−1.62 ± 1.23	−1.51 ± 0.57	−1.32 ± 0.81	−1.70 ± 1.23
	Valencian Community	−1.32 ± 0.89	−1.78 ± 1.97	−1.25 ± 0.78	−3.65 ± 1.43	−1.48 ± 0.92	−1.35 ± 1.01
	Catalonia	−0.99 ± 0.82	−1.38 ± 0.98	−1.47 ± 1.06	−2.16 ± 2.68	−2.30 ± 2.83	−1.34 ± 9.02
	Castile and Leon	−1.20 ± 0.52	−1.37 ± 0.52	−1.55 ± 1.22	−1.34 ± 0.91	−1.12 ± 0.76	−1.77 ± 1.16
	Galicia	−1.10 ± 0.39	−1.67 ± 1.43	−1.89 ± 0.58	0.35 ± 3.02	−1.55 ± 0.90	−1.70 ± 2.02
	Community of Madrid	−1.05 ± 0.64	−1.47 ± 1.13	−2.14 ± 2.29	−2.26 ± 3.23	−1.39 ± 1.44	−1.51 ± 1.28
	Aragon	−0.91 ± 0.39	−2.80 ± 1.30	−1.57 ± 0.68	−3.20 ± 2.75	−1.37 ± 0.77	−2.08 ± 1.28
	Cantabria	−1.46 ± 0.67	−0.50 ± —	−2.18 ± 2.45	−3.19 ± 1.99	−1.50 ± 0.90	—
	Navarra	−7.75 ± 0.00	−0.50 ± 0.00	−1.28 ± 0.47	−1.62 ± 1.66	−1.22 ± 0.61	−1.42 ± 0.62
	Extremadura	−1.12 ± 0.63	−1.06 ± 0.80	−1.39 ± 1.03	−1.94 ± 0.88	−1.73 ± 0.77	−1.15 ± 0.36
	Castile-la Mancha	−1.41 ± 0.79	−1.41 ± 0.91	−1.46 ± 1.14	−2.00 ± —	−1.56 ± 0.33	−2.15 ± 1.23

With regards to the use of electronic devices, 48.3% of the children (57.9% in 2016 and 33.1% in 2017) used them >50% of the time in near activities. Only 26.2% (21.9% in 2016 and 32.9% in 2017) used them <25% of the time and 25.6% (20.2% in 2016 and 34% in 2017) between 25% and 50%.

Figure 2 shows that the more time spent performing near activities and using a phone, tablet, or videogames, the higher the prevalence of myopia ($p < 0.05$).

On the other hand, a moderate correlation was found between the spherical equivalent value with regards to the time spent in near activities and using electronic devices ($p < 0.05$).

With regards to the predisposition, as shown in Figure 3, a significant association has been found between the presence of myopia in one or both parents and the refractive condition of the children ($p = 0.013$). Therefore, the risk of having myopia increases from 9.7% if neither parent is myopic to 28.3%, if both are, respectively.

3.2. Prevention Factors. Each child was allocated to a group depending on the hours he spent outdoors each day: low (between 0 and 1.6 hours), moderate (between 1.6 and 2.7 hours), and high (>2.7 hours). 80.7% of the participants spent short time outdoors, while only a 9.9% of the children spent a moderate amount of time, and 9.4% of children spent long time outdoors, respectively.

However, in this study, we did not obtain statistically significant differences between the prevalence of myopia and the time they spend outdoors ($p = 0.961$).

4. Discussion

According to the WHO, myopia is considered as one of the main public health problems worldwide [20]. Our study included a group of children between 5 and 7 years of age, of which 18% were myopic in 2016 and 2017. Therefore, it has been concluded that figures of myopia prevalence in our sample of children in Spain are similar to that of Australia (14.02%) [21], Central Asia (17%), Andean Latin America (20.5%), and Tropical Latin America (14.5%) [6]. Contrasting, figures of prevalence are higher in Pakistan (36.5%) [22] and in Saudi Arabia (53.71%) [23].

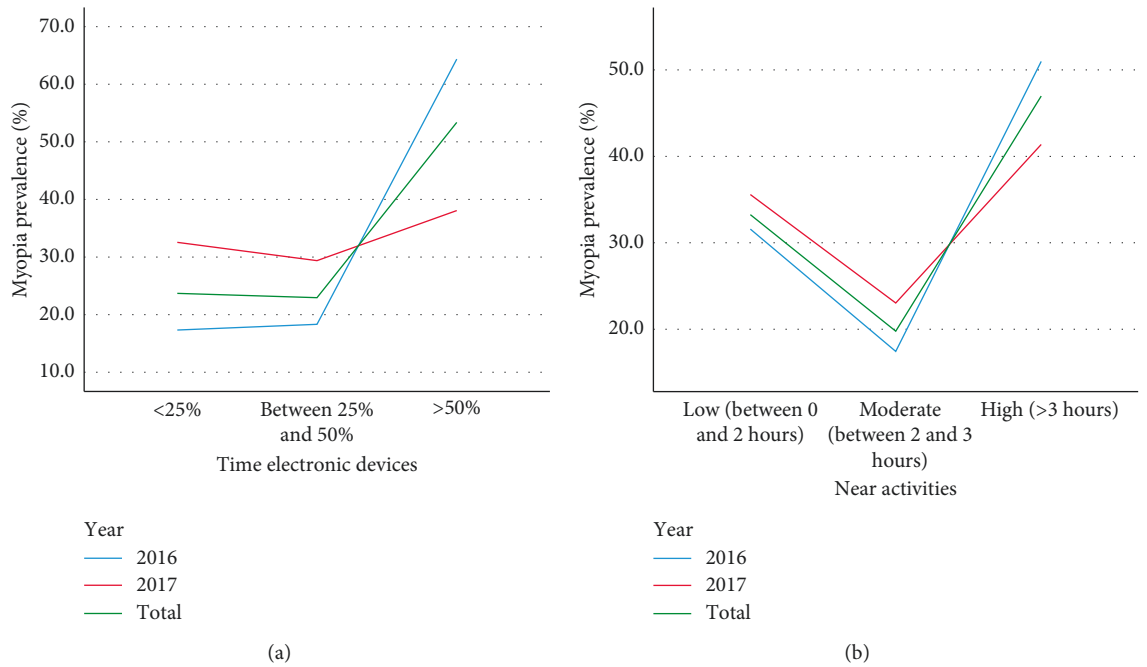

Figure 2: Prevalence of myopia according to (a) the use of electronic devices and (b) the time spent performing activities in near vision.

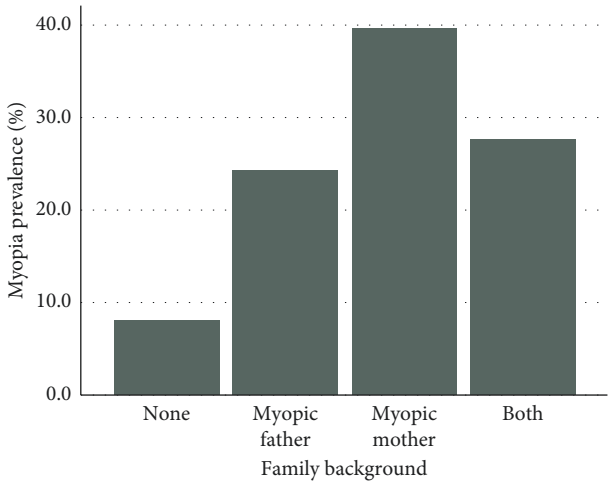

Figure 3: Percentage of refractive condition of children in relation with their family history.

Regarding gender, we did not find any significant differences in the prevalence of myopia. These results agree with those obtained by Uchenna et al. [24] and COMET [25], showing that there is no connection between sex and myopia and that figures can vary along time. However, there are studies, like the ones carried out in China [26, 27] and Saudi Arabia [28], that show higher figures of myopia prevalence in female than in male.

According to other studies, the prevalence of myopia increases with age. Thus, in 2016, Ma et al. [29] indicated an increase of 50.4% in children from 3 to 10 years old. When comparing the SE value of our research with the one carried out by Pi et al. [30] in 2010, a tendency of myopisation is observed, going from +1.25*D* in 2010 versus +0.78*D*, found in our study, in 2017. Likewise, similar studies show an increase in S.E. value of −0.27*D* per year, in 50% of the children [31].

With regards to lifestyle, the latest reviews indicate that children spend on average 4.8 ± 1.6 hours each day doing near activities. Likewise, it was shown that male spend more time doing near activities than female (4.9 ± 1.7 vs 4.6 ± 1.5) [32]. In 2006, Khader et al., proved that children with myopia spend around 0.95 hours/day in front of a computer, as opposed to the 0.69 hours/day spent by nonmyopic children [33]. These results agree with the ones obtained in our study in Spain. On the other hand, Lu et al. [34], Rose et al. [35], and Lin et al. [36] have pointed out that near activities are not a risk factor in the development of myopia.

With regards to the time spent outdoors, we found that most children spend between 0 and 1.6 hours outdoors. Similar results were obtained in Sydney in 2008, where children spend around 2.3 hours/day outdoors [37]. This difference could be due to the greater use of electronic devices nowadays and the geographical location.

There are a lot of studies that look for relations between spending outdoors time and myopia. Jin et al. [38] found the less figures of myopia, by means of pupil constriction and the release of dopamine, the greater the exposure to sunlight. However, we did not find a connection between the time spent outdoors and prevalence of myopia. This leads us to believe that in Spain, no association has been found due to the lack of children in our sample who spend more than 2.5 hours per day exposed to sunlight; therefore, it would be interesting to confirm these results through future research.

With regards to the limitations of our study, it is important to highlight the low number of participants aged 5 years (23%), in comparison with 37% of 6-year-old children and 40% of 7-year-old children, respectively. It is also

important to say that centres from Balearic Islands, Melilla, and La Rioja did not participate in the 2017 collection, so comparison between 2016 and 2017 has not been included for these autonomous communities in Tables 3 and 4. In addition, only noncycloplegic refraction has been taken in this study, so it must be taken into consideration when compared to other studies. Similar studies have found that the difference between noncycloplegic and cycloplegic refraction is 0.95*D* in young children [39]. Finally, it should also be noted that the campaign offered a free spectacle to children that needed, so it could suppose a bias in the study.

5. Conclusion

Myopia prevalence appears to be increasing in Spain. Lifestyle factors appear to be increasing the risk of myopia.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

[1] D. Pascolini and S. P. Mariotti, "Global estimates of visual impairment: 2010," *British Journal of Ophthalmology*, vol. 96, no. 5, pp. 614–618, 2012.

[2] R. Varma, K. Tarczy-Hornoch, and X. Jiang, "Visual impairment in preschool children in the United States," *JAMA Ophthalmology*, vol. 135, no. 6, pp. 610–616, 2017.

[3] R. R. A. Bourne, B. P. Dineen, D. M. N. Huq, S. M. Ali, and G. J. Johnson, "Correction of refractive error in the adult population of Bangladesh: meeting the unmet need," *Investigative Opthalmology & Visual Science*, vol. 45, no. 2, pp. 410–417, 2004.

[4] P. Mitchell, F. Hourihan, J. Sandbach, and J. J. Wang, "The relationship between glaucoma and myopia: the blue mountains eye study," *Ophthalmology*, vol. 106, no. 10, pp. 2010–2015, 1999.

[5] H. Hashemi, A. Fotouhi, A. Yekta, R. Pakzad, H. Ostadimoghaddam, and M. Khabazkhoob, "Global and regional estimates of prevalence of refractive errors: systematic review and meta-analysis," *Journal of Current Ophthalmology*, vol. 30, no. 1, pp. 3–22, 2018.

[6] B. A. Holden, T. R. Fricke, D. A. Wilson et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050," *Ophthalmology*, vol. 123, no. 5, pp. 1036–1042, 2016.

[7] D. R. Fredrick, "Myopia," *BMJ*, vol. 324, no. 7347, pp. 1195–1199, 2002.

[8] Group TEDPR, "The prevalence of refractive errors among adults in the United States, Western Europe, and Australia," *Archives of Ophthalmology*, vol. 122, no. 4, pp. 495–505, 2004.

[9] P. J. Foster and Y. Jiang, "Epidemiology of myopia," *Eye*, vol. 28, no. 2, pp. 202–208, 2014.

[10] S.-M. Saw, G. Gazzard, E. C. Shih-Yen, and W.-H. Chua, "Myopia and associated pathological complications," *Ophthalmic and Physiological Optics*, vol. 25, no. 5, pp. 381–391, 2005.

[11] R. M. Mico and T. F. Blasco, "Distribution of refractive errors in Spain," *Documenta Ophtalmologica*, vol. 101, no. 1, pp. 25–23, 2000.

[12] K. Rajendran, M. Haneef, K. Chandrabhanu, K. Moorthy, M. Muhammed, and R. T. Pillai, "A prevalence study on myopia among school going children in a rural area of south India," *Indian Journal of Clinical Practice*, vol. 25, no. 4, pp. 374–380, 2014.

[13] M. J. Smith and J. J. Walline, "Controlling myopia progression in children and adolescents," *Adolescent Health, Medicine and Therapeutics*, vol. 6, pp. 133–140, 2015.

[14] A. N. French, R. S. Ashby, I. G. Morgan, and K. A. Rose, "Time outdoors and the prevention of myopia," *Experimental Eye Research*, vol. 114, pp. 58–68, 2013.

[15] K. L. Gifford, K. Richdale, P. Kang et al., "IMI–clinical management guidelines report," *Investigative Ophthalmology & Visual Science*, vol. 60, no. 3, pp. 184–203, 2019.

[16] S. M. Saw, Y. Zheng, J. Chay et al., "The economic cost of myopia in Singapore," *Investigative Ophthalmology & Visual Science*, vol. 54, no. 13, p. 5711, 2013.

[17] P. Funarunart, S. Tengtrisorn, P. Sangsupawanich et al., "Accuracy of noncycloplegic refraction in primary school children in Southern Thailand," *Journal of the Medical Association of Thailand*, vol. 92, no. 6, pp. 806–812, 2009.

[18] American Optometric Association, *Care of the Patient with Myopia*, American Optometric Association, St. Louis, MO, USA, 2018, http://www.myopiaprofile.com/.

[19] Gifford and Myopia Profile, *Myopia Profile: An Information Resource for Optometrists*, 2018, https://www.aoa.org/.

[20] World Health Organization, *The Impact of Myopia and High Myopia*, World Health Organization, Geneva, Switzerland, 2018, https://www.who.int/.

[21] B. M. Junghans and S. G. Crewther, "Little evidence for an epidemic of myopia in Australian primary school children over the last 30 years," *BMC Ophthalmology*, vol. 5, no. 1, 2005.

[22] A. Das, H. Dutta, G. Bhaduri, A. De Sarkar, K. Sarkar, and M. Bannerjee, "A study on refractive errors among school children in Kolkata," *Journal of the Indian Medical Association*, vol. 105, no. 4, pp. 169–172, 2017.

[23] M. A. AI Rowaily and B. M. Alanizi, "Prevalence of uncorrected refractive errors among adolescents at king Abdul-Aziz Medical City, Riyadh, Saudi Arabia," *Journal of Clinical & Experimental Ophthalmology*, vol. 1, no. 3, 2010.

[24] U. C. Otawa, A. J. Munsamy, and S. O. Wajuihian, "Prevalence and risk factors for myopia among school children in Aba, Nigeria," *African Vision and Eye Health*, vol. 76, no. 1, 2017.

[25] COMET Group, "Myopia stabilization and associated factors among participants in the correction of myopia evaluation trial (COMET)," *Investigative Ophthalmology & Visual Science*, vol. 54, no. 13, pp. 7871–7884, 2013.

[26] C. Xu, C. Pan, M. Bi et al., "Prevalence and risk factors for myopia in older adult East Chinese population," *BMC Ophthalmology*, vol. 17, no. 1, p. 191, 2017.

[27] M. Chen, A. Wu, L. Zhang et al., "The increasing prevalence of myopia and high myopia among high school students in Fenghua city, eastern China: a 15-year population-based survey," *BMC Ophtalmology*, vol. 18, no. 1, p. 159, 2018.

[28] H. G. Ahmed, R. M. Algorinees, N. T. Alqatani et al., "Prevalence of myopia and its related risk factors among medical students in Saudi Arabia," *Advances in Ophthalmology & Visual System*, vol. 6, no. 1, 2017.

[29] Y. Ma, X. Qu, X. Zhu et al., "Age-specific prevalence of visual impairment and refractive error in children aged 3–10 years in Shanghai, China," *Investigative Opthalmology & Visual Science*, vol. 57, no. 14, pp. 6188–6191, 2016.

[30] L. H. Pi, L. Chen, Q. Liu et al., "Refractive status and prevalence of refractive errors in suburban school-age children," *International Journal of Medical Sciences*, vol. 7, no. 6, pp. 324–353, 2010.

[31] R. Saxena, P. Vashist, R. Tandon et al., "Incidence and progression of myopia and associated factors in urban school children in Delhi: the North India myopia study (NIM study)," *PLoS One*, vol. 12, no. 12, Article ID e0189774, 2017.

[32] L. Zhong, T. Y. Gao, B. Vasudevan et al., "Near work, outdoor activity, and myopia in children in rural China: the Handan offspring myopia study," *BMC Ophtalmology*, vol. 17, no. 1, p. 203, 2017.

[33] Y. S. Khader, W. Q. Batayha, S. M. Abdul-Aziz, and M. I. Al-Shiekh-Khalil, "Prevalence and risk indicators of myopia among school children in Amman, Jordan," *Eastern Mediterranean Health Journal*, vol. 12, no. 3-4, pp. 434–439, 2006.

[34] B. Lu, N. Congdon, X. Liu et al., "Associations between near work, outdoor activity, and myopia among adolescent students in rural China," *Archives of Ophthalmology*, vol. 127, no. 6, pp. 769–775, 2009.

[35] K. A. Rose, I. G. Morgan, W. Smith, G. Burlutsky, P. Mitchell, and S. Saw, "Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney," *Archives of Ophthalmology*, vol. 126, no. 4, pp. 527–530, 2008.

[36] Z. Lin, B. Vasudevan, V. Jhanji et al., "Near work, outdoor activity, and their association with refractive error," *Optometry and Vision Science*, vol. 91, no. 4, pp. 376–382, 2014.

[37] K. A. Rose, I. G. Morgan, J. Ip et al., "Outdoor activity reduces the prevalence of myopia in children," *Ophthalmology*, vol. 115, no. 8, pp. 1279–1285, 2008.

[38] J. X. Jin, W. J. Hua, X. Jiang et al., "Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun eye care study," *BMC Ophtalmology*, vol. 15, no. 1, p. 73, 2015.

[39] P. Sankaridurg, H. Xiangui, T. Naduvilath et al., "Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children," *Acta Ophtalmologica*, vol. 95, no. 7, pp. e633–e640, 2017.

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Research Article

Risk Factors for Incident Myopia among Teenaged Students of the Experimental Class of the Air Force in China

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Background. In recent decades, the prevalence rate of myopia has markedly increased, especially among teenagers. Our purpose was to determine the incidence of myopia and identify the related risk factors among schoolchildren in the experimental classes of the Air Force in China. *Methods*. In May 2015, this 3-year prospective cohort study enrolled 522 boys (age, 14–16 years) attending grade 10 in 16 high schools in 15 cities in China. Cycloplegic refraction was examined using retinoscopy in both eyes at the baseline and follow-up (3 years). A detailed questionnaire was completed by the students at the 3-year follow-up and included questions on parental myopia and on the total time spent doing near work and outdoor activities each week. *Results*. The incidence of myopia at the 3-year follow-up was 27.01% (141/522, 95% confidence interval (CI): 23.38% to 30.98%). The refractive change was −0.46 D (95% CI: −0.49 to −0.42 D). More hyperopic or less myopic baseline refraction, outdoor activity time per week ≥14 h (odds ratio (OR) = 0.464, 95% CI: 0.227 to 0.950), and reading/writing distance ≥ 30 cm (OR = 0.505, 95% CI: 0.270 to 0.944) were significant protective factors against incident myopia. Near-work time ≥28 h per week was a significant risk factor (OR = 2.579, 95% CI: 1.314 to 5.061). Parental myopia, age at the start of primary school, continuous reading/writing for ≥1 h, sleep duration per week <49 h, and one or more dietary biases were not significant risk factors ($P > 0.05$). *Conclusion*. A more hyperopic baseline refraction, more time spent outdoors, and longer writing/reading distance were protected against myopia onset, while more near-work time was a risk factor.

1. Background

Myopia is an important and widespread public health problem [1]. Indeed, the worldwide prevalence rate of myopia (defined as a spherical equivalent refraction (SER) of −0.5 D or less) is around 23% and that of high myopia is nearly 3% [2]. It has been estimated that by 2050, myopia will affect nearly half (49.8%) of the world's population, and high myopia will be found in almost a tenth (9.8%) of all people [2]. High myopia can result in cataract, glaucoma, macular degeneration, and even retinal detachment and choroidal neovascularisation, which could lead to vision loss. Myopia is highly prevalent in East Asia, particularly Japan, Singapore, China, and South Korea [3]. In China, prevalence rates of 30%–60% have been reported among children aged 15–18 years [4–7] and 80.7% among high school-aged children [4]. Myopia is an important factor that impacts the health of schoolchildren. Furthermore, in China, myopia limits the career choices of teenagers graduating from high school; for example, teenagers with myopia may not be able to become pilots or join the armed forces.

The potential causes of myopia include both hereditary and environmental factors [8]. Saw et al. [9] showed that compared to children of nonmyopic parents, children of myopic parents have a higher degree of myopia (average, 0.39 D for those with one myopic parent and 0.74 D for those with two myopic parents). Genetic factors are an

important cause of myopia, especially early-onset high myopia. In contrast, school myopia has a multifactorial etiology, with environmental factors playing a major role, such as reading habits, outdoor activities, and near work [10–14]. Studies [10, 15–17] suggest that increased outdoor activity time, longer near-work distance, and decreased near-work time could reduce the incidence of myopia. However, most of these studies have focused on children in junior high school or primary school. As many students are already myopic before the age of 14, prospective studies on myopia onset in students attending senior high school are less common.

The Chinese Ministry of Education and Air Force conducts an experimental class that enrolls children aged 14–16 years who have graduated from junior high schools from all over the country, provided they pass physical examinations and academic tests. There are 16 experimental classes of the Air Force in 15 cities of China. The aim of the present study was to determine the incidence of myopia and track the progression of myopia among grade-10 to grade-12 students of the experimental class over a 3-year period in order to identify the risk factors for myopia, understand the underlying aetiological mechanisms, and formulate potential management strategies.

2. Methods

2.1. Patients and Consent. This was a 3-year-long prospective longitudinal study. All participants were recruited from the experimental classes of the Air Force. This study was approved by the ethics committee of the General Hospital of the Air Force. The study protocol complies with the tenets of the Declaration of Helsinki. We explained the objectives and methods of the study to the students and their parents and obtained both oral and written consent from both. The participants were enrolled in the study in May 2015 and were followed up for 3 years until May 2018.

The inclusion criteria were as follows: (1) uncorrected visual acuity ≥1.0 in both eyes and (2) SER between −0.25 D and +2.00 D in both eyes. The SER was calculated as the spherical power plus half of the cylindrical power. The exclusion criteria were a history of ocular surgery, ocular trauma, or an ocular disease that affected the vision.

2.2. Ocular Examination. All students underwent a comprehensive ocular examination including fundoscopy, slit-lamp examination, cycloplegic refraction, and 5 m distance visual acuity (Landolt C chart). The examinations were performed by two optometrists and two ophthalmologists, all of whom were trained to use standardized protocols. The pupils were dilated by instilling one drop of 0.5% tropicamide-phenylephrine ophthalmic solution (Mydrin-P, Santen, Osaka, Japan) every 5 min for 20 min in both eyes. Cycloplegic retinoscopy was performed 20 min after the administration of the last eye drops. The right eyes of the children were included in the analysis. SER ≤ −0.5 D indicated myopia, while −0.5 D < SER ≤ +2.00 D indicated nonmyopia, as children with refractions of +2.00 D or more may have other visual problems [18]. We defined incident myopia as the absence of myopia at the baseline and the development of myopia during the 3-year follow-up period.

2.3. Questionnaire. All participants completed a questionnaire including questions about age, age at the start of primary school, and daily activities such as near reading/writing time per week (<21 h, ≥21 h to <28 h, or ≥28 h), outdoor activity time per week (<9.33 h, ≥9.33 h to <14 h, or ≥14 h), near-work distance (≥30 cm or <30 cm), continuous reading/writing for 1 h or more (seldom/none or frequently), parental myopia (at least one parent or none), sleep duration per week (≤49 h or >49 h), and dietary bias (one/more than one or none). We defined near-reading/writing time as the total amount of time spent each week on near-work activities such as reading books, writing homework, and practicing calligraphy. We defined outdoor-activity time as the total amount of time spent each week on outdoor sports and leisure.

2.4. Statistical Analysis. Statistical analysis was conducted using SPSS for Windows, v24.0 (SPSS Inc., Chicago, IL, USA). We used the data of only those students who completed both the questionnaire and ocular examination. Continuous variables were expressed as mean and standard deviation or as mean (95% confidence interval (CI)). Categorical variables were compared between the myopia and nonmyopia groups by using the chi-squared test. Univariate and multivariate logistic regression analyses were used to identify the factors associated with incident myopia. Two-sided P values less than 0.05 were deemed statistically significant.

3. Results

3.1. Rate of Incident Myopia. A total of 522 male students completed both the questionnaire and ocular examination. Their average age was 15.5 ± 0.6 years, and their average baseline SER (right eye) was 0.40 ± 0.46 D (Table 1). The baseline age, height, weight, and BMI did not differ between those who remained nonmyopic and those who developed myopia. By the 3-year follow-up, 141 of the 522 students had developed myopia (SER ≤ −0.5 D). Thus, the incidence of myopia was 27.01% (95% CI: 23.38% to 30.98%). The students were divided into subgroups based on their baseline SER (Figure 1). We noticed that the rate of incident myopia was greatest in the lowest two refractive categories, i.e., −0.05 D < SER ≤ 0 D (69/131 students, 52.67%, 95% CI: 44.17% to 61.02%) and 0 D < SER ≤ +0.50 D (61/226 students, 26.99%, 95% CI: 21.62% to 33.13%). The rates in the other categories were as follows: +0.50 D > SER ≤ +1.00 D, 11/123 students (8.94%, 95% CI: 5.07% to 15.31%); +1.00 D > SER ≤ +1.50 D, 0/35 students (0%, 95% CI: 0% to 9.89%); and +1.50 D > SER ≤ +2.00 D, 0/7 students (0%, 95% CI: 0% to 35.43%). The prevalence of incident myopia

Table 1: Baseline characteristics of students with and without incident myopia.

	Incident myopia	Nonmyopic	P value
Baseline age (years)	17.6 ± 0.6	17.6 ± 0.6	0.567
Baseline height (cm)	172.20 ± 4.63	171.58 ± 4.62	0.181
Baseline weight (Kg)	60.49 ± 7.92	59.42 ± 7.36	0.148
Baseline BMI	20.36 ± 2.37	20.16 ± 2.13	0.348

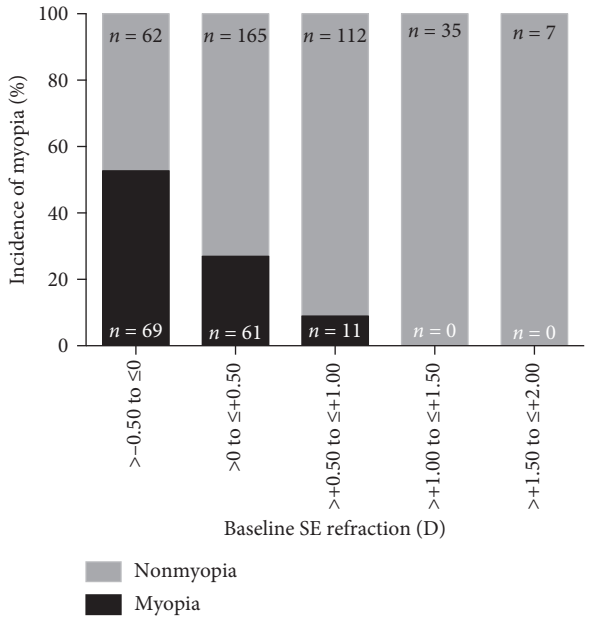

Figure 1: Proportion of children with and without incident myopia according to the baseline spherical equivalent refraction.

decreased with increasing baseline SER ($P_{\text{trend}} < 0.0001$; Figure 1).

3.2. Changes in Refractive Power. At the 3-year follow-up, the average SER was −0.05 ± 0.57 D. The refractive error decreased on average by −0.46 D (95% CI: −0.49 to −0.42 D, $P < 0.0001$) compared to the baseline measures. The magnitude of the SER change at the 3-year follow-up increased with increasing baseline SER as follows (Figure 2).

(1) −0.50 D > SER ≤ 0 D: −0.37 D (95% CI: −0.44 to −0.30 D), $P < 0.0001$

(2) 0 D > SER ≤ +0.50 D: −0.43 D (95% CI: −0.49 to −0.37 D), $P < 0.0001$

(3) +0.50 D > SER ≤ +1.00 D: −0.55 D (95% CI: −0.63 to −0.48 D), $P < 0.0001$

(4) +1.00 D > SER ≤ +1.50 D: −0.55 D (95% CI: −0.68 to −0.42 D), $P < 0.0001$

(5) +1.50 D > SER ≤ +2.00 D: −0.74 D (95% CI: −1.14 to −0.33 D), $P = 0.016$

3.3. Univariate Analysis. Univariate analyses (Table 2) revealed that the following factors were significantly associated with a decrease in incident myopia: more outdoor activity time per week ($P = 0.006$, $P_{\text{trend}} = 0.002$), less near-work time per week ($P = 0.001$, $P_{\text{trend}} = 0.001$), and reading/writing distance ≥ 30 cm ($P = 0.035$). In contrast, having at least one myopic parent, starting primary school at ≤6 years of age, frequently reading/writing for 1 h or more, sleep

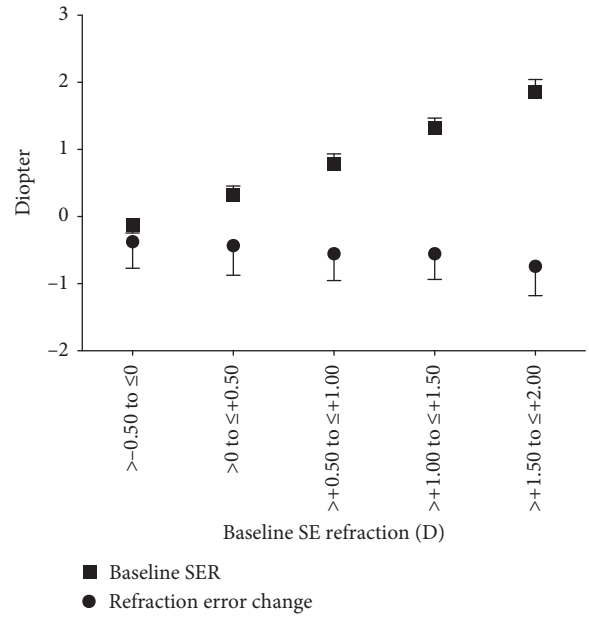

Figure 2: Baseline spherical equivalent refraction (SER) and change in SER from the baseline.

Table 2: Univariate analysis of potential risk factors for incident myopia.

Risk factor	Incident myopia, % (n)	P value (χ^2)	P_{trend}
Parental myopia			
0 parents	27.48 (119)		
1 parent	23.68 (18)	0.7525	0.1330
2 parents	30.77 (4)		
Outdoor activity time (per week)			
≥14 h	17.72 (14)		
≥9.33 h to <14 h	21.66 (34)	**0.0063**	**0.0020**
<9.33 h	32.52 (93)		
Near-work time (per week)			
≥28 h	30.62 (128)		
≥21 h to <28 h	12.60 (9)	**0.0010**	**0.0005**
<21 h	12.00 (4)		
Reading/writing distance			
<30 cm	42.86 (27)	**0.0065**	—
≥30 cm	24.84 (114)		
Continuous reading/writing for 1 h or more			
Seldom or none	26.64 (69)	0.8499	—
Frequently	27.38 (72)		
Age at the start of primary school			
>6 years	25.64 (40)	0.6452	—
≤6 years	27.60 (101)		
Sleep duration (per week)			
≤49 h	28.57 (90)	0.3221	—
>49 h	24.64 (51)		
Dietary bias			
One or more	30.04 (67)	0.1777	—
None	24.75 (74)		

duration per week ≤49 h, and one or more dietary biases were not associated with myopia onset ($P > 0.05$).

3.4. Multivariate Analysis. Multivariate analysis (Table 3) showed that the following factors protected against myopia onset: less myopic or more hyperopic SER at the baseline (odds ratio (OR) = 0.070, 95% CI: 0.036 to 0.137), outdoor activity time per week ≥ 14 h (OR = 0.464, 95% CI: 0.227 to 0.950), and reading/writing distance ≥ 30 cm (OR = 0.505, 95% CI: 0.270 to 0.944). In contrast, near-work time per week ≥28 h (OR = 2.579, 95% CI: 1.314 to 5.061) was associated with an increased risk for incident myopia. Parental myopia, age at the start of primary school, continuous reading/writing for 1 h or more, and sleep duration per week were not associated with myopia onset ($P > 0.05$).

Table 3: Multivariate analysis of factors associated with incident myopia.

Risk factor	OR	95% CI	*P* value
Parental myopia			
One or both	0.564	0.304–1.046	0.069
None		Reference	
Baseline SER	0.070	0.036–0.137	**<0.001**
Outdoor activity time (per week)			
≥14 h	0.464	0.227–0.950	**0.036**
≥9.33 h to <14 h	0.771	0.460–1.293	0.324
<9.33 h		Reference	
Near-work time (per week)			
≥28 h	2.579	1.314–5.061	**0.006**
<28 h		Reference	
Reading/writing distance			
≥30 cm	0.505	0.270–0.944	**0.032**
<30 cm		Reference	
Reading/writing for ≥1 h			
Frequently	0.780	0.491–1.240	0.294
None or seldom		Reference	
Age at start of primary school			
>6 years	0.855	0.527–1.388	0.526
≤6 years		Reference	
Sleep duration (per week)			
>49 h	0.968	0.600–1.562	0.895
≤49 h		Reference	

4. Discussion

In the present study, we found that the cumulative change in the refractive index over 3 years was −0.46 D (95% CI: −0.49 to −0.42), and the proportion of children with incident myopia was 27.01%. More hyperopic or less myopic SER at the baseline, outdoor activity time per week ≥14 h, and reading/writing distance ≥30 cm were protective factors against incident myopia, while near-work time per week ≥28 h was a risk factor. Parental myopia, age at the start of primary school, and weekly sleep duration were not associated with the onset of myopia. The results of the present study were similar to those of another study by our research team [19]. In that study, Yao et al. found that more hyperopic baseline refraction was a protective factor for incident myopia, and less outdoor activity time and more near work time were risk factors for not only incident myopia but also refractive change. The students in the study by Yao et al. underwent a 20 min physical training class outdoors every day. Furthermore, that study focused on myopic shift and its risk factors at intermediate time points during a 2-year follow-up period. In the present study, we focused on detecting the general onset of myopia and its risk factors. To the best of our knowledge, the present study is the first to determine the incidence of myopia among high school-aged children in mainland China who were nonmyopic at the baseline and not given any intervention. Furthermore, our study is the first to determine the factors influencing the incidence of myopia over a 3-year follow-up period.

The SER at the baseline is the greatest individual predictor of incident myopia in schoolchildren [12, 20, 21]. French et al. [12] found that in a cohort of Australian children aged 12 years, those with a baseline refraction ≤+0.50 D were at a higher risk for developing incident myopia. A study from western China revealed that over a period of 5 years, the incidence of myopia was lower among those who were hyperopes (SER ≥ +0.50 D) at the baseline than among those who were emmetropes (−0.50 D < SER < +0.50 D) [21]. Baseline SER predicts myopia onset more accurately than even ocular measures such as axial length and corneal power [20]. Consistent with the above studies, we found that children with a more hyperopic or less myopic SER at the baseline (>+0.50 D) had a low incidence of myopia during the 3-year study period. This implies that slightly hyperopic refraction may prevent myopia onset among children aged 14–16 years, while a baseline SER ≤ +0.50 D is a potential risk factor for incident myopia.

Longer reading and writing times increase the near-work burden of the eyes. The accommodative demand increases when the eyes focus on a close target, and hence, the lens has to perform more work to ensure clarity of vision. However, the accuracy of accommodation tends to be biased because of the shortened distance, which results in accommodation lead or lag. Compared with accommodation lead, accommodation lag is more common in the development of hyperopic defocus and axial elongation. Therefore, accommodation lag has a greater impact on the incidence and development of myopia [22–24].

In our study, near-work time per week ≥28 h was obviously associated with myopia onset, which is consistent with the previous studies [16, 17, 25]. Ip et al. [17] revealed that the incidence of myopia was significantly higher in East Asian children who read 6.5 h or more per week than in Caucasian European children (32.5 h/week vs. 26.0 h/week). Furthermore, a close reading or near-work distance (<30 cm) was independently associated with incident myopia in children [17], which is consistent with our study. Wu et al. [14, 26] reported that smaller near-work distances were associated with greater myopia prevalence and greater myopic shift. Saw et al. [16] found that children in Singapore with higher myopia read nearly two more books per week than did those with lower myopia or nonmyopes. In Shanghai, China, reading/writing at close distances and 30–40 min of uninterrupted near work were found to be risk

factors for myopic shift [25]. A meta-analysis showed a 2% increase in the odds of myopia onset with each additional diopter-hour per week spent doing near work [27]. These results may provide valuable information about the relationship between near work and incident myopia.

The present study showed that more outdoor activity time per week (≥9.33 h) protected against incident myopia. Numerous studies have reported that more time spent outdoors effectively prevents myopia onset and myopic shifts [15, 28, 29]. In early 1993, Parssinen and Lyyra [28] reported that myopic shifts occurred faster in schoolchildren in Finland who spent only 1.1 h per day outdoors than in schoolchildren who spent 3.2 h per day outdoors. The CLEERE group [30] found that emmetropes had longer outdoor activity hours 4 years before myopia onset and continuing till the fourth year after onset. The Sydney Myopia Study [12], which included two age cohorts of children (6 and 12 years), showed that the time spent outdoors was lower among children with incident myopia than among children who remained nonmyopic over a 5- to 6-year follow-up period. An intervention trial in Guangzhou [31] reported that one additional 40 min class of outdoor activities significantly decreased the 3-year incidence of myopia (30.4% vs. 39.5%) and change in SER (−1.42 D vs. −1.59 D). In northeast China, Jin et al. [29] found that two extra 20 min recess programs outdoors per day decreased myopia incidence by 50% over a 1-year follow-up period. Another intervention study showed that children in a suburban area in southern Taiwan who spent 80 min per day outdoors had a lower rate of myopia onset than a control group after only 1 year (8.41% vs. 17.65%) [15]. A meta-analysis found a 2% decrease in the odds of myopia for each additional hour spent outdoors per week [32]. It was also reported that children with myopic refraction had shorter outdoor activity time [33], and those who combined lower near work with higher outdoor activity had a more hyperopic refraction [34]. However, the time outdoors was not associated with progression following myopia onset [35]. The mechanism underlying the protective effect of being outdoors may be related to strong light intensity and increased dopamine release in the retina [10, 34, 36, 37].

This study has certain limitations. First, this was a 3-year observational cohort study, and there was no additional follow-up during the 3-year period. Second, the data about near work, time spent outdoors, reading/writing habits, and other related factors were obtained from questionnaires and may have been subject to recall bias. Third, the enrolled children represented a relatively homogenous group in terms of gender and age. Although the findings of our study may not be easily extrapolated to other populations, they nevertheless impart valuable information about incident myopia among high school-aged children in China who have similar academic workloads.

5. Conclusion

To summarize, having a more hyperopic or less myopic refraction at the baseline was an important predictor of myopia onset among high school-aged children. Additionally, spending more time on near work and less time on outdoor activities and reading/writing at a close distance were associated with an increased risk of incident myopia.

Abbreviations

SER: Spherical equivalent refraction
OR: Odds ratio
CI: Confidence interval.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study protocol complied with the principles of the Helsinki Declaration and was approved by the Ethics Committee of Air Force General Hospital.

Consent

Verbal and written consent was obtained from all participants and their parents.

Conflicts of Interest

The authors have no conflicts of interest pertaining to this work.

Authors' Contributions

All the authors have made substantial contributions to the work. Lin-song Qi contributed to the study conception and design and helped acquire and analyse the data and draft the article. Lu Yao also contributed to the study conception and design and helped analyse the data and draft the article. Xuefeng Wang helped with data acquisition and physical examination of all the participants. Jiu-mei Shi helped with data acquisition and analyse the data. Yong Liu helped with ocular examinations and participated in data analysis and manuscript revision. Teng-yun Wu helped with ocular examinations and data acquisition. Zhi-kang Zou oversaw all aspects of the study and participated in study conception and design, data analysis and interpretation, and critical revision of the manuscript for intellectual content. All the authors have read and approved the final manuscript. Lin-song Qi and Lu Yao equally contributed to this work.

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References

[1] I. G. Morgan, K. Ohno-Matsui, and S.-M. Saw, "Myopia," *The Lancet*, vol. 379, no. 9827, pp. 1739–1748, 2012.

[2] B. A. Holden, T. R. Fricke, D. A. Wilson et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050," *Ophthalmology*, vol. 123, no. 5, pp. 1036–1042, 2016.

[3] B.-Y. Ding, Y.-F. Shih, L. L. K. Lin, C. K. Hsiao, and I.-J. Wang, "Myopia among schoolchildren in East Asia and Singapore," *Survey of Ophthalmology*, vol. 62, no. 5, pp. 677–697, 2017.

[4] Q. S. You, L. J. Wu, J. L. Duan et al., "Factors associated with myopia in school children in China: the Beijing childhood eye study," *PLoS One*, vol. 7, no. 12, Article ID e52668, 2012.

[5] M. He, J. Zeng, Y. Liu, J. Xu, G. P. Pokharel, and L. B. Ellwein, "Refractive error and visual impairment in urban children in southern China," *Investigative Opthalmology & Visual Science*, vol. 45, no. 3, pp. 793–799, 2004.

[6] M. He, W. Huang, Y. Zheng, L. Huang, and L. B. Ellwein, "Refractive error and visual impairment in school children in rural southern China," *Ophthalmology*, vol. 114, no. 2, pp. 374–382, 2007.

[7] S.-M. Li, L.-R. Liu, S.-Y. Li et al., "Design, methodology and baseline data of a school-based cohort study in Central China: the Anyang childhood eye study," *Ophthalmic Epidemiology*, vol. 20, no. 6, pp. 348–359, 2013.

[8] R. Wojciechowski, "Nature and nurture: the complex genetics of myopia and refractive error," *Clinical Genetics*, vol. 79, no. 4, pp. 301–320, 2011.

[9] S.-M. Saw, A. Carkeet, K.-S. Chia, R. A. Stone, and D. T. H. Tan, "Component dependent risk factors for ocular parameters in Singapore Chinese children," *Ophthalmology*, vol. 109, no. 11, pp. 2065–2071, 2002.

[10] I. G. Morgan, A. N. French, R. S. Ashby et al., "The epidemics of myopia: aetiology and prevention," *Progress in Retinal and Eye Research*, vol. 62, pp. 134–149, 2018.

[11] A. Mirshahi, K. A. Ponto, R. Hoehn et al., "Myopia and level of education: results from the gutenberg health study," *Ophthalmology*, vol. 121, no. 10, pp. 2047–2052, 2014.

[12] A. N. French, I. G. Morgan, P. Mitchell, and K. A. Rose, "Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study," *Ophthalmology*, vol. 120, no. 10, pp. 2100–2108, 2013.

[13] A. N. French, R. S. Ashby, I. G. Morgan, and K. A. Rose, "Time outdoors and the prevention of myopia," *Experimental Eye Research*, vol. 114, pp. 58–68, 2013.

[14] L. J. Wu, Q. S. You, J. L. Duan et al., "Prevalence and associated factors of myopia in high-school students in Beijing," *PLoS One*, vol. 10, no. 3, Article ID e0120764, 2015.

[15] P.-C. Wu, C.-L. Tsai, H.-L. Wu, Y.-H. Yang, and H.-K. Kuo, "Outdoor activity during class recess reduces myopia onset and progression in school children," *Ophthalmology*, vol. 120, no. 5, pp. 1080–1085, 2013.

[16] S. M. Saw, W. H. Chua, C. Y. Hong et al., "Nearwork in early-onset myopia," *Investigative Ophthalmology & Visual Science*, vol. 43, no. 2, pp. 332–339, 2002.

[17] J. M. Ip, S.-M. Saw, K. A. Rose et al., "Role of near work in myopia: findings in a sample of Australian school children," *Investigative Opthalmology & Visual Science*, vol. 49, no. 7, pp. 2903–2910, 2008.

[18] M. S. Borchert, R. Varma, S. A. Cotter et al., "Risk factors for hyperopia and myopia in preschool children the multi-ethnic pediatric eye disease and baltimore pediatric eye disease studies," *Ophthalmology*, vol. 118, no. 10, pp. 1966–1973, 2011.

[19] L. Yao, L.-S. Qi, X.-F. Wang et al., "Refractive change and incidence of myopia among a group of highly selected senior high school students in China: a prospective study in an aviation cadet prerecruitment class," *Investigative Opthalmology & Visual Science*, vol. 60, no. 5, pp. 1344–1352, 2019.

[20] K. Zadnik, D. O. Mutti, N. E. Friedman et al., "Ocular predictors of the onset of juvenile myopia," *Investigative Opthalmology & Visual Science*, vol. 40, no. 9, pp. 1936–1943, 1999.

[21] W.-J. Zhou, Y.-Y. Zhang, H. Li et al., "Five-year progression of refractive errors and incidence of myopia in school-aged children in western China," *Journal of Epidemiology/Japan Epidemiological Association*, vol. 26, no. 7, pp. 386–395, 2016.

[22] S. K. Wang, Y. Guo, C. Liao et al., "Incidence of and factors associated with myopia and high myopia in Chinese children, based on refraction without cycloplegia," *JAMA Ophthalmology*, vol. 136, no. 9, pp. 1017–1024, 2018.

[23] S. Rusnak, V. Salcman, L. Hecova, and Z. Kasl, "Myopia progression risk: seasonal and lifestyle variations in axial length growth in Czech children," *Journal of Ophthalmology*, vol. 2018, Article ID 5076454, 5 pages, 2018.

[24] W. Hou, T. T. Norton, L. Hyman, J. Gwiazda, and C. Group, "Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation trial," *Eye & Contact Lens*, vol. 44, no. 4, pp. 248–259, 2018.

[25] X. You, L. Wang, H. Tan et al., "Near work related behaviors associated with myopic shifts among primary school students in the Jiading district of Shanghai: a school-based one-year cohort study," *PLoS One*, vol. 11, no. 5, Article ID e0154671, 2016.

[26] L.-J. Wu, Y.-X. Wang, Q.-S. You et al., "Risk factors of myopic shift among primary school children in Beijing, China: a prospective study," *International Journal of Medical Sciences*, vol. 12, no. 8, pp. 633–638, 2015.

[27] H. M. Xu, D. S. Chang, and P.-C. Wu, "The association between near work activities and myopia in children-A systematic review and meta-analysis," *PLoS One*, vol. 10, no. 10, Article ID e0140419, 2015.

[28] O. Parssinen and A. L. Lyyra, "Myopia and myopic progression among schoolchildren: a three-year follow-up study," *Investigative Ophthalmology & Visual Science*, vol. 34, no. 9, pp. 2794–2802, 1993.

[29] J.-X. Jin, W.-J. Hua, X. Jiang et al., "Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun eye care study," *BMC Ophthalmology*, vol. 15, no. 1, 2015.

[30] L. A. Jones-Jordan, G. L. Mitchell, S. A. Cotter et al., "Visual activity before and after the onset of juvenile myopia," *Investigative Opthalmology & Visual Science*, vol. 52, no. 3, pp. 1841–1850, 2011.

[31] M. He, F. Xiang, Y. Zeng et al., "Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial," *JAMA*, vol. 314, no. 11, pp. 1142–1148, 2015.

[32] J. C. Sherwin, M. H. Reacher, R. H. Keogh, A. P. Khawaja, D. A. Mackey, and P. J. Foster, "The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis," *Ophthalmology*, vol. 119, no. 10, pp. 2141–2151, 2012.

[33] D. O. Mutti, G. L. Mitchell, M. L. Moeschberger, L. A. Jones, and K. Zadnik, "Parental myopia, near work, school achievement, and children's refractive error," *Investigative*

Ophthalmology & Visual Science, vol. 43, no. 12, pp. 3633–3640, 2002.

[34] K. A. Rose, I. G. Morgan, J. Ip et al., "Outdoor activity reduces the prevalence of myopia in children," *Ophthalmology*, vol. 115, no. 8, pp. 1279–1285, 2008.

[35] L. A. Jones-Jordan, L. T. Sinnott, S. A. Cotter et al., "Time outdoors, visual activity, and myopia progression in juvenile-onset myopes," *Investigative Opthalmology & Visual Science*, vol. 53, no. 11, pp. 7169–7175, 2012.

[36] X. Zhou, M. T. Pardue, P. M. Iuvone, and J. Qu, "Dopamine signaling and myopia development: what are the key challenges," *Progress in Retinal and Eye Research*, vol. 61, pp. 60–71, 2017.

[37] C. S. McCarthy, P. Megaw, M. Devadas, and I. G. Morgan, "Dopaminergic agents affect the ability of brief periods of normal vision to prevent form-deprivation myopia," *Experimental Eye Research*, vol. 84, no. 1, pp. 100–107, 2007.

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Research Article

Role of Gender in the Prevalence of Myopia among Polish Schoolchildren

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Purpose. The aim of the paper was to study the role of gender in the progression of myopia among Polish schoolchildren. *Materials and Methods*. 4875 children from elementary schools and high schools were examined (2470 boys, aged 6–16 years, mean age 11.0, SD = 2.6 and 2405 girls, aged 6–16 years, mean age 11.1, SD = 2.6). The examined students were Caucasian and resided in and around Szczecin, Poland. The examination included retinoscopy under cycloplegia. The refractive error readings were reported as spherical equivalent (SE). Myopia was defined as SE of at least −0.5 D. Data analysis was performed using the Mann–Whitney *U* test and 2-sided Fisher's exact test. p values of less than 0.05 were considered statistically significant. *Results*. It was found that the SE among Polish boys is similar to the SE among Polish girls before the age of 9 years. However, in older children, lower SE values and higher prevalence of myopia were found among girls than boys, both at 9–13 years range (0.45 ± 1.05 vs 0.55 ± 1.23 D, $p = 0.047$ and 8.30% vs 5.71%, $p = 0.015$, respectively) and at 13–16 years range (0.32 ± 1.14 vs 0.54 ± 1.08 D, $p = 0.0093$ and 10.37% vs 5.96%, $p = 0.0050$), respectively. *Conclusions*. Gender is associated with the prevalence of myopia among Polish schoolchildren ranging from 9 to 16 years of age.

1. Introduction

Several studies have been carried out in different countries on the role of gender in the progression of myopia among schoolchildren. In Poland, only one paper dealing with the issue has been published [1–12].

Several contradictory results from these studies can be found in the world literature. However, most researchers point to a more frequent occurrence of myopia in girls [1–6, 9, 11, 12] than in boys [7, 8] (Table 1).

Due to the discrepancies in the obtained data, we decided to examine the spherical equivalent (SE) on a large population of 4875 Polish students after cycloplegia with 1% tropicamide.

2. Materials and Methods

The studies were carried out from October 2000 to March 2009. 4875 children from elementary schools and high schools were examined (2470 boys, aged 6–16 years, mean age 11.0, SD = 2.6 and 2405 girls aged 6–16 years, mean age 11.1, SD = 2.6). The examined students were Caucasian and resided in and around Szczecin, Poland.

Twenty-one schools were selected by random sampling out of 210 schools from the area of Szczecin. All children from the selected schools were invited to participate in the study. However, only 95.8% accepted to participate. We did not observe differential dropout.

Every examined student had undergone the following examinations: distance visual acuity testing, cover test, anterior segment evaluation, and cycloplegic retinoscopy after instillation of 1% tropicamide, and a questionnaire was taken. The methodology of the examinations has been described in detail in previous work.

Data analysis was performed using the Mann–Whitney *U* test and 2-sided Fisher's exact test. p values of less than 0.05 were considered statistically significant [13].

Table 1: Dependency between gender and myopia.

Reference	Country	Time of data collection (years)	Age (years)	Prevalence of myopia		Girls and boys (%)
				Girls (%)	Boys (%)	
Ahmed et al. [1]	India	2007	6–22	5.4	3.6	1.8
Czepita et al. [2]	Poland	2000–2005	6–18	7.4	5.1	2.3
Giloyan et al. [3]	Armenia	2011	10–16	53.4	46.6	6.8
Goh et al. [4]	Malaysia	2003	7–15	21.2	17.5	3.7
Hsu et al. [5]	Taiwan	2005-2006	7–13	25.9	25.3	0.6
Ip et al. [6]	Australia	2003–2005	11–15	14.1	9.7	4.4
Lam and Goh [7]	Hong Kong	1990-1991	6–17	55.9	57.4	−1.5
Maul et al. [8]	Chile	1998	5–15	14.7	19.4	−4.7
Mäntyjärvi [9]	Finland	1980-1981	7–15	26.6	19.5	7.1
Pokharel et al. [10]	Nepal	1980-1981	5–15	1.5	1.5	0
Quek et al. [11]	Singapore	2002	15–19	72.7	67.7	5.0
Zhao et al. [12]	China	1998	5–15	23.5	14.1	9.4

3. Results

It was found that the spherical equivalent among Polish boys is similar to the SE among Polish girls before the age of 9 years. However, in older children, lower SE values and higher prevalence of myopia were found among girls than boys, both at 9–13 years range (0.45 ± 1.05 vs 0.55 ± 1.23 D, $p = 0.047$ and 8.30% vs 5.71%, $p = 0.015$, respectively) and at 13–16 years range (0.32 ± 1.14 vs 0.54 ± 1.08 D, $p = 0.0093$ and 10.37% vs 5.96%, $p = 0.0050$), respectively (Figure 1, Tables 2 and 3).

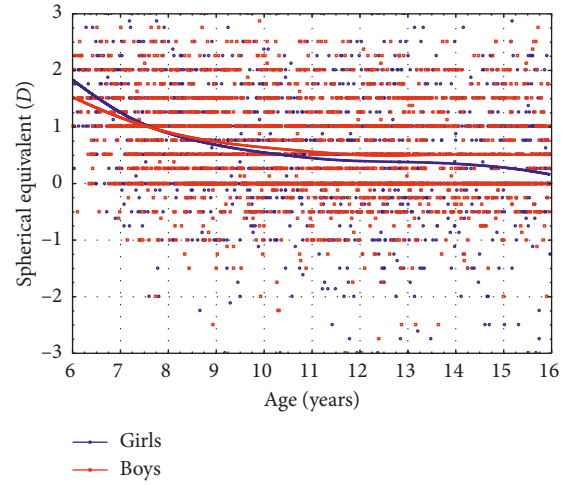

Figure 1: Spherical equivalent in relation to the age of boys (red line) and girls (blue line). Regression lines are obtained using distance-weighted least squares fitting method.

4. Discussion

It is widely known that myopia occurs more often in pupils who spend a lot of time reading, writing, or using a computer [13–15]. Myopia occurs less often in pupils who spend a lot of time doing outdoor activities [13, 14, 16]. It is widely regarded that myopia occurs more often in girls than in boys, especially in older children. In our study, we also observed a higher occurrence of myopia in girls aged 9 to 16 years. A similar relationship was observed by other authors. Only Maul et al. [8] in Chile concluded that myopia occurs more often in boys aged 5–15 years.

In order to reduce the possibility of making a mistake, we decided to conduct the examinations on a large population of 4875 students after cycloplegia with 1% tropicamide. Besides, the examinations were performed only by two doctors. According to Zadnik et al. [17], 95% limits of agreement for cycloplegic retinoscopy are ±0.95 D.

Based on the conducted examinations, we found that in Polish schoolchildren, with age, a decrease in the spherical equivalent occurs. A faster and larger decrease was observed in girls compared to boys. This may indicate that myopia occurs earlier and more often in girls than in boys. In 2007, we published a similar paper on the prevalence of refractive errors among children aged 6–18 years. We concluded that the prevalence of myopia among boys was 5.1% and among girls was 7.4% [2].

The data obtained by us are similar to the results of investigations performed in India [1], Poland [2], Armenia [3], Malaysia [4], Taiwan [5], Australia [6], Finland [9], Nepal [10], Singapore [11], and China [12]. However, they differ from the results gathered in Hong Kong [7] and Chile [8].

It is widely accepted that there are two possibilities for gender differences. The first is that the differences are biologically determined. The second possibility is that they are socially/behaviorally determined.

Zylbermann et al. [18] determined that Orthodox Jewish boys, who receive an intensive religious education, are much more myopic than their sisters and the rest of their age cohort who receive a more secular education. Probably, the high degree and prevalence of myopia observed in the Orthodox male group may be due to their heavy accommodative eye use attributed to their different study habits.

Recent extensive studies carried out in China on the prevalence of myopia have concluded that myopia occurs more often in girls. Ma et al. [19] have shown that myopia occurs more often in girls below 3 years of age. However, Li et al. [20] concluded that myopia occurs more often in 12.7-year-old girls.

Table 2: Spherical equivalent (D) among examined boys and girls.

Age (years)	Boys Mean ± SD	Girls Mean ± SD	p^*
6–9 (≥6 and <9)	+0.95 ± 1.04	+0.99 ± 1.21	0.91
9–13 (≥9 and <13)	+0.55 ± 1.23	+0.45 ± 1.05	0.047
13–16 (≥13 and <16)	+0.54 ± 1.08	+0.32 ± 1.14	0.0093

SD: standard deviation. *Mann–Whitney U test.

Table 3: Prevalence of myopia defined as spherical equivalent of at least −0.5 D among examined boys and girls.

Age (years)	Boys (%) (95% CI)	Girls (%) (95% CI)	p^*
6–9 (≥6 and <9)	3.65 (2.35–5.38%)	3.35 (2.11–5.03%)	0.88
9–13 (≥9 and <13)	5.71 (4.46–7.18%)	8.30 (6.76–10.07%)	0.015
13–16 (≥13 and <16)	5.96 (4.23–8.12%)	10.37 (8.08–13.05%)	0.0050

95% CI: 95% confidence interval. *Fisher's exact test.

According to Krause et al. [21], the reasons for sex differences are determined by genetic factors, dietary factors, and amount of close work, as well as are connected with puberty. Girls reach puberty earlier than boys and therefore reach their final body height one or two years earlier than boys. This leads to a rise in the prevalence of myopia.

Our results are similar to the results obtained by other authors. We also demonstrated that gender is associated with the prevalence of myopia.

5. Conclusions

Gender is associated with the prevalence of myopia among Polish schoolchildren ranging from 9 to 16 years of age.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

[1] I. Ahmed, S. Mian, S. Mudasir, and K. I. Andrabi, "Prevalence of myopia in students of Srinagar City of Kashmir, India," *International Journal of Health Sciences*, vol. 2, no. 1, pp. 77–81, 2008.

[2] D. Czepita, A. Mojsa, M. Ustianowska, M. Czepita, and E. Lachowicz, "Role of gender in the occurrence of refractive errors," *Annales Academiae Medical Stetinensis*, vol. 53, no. 2, pp. 5–7, 2007.

[3] A. Giloyan, T. Harutyunyan, and V. Petrosyan, "Risk factors for developing myopia among schoolchildren in Yerevan and Gegharkunik Province, Armenia," *Ophthalmic Epidemiology*, vol. 24, no. 2, pp. 97–103, 2017.

[4] P. Goh, Y. Abqariyah, G. Pokharel, and L. Ellwein, "Refractive error and visual impairment in school-age children in Gombak District, Malaysia," *Ophthalmology*, vol. 112, no. 4, pp. 678–685, 2005.

[5] S.-L. Hsu, C.-H. Chang, Y.-H. Lai, M.-H. Wen, K.-C. Cheng, and C.-K. Ho, "Refractive status of mountain Aborigine schoolchildren in Southern Taiwan," *Kaohsiung Journal of Medical Sciences*, vol. 24, no. 3, pp. 120–125, 2008.

[6] J. M. Ip, S. C. Huynh, D. Robaei et al., "Ethnic differences in refraction and ocular biometry in a population-based sample of 11–15-year-old Australian children," *Eye*, vol. 22, no. 5, pp. 649–656, 2008.

[7] C. S. Lam and W. S. Goh, "The incidence of refractive errors among school children in Hong Kong and its relationship with the optical components," *Clinical and Experimental Optometry*, vol. 74, no. 3, pp. 97–103, 1991.

[8] E. Maul, S. Barroso, S. R. Munoz, R. D. Sperduto, and L. B. Ellwein, "Refractive error study in children: results from La Florida, Chile," *American Journal of Ophthalmology*, vol. 129, no. 4, pp. 445–454, 2000.

[9] M. Mäntyjärvi, "Incidence of myopia in a population of Finnish school children," *Acta Ophthalmologica*, vol. 61, no. 3, pp. 417–423, 1983.

[10] G. P. Pokharel, A. D. Negrel, S. R. Munoz, and L. B. Ellwein, "Refractive error study in children: results from Mechi Zone, Nepal," *American Journal of Ophthalmology*, vol. 129, no. 4, pp. 436–444, 2000.

[11] T. P. L. Quek, C. G. Chua, C. S. Chong et al., "Prevalence of refractive errors in teenage high school students in Singapore," *Ophthalmic and Physiological Optics*, vol. 24, no. 1, pp. 47–55, 2004.

[12] J. Zhao, J. Mao, R. Luo, F. Li, S. R. Munoz, and L. B. Ellwein, "The progression of refractive error in school-age children: Shunyi District, China," *American Journal of Ophthalmology*, vol. 134, no. 5, pp. 735–743, 2002.

[13] M. Ellwein, D. Czepita, and W. Lubiński, "The influence of environmental factors on the prevalence of myopia in Poland," *Journal of Ophthalmology*, vol. 2017, p. 5, 2017.

[14] D. Czepita, "Myopia: incidence, pathogenesis, management and new possibilities of treatment," *Russian Ophthalmological Journal*, vol. 7, no. 1, pp. 96–101, 2014.

[15] M. Czepita, L. Kuprjanowicz, K. Safranow et al., "The role of reading, writing, using a computer, or watching television in the development of myopia," *Ophthalmology Journal*, vol. 1, no. 2, pp. 53–57, 2016.

[16] M. Czepita, L. Kuprjanowicz, K. Safranow et al., "The role of outdoor activity in the development of myopia in

schoolchildren," *Pomeranian Journal of Live Sciences*, vol. 62, no. 4, pp. 30–32, 2016.

[17] K. Zadnik, D. O. Mutti, and A. Adams, "The repeatability of measurement of the ocular components," *Investigative Ophthalmology & Visual Science*, vol. 33, no. 7, pp. 2325–2333, 1992.

[18] R. Zylbermann, D. Landau, and D. Berson, "The influence of study habits on myopia in Jewisch teenagers," *Journal of Pediatric Ophthalmology & Strabismus*, vol. 30, no. 5, pp. 319–322, 1993.

[19] Q. Ma, W. Xu, X. Zhou, C. Cui, and C. W. Pan, "The relationship of season of birth with refractive error in very young children in Eastern China," *PLoS One*, vol. 9, no. 6, Article ID e100472, 2014.

[20] S. M. Li, S. Y. Li, M. T. Kang et al., "Near work related parameters and myopia in Chinese children: the Anyang Childhood Eye Study," *PLoS One*, vol. 10, no. 8, Article ID e0134514, 2015.

[21] U. Krause, K. Krause, and P. Rantakallio, "Sex differences in refraction errors up to the age of 15," *Acta Ophthalmologica*, vol. 60, no. 6, pp. 917–926, 1982.

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Research Article

Simultaneous Changes in Astigmatism with Noncycloplegia Refraction and Ocular Biometry in Chinese Primary Schoolchildren

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Purpose. To assess the changing profile of astigmatism in Chinese schoolchildren and the association between astigmatism changes and ocular biometry. *Methods*. We examined and followed up 1,463 children aged 6–9 years from Wenzhou, China. We measured noncycloplegic refraction twice each year and tested axial length (AL) and corneal radius of curvature (CRC) annually for two years. We defined clinically significant astigmatism (CSA) as ≤−0.75 diopter (D) and non-CSA astigmatism as ≤0 to >−0.75 D. *Results*. Prevalence of CSA at baseline was 22.4% ($n = 327$) and decreased to 20.3% ($n = 297$) at the two-year follow-up ($P = 0.046$). Ninety-two (8.1%) non-CSA children developed CSA. In multiple regression, after adjusting for age, gender, baseline cylinder refraction, and axis, children who had longer baseline ALs (>23.58 mm; odds ratio (OR) = 5.19, 95% confidence interval (CI): 2.72–9.90) and longer baseline AL/CRC ratio (>2.99, OR = 4.99, 95% CI: 2.37–10.51) were more likely to develop CSA after two years. Four-hundred and two (27.5%) children had increased astigmatism, 783 (53.5%) had decreased, and 278 (19.0%) had no change during the two-year follow-up. Children with increased astigmatism had longer baseline ALs (23.33 mm, $P < 0.001$), higher AL/CRC ratios (2.99 mm, $P < 0.001$), and more negative spherical equivalent refraction (SER) (−0.63 D, $P < 0.001$) compared with the decreased and no astigmatism change subgroups. Also, children in the increased astigmatism subgroup had more AL growth (0.68 mm, $P < 0.001$), higher increases in AL/CRC ratio (0.08, $P < 0.001$), and more negative SER change (−0.86 D, $P < 0.001$) compared with the decreased and no astigmatism change subgroups. *Conclusions*. The prevalence of astigmatism decreased slightly over the two-year study period. Longer ALs and higher AL/CRC ratios were independent risk factors for developing CSA. Increased astigmatism was associated with AL growth, AL/CRC ratio increases, and the development of myopia. This trial is registered with ChiCTR1800019915.

1. Introduction

Astigmatism is a frequent, correctable cause of visual impairment in children, whether or not this coexists with myopia or hyperopia [1]. We know that the high prevalence of astigmatism at birth decreases throughout infancy [2], but its change with age is less certain. In a longitudinal study in the USA, Harvey et al. [3] reported that schoolchildren showed clinically stable astigmatic refractions. However, in Taiwan, Chan et al. [4] found that Chinese primary schoolchildren showed a decrease in astigmatism at the one-year follow-up. Although the prevalence of astigmatism may decrease during the school years, changes in astigmatism in individual children vary.

In European children (Pärssinen et al. [5]) and native American populations (Twelker et al. [6]), the presence of astigmatism predisposes development of progressive myopia. In Twelker's et al.'s [6] study of native American population, Dobson et al. [7] found rates of myopia progression in astigmatic and nonastigmatic preschool children over a 4- to 8-year follow-up to be similar. Pärssinen [8] observed that myopia progression appeared unrelated to the

initial astigmatism. Thus, the association between astigmatism and myopia is controversial [9].

Despite a large refractive database of Chinese schoolchildren, the changing profile of astigmatism has not been reported, and the relationship between the change in astigmatism and myopia is not clear in the literature. Two studies [10, 11] found axial length (AL) growth to be a more accurate predictor of myopic shift. Ratio of AL to corneal radius of curvature (CRC) (AL/CRC ratio) is an objective measure that can be used as a proxy for refractive error in the absence of cycloplegic refraction [12].

Hence, the study aims to investigate the prevalence of astigmatism, its changing profile, and how its change is associated with ocular biometry as surrogate for refractive error in 6–9-year-old Chinese schoolchildren.

2. Methods

2.1. Design and Subjects. Our study was a prospective, school-based investigation using random cluster sampling. Three schools were selected. Fifty-six children with ocular diseases or contact lens wear were excluded, and 1523 children participated. Of the enrolled children, 1463 (96.1%) completed all the eye examinations during the two-year follow-up. The purpose and details of the study examination were explained to participating parents and children before obtaining parental consent. This study was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University and followed the tenets of the Declaration of Helsinki.

2.2. Procedures. Each school provided a private room where vision screenings were conducted by four professional optometrists. Before the examination, each child was informed again about the purpose and procedure of every technique. Once the children met all the requirements, examination commenced. Manifest (noncycloplegic) refraction was assessed each semester (5 times total). We used a Topcon RM8900 autorefractor (Topcon Co., Tokyo, Japan) to measure each eye at least three times to determine an average refractive error. Each eye was examined again if one value deviated from the other two by ≥±0.50 diopters (D). The IOL Master (Carl Zeiss Meditec) was used to measure AL and CRC every year.

2.3. Definitions. Refractive data for both eyes of each child were strongly correlated (Spearman's ρ 0.78–0.90, all $P < 0.001$), so only the right eye data were analyzed. Children with astigmatism ≤−0.75 D were classified as having clinically significant astigmatism (CSA), and those with astigmatism ≤0 to >−0.75 D were classified as non-CSA. The spherical equivalent of refraction (SER) was calculated as the sphere value plus half the cylinder value. Refraction was defined by spherical equivalent: myopia as ≤−0.5 D, hyperopia as ≥+0.5 D, and emmetropia as −0.5 D < SER <+0.5 D. Axis of 180° ± 15° was defined as with-the-rule (WTR), axis of 90° ± 15° as against-the-rule (ATR), and intermediate values as oblique (OBL). These standards were chosen for better comparison with other studies [4, 13–16].

2.4. Statistical Analysis. Statistical analysis was performed using SPSS (version 18.0). The means ± standard deviations (SD) were calculated for normally distributed data. The Pearson χ^2 test was used to compare categorical variables and *t*-tests for continuous variables. Multiple sets of continuous variables were analyzed using the ANOVA test. Multiple logistic regression was utilized to examine the effect of various factors on the dependent variable (e.g., children who developed CSA or remained as non-CSA). Two-tailed *P* values were used in all analyses, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Astigmatism Prevalence. Participants comprised 787 (53.8%) boys and 676 (46.2%) girls. The age was 7.3 ± 0.9 years (range 6 to 9 years). At baseline, the cylinder refraction for all children was −0.52 ± 0.63 D (range −5.75 D to 0 D). For children with non-CSA, the cylinder refraction was −0.27 ± 0.22 D and −1.40 ± 0.79 D for children who had CSA. The prevalence of CSA was 22.4% ($n = 327$). There was no significant difference for age ($\chi^2 = 3.94$, $P = 0.27$) or gender ($\chi^2 = 0.27$, $P = 0.61$). Of the 327 children with CSA, 249 (76.1%) had WTR astigmatism, 11 (3.4%) had ATR, and 67 (20.5%) had OBL astigmatism. The mean cylinder refraction and axis of CSA did not differ across each age group ($F = 0.53$, $P = 0.670$; $\chi^2 = 3.81$, $P = 0.700$) (Table 1).

3.2. Changes in Astigmatism. Cylinder refraction in all children changed from −0.52 ± 0.63 D to −0.43 ± 0.65 D ($P < 0.001$) after two years. In the children with CSA, cylinder refraction decreased from −1.40 ± 0.79 D to −1.14 ± 0.96 D ($P < 0.001$). In the children with non-CSA, cylinder refraction decreased from −0.27 ± 0.22 D to −0.22 ± 0.30 D ($P < 0.001$, Figure 1). The prevalence of CSA decreased from 22.4% to 20.3% ($n = 297$) by study completion ($\chi^2 = 467.72$, $P < 0.001$). In the non-CSA group ($n = 1{,}136$), astigmatism increased for 29.2% ($n = 332$) of the children, decreased for 48.2% ($n = 547$), and did not change for 22.6% ($n = 257$). In the CSA group ($n = 327$), astigmatism increased for 21.4% ($n = 70$) of the children, decreased for 72.2% ($n = 236$), and did not change for 6.4% ($n = 21$). Most of the absolute dioptric changes in cylinder refraction were between >0 and < 0.5 D for the two groups (Figure 2). Such changes occurred in 59.3% ($n = 194$) of the CSA children and 60.2% ($n = 684$) of the non-CSA children. In another, such changes occurred in 76.1% ($n = 306$) of the increased subgroup. Change of ≥0.5 D to <1.0 D occurred in 28.8% ($n = 94$) of the CSA children and 16.2% ($n = 184$) of the non-CSA children. Also, such changes occurred in 20.1% ($n = 81$) of the increased subgroup. Change of ≥1.0 D occurred in 5.5% ($n = 18$) of the CSA children and 1.0% ($n = 11$) of the non-CSA children. And, such changes occurred in 3.7% ($n = 15$) of the increased subgroup. Table 2 showed the proportion of the type of astigmatism changes. There was a significant

Table 1: Cylinder refraction and axis of CSA children in different age groups.

Age (y)	Cylinder refraction[a] (D)	P value*	Axis of astigmatism[b] (≤−0.75 D)			P value#
			WTR	ATR	OBL	
6	−1.38 ± 0.85	0.67	66 (78.6%)	2 (2.4%)	16 (19.0%)	0.7
7	−1.34 ± 0.78		88 (72.7%)	6 (5.0%)	27 (22.3%)	
8	−1.47 ± 0.78		79 (79.0%)	3 (3.0%)	18 (18.0%)	
9	−1.38 ± 0.71		16 (72.7%)	0 (0.0%)	6 (27.3%)	

D, diopters; y, years; WTR, with-the-rule; ATR, against-the-rule; OBL, oblique. [a]Means ± standard deviations; [b]number of eyes (%); *ANOVA; #χ^2 test.

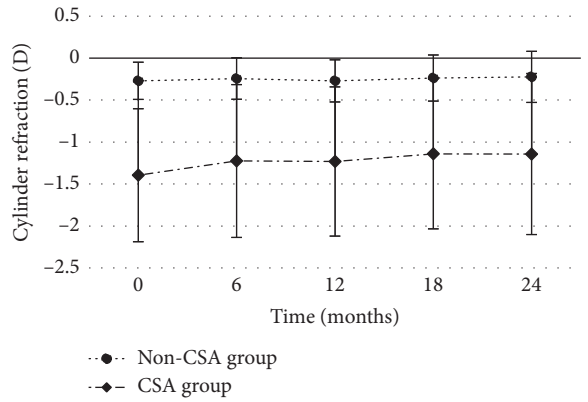

Figure 1: CSA and non-CSA changes in cylinder refraction.

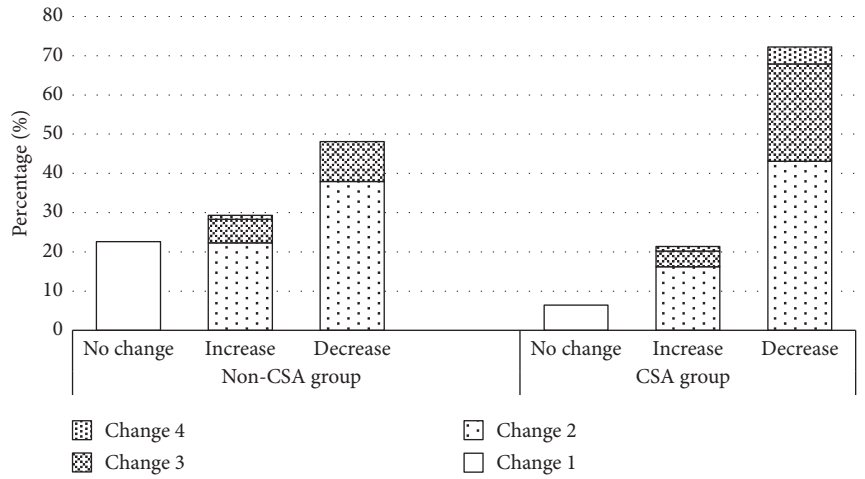

Figure 2: Absolute value of dioptric changes in cylinder refraction changes in the non-CSA and CSA groups. No-change subgroup, no change in diopters; increase subgroup, increases in diopters; decrease subgroup, decreases in diopters. Change 1: dioptric change = 0 D; Change 2: dioptric change >0 to <0.5 D; Change 3: dioptric change ≥0.5 D to <1.0 D; Change 4: dioptric change ≥1.0 D.

Table 2: Comparison of the type of astigmatism at initial examination and final examination in the 1463 children who underwent follow-up examination at 2 years.

Group at baseline	Group at final (2 years later)									
	Non-CSA		Hyperopic astigmates		Mixed astigmates		Myopic astigmates		Total	
	n	%	n	%	n	%	n	%	n	%
Non-CSA	1044	91.9	3	0.3	21	1.8	68	6.0	1136	100
Hyperopic astigmates	34	47.2	28	38.9	6	8.3	4	5.6	72	100
Mixed astigmates	50	35.2	6	4.2	44	31	42	29.6	142	100
Myopic astigmates	38	33.6	0	0	9	8	66	58.4	113	100
Total	1166	79.7	37	2.5	80	5.5	180	12.3	1463	100

difference between the baseline and final examination for the proportion of the type of astigmatism ($\chi^2 = 71.66$, $P < 0.001$). The proportion of CSA children who had hyperopic astigmatism decreased from 22.0% (72/327) to 12.5% (37/297), and the proportion with mixed astigmatism decreased from 43.4% to 26.9%. However, the proportion with myopic astigmatism increased from 34.6% to 60.6% at the two-year follow-up. For the astigmatism increased subgroup, hyperopic astigmatism decreased from 2.0% (8/402) to 1.7% (7/402), mixed astigmatism increased from 5.5% (22/402) to 9.2% (37/402), and myopic astigmatism increased from 10.0% (40/402) to 29.4% (118/402) ($\chi^2 = 100.57$, $P < 0.001$).

3.3. Association between Change of Astigmatism and Ocular Biometry. For non-CSA children, 8.1% ($n = 92$) developed CSA and 91.9% ($n = 1{,}044$) remained non-CSA. In the multiple logistic regression model (Table 3), after adjusting for age, gender, baseline cylinder refraction, and baseline axis of astigmatism, the higher baseline AL (odds ratio [OR] = 5.19, 95% confidence interval [CI]: 2.72–9.90 for the top quartile compared with the bottom quartile) was significantly associated with the development of CSA from non-CSA eyes. Similarly, the higher AL/CRC ratio (OR = 4.99, 95% CI: 2.37–10.51 for the top quartile compared with the bottom quartile) was also significantly associated with the development of CSA from non-CSA eyes. However, there were no differences between the ALs of 22.53 to 23.58 mm and the ALs <22.53 mm for the development of CSA from non-CSA. AL/CRC ratios of 2.89 to 2.99 were also not associated with the development of CSA compared with the bottom quartile. In another, 73.9% (68/92) developed myopic astigmatism of children who had non-CSA at baseline. Of them, the radius of CR of the horizontal meridian increased from 7.90 mm to 7.94 mm after the two-year follow-up ($P = 0.02$). However, there was no significant difference for the change of the radius of CR of the steep meridian ($P = 0.84$).

The percentage of baseline ALs (>23.58 mm) in the top quartile of non-CSA eyes was significantly higher in myopes (47.8%) compared with emmetropes (19.2%) and hyperopes (7.1%) ($P < 0.001$ each, Table 4). However, the percentage of baseline ALs (<22.53 mm) in the bottom quartile of non-CSA eyes was significantly higher in hyperopes (44.0%) compared with emmetropes (25.4%) and myopes (12.4%) ($P < 0.001$ each). For baseline AL/CRC ratios (>2.99), the percentage of eyes in the top quartile was higher in myopes (52.5%) compared with emmetropes (15.6%) and hyperopes (5.5%) ($P < 0.001$ each). However, the percentage of baseline AL/CRC ratios (<2.89) in the bottom quartile was higher in hyperopes (37.9%) compared with emmetropes (20.5%) and myopes (10.0%) ($P < 0.001$ each). The AL was 23.59 ± 0.96 mm for myopes, and it decreased to 22.97 ± 0.66 mm for emmetropes and 22.63 ± 0.76 mm for hyperopes ($F = 103.45$, $P < 0.001$). The AL/CRC ratio was 3.01 ± 0.11 for myopes, and it decreased to 2.94 ± 0.06 for emmetropes and 2.90 ± 0.08 for hyperopes ($F = 145.16$, $P < 0.001$).

Children with CSA ($n = 327$) had two outcomes after the two-year study. Astigmatism either decreased to non-CSA (37.0%, $n = 122$), or it remained CSA (63.0%, $n = 205$). After adjusting for age, gender, and baseline axis of astigmatism, the AL/CRC ratio (OR = 0.31, 95% CI: 0.15–0.64 for the top quartile compared with the bottom quartile) was associated with the decrease of CSA to non-CSA. However, the baseline AL was not associated with the decrease of CSA to non-CSA (Supplementary Table 1).

Among the study participants, 402 (27.5%) had increased astigmatism, 783 (53.5%) had decreased astigmatism, and 278 (19.0%) children had no change in astigmatism at follow-up. Using the least significant difference (LSD) pairwise comparison methods (Table 5), we found that the subgroup of children with increased CSA had longer ALs (23.33 mm), larger AL/CRC ratios (2.99), and more myopic SERs (−0.63 D) compared with children who had decreases in these biometric parameters (AL = 22.89 mm, AL/CRC ratio = 2.94, SER = −0.07 D, $P < 0.001$ for each). Similarly, the subgroup with increased CSA had longer ALs, larger AL/CRC ratios, and more myopic SERs than the subgroup that had no changes in CSA (AL = 23.06 mm, AL/CRC ratio = 2.93, SER = −0.01 D, $P < 0.001$ for each). Moreover, AL growth (0.68 mm), AL/CRC ratio change (0.08), and myopic progression (−0.86 D) were all greater in the subgroup with increased CSA compared with the subgroup with decreased CSA (AL = 0.56 mm, AL/CRC ratio = 0.07, SER = −0.31 D, $P < 0.001$ for each) and with the subgroup without change in CSA (AL = 0.53 mm, AL/CRC ratio = 0.07, SER = −0.39 D, $P < 0.001$ for each).

4. Discussion

4.1. Prevalence of Astigmatism. The prevalence of astigmatism varies according to ethnicity, population, and measurement standards. We found the prevalence of CSA at baseline (≤0.75 D, 22.4%) to be higher than findings in South African populations [17] (≤−0.75 D, 5–15 years, 9.2%) and in other populations including those in Iran (≤−0.75 D, 6–17 years, 11.5%) [18] and Nepal (≤−0.75 D, 5–15 years, 3.5%) [19]. Our prevalence was lower than that in another Chinese study [20], where prevalence was 42.7% in urban districts (≤−0.75 D, 5–15 years) and 25.3% (≤−0.75 D, 13–17 years) in rural districts [21]. Chan et al. [4] reported that 32.9% of Taiwanese schoolchildren had astigmatism >1.0 D, a prevalence higher than that of our study. We did not detect correlations with either gender or age like those reported by Chebil et al. [22] and Fotouhi et al. [9]. Our results also agreed with others [4, 23, 24], where most schoolchildren had WTR astigmatism. We found no significant association between age and CSA, consistent with data from Fotouhi et al. [9] and Chan et al. [4].

4.2. Changes in Astigmatism. Over the two years of this study, the prevalence of astigmatism decreased, declining in both the non-CSA group (−0.27 D to −0.22 D) and the CSA group (−1.40 D to −1.14 D). In a study of 4,662 Chinese schoolchildren (5–13 years), the magnitude of astigmatic

Table 3: Logistic regressions of baseline factors for development of CSA from non-CSA eyes after two years.

Baseline characteristic[a]	Univariate regression			Multiple regression[b]			Multiple regression[c]		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (y)*#	1.32	1.05–1.67	**0.02**						
Gender (%)*#									
Boys	Reference								
Girls	0.76	0.49–1.17	0.2						
Cylinder refraction (D)									
0 (75th percentile)	Reference			Reference			—		
−0.5 to 0	2.22	1.18–4.19	**0.014**	2.45	1.29–4.68	**0.006**	—	—	—
<−0.5 (25th percentile)	5.84	2.76–12.34	**<0.001**	8.17	3.74–17.85	**<0.001**	—	—	—
Axis (%)									
OBL	Reference			—			Reference		
Nil	0.5	0.25–0.97	**0.04**	—	—	—	0.48	0.24–0.95	**0.035**
WTR	2.01	1.24–3.24	**0.004**	—	—	—	1.98	1.21–3.22	**0.006**
ATR	0.41	0.12–1.36	0.15	—	—	—	0.43	0.13–1.46	0.18
AL (mm)									
<22.53 (25th percentile)	Reference			Reference			—		
22.53–23.58	1.07	0.56–2.05	0.844	1.26	0.65–2.46	0.49	—	—	—
>23.58 (75th pencentile)	3.96	2.13–7.36	**<0.001**	5.19	2.72–9.90	**<0.001**	—	—	—
AL/CRC ratio									
<2.89 (25th percentile)	Reference			—			Reference		
2.89–2.99	1.55	0.74–3.26	0.25	—	—	—	1.5	0.71–3.17	0.29
>2.99 (75th pencentile)	5.13	2.45–10.74	**<0.001**	—	—	—	4.99	2.37–10.51	**<0.001**

CSA, clinically significant astigmatism; 95% CI, 95% confidence interval; y, years; AL, axial length; CRC, corneal radius of curvature; D, diopters; Nil, cylinder refraction of zero. [a]Percentiles correspond to baseline values for children with non-CSA; [b]Logistic functions were adjusted for age, gender, and baseline cylinder refraction; [c]Logistic function were adjusted for age, gender, and axis of baseline non-CSA (≤0 to > −0.75 D). *$P > 0.05$ in multiple regression[b]; #$P > 0.05$ in multiple regression[c].

Table 4: Baseline ocular biometry percentages associated with refractive status of non-CSA children.

Variables	Hyperopes (≥+0.5 D)		Emmetropes (−0.5 D to +0.5 D)		Myopes (≤−0.5 D)		*P* value[a]
	n	%	*n*	%	*n*	%	
AL (mm)							
<22.53 (25th percentile)	80	44	166	25.4	37	12.4	
22.53–23.58	89	48.9	362	55.4	119	39.8	<0.001
>23.58 (75th percentile)	13	7.1	125	19.2	143	47.8	
AL/CRC ratio							
<2.89 (25th percentile)	69	37.9	134	20.5	30	10	
2.89–2.99	103	56.6	417	63.9	112	37.5	<0.001
>2.99 (75th percentile)	10	5.5	102	15.6	157	52.5	
Total	182	100	653	100	299	100	

AL, axial length; CRC, corneal radius of curvature; D, diopters. [a]Determined using Pearson χ^2 test.

Table 5: Comparison of ocular biometry among the three astigmatism change subgroups.

Ocular parameter	Astigmatism subgroups			*F*	*P* value
	Increase	Decrease	No change		
Baseline AL (mm)	23.33 ± 0.98*#	22.89 ± 0.84	23.06 ± 0.75	74.562	<0.001
AL change (mm)	0.68 ± 0.41*#	0.56 ± 0.36	0.53 ± 0.33	16.466	<0.001
Baseline AL/CRC ratio	2.99 ± 0.08*#	2.94 ± 0.08	2.93 ± 0.08	45.005	<0.001
AL/CRC ratio change	0.08 ± 0.06*#	0.07 ± 0.04	0.07 ± 0.04	9.312	<0.001
Baseline SER (D)	−0.63 ± 1.40*#	−0.07 ± 1.04	−0.01 ± 0.74	39.142	<0.001
SER change (D)	−0.86 ± 1.15*#	−0.31 ± 0.86	−0.39 ± 0.77	33.222	<0.001

AL, axial length; CRC, corneal radius of curvature; SER, spherical equivalent refraction; D, diopters; values are means ± standard deviations. *Compared to the decrease subgroup, $P < 0.001$; #compared to the no-change group, $P < 0.001$.

error showed little change (0.004 D) over the 28.5-month duration follow-up [25]. Chan et al. [4] found that the cylinder refraction decreased from −0.74 D to −0.58 D after a one-year follow-up in children aged 7–11 years. However, the Northern Ireland Childhood Errors of Refraction (NICER) study [26] reported that the prevalence of 6–7 years

old astigmates remained stable after a 3-year follow-up. The reasons for these differences may be attributed to the different populations and the standards used for astigmatism. Although both groups had overall reductions in astigmatism, astigmatism in diopters may increase, decrease, or remain unchanged for individual children. Dioptric changes of the absolute value of astigmatism was mostly in the range of >0 to <0.5 D in the two groups, which means that most of the changes were relatively small. In our study, we found that hyperopic astigmatism decreased and myopic astigmatism increased after two-year follow-up which was consistent with the data from Dobson et al. [7].

4.3. Association between Change of Astigmatism and Ocular Biometry. In our non-CSA group, 8.1% of the children developed CSA after two years. This incidence of CSA conversion from non-CSA was relatively low compared with the 11.5% of Singaporean children aged 7–9 who developed CSA (defined as cylinder refraction ≤−1.0 D) over a three-year duration [27] and the 9.1% of the children aged 6-7 years in the three years of the NICER study [26]. After accounting for the baseline age, gender, cylinder refraction, and axis of astigmatism, our multiple analyses showed that children with a baseline AL >23.58 mm, i.e., higher than the 75th percentile, were 5.19 times more likely to develop CSA. The baseline AL/CRC ratio >2.99, i.e., higher than the 75th percentile, was the independent factor most strongly associated with non-CSA developing to CSA after two years.

AL is correlated with SER in longer eyes more likely to be myopic [28]. Zhang et al. [29] reported that AL predicts the onset of myopia, and the AL/CRC ratio is strongly correlated with the SER [13, 30, 31]. AL/CRC ratio can be a useful marker of the onset and the progression of myopia [32]. Several studies [33–35] reported no significant change in the AL or AL/CRC ratio before and after mydriasis which compares well with measurements in other studies with or without cycloplegia. We speculate that eyes with ALs longer than 23.58 mm and with AL/CRC ratios higher than 2.99, both of which indicate a high likelihood of myopia, are more likely to develop CSA. In our study, the percentage of baseline AL (>23.58 mm) and AL/CRC ratio (>2.99) for the top quartile was significantly higher in myopes compared with that in emmetropes and hyperopes. The mean ALs and AL/CRC ratios were also larger among myopes than emmetropes and hyperopes, a finding consistent with our hypothesis. In a cross-sectional study, Huang et al. [36] found that myopia was associated with an increased risk of astigmatism. Tong et al. [27] reported a similar result that children who were myopic at baseline had a higher incidence of astigmatism than nonmyopes. Increased myopia is often accompanied by changes in axial length and corneal curvature [37]. In this study, we found that for non-CSA children who developed myopic astigmatism, the radius of CR of the horizontal meridian increased and the radius of CR of the steep meridian was of no change. The AL growth may cause corneal morphologic changes which result in curvature and axial asymmetries and increased chance of developing astigmatism. However, due to the limited sample size, the specific change of the radius of CR and the reasons should be further studied.

In another, among the non-CSA eyes that converted to CSA, the percentages of baseline ALs <22.53 mm and AL/CRC ratios <2.89 for the bottom quartile were significantly higher in hyperopes compared to emmetropes and myopes. The lower ALs and lower AL/CRC ratios are more likely to be in hyperopic eyes [28]. Compared with the bottom quartile for AL or AL/CRC ratio, ALs of 22.53–23.58 mm or AL/CRC ratios of 2.89–2.99 were not independent factors associated with non-CSA developing to CSA even though it has been reported that hyperopic eyes are more likely to be astigmatic than myopic eyes [7]. Fotouhi et al. [9] found that the association between astigmatism and myopia (odds ratio = 8.81) was stronger than its association with hyperopia (Odds ratio = 3.81). However, our study showed the opposite results. The relationship between astigmatism and hyperopia is still unclear and should be further studied.

Our results showed that compared with the decreased CSA subgroup and the unchanged subgroup, children in the increased CSA subgroup had longer ALs, higher AL/CRC ratios, and greater increases in AL and AL/CRC. Also, the increased astigmatism was correlated with higher myopic refraction and myopic development. This indicates that increased astigmatism is associated with visual blurring perturbations that might influence the development of myopia [38].

A limiting factor in our study was our use of manifest (noncycloplegic) refraction data. Zhang et al. [39] and Fotouhi et al. [9] both reported that dioptric astigmatism measured in children who consented to cycloplegia was similar to that measured in those who refused consent ($P = 0.248$; $P = 0.296$). However, obtaining refractive error in the absence of cycloplegia may overestimate myopic power and underestimate hyperopia [40]. Therefore, we used AL and AL/CRC ratio to serve as objective indicators for the development of myopia.

Other factors associated with astigmatism, such as ethnicity, body mass index, and parental astigmatism, were not included in our study. Neither did we analyze how internal astigmatism and corneal astigmatism changed, or how their individual effects related to the change of cylinder refraction.

5. Conclusion

The prevalence of astigmatism decreased slightly during the two-year follow-up. Children who had longer ALs and higher AL/CRC ratios were more likely to develop CSA. Increased astigmatism was associated with AL growth, AL/CRC ratio increase, and myopic development.

Data Availability

The original data, figures, and tables that were used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary Table 1 analyzed the baseline factors associated with CSA decreased to non-CSA after two years. However, the result was just the opposite of Table 2, and no more meaningful conclusions were reached. (*Supplementary Materials*)

References

[1] D. Robaei, K. Rose, E. Ojaimi, A. Kifley, S. Huynh, and P. Mitchell, "Visual acuity and the causes of visual loss in a population-based sample of 6-year-old Australian children," *Ophthalmology*, vol. 112, no. 7, pp. 1275–1282, 2005.

[2] E. M. Harvey, J. M. Miller, J. Schwiegerling, D. Sherrill, D. H. Messer, and V. Dobson, "Developmental changes in anterior corneal astigmatism in Tohono O'odham native American infants and children," *Ophthalmic Epidemiology*, vol. 20, no. 2, pp. 102–108, 2013.

[3] E. M. Harvey, J. M. Miller, J. D. Twelker, and D. L. Sherrill, "Longitudinal change and stability of refractive, keratometric, and internal astigmatism in childhood," *Investigative Ophthalmology & Visual Science*, vol. 56, no. 1, pp. 190–198, 2015.

[4] S.-E. Chan, H.-K. Kuo, C.-L. Tsai, and P.-C. Wu, "Astigmatism in Chinese primary school children: prevalence, change, and effect on myopic shift," *Japanese Journal of Ophthalmology*, vol. 62, no. 3, pp. 321–326, 2018.

[5] O. Pärssinen, M. Kauppinen, and A. Viljanen, "Astigmatism among myopics and its changes from childhood to adult age: a 23-year follow-up study," *Acta Ophthalmologica*, vol. 93, no. 3, pp. 276–283, 2015.

[6] J. D. Twelker, J. M. Miller, D. L. Sherrill, and E. M. Harvey, "Astigmatism and myopia in Tohono O'odham native American children," *Optometry and Vision Science*, vol. 90, no. 11, pp. 1267–1273, 2013.

[7] V. Dobson, E. M. Harvey, and J. M. Miller, "Spherical equivalent refractive error in preschool children from a population with a high prevalence of astigmatism," *Optometry and Vision Science*, vol. 84, no. 2, pp. 124–130, 2007.

[8] O. Pärssinen, "Astigmatism and school myopia," *Acta Ophthalmologica*, vol. 69, no. 6, pp. 786–90, 2009.

[9] A. Fotouhi, H. Hashemi, A. A. Yekta, K. Mohammad, and M. K. Khoob, "Characteristics of astigmatism in a population of schoolchildren, Dezful, Iran," *Optometry and Vision Science*, vol. 88, no. 9, pp. 1054–1059, 2011.

[10] H.-B. Wong, D. Machin, S.-B. Tan, T.-Y. Wong, and S.-M. Saw, "Ocular component growth curves among Singaporean children with different refractive error status," *Investigative Opthalmology & Visual Science*, vol. 51, no. 3, pp. 1341–1347, 2010.

[11] J. W. L. Tideman, J. R. Polling, J. R. Vingerling et al., "Axial length growth and the risk of developing myopia in European children," *Acta Ophthalmologica*, vol. 96, no. 3, pp. 301–309, 2018.

[12] V. H. Foo, P. K. Verkicharla, M. K. Ikram et al., "Axial length/corneal radius of curvature ratio and myopia in 3-year-old children," *Translational Vision Science & Technology*, vol. 5, no. 1, p. 5, 2016.

[13] S. K. Wang, Y. Guo, C. Liao et al., "Incidence of and factors associated with myopia and high myopia in Chinese children, based on refraction without cycloplegia," *JAMA Ophthalmology*, vol. 136, no. 9, pp. 1017–1024, 2018.

[14] V. Galvis, A. Tello, J. Otero et al., "Prevalence of refractive errors in Colombia: MIOPUR study," *British Journal of Ophthalmology*, vol. 102, no. 10, pp. 1320–1323, 2018.

[15] S. O. Wajuihian, "Characteristics of astigmatism in black south African high school children," *African Health Sciences*, vol. 17, no. 4, pp. 1160–1171, 2018.

[16] X. Han, X. Guo, P. Y. Lee, I. G. Morgan, and M. He, "Six-year changes in refraction and related ocular biometric factors in an adult Chinese population," *PLoS One*, vol. 12, no. 8, Article ID E0183364, 2017.

[17] K. S. Naidoo, A. Raghunandan, K. P. Mashige et al., "Refractive error and visual impairment in African children in south Africa," *Investigative Opthalmology & Visual Science*, vol. 44, no. 9, pp. 3764–3770, 2003.

[18] F. Rezvan, M. Khabazkhoob, A. Fotouhi et al., "Prevalence of refractive errors among school children in northeastern Iran," *Ophthalmic and Physiological Optics*, vol. 32, no. 1, pp. 25–30, 2012.

[19] G. P. Pokharel, A. D. Negrel, S. R. Munoz, and L. B. Ellwein, "Refractive error study in children: results from Mechi zone, Nepal," *American Journal of Ophthalmology*, vol. 129, no. 4, pp. 436–444, 2000.

[20] M. He, J. Zeng, Y. Liu, J. Xu, G. P. Pokharel, and L. B. Ellwein, "Refractive error and visual impairment in urban children in southern China," *Investigative Opthalmology & Visual Science*, vol. 45, no. 3, pp. 793–799, 2004.

[21] M. He, W. Huang, Y. Zheng, L. Huang, and L. B. Ellwein, "Refractive error and visual impairment in school children in rural southern China," *Ophthalmology*, vol. 114, no. 2, pp. 374.e1–382.e1, 2007.

[22] A. Chebil, L. Jedidi, N. Chaker et al., "Characteristics of astigmatism in a population of Tunisian school-children," *Middle East African Journal of Ophthalmology*, vol. 22, no. 3, pp. 331–334, 2015.

[23] S. O. Wajuihian and R. Hansraj, "Refractive error in a sample of black high school children in south Africa," *Optometry and Vision Science*, vol. 94, no. 12, pp. 1145–1152, 2017.

[24] H. S. Lin, H. Zhou, X. M. Li et al., "The distribution of astigmatism in children and adolescents in Wenzhou area and risk factor analysis," *Chinese Journal of Optometry Ophthalmology and Visual Science*, vol. 19, no. 6, pp. 369–375, 2017.

[25] J. Zhao, J. Mao, R. Luo, F. Li, S. R. Munoz, and L. B. Ellwein, "The progression of refractive error in school-age children: Shunyi district, China," *American Journal of Ophthalmology*, vol. 134, no. 5, pp. 735–743, 2002.

[26] L. O'Donoghue, K. M. Breslin, and K. J. Saunders, "The changing profile of astigmatism in childhood: the NICER study," *Investigative Opthalmology & Visual Science*, vol. 56, no. 5, pp. 2917–2925, 2015.

[27] L. Tong, S.-M. Saw, Y. Lin, K.-S. Chia, D. Koh, and D. Tan, "Incidence and progression of astigmatism in Singaporean children," *Investigative Opthalmology & Visual Science*, vol. 45, no. 11, pp. 3914–3918, 2004.

[28] R. P. C. Lira, C. E. L. Arieta, T. H. M. Passos et al., "Distribution of ocular component measures and refraction in Brazilian school children," *Ophthalmic Epidemiology*, vol. 24, no. 1, pp. 29–35, 2017.

[29] M. Zhang, G. Gazzard, Z. Fu et al., "Validating the accuracy of a model to predict the onset of myopia in children," *Investigative Opthalmology & Visual Science*, vol. 52, no. 8, pp. 5836–5841, 2011.

[30] E. Iyamu, J. Iyamu, and C. I. Obiakor, "The role of axial length-corneal radius of curvature ratio in refractive state categorization in a Nigerian population," *ISRN Ophthalmology*, vol. 2011, Article ID 138941, 6 pages, 2011.

[31] Z. G. Chen, M. C. Chen, J. Y. Zhang et al., "Analysis of the influence factors of school-age children's refractive status," *Chinese Journal of Ophthalmology*, vol. 52, no. 11, pp. 831–835, 2016.

[32] X. He, H. Zou, L. Lu et al., "Axial length/corneal radius ratio: association with refractive state and role on myopia detection combined with visual acuity in Chinese schoolchildren," *PLoS One*, vol. 10, no. 2, Article ID e0111766, 2015.

[33] X. Wang, J. Dong, M. Tang, X. Wang, H. Wang, and S. Zhang, "Effect of pupil dilation on biometric measurements and intraocular lens power calculations in schoolchildren," *PLoS One*, vol. 13, no. 9, Article ID e203677, 2018.

[34] B. Khambhiphant, N. Chatbunchachai, and K. Pongpirul, "The effect of pupillary dilatation on IOL power measurement by using the IOLMaster," *International Ophthalmology*, vol. 35, no. 6, pp. 853–859, 2015.

[35] J. Huang, C. McAlinden, B. Su et al., "The effect of cycloplegia on the lenstar and the IOLMaster biometry," *Optometry and Vision Science*, vol. 89, no. 12, pp. 1691–1696, 2012.

[36] J. Huang, M. G. Maguire, E. Ciner et al., "Risk factors for astigmatism in the vision in preschoolers study," *Optometry and Vision Science*, vol. 91, no. 5, pp. 514–521, 2014.

[37] F. González Blanco, J. C. Sanz Ferńandez, and M. A. Muńoz Sanz, "Axial length, corneal radius, and age of myopia onset," *Optometry and Vision Science*, vol. 85, no. 2, pp. 89–96, 2008.

[38] J. Gwiazda, K. Grice, R. Held, J. McLellan, and F. Thorn, "Astigmatism and the development of myopia in children," *Vision Research*, vol. 40, no. 8, pp. 1019–1026, 2000.

[39] L. Zhang, X. He, X. Qu et al., "Refraction and ocular biometry of preschool children in Shanghai, China," *Journal of Ophthalmology*, vol. 2018, Article ID 5205946, 10 pages, 2018.

[40] H. Hashemi, M. Khabazkhoob, A. Asharlous et al., "Cycloplegic autorefraction versus subjective refraction: the Tehran eye study," *British Journal of Ophthalmology*, vol. 100, no. 8, pp. 1122–1127, 2016.

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Research Article

Novel Method of Remotely Monitoring the Face-Device Distance and Face Illuminance Using Mobile Devices: A Pilot Study

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Specially developed software (app) was written for handheld electronic devices that uses the device camera and light detector for real-time monitoring of near-work distance and environmental lighting. A pilot study of this novel app employed children using tablet computers in a classroom. Measurements of face-device distance and face illuminance were obtained from two schools where tablets were used regularly. Children were divided randomly into a control group (CG) and intervention group (IG). The app was calibrated in a lab and configured to store average values every 20 seconds in a remote database. In both groups, the app recorded data only when a child's face was present in the camera image. The app darkened the screen for the IG when the face-device distance was shorter than 40 cm. The total mean face-device distance was 36.8 ± 5.7 cm in CG and 47.2 ± 6.5 cm in IG. Children in IG had to accommodate approximately 0.6 D less when using their devices. The mean classroom face illuminance was 980 ± 350 lux in School #1 and 750 ± 400 lux in School #2. The novel method of remotely monitoring and controlling the face-device distance and illuminance can potentially open new paths for myopia prevention and myopia control.

1. Introduction

Myopia is one of the principal causes of vision loss worldwide, and its prevalence is increasing [1, 2]. It has become a major public health concern due to comorbidities that can potentially result in blindness [3]. There is an increasing urgency in identifying factors with the highest impact on myopia onset and progression, as well as interventions that could prevent its onset or slow its progression.

Numerous studies show that myopia can be a consequence of an interaction of genetic [4, 5] and environmental factors [6] such as near work [7] and environmental light levels [8, 9]. At the same time, the almost universal use of personal electronic devices in recent years has increased the amount of daily near-work activities, as screens are often viewed closer than printed text [10, 11]. It has been hypothesized that intensive use of electronic devices by young children might trigger the onset and accelerate the progression of myopia [12], and yet children start using them at increasingly young age [13]. In the USA, 2015, the average time spent with mobile devices by children 8 and under was 2.3 h, a threefold increase from 2013, while 38% of the children under the age of 2 have used a mobile device [13].

A meta-analysis published in 2015 involving over 25 thousand subjects between 6 and 18 years of age found a strong correlation between near work and myopia [14]. The association between near work and odds of myopia increased by 2% per each additional diopter-hour of near-work activity. Another meta-analysis evaluating the impact of outdoor activities on the odds of myopia onset indicated a

2% decrease per each additional hour of time spent outdoors per week [15]. These results have been confirmed by a more recent work by Xiong et al. who reported that time spent by children engaged in outdoor activities in high-illumination conditions had a protective effect on myopia onset but not myopia progression [16]. They found a reduction between 2% and 5% in the odds of myopia onset due to an increase of outdoor activity.

In a 2018 study, Wu et al. [17] concluded that high environmental light levels can aid the emmetropization process. It is estimated that the illumination level on a sunny day can be approximately 100,000 lux, while indoors it is typically between 100 and 500 lux [18]. Several schools in Taiwan have implemented more outdoor activities so that children could rest from near-work indoors, and after a one-year study, it was found that the myopia incidence in these children dropped to 8.4% compared to 17.6% in children who did not participate in the study [19].

Performing near work indoors and performing activities outdoors are intertwined parts of everyday lives, and the extent of their separate influence on myopia onset and progression is still not well known due to the fact that it is very difficult to measure these factors in real life conditions and they are inherently correlated with each other (negative correlation). At the same time, if behavioral interventions to address myopia (such as modifying the visual demand during near work, increasing the time outdoors, or increasing classroom illumination) are to be implemented, it is critical to quantify the "dose" and ensure subject compliance with such interventions. This urgently calls for tools and methods that can measure and monitor these factors independently and accurately in real-time.

Unfortunately, until recently, methods were limited to questionnaire responses obtained from children or their parents [20–22]. Example questions include: "how many pages did the child read last week?" or "how many hours did the child spend outside?" Results obtained in this way inherently suffer from poor accuracy and precision because they depend on human memory and biases. As an example, Li et al. found that the correlation between two subsequent surveys related to outdoor activity conducted in an interval of three weeks was just 0.63 and Cronbach's α coefficient was an unacceptable 0.61 [23]. Although parents can estimate time spent outside, they are unable to quantify their children's near-work viewing distances and room illumination.

Most recently, modern range-finding technologies have been implemented as wearable clip-on devices that can attach to spectacle frames, which can measure the distance between the device and diffusely reflective objects (such as books) [24]. Other examples include a wearable light-sensing device in the form of a wristband [25] and novel methods to measure the time spent outdoors using ultraviolet exposure biomarkers [26, 27]. A common disadvantage of all of these methods is the fact that they require children to consistently wear unfamiliar pieces of technology.

On the other hand, modern mobile devices, which children already use extensively [12, 13], come equipped with a light sensor, front-facing camera, wireless connectivity, and processing power, which can be used to accurately measure both the face-device distance and face illuminance from the image of the face captured by the camera. Therefore, while being used normally and potentially contributing to myopia development, these devices can automatically monitor myopia-related behaviors, and, if desired, perform interventions, such as showing warnings on the electronic screen.

This study evaluated a novel method of real-time monitoring of near-work distance and face illuminance of children using mobile devices that were equipped with software developed for this purpose.

2. Materials and Methods

2.1. Overview and Principle of Operation of the App. Software was loaded onto each tablet as a custom app (not available in the market at the time), which once activated is designed to run continuously in the background of the operating system. This software and the device hardware are together capable of measuring the face-device distance and face illuminance in real-time during normal use of the device. User-determined options can activate "warnings" when certain device-user characteristics were evaluated by the app exceeded user-defined parameters such as a minimum viewing distance. For example, the screen could be darkened when the measured distance was shorter than a certain preselected minimum distance (Figure 1).

The face-device distance measurement algorithm required an individual one-time (per subject and device) calibration procedure, the principle of which is expressed in

$$K = d_c \cdot n_c, \tag{1}$$

where K is a constant value which depends on the device and can be calculated by equation (1) knowing the value of d_c, which is the calibration distance, and the value of n_c, the number of pixels in the image of the user's head captured by a front camera of the device during the calibration.

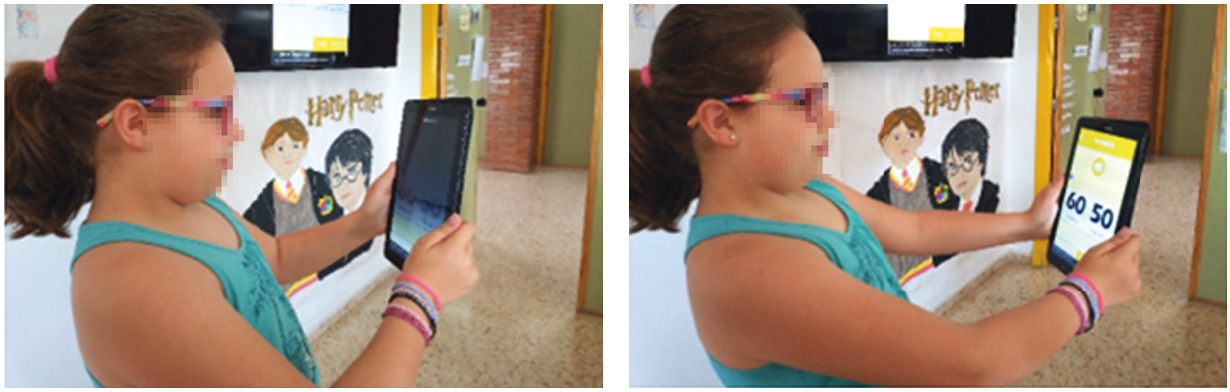
The face-device distance d_t could then be estimated in real-time using the following equation:

$$d_t = \frac{K}{n_t}, \tag{2}$$

where n_t is the number of pixels in the image of the user's head captured by a front camera of the device at time t. The methodology is further described in detail in the application patent from López Gil and Liu [28].

Additionally, the app was capable of measuring the face illuminance using two methods: with a built-in, wide field-of-view ambient light sensor (typically situated close to the front camera) [29] and with the front camera itself—by using the pixels in the image of a user's head. In the present study, the former method was used.

The app was configured to store average values of distance (in mm) and illuminance (in lux) along with a timestamp every 20 seconds in a remote database. The app recorded data only when the child's face was present in the image from the front camera with a frame rate of 30 fps.



(a) (b)

Figure 1: When the student's face-device distance is shorter than a preconfigured distance (in this case, 40 cm), the screen is partially darkened (a), making the student move the device further away (b) to restore normal screen brightness.

2.2. Calibration of Face-Device Distance Measurements. The accuracy of distance and illuminance measurements was evaluated in laboratory conditions using the same model device that was to be used in schools (Samsung Galaxy™ Tab A SM-P580 with a 10-inch screen). Repeat measurements were collected from one subject, who used a chinrest to stabilize the position of the head. An optical bench was placed in front of the chinrest, allowing for accurate positioning of the device (±1 mm) between 40 and 250 cm (Figure 2). The minimum distance was limited by the FOV of the camera (46° for a 28 mm equivalent focal length lens). The 2 megapixel images (1920 × 1080 pixel) were sufficient to assess face image size at distances up to 250 cm.

The face-distance measurement calibration was carried out using two different calibration distances ($d_c = 60$ cm and 200 cm) to verify how it affected the measurement accuracy. At each calibration distance, the software detected the face, and the operator entered the distance and the software calculated K (equation (1)). Subsequently, the position of the device in the optical bench was changed in 10 cm increments, three measurements of face-device distance were recorded by the app, and the average and standard deviation were calculated. Figure 3 shows the difference between the device-determined vergence (inverse of distance in meters) and the actual face-device vergence. A positive sign for the vergence convention has been used for real stimulus.

The distance measurement error did not exceed 5 mm (equivalent to a vergence error <0.03 D at a viewing distance of 40 cm). These results are similar to those previously reported using the same methodology in other devices [30]. The mean and 95% limit (±1.96 ∗ SD) of the agreement in the vergence measurement (Figure 3(b)) were −0.01 ± 0.05 D and 0.02 ± 0.04 D for the 60 cm and 200 cm calibration, respectively.

2.3. Calibration of Face Illuminance Measurements. Calibration of illumination measurement (Figure 4) used a chinrest and optical bench with the face-device distance fixed at 30 cm. A dome-type lux meter (Hanna HI 97500) was situated at the eye level (temporal to right eye). The

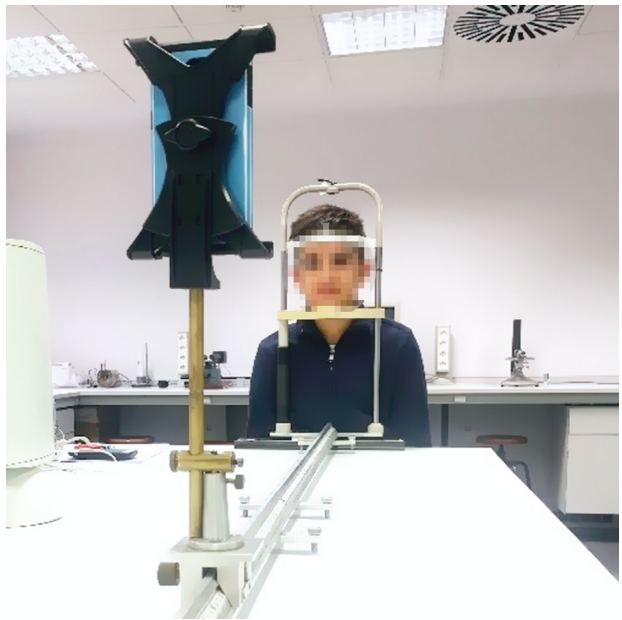


Figure 2: Laboratory setup used for testing the accuracy of face-device distance measurements. Face position was stabilized with a chin and forehead rest, and the mobile device position was adjusted along the optical bench.

room was illuminated with two variable-power 500 W incandescent lights placed on the table top at a distance of approximately 40 cm from the face, and the room's ceiling fluorescent lights were either on or off.

In total, 21 single measurements of illumination were taken within the range from 10 to 1200 lux (Figure 5). The standard deviation of repeat measures of face illumination obtained by the tablet with the app was corresponded to the instrument error: ±1 lux.

The slope of 0.292 in the linear fit to the data in Figure 5(a) indicates that, in order to obtain real face illumination values, the tablet lux meter readings needed to be multiplied by its inverse (3.425). The lower tablet lux meter [29] readings reflect its wide angle of integration (typically

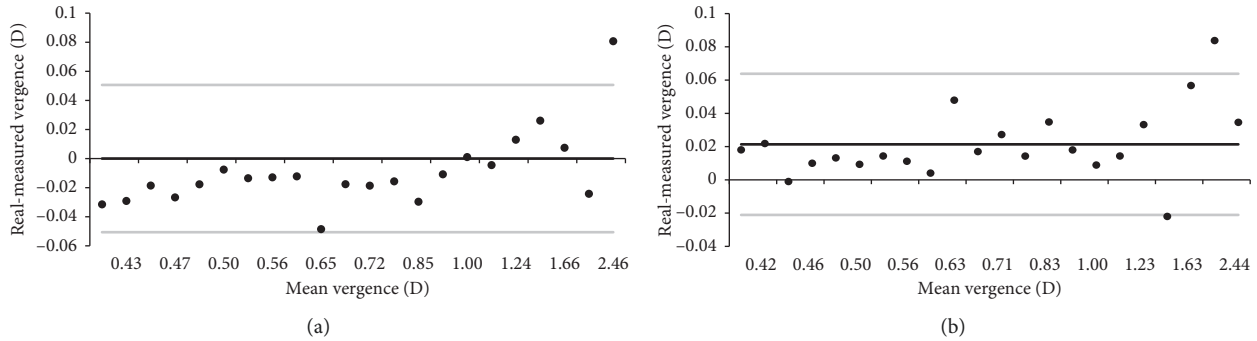


Figure 3: Bland-Altman plots of differences between observed and actual face-device vergence after calibration at 60 cm (a) and 200 cm (b). Black line represents the mean value and grey lines the 5th and 95th percentiles of the difference distributions.

Figure 4: Laboratory setup for evaluating accuracy of illumination measurements. Face position was fixed with a chin and forehead rest. A lux meter was placed temporal to the right eye and in the eye plane.

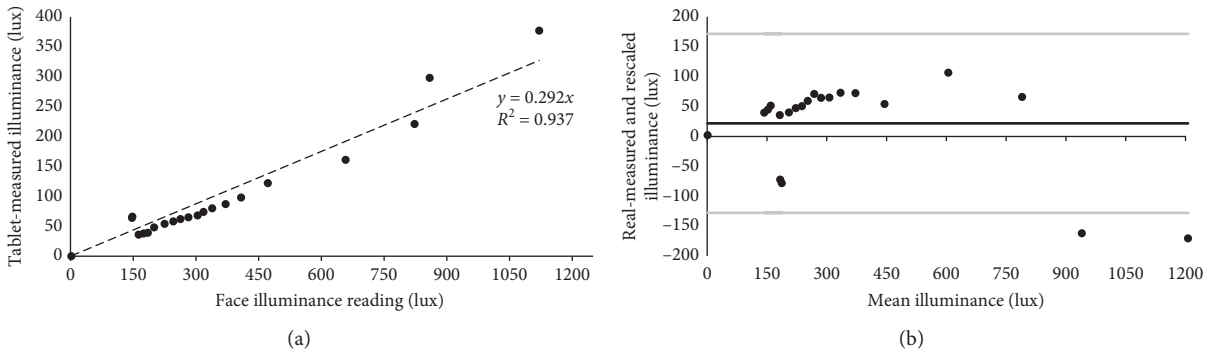


Figure 5: Illuminance measurements as a function of light meter readings. The dotted line in (a) shows the fitting straight line with a slope of 0.292. Bland-Altman plot in (b) shows the same measurement results but rescaled after using the slope value. Black line in (b) represents the mean value and grey lines the 5th and 95th percentiles of the difference distributions.

~60 degrees). The illuminated face subtended only a portion of this angle, and the wall of the lab, being further away, had lower illuminance from the halogen lights (inverse square law); hence, the solid angle integration (approximately 1.05 sr) resulted in the lower average illuminance. Future developments which measure light only in the pixels in the

image of the face taken with the front camera will eliminate the need for this scaling factor.

The four out-lying points seen in Figure 5(a) appear to be aligned together. This occurred because the fluorescent ceiling lights were on for these measurements and the wide angle of integration of the tablet light sensor included light coming from the fluorescent lights on the ceiling in addition to the light reflected from the face. When the four points are not taken into account the fitting parameter, R^2, increases to 0.986. These four out-lying points also increase the interval of confidence in the Bland-Altman plots in Figure 5(b). In order to improve the accuracy of the calibration, the lab conditions should ideally reflect classroom conditions, which are not standardized and can vary significantly between schools.

The mean and 95% limit ($\pm 1.96 * \mathrm{SD}$) of the agreement in the rescaled illuminance measurement (Figure 5(b)) were 21 ± 150 lux.

Face illuminance yielded by light emitted by the screen of a device is usually much lower than room illumination. For instance, illuminance of 190 lux was obtained when the room lights were on and the screen was off, which increased only by 8 lux when the screen was turned on, displaying a white target at full brightness. This result emphasizes that the measured illuminance is reflective of general environmental lighting (e.g., room or sky).

2.4. Measurements in Schools. Distance and illuminance measurements were obtained from two schools where tablets were used as a part of their regular teaching programme: CEIP Torrealta in Molina de Segura (School #1) and CEIP Esparragal in Puerto Lumbreras (School #2), both located in the region of Murcia (Spain). The number of participants was 11 and 34 in School #1 and School #2, respectively. Ages ranged from 10 to 13 years (10.6 ± 0.5 years in School #1 and 11.1 ± 0.7 years in School #2). No subjects suffered from any vision problems which would impair their ability to use a tablet at a distance greater than 40 cm. The participation in the study was voluntary. Before the commencement of the study, it was approved by the Ethics Committee of the University of Murcia and the participants were informed about their rights and their parents or legal guardians received an informed consent form in accordance with the guidelines of the Ethics Committee. The research followed the tenets of the Declaration of Helsinki.

The app was installed in 45 tablets (Samsung Galaxy™ Tab A SM-P580), used daily during classes in both schools. Each tablet was associated with one child, and the near-work distance measurement calibration was performed individually to ensure the accuracy of measurements. The room illuminance in both classes was measured using a lux meter (Hanna HI 97500) at three different places, and the range of illuminance was similar to the one used during the accuracy testing.

The children wore their habitual refractive correction and were randomly divided into two groups: control group (CG) with 21 subjects and intervention group (IG) with 24 subjects. The intervention group experienced the partial darkening effect applied to the screen of the device whenever the face-device distance measured by the app was shorter than the preconfigured distance of 40 cm. Children could still interact with the devices but had to move it beyond the preconfigured distance for the screen brightness to recover. There was no intervention in the CG, but in both IG and CG, the app carried out measurements (near-work distance, time, and illumination) in the background of the operating system and synchronized the data with a remote database using the wireless connection of the tablets. These were the only data that were synchronized (no personal details, photos, or other data were recorded). Due to the limited time we had for the measurements, it was decided to avoid a crossover design in which each child would be their own control.

The study was carried out over 15 days. In School #1, the total time the children used the app was 15 hours, on average 82 min per student. In School #2, the total time was 29 hours, on average 51 min per student. In total, over 10000 data samples were obtained.

3. Results

3.1. Face-Device Distance Measurements. Figures 6(a) and 6(b) show the near-work distance measurements for each child in the CG and IG, respectively.

The mean face-device distance (grey bar) was 36.8 ± 5.7 cm in CG and 47.2 ± 6.5 cm in IG (grey bars on right of Figure 6), corresponding to 2.7 and 2.1 D of vergence, respectively. The percentage of children who used their devices at a distance greater than 40 cm was 24% and 92% in the CG and IG, respectively. When no distinction is made between children from different schools, the difference was statistically significant ($p = 9.85\ 10^{-7}$), just as when the same t-test was applied to the data from each school separately ($p = 0.001$ and 0.0001 for Schools #1 and #2, respectively). Habitual near-work distance did not differ between schools ($p = 0.56$).

3.2. Illumination Measurements. Figures 7(a) and 7(b) show the mean and SD face illuminance measurements for each child in School #1 and School #2, respectively.

The total mean classroom face illuminance (grey bar) was 980 ± 350 lux in School #1 and 750 ± 400 lux in School #2. The difference in face illuminance measurements between both Schools was significant ($p = 0.048$).

4. Discussion

4.1. Face-Device Distance. Calibration revealed that devices equipped with the face-distance measuring app could measure viewing distance with an accuracy below 5 mm and a precision of approximately 1 cm or better (vergence error <0.03 D) within the range from 40 to 250 cm. This includes the typical mobile device use distance, which usually does not exceed one meter [11]. Additionally, it was found that the calibration performed at 200 cm resulted in slightly more accurate measurements compared to data collected after calibration at 60 cm.

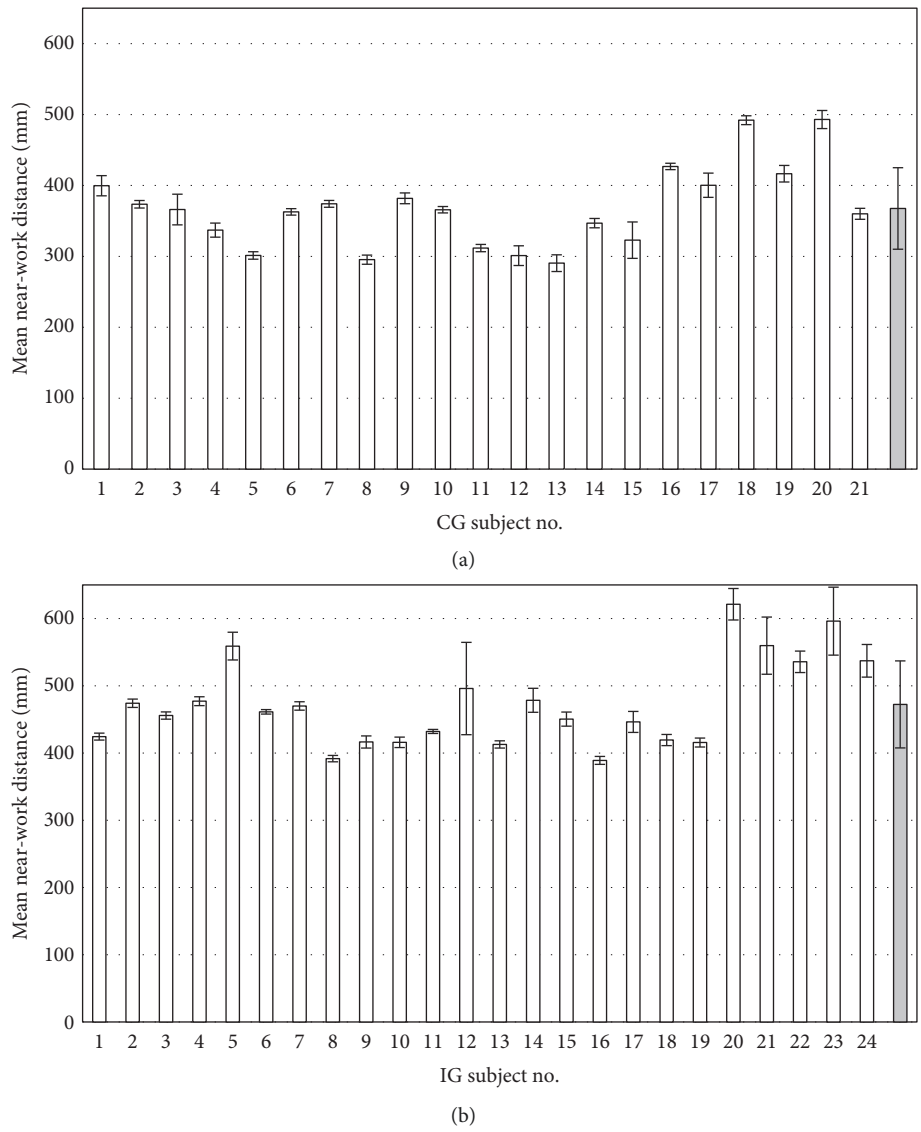


Figure 6: Mean (±1 SD) intersubject near-work distance of each child in the control group (CG) (a) and intervention group (IG) (b). The grey bars represent the mean for the entire group.

Most students became familiar with the app very quickly, and after several times, the tablet's screen became dark, they learned to use and maintain it beyond the preconfigured distance of 40 cm (mean distance in the IG was 47.2 ± 6.5 cm). The results from CG indicate that the students' habitual face-device distance was 36.8 ± 5.7 cm when they performed near-work with their 10-inch tablets. There were no significant differences in habitual near-work distance in children from both schools ($p > 0.05$ between subjects in CG subdivided into both schools).

The total mean face-device distance in IG was 10.3 cm greater than in CG. The mean face-device distance in IG was greater than 40 cm for all subjects except for subjects #8 and #16, who were close (39.1 cm and 38.9 cm, respectively), which can be due to small individual calibration errors, forcing the darkness of the screen of the mobile device by under 40 cm. In dioptric terms, without taking into account errors of accommodation (or assuming that it was the same in both groups), this translated to a 0.6 D decrease in visual demand in IG compared to CG. In other words, the IG subjects had to accommodate less when using their devices. The precision with which the threshold for dimming was adapted to by the children indicate larger reductions in dioptric demand can be introduced by a simple adjustment to the app, e.g., set the preconfigured intervention distance to 50 cm and these students would have reduced their accommodative demand by approximately 1 D. The differences between mean intersubject near-work distances between IG and CG were significant ($p < 0.05$), with and without the Bonferroni correction [31], both when analyzing schools separately and together.

The tilt of the device with respect to the face of the user could potentially give a wrong reading of the distance user-device. Figure 8 shows a schematic of this limitation.

The error b—a of the measurement can be approximated by the formula in equation (1):

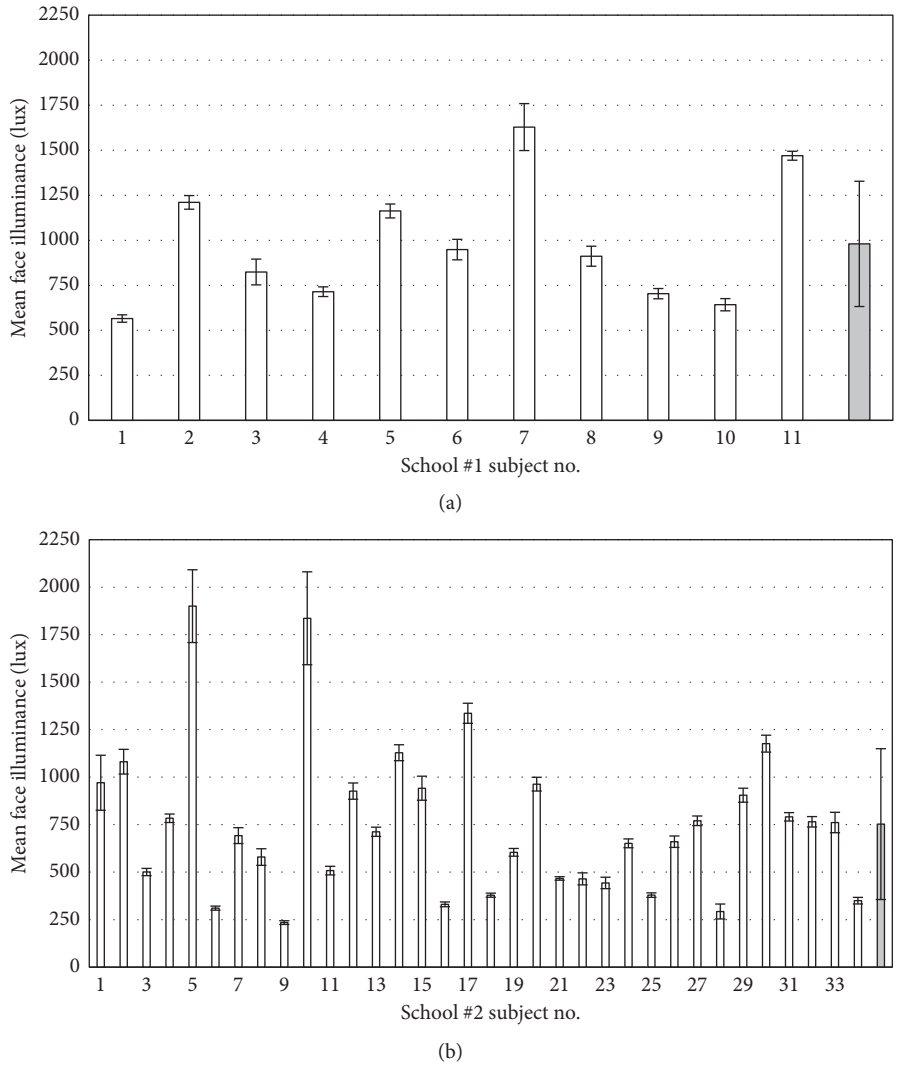


Figure 7: Mean (±1 SD) intersubject face illuminance in School #1 (a) and School#2 (b). The grey bars (last "subject") represent the total mean for the entire group.

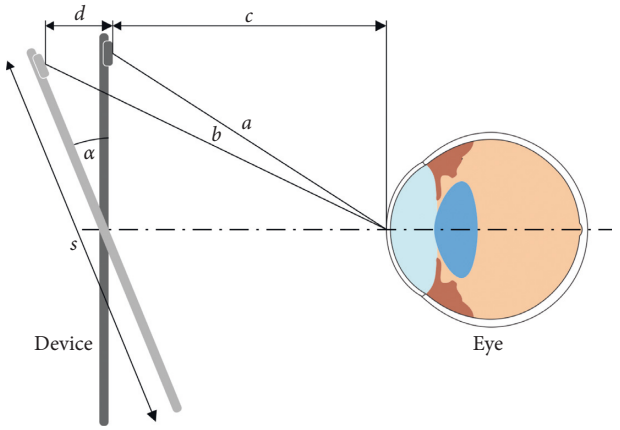


Figure 8: Change of distance from the camera C to the eye E of a tablet of height s when tilted by an angle α with respect to its original orientation parallel to the face.

$$b - a \approx d = \frac{s}{2} \cdot \sin \alpha, \tag{3}$$

where d is the approximate measurement error, s is the tablet height ($c > s/2$), and α is the tablet tilt.

In the present study, $s = 25.4$ cm and half of the field of view (FOV) of the camera of the device was 23°. Although the maximum error obtained from equation (1) is 5 cm, the face detection algorithm in the app used the whole height of the face, so the real maximum tilt angle is lower than 23°. Additionally, since the measurement error in equation (1) is linearly dependent on the tablet height, it can be expected to be lower when a smartphone is used instead.

4.2. Face Illuminance. Activities in School #1 were carried out with the blinds wide open and often with ceiling lights on. Meanwhile, in School #2, the majority of the blinds were

(a) (b)

Figure 9: Use of tablets in two schools: School #1 (a) and School #2 (b).

rolled down and the ceiling lights were on (Figure 9). These observations were confirmed by the total mean values of face illuminance measured by tablets with the app: 980 ± 350 and 750 ± 400 lux in Schools #1 and #2, respectively (Figure 7). The measured illuminance levels were both higher than 300 lux required by law in the state of Murcia [32] and 652 lux reported by Read et al. as the average daily illuminance values which yielded low risk to increase myopia [33].

On the other hand, the measured mean illuminance values were 3 to 4 times higher than 248 ± 168 lux obtained in 2017 by Ostrin et al. using a wrist band device in school [25]. Since ambient light sensors included in smart watches and wrist bands are semiconductor devices similar to the ones included in smart phones and tablets, the higher measured illuminance with the tablets likely reflects the measurement geometry. A hand wearing a wrist band can often be lowered to the level of the hip or covered by clothes, whereas the tablets are always directed towards the face of the user and precalibrated in the lab to measure face illuminance. The app recorded data only when the child's face was present in the image from the front camera. The differences with previous studies can also be explained by the different geographical locations, season, and time of day. Both locations (Murcia and Houston) share similar latitudes (37 and 30 degrees North), but the former has a slightly larger annual solar exposure levels (2069 kWh/m^2 compared to 1870 in Houston) [34].

The large variations in illumination between subjects (Figure 7) can be explained by the inhomogeneity in the illumination of the class in both schools. To test this hypothesis, the illuminance in different locations of the classroom in School #1 was measured using a lux meter at the same time of a sunny day. The difference between the minimum and maximum readings exceeded 600 lux. Direct exposure of the lux meter to sunlight was avoided (just like children would avoid direct sun in their face during a class). These values indicate that the illumination can vary as much as three times (possibly more) throughout the classroom.

During the measurement of illumination was being proceeded, we found a limitation which is the same as to the measure of distance. This restriction is on the tilt of the distance which can influence the measurement. In this particular case, it is highly important to bear in mind that the sensor must avoid a luminous focus above because it could cause the alteration of the measure, as a consequence. Thus, the most appropriate environment for this sensor is a room with a homogenous illumination due to the few changes, which could emerge in the measurement. The same would happen if whether we have a different skin tone, different clothing, or different background since it would not have as much impact as a bright focus above the sensor.

5. Conclusions

In summary, the results show that the proposed novel method of intervening with an app in excessive near work performed by schoolchildren while studying has accomplished its purpose of extending their habitual near-work distance without introducing any new elements into their environment. Thus, the novel method implemented in an app which was developed and tested in the present work can have potential impact on myopia onset and progression. By accurately measuring the near-work distance and face illuminance, the app has the ability to disentangle the independent contribution of each factor in myopia onset and progression. This needs to be tested in properly designed clinical trials, now made possible by the advances in the hardware of mobile devices.

It is also important to point out that there are many near work activities that children perform in the classroom that do not involve the use of an electronic devices (i.e., reading text books, or writing in their note books). For future research, other measures should be taken to control those activities carried out without the use of an electronic device.

Data Availability

The data used in this study are available upon request to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

[1] B. A. Holden, T. R. Fricke, D. A. Wilson et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050," *Ophthalmology*, vol. 123, no. 5, pp. 1036–1042, 2016.

[2] E. Dolgin, "The myopia boom," *Nature*, vol. 519, no. 7543, pp. 276–278, 2015.

[3] D. I. Flitcroft, "The complex interactions of retinal, optical and environmental factors in myopia aetiology," *Progress in Retinal and Eye Research*, vol. 31, no. 6, pp. 622–660, 2012.

[4] F. Douglas, "Myopia," *BMJ*, vol. 324, pp. 1195–1199, 2002.

[5] V. J. M. Verhoeven, G. S. H. Buitendijk, G. H. S. Buitendijk et al., "Education influences the role of genetics in myopia," *European Journal of Epidemiology*, vol. 28, no. 12, pp. 973–980, 2013.

[6] J. M. Ip, K. A. Rose, I. G. Morgan, G. Burlutsky, and P. Mitchell, "Myopia and the urban environment: findings in a sample of 12-year-old Australian school children," *Investigative Opthalmology & Visual Science*, vol. 49, no. 9, pp. 3858–3863, 2008.

[7] D. Mutti, G. L. Mitchell, M. L. Moeschberger, L. A. Jones, and K. Zadnik, "Parental myopia, near work, school achievement, and children's refractive error," *Investigative Ophthalmology & Visual Science*, vol. 43, pp. 3633–3640, 2002.

[8] T. T. Norton and J. T. Siegwart, "Light levels, refractive development, and myopia—a speculative review," *Experimental Eye Research*, vol. 114, pp. 48–57, 2013.

[9] J. C. Sherwin, M. H. Reacher, R. H. Keogh, A. P. Khawaja, D. A. Mackey, and P. J. Foster, "The association between time spent outdoors and myopia in children and adolescents," *Ophthalmology*, vol. 119, no. 10, pp. 2141–2151, 2012.

[10] C. Myrberg and N. Wiberg, "Screen vs. paper: what is the difference for reading and learning?," *Insights the UKSG journal*, vol. 28, no. 2, pp. 49–54, 2015.

[11] Y. Bababekova, M. Rosenfield, J. E. Hue, and R. R. Huang, "Font size and viewing distance of handheld smart phones," *Optometry and Vision Science*, vol. 88, no. 7, pp. 795–797, 2011.

[12] S. McCrann, I. Flitcroft, K. Lalor, J. Butler, A. Bush, and J. Loughman, "Parental attitudes to myopia: a key agent of change for myopia control?," *Ophthalmic and Physiological Optics*, vol. 38, no. 3, pp. 298–308, 2018.

[13] V. Rideout, *The Common Sense Census: Media Use By Kids Age Zero To Eight*, Common Sense Media, San Francisco, CA, USA, 2017.

[14] H. M. Huang, D. S. Chang, and P. C. Wu, "The association between near work activities and myopia in children-a systematic review and meta-analysis," *PLoS One*, vol. 10, no. 10, Article ID e0140419, 2015.

[15] J. Wang, X. G. He, and X. Xu, "The measurement of time spent outdoors in child myopia research: a systematic review," *Int J Ophthalmol.*vol. 11, no. 6, pp. 1045–1052, 2018.

[16] S. Xiong, P. Sankaridurg, T. Naduvilath et al., "Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review," *Acta Ophthalmologica*, vol. 95, no. 6, pp. 551–566, 2017.

[17] P.-C. Wu, C.-T. Chen, K.-K. Lin et al., "Myopia prevention and outdoor light intensity in a school-based cluster randomized trial," *Ophthalmology*, vol. 125, no. 8, pp. 1239–1250, 2018.

[18] R. A. Stone, Y. Cohen, A. M. McGlinn et al., "Development of experimental myopia in chicks in a natural environment," *Investigative Opthalmology & Visual Science*, vol. 57, no. 11, pp. 4779–4789, 2016.

[19] P.-C. Wu, C.-L. Tsai, C.-H. Hu, and Y.-H. Yang, "Effects of outdoor activities on myopia among rural school children in Taiwan," *Ophthalmic Epidemiology*, vol. 17, no. 5, pp. 338–342, 2010.

[20] J. M. Ip, S.-M. Saw, K. A. Rose et al., "Role of near work in myopia: findings in a sample of Australian school children," *Investigative Opthalmology & Visual Science*, vol. 49, no. 7, pp. 2903–2910, 2008.

[21] B. Kinge, A. Midelfart, G. Jacobsen, and J. Rystad, "The influence of near-work on development of myopia among university students. A three-year longitudinal study among engineering students in Norway," *Acta Ophthalmologica Scandinavica*, vol. 78, no. 1, pp. 26–29, 2000.

[22] S.-M. Saw, A. Carkeet, K.-S. Chia, R. A. Stone, and D. T. H. Tan, "Component dependent risk factors for ocular parameters in Singapore Chinese children," *Ophthalmology*, vol. 109, no. 11, pp. 2065–2071, 2002.

[23] S. M. Li, S. Y. Li, M. T. Kang et al., "Near work related parameters and myopia in Chinese children: the Anyang Childhood Eye Study," *PLoS One*, vol. 10, Article ID e0134514, 2015.

[24] L. Wen, W. Lan, Y. Huang, Y. Wu, X. Li, and Z. Yang, "A novel device to record the behavior related to myopia development—preliminary results in the lab," *Investigative Ophthalmology & Visual Science*, vol. 57, no. 12, p. 2491, 2016.

[25] L. A. Ostrin, "Objectively measured light exposure in emmetropic and myopic adults," *Optometry and Vision Science*, vol. 94, no. 2, pp. 229–238, 2017.

[26] J. C. Sherwin, C. M. McKnight, A. W. Hewitt, L. R. Griffiths, M. T. Coroneo, and D. A. Mackey, "Reliability and validity of conjunctival ultraviolet autofluorescence measurement," *British Journal of Ophthalmology*, vol. 96, no. 6, pp. 801–805, 2012.

[27] J. C. Sherwin, A. W. Hewitt, M. T. Coroneo, L. S. Kearns, L. R. Griffiths, and D. A. Mackey, "The association between time spent outdoors and myopia using a novel biomarker of outdoor light exposure," *Investigative Opthalmology & Visual Science*, vol. 53, no. 8, pp. 4363–4370, 2012.

[28] N. López Gil and Y. Liu, "System and Method for Preventing sight Deterioration caused by near work with devices with electronic screens," Patent No. WO 014960 A1, 2018.

[29] Capella Microsystems Inc, *CM3323 Color Sensor with I2C Interface*, Capella Microsystems Inc, Santa Clara, CA, USA, 2012, http://www.capellamicro.com.tw/EN/index.php.

[30] M. T. Jaskulski, Y. Liu, and N. López-Gil, "Measuring face illumination and near work distance using personal mobile devices," *Invest. Ophthalmol. Vis. Sci.*vol. 59, no. 9, p. 2152, 2018.

[31] R. A. Armstrong, "When to use the Bonferroni correction," *Ophthalmic and Physiological Optics*, vol. 34, no. 5, pp. 502–508, 2014.

[32] IDAE Instituto para la Diversificación y Ahorro de la Energía, *Guía Técnica de Eficiencia Energética en Iluminación*, Centros docentes, Madrid, Spain, 2001, http://www.idae.es/.

[33] S. A. Read, M. J. Collins, and S. J. Vincent, "Light exposure and eye growth in childhood," *Investigative Opthalmology & Visual Science*, vol. 56, no. 11, pp. 6779–6787, 2015.

[34] O. Knight, *Assessing and Mapping Renewable Energy Resources*, ESMAP Knowledge Series, Washington, DC, USA, 2016.

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Research Article

Changes in Retinal Vasculature and Thickness after Small Incision Lenticule Extraction with Optical Coherence Tomography Angiography

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Purpose. To evaluate the changes in retinal vessel density and thickness after small incision lenticule extraction (SMILE) with optical coherence tomography angiography (OCTA) in myopic patients. *Methods*. In this prospective study, SMILE surgeries were done in 46 eyes of 24 patients with spherical equivalent (SE) more than −6.0 diopters (*D*). Retinal vessel density and thickness at the macula and optic nerve were recorded with OCTA before and 1 day, 2 weeks, and 1 month after surgery. Intraocular pressure (IOP), uncorrected distance visual acuity (UDVA), and refraction were taken at the same time. *Results*. The superficial retinal vessel density and deep foveal retinal vessel density 1 day after surgery were less than those before surgery; however, the changes at any timepoints were not statistically significant ($p = 0.2736$ and $p = 0.1590$, respectively). Both the superficial vessel density and deep vessel density at the parafoveal and perifoveal regions decreased significantly 1 day postoperatively (all $p < 0.05$) and then returned to the preoperative level at 2 weeks and stabilized thereafter. There were no significant changes in any of the 4 vessel densities in the area of peripapillary before and 1 day, 2 weeks, and 1 month after surgery ($p = 0.3345$). No statistically significant differences between preoperative and postoperative retinal thickness were detected for the area of macula and optic nerve (all $p > 0.5$). *Conclusions*. The vessel density at the parafoveal and perifoveal regions decreased at 1 day after SMILE with no effect on the visual acuity and relieved within 2 weeks. Decreased ocular blood flow in response to the spike in IOP may account for such changes.

1. Introduction

Femtosecond laser-assisted corneal refractive surgeries hold major part in treating refractive errors nowadays. During these procedures, vacuum suction is inevitable. Previous studies have shown intraocular pressure (IOP) increased during suction-mediated application of the glass contact, which is used in flap creation and refractive cut during the femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK) and femtosecond lenticule extraction (FLEx) and even femtosecond laser-assisted cataract surgery [1–3]. The sudden spike in IOP to levels exceeding 65 mmHg, which can damage the eye, has been observed during the traditional microkeratome flap creation of laser in situ keratomileusis (LASIK) [4, 5]. Femtosecond laser creation exerts less extreme IOP fluctuations but requires more procedural time than LASIK [3, 6, 7]. It is suggested that acute increases in IOP can induce ischemia-reperfusion injury, which may cause retinal ganglion cell death as well as damage to the optic nerve and retina [8, 9]. Though most researchers showed suction had no significant clinical effects on the macular and retinal nerve fiber layer (RNFL) thickness during FS-LASIK or FLEx [10–12], macular hemorrhage after FS-LASIK was reported in a patient with a moderate

degree of myopia and no macular pathology [13]. Thus, the effect of sudden spike in IOP on the retina caused by suction during the femtosecond laser procedures is still a widespread concern among ophthalmologists.

Since 2011, the VisuMax femtosecond laser has been used to make the refractive cut in the small incision lenticule extraction (SMILE) procedure [14]. Studies have showed SMILE to be precise and accurate in treating refractive errors [15, 16]. The procedure of SMILE has two steps: creation of the lenticule with femtosecond laser and separation/extraction of the lenticule from the corneal stroma. However, whether the sudden spike in IOP and the lenticule separation during SMILE damage the retina remains unknown. Furthermore, Shoji et al. showed that a change in retinal vessel density could be detected before a change in ganglion cell complex (GCC) thickness occurs [17]. Therefore, the aim of this prospective study was to evaluate the changes in retinal vasculature and thickness after uncomplicated SMILE with optical coherence tomography angiography (OCTA) in myopic patients.

2. Methods

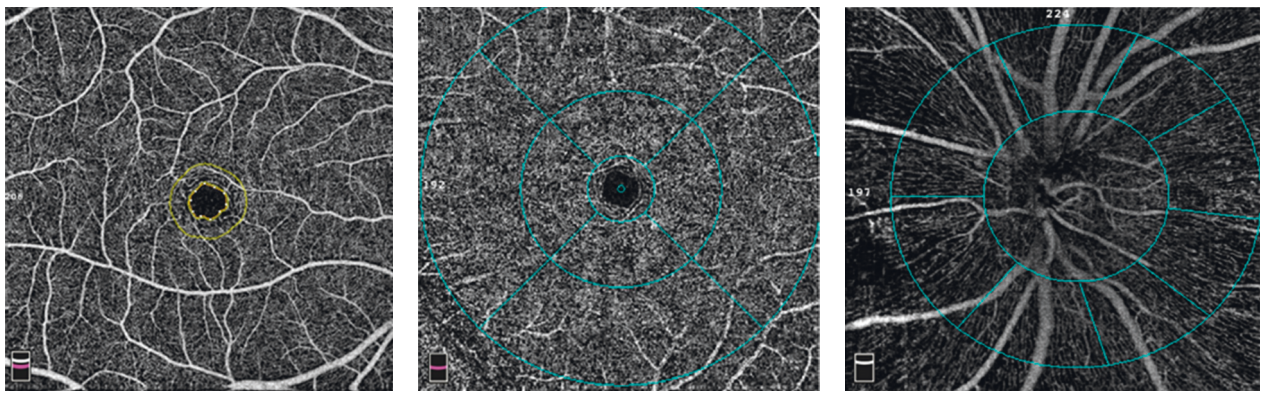
2.1. Participants. This study was approved by the Institutional Review Board of the Eye & ENT Hospital of Fudan University. All procedures adhered to the Declaration of Helsinki and were conducted in accordance with the approved research protocol. Informed consent was obtained from all participants before enrollment. Twenty-four patients (46 eyes) undergoing SMILE were enrolled in this prospective study from May 2018 to August 2018. Inclusion criteria were age 18 years or older, stable myopia for ≥2 years, corrected distance visual acuity of 20/25 or better, and spherical equivalent (SE) with subjective refraction more than −6.0 diopters (*D*). Exclusion criteria were a calculated postoperative residual stromal bed of <250 μm and abnormal corneal topography. Eyes with media opacities that prevented good quality scans and any retinal or neurological disease were excluded (e.g., diabetics and evidence of glaucomatous optic nerve damage). The eyes with a past history of surgery, trauma, or inflammation were also excluded.

2.2. Surgical Techniques. A VisuMax (Carl Zeiss Meditec) femtosecond laser platform was used for all surgical procedures. Surgery was performed as described by a previous study and was done by the same experienced surgeon [18]. The suction time lasted for 24 seconds during the lenticule creation. Postoperatively, in addition to the regular topical antibiotics (ofloxacin ophthalmic solution 0.5%; Santen Pharmaceutical Co., Ltd.) and artificial tears (sodium hyaluronate eye drops 0.3%; Santen Pharmaceutical Co., Ltd.), topical steroids (fluorometholone 0.1%; Santen Pharmaceutical Co., Ltd.) were initially administered 6 times a day and tapered off over 20 days.

2.3. OCTA Data Acquisition and Processing. OCTA scans were obtained with a spectral-domain system (software version 2017.1.0.155; Optovue Inc., Fremont, CA, USA), a split-spectrum amplitude-decorrelation angiography algorithm to perform quantitative angiography of the retina. En face retinal angiograms were automatically created with projection from the internal limiting membrane to the retinal pigment epithelium. The software automatically calculated the perfused vessel density in the specific area of retina. Macular data were acquired over a 6.0 × 6.0 mm area. Retinal segmentation was automatically performed by the viewing software to generate en face projection images of the superficial retinal capillary plexus (SCP) and the deep retinal capillary plexus (DCP). The SCP en face OCTA image was segmented with an inner boundary 3 μm below the internal limiting membrane and an outer boundary 15 μm below the inner plexiform layer. The DCP en face OCTA image was set at 15 to 70 μm beneath the inner plexiform layer. The foveal avascular zone (FAZ) was outlined and measured automatically by the software (Figure 1). The fovea is the 1.0 mm ring area at the center (Figure 1). The parafoveal region was defined as an annulus with an outer diameter of 3.0 mm and an inner diameter of 1.0 mm, and the perifoveal region was defined as an annulus with an outer diameter of 5.0 mm and an inner diameter of 3.0 mm (Figure 1). The optic nerve head data were covered by 4.5 × 4.5 mm OCTA scans. The peripapillary area was defined as a 700 mm wide elliptical annulus extending outward from the optic disc boundary (Figure 1). The software automatically calculated the perfused vessel density. Vessel density was defined as the percentage of the area occupied by vessels within the segmented area, as acquired by the provided RTVue-XR Avanti software.

Retinal thickness was obtained by the same OCT system at the same time as the retinal vasculature using the retina map mode. Retinal thickness referred to the mean thickness of that specific area. Macular thickness was calculated in the foveal, parafoveal, and perifoveal zones. The peripapillary RNFL was determined using the optic nerve head protocol. Measurements were automatically performed at four peripapillary quadrants: superior, inferior, nasal, and temporal according to the previous study [19]. We had a single observer to perform the OCTA examination who was blind to the study.

At the same time, heart rate (HR) and blood pressure (BP) were also measured and the mean arterial pressure was calculated as the diastolic blood pressure plus one-third of the difference between the diastolic and the systolic blood pressure [20, 21]. The ocular perfusion pressure was determined by subtracting the IOP from two-thirds of the mean arterial pressure. The signal strength index was used to control for image quality. Images with a signal strength index of less than 50 were excluded, and scans with movement or decentration artifacts were repeated. OCTA, uncorrected distance visual acuity (UDVA), HR, BP, and IOP (NIDEK TONOREF II; NIDEK Co., Ltd, Gamagori, Japan) and automated refraction (RK-8100, Topcon, Tokyo, Japan) measurements were recorded before and 1 day, 2 weeks, and 1 month after surgery. Subjective refraction was also measured before the surgery. To avoid the effects of diurnal variations, all measurements were obtained before the noon.



(a) (b) (c)

Figure 1: Optic coherence tomographic angiogram of the macular area and optic nerve from a 22-year-old male. (a) Foveal avascular zone (the area within the inner annulus). (b) Foveal area (the area within the inner circles) comprising the parafoveal area (the annulus between the inner and middle circles) and perifoveal area (the annulus between the middle and outer circles). The diameter of inner, middle, and outer circles is 1.0 mm, 3.0 mm, and 5.0 mm, respectively. (c) Peripapillary (the annulus between the inner and outer circles).

2.4. Statistical Analysis. Statistical analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA). Quantitative data were expressed as the mean ± SD. Visual acuity was converted to LogMAR for data analysis. Analysis of variance (ANOVA) or the Kruskal–Wallis test was used to test for difference among different groups, and the Bonferroni test was used to identify which pairs of treated groups were significantly different. We also used multivariable linear regression model to detect parameters that could significantly predict the changes in vessel density after the surgery. Statistical significance was assumed at $p < 0.05$.

Table 1: Demographic data.

Characteristics	Mean ± SD
Age (years)	21.00 ± 2.47
SE (diopters)	−4.43 ± 1.80
Axial length (mm)	25.77 ± 0.99
UDVA	0.61 ± 0.33
IOP (mmHg)	15.98 ± 2.37
CCT (μm)	538.61 ± 24.38
AD (μm)	98.17 ± 27.37

SE, spherical equivalent; UDVA, uncorrected distance visual acuity; IOP, intraocular pressure; CCT, central corneal thickness; AD, ablation depth; SD, standard deviation.

3. Results

Totally, 46 eyes (24 patients (20 men, 4 women)) were included in the final analysis. The demographic and clinical information of subjects is listed in Table 1. After the SMILE surgery, the LogMAR UDVA were −0.05 ± 0.06, −0.07 ± 0.04, and −0.08 ± 0.04 at 1 day, 2 weeks, and 1 month, which were significantly improved compared to the UDVA before surgery ($p = 0.0001$). The difference in UDVA between 1 day and 2 weeks was insignificant ($p = 0.180$). The similar result was found between 2 weeks and 1 month ($p = 0.527$). However, the UDVA in 1 month postoperatively was significantly improved compared to that at 1 day ($p = 0.004$). The IOP was 11.50 ± 2.09 mmHg, 11.95 ± 2.32 mmHg, and 11.38 ± 2.33 mmHg at 1 day, 2 weeks, and 1 month postoperatively, respectively (all $p > 0.5$). The mean BP and HR remained unchanged during all visits (all $p > 0.5$). A significant improvement was seen in SE at all follow-ups in contrast to the value preoperatively ($p = 0.0001$), whereas the SE remained unchanged from 1 day to 1 month (all $p > 0.5$).

There were no significant changes in any of the 4 vessel densities in the area of peripapillary before and after surgery ($p = 0.3345$) (Table 2). The superficial and deep foveal retinal vessel density at 1 day after surgery were less than those before surgery; however, the changes were not statistically significant ($p = 0.2736$ and $p = 0.1590$, respectively). The superficial retinal vessel density of the parafoveal and perifoveal regions decreased significantly at 1 day after surgery ($p = 0.006$ and $p < 0.001$, respectively). At 2 weeks after surgery, there was a recovery in vessel density to the preoperative level at the parafoveal and perifoveal regions, respectively ($p = 0.011$ and $p = 0.001$, respectively) (Figure 2). There were no significant differences among the 3 superficial retinal vessel densities in the parafoveal and perifoveal regions before and 2 weeks and 1 month after surgery (all $p > 0.5$) (Table 2). The similar changes were seen in the deep retinal vessel density of the parafoveal and perifoveal regions (Table 2). The FAZ was 0.30 ± 0.10 mm^2 before surgery and increased to be 0.50 ± 1.32 mm^2 at 1 day after surgery. Then, the FAZ returned to the preoperative level of 0.30 ± 0.11 mm^2 at 2 weeks and 0.30 ± 0.10 mm^2 at 1 month after the surgery. Nevertheless, the differences in FAZ at the four timepoints were not statistically significant ($p = 0.9221$).

Furthermore, we studied the parameters that could predict the changes in retinal vessel density of the parafoveal and perifoveal regions 1 day after the surgery. However, neither the ablation depth (AD) nor the preoperative SE was significantly correlated with the changes in retinal vessel density of the parafoveal and perifoveal regions 1 day after the surgery (all $p > 0.5$). Moreover, the changes in retinal

Table 2: Vessel density (%) before and after SMILE with OCTA.

	Follow-up visits				
	Before surgery	1 day after surgery	2 weeks after surgery	1 month after surgery	p
Peripapillary	51.07 ± 3.22	51.84 ± 2.80	52.29 ± 3.90	51.42 ± 3.24	0.3345
SCP					
Fovea	21.19 ± 7.17	18.65 ± 7.14	20.50 ± 7.43	20.95 ± 7.31	0.2736
Parafovea	52.91 ± 8.13	48.97 ± 4.66	52.75 ± 4.94	53.25 ± 3.98	0.0001
Perifovea	51.77 ± 3.40	48.45 ± 3.53	51.19 ± 3.57	51.25 ± 3.27	0.0001
DCP					
Fovea	36.49 ± 9.35	33.26 ± 7.85	36.23 ± 7.94	36.33 ± 7.75	0.1590
Parafovea	56.02 ± 4.64	51.13 ± 4.45	55.41 ± 4.33	55.06 ± 4.39	<0.0001
Perifovea	52.34 ± 6.89	44.57 ± 5.74	51.10 ± 6.66	50.84 ± 7.17	0.0001

SMILE, small incision lenticule extraction; OCTA, optical coherence tomography angiography; SCP, superficial retinal capillary plexus; DCP, deep retinal capillary plexus.

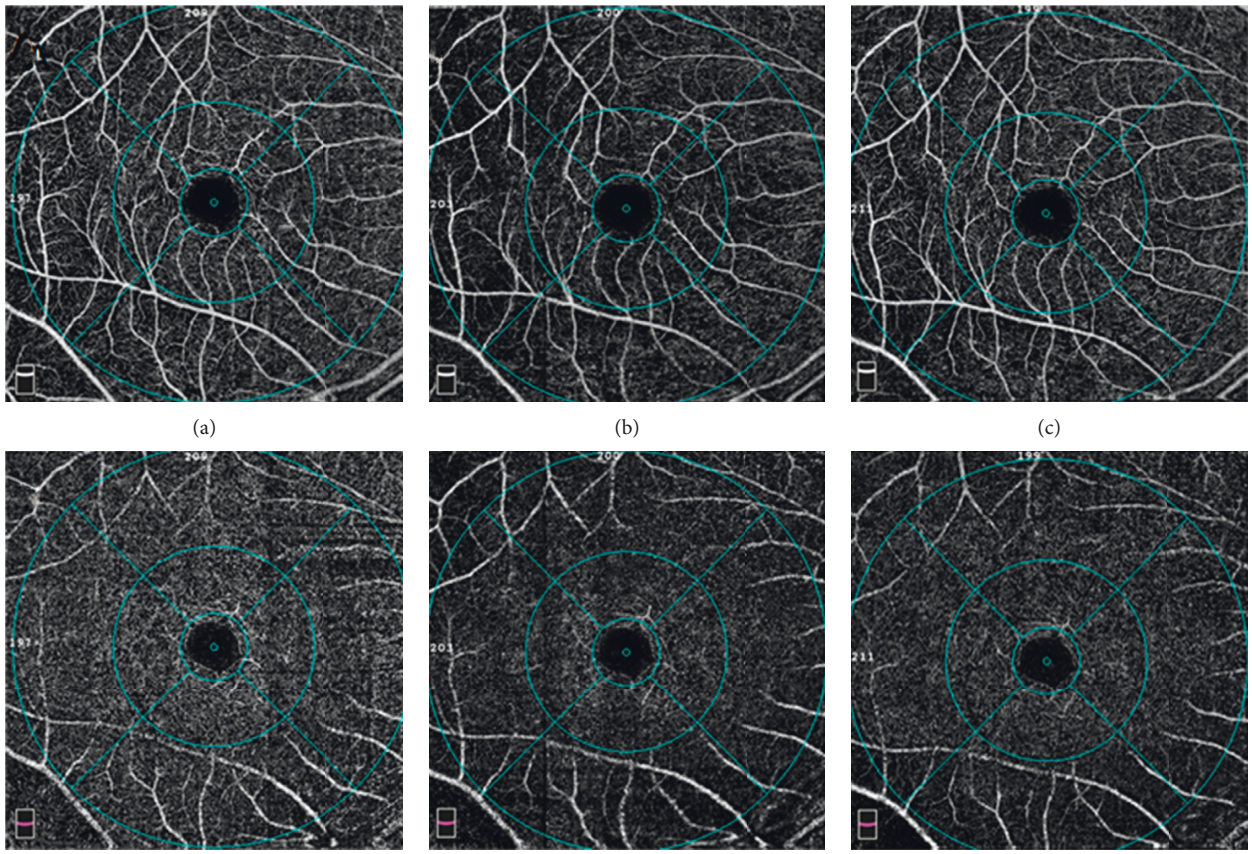


Figure 2: Optic coherence tomographic angiogram of the macular area from a 24-year-old female. The superficial vessel density at the fovea, parafovea, and perifovea was 16.3%, 55.4%, and 51.9% before surgery (a). The superficial vessel density at the fovea, parafovea, and perifovea was 12.2%, 43.5%, and 41.9% at 1 day postoperatively (b). The superficial vessel density at the fovea, parafovea, and perifovea was 14%, 51.3%, and 47.9% at 2 weeks postoperatively (c). The deep vessel density at the fovea, parafovea, and perifovea was 28%, 56.5%, and 51.3% preoperatively (d). The deep vessel density at the fovea, parafovea, and perifovea was 26%, 54%, and 42.3% at 1 day postoperatively (e). The deep vessel density at the fovea, parafovea, and perifovea was 26.4%, 54.1%, and 45.7% at 2 weeks postoperatively (f).

vessel density of the parafoveal and perifoveal regions 1 day after the surgery had no significant influence on the improvement of UDVA at 1 day ($r = 0.1137$, $p = 0.4519$; and $r = 0.0225$, $p = 0.8820$, respectively). The preoperative IOP value and axial length were not correlated with the changes in retinal vessel density of the parafoveal and perifoveal regions 1 day after the surgery (all $p > 0.5$).

The foveal, parafoveal, and perifoveal retinal thicknesses at 3 timepoints postoperatively were not statistically different from those before the SMILE procedure (Table 3; all

Table 3: Peripapillary RNFL and macular thickness values before and after surgery (μm).

	Before surgery	1 day after surgery	2 weeks after surgery	1 month after surgery	p
Peripapillary RNFL					
Mean	115.50 ± 12.63	117.33 ± 12.99	119.53 ± 16.44	116.75 ± 12.53	0.5893
Superior	137.04 ± 16.47	137.96 ± 17.60	140.16 ± 15.34	139.14 ± 15.81	0.7312
Inferior	139.87 ± 16.08	142.68 ± 18.55	141.76 ± 15.54	141.53 ± 15.70	0.9236
Temporal	89.41 ± 15.90	89.75 ± 12.38	87.06 ± 12.81	87.18 ± 14.07	0.7014
Nasal	99.52 ± 22.04	104.67 ± 30.64	109.56 ± 41.97	102.86 ± 22.44	0.3786
Macular thickness					
Foveal	244.46 ± 17.47	244.22 ± 17.51	245.07 ± 18.17	243.59 ± 17.28	0.9902
Parafoveal	321.15 ± 11.07	320.57 ± 10.74	320.05 ± 11.71	319.86 ± 11.83	0.9047
Perifoveal	279.78 ± 9.06	279.02 ± 9.17	279.14 ± 10.34	279.05 ± 10.14	0.9241

RNFL, retinal nerve fiber layer.

$p > 0.5$). Similarly, no statistically significant differences between preoperative and postoperative RNFL thickness values were detected for any of the examined sectors and the average peripapillary area (Table 3).

4. Discussion

OCTA is an imaging technology in vivo that provides detailed morphologic and quantitative microvascular information. A study with OCTA reported a reduced retinal vessel density in eyes with high myopia [22]. However, others found no significant differences among patients with mild myopia, moderate myopia, and high myopia [23–25]. It was speculated that pathologic changes in high myopia affect the macular vascular density rather than the SE. Nevertheless, in the present study, a significant decrease in vessel density at the parafovea and perifovea regions was found at 1 day after SMILE surgery in non-high myopia.

In eyes with high myopia, excessive axial elongation of the eyeball is usually accompanied with mechanical stretching of the retina, choroid, and sclera, leading to straightening and narrowing of the vessels [26, 27]. It should not be applied to the subjects of the non-high myopia in our study. Although the decrease in vessel density was reversible and completely recovered within 2 weeks in our study, it was proved for the first time that the procedure of SMILE had influence on the retinal vasculature at the macular area. We assumed the sudden spike in IOP during the SMILE procedure accounts for the changes. It was supported by Grunwald et al.'s study with a significantly faster leukocyte speed in the macula responding to a drop in IOP [28] and Weigert et al.' report with decreased fundus pulsation amplitude in response to an increase in IOP [29]. The refractive cut by femtosecond laser in SMILE was almost identical with the process in FLEx. It was reported that the increase in IOP during FLEx was similar to that in FS-LASIK, except for the duration of elevated IOP in FLEx was twice than that in FS-LASIK [2]. In another word, in addition to the elevation of the IOP (about 30 mmHg), the longer duration with the suction in SMILE may also cause a decrease in the ocular blood flow. Though the IOP fell steeply down in the suction off stage, the IOP was monitored to be still elevated during the process of lenticule separation/extraction in the animal model [30]. The long-lasting duration of elevated IOP in the eyes with SMILE surgery may lead to decreased fundus pulsation amplitude [29]. Consequently, the decreases in vessel density were observed by OCTA at 1 day postoperatively in the current study. However, the changes in vessel density at the parafoveal and perifoveal regions were transient and reversible as evidenced by the complete recovery at 2 weeks and 1 month after surgery. Moreover, the UDVA was significantly improved and remained stable at 3 postoperative timepoints in spite of the decrease in macular retinal vessel density. Thus, the temporary changes in retinal vessel density did not have impact on the recovery of visual acuity after the SMILE.

Though a significant decrease in macular vessel density was found 1 day after surgery in our study, the changes in retinal thickness and RNFL thickness were not detectable. This finding is in agreement with Shoji et al.'s indication that the change in retinal vessel density could be detected before a change in GCC thickness occurs [17]. It is also consistent with a previous study in which suction had no significant clinical effects on the macular thickness and RNFL thickness during FLEx or FS-LASIK [10]. However, it was demonstrated in another study that the average foveal and parafoveal retinal thicknesses were significantly thicker 1 day after surgery [11]. And the changes were reversible and recovered within 1 week without effect on the visual acuity [11]. We speculated the disparity of age accounts for the difference as the age is 9.68 ± 2.56 years in previous study compared to 21.00 ± 2.47 years in ours. It seemed that the SMILE procedure had no impact on the optic nerve as there were no changes either in the RNFL thickness or in the vessel density. Patients were instructed to stare at a specific light source for gaze fixation during the procedure. Thus, we speculated that the sudden spike in IOP may directly deliver to the macular area rather than to the optic nerve.

There are some limitations in our study. First, the small sample and the involvement of both right and left eyes are big issues. Though changes were seen in foveal vessel density and FAZ at 1 day after the surgery, neither of the differences were significant. The relatively small sample may account for the insignificance. Then, the interval between the 1 day and 2 weeks may not be appropriate. Because it has been reported in previous study that the foveal center retinal thickness after FS-LASIK was always relieved within 1 week [11]. Consequently, the duration of the alterations in the

retinal vasculature after SMILE cannot be concluded in the present study. Finally, there were only 4 females in present study, and the proportion (20 males/4 females) may be not appropriate. However, several studies indicated gender did not significantly influence perfused vessel density in either the parafoveal or peripapillary region [20, 29].

5. Conclusion

The vessel density at the parafoveal and perifoveal regions decreased significantly at 1 day after the SMILE procedure, and these changes were not accompanied with the changes in macular thickness and with no effect on the visual acuity. Moreover, such decrease in vessel density was completely relieved at 2 weeks postoperatively. The SMILE procedure had no significant influence on the RNFL thickness and vessel density of the optic nerve. Decreased ocular blood flow in response to the spike in IOP may account for such changes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] N. B. Baig, G. P. Cheng, J. K. Lam et al., "Intraocular pressure profiles during femtosecond laser-assisted cataract surgery," *Journal of Cataract & Refractive Surgery*, vol. 40, no. 11, pp. 1784–1789, 2014.

[2] M. Ang, S. S. Chaurasia, R. I. Angunawela et al., "Femtosecond lenticule extraction (FLEx): clinical results, interface evaluation, and intraocular pressure variation," *Investigative Ophthalmology & Visual Science*, vol. 53, no. 3, pp. 1414–1421, 2012.

[3] J. M. Vetter, M. P. Holzer, C. Teping et al., "Intraocular pressure during corneal flap preparation: comparison among four femtosecond lasers in porcine eyes," *Journal of Refractive Surgery*, vol. 27, no. 6, pp. 427–433, 2011.

[4] C. J. Flaxe, Y. H. Choi, M. Sheety, S. C. Oeinck, J. Y. Lee, and P. J. McDonnell, "Proposed. mechanism for retinal tears alters LASIK: an experimental model," *Ophthalmology*, vol. 111, no. 1, pp. 24–27, 2004.

[5] S. Hori, H. Shimada, T. Hattori, H. Nakashizuka, Y. Mizutani, and M. Yuzawa, "Early onset of rhegmatogenous retinal detachment after LASIK with femtosecond laser," *Japanese Journal of Ophthalmology*, vol. 53, no. 1, pp. 75-76, 2009.

[6] A. P. Aisteidou, G. Labiris, E. I. Paschalis, N. C. Foudoulakis, S. C. Koukoula, and V. P. Kozobolis, "Evaluation of the retinal nerve fiber layer measurements, after photorefractive keratectomy and laser in situ keratomileusis, using scanning laser polarimetry (GDX VCC)," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 248, no. 5, pp. 731–736, 2010.

[7] S. S. Chaurasia, F. Gimeno Luengo, K. Tan et al., "In vivo real-time intraocular pressure variations during LASIK flap creation," *Investigative Ophthalmology & Visual Science*, vol. 51, no. 9, pp. 4641–4645, 2010.

[8] C. Nucci, R. Tartaglione, L. Rombolà, L. A. Morrone, E. Fazzi, and G. Bagetta, "Neurochemical evidence to implicate elevated glutamate in the mechanisms of high intraocular pressure (IOP)-induced retinal ganglion cell death in rat," *NeuroToxicology*, vol. 26, no. 5, pp. 935–941, 2005.

[9] K. J. Cho, J. H. Kim, H. Y. Park, and C. K. Park, "Glial cell response and iNOS expression in the optic nerve head and retina of the rat following acute high IOP ischemia-reperfusion," *Brain Research*, vol. 1403, pp. 67–77, 2011.

[10] J. Zhang, Y. Zhou, Y. Zheng, Q. Liu, C. Zhai, and Y. Wang, "Effect of suction on macular and retinal nerve fiber layer thickness during femtosecond lenticule extraction and femtosecond laser-assisted laser in situ keratomileusis," *Journal of Cataract & Refractive Surgery*, vol. 40, no. 12, pp. 1994–2001, 2014.

[11] P. F. Zhao, Y. H. Zhou, J. Zhang, and W. B. Wei, "Analysis of macular and retinal nerve fiber layer thickness in children with refractory amblyopia after femtosecond laser-assisted laser in situ keratomileusis: a retrospective study," *Chinese Medical Journal*, vol. 130, no. 18, pp. 2234–2240, 2017.

[12] M. Hosny, R. M. Zaki, R. A. Ahmed, N. Khalil, and H. M. Mostafa, "Changes in retinal nerve fiber layer thickness following mechanical microkeratome-assisted versus femtosecond laser-assisted LASIK," *Clinical Ophthalmology*, vol. 7, pp. 1919–1922, 2013.

[13] A. H. Principe, D. Y. Lin, K. W. Small, and A. J. Aldave, "Macular hemorrhage after laser in situ keratomileusis (LASIK) with femtosecond laser flap creation," *American Journal of Ophthalmology*, vol. 138, no. 4, pp. 657–659, 2004.

[14] R. Shah, S. Shah, and S. Sengupta, "Results of small incision lenticule extraction: all-in-one femtosecond laser refractive surgery," *Journal of Cataract and Refractive Surgery*, vol. 37, no. 1, pp. 127–137, 2011.

[15] H. Kobashi, K. Kamiya, A. Igarashi, M. Takahashi, and K. Shimizu, "Two-years results of small-incision lenticule extraction and wavefront-guided laser in situ keratomileusis for Myopia," *Acta Ophthalmologica*, vol. 96, no. 2, pp. e119–e126, 2018.

[16] M. A. Torky and Y. A. Alzafiri, "Visual and refractive outcomes of small-incision lenticule extraction in mild, moderate, and high myopia: six-month results," *Journal of Cataract and Refractive Surgery*, vol. 43, no. 4, pp. 459–465, 2017.

[17] T. Shoji, L. M. Zangwill, T. Akagi et al., "Progressive macula vessel density loss in primary open angle glaucoma: a longitudinal study," *American Journal of Ophthalmology*, vol. 182, pp. 107–117, 2017.

[18] M. J. Chen, M. R. Yu, and J. H. Dai, "Comparison of biomechanical effects of small incision lenticule extraction and laser-assisted subepithelial keratomileusis," *Acta Ophthalmologica*, vol. 94, no. 7, pp. e586–e591, 2016.

[19] Y. Li, H. Miara, P. Ouyang, and B. Jiang, "The comparison of regional RNFL and fundus vasculature by OCTA in Chinese myopia population," *Journal of Ophthalmology*, vol. 2018, Article ID 3490962, 10 pages, 2018.

[20] Y. Zong, H. Xu, J. Yu et al., "Retinal vascular autoregulation during phase IV of the valsalva maneuver: an optical coherence tomography angiography study in healthy Chinese adults," *Frontiers in Physiology*, vol. 8, p. 553, 2017.

[21] Z. N. Zhao, W. Wen, C. H. Jiang, and Y. Lu, "Changes in macular vasculature after uncomplicated phacoemulsification surgery: optical coherence tomography angiography study,"

Journal of Cataract and Refractive Surgery, vol. 44, no. 4, pp. 453–458, 2018.

[22] M. Al-Sheikh, N. Phasukkijwatana, R. Dolz-Marco et al., "Quantitative OCT angiography of the retinal microvasculature and the choriocapillaris in myopic eyes," *Investigative Ophthalmology & Visual Science*, vol. 58, no. 4, pp. 2063–2069, 2017.

[23] X. Wang, X. M. Kong, C. H. Jiang, M. Li, J. Yu, and X. H. Sun, "Is the peripapillary retinal perfusion related to myopia in healthy eyes? A prospective comparative study," *BMJ Open*, vol. 6, no. 3, article e010791, 2016.

[24] J. Mo, A. Duan, S. Chan, X. Wang, and W. Wei, "Vascular flow density in pathological myopia: an optical coherence tomography angiography study," *BMJ Open*, vol. 7, no. 2, article e013571, 2017.

[25] S. Yang, M. Zhou, B. Lu et al., "Quantification of macular vascular density using optical coherence tomography angiography and its relationship with retinal thickness in myopic eyes of young adults," *Journal of Ophthalmology*, vol. 2017, Article ID 1397179, 10 pages, 2017.

[26] D. S. Lam, K. S. Leung, S. Mohamed et al., "Regional variations in the relationship between macular thickness measurements and myopia," *Investigative Ophthalmology & Visual Science*, vol. 48, no. 1, pp. 376–382, 2007.

[27] P. C. Wu, Y. J. Chen, C. H. Chen et al., "Assessment of macular retinal thickness and volume in normal eyes and highly myopic eyes with third-generation optical coherence tomography," *Eye (London)*, vol. 22, no. 4, pp. 551–555, 2008.

[28] J. E. Grunwald, S. H. Sinclair, and C. E. Riva, "Autoregulation of the retinal circulation in response to decrease of intraocular pressure below normal," *Investigative Ophthalmology & Visual Science*, vol. 23, no. 1, pp. 124–127, 1982.

[29] G. Weigert, O. Findl, A. Luksch et al., "Effects of moderate changes in intraocular pressure on ocular hemodynamics in patients with primary open-angle glaucoma and healthy controls," *Ophthalmology*, vol. 112, no. 8, pp. 1337–1342, 2005.

[30] W. Cheng, L. Liu, S. Yu et al., "Real-time intraocular pressure measurements in the vitreous chamber of rabbit eyes during small incision lenticule extraction (SMILE)," *Current Eye Research*, vol. 43, no. 10, pp. 1260–1266, 2018.

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Research Article

Threshold Values of Myopic Anisometropia Causing Loss of Stereopsis

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Purpose. The aim of the study was to determine the threshold values of myopic anisometropia that lead to the loss of stereoacuity in most of patients. *Materials and Methods*. Forty healthy subjects were included in the study. The inclusion criteria were as follows: lack of any functional or morphological ophthalmological disorders, or detectable damage to the visual system, anisometropia equal or less than 0.25 D in a spherical equivalent, and full stereoscopic vision for near and for distance. Myopic anisometropia was evoked by placing different focusing lenses in front of the right eye of the subject in the trial frame. Stereoscopic vision was assessed with the use of the Titmus test (dots) (Stereo Fly Test Stereo Optical Co. Inc.) for near and the Randot test for distance (Distance Randot Stereotest Stereo Optical Co. Inc.). *Results*. The threshold values for different types of myopic anisometropia for the loss of stereopsis in more than 50% of patients were determined. For near, this value was 3 D for sphere and "against the rule astigmatism" and 4 D for "with the rule astigmatism". For distance, the values were 2 D for sphere and "against the rule astigmatism" and 3 D for "with the rule astigmatism." *Conclusions*. Myopic anisometropia of more than 2 D can cause a significant impairment of binocular vision. Stereoacuity at distance is more sensitive to myopic anisometropia than stereoacuity at near. Myopic anisometropia involving "against the rule" astigmatism potentially affects binocularity more than anisometropia with regular astigmatism. A prompt correction of anisometropia of more than 2 D is needed in children to prevent the development of amblyopia.

1. Introduction

Anisometropia is a well-known risk factor for the development of amblyopia and sometimes strabismus. If significant and not corrected in the first years of life, it can disturb the normal development of the visual system. Visual acuity in the eye with a larger refraction error is usually decreased, and image in that eye is defocused. This leads to the asymmetry of the signals emerging from both eyes and the underdevelopment of the neurons driven by the defocused image on the level of the brain [1, 2]. Hypermetropic anisometropia is thought to be a more significant risk factor for the development of amblyopia than myopic anisometropia [3]. It can lead to fixation instability and mimic microstrabismus [4]. Myopic anisometropia is often treated as a benign form of anisometropia, which can be successfully treated even in older children. However, relatively little is known about its negative influence on the development of stereopsis. Stereoscopic vision is one of the most important properties of the visual system, which determines the quality of life and has an impact on the future professional career. Deficits in stereoscopic vision affect precision movements, precision grasping, and sense of distance [5]. Therefore, a lack of stereoscopic vision can limit personal engagement in professional life and hence causes frustration or even depression [6, 7]. Impaired stereoscopic vision is one of the most important deficits associated with anisometropic amblyopia [8]. The relationship between the amount of anisometropia and the loss of stereoacuity is yet to still be discussed in the medical literature. Controversies refer to the number of dioptres of anisometropia and the type of anisometropia (myopic, hyperopic, or astigmatic) that are the most likely to cause abnormalities in the visual system. Most of the studies that analyse the relationship between stereoscopic vision and the amount of anisometropia are population based—they study patients that are

anisometropic and often amblyopic already [9]. As we know, the refraction error can change during the first years of life, so measurements that are taken in a few-year-old patient do not necessary reflect the maximum amount of anisometropia that was previously present in a subject, hence the idea of measuring stereopsis in healthy subjects after experimentally induced myopic anisometropia. Our study sought to determine the threshold amounts of myopic anisometropia for sphere and cylinder, which cause a loss of binocularity for near and for distance in healthy young individuals.

2. Materials and Methods

The study was conducted on 40 healthy subjects with no visual problems: 21 females and 19 males. The mean age of the patients was 34.9 ± 11.26 years. The inclusion criteria were as follows: lack of any functional or morphological ophthalmological disorders or detectable damage to the visual system, anisometropia equal or less than 0.25 D in spherical equivalent (SE), and full stereoscopic vision for distance and for near.

All subjects have undergone a routine ophthalmological examination that included the assessment of best-corrected visual acuity (BCVA) for distance and for near, slit lamp examination of the anterior segment of the eye, and indirect fundus examination by plus 90 D lens.

The refraction error was measured after cycloplegia with topical 1% tropicamide. Drops were administered twice with an interval of 5 minutes, and refraction was than measured after 40 minutes with an Oculus Park 1 autorefractometer (OCULUS, Germany 2008). The result was converted to SE, and the amount of anisometropia was than calculated. All subjects with anisometropia of more than 0.25 D were excluded from the study.

BCVA and stereopsis were measured on another day than the refraction error was determined. BCVA was measured on the Snellen chart. None of the patients required a distance optical correction. All subjects had full-distance visual acuity (BCVA) without correction: 1.0 Snellen. Some patients required a simple spherical optical correction for near, which was determined after the presence of anisometropia was excluded. Patients who did not achieve full near visual acuity after optical correction were excluded from the study.

Stereoscopic vision was assessed with the use of the Titmus test (dots) (Stereo Fly Test Stereo Optical CO Inc) for near and the Randot test for distance (Distance Randot Stereotest Stereo Optical Co Inc). The Titmus test with dots was suitable for adults as it provides precise grading of values of stereopsis for near expressed in seconds of arch. Unfortunately, there are not many distance stereotests available on the market. Randot stereotest for distance is one of the few officially approved for such testing, so it became our choice in current research. However, it has to be taken into consideration that distance Randot stereotest provides only 4 values of grading of stereoacuity. Only patients with full stereoscopic vision for distance and for near after optical correction were included in the study. Full stereoscopic vision was considered 40 sec of arch for near and 60 sec of arch for distance, as these were the minimal arch values measured on the abovementioned tests.

Myopic anisometropia was evoked by placing focusing lenses in front of the right eye of the subject in the trial frame. First in order, spherical focusing lenses were placed in the trial frame. Stereotest for distance and for near was than performed for +1 D, +2 D, +3 D, and +4 D powers of the lens. The same procedure was conducted for cylindrical lenses for + 1 D, +2 D, +3 D, and +4 D values. The cylinder was placed first in a 90-degree position (evoking "with the rule" astigmatism) and then in a 180-degree position (evoking "against the rule" astigmatism). Both stereotests were performed for each position of the cylinder lens.

As stereotests do not measure the amount of stereopsis in a linear way; therefore, grading of the results was established according to the achieved angle of stereopsis in the test.

Grading of stereoscopic vision is presented in Table 1.

The percentage of patients with different levels of stereopsis was then referred to each amount of anisometropia. The study sought the threshold amount of anisometropia that caused a loss of stereopsis in more than 50% of subjects.

3. Statistical Analysis

The statistical analysis was conducted with Statistica 13.0 software (StatSoft Inc., 2011). For the verification of statistical hypothesis, the ANOVA test of Friedman rank was used, including a post hoc test. The level of confidence was set at 0.05. The results were considered statistically significant if the calculated test probability was <0.05.

4. Results

The results for the loss of stereopsis at near for different forms of myopic anisometropia are presented below.

The distribution of patients losing stereopsis with an increasing amount of spherical anisometropia for near is presented in Table 2 and Figure 1. The results of the post hoc ANOVA test are presented in Table 3.

Result of χ^2 ANOVA ($N = 40$, $\mathrm{df} = 3$) $= 108.0763$, $p = 0.00000$, so an increasing amount of spherical myopic anisometropia impairs stereopsis at near.

As we see in Table 3, there are significant differences for sph +1.0 D versus sph +3.0 D and sph +4.0 D and sph +2.0 D versus + sph +3.0 D and sph +4.0 D.

Most of the patients lose stereopsis when spherical myopic anisometropia equals 4.0 D; however, as the measurements of stereopsis show no statistical difference between +3.0 and +4.0 D, we can assume that 3.0 D is a threshold value of spherical myopic anisometropia for the loss of stereopsis at near.

The results for the loss of stereopsis at near in astigmatic myopic anisometropia ("with the rule" astigmatism) are presented in Tables 4 and 5 and Figure 2.

Results of χ^2 ANOVA ($N = 40$, $\mathrm{df} = 3$) $= 105.7009$ $p = 0.00000$. An increasing amount of "with the rule" astigmatism significantly impairs stereopsis.

Table 1: Classification of the degree of stereopsis.

Grade of stereopsis	Near (sec. of arch)	Distance (sec. of arch)
Good	40, 50, 60, 80, 100	60, 100
Moderate	140, 200, 400	200
Poor	800	400
Absence	∝	∝

Table 2: Distribution of patients with different degrees of stereopsis for near according to the amount of spherical anisometropia.

Grade of stereopsis	(Near) sph +1		(Near) sph +2		(Near) sph +3		(Near) sph +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	0	0.0	1	2.5	13	32.5	32	80.0
Poor	0	0.0	2	5.0	13	32.5	5	12.5
Moderate	5	12.5	24	60.0	13	32.5	3	7.5
Good	35	87.5	13	32.5	1	2.5	0	0.0
Total	40	100.0	40	100.0	40	100.0	40	100.0

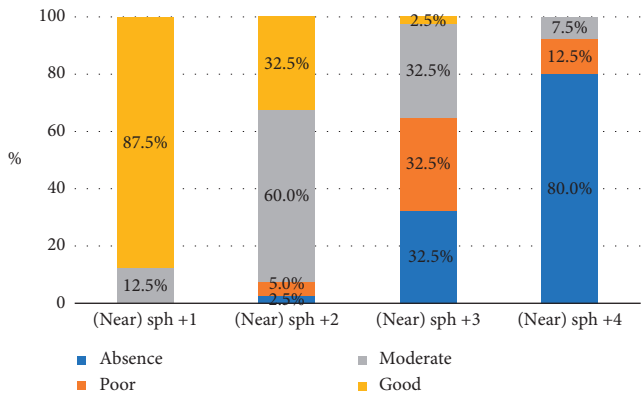

Figure 1: Distribution of patients with different grades of stereopsis according to the level of spherical myopic anisometropia presented on the graph.

Table 3: Results of the post hoc ANOVA test showing the statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Near) sph +1	(Near) sph +2	(Near) sph +3	(Near) sph +4
(Near) sph +1	—	0.6375	1.875	2.5375
(Near) sph +2	0.6375	—	1.2375	1.9
(Near) sph +3	1.875	1.2375	—	0.6625
(Near) sph +4	2.5375	1.9	0.6625	—

As we see from Table 5, the difference in measurements between cyl 90° +1.0 and cyl 90° +2.0 is not significant. All other pairs of measurements show a statistical difference.

Most of the patients lose stereopsis when myopic astigmatic anisometropia for "with the rule" astigmatism is 4 D. +3 D cyl 90° value also significantly impairs stereopsis; however, most of the patients in this group preserve some degree of binocularity.

Analogous results for the measurements of stereopsis in myopic astigmatic anisometropia ("against the rule" astigmatism) are presented in Tables 6 and 7 and Figure 3.

Table 4: Distribution of patients with different degrees of stereopsis for near according to the amount of astigmatic anisometropia ("with the rule" astigmatism).

Grade of stereopsis	(Near) cyl 90° +1		(Near) cyl 90° +2		(Near) cyl 90° +3		(Near) cyl 90° +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	0	0.0	0	0.0	7	17.5	28	70.0
Poor	0	0.0	1	2.5	13	32.5	7	17.5
Moderate	7	17.5	29	72.5	18	45.0	5	12.5
Good	33	82.5	10	25.0	2	5.0	0	0.0
Total	40	100.0	40	100.0	40	100.0	40	100.0

Table 5: Results of the post hoc ANOVA test showing the statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Near) cyl 90° +1	(Near) cyl 90° +2	(Near) cyl 90° +3	(Near) cyl 90° +4
(Near) cyl 90° +1	—	0.725	1.6625	2.6125
(Near) cyl 90° +2	0.725	—	0.9375	1.8875
(Near) cyl 90° +3	1.6625	0.9375	—	0.95
(Near) cyl 90° +4	2.6125	1.8875	0.95	—

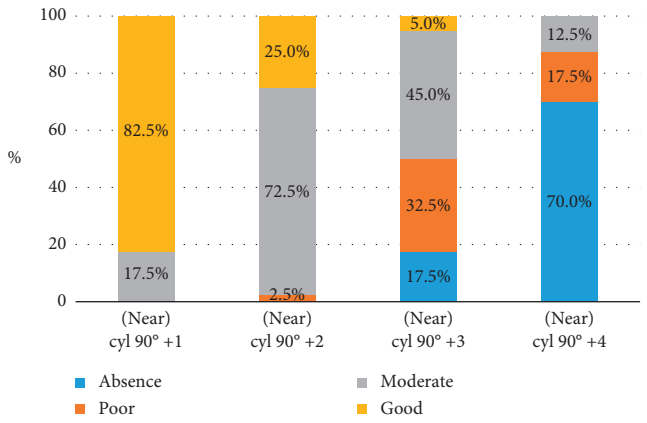

Figure 2: Distribution of patients with different grades of stereopsis for near according to the level of astigmatic myopic anisometropia ("with the rule" astigmatism) presented on the graph.

Results of χ^2 ANOVA ($N = 40$, df = 3) = 101.3104 $p = 0.00000$. An increasing amount of astigmatic anisometropia ("against the rule" astigmatism) significantly impairs stereopsis.

As we see from Table 7, there is no statistical difference for the stereopsis loss between +3.0 D cyl 180° and +4.0 D cyl 180°, so a value of 3 D of astigmatism, in this case, has to be treated as the threshold value for the loss of stereoacuity.

The results for the loss of stereopsis at distance for different forms of myopic anisometropia are presented below.

Tables 8 and 9 and Figure 4 present the impairment of stereopsis in spherical myopic anisometropia at distance.

Table 6: Distribution of patients with different degrees of stereopsis for near according to the amount of astigmatic anisometropia ("against the rule" astigmatism).

Grade of stereopsis	(Near) cyl 180° +1		(Near) cyl 180° +2		(Near) cyl 180° +3		(Near) cyl 180° +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	0	0.0	1	2.5	8	20.0	28	70.0
Poor	0	0.0	3	7.5	13	32.5	3	7.5
Moderate	10	25.0	25	62.5	19	47.5	9	22.5
Good	30	75.0	11	27.5	0	0.0	0	0.0
Total	40	100.0	40	100.0	40	100.0	40	100.0

Table 7: Results of the post hoc ANOVA test showing a statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Near) cyl 180° +1	(Near) cyl 180° +2	(Near) cyl 180° +3	(Near) cyl 180° +4
(Near) cyl 180° +1	—	0.7	1.7625	2.4375
(Near) cyl 180° +2	0.7	—	1.0625	1.7375
(Near) cyl 180° +3	1.7625	1.0625	—	0.675
(Near) cyl 180° +4	2.4375	1.7375	0.675	—

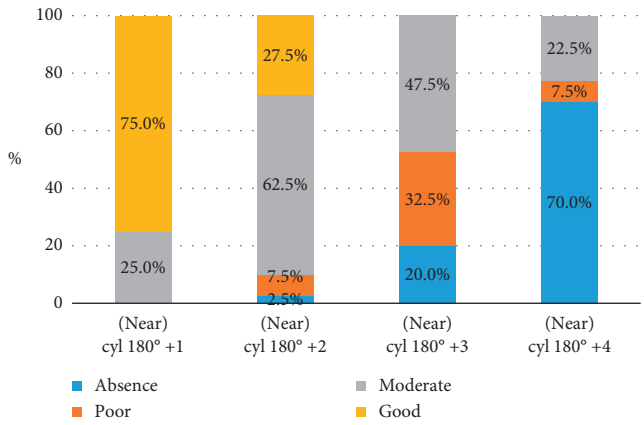

Figure 3: Distribution of patients with different grades of stereopsis according to the level of astigmatic myopic anisometropia ("against the rule" astigmatism) presented on the graph.

Table 8: Distribution of patients with different degrees of stereopsis for distance according to the amount of spherical anisometropia.

Grade of stereopsis	(Distance) sf +1		(Distance) sf +2		(Distance) sf +3		(Distance) sf +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	2	5.0	28	70.0	37	92.5	40	100.0
Poor	8	20.0	3	7.5	2	5.0	0	0.0
Moderate	7	17.5	7	17.5	1	2.5	0	0.0
Good	23	57.5	2	5.0	0	0.0	0	0.0
Total	40	100.0	40	100.0	40	100.0	40	100.0

Tables 10 and 11 and Figure 5 show the results of the change of stereoacuity with an increasing amount of myopic astigmatic anisometropia ("with the rule" astigmatism) at distance.

Table 9: Results of the post hoc ANOVA test showing a statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Distance) sf +1	(Distance) sf +2	(Distance) sf +3	(Distance) sf +4
(Distance) sf +1	—	1.5	1.9625	2.0375
(Distance) sf +2	1.5	—	0.4625	0.5375
(Distance) sf +3	1.9625	0.4625	—	0.075
(Distance) sf +4	2.0375	0.5375	0.075	—

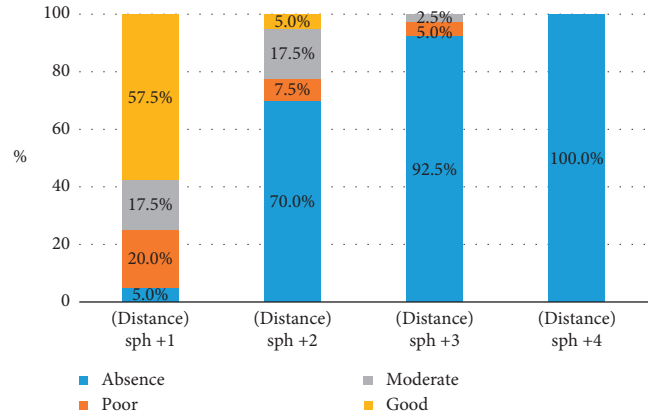

Figure 4: Distribution of patients with different grades of stereopsis at distance according to the level of spherical myopic anisometropia presented on the graph.

Results of χ^2 ANOVA ($N = 40$, df = 3) = 98.20152 $p = 0.00000$. An increasing amount of spherical myopic anisometropia impairs stereopsis at distance.

As we see from Table 9 and Figure 4, as low as 2 D of myopic spherical anisometropia causes a loss of stereopsis at distance in most of the subjects.

Results of χ^2 ANOVA ($N = 40$, df = 3) = 90.07807 $p = 0.00000$. An increasing amount of "with the rule" astigmatism impairs grade of stereoacuity.

As can be seen, most of the subjects lose stereoacuity at the level of anisometropia of 3 D for "with the rule" myopic astigmatism; however, a value of 2 D also significantly reduces the level of binocularity.

Tables 12 and 13 and Figure 6 present the results for the measurements of stereopsis at distance in myopic anisometropia involving "against the rule" astigmatism.

Results of χ^2 ANOVA ($N = 40$, df = 3) = 90.07807 $p = 0.00000$. An increasing amount of "against the rule" astigmatism impairs grade of stereoacuity.

As can be seen from the above data, 2 D of myopic anisometropia with "against the rule" astigmatism leads to a loss of binocularity in most patients.

A summary of the threshold values of myopic anisometropia causing a loss of stereopsis is presented in Table 14.

Table 10: Distribution of patients with different degrees of stereopsis for near according to the amount of astigmatic anisometropia ("with the rule" astigmatism).

Grade of stereopsis	(Distance) cyl 90° +1		(Distance) cyl 90° +2		(Distance) cyl 90° +3		(Distance) cyl 90° +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	3	7.5	15	37.5	35	87.5	39	97.5
Poor	4	10.0	12	30.0	3	7.5	1	2.5
Moderate	14	35.0	8	20.0	1	2.5	0	0.0
Good	19	47.5	5	12.5	1	2.5	0	0.0
Total	40	100.0	40	100.0	40	100.0	40	100.0

Table 11: Results of the post hoc ANOVA test showing a statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Distance) cyl 90° +1	(Distance) cyl 90° +2	(Distance) cyl 90° +3	(Distance) cyl 90° +4
(Distance) cyl 90° +1	—	1.05	1.925	2.075
(Distance) cyl 90° +2	1.05	—	0.875	1.025
(Distance) cyl 90° +3	1.925	0.875	—	0.15
(Distance) cyl 90° +4	2.075	1.025	0.15	—

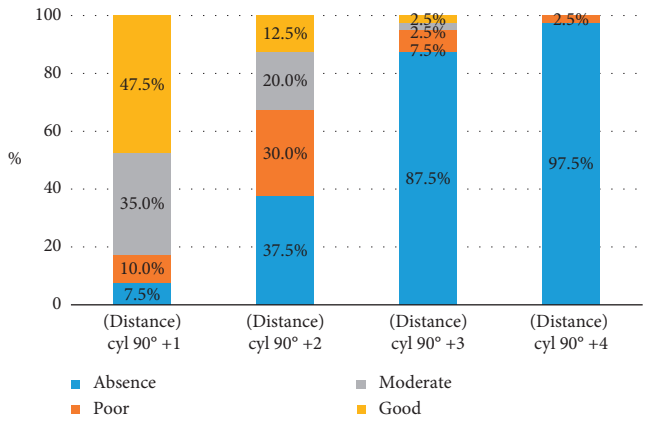

Figure 5: Distribution of patients with different grades of stereopsis for distance according to the level of astigmatic myopic anisometropia ("with the rule" astigmatism) presented on the graph.

5. Discussion

In population-based studies, anisometropia is indicated as an important factor affecting stereoacuity although there are controversies regarding threshold values for its loss. Levi et al. analysed 84 pure anisometropes according to the loss of stereopsis. Myopic anisometropes showed much better stereopsis than analogues anisohypermetropes. In pure anisometropia, there was a linear relationship between the increasing amount of anisometropia and the loss of stereopsis [9]. Dobson et al. depicted a population of school-aged children with a high prevalence of astigmatism [10]. In this study, a significant increase in the presence of amblyopia referred only to hyperopic anisometropia of 1 D or more in sphere or 2-3 D or more in astigmatism. However, a significant reduction of stereoacuity was noted in anisometropia as low as 0.5 D or more in sphere or cylinder for all refraction errors. Jeon and Choi analysed 107 children with anisometropia [11]. The children were divided into 2 groups: amblyopic and nonamblyopic. The average degree of anisometropia was 2.54 in the nonamblyopic group and 4.29 D in the amblyopic group. Stereopsis was significantly worse in the amblyopic group: 641.71 sec. of arch versus 76.25 sec. of arch., while it was 54.52 sec. arch in the controls. In the study by Chen et al., pure anisometropes of 3 D or less retain fusion and some stereopsis. A complete loss of binocularity was noted in anisometropia as high as 6 D or more [12]. Yan et al. report an impairment of stereopsis in children with myopic anisometropia of more than 1 D in sphere or cylinder [13].

As can be reasoned from the abovementioned studies, anisometropia affects stereoacuity, but it is difficult to name the amount of anisometropia that significantly reduces stereoscopic vision. In population-based studies, researchers often deal with stereoacuity defects of different origins (anisometropia, microstrabismus, and deprivation), which makes such an analysis difficult.

On the contrary, studies analysing stereopsis in experimentally induced anisometropia enable to precisely measure the deficiency of stereoacuity per 1 D of ametropia.

Oguz and Oguv experimentally induced anisometropia in healthy adults [14]. In this study, stereoacuity was reduced by 57–59 sec. of arch for 1 D of spherical anisometropia and 51–56 sec. of arch for astigmatism. The threshold value of anisometropia, which significantly reduced stereoacuity, was 3 D for both sphere and cylinder. Similar results were reported by Dadeya et al. and Gawęcki and Adamski [15, 16]. Kulkarni et al. analysed the influence of experimentally induced astigmatism on stereoacuity [17]. The authors used 2 values of astigmatism: 1 D or 2 D placed on a different axis. The stereoacuity levels decreased with the increase of the dioptre power of astigmatism. They were affected the most by the oblique astigmatism and the least by the astigmatism at the 180 axis. A similar study for astigmatism was performed by Al-Qahtani, and Al-Debasi confirmed these results [18].

The present study analyses myopic anisometropia in particular. In comparison to previous reports, it employs grading of stereopsis and is performed on a relatively large number of patients. In this research, the threshold values of

Table 12: Distribution of patients with different degrees of stereopsis at distance according to the amount of astigmatic anisometropia ("against the rule" astigmatism).

Grade of stereopsis	(Distance) cyl 180° +1		(Distance) cyl 180° +2		(Distance) cyl 180° +3		(Distance) cyl 180° +4	
	n	%	*n*	%	*n*	%	*n*	%
Absence	3	7.5	23	57.5	34	85.0	37	92.5
Poor	6	15.0	7	17.5	3	7.5	3	7.5
Moderate	5	12.5	3	7.5	3	7.5	0	0.0
Good	26	65.0	7	17.5	0	0.0	0	0.0
Ogółem	40	100.0	40	100.0	40	100.0	40	100.0

Table 13: Results of the post hoc ANOVA test showing a statistical difference between all possible pairs of measurements. Absolute differences between mean rank values are significant if larger than 0.761599273516645 at a confidence level = 0.05.

	(Distance) cyl 180° +1	(Distance) cyl 180° +2	(Distance) cyl 180° +3	(Distance) cyl 180° +4
(Distance) cyl 180° +1	—	1.175	1.8625	2.0125
(Distance) cyl 180° +2	1.175	—	0.6875	0.8375
(Distance) cyl 180° +3	1.8625	0.6875	—	0.15
(Distance) cyl 180° +4	2.0125	0.8375	0.15	—

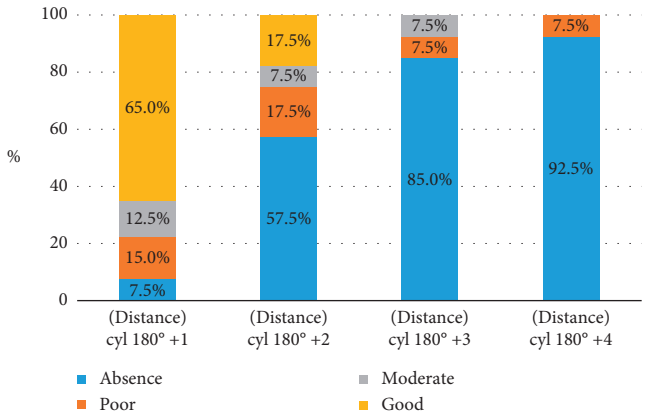

Figure 6: Distribution of patients with different grades of stereopsis at distance according to the level of astigmatic myopic anisometropia ("against the rule" astigmatism) presented on the graph.

Table 14: Threshold values of myopic anisometropia causing a loss of stereopsis in more than 50% of subjects.

Type of myopic anisometropia	Value in D for near	Value in D for distance
Spherical	3	2
Astigmatism "with the rule"	4	3
Astigmatism "against the rule"	3	2

myopic anisometropia, which lead to a complete loss of stereoacuity, differ in near and distance measurements. Myopic anisometropia is better tolerated for near, where values of 3-4 D cause a loss of binocularity. At distance, as low as 2 D of anisometropia can significantly decrease or cause a loss of binocularity. We also observe that "against the rule" astigmatism can affect stereoacuity more than regular astigmatism. These results are in consent with previous studies; however, this paper additionally presents intermediate values of anisometropia that impair stereoacuity, but not suppress it totally. It has to be remembered that lower threshold values of myopic anisometropia also put patients at risk of developing amblyopia.

Determining the threshold values for the loss of stereoacuity has practical therapeutic implications. Diagnosing a child with myopic anisometropia of 2 D or more implicates the need for immediate treatment. Therapeutic decisions have to be determined by the presence of the sensitive period for the treatment of amblyopia, available therapeutic methods, and potential risks associated with the application of those methods.

Most of the studies indicate the sensitive period for visual development as age 0–7 [19–21]. However, there is evidence that supports more effective treatment of amblyopia in younger children [22, 23]. Donahue reports a low prevalence of amblyopia in anisometropic children aged less than 3 [24]. After the age of 3, in most children with anisometropia, amblyopia is already developed.

Correction of the refraction error including anisometropia is a key for preserving and restoring binocularity. Without such treatment chances for normal development of the visual system are significantly diminished. A smaller amount of anisometropia can be successfully corrected with glasses, and a larger amount with contact lenses [25]. However, there exist a number of children uncompliant to optical correction by those means. In such cases, laser correction of the refraction error should be considered. Medical literature presents successful functional results of PRK in anisometropic children. Autrata et al. reports good binocular function in 13 children aged 7–15 who underwent photorefractive keratectomy (PRK) in high myopic anisometropia [26]. Twelve of the thirteen patients had a fusional potential, and 6 of them had stereopsis. In a later study, the same authors present a better binocular function in anisometropic children after PRK or laser-assisted subepithelial keratectomy (LASIK) than in anisometropic children treated by contact lenses (fusion and stereopsis gain in 78% versus 33%) [27]. Paysee et al. also report optimistic results in anisometropia treated by PRK [28, 29]. Stereopsis improved in 33% of cases (short term) and 55% of cases (long term) of children between 2 and

11 years of age. Yin et al. analysed 32 myopic children who underwent LASIK due to myopic anisometropia [30]. The number of patients who had stereopsis improved from 19% before to 89% after the surgery. Astle et al. reported the percentages of stereopsis gain from 39.4% to 87.9% for the whole cohort of children with hyperopic and myopic anisometropia [31]. The improvement of stereopsis in anisometropic patients after corneal refractive surgery also applies to adults [32].

Magli et al. published less optimistic results [33]. Just 2 of 18 patients with myopic anisometropia improved stereopsis after PRK. Similar results were reported by Zangh and Yu in juvenile patients with myopic anisometropic amblyopia, who had no stereopsis before femtosecond laser corneal surgery [34]. There was a stereopsis gain in 21.2% of these patients.

The other method of correcting large anisometropia is phakic intraocular lens (p-IOL) implantation. The procedure involves the implantation of an artificial lens either into the anterior chamber or into the ciliary sulcus with a preservation of the natural lens of the patient. Tian et al. performed a meta-analysis of the literature on the subject [35]. They compared the functional improvement of vision in children with myopic anisometropia after corneal refractive surgery and after p-IOL implantation. Binocular vision improved in more than half of the patients in both groups.

Just recently, implantable collamer lenses (ICL) have been introduced for the correction of large refractive errors. They are p-IOLs implanted to the ciliary sulcus. Zhang et al. report a treatment of 11 eyes of children with unilateral high myopia (average age of 11 years) treated with ICL. The procedure resulted in a significant improvement of BCVA; however, none of the patients had a stereopsis recovery for near after the surgery [36]. The same author reports the effects of ICL treatment in adults with myopic anisometropia [37]. A basic stereopsis gain for near was noted in 4 of 13 patient who underwent the procedure.

As we see from the listed studies, the results of surgical treatment are satisfactory just in some cases. This may be due to the age of patients that undergo the surgery, which is usually advanced as for the amblyopia treatment. Like in every therapy, the potential risks of such a surgery have to be balanced with the potential benefits. Phakic IOLs, especially ICLs, seem to be reasonable treatment options for children with large anisometropia in whom correction with contact lenses or glasses is impossible or troublesome. This applies especially to high myopic anisometropia, as high myopia is often difficult to be corrected by corneal laser surgery. Besides, myopia is a refraction error that is willingly corrected by many patients when they reach adult age. In the case of myopic anisometropia, a decision about the surgery should be undertaken within the sensitive period for visual development.

6. Conclusion

Myopic anisometropia of more than 3 D in sphere or cylinder causes a total loss of stereopsis for near in most patients. At distance, myopic anisometropia as low as 2 D results in a significant impairment or loss of binocularity. Myopic anisometropia involving "against the rule" astigmatism disturbs stereoacuity more than anisometropia involving "with the rule" astigmatism. Immediate measures for optical or sometimes surgical correction should be undertaken if myopic anisometropia of 2 D or more is diagnosed during screening for the refraction error in children. There is a need for creating an algorithm for the treatment of anisometropic amblyopia that would consider the age of patients, their compliance, and the amount of anisometropia.

Data Availability

The electronic data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The author declares that there are no conflicts of interest.

References

[1] D. R. Weakley Jr., "The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity," *Ophthalmology*, vol. 108, no. 1, pp. 163–171, 2001.

[2] R. J. Babu, S. R. Clavagnier, W. Bobier, B. Thompson, and R. F. Hess, "The regional extent of suppression: strabismics versus nonstrabismics," *Investigative Opthalmology & Visual Science*, vol. 54, no. 10, pp. 6585–6593, 2013.

[3] M. T. Kulp, G.-S. Ying, J. Huang et al., "Associations between hyperopia and other vision and refractive error characteristics," *Optometry and Vision Science*, vol. 91, no. 4, pp. 383–389, 2014.

[4] E. E. Birch, V. Subramanian, and D. R. Weakley, "Fixation instability in anisometropic children with reduced stereopsis," *Journal of American Association for Pediatric Ophthalmology and Strabismus*, vol. 17, no. 3, pp. 287–290, 2013.

[5] D. R. Melmoth, A. L. Finlay, M. J. Morgan, and S. Grant, "Grasping deficits and adaptations in adults with stereo vision losses," *Investigative Opthalmology & Visual Science*, vol. 50, no. 8, pp. 3711–3720, 2009.

[6] E. S. van de Graaf, G. W. van der Sterre, H. van Kempen-du Saar, B. Simonsz, C. W. N. Looman, and H. J. Simonsz, "Amblyopia and strabismus questionnaire (A&SQ): clinical validation in a historic cohort," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 245, no. 11, pp. 1589–1595, 2007.

[7] S. L. Pineles, F. G. Velez, S. J. Isenberg et al., "Functional burden of strabismus," *JAMA Ophthalmology*, vol. 131, no. 11, pp. 1413–1419, 2013.

[8] A. L. Webber and J. Wood, "Amblyopia: prevalence, natural history, functional effects and treatment," *Clinical and Experimental Optometry*, vol. 88, no. 6, pp. 365–375, 2005.

[9] D. M. Levi, S. P. McKee, and J. A. Movshon, "Visual deficits in anisometropia," *Vision Research*, vol. 51, no. 1, pp. 48–57, 2011.

[10] V. Dobson, J. M. Miller, C. E. Clifford-Donaldson, and E. M. Harvey, "Associations between anisometropia, amblyopia, and reduced stereo acuity in a school-aged population with a high prevalence of astigmatism," *Investigative Opthalmology & Visual Science*, vol. 49, no. 10, p. 4427, 2008.

[11] H. S. Jeon and D. G. Choi, "Stereopsis and fusion in anisometropia according to the presence of amblyopia," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 255, no. 12, pp. 2487–2492, 2017.

[12] B. B. Chen, F. W. Song, Z. H. Sun, and Y. Yang, "Anisometropia magnitude and visual deficits in previously untreated anisometropic amblyopia," *International Journal of Ophthalmology*, vol. 6, no. 5, pp. 606–610, 2013.

[13] J.-W. Yang, T.-Y. Huang, J.-S. Lee, L. Yeung, Y.-F. Lin, and C.-C. Sun, "Correlation between myopic ametropia and stereo acuity in school-aged children in Taiwan," *Japanese Journal of Ophthalmology*, vol. 57, no. 3, pp. 316–319, 2013.

[14] H. Oguz and V. Oguz, "The effects of experimentally induced anisometropia on stereopsis," *Journal of Pediatric Ophthalmology and Strabismus*, vol. 37, no. 4, pp. 214–218, 2000.

[15] S. Dadeya, S. F. Kamlesh, and F Shibal, "The effect of anisometropia on binocular visual function," *Indian Journal of Ophthalmology*, vol. 49, no. 4, pp. 261–263, 2001.

[16] M. Gawecki and J. Adamski, "Anisometropia and stereopsis," *Klin Oczna*, vol. 106, no. 4-5, pp. 561–563, 2004.

[17] V. Kulkarni, N. Puthran, and B. Gagal, "Correlation between stereoacuity and experimentally induced graded monocular and binocular astigmatism," *Journal of Clinical and Diagnostic Research*, vol. 10, no. 5, pp. NC14–NC17, 2016.

[18] H. Al-Qahtani and H. Al-Debasi, "The effects of experimentally induced graded monocular and binocular astigmatism on near stereo acuity," *Saudi Journal of Ophthalmology*, vol. 32, no. 4, pp. 275–279, 2018.

[19] C. C. Bretas and R. N. Soriano, "Amblyopia: neural basis and therapeutic approaches," *Arquivos Brasileiros de Oftalmologia*, vol. 79, no. 5, pp. 346–351, 2016.

[20] S. West and C. Williams, "Amblyopia in children (aged 7 years or less)," *BMJ Clinical Evidence*, vol. 2016, 2016.

[21] M. Fronius, L. Cirina, H. Ackermann, T. Kohnen, and C. M. Diehl, "Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: new insight into declining susceptibility of the visual system," *Vision Research*, vol. 103, pp. 11–19, 2014.

[22] K. Simons, "Amblyopia characterization, treatment, and prophylaxis," *Survey of Ophthalmology*, vol. 50, no. 2, pp. 123–166, 2005.

[23] C. Williams, K. Northstone, R. A. Harrad, J. M. Sparrow, I. Harvey, and ALSPAC Study Team, "Amblyopia treatment outcomes after preschool screening v school entry screening: observational data from a prospective cohort study," *British Journal of Ophthalmology*, vol. 87, no. 8, pp. 988–993, 2003.

[24] S. P. Donahue, "Relationship between anisometropia, patient age, and the development of amblyopia," *American Journal of Ophthalmology*, vol. 142, no. 1, pp. 132–140, 2006.

[25] J. Y. Lee, J. Y. Seo, and S. U. Baek, "The effects of glasses for anisometropia on stereopsis," *American Journal of Ophthalmology*, vol. 156, no. 6, pp. 1261–1266, 2013.

[26] R. Autrata, J. Rehůrek, and M. Holousová, "Photorefractive keratectomy in high myopic anisometropia in children," *Ceská a Slovenská Oftalmologie*, vol. 55, no. 4, pp. 216–221, 1999.

[27] R. Autrata and J. Rehurek, "Laser-assisted subepithelial keratectomy and photorefractive keratectomy versus conventional treatment of myopic anisometropic amblyopia in children," *Journal of Cataract & Refractive Surgery*, vol. 30, no. 1, pp. 74–84, 2004.

[28] E. A. Paysse, M. B. Hamill, M. A. W. Hussein, and D. D. Koch, "Photorefractive keratectomy for pediatric anisometropia: safety and impact on refractive error, visual acuity, and stereopsis," *American Journal of Ophthalmology*, vol. 138, no. 1, pp. 70–78, 2004.

[29] E. Paysse, D. Coats, M. Hussein, M. Hamill, and D. Koch, "Long-term outcomes of photorefractive keratectomy for anisometropic amblyopia in children," *Ophthalmology*, vol. 113, no. 2, pp. 169–176, 2006.

[30] Z. Q. Yin, H. Wang, T. Yu, Q. Ren, and L. Chen, "Facilitation of amblyopia management by laser in situ keratomileusis in high anisometropic hyperopic and myopic children," *Journal of American Association for Pediatric Ophthalmology and Strabismus*, vol. 11, no. 6, pp. 571–576, 2007.

[31] W. F. Astle, J. Rahmat, A. D. Ingram, and P. T. Huang, "Laser-assisted subepithelial keratectomy for anisometropic amblyopia in children: outcomes at 1 year," *Journal of Cataract & Refractive Surgery*, vol. 33, no. 12, pp. 2028–2034, 2007.

[32] M. Jabbarvand, H. Hashemian, M. Khodaparast, and P. Anvari, "Changes in stereopsis after photorefractive keratectomy," *Journal of Cataract & Refractive Surgery*, vol. 42, no. 6, pp. 899–903, 2016.

[33] A. Magli, A. Iovine, V. Gagliardi, F. Fimiani, and P. Nucci, "Photorefractive keratectomy for myopic anisometropia: a retrospective study on 18 children," *European Journal of Ophthalmology*, vol. 18, no. 5, pp. 716–722, 2008.

[34] J. Zhang and K. M. Yu, "Femtosecond laser corneal refractive surgery for the correction of high myopic anisometropic amblyopia in juveniles," *International Journal of Ophthalmology*, vol. 10, no. 11, pp. 1678–1685, 2017.

[35] C. Tian, X. Peng, Z. Fan, and Z. Yin, "Corneal refractive surgery and phakic intraocular lens for treatment of amblyopia caused by high myopia or anisometropia in children," *Chinese Medical Journal*, vol. 127, no. 11, pp. 2167–2172, 2014.

[36] J. Zhang, J. R. Li, Z. D. Chen, M. B. Yu, and K. M. Yu, "Phakic posterior chamber intraocular lens for unilateral high myopic amblyopia in Chinese pediatric patients," *International Journal of Ophthalmology*, vol. 9, no. 12, pp. 1790–1797, 2016.

[37] J. Zhang, J. Zhuang, and K. M. Yu, "Posterior chamber phakic intraocular lens for the correction of high myopic anisometropic amblyopia in adults," *International Journal of Ophthalmology*, vol. 11, no. 11, pp. 1870–1874, 2018.

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Research Article

Long-Term Natural Course of Pathologic Myopia in Chinese Patients

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Purpose. To investigate the natural progression in Chinese patients with pathological myopia (PM) and its associated factors. *Methods*. The medical records of 28 patients with PM (worse than −6 diopter), including 31 eyes of 21 children and 12 eyes of 7 adults, were studied. All of the patients underwent a complete ophthalmologic examination at least twice over 3-year period, including the measurement of refractive error (shown as spherical equivalent, SE), axial length (AL), intraocular pressure, visual acuity (uncorrected visual acuity, UCVA, and best-corrected visual acuity, BCVA), and dilated fundus examination. *Results*. The median AL of adults increased significantly from 29.8 mm to 31.43 mm over 5.4 years follow-up ($P = 0.0037$), accompanied with the median SE progressing significantly from −16.4 D to −18.94 D ($P = 0.0005$). Similarly, the median AL of children increased significantly from 26.13 mm to 27.81 mm over 3.9 years ($P = 0.0001$). However, the improvements of UCVA and BCVA in children were significant ($P = 0.0304, 0.0001$), and they had a negative correlation with age ($P = 0.0010, 0.0005$). Also, UCVA and BCVA in children with bilateral PM were significantly better than those with unilateral PM ($P = 0.0385, 0.0210$). *Conclusions*. Fundus degenerations in children with pathological myopia may lead its way since the age of 10 years. Besides, children with bilateral pathological myopia can have parallel development in visual acuity.

1. Introduction

Myopia has emerged as a major public health concern nowadays with the striking evidence existing for rapid increases in its prevalence [1]. Among which, interethnic comparisons showed that the incidence of myopia was higher in Chinese than in non-Chinese [2–5]. The similar findings observed in the Correction of Myopia Evaluation Trial (COMET), a randomized double-masked multicenter clinical study, identified that Asian populations in America experienced a greater prevalence of myopia [6]. A multicenter observational study, which included 4 ethnic groups from 4 different locations in the United States, also found Asian children tend to have the highest prevalence of myopia, compared with Hispanics and African Americans [7]. Therefore, ethnicity may play an important role in myopic prevalence even in its progression.

With the increasing prevalence of myopia in most populations worldwide, the prevalence of pathological myopia (PM) has also increased. Pathological myopia, clinically characterized by continuous eye elongation, resulting from scleral thinning and posterior staphyloma, initiates serious intraocular complications, and leads to varying degrees of visual deterioration [8, 9]. The prevalence of PM is also known to be different among races, more common in the adult Asian population, at approximately 9% [10], than in the Caucasians in the United States at 2% [5]. In addition, PM was the second most common cause of low vision and blindness for people aged 40 years and older Chinese individuals [11] and was also reported to be the leading cause of visual impairment [12–14].

However, little is known about the natural history of pathological myopia. A PubMed search extracted no more than 5 articles describing a natural course of PM, and none

of which was conducted in Chinese population [15–18]. Considering the interethnic difference, the purpose of this study was to investigate the natural changes of axial length, refraction, and intraocular complications in Chinese patients with PM, as well as the potential associated factors.

2. Patients and Methods

The study followed the tenets of the Declaration of Helsinki (1964) and was approved by Ethics Committee of Eye and ENT Hospital of Fudan University. Since this was a retrospective study with no interventions involved, patients or their guardians were acknowledged with the study protocol verbally without signing written consent form.

The medical records of consecutive patients with PM who were examined in Eye and ENT Hospital of Fudan University from 2008 through 2012 and a minimum follow-up of 2 years were retrospectively analyzed. Eligible subjects were diagnosed with PM accompanied with the following criteria: refractive error should be worse than −6.0 D (spherical equivalent, SE) when patients were younger than 8 years old, worse than −8.0 D when aged between 8 and 12 years old, worse than −10.0 D when aged between 12 and 18 years old, and worse than −12.0 D when older than 18 years old; and the best-corrected visual acuity (BCVA) should be no better than 20/20. The exclusion criteria were (1) nonspectacles myopia corrections, such as contact lenses, pharmaceuticals, and surgeries; (2) history of vitreoretinal surgery or cataract surgery; (3) moderate to severe cataract obstructing an accurate measurement of the axial length; (4) any history of nystagmus, glaucoma, lens abnormality, or retinal disorders which would influence axial length measurement or fixation; and (5) active choroidal neovascularization at the initial examination or during the follow-up, where exudative changes such as serous retinal detachment would change axial length.

All of the patients underwent a complete ophthalmologic examination at each visit, including the measurement of the refractive error (spherical equivalent), axial length (AL), intraocular pressure (IOP), visual acuity, and dilated fundus examination. AL was measured using noncontact IOLMaster (Carl Zeiss Meditec AG, Jena, Germany) at least 5 times for each eye at each examination and was averaged for statistical analyses. The uncorrected visual acuity (UCVA) was examined with a standard logarithmic visual acuity chart. Subjective refraction of children was examined by experienced optometrists using autorefractor (ARK-700A autorefractor and SSC-330 scientific subjective refractor, NIDEK, Japan) half an hour after cycloplegia induced with three drops of 0.5% tropicamide with five-minute intervals. Refractive error examination for children younger than 3 years old was conducted using retinoscopy after cycloplegia. IOP was tested at least 3 times with Canon TXF-noncontact tonometer and averaged for analysis. All technicians were blind to the study.

2.1. Statistical Analysis. All statistical analyses were performed with Stata software version 11.0 (Stata Corp., College Stations, TX, USA). Visual acuity was converted to logMAR for data analysis. Changes within groups were analyzed using the Wilcoxon signed-rank test. Comparisons between the groups were performed with Student's *t*-test or the Mann–Whitney rank-sum test. In addition, factors that might be associated with the AL increase and myopic progression were analyzed using regression analysis. P value < 0.05 was considered statistically significant.

3. Results

Of all the eligible medical records, 43 eyes of 28 patients met the inclusion criteria, where 14 patients were diagnosed with unilateral PM and 21 patients (31 eyes) were younger than 18 years. The clinical characteristics of children and adults at the initial examination are shown in Table 1.

During the follow-up period, the median AL increased significantly from 26.13 mm at the initial visit to 27.81 mm at the final examination in the 31 eyes of children ($P = 0.0001$), equivalent of 1.68 mm axial elongation over 3.9 years (0.43 mm per year). Among which, 18 eyes (58%) experienced an axial elongation no more than 2.0 mm during the period, equal to 0.5 mm per year, while 7 eyes (23%) elongated more than 2.0 mm. Compared to children, the median AL in the 12 eyes of adults increased significantly from 29.8 mm to 31.43 mm during the follow-up ($P = 0.0037$), equal to 1.63 mm axial elongation over a period of 5.4 years (0.30 mm per year). Six eyes (50%) experienced an axial elongation no more than 1 mm during the course, equal to 0.2 mm per year; among which, 5 eyes (42%) elongated no more than 0.5 mm (0.1 mm/year). However, 4 eyes (33%) of adults had an axial elongation more than 2.0 mm.

In terms of refractive error, 31 eyes of children experienced a median myopia progression of −3.35 D during the 3.9-year follow-up, ending up with −12.25 D at the final visit ($P = 0.0001$), equal to 0.86 D progression per year. Of all the children, 3 eyes (10%) remained stable (no more than 0.5 D), whereas 8 eyes (26%) progressed significantly by more than 4 D. As for the refractive changes in adults, the median SE changed significantly from −16.4 D at the first visit to −18.94 D at the last examination in all 12 eyes ($P = 0.0005$), equal to −2.54 D over 5.4 years of follow-up (−0.47 D per year). Among which, only one eye was stable (no more than 0.5 D), while two eyes (17%) progressed more than 4 D.

As we expected, myopia progression had a significantly positive relationship with the increase of AL for both children and adults ($P = 0.0136$, 0.0002) (Figures 1 and 2). However, neither AL nor the IOP at the initial visit was significantly correlated with the increase of AL ($P > 0.05$). For children, axial elongation and myopic progression had no association with the age at their initial visits ($P = 0.0840$, 0.8711). However, the myopic progression was negatively correlated with the SE at the initial visit ($P = 0.0013$).

With regard to the IOP, no significant difference was found in both children and adults at the final visit when compared to that at the first visit ($P = 0.1325$, 0.8377). But for visual acuity, significant improvement was observed in

Table 1: Clinical characteristics of children and adults at the initial examination.

	Children (31 eyes of 21 patients)	Adults (12 eyes of 7 patients)
Median age at initial examination (range) (yrs)	6.6 (1.1 to 14.3)	38.1 (25.7 to 45.6)
Median SE (range) (D)	−8.9 (−6 to −21.5)	−16.4 (−12.5 to −22.5)
Median axial length (range) (mm)	26.13 (21.53 to 30.11)	29.8 (27.16 to 32.35)
Median follow-up (range) (yrs)	3.9 (2 to 7.2)	5.4 (2.4 to 6)

D: diopters; yrs: years; SE: spherical equivalent.

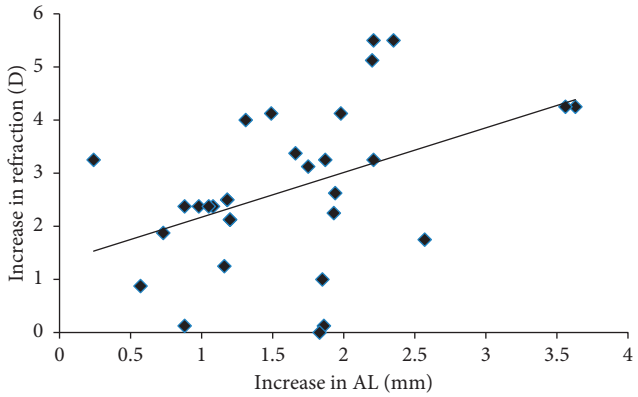

Figure 1: The correlation between myopia progression and axial elongation during the follow-up period in children. AL: axial length; D: diopter.

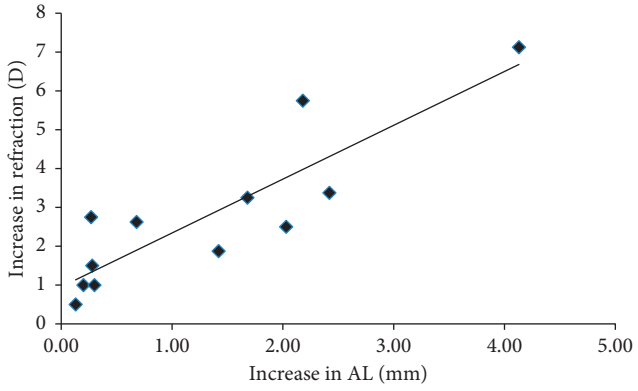

Figure 2: The relationship between myopia progression and change in axial length during the follow-up period in adults. AL: axial length; D: diopter.

both UCVA and BCVA of children at the final visit, compared to those of the initial visit ($P = 0.0304$, 0.0001). However, deterioration of UCVA was found in adults during the follow-up ($P = 0.0293$), whereas BCVA remained unchanged ($P = 0.1545$). Children were divided into four groups according to the age at the initial visit (Table 2). In general, the improvement of both UCVA and BCVA was negatively correlated with age ($P = 0.0010$, 0.0005). Three younger groups of children experienced significant improvement of UCVA but children older than 10 years old had UCVA deterioration (Table 2). In addition, BCVA improvement was observed in two younger groups but not in two older groups (Table 2), suggesting that children with extensive myopia older than 10 may have little opportunity in BCVA improvement.

Table 2: Comparison of visual acuity (UCVA and BCVA separately) of children at different ages between the first and last visits.

Grouping by age (yrs)	<4 ($n = 6$)	≥4 and <7 ($n = 9$)	≥7 and <10 ($n = 9$)	≥10 ($n = 7$)
Follow-up periods (yrs)	3.23 ± 0.90	3.91 ± 1.06	5.20 ± 1.53	3.74 ± 1.84
P value for UCVA	0.0063	0.0465	0.0404	0.0202
P value for BCVA	0.0284	0.0076	0.5733	0.5292

n: number of eyes; yrs: years; UCVA: the uncorrected visual acuity; BCVA: best-corrected visual acuity.

Children were also grouped by unilateral or bilateral PM, and the clinical characteristics of the initial examination are shown in Table 3. UCVA and BCVA were significantly better in the bilateral group ($P = 0.0385$, 0.0210) despite that the refractive error and AL were comparable between the two groups. During the follow-up period, no significant between-group difference was found in the axial elongation or myopic progression ($P = 0.7981$, 0.5631). However, UCVA of the unilateral group improved more than the bilateral group ($P = 0.0344$, Table 3, Figure 3), as well as the BCVA, though not significantly ($P = 0.0557$).

4. Discussion

Although more and more pathological myopia patients have been visiting our clinics, we had rare chance to follow the natural course of PM since high myopia and related complications were usually treated, preventing us from enrolling more cases in our study. However, to our knowledge, it was the first report focusing on the natural progression of PM in Chinese patients as well as the first study concerning the natural course of PM development in children.

It was acknowledged that AL would reach adult length and remained stable by the age of 13 [19, 20], it was not the case for patients with progressive PM. Saka et al. reported that the median increase of AL in high myopic eyes with and without various pathologic changes was 0.08 mm per year (0.06 mm/year in the age group of <45 years and 0.12 mm/year in the age group of ≥45 years [15]), as determined by A-scan ultrasound. In another study, Takahashi et al. used IOLMaster to determine the mean AL increase by 0.085 mm per year [21]. In the current study, the median axial elongation per year was about 0.3 mm in adults, much longer than that reported by previous studies. Even with the acknowledged disparity of axial measurement 0.09 mm longer with IOLMaster than ultrasound [22], a 0.21 mm/year-axial elongation difference still remained in our study,

Table 3: Comparison of clinical characteristics between bilateral and unilateral pathological myopia in children at the initial visit.

	Unilateral PM (11 eyes of 11 children)	Bilateral PM (20 eyes of 10 children)	P value
Median age at initial examination (yrs)	5.5	8.9	0.1286
Median SE (D)	−7.25	−9.19	0.0630
Median axial length (mm)	25.94	26.53	0.1795
Median UCVA at initial visit (logMAR)	1.05	0.70	0.0385
Median UCVA at final visit (logMAR)	0.67	0.60	0.772
Follow-up (range) (yrs)	3.9	3.8	0.5356

yrs: years; SE: spherical equivalent; PM: pathological myopia; UCVA: uncorrected visual acuity.

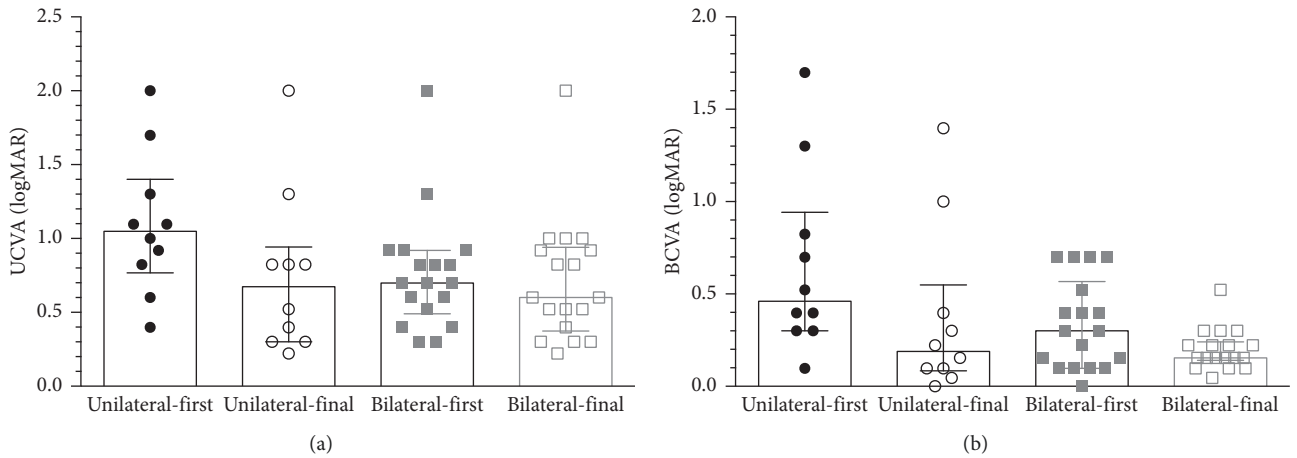

Figure 3: Comparison of visual acuity ((a) UCVA and (b) BCVA) between children with unilateral pathological myopia and bilateral myopia at their first and final visits. UCVA: uncorrected visual acuity; BCVA: best-corrected visual acuity; logMAR: Logarithm of the Minimum Angle of Resolution.

which may be resulted from the different inclusion criteria. In the previous studies, the definition of high myopia was refractive error equal to or worse than −6.0 diopters (D) or AL ≥ 26.5 mm. However, adult patients enrolled in the current study had a refractive error of −12.0 D or more, much more myopic than previous studies. It was acknowledged that PM was characterized by progressive axial elongation and myopia development. Thus, our results may reflect that the axial elongation increased with the degree of PM, or Chinese PM patients may be more susceptible to axial elongation. Since the studies of Saka and Takahashi were both conducted in Japan, another high-prevalence area, interethnic progression of AL in PM also existed. In the western area, Fledelius and Goldschmidt reported a significant mean AL increase, from 26.7 ± 1.3 mm at age 26 to 27.5 ± 2.1 mm at age 54, in 39 high myopic patients, equivalent to 0.03 mm elongation per year [22]. The much longer follow-up periods may be responsible for the obvious difference. Nevertheless, these findings suggest that further studies warrant to determine whether the myopia progression was affected by ethnic difference.

Numerous studies focused on myopia progression in children, but neither of them paid attention to the progression of PM to date. In the current study, the median AL growth was 1.68 mm over 3.9-year follow-up (0.43 mm/year) in children, equal to a 0.86 D myopic progression per year. However, Saw et al. reported a myopia progression rate of −2.40 D in 7-year old, −1.97 D in 8-year old, and −1.71 D in 9-year old during 3 years, about −0.8 D per year in 7-year old children [23]. Also, in a Hong Kong myopia study of school children aged 5 to 16 years, the myopia progression rate was −0.63 D per year [24], slightly less than the rate in the current study. As for the AL elongations, Saw et al. reported an average increase of 0.89 mm over 3 years [25], similar to the myopic children aged 7–10.5 years (n = 133) in the Hong Kong study who showed AL increase by 0.32 mm per year (0.96 mm over 3 years) [26]. In contrast, in the COMET trial, the rate of axial elongation was slightly lower in myopic children aged 6–11 years which was 0.75 mm over 3 years [27]. Previous studies have demonstrated an evident greater rate of myopia progression in Asian children than in age-matched European children [23, 27], but none of them defined the PM. Now, we deemed that the Chinese pathological myopic children experienced faster axial elongation but similar myopic development annually compared to children with mild to moderate myopia. Besides, the negative correlation between the myopic progression and the refractive error at the initial visit was different from previous studies. PM in children was mostly infantile-onset myopia and considered to be associated with the onset of amblyopia [28, 29]. Since the lazy eye may not be so engaged in visual activity, the myopic development could be slowed down to some extent. Considering the difference between bilateral and unilateral PM, the former performed much better in visual acuity than the latter one. Visual acuity was usually worse in the pathological myopic eye than the fellow eye in

unilateral myopia and had unbalanced development interocularly, but improved simultaneously between the two eyes in bilateral PM. However, no notable difference was observed in axial elongation or myopia progression between the two groups.

It is well known that the change of refractive error is associated with the elongation of eyeball. Our data were consistent with previous results that the myopia progression was positively correlated with the increase of AL both for children and adults. The result that AL elongation had no relationship with axial length at the initial examination or IOP was in agreement with Saka's research [15]. Also, no correlations between the age and AL elongation or myopia progression in children were demonstrated.

In comparison with the deteriorated UCVA in adult pathological myopes, UCVA and BCVA in PM children improved during the follow-up period. Posterior staphyloma and fundus degenerations are not common in highly myopic children [30], but the incidence and severity of pathological changes in high myopia increase with age [31]. The improvement of visual acuity in highly myopic children may be resulted from ongoing visual development as well as mild pathological features. In addition, children younger than 10 years showed improvement of UCVA, while their older counterpart showed deteriorations. These findings suggest that the visual acuity of infantile-onset PM eyes may first improve with ocular development; then at a certain age, it deteriorates due to that the incidence and severity of pathological disorders increase with age, and the certain age may be 10 years of age according to our results. Though the dividing age was not clear in BCVA, the consistent trend of visual acuity development suggested that the certain age would probably be older than 10 years old, while this hypothesis needs further confirmation. The insufficient sample was a limitation, so a larger population is necessary to extract the exact age when fundus deterioration appears in highly myopic children. Moreover, this retrospective study was limited by the existing medical records, providing at most 7-year follow-up.

5. Conclusions

In conclusion, this is the first study reporting the natural progression in Chinese patients with PM and its possible associated factors, in which we demonstrated a 1.68 mm median axial elongation over 3.9 years, accompanied with a −3.35 D myopia progression in children, whereas in adults, it was 1.63 mm over 5.4 years and −2.54 D. However, neither the AL at the initial examination nor the IOP was significantly correlated with the increase in the AL. Children with PM had their UCVA and BCVA improved with age before 10 years old, whereas fundus degeneration may lead visual acuity deteriorations thereafter. Besides, children with bilateral PM showed better performance in visual acuity than their unilateral counterparts.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

All the authors declare that they have no conflicts of interest.

Authors' Contributions

Chen MJ and Yu MR contributed equally to this work and should be considered as co-first authors.

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References

[1] I. G. Morgan, K. Ohno-Matsui, and S.-M. Saw, "Myopia," *The Lancet*, vol. 379, no. 9827, pp. 1739–1748, 2012.

[2] I. Morgan and K. Rose, "How genetic is school myopia?," *Progress in Retinal and Eye Research*, vol. 24, no. 1, pp. 1–38, 2005.

[3] M. He, W. Huang, Y. Zheng, L. Huang, and L. B. Ellwein, "Refractive error and visual impairment in school children in rural southern China," *Ophthalmology*, vol. 114, no. 2, pp. 374–382, 2007.

[4] D.-C. Tsai, S.-Y. Fang, N. Huang et al., "Myopia development among young schoolchildren: the myopia investigation study in Taipei," *Investigative Opthalmology & Visual Science*, vol. 57, no. 15, pp. 6852–6860, 2016.

[5] S. Vitale, R. D. Sperduto, and F. L. Ferris, "Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004," *Archives of Ophthalmology*, vol. 127, no. 12, pp. 1632–1639, 2009.

[6] L. Hyman, J. Gwiazda, M. Hussein et al., "Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial," *Archives of Ophthalmology*, vol. 123, no. 7, pp. 977–987, 2005.

[7] R. N. Kleinstein, L. A. Jones, S. Hullett et al., "Refractive error and ethnicity in children," *Archives of Ophthalmology*, vol. 121, no. 8, pp. 1141–1147, 2003.

[8] S.-M. Saw, G. Gazzard, E. C. Shih-Yen, and W.-H. Chua, "Myopia and associated pathological complications," *Ophthalmic and Physiological Optics*, vol. 25, no. 5, pp. 381–391, 2005.

[9] T. Grosvenor, "Why is there an epidemic of myopia?," *Clinical and Experimental Optometry*, vol. 86, no. 5, pp. 273–275, 2003.

[10] T. Wong, P. Foster, J. Hee et al., "The prevalence and risk factors for refractive errors in an adult Chinese population in Singapore," *Investigative Ophthalmology & Visual Science*, vol. 38, no. 2, pp. 334–340, 2000.

[11] L. Xu, Y. Wang, Y. Li et al., "Causes of blindness and visual impairment in urban and rural areas in beijing," *Ophthalmology*, vol. 113, no. 7, pp. 1134.e1–1134.e11, 2006.

[12] M. Yamada, Y. Hiratsuka, C. B. Roberts et al., "Prevalence of visual impairment in the adult Japanese population by cause and severity and future projections," *Ophthalmic Epidemiology*, vol. 17, no. 1, pp. 50–57, 2010.

[13] B. A. Holden, T. R. Fricke, D. A. Wilson et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050," *Ophthalmology*, vol. 123, no. 5, pp. 1036–1042, 2016.

[14] K. Ohno-Matsui, Y. Ikuno, T. Y. Y. Lai, and C. M. Gemmy Cheung, "Diagnosis and treatment guideline for myopic

choroidal neovascularization due to pathologic myopia," *Progress in Retinal and Eye Research*, vol. 63, pp. 92–106, 2018.

[15] N. Saka, K. Ohno-Matsui, N. Shimada et al., "Long-term changes in axial length in adult eyes with pathologic myopia," *American Journal of Ophthalmology*, vol. 150, no. 4, pp. 562–568, 2010.

[16] C. Melzer, F. Ziemssen, N. Eter et al., "Design and baseline characteristics of the HELP study: an extended and long-term observation of pathological myopia in Caucasians," *Ophthalmologica*, vol. 240, no. 3, pp. 167–178, 2018.

[17] H. Ohsugi, Y. Ikuno, T. Shoujou, K. Oshima, E. Ohsugi, and H. Tabuchi, "Axial length changes in highly myopic eyes and influence of myopic macular complications in Japanese adults," *PLoS One*, vol. 12, no. 7, Article ID e0180851, 2017.

[18] K. Hayashi, K. Ohno-Matsui, N. Shimada et al., "Long-term pattern of progression of myopic maculopathy," *Ophthalmology*, vol. 117, no. 8, pp. 1595.e4–1611.e4, 2010.

[19] J. S. Larsen, "The sagittal growth of the eye," *Acta Ophthalmologica*, vol. 49, no. 6, pp. 873–886, 1971.

[20] R. A. Gordon and P. B. Donzis, "Refractive development of the human eye," *Archives of Ophthalmology*, vol. 103, no. 6, pp. 785–789, 1985.

[21] A. Takahashi, Y. Ito, Y. Iguchi, T. R. Yasuma, K. Ishikawa, and H. Terasaki, "Axial length increases and related changes in highly myopic normal eyes with myopic complications in fellow eyes," *Retina*, vol. 32, no. 1, pp. 127–133, 2012.

[22] H. C. Fledelius and E. Goldschmidt, "Oculometry findings in high myopia at adult age: considerations based on oculometric follow-up data over 28 years in a cohort-based Danish high-myopia series," *Acta Ophthalmologica*, vol. 88, no. 4, pp. 472–478, 2010.

[23] S.-M. Saw, L. Tong, W.-H. Chua et al., "Incidence and progression of myopia in Singaporean school children," *Investigative Opthalmology & Visual Science*, vol. 46, no. 1, pp. 51–57, 2005.

[24] D. S. P. Fan, D. S. C. Lam, R. F. Lam et al., "Prevalence, incidence, and progression of myopia of school children in Hong Kong," *Investigative Opthalmology & Visual Science*, vol. 45, no. 4, pp. 1071–1075, 2004.

[25] S. M. Saw, W. H. Chua, G. Gazzard, D. Koh, D. T. H. Tan, and R. A. Stone, "Eye growth changes in myopic children in Singapore," *British Journal of Ophthalmology*, vol. 89, no. 11, pp. 1489–1494, 2005.

[26] M. H. Edwards, R. W. Li, C. S. Lam, J. K. Lew, and B. S. Yu, "The Hong Kong progressive lens myopia control study: study design and main findings," *Investigative Ophthalmology & Visual Science*, vol. 43, no. 9, pp. 2852–2858, 2002.

[27] Y.-F. Shih, T.-C. Ho, C. K. Hsiao, and L. L.-K. Lin, "Long-term visual prognosis of infantile-onset high myopia," *Eye*, vol. 20, no. 8, pp. 888–892, 2006.

[28] L.-H. Pi, L. Chen, Q. Liu et al., "Prevalence of eye diseases and causes of visual impairment in school-aged children in western China," *Journal of Epidemiology*, vol. 22, no. 1, pp. 37–44, 2012.

[29] J. Gwiazda, L. Hyman, M. Hussein et al., "A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children," *Investigative Opthalmology & Visual Science*, vol. 44, no. 4, pp. 1492–1500, 2003.

[30] H. W. Hsiang, K. Ohno-Matsui, N. Shimada et al., "Clinical characteristics of posterior staphyloma in eyes with pathologic myopia," *American Journal of Ophthalmology*, vol. 146, no. 1, pp. 102–110, 2008.

[31] T. Barth, F. Zeman, H. Helbig, and I. Oberacher-Velten, "Etiology and treatment of choroidal neovascularization in pediatric patients," *European Journal of Ophthalmology*, vol. 26, no. 5, pp. 388–393, 2016.