ASTIGMATISM AND

AXIAL LENGTH IN HUMANS

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Thesis Abstract

Purpose: Astigmatism plays an important role in emmetropization and refractive development, but its impact on ocular structural changes remains largely unexplored in humans. The main purpose of this thesis was to investigate the associations between astigmatism – including its magnitude and axis orientation – and ocular axial length in humans. Specifically, the **meta-analysis** aimed to determine the association between baseline astigmatism and myopia development in children. **Study I** aimed to examine the impact of baseline astigmatism on axial elongation in school-age children. **Study II** aimed to characterize retinal thickness in eyes with different types of astigmatism. **Study III** aimed to develop prediction models for axial elongation and explore how astigmatism affects these models.

Meta-Analysis – Impact of Astigmatism on Refractive Development

***Methods*:** A systematic literature search was conducted using PubMed, Embase, Cochrane Library, and Web of Science databases from inception through January 31, 2023. Longitudinal studies reporting the progression rates of spherical-equivalent refraction (SER) in children (<18 years) with different astigmatism magnitudes (lower *vs.* higher) or axis orientations (With-the-Rule [WTR] *vs.* Against-the-Rule [ATR]) were included. SER progression rates were extracted and pooled with random-effects model meta-analysis.

***Results*:** Eight studies comprising 3,964 children (WTR, n = 3,021; ATR, n = 943) were included in the meta-analysis on the impact of astigmatism axis orientation. Children with baseline ATR astigmatism (SER, −0.44 ± 0.21 D/year) exhibited significantly faster myopic progression compared to those with WTR astigmatism (SER, −0.36 ± 0.16 D/year; P = 0.008). Regarding the impact of astigmatism magnitude, ten studies involving 7,554 children (lower, n = 2,933; higher, n = 4,621) were included, and revealed no statistically significant difference in myopia development between lower (SER, −0.36 ± 0.15 D/year) and higher magnitudes of baseline astigmatism (SER, −0.32 ± 0.14 D/year; P = 0.510).

Study I – Impact of Astigmatism on Axial Elongation: A Five-Year Population-Based Study

***Methods*:** Annual vision screenings were conducted at seven schools in Tianjin, China, from 2018 to 2022. Ocular biometry and non-cycloplegic autorefraction were collected. Children aged 5–16 years without any myopia interventions were included and categorized by their baseline astigmatism magnitude (Controls *vs.* Low *vs.* High) and axis orientation (WTR *vs.* Oblique *vs.* ATR). Additionally, children were classified by baseline spherical ametropia (Compound Hyperopic *vs.* Compound Myopic *vs.* Other). Annual progression rates of axial length (AXL) were calculated using regression models and compared across different types of astigmatism and spherical ametropia, adjusting for baseline age, sex, AXL, and follow-up duration as covariates. Only the right eyes were analyzed.

***Results*:** A total of 10,732 Chinese children (baseline age, 9.26 ± 2.42 years; follow-up, 2.63 ± 1.01 years; 53.2% male) were included and divided into a younger cohort (age < 11 years; n = 7,880) and an older cohort (age ≥ 11 years; n = 2,852). Across both age groups and all astigmatic magnitudes, ATR astigmatism exhibited the most rapid AXL progression, followed by oblique and WTR astigmatism. Two-way ANCOVA of the combined cohort revealed that both high-magnitude and ATR astigmatism were significantly associated with increased AXL progression ($P \leq 0.018$). However, the impact of astigmatism on AXL progression varied depending on baseline spherical ametropia, as high-magnitude and ATR astigmatism increased AXL progression in compound myopic eyes but decreased progression in compound hyperopic eyes.

Study II – Impact of Astigmatism on Retinal Thickness: A Case-Control Study

***Methods*:** This case-control study included 101 Chinese young adults (age, 31.67 ± 7.84 years; 38% male) from the Hong Kong Polytechnic University (PolyU) Optometry Clinic. Non-cycloplegic subjective refractions, optical coherence tomography (OCT), and best-corrected distance visual acuity (BCDVA) were collected. Participants were categorized by different types of astigmatism (WTR, n = 41; ATR, n = 25; Controls, n = 35). Inclusion criteria were ages between 18–45 years, BCDVA no worse than 0.10 LogMAR, SER ≥ −10.00 D, and astigmatism ≤ −0.75 D for WTR and ATR groups or astigmatism ≥ −0.25 D for controls. OCT-based retinal thickness and BCDVA were compared across

three astigmatism groups, adjusting for age, sex, and AXL. Only the right eyes were analyzed, and groups were matched for age, sex, SER, AXL, and corneal curvature.

***Results*:** Significant differences were found across the astigmatism groups in both retinal thickness (P = 0.028) and BCDVA (P = 0.039), with thicker retina and poorer BCDVA found in eyes with WTR astigmatism. Bonferroni's *post-hoc* test revealed significant between-group differences in BCDVA (WTR *vs.* Controls, P = 0.041), as well as in retinal thickness at the inner-nasal (WTR *vs.* ATR, P = 0.034) and outer-temporal subfields (WTR *vs.* Controls, P = 0.042). BCDVA was positively associated with macular retinal thickness (r = 0.206, P = 0.041) after adjusting for age, sex, and AXL.

Study III – Impact of Astigmatism on Predicting Axial Elongation: A Machine-Learning Study

***Methods*:** This study included longitudinal eye examination data from 8,296 children in the Tianjin Vision Screening Programme (*Centre 1*) and the PolyU Optometry Clinic (*Centre 2*). Inclusion criteria were ages between 5–16 years, with at least three visits over more than one year of follow-up, and no myopia control interventions. Baseline variables, including age, sex, SER, astigmatism, AXL, and previous AXL progression rate, were used to develop two machine-learning algorithms: 1) AXL-Estimator, to predict future axial length; and 2) AXL-Classifier, to identify children with progressive myopia (axial elongation ≥ 0.30 mm/year) over the next three years. Random forest algorithms with ten-fold cross-validation were employed to train the models on the training dataset (n = 5,734 from *Centre 1*). Independent validations were conducted on the internal validation (n = 1,419 from *Centre 1*) and external validation (n = 1,143 from *Centre 2*) datasets. The performance of the AXL-Estimator and AXL-Classifier was evaluated by mean absolute error (MAE) and the area under the ROC curve (AUROC), respectively. The impact of astigmatism on these prediction models was assessed using Gini feature importance and stratification analysis. Only the right eyes were analyzed.

***Results*:** The AXL-Estimator demonstrated high prediction accuracy across all datasets, with one-year MAEs of 0.126–0.146 mm, two-year MAEs of 0.222–0.277 mm, and three-year MAEs of 0.292–0.310 mm. The corresponding R^2 values ranged from 0.884 to 0.985, indicating a good fit for our models. The

AXL-Classifier also yielded significant and robust diagnostic performance in differentiating progressive myopia, achieving AUROCs from 0.893 to 0.974 for up-to-three-year predictions across all datasets (all $P < 0.001$). While both astigmatic magnitude (6.66% to 13.10%) and axis orientation (1.85% to 3.32%) had generally relatively low feature importance in these models, stratification analysis revealed consistent and significant decreases in models' performance when predicting for eyes with astigmatism, particularly high astigmatism.

Conclusions: These studies collectively highlight the significant impact of astigmatism on refractive development (**meta-analysis**) and axial length in humans. Both the magnitude and axis orientation of baseline astigmatism significantly influence axial elongation in school-age children (**Study I**), potentially leading to significant alterations in retinal thickness and visual acuity (**Study II**). Furthermore, while our machine learning models can accurately predict axial elongation, their performance may decrease in children with significant astigmatism (**Study III**). These findings not only improve our understanding of how astigmatism influences ocular structural growth but also provide valuable insights for personalized management and interventions for refractive development involving astigmatism.

Publications Arising from the Thesis

Publications

1. Liang D, Leung T-W, Kee C-S (**2023**). Measuring Retinal Thickness and Visual Acuity in Eyes with Different Types of Astigmatism in a Cohort of Hong Kong Chinese Adults. *Investigative Ophthalmology & Visual Science*, 64(1), 2. https://doi.org/10.1167/iovs.64.1.2
2. Liang D, Du B, Leung T-W, Liu Z, Su Q, Jin N, Zhang Z, He M, Yan H, Wei R, Kee C-S (**2024**). Impact of Astigmatism on Axial Elongation in School-Age Children: A Five-Year Population-based Study in Tianjin, China. *Investigative Ophthalmology & Visual Science*, 65(13), 45. https://doi.org/10.1167/iovs.65.13.45

Conference Presentations

1. Poster Presentation. "Retinal Thickness and Visual Acuity in Eyes with Different Types of Astigmatism". In: *ARVO Annual Meeting*, Denver, USA, May 1–4, **2022**.
2. Poster Presentation. "Long-Term Study Reveals Astigmatism's Effect on Eye Development". In: *ARVO Annual Meeting*, Seattle, USA, May 4–9, **2024**.
3. Poster Presentation. "Impact of Astigmatism on Eye Growth in School-Age Children: A Five-Year, Population-based Study in Tianjin, China". In: *International Conference of Vision and Eye Research (iCover)*, Hong Kong, May 23–24, **2024**. (Best Poster Award)
4. Poster Presentation. "Predicting Axial Elongation in School-Age Chinese Children Using Machine Learning: A Longitudinal Two-Centre Study". In: *International Myopia Conference (IMC)*, Sanya, China, Sept 25–28, **2024**.

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List of Abbreviations

ACC	Accuracy
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ATR	Against-the-Rule
AUROC	Area under the Receiver Operating Characteristic Curve
AXL	Axial Length
BM	Bruch's Membrane
CI	Confidence Interval
CV	Cross-Validation
D	Diopter
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study Grid
FU	Follow-up
IC	Induced Component
ICC	Intraclass Correlation Coefficient
ILM	Inner Limiting Membrane
IOP	Intraocular Pressure
IQR	Interquartile Range
LogMAR	Logarithm of the Minimal Angle of Resolution
MAE	Mean Absolute Error
ML	Machine Learning
NOS	Newcastle-Ottawa Quality Assessment Scale for Cohort Studies
OBL	Oblique Astigmatism
OCT	Optical Coherence Tomography
PolyU	The Hong Kong Polytechnic University
PRAXL	Previous Progression Rate of Axial Length

REML	Restricted Maximum Likelihood
RF	Random Forest
RMSE	Root Mean Square Error
ROC	Receiver Operating Characteristic Curve
RT	Retinal Thickness
SD	Standard Deviation
SEN	Sensitivity
SER	Spherical-Equivalent Refraction
SPEC	Specificity
SNR	Signal-to-Noise Ratio
THRiVE	Tianjin and Hong Kong Research in Vision and Eye
WMD	Weighted Mean Difference
WTR	With-the-Rule

Thesis Overview

This thesis consists of **six** chapters.

Chapter 1 provides a comprehensive introduction to the study background, beginning with an overview of astigmatism and ocular development. It then describes the association between astigmatism and ocular development, including the changes in refractive status and ocular structures. This chapter concludes by presenting the general hypothesis, research aims, and four key research questions to be addressed in this thesis.

Chapter 2 presents the first meta-analysis on the impact of baseline astigmatism, including its magnitude and axis orientation, on refractive development. By synthesizing data from 11 published original studies covering 7,554 subjects worldwide, this meta-analysis reveals a significantly higher myopia progression in ATR astigmatism compared to WTR astigmatism. This chapter provides robust evidence on how astigmatism affects refractive development in children and offers valuable insights for the following studies in this thesis.

Chapter 3 (**Study I**) presents a five-year longitudinal study involving 10,732 Chinese children to investigate the progression rates of axial length across different baseline astigmatism. This study is the first to demonstrate that both high magnitude and ATR astigmatism are significantly associated with increased AXL progression, with the impact of astigmatism modulated by baseline spherical ametropia. These findings underscore the significant and complex association between astigmatism and ocular growth.

Chapter 4 (**Study II**) presents a case-control study to investigate the retinal thickness profile and visual acuity across eyes with different types of astigmatism, matched for variables including age, sex, spherical-equivalent refraction, axial length, and corneal curvature. This study is the first to show a

significant association between astigmatism and retinal thickness, with thicker retina and poorer visual acuity found in eyes with WTR astigmatism compared to ATR astigmatism and non-astigmatic controls. These findings suggest the significant impact of astigmatism, both magnitude and axis orientation, on retinal structures.

Chapter 5 (**Study III**) presents a machine-learning study investigating the influence of astigmatism on prediction models for axial elongation. The study begins by developing machine-learning algorithms to predict future axial elongation using baseline variables, achieving remarkable accuracy and robustness. The impact of astigmatism on these models is then evaluated by Gini feature importance and stratification analyses. The results indicate that, although astigmatic magnitude and axis orientation exhibit relatively low feature importance in the prediction models, the predictive performance significantly decreases when predicting for eyes with high magnitude of astigmatism.

Chapter 6 summarises the findings of this thesis and discusses their significance for future research. This chapter synthesizes insights gained from the studies conducted within this thesis, along with previous research, emphasizing the significant impact of astigmatism on axial eye growth and its possible underlying mechanisms.

Chapter 1

General Introduction

1.1 Astigmatism

1.1.1 Definitions of Astigmatism

Astigmatism is a common refractive error caused by differential refractive powers across different meridians, leading to asymmetric refraction of light rays (Duke-Elder, 1970). This condition is mainly attributed to the anterior corneal surface and lenticular toricity (Grosvenor, 1976; Grosvenor et al., 1988; Dobson et al., 1999). In regular astigmatism, the two principal power meridians are separated orthogonally, while in irregular astigmatism, refractions in different meridians are not orthogonal (Duke-Elder, 1970; Kee, 2013; Read et al., 2007a). In this thesis, "*astigmatism*" refers to regular astigmatism.

Astigmatism is more complex than spherical refractive errors (*i.e.*, myopia and hyperopia), as it can simultaneously produce two line foci with specific orientations. Consequently, both the magnitude and axis orientation of astigmatism should be considered. The varying positions of these two line foci relative to the retinal plane lead to different astigmatic conditions:

- Compound astigmatism, where both principal meridians are either farsighted (*i.e.*, compound-hyperopic) or nearsighted (*i.e.*, compound-myopic).
- Simple astigmatism, where one principal meridian is emmetropic, and the other is either farsighted (*i.e.*, simple-hyperopic) or nearsighted (*i.e.*, simple-myopic).
- Mixed astigmatism, where one principal meridian is farsighted, and the other is nearsighted.

In addition, based on the axis orientation of the principal meridians, astigmatism is further categorized into three types:

- With-the-rule astigmatism (WTR), where the vertical meridian has the strongest refractive power, *i.e.*, negative-cylinder axes oriented within 180° ± 30°.

- Against-the-rule astigmatism (ATR), where the horizontal meridian has the strongest refractive power, *i.e.*, negative-cylinder axes oriented within 90° ± 30°.
- Oblique astigmatism (OBL), where the strongest power meridian is oriented obliquely, *i.e.*, negative-cylinder axes oriented within 31°–59° or 121°–149°.

1.1.2 Prevalence of Astigmatism

A meta-analysis conducted in 2018 identified astigmatism as the most prevalent refractive error globally, with an estimated prevalence of 14.9% in children and 40.4% in adults (Hashemi et al., 2018). The prevalence of astigmatism varies significantly across regions and ethnicities. Higher prevalence rates have been observed in Native American, Hispanic, and Asian children (Fozailoff et al., 2011; Harvey et al., 2006; Huang et al., 2014; Kleinstein et al., 2003; Wen et al., 2013). In Chinese children, the prevalence of astigmatism varies widely depending on the definition of astigmatism used. Epidemiological studies have reported prevalence rates ranging from 13.3%–33.0% for astigmatism of 1.00 D or more, 4.0%–14.2% for astigmatism of 1.50 D or more, and approximately 2.2% for astigmatism of 3.00 D or more (J. Wang et al., 2020; Tong et al., 2002; Quek et al., 2004; Shih et al., 2004; Lai et al., 2010; Zhang et al., 2018; Lan et al., 2013; H. Li et al., 2019; Lai et al., 2010).

The prevalence of astigmatism also varies with age (Kee, 2013). Studies have shown that most infants are born with significant astigmatism, although there is considerable variability in the common axis orientation. Some studies found a predominance of WTR astigmatism (Ehrlich et al., 1997; Mutti et al., 2004; Varughese et al., 2005), while others reported a predominance of ATR astigmatism (Abrahamsson et al., 1988; Dobson et al., 1984; Friling et al., 2004; Gwiazda et al., 1984; Howland and Sayles, 1985). The infantile astigmatism declines substantially throughout infancy and childhood, suggesting a process termed "*sphericalization*" (Dobson et al., 1984; Abrahamsson et al., 1988; Harvey et al., 2013; Atkinson et al., 1980). However, the prevalence of astigmatism increases during school ages (Harvey et al., 2015; Kee, 2013), appears to stabilize during young adulthood (Leung et al., 2012), and rises again in older age. In addition, there is a general shift in the axis orientation of astigmatism in older age (J. Zhang et

al., 2023): the prevalence of WTR astigmatism decreases, and the prevalence of ATR and oblique astigmatism increases (Antón et al., 2009; He et al., 2009; Leung et al., 2012; Li et al., 2009; Liu et al., 2011; Naeser et al., 2018; Sawada et al., 2008; Varma et al., 2017; Wolfram et al., 2014; J. Yu et al., 2017).

1.1.3 Causes of Astigmatism

Astigmatism most commonly arises from unequal corneal curvature (Friling et al., 2004; Howland and Sayles, 1985), with its changes also primarily attributed to corneal changes (Read et al., 2007a; Mutti et al., 2004; Hayashi et al., 1995; De Bernardo et al., 2020). Although the exact aetiology of astigmatism remains unclear, the onset and development of astigmatism have been associated with various genetic and environmental factors (Harb and Wildsoet, 2019; Read et al., 2007a).

Genetic Factors. The genetic factors contributing to astigmatism have been investigated through twin-based studies and genome-wide association studies; however, these studies yielded mixed results. While most twin-based studies reported a low genetic contribution to astigmatism (Teikari et al., 1989; Teikari and O'Donnell, 1989; Valluri et al., 1999), Hammond et al. reported higher correlations for astigmatism among monozygotic twins compared to dizygotic twins, suggesting that 50%–65% of the variance in astigmatism is attributed to genetic effects (Hammond et al., 2001). In addition, genome-wide association studies have identified specific genetic loci associated with astigmatism (Mishra et al., 2012; Lopes et al., 2013; Guggenheim et al., 2013; Shah et al., 2018), which are linked to biological processes related to eye growth and matrix remodelling (Namba et al., 2020). These genetic factors are believed to mainly influence the development of corneal curvature and, therefore, contribute to the development of astigmatism.

Eyelid pressure. The pressure exerted by the eyelids on the cornea is considered a significant factor associated with corneal astigmatism. For instance, Wilson reported decreased WTR astigmatism when the eyelids were lifted in subjects with astigmatism (Wilson, 1982). Other studies have also reported a significant association between corneal astigmatism and factors related to eyelid pressure, which

include:

- Eyelid morphology, such as fissure angle (Read et al., 2007b) and palpebral fissure width (Grey and Yap, 1986; Lieberman and Grierson, 2000).
- Eyelid pathologies, such as chalazion (Nisted and Hofstetter, 1974; Park and Lee, 2014; Jin et al., 2017; Ouyang et al., 2022), congenital ptosis (Paik et al., 2016; Uğurbaş and Zilelioğlu, 1999), and haemangioma (Plager and Snyder, 1997; Herlihy et al., 2016).
- Specific visual tasks, such as sustained downward gaze (Buehren et al., 2003; Collins et al., 2006; Leung et al., 2020).

In summary, the evidence for eyelid pressure as an etiological factor in corneal astigmatism is compelling (Read et al., 2007b). This may explain the high prevalence of WTR astigmatism in East Asian and Native American populations (Dobson et al., 1999; Goss, 1989; Kame et al., 1993; Leung et al., 2012), as well as the shift from WTR to ATR astigmatism in older age (Antón et al., 2009; He et al., 2009; Leung et al., 2012; Li et al., 2009; Liu et al., 2011; Naeser et al., 2018; Sawada et al., 2008; Varma et al., 2017; Wolfram et al., 2014; J. Yu et al., 2017), which may be attributed to reduced lid tension in older adults.

Corneal and Scleral Biomechanics. The corneal biomechanical properties, including rigidity and elasticity, may influence the changes in corneal curvature, thereby contributing to the development of astigmatism (Namba et al., 2020; Franco and Lira, 2009). Factors that reduce corneal rigidity, such as poor nutrition, have been identified as potential risk factors for astigmatism (Lyle et al., 1972; Marasini, 2016). Furthermore, surgical procedures (e.g., cataract surgery) that alter the cornea's biomechanical properties, such as the arrangement of collagen fibrils, can also result in significant changes in astigmatism (Meek and Newton, 1999). Unequal extraocular muscle tension on the cornea (Howland and Sayles, 1985; Kwitko et al., 1992; Preslan et al., 1992), or irregularity in scleral shape (Consejo and Rozema, 2018) have also been associated with corneal astigmatism.

Nicotine Exposure. Early exposure to nicotine has been linked to an increased risk of astigmatism in several studies. A population-based study involving 9,970 multi-ethnic infants found an association between maternal smoking during pregnancy and a higher risk of astigmatism in the offspring (McKean-Cowdin et al., 2011). Another study of 27,890 Chinese preschoolers suggested a dose-response effect of nicotine exposure on the risk of astigmatism (C.-G. Li et al., 2019). One potential biological mechanism may involve nicotinic acetylcholine receptors in the retina, which are crucial for neuronal migration and growth cone guidance (Lindstrom, 1997), thereby affecting the development of astigmatism. In addition, recent research suggests that nicotine exposure decreases choroidal vascularity (Wei et al., 2019), which might slow postnatal eye growth and potentially impede the process of sphericalization.

Visual Environment. It is hypothesized that astigmatism may develop in response to environmental visual cues, and several experimental studies support this idea. Altered ocular growth that partially compensates for the imposed astigmatism has been reported in chicks (Chu and Kee, 2015; Irving et al., 1995; Popa et al., 2020; Vyas and Kee, 2021) and monkeys (Kee et al., 2003), suggesting that optical cues affect the development of both corneal and refractive astigmatism. In humans, bi-directional changes in refractive astigmatism have been observed in young adults after exposure to 60 minutes of either WTR or ATR astigmatic blur using +3.00 DC cylindrical lenses. Specifically, J0 astigmatism became less positive in the WTR condition and less negative in the ATR condition, indicating that visual cues can lead to compensatory changes in astigmatism (Chan et al., 2022).

Other Factors. Several other factors have been associated with the development of astigmatism, including digital screen exposure (Huang et al., 2020; Yang et al., 2022) and nystagmus (Dickinson and Abadi, 1984; Fresina et al., 2013). These factors likely influence astigmatism through mechanisms involving increased eyelid pressure or extraocular muscle tension onto the cornea.

1.1.4 Impacts of Astigmatism

The visual and clinical impacts of astigmatism have been well-documented (Read et al., 2014).

Astigmatism significantly affects visual acuity and contrast sensitivity (Guo and Atchison, 2010; Atchison and Mathur, 2011; Mohammadi et al., 2019), leading to reduced performance in both distant and near tasks, such as near-work activities (Casagrande et al., 2014; Wills et al., 2012) and driving (Wolffsohn et al., 2011; Wood et al., 2012). Several studies have suggested significant associations between uncorrected astigmatism and decreased performance on cognitive, language, and behavioural tasks (Orlansky et al., 2015; Harvey et al., 2017, 2018) in school-age children.

Additionally, significant astigmatism during early childhood is associated with various ocular and visual disorders (Dobson et al., 2003; Cotter et al., 2011; Flitcroft, 2005; Read et al., 2014; Mitchell et al., 1973). For instance, astigmatism during early visual development may result in a form of meridian-specific visual impairment, termed "meridional amblyopia" (Dobson et al., 2003; Mitchell et al., 1973), which is hypothesized to be due to abnormal development in the primary visual cortex and may lead to visual deficits across a range of visual functions (Freeman et al., 1972; Harvey et al., 2007; Mitchell et al., 1973).

1.2 Ocular Development

1.2.1 Emmetropization

Human eyes are generally born with a substantial degree of hyperopia (Atkinson et al., 1984; Flitcroft, 2014; Mehra et al., 1965). This hyperopic defocus is thought to trigger the eye to grow towards the focal plane, thereby reducing the refractive error and finally achieving emmetropia – the refractive state where the optical image of distant objects is sharply focused on the retina (Brown et al., 1999). This process, termed "*emmetropization*" (Troilo et al., 2019), occurs during the first two years of infancy (Mutti et al., 2005), typically peaking at the end of around two years of age (Ehrlich et al., 1997), and is mainly completed by six years of age (Flitcroft, 2014). During emmetropization, postnatal hyperopia rapidly decreases towards not emmetropia but a mild hyperopia of around 0.50 to 2.00 D, allowing ocular accommodation to produce good visual acuity (Ehrlich et al., 1997; Flitcroft, 2014; Morgan et al., 2010).

The refractive development of the human eyes involves several key components, including changes in corneal power (Inagaki, 1986), crystalline lens power (Gordon and Donzis, 1985), and axial length (Fledelius and Christensen, 1996). Most infants are initially hyperopic; during emmetropization, reductions in corneal power and crystalline lens power, along with an increase in axial length, collectively contribute to moving the focal plane closer to the retina. After infancy, normal eye growth results in the cessation of changes in corneal power (Baird et al., 2020), while changes in crystalline lens power and axial length continue, albeit at a relatively slower rate. During this period, the crystalline lens undergoes thinning, flattening, and a reduction in power to maintain a balance between the focal length and the increased axial length (Mutti et al., 2012). The balance is not broken until myopia develops, at which point the crystalline lens is no longer able to compensate for the excessive axial elongation adequately.

1.2.2 Mechanisms

The optical geometry and refractive state of the eye are initially established during embryonic development and then refined during the postnatal emmetropization process (Summers et al., 2021). While embryonic eye growth is primarily determined by genetic factors (Graw, 1996; Cvekl and Zhang, 2017; Tedja et al., 2019), postnatal ocular development is influenced by a combination of genetic and environmental factors (Baird et al., 2010; Morgan, 2003; Tedja et al., 2019). During emmetropization, eye growth in the posterior segment is regulated by visual inputs to match the refraction produced by the refractive components at the anterior segment, ensuring that the focal plane aligns with the retina to produce sharp vision (Wallman and Winawer, 2004). In other words, visual inputs are critical for emmetropization during postnatal ocular development (Troilo et al., 2019).

Experimental research across various animal species has demonstrated the importance of optical defocus in guiding emmetropization. The eye compensates for imposed hyperopic or myopic defocus by accelerating or slowing its growth rate, respectively (Summers et al., 2021; Troilo et al., 2019). This bi-directional response to opposite signs of defocus *(e.g.*, inducing myopia by imposing hyperopic

defocus on the retina) has been observed in species including tree shrews, guinea pigs, chicks, mice, and primates (Troilo et al., 2019). Astigmatic defocus has also been reported to guide emmetropization and refractive development (Kee, 2013) (see "*1.3 Astigmatism and Ocular Development*" for details).

The question of which visual cue is used by the retina to determine the response direction specific to the defocus sign (*i.e.*, whether myopic or hyperopic) has long been investigated. Several potential visual cues have been proposed, including longitudinal chromatic aberration (Rucker and Wallman, 2009; Rucker, 2013; Rucker et al., 2020), high-order monochromatic aberrations (Ramamirtham et al., 2006; Hughes et al., 2020), spatial frequency (Tran et al., 2008; Bowrey et al., 2015; Flitcroft et al., 2020), retinal image magnification (Swiatczak and Schaeffel, 2021), contrast perception (Rucker, 2013; Swiatczak and Schaeffel, 2022a), the Stiles-Crawford effect (Carmichael-Martins and Vohnsen, 2018; Vohnsen, 2021), and factors such as relative distance and optical vergence (Wildsoet and Schmid, 2001). However, identifying the exact visual cues involved in the emmetropization process and eye growth is challenging, as these cues are likely integrated and function together (Troilo et al., 2019).

Moreover, several experiments have reported visually-mediated refractive development in animals even when the retinal circuit is destroyed (Norton et al., 1994; Popa et al., 2020), the optic nerve is sectioned (Troilo et al., 1987; Troilo and Wallman, 1991; Wildsoet and Pettigrew, 1988), or different regions of the retina are simultaneously exposed to optical defocus of opposite signs (Smith et al., 2013). These findings indicate the presence of a local retinal mechanism of emmetropization and eye growth. The retina locally detects and decodes the visual cues from form-deprivation or imposing defocus, and converts these visual signals into molecular signals, such as dopamine and transforming growth factor (TGF)-β (Feldkaemper and Schaeffel, 2013; Ku et al., 2024). These molecular signals are then transmitted through the retinal pigment epithelium layer (Jonas et al., 2017) and act on choroid (Wallman et al., 1995; Hung et al., 2000; Wildsoet and Wallman, 1995) and sclera (McBrien and Gentle, 2003; Norton and Siegwart, 1995; Wildsoet and Wallman, 1995). The choroidal and scleral structures can directly control ocular growth even without much direct contribution from the central nervous system (Summers et al., 2021; Troilo et al., 2019).

1.3 Astigmatism and Ocular Development

Sign-dependent ocular compensatory responses to imposed spherical defocus have been reported in various species (Troilo et al., 2019). While other visual cues may also influence the emmetropization process, astigmatism has received relatively little attention despite its high prevalence in newborns (Abrahamsson et al., 1988; Dobson et al., 1984; Ehrlich et al., 1997; Gwiazda et al., 1984; Mutti et al., 2004) and its frequent co-existence with spherical ametropia (Farbrother et al., 2004; Fulton et al., 1982; Pärssinen, 1991).

1.3.1 Refractive Status

The degradation of retinal image quality produced by astigmatism has been hypothesized to serve as a visual cue guiding emmetropization (Charman, 2011; Flitcroft, 2012; Howland, 1982). Conversely, the optical blur resulting from astigmatism could disrupt the normal process of emmetropization, potentially leading to myopia development (Fulton et al., 1982; Gwiazda et al., 2000). Ample evidence supports that the presence of astigmatism can alter refractive development in both chicks (Irving et al., 1995; Chu and Kee, 2015; Popa et al., 2020; Vyas and Kee, 2021; McLean and Wallman, 2003; Schmid and Wildsoet, 1997) and monkeys (Kee et al., 2003, 2004; Smith et al., 1998), although the endpoint varied across studies. For instance, while some studies found a refractive shift towards the circle of least confusion after imposing astigmatic defocus (Chu and Kee, 2015; Irving et al., 1995), others reported the endpoint directed towards one of the two principal power meridians that are associated with the imposed astigmatism (Kee et al., 2004; McLean and Wallman, 2003; Schmid and Wildsoet, 1997; Vyas and Kee, 2021). In humans, significant positive associations between the presence of astigmatism and the development of myopia have been observed in several cross-sectional and longitudinal studies (Fan et al., 2004; Fulton et al., 1982; Gwiazda et al., 2000; Twelker et al., 2013).

With respect to the effects of astigmatic axis orientation, studies in chicks (Chu and Kee, 2015; Vyas and Kee, 2021) and monkeys (Kee et al., 2004) have demonstrated orientation-dependent alterations in

refractive development, supporting the important role of astigmatic axis orientation in the process of emmetropization. Similarly, children with ATR astigmatism are more likely to develop myopia or experience more rapid myopia progression (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964).

1.3.2 Anterior Segment

Significant changes in corneal shape after the imposition of astigmatism have been reported in both chicks (Chu et al., 2014; Chu and Kee, 2015; Irving et al., 1992; Vyas and Kee, 2021) and monkeys (Kee et al., 2003). In addition, meridional changes in corneal curvature were observed in chicks when different types of astigmatism were induced using cylindrical lenses, with WTR and ATR astigmatism resulting in compensatory changes in corneal curvature along the principal meridians (Chu and Kee, 2015; Vyas and Kee, 2021). Similarly, imposing astigmatic defocus with different axis orientations significantly affected vitreous chamber depths in chicks (Vyas and Kee, 2021).

1.3.3 Posterior Structure

Altered ocular axial elongation in response to astigmatic defocus has been reported in both chicks (Chu and Kee, 2015; McLean and Wallman, 2003; Schmid and Wildsoet, 1997; Vyas and Kee, 2021) and monkeys (Kee et al., 2004; Smith et al., 1998). Specifically, in chicks treated with plus-cylindrical lenses, equatorial choroidal thickening was observed (Irving et al., 1995). Furthermore, imposing ATR astigmatism in chicks resulted in significantly greater equatorial diameter and posterior expansions in the horizontal meridian compared to the vertical meridian; however, this effect was not observed in imposed WTR astigmatism (Chu and Kee, 2015). An experimental study in humans has also shown that even short-term exposure (*i.e.*, 60 minutes) to WTR and ATR astigmatic blur using +3.00 DC cylindrical lenses triggered bi-directional trends of changes in choroidal thickness. Specifically, mean choroidal thickness significantly increased with WTR, but it decreased with ATR astigmatic defocus (Hoseini-Yazdi et al., 2020).

1.3.4 Retinal Electrophysiology

Converging evidence indicates a local retinal mechanism for emmetropization and refractive

development (Norton et al., 1994; Popa et al., 2020; Smith et al., 2013; Troilo et al., 1987; Troilo and Wallman, 1991; Wildsoet and Pettigrew, 1988), highlighting the crucial role of the retina in eye growth. While the exact response of the retina to astigmatic defocus in altering eye growth remains unclear, previous research has found dysfunctions in retinal electrophysiological response in astigmatic eyes. Flitcroft et al. recorded electroretinographic (ERG) signals from 123 children with reduced vision and found that children with high astigmatism more frequently exhibited ERG abnormalities compared to those with low or no astigmatism (Flitcroft, 2005). Studies in chicks also showed significant correlations between experimentally induced WTR and ATR astigmatism and multifocal ERG responses (Vyas et al., 2022). Specifically, in chicks that developed ATR astigmatism, the magnitude of the induced astigmatism was inversely correlated with the amplitude of the induced component (IC) of the multifocal ERG signal, while the magnitude of induced WTR astigmatism was correlated with increased IC amplitude.

1.4 Hypotheses and Aims of the Thesis

Based on the accumulated evidence presented above, it is clear that astigmatism plays an important role in emmetropization and refractive development. This leads to the **general hypothesis** that astigmatism, including its magnitude and axis orientation, can significantly influence ocular structural growth in humans.

The **general aim** of this thesis is to determine whether and how astigmatism affects ocular structures, particularly axial length and retinal thickness, in human eyes. Specifically, this thesis aims to address the following research questions:

1.4.1 Systematic Review – Impact of Astigmatism on Refractive Development

Several studies have investigated the impact of astigmatism on refractive development in children, but the findings are controversial: significant associations between myopia development and baseline astigmatism – either in terms of its magnitude (Fulton et al., 1982; Fan et al., 2004; Twelker et al., 2013)

or axis orientation (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964) – have been reported in some studies, but not in others (Ehrlich et al., 1995; Goss and Shewey, 1990; Mutti et al., 2004). Whether and how astigmatism affects refractive development in humans remains to be determined. In this thesis, **Chapter 2** will present a systematic review and meta-analysis aimed at quantitatively estimating the progression rates of myopia across eyes with different baseline astigmatism, by synthesizing published data from previous studies in children.

1.4.2 Study I – Impact of Astigmatism on Axial Elongation

Axial length is the primary ocular parameter associated with refractive status, and serves as a useful diagnostic bio-index for assessing the development of myopia (Flitcroft et al., 2019). While some studies have reported the association between astigmatism and refractive development (Gwiazda et al., 2000; Fulton et al., 1982; Fan et al., 2004; Twelker et al., 2013; Hirsch, 1964; Grosvenor et al., 1987), the impact of early astigmatism on ocular axial elongation in humans remains largely unexplored. In this thesis, **Chapter 3** will present a population-based longitudinal study investigating the progression rates of axial length across school-age children with different baseline astigmatism.

1.4.3 Study II – Impact of Astigmatism on Retinal Thickness

The retina plays an essential role in eye growth by detecting optical defocus and generating signals that regulate structural changes in the retina, choroid, and sclera (Troilo et al., 2019). Previous studies have reported associations between retinal ERG responses and astigmatism (Flitcroft, 2005; Vyas et al., 2022), and it is known that retinal ERG responses may relate to retinal thickness (Koh et al., 2014; Wolsley et al., 2008). However, it remains unclear how astigmatism directly relates to changes in retinal thickness. In this thesis, **Chapter 4** will present a case-control study to characterize the retinal thickness profiles across eyes with different types of astigmatism.

1.4.4 Study III – Impact of Astigmatism on Predicting Axial Elongation

The significant association between astigmatism and refractive development, as reported in previous studies, suggests that astigmatism could potentially serve as a valuable predictor for myopia

development. However, while prediction models for refractive development have been proposed in several studies (Guo et al., 2022; Li et al., 2022; Lin et al., 2018), a significant research gap remains in developing reliable prediction models for axial elongation. In addition, whether and how astigmatism contributes to the prediction of axial elongation remains unknown. **Chapter 5** will present a machine-learning study, in which we first develop models for predicting axial elongation accurately and then evaluate the impact of astigmatism on these prediction models, based on two-centre longitudinal cohorts of school-age children.

The study design of this thesis is presented in **Figure 1.1**.

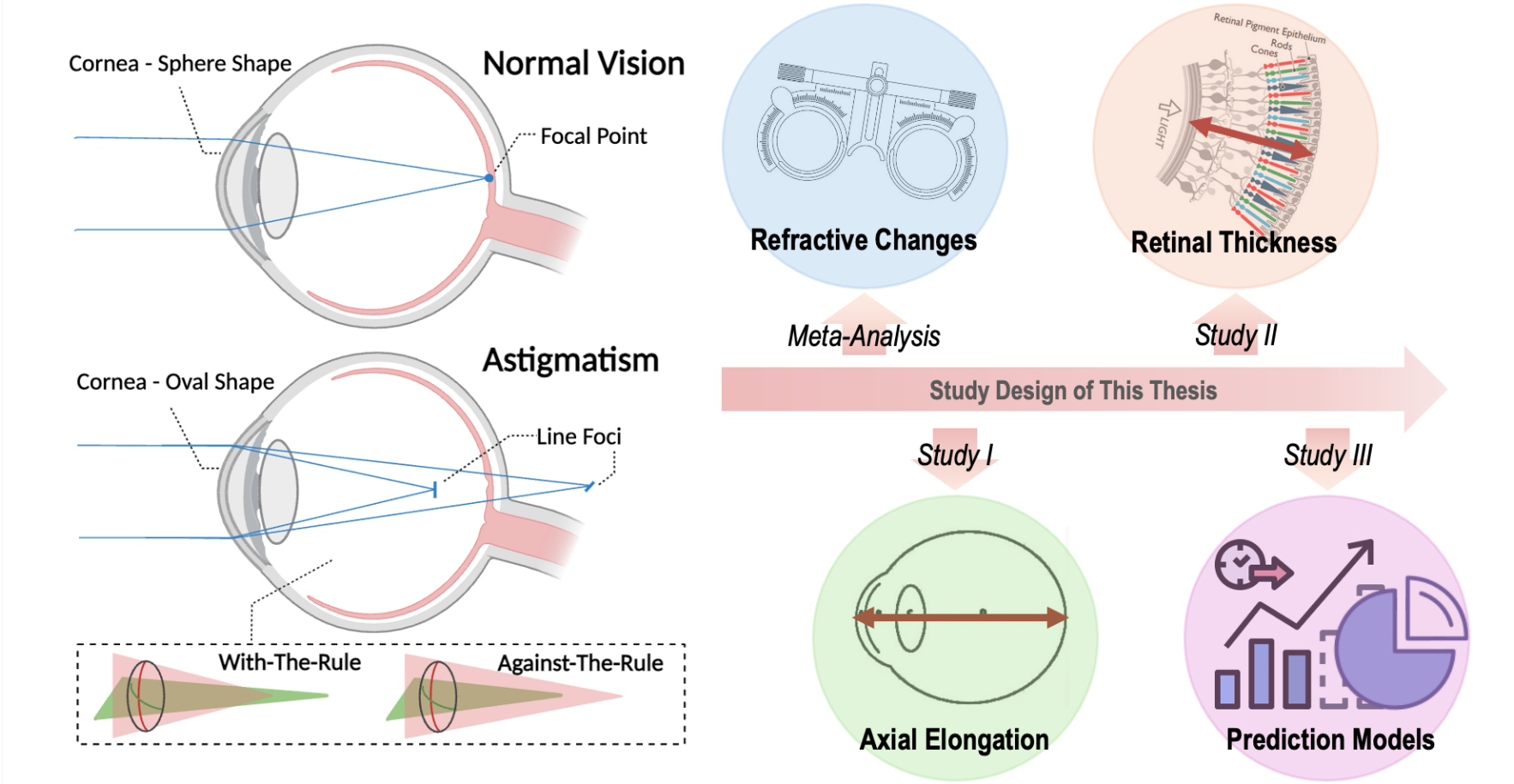

Figure 1.1 **Study Design of This Thesis**

Chapter 2

Impact of Astigmatism on Refractive Development

A Systematic Review and Meta-analysis

2.1 Introduction

Astigmatism is a refractive error due to differential refractive powers across two principal meridians, and consequently, each point of an object is refracted into light spreading between two line foci with specific orientations. Astigmatism is highly prevalent in infants (Abrahamsson et al., 1988; Dobson et al., 1984; Ehrlich et al., 1997; Gwiazda et al., 1984; Mutti et al., 2004) and is the most common refractive problem in children and adults globally (Hashemi et al., 2018). Several studies have noted that astigmatism frequently co-exists with myopia (Farbrother et al., 2004; Fulton et al., 1982; Pärssinen, 1991) and is associated with higher degrees of myopia (Farbrother et al., 2004; Heidary et al., 2005; Kaye and Patterson, 1997; H. Li et al., 2019), suggesting a possible role of astigmatism in myopia development. It has been hypothesized that astigmatism could act as a visual cue to guide the emmetropization by integrating the optical signals associated with the two principal meridians (Charman, 2011; Flitcroft, 2012; Howland, 1982). Conversely, the optical blur resulting from astigmatism could also disrupt the normal process of emmetropization, leading to the development of myopia (Fulton et al., 1982; Gwiazda et al., 2000).

Experimental studies in chicks (Irving et al., 1995; Chu and Kee, 2015; Popa et al., 2020; Vyas and Kee, 2021; McLean and Wallman, 2003; Schmid and Wildsoet, 1997) and monkeys (Kee et al., 2004, 2003; Smith et al., 1998) have observed an altered course of refractive development with imposed astigmatism, although the endpoints varied across studies. In addition, astigmatism has been associated with a series of alterations in ocular structures, including corneal shape (Chu et al., 2014; Chu and Kee, 2015; Irving et al., 1992; Kee et al., 2003; Vyas and Kee, 2021), axial components (Chu and Kee, 2015; McLean and Wallman, 2003; Schmid and Wildsoet, 1997; Vyas and Kee, 2021), choroidal thickness (Hoseini-Yazdi et al., 2020; Vyas and Kee, 2021), and compensatory refractive components (Chan et al., 2022) in animal

or human studies. Taken together, existing evidence supports the hypothesis that astigmatism plays a role in guiding or interfering with the process of emmetropization, and potentially influencing the development of myopia.

However, findings from longitudinal data on the association between early astigmatism and the later development of myopia are inconclusive. Some studies have indicated that children with a higher magnitude of astigmatism are more likely to develop myopia later in life or experience increased myopia progression (Fulton et al., 1982; Gwiazda et al., 2000; Fan et al., 2004; Twelker et al., 2013). In contrast, several studies have reported no relationship (Chan et al., 2018; Ehrlich et al., 1995; Goss and Shewey, 1990; Hu et al., 2016; Mutti et al., 2004; Pärssinen, 1991) between astigmatic magnitude and myopia development.

Regarding the axis orientation of astigmatism, ATR astigmatism has been associated with the onset and increased progression of myopia compared to WTR astigmatism (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964), even when astigmatism is defined at a low magnitude, *e.g.*, ≤ -0.12 DC (Hirsch, 1964). However, other studies have not found significant differences in myopia progression between eyes with baseline WTR and ATR astigmatism (Chan et al., 2018; Ehrlich et al., 1995; Fan et al., 2004; Goss and Shewey, 1990; Hu et al., 2016, 2019; Mutti et al., 2004; O'Donoghue et al., 2015; Pärssinen, 1991; Pärssinen et al., 2015).

To better understand the role of astigmatism in myopia development, we conducted a systematic review and meta-analysis to comprehensively evaluate the progression rate of myopia in eyes with different types of astigmatism, by synthesizing existing evidence from longitudinal studies in children. Specifically, this review aims to determine the differences in the progression rates of spherical-equivalent refraction (SER) between groups with different baseline astigmatism, considering the effects of its relative magnitude (lower *vs.* higher) and axis orientation (WTR *vs.* ATR). We hypothesize that both the magnitude and axis orientation of astigmatism can have distinctive effects on refractive development. If the relationship is confirmed, it would provide critical insights into the mechanisms

underlying refractive development and ocular growth, and inform healthcare strategies to improve myopia control in the future. This meta-analysis focuses on refractive development rather than axial elongation due to the lack of longitudinal data on axial length in the existing literature.

2.2 Methods

This systematic review and meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). The title and protocol were registered prospectively on the International Prospective Register of Systematic Reviews database (PROSPERO, CRD42023416177). This study was approved by the Hong Kong Polytechnic University (PolyU) Human Ethics Committee, which waived the requirement for patient informed consent owing to the use of publicly aggregated de-identified data.

2.2.1 Literature Search and Eligibility Criteria

A systematic literature search was performed using PubMed, Embase, Cochrane Library, and Web of Science databases from inception through January 31, 2023, targeting longitudinal studies that reported differences in progression rates of myopia between children with different astigmatism, either in terms of magnitude or axis orientation. Reference lists of included studies and relevant reviews were manually searched to identify additional relevant studies. The search strategies with syntax specific to each database are detailed in **Supplementary Table S2.1**.

Studies were included if the following criteria were met: **(A)** longitudinal studies with either a prospective or retrospective design; **(B)** human studies enrolling participants aged no more than 18 years; and **(C)** studies investigating the progression rates of myopia (measured by either cycloplegic or non-cycloplegic refraction) in groups with different types of astigmatism at baseline. Depending on the results reported in the original articles, some studies included were available for only one of the review objectives (*i.e.*, the effect of either magnitude or axis orientation), while others contributed to both. To cover more original studies and a larger sample size, available studies were included regardless of the

definition of astigmatism used. In addition, studies that did not specifically report the SER progression rate but presented the interval changes in SER, enabling secondary calculation of progression rates, were also included.

The following studies were excluded: **(A)** studies of specific risk groups (*e.g.*, populations with strabismus, retinopathy of prematurity, Down's syndrome); **(B)** studies in which a specific intervention for myopia control (*e.g.*, atropine) or myopia treatment (*e.g.*, refractive surgery) was performed on the whole population; **(C)** qualitative studies, case reports or series, reviews, and conference abstracts; **(D)** studies with any form of data insufficiency that failed to calculate the SER progression rates; **(E)** non-English or inaccessible abstract and full-text; and **(F)** duplicate reports or analyses of the same dataset.

2.2.2 Study Selection, Data Extraction, and Risk-of-Bias Assessment

The systematic search and study selection were performed independently by two investigators (D.L. and P.A.A) at both the title/abstract and full-text stages. Specifically, the investigators reached a consensus on the search strategies for each database and the eligibility criteria for included studies. Then, the investigators independently screened the title and abstract of the articles retrieved from the preliminary search according to the predefined criteria. Full texts of the potentially eligible studies were accessed to evaluate their eligibility for inclusion in the final analysis.

Relevant data were extracted from each included study by one investigator and independently verified by another. The extracted data included: **(A)** study characteristics, including the first author, publication year, country, study design, sample size, baseline age of subjects, duration of follow-up, and baseline refractions of subjects; **(B)** methodological details, including the method of refractive assessment and definition of astigmatism; and **(C)** analysis and results, including the adjusted variables and outcome of interest. Data available only in graphical format were extracted by the two investigators independently using a graph digitizer (PlotDigitizer). Intraclass correlation coefficients (ICCs) were calculated to determine the inter- and intra-operator reproducibility of these extracted data from the graphs.

The risk of bias in the individual observational studies was independently assessed by the two investigators using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS) (Wells et al., 2014). The NOS system can evaluate three domains (*i.e.*, patient selection, comparability, and outcome) of cohort studies, with a maximum score of nine. A study was defined as high quality if it scored 7 or more, medium quality if it scored 4–6, and low quality if it scored less than 4. Only studies with medium and high quality were included in this meta-analysis.

Any disagreement during the literature search, study selection, data extraction, and risk-of-bias assessment was settled by discussion between the two investigators or adjudication by a senior third investigator when needed.

2.2.3 Statistical Analysis

Meta-analysis. All statistical analyses were performed using Stata software (v16.1, Stata Corp., USA). Only data from studies with a low risk of bias (*i.e.*, an NOS score of 4–9 points) were included in the final meta-analysis. A restricted maximum likelihood (REML) random-effects model (Harville, 1977; Langan et al., 2019) was used to calculate the pooled estimate and 95% confidence interval (CI) of the SER progression rates. A $P < 0.05$ was considered statistically significant.

Effect Measure. The differences in the SER progression rate between different astigmatism, in terms of astigmatic magnitude (lower *vs.* higher) and axis orientation (WTR *vs.* ATR), were calculated and synthesized. Exact values of the progression rate (in Dioptres/Year) were extracted from original studies if available. For studies that did not specifically report the exact SER progression rates, estimated values were calculated by dividing the interval change of myopia (in Dioptres) by the follow-up duration (in Years).

Heterogeneity. Between-study heterogeneity was assessed with the τ^2 test and quantified via the contribution of heterogeneity to the total variability across studies (I^2). Significant heterogeneity was defined by an $I^2 \geq 50\%$ coupled with a τ^2 test statistic corresponding to a two-sided $P < 0.05$ (Higgins,

2003; Higgins et al., 2019). Subgroup analyses were performed to identify potential causes of heterogeneity (Higgins et al., 2019), including baseline age and SER of the study population, definition of astigmatism used, and follow-up duration. Subgroup analyses on other potentially confounding factors, such as astigmatic subtype (*e.g.*, mixed *vs.* myopic astigmatism) (Goss, 1999; Goss and Shewey, 1990) and correction details (*e.g.*, fully corrected *vs.* under-corrected), were not performed due to insufficient information and data.

Sensitivity & Publication Bias. A leave-one-out sensitivity analysis was performed on those meta-analyses with a significant pooled estimate, by omitting one study at a time to observe its influence on the overall effect. Publication bias was evaluated using the asymmetry of funnel plots and Egger's bias test for small study effects (Egger et al., 1997; Sterne et al., 2000, 2011). If publication bias was suspected (*i.e.*, a $P < 0.05$ in Egger's test), the trim-and-fill method was used to re-estimate the pooled effect measures after imputing studies that were potentially missing (Duval and Tweedie, 2000a, 2000b).

2.3 Results

2.3.1 Characteristics of Included Studies

The PRISMA flowchart for literature search and study inclusion is shown in **Figure 2.1**. A total of 7,909 non-duplicated publications were identified from the systematic search, and an additional 5 records were identified through citation searching. Furthermore, one study that was in press but not yet listed electronically at the time was provided by co-authors (Y. Liang et al., 2024). The titles and abstracts of 7,915 articles were screened, of which 134 full-text articles were retrieved. Finally, 26 studies were considered relevant to the review topic, among which 11 studies had sufficiently well-reported data for meta-analysis (10 studies available for the effect of astigmatic magnitude, and 8 studies for the effect of axis orientation).

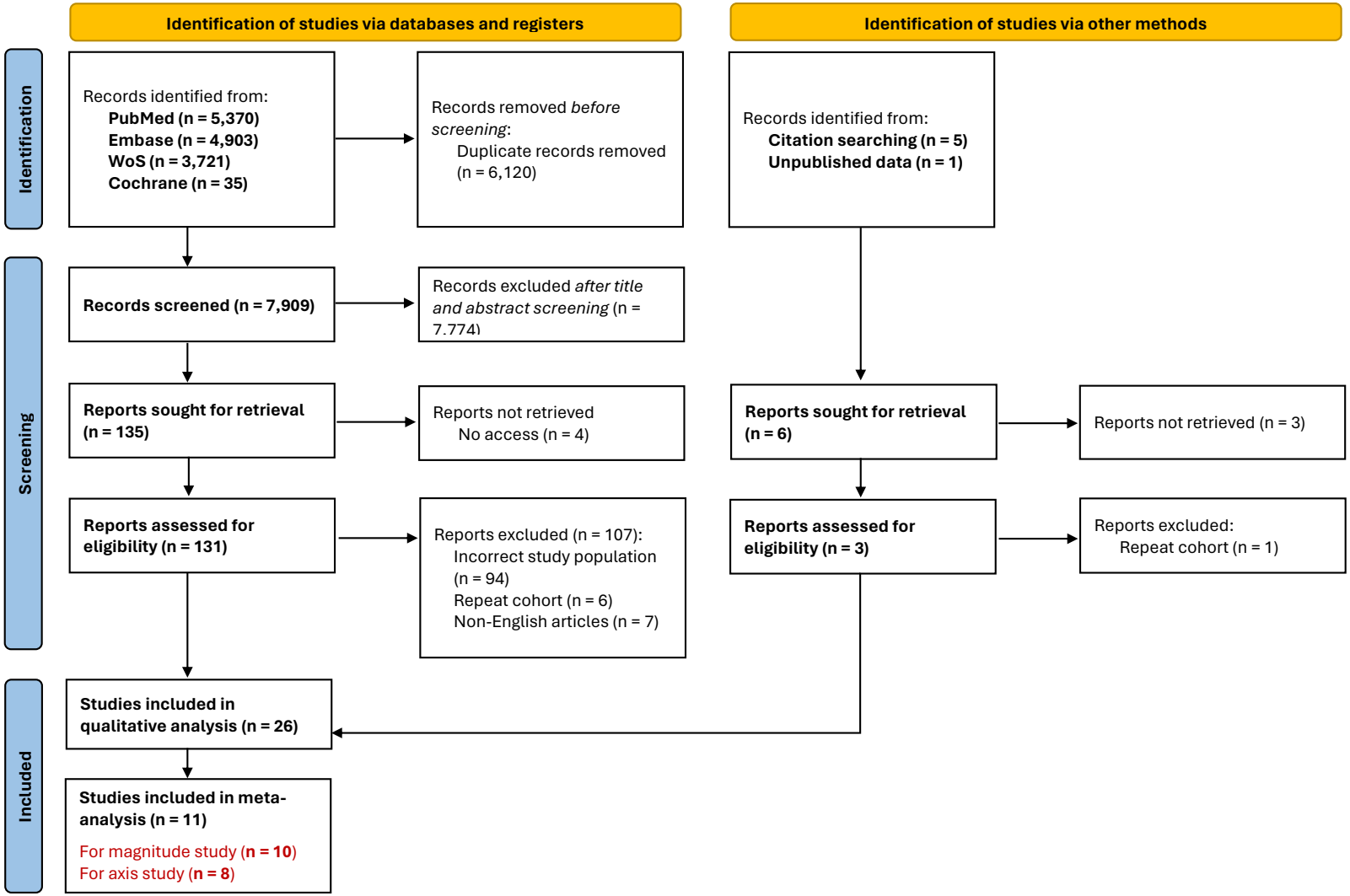

Figure 2.1 PRISMA Flowchart for Literature Search and Study Selection (through January 31, 2023)

The characteristics of the included studies are shown in **Table 2.1**. Of the 11 studies included in the meta-analysis, four were conducted in America, six in Asia, and one in Europe. All studies utilized a longitudinal design. The mean age of study populations at baseline ranged from <1 year to 12.2 years, and the mean duration of follow-up ranged from 1 year to 12.7 years. Three studies exclusively enrolled subjects with a negative SER (Goss and Shewey, 1990; Grosvenor et al., 1987; Pärssinen, 1991), one study only enrolled subjects with hyperopia (Hu et al., 2016), and the remaining seven studies recruited subjects with myopia, emmetropia, or hyperopia at baseline. Additionally, three studies reported subjective refractions, whereas three other studies and five studies reported objective refractions using retinoscopy and autorefractors, respectively. Cycloplegia was used when measuring refractions in six studies.

The risk of bias assessment of the included studies is shown in **Supplementary Table S2.2**. Of the 10 studies contributing to the meta-analysis of the magnitude effect, six studies were rated as high quality, and four were medium quality (average NOS score, 6.4). Of the 8 studies available for the meta-analysis of the astigmatic axis orientation, six studies were rated as high quality, and two were medium (average NOS score, 7.0). The primary reason for the loss of NOS score in those medium-quality studies was the lack of control for potentially confounding factors (*e.g.*, baseline age and SER) in their study designs or data analyses.

2.3.2 SER Progression between WTR *vs.* ATR Astigmatism

Qualitative Analysis: A total of 17 relevant studies investigated the associations between myopia progression and axis orientation of astigmatism in children, by examining the differences in myopia progression rates between groups with different astigmatic axis orientations (Chan et al., 2018; Ehrlich et al., 1997; Goss, 1999; Grosvenor et al., 1987; Gwiazda et al., 2000, 1993; Hirsch, 1964; Hu et al., 2016; Pärssinen, 1991; Pärssinen et al., 2015; Verkicharla et al., 2020), or by studying the correlations between myopia progression rate and the J0 astigmatic component (Ehrlich et al., 1995; Fan et al., 2004; Hu et al., 2019; Mutti et al., 2004; O'Donoghue et al., 2015). However, the findings were inconclusive (see **Table 2.2** for details).

Source, location	Sample size	Baseline age, year [a]	FU duration, year [a]	Baseline SER, dioptre [a]	Refraction measurement	Cycloplegia used	Definition of astigmatism, D	NOS Quality score	
								Magnitude study	Axis study
Grosvenor et al, 1987, US	124	[6, 15]	3	≤-0.25	Retinoscopy	Yes	≥0.25	7	7
Goss and Shewey, 1990, US	275	[6, 15]	nr.	≤-0.50 [b]	Subjective	No	≥0.25	6	6
Pärssinen, 1991, Finland	238	10.39 (1.08)	3	-1.43 (0.59)	Subjective	Yes	≥0.25	na.	9
Gwiazda et al, 2000, US	245	<1	12.7 [6, 23]	1.05 (1.18) [c]	Retinoscopy	No	≥1.00	7	7
Twelker et al, 2013, US	777	4.17 (0.62)	7.15 (3.15)	1.03 (1.19)	Autorefraction	Yes	≥1.00	7	na.
Hu et al, 2016, China	890	6.39 [2.47, 10]	4.0 [3.1, 5.3]	7.16 (1.70)	Subjective	Yes	≥0.75	6	6
Kim et al, 2017, Korea	221	4.42 (1.57)	11.19 (1.81)	0.92 (2.57) [c]	Autorefraction	Yes	≥1.00	5	na.
Chan et al, 2018, Taiwan	183	9.04 (1.38)	1	-0.78 (1.68)	Autorefraction	Yes	≥1.00	5	na.
Verkicharla et al, 2020, India	4,281	12.20 (3.74)	1	-2.38 (1.36)	Retinoscopy	Partly used	≥0.25	7	7
Liang et al, 2022, Hong Kong	38	[8, 10]	2	-0.57 (1.57)	Autorefraction	No	≥1.00	7	7
Liang et al, 2024, Hong Kong	72	[8, 10]	2	-1.60 (1.16)	Autorefraction	No	≥1.00	7	7

Table 2.1 Characteristics of Included Studies for Meta-Analysis

Note: FU, follow-up. SER, spherical-equivalent refraction. nr, not reported in the original article. na, not available.

[a] Data were presented as mean (SD) or [range], if applicable.

[b] Spherical power ≤ −0.50 Dioptre in both principal meridians during follow-up in this study.

[c] Data were not directly reported in the original article but extracted from graphs or tables by investigators.

Source, location	Sample size	Baseline age, year [a]	Follow-up, year [a]	Baseline SER, Diopter [a]	Cyclo-plegic	Outcome of interest [b]
Hirsch, 1964, US	261	[5, 6]	8	Not reported	No	• ATR astigmatism occurring in children starting school was predictive of later development of myopia.
Fulton et al, 1982, US	298	FU within 2 to 36 months of age		-2.90 (3.90)	Yes	• The presence of astigmatism was associated with an increased progression of myopia.
Grosvenor et al, 1987, US	124	[6, 15]	3	≤-0.25	Yes	• WTR astigmatism progressed more slowly than those having no or ATR astigmatism.
Goss and Shewey,1990, US	275	FU within 6 to 15 years of age		*≤-0.50*	No	• No significant difference in myopia progression rates across WTR, ATR, and zero astigmatism groups.
Pärssinen, 1991, Finland	238	10.39 (1.08)	3	-1.43 (0.59)	Yes	• No significant correlation between the amount of baseline astigmatism and myopia progression after controlling for baseline SER. • No significant difference in the myopia progression between baseline WTR and ATR astigmatism.
Gwiazda et al, 1993, US	72	<6 months	[9, 16]	nr.	No	• Infants exhibiting WTR-hyperopic or ATR-myopic astigmatism developed more myopic refractive errors during childhood.
Ehrlich et al, 1995, UK	254	8.5 months	12 months	2.19 (1.31)	Yes	• No significant correlation between the change in mean SER with baseline absolute astigmatism • No significant correlation between the change in mean SER with baseline signed astigmatism in myope group, and a weak correlation observed in control group
Ehrlich et al, 1997, UK	88	8.5 months	30 months	0.67 (1.15)	Yes	• The correlation between the rate of SER change with baseline astigmatic magnitude was weak ($r = -0.20$, $P < 0.001$). • The axis orientation of astigmatism did not influence the mean proportional rate of change in SER.
Edwards and Shing, 1999, Hong Kong	32	3 months	[7, 8]	2.81 (1.89)	Yes	• Myopia at age 7 to 8 years was associated with high infantile astigmatism.
Gwiazda et al, 2000, US	245	<1	12.7 [6, 23]	1.05 (1.18) [d]	No	• Subjects with significant ATR astigmatism in infancy were more likely to develop myopia at school age.
Fan et al, 2004, Hong Kong	108	[27, 77] months	5	0.89 (0.84)	Yes	• Higher astigmatism was associated with more myopic shift and more axial length growth. • The axis orientation of astigmatism was not related to the myopic shift and axial length growth.
Mutti et al, 2004, US	183	3 months	3	-2.14 (1.33)	Yes	• Astigmatism in infancy appeared to be unrelated to emmetropization of SER. • SER changes from 3-9 months of age were unrelated to baseline J0.
Dobson et al, 2007, US	146	[3, 4]	[4.0, 7.9]	1.08 (1.25)	Yes	• The presence/absence of high astigmatism (≥ 1.00DC) at baseline was not significantly related to change in mean SER from baseline to follow-up.
Twelker et al, 2013, US	777	4.17 (0.62)	7.15 (3.15)	1.03 (1.19)	Yes	• Relation between SER slope and level of baseline astigmatism was statistically significant.

Table 2.2 Systematic Review and Quantitative Summary of Studies Related to the Topic of This Meta-Analysis

Source, location	Sample size	Baseline age, year [a]	Follow-up, year [a]	Baseline SER, Diopter [a]	Cyclo-plegic	Outcome of interest [b]
Pärssinen et al, 2015, Finland	163	[9, 11]	23	−0.25 to −3.00 D	Yes	• Spherical refraction showed a greater increase in WTR up to 3-year and 13-year follow-up. • No significant correlation between baseline astigmatism and myopic progression throughout the 23-year follow-up period.
O'Donoghue et al,2015, UK	295	[6, 7]	3	-1 to 10.75D	Yes	• The J0 and J45 values at baseline were not statistically significantly correlated with the change in the spherical component of refraction in either the younger or the older groups.
	429	[12, 13]		-5.5 to 11.25D		
Zadnik et al, 2015, US	4,512	FU within 6 to 13 years of age		> −0.75D	Yes	• Baseline astigmatism was found to be an independent influencing factor for myopia development.
Hu et al, 2016, China	890	6.39 [2.47, 10]	4.0 [3.06, 5.3]	7.16 (1.70)	Yes	• No significant difference in the change of mean spherical refraction among groups with different extents or axes of astigmatism.
Kim et al, 2017, Korea	221	4.42 (1.57)	11.19 (1.81)	0.92 (2.57) [d]	Yes	• Changes in SER were not associated with the baseline degrees of astigmatism (P = 0.684).
Chan et al, 2018, Taiwan	183	9.04 (1.38)	1	-0.78 (1.68)	Yes	• No significant correlation between baseline astigmatism with change in SER or axial length. • No significant differences in SER change across the WTR, ATR, and OBL groups.
Hu et al, 2019, China	495	5	3.7	-3.00 [-5.25, −1.75]	Yes	• Baseline J0 was not correlated with the rate of change in SER. • Children with baseline J45 smaller than −0.50 D showed greater rates of myopia progression.
Verkicharla et al,2020, India [c]	4,281	12.20 (3.74)	1	-2.38 (1.36)	Partly	• Significant difference in myopia progression between groups with different magnitudes or axes of astigmatism, in subjects aged ≤ 18 years and with SER ≥ −6.00 D.
Liang et al, 2022, Hong Kong [c]	38	[8, 10]	2	-0.57 (1.57)	No	• No significant difference in the SER progression rate between groups with different magnitudes of astigmatism after controlling for the baseline age and SER. • ATR astigmatism had significantly greater myopic shift than those with WTR astigmatism.
Schein et al, 2022, US	194	FU within 9 to 20 months of age		nr.	Yes	• The greatest degree of emmetropization occurred among eyes with high astigmatism, followed by moderate astigmatism, moderate hyperopia, and high hyperopia, in that order.
You et al, 2022, China	4,921	[1, 6]	[1, 2]	0.62 (1.13)	No	• Baseline astigmatism was significantly associated with subjects having SER changes < −0.50 D.
Liang et al, 2024, Hong Kong [c]	72	[8, 10]	2	-1.60 (1.16)	No	• No significant difference in SER progression rate between groups with different magnitudes or axis orientation of astigmatism after controlling for baseline age and SER.

Note: ATR, against-the-rule. WTR, with-the-rule. OBL, oblique astigmatism. SER, spherical-equivalent refractions. FU, follow-up. D, dioptre. nr, no reported in the original article.
[a] Data are presented as mean (SD) or [range], if applicable. [b] Only conclusions from original article be relevant to our topic are summarised in this table.
[c] Data were calculated from the raw data of the original study. [d] Data was not directly reported in the original article but extracted from graphs or tables by investigators.

Table 2.2 (continued)

The associations between myopia progression and axis orientation of baseline astigmatism reached significance in 6 studies, and were insignificant or inconclusive in 11 studies. Of those significant findings, most studies (n = 5) found that baseline ATR astigmatism was associated with the future presence or increased progression of myopia (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964; Liang et al., 2022; Verkicharla et al., 2020), while only 1 study observed a more myopic shift in WTR astigmatism after a 3- and 13-year follow-up (Pärssinen et al., 2015).

Meta-analysis: A total of 3,964 children from 8 studies fulfilled the criteria for the meta-analysis on the impact of axis orientation of astigmatism, among which 3,021 (76.2%) were WTR astigmatism and 943 (23.8%) were ATR astigmatism at baseline (Goss and Shewey, 1990; Grosvenor et al., 1987; Gwiazda et al., 2000; Hu et al., 2016; Liang et al., 2022; Y. Liang et al., 2024; Pärssinen, 1991; Verkicharla et al., 2020). The average SER progression rate was −0.36 D/year (SD, 0.16; range, −0.50 to −0.06 D/year) for WTR astigmatism and −0.44 D/year (SD, 0.21; range, −0.82 to −0.10 D/year) for ATR astigmatism. Meta-analysis showed that children with baseline ATR astigmatism had a statistically significantly higher progression towards myopia compared to those with WTR astigmatism ($P = 0.008$). The forest plot of SER progression between WTR and ATR astigmatism is shown in **Figure 2.2**.

Publication Bias, Sensitivity, and Subgroup Analysis. The funnel plot and Egger's test showed no clear evidence of publication bias ($P = 0.28$). The leave-one-out sensitivity analysis showed a persistently significant difference in SER progression between WTR and ATR astigmatism, except when the study by Verkicharla et al. (Verkicharla et al., 2020) was removed (omitted WMD, 0.07 D/year; $P = 0.095$; **Figure 2.3**). There was no significant heterogeneity among the included studies for the overall meta-analysis ($I^2 = 0.01\%$; $\tau^2 < 0.01$; $P = 0.09$) or within subgroup analyses regarding the definition of astigmatism, study region, follow-up duration, measurements of refraction, baseline age or SER categories (all $P \geq 0.35$ for between-subgroup tests, **Supplementary Table S2.3**). Notably, ATR astigmatism showed a higher myopia progression than WTR astigmatism in all subgroups, except in those with baseline hyperopia (WMD, −0.05 [-0.25, +0.15] D/year; $P = 0.62$).

Source	With-the-Rule		Against-the-Rule		Effect Size WMD [95%CI]	Weight %	Forest Plot
	n	RP, mean (SD)	n	RP, mean (SD)			
Grosvenor et al, 1987	52	-0.230 (0.270)	36	-0.370 (0.270)	0.140 [0.025, 0.255]	15.30	
Goss and Shewey, 1990	37	-0.430 (0.290)	73	-0.425 (0.280)	-0.005 [-0.117, 0.107]	15.57	
Pärssinen et al, 1991	24	-0.500 (0.340)	106	-0.530 (0.340)	0.030 [-0.121, 0.181]	12.06	
Gwiazda et al, 2000	10	-0.060 (0.119)	19	-0.100 (0.138)	0.041 [-0.060, 0.142]	16.69	
Hu et al, 2016	871	-0.478 (0.483)	23	-0.428 (0.352)	-0.050 [-0.249, 0.149]	8.77	
Liang et al, 2022	27	-0.720 (0.270)	5	-1.230 (0.300)	0.510 [0.248, 0.772]	5.98	
Verkicharla et al, 2020	1,942	-0.361 (0.665)	675	-0.409 (0.677)	0.048 [-0.011, 0.107]	21.10	
Liang et al, 2024	58	-0.300 (0.370)	6	-0.540 (0.390)	0.240 [-0.072, 0.552]	4.52	
Overall (*P* = 0.008)	**3,021**		**943**		**0.054 [0.015, 0.094]**	**100**	
Heterogeneity (I^2 = 0.01%, τ^2 < 0.001, *P* = 0.090)							
Random-effects REML model was used. PR, progression rate of myopia (D/year). WMD, weighted mean difference.							

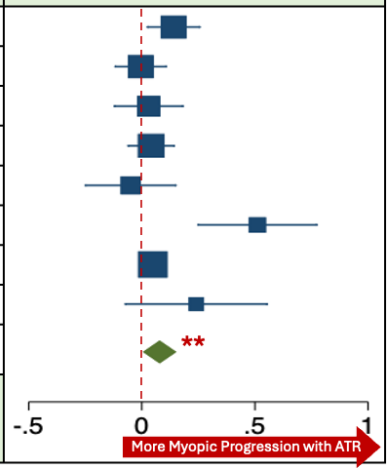

Figure 2.2 Forest Plot of the Weighted Mean Difference in SER Progression between With-the-Rule and Against-the-Rule Astigmatism

Omitted Study (Axis Orientation)	Effect Size WMD [95%CI]	*P*	Leave-one-out Sensitivity Analysis
Grosvenor et al, 1987	0.083 [0.001, 0.166]	**0.046**	
Goss and Shewey, 1990	0.096 [0.011, 0.180]	**0.026**	
Pärssinen et al, 1991	0.088 [0.004, 0.171]	**0.040**	
Gwiazda et al, 2000	0.090 [0.001, 0.180]	**0.049**	
Hu et al, 2016	0.091 [0.013, 0.170]	**0.022**	
Liang et al, 2022	0.049 [0.009, 0.089]	**0.016**	
Verkicharla et al, 2020	0.074 [-0.025, 0.173]	0.095	
Liang et al, 2024	0.081 [0.005, 0.156]	**0.037**	
Total	**0.054 [0.015, 0.094]**	**0.008**	
Random-effects REML model was used. WMD, weighted mean difference.			

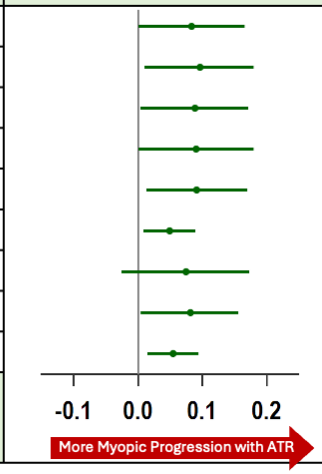

Figure 2.3 Leave-One-Out Sensitivity Analysis of the Weighted Mean Difference in SER Progression between With-the-Rule and Against-the-Rule Astigmatism

2.3.3 SER Progression between Lower *vs.* Higher Astigmatism

Qualitative Analysis. A total of 21 relevant studies investigated the associations between myopia development and baseline astigmatic magnitude in children, either by comparing the myopia progression between groups with different magnitudes of astigmatism (S.-E. Chan et al., 2018; Dobson et al., 2007; Goss & Shewey, 1990; Grosvenor et al., 1987; Gwiazda et al., 2000; H. Hu et al., 2016; Y. S. Kim et al., 2017; Verkicharla et al., 2020; Twelker et al., 2013), or by studying the correlations between the myopia progression and astigmatic magnitude (Chan et al., 2018; Ehrlich et al., 1997, 1995; Fan et al., 2004; Pärssinen, 1991; Pärssinen et al., 2015). However, the findings were also equivocal (**Table 2.2**).

In summary, ten studies reported a significant association between myopia progression and baseline magnitude of astigmatism. Among these, seven studies found that the presence or higher magnitude of baseline astigmatism was associated with a higher risk or increased progression of myopia (Edwards and Shing, 1999; Ehrlich et al., 1997; Fan et al., 2004; Fulton et al., 1982; Gwiazda et al., 2000; Twelker et al., 2013; You et al., 2022), while three studies reported a contradictory conclusion (Grosvenor et al., 1987; Verkicharla et al., 2020; Zadnik et al., 2015). However, the other 11 studies did not report any significant association.

Meta-analysis. A total of 7,554 subjects from 10 studies (Chan et al., 2018; Goss and Shewey, 1990; Grosvenor et al., 1987; Gwiazda et al., 2000; Hu et al., 2016; Kim et al., 2017; Kumar Verkicharla et al., 2020; Liang et al., 2022; Twelker et al., 2013) met the criteria for meta-analysis of the magnitude effect, with 2,933 (38.8%) and 4,621 (61.2%) subjects divided into groups of lower and higher magnitudes of baseline astigmatism, respectively. The average SER progression rate was −0.36 D/year (SD, 0.15; range, −0.49 to −0.09 D/year) in the lower-magnitude group and −0.32 D/year (SD, 0.14; range, −0.48 to −0.10 D/year) in the higher-magnitude group. The meta-analysis showed no significant difference in SER progression rates between different magnitudes of baseline astigmatism (P = 0.51; **Figure 2.4**).

Source	Higher-magnitude		Lower-magnitude		Effect Size WMD [95%CI]	Weight %	Forest Plot
	n	PR, mean (SD)	n	PR, mean (SD)			
Grosvenor et al, 1987	93	-0.307 (0.255)	31	-0.400 (0.255)	0.093 [-0.011, 0.197]	7.70	
Goss and Shewey, 1990	110	-0.427 (0.282)	165	-0.400 (0.225)	-0.027 [-0.087, 0.033]	12.46	
Gwiazda et al, 2000	30	-0.095 (0.128)	39	-0.086 (0.087)	-0.009 [-0.060, 0.042]	13.69	
Twelker et al, 2013	402	-0.170 (0.200)	375	-0.150 (0.150)	-0.020 [-0.045, 0.005]	16.82	
Hu et al, 2016	1,063	-0.484 (0.501)	451	-0.448 (0.526)	-0.036 [-0.092, 0.020]	13.00	
Kim et al, 2017	119	-0.335 (0.172)	102	-0.319 (0.181)	-0.016 [-0.063, 0.031]	14.24	
Chan et al, 2018	60	-0.220 (0.650)	123	-0.470 (0.700)	0.250 [0.039, 0.461]	2.74	
Liang et al, 2022	6	-0.840 (0.360)	32	-0.810 (0.300)	-0.030 [-0.299, 0.239]	1.79	
Verkicharla et al, 2020	2,724	-0.374 (0.666)	1,557	-0.462 (0.641)	0.088 [0.047, 0.129]	14.98	
Liang et al, 2024	14	-0.350 (0.530)	58	-0.310 (0.330)	-0.040 [-0.259, 0.179]	2.57	
Overall (*P* = 0.510)	**4,621**		**2,933**		**0.013 [-0.026, 0.052]**	**100**	
Heterogeneity (I^2 = 74.80%, τ^2 = 0.002, *P* < 0.001)							
Random-effects REML model was used. PR, progression rate of myopia (D/year). WMD, weighted mean difference.							

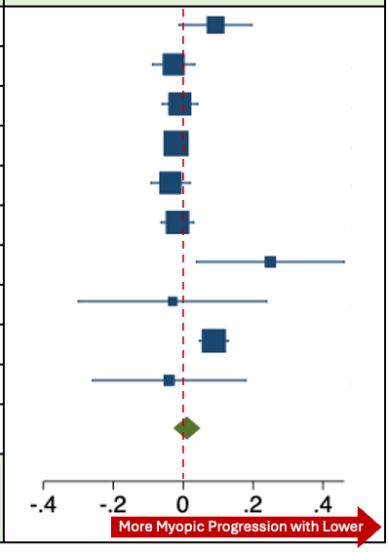

Figure 2.4 Forest Plot of the Weighted Mean Difference in SER Progression between Lower and Higher Magnitude of Astigmatism

Omitted Study (Magnitude)	Effect Size WMD [95%CI]	*P*	Leave-one-out Sensitivity Analysis
Grosvenor et al, 1987	0.004 [-0.035, 0.042]	0.851	
Goss and Shewey, 1990	0.017 [-0.026, 0.059]	0.439	
Gwiazda et al, 2000	0.015 [-0.029, 0.059]	0.507	
Twelker et al, 2013	0.018 [-0.028, 0.064]	0.441	
Hu et al, 2016	0.018 [-0.024, 0.060]	0.397	
Kim et al, 2017	0.016 [-0.028, 0.061]	0.473	
Chan et al, 2018	0.004 [-0.032, 0.040]	0.833	
Liang et al, 2022	0.012 [-0.027, 0.051]	0.556	
Verkicharla et al, 2020	-0.011 [-0.037, 0.014]	0.379	
Liang et al, 2024	0.012 [-0.027, 0.051]	0.537	
Total	**0.013 [-0.026, 0.052]**	**0.510**	
Random-effects REML model was used. WMD, weighted mean difference.			

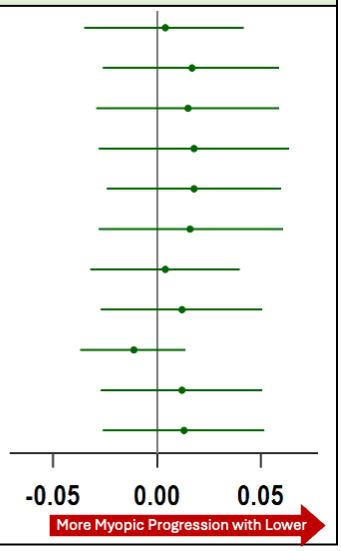

Figure 2.5 Leave-One-Out Sensitivity Analysis of the Weighted Mean Difference in SER Progression between Lower and Higher Magnitude of Astigmatism

Publication Bias, Sensitivity, and Subgroup Analysis. The funnel plot and Egger's test showed no clear evidence of publication bias ($P = 0.09$). The overall results did not change after the leave-one-out sensitivity analysis (all $P > 0.37$; **Figure 2.5**). Significant heterogeneity was observed among included studies ($I^2 = 74.8\%$; $\tau^2 = 0.002$; $P < 0.01$); therefore, subgroup analyses were performed to identify the possible causes of heterogeneity. Our results showed that the high heterogeneity was markedly reduced after accounting for follow-up duration (less than 2 years *vs.* others, $I^2 < 0.03\%$ in both subgroups; **Supplementary Table S2.4**).

2.4 Discussion

In this systematic review and meta-analysis, we searched for longitudinal studies that compare the differences in the progression rate of myopia between children with different baseline astigmatism, in terms of both its magnitude and axis orientation. Using 3,021 WTR and 943 ATR astigmatic eyes from 8 longitudinal studies worldwide, our meta-analysis found that ATR astigmatism was significantly associated with faster myopia progression compared to WTR astigmatism (−0.44 *vs.* −0.36 D/year, $P = 0.008$). This finding supports our general hypothesis that the axis orientation of baseline astigmatism can alter the course of refractive development. However, no significant difference in myopia progression was found between different magnitudes of astigmatism based on 7,554 eyes from 9 studies (lower, −0.36 D/years; higher, −0.32 D/year; $P = 0.510$), which was likely caused by the considerable methodological heterogeneity among the included studies.

2.4.1 Impact of Astigmatic Axis Orientation on SER Progression

Our meta-analysis revealed a significant difference in myopia progression between ATR and WTR astigmatism. Previous experimental studies in chicks (Chu and Kee, 2015; Vyas and Kee, 2021) and monkeys (Kee et al., 2004) have demonstrated that astigmatic axis orientation can influence emmetropization. In human studies, the associations between baseline astigmatic axis orientation and myopia development have been systematically summarized in **Table 2.2**. Specifically, children with ATR astigmatism were more likely to develop myopia subsequently (Gwiazda et al., 2000; Hirsch, 1964)

or experience more myopia progression (Grosvenor et al., 1987; Liang et al., 2022; Verkicharla et al., 2020). However, many of these studies were limited by their relatively small sample size and lacked statistical significance. In contrast, our meta-analysis, which included a substantial number of subjects from multiple studies, provided greater statistical power and a more robust evaluation than each independent study.

Another interesting finding was that ATR astigmatism showed higher myopia progression across all subgroups, except in those with baseline hyperopia only (**Supplementary Table S2.3**), suggesting that the impact of baseline astigmatic axis orientation on myopia development may vary depending on baseline refractive status (Goss, 1999). This observation has been supported by previous studies in hyperopic infants (Ehrlich et al., 1997; Gwiazda et al., 1993), which found that hyperopic WTR astigmatism was more likely to develop myopia during childhood (Gwiazda et al., 1993) or had a greater, albeit insignificant, proportional rate of SER change (the rate of change as a proportion of the initial value; WTR: −33%, ATR: −24%) from 9 to 20 months of age (Ehrlich et al., 1997). However, a more recent experimental study in chicks found that imposing ATR astigmatism together with hyperopic defocus promoted more myopic changes than hyperopic-WTR astigmatism (Vyas and Kee, 2021). Nevertheless, these findings collectively support the hypothesis of the differential impacts of astigmatic axis orientation on myopia development in children.

2.4.2 Impact of Astigmatic Magnitude on SER Progression

Our meta-analysis, which included 7,554 eyes from 9 longitudinal studies, found no statistically significant difference in myopia progression between different magnitudes of astigmatism (mean difference, 0.01 D/year). However, it is noteworthy that considerable heterogeneity was observed in this meta-analysis of the magnitude effect (I^2 = 74.80%, P < 0.01). Subgroup analyses suggested that the high heterogeneity was likely due to the differences in study methodology, particularly in follow-up duration. When analysing studies with a follow-up duration of two years or less (totalling 4,574 subjects from 4 studies), we found that eyes with lower astigmatism exhibited significantly more myopia progression compared to those with higher astigmatism (mean difference, 0.09 D/year). However, this

significant difference was not observed in those studies with follow-up durations longer than 2 years or in any other subgroup analyses (**Supplementary Table S2.4**).

Previous animal studies have shown that the degradation of retinal image quality produced by astigmatism can influence defocus-guided emmetropization, although the endpoints varied across studies (Kee et al., 2004, 2003; McLean and Wallman, 2003; Popa et al., 2020; Smith et al., 1998; Vyas and Kee, 2021). However, in human studies, there is limited evidence to suggest that astigmatism promotes myopia (Troilo et al., 2019), and how astigmatism affects myopia development remains controversial. On the one hand, several longitudinal studies have identified significant positive associations between the presence of astigmatism and myopia progression (Fan et al., 2004; Fulton et al., 1982; Gwiazda et al., 2000; Twelker et al., 2013). On the other hand, other studies have not supported this relationship (Chan et al., 2018; Dobson et al., 2007; Ehrlich et al., 1995; Goss and Shewey, 1990; Hu et al., 2016; Mutti et al., 2004; Pärssinen, 1991), with some even reporting contrasting findings (Grosvenor et al., 1987).

Grosvenor et al. suggested that myopes with high astigmatism tend to progress slower than those with little or no astigmatism (Grosvenor et al., 1987), which aligns with our findings. One possible explanation is that children with higher baseline astigmatism may be more likely to experience sphericalization, a process in which astigmatism declines over time, potentially leading to a less negative shift in SER. Additionally, in most existing studies, SER rather than spherical refraction was matched and controlled between different astigmatism groups. This approach may have resulted in differences in the spherical component between lower and higher astigmatism groups. For instance, under equal SER conditions, astigmatic eyes with lower magnitudes might have more myopic spherical refraction, which is likely to progress faster in myopia compared to those with less myopic spherical refraction (Ehrlich et al., 1995; Hagen et al., 2019).

It is worth noting that other factors, such as baseline age, may have also contributed to the high heterogeneity observed in the meta-analysis of astigmatic magnitude, although there was no remarkable

reduction of heterogeneity after accounting for these factors in subgroup analyses. Previous studies have suggested that methodological varieties, such as differences in baseline age, SER, and the definition of astigmatism, can lead to different findings on the associations between astigmatism and myopia development (Goss and Shewey, 1990; Pärssinen, 1991). Therefore, interpreting the results of the meta-analysis on the effect of astigmatic magnitude requires caution due to the substantial methodological heterogeneity across the included studies.

2.4.3 Limitations

This meta-analysis has several limitations. **First**, our analysis was limited to data from published studies, which could introduce potential bias due to the exclusion of unpublished work that might exhibit small or insignificant effects. However, our funnel plots and Egger's bias test did not indicate significant publication bias among the included studies. **Second**, we employed manual graph digitization when original data were only accessible in graphical form, which could introduce operative bias. Nevertheless, the high ICCs ranging from 0.96 to 0.99 suggest robust inter- and intra-operator reproducibility in digitization between the two independent investigators. **Third**, a number of the included studies did not provide detailed information on optical corrections, limiting our ability to draw clear conclusions about the specific influence of astigmatism on myopia progression (Dobson et al., 2007). **Fourth**, the inclusion of non-cycloplegic refractions in some included studies would introduce potential bias in refractive measurement. Additional, the use of SER rather than spherical refraction in most of the included studies could also introduce bias, given the strong correlation between astigmatism and SER measures (Farbrother et al., 2004). **Lastly**, the methodological heterogeneity observed in the magnitude meta-analysis may arise from multiple factors such as baseline age and follow-up duration. However, unravelling the interaction between these factors was not feasible due to insufficient information provided in the included studies.

These limitations highlight the need for more comprehensive investigations, particularly those focusing on the effect of astigmatism on axial elongation – a key biometric factor in myopia development that is independent of astigmatism. Future studies should also consider and control for various possible

covariates that may cause methodological heterogeneity and influence the relationship between astigmatism and myopia development. Additionally, it would be valuable to explore how the impact of astigmatism on myopia development varies across eyes with different baseline characteristics, such as age, sex, and refractive status. In the following **Study I** (**Chapter 3**) of this thesis, a more comprehensive analysis of the impact of astigmatism on axial elongation, considering other potential confounding factors, will be presented to address these limitations.

2.5 Conclusions

This meta-analysis is the first to investigate the association between baseline astigmatism and myopia progression in children, using data from 11 longitudinal studies covering 7,554 subjects worldwide. Our findings reveal that children with ATR astigmatism exhibit significantly higher myopia progression compared to those with WTR astigmatism, indicating the crucial role of astigmatic axis orientation in myopia development and its clinical significance. However, no significant difference in myopia progression was observed among subjects with different magnitudes of astigmatism, possibly due to the high methodological heterogeneity across the included studies. Therefore, future research with standardized methodologies is needed to reduce bias and validate these observations. The findings of this meta-analysis not only provide robust evidence supporting our hypothesis regarding the impact of baseline astigmatism on refractive development but will also inform and guide future studies within this thesis.

2.6 Supplementary Materials

Database	Step	Search Terms (Date: January 31, 2023)	Results
PubMed	1	(astigmatism) AND (emmetropization OR emmetropisation)	279
	2	(astigmatism) AND (myopia OR hyperopia OR refractive error OR spherical equivalent OR axial length) AND (develop OR progress OR onset OR predict)	3,146
	3	(astigmatism) AND (myopia OR hyperopia OR refractive error OR spherical equivalent OR axial length) AND (longitudinal OR follow up OR follow-up OR baseline)	3,288
	4	2 OR 3	5,233
	5	1 OR 4	**5,370**
Embase	1	'astigmat*' AND ('emmetropization' OR 'emmetropisation')	117
	2	'astigmat*' AND ('myopi*' OR 'hyperopi*' OR 'refractive error*' OR 'spherical equivalent' OR 'axial length') AND ('develop*' OR 'progress*' OR 'onset' OR 'predict*')	3,292
	3	'astigmat*' AND ('myopi*' OR 'hyperopi*' OR 'refractive error*' OR 'spherical equivalent' OR 'axial length') AND ('longitudinal*' OR 'follow up' OR 'follow-up' OR 'baseline')	2,752
	4	2 OR 3	4,851
	5	1 OR 4	**4,903**
Web of Science	1	astigmat* AND (emmetropization OR emmetropisation)	148
	2	astigmat* AND (myopi* OR hyperopi* OR refractive error* OR spherical equivalent OR axial length) AND (develop* OR progress* OR onset OR predict*)	2,600
	3	astigmat* AND (myopi* OR hyperopi* OR refractive error* OR spherical equivalent OR axial length) AND (longitudinal OR follow up OR follow-up OR baseline)	2,071
	4	2 OR 3	3,684
	5	1 OR 4	**3,721**
Cochrane	1	(astigmatism) AND (emmetropization OR emmetropisation)	2
	2	(astigmatism) AND (myopia OR hyperopia OR refractive error OR spherical equivalent OR axial length) AND (develop OR progress OR onset OR predict)	25
	3	(astigmatism) AND (myopia OR hyperopia OR refractive error OR spherical equivalent OR axial length) AND (longitudinal OR follow up OR follow-up OR baseline)	35
	4	2 OR 3	35
	5	1 OR 4	**35**

Supplementary Table S2.1 Search Strategies with Syntax and Search Results for Each Database

Study	Selection				Comparability		Outcome of Interest			NOS Quality Score [f]	
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Magnitude	Axis
Grosvenor et al, 1987	1	1	1	1	0 [b]	0 [c]	1	1	1	7	7
Goss and Shewey, 1990	1	1	1	1	0 [b]	0 [c]	1	1	0 [e]	6	6
Pärssinen, 1991	1	1	1	1	1	1	1	1	1	na.	9
Gwiazda et al, 2000	1	1	1	1	0 [b]	1	1	1	0 [e]	7	7
Twelker et al, 2013	1	1	1	1	0 [b]	1	1	1	0 [e]	7	na.
Hu et al, 2016	0 [a]	1	1	1	1	0 [c]	1	1	0 [e]	6	6
Kim et al, 2017	0 [a]	1	1	1	0 [b]	0 [c]	1	1	0 [e]	5	na.
Chan et al, 2018	1	1	1	1	0 [b]	0 [c]	1	0 [d]	0 [e]	5	na.
Verkicharla et al, 2020	1	1	1	1	1	1	1	0 [d]	0 [e]	7	7
Liang et al, 2022	1	1	1	1	1	1	1	0 [d]	0 [e]	7	7
Liang et al, 2024	1	1	1	1	1	1	1	0 [d]	0 [e]	7	7

Supplementary Table S2.2 Risk of Bias Assessment of Included Studies

Note: The quality scores of the included studies were assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS). High quality: more than 6; moderate quality: 4-6; low quality: less than 4. Only studies with moderate and high quality were included in the meta-analysis. na, not applicable due to unavailable data for this analysis.

[a] The study selected a specific subset of participants (*e.g.*, referral patients in eye hospitals) instead of a general population, which might introduce bias in the representativeness of the study cohort.

[b] The study did not control for the most important factor (*i.e.*, baseline SER) in the study design or statistical analyses.

[c] The study did not control for other relevant factors (*e.g.*, baseline age) in the study design or statistical analyses.

[d] The study had a relatively inadequate follow-up period for the outcome of interest (*i.e.*, less than 3 years for this meta-analysis).

[e] The study did not report the follow-up rate or had a follow-up rate of less than 80% without describing those lost to follow-up.

Subgroup Analysis for Axis Effect	# of Studies	# of Subjects		Subgroup Meta-analysis		Heterogeneity		Between-subgroup *P* [c]
		WTR	ATR	Weighted Mean Difference, D/year	*P* [a]	I^2 (%)	*P* [b]	
Definition of Astigmatism								
Cylinder ≥ 0.75 DC	2	881	42	+0.02 (-0.07, +0.11)	0.63	<0.01	0.42	0.35
Others	6	2,140	901	+0.08 (+0.00, +0.16)	0.05	54.3	0.05	
Study Region								
America	3	99	128	+0.06 (-0.02, +0.14)	0.16	37.9	0.19	0.85
Europe	1	24	106	+0.03 (-0.12, +0.18)	0.70	na.	na.	
Asia	4	2,898	709	+0.11 (-0.12, +0.34)	0.35	82.0	0.02	
Follow-up Duration								
Average FU ≤ 2 years	3	2,027	686	+0.19 (-0.13, +0.52)	0.25	84.0	0.01	0.38
Average FU > 2 years	5	994	257	+0.04 (-0.02, +0.10)	0.15	11.7	0.37	
Measurement of Refractions								
Cycloplegia	3	947	165	+0.06 (-0.05, +0.17)	0.27	36.6	0.21	0.83
Non-Cycloplegia	5	2,074	778	+0.05 (+0.00, +0.09)	0.04	0.01	0.06	
Baseline SER								
All Myopia or All with Negative SER	3	113	215	+0.06 (-0.04, +0.15)	0.23	41.3	0.19	0.45
All Hyperopia	1	871	23	-0.050 (-0.25, +0.15)	0.62	na.	na.	
Others	4	2,037	705	+0.12 (-0.05, +0.30)	0.18	86.2	0.04	
Baseline Age								
Infancy	1	10	19	+0.04 (-0.06, +0.14)	0.43	na.	na.	0.71
Others	7	3,011	924	+0.06 (-0.00, +0.13)	0.06	40.3	0.06	
Overall	**8**	**3,021**	**943**	**+0.05 (+0.01, +0.09)**	**0.007**	**0.01**	**0.09**	-

Supplementary Table S2.3 Subgroup Analyses for the Impact of Astigmatic Axis Orientation on SER Progression

Note: WTR, with-the-rule. ATR, against-the-rule. D, diopter. A WMD > 0 indicates that ATR astigmatism has more myopic progression than WTR astigmatism.

[a] *P*-value for the comparisons of SER progression between WTR and ATR within each subgroup.

[b] *P*-value for the heterogeneity of SER across studies within the same subgroup.

[c] *P*-value for the comparisons of weighted mean differences between subgroups.

Subgroup Analysis for Magnitude Effect	# of Studies	# of Subjects		Subgroup Meta-analysis		Heterogeneity		Between-subgroup *P* [c]
		Higher	Lower	Weighted Mean Difference, D/year	*P* [a]	I^2 (%)	*P* [b]	
Definition of Astigmatism								
Cylinder ≥ 0.75 DC	7	1,694	1,180	-0.02 (-0.04, +0.00)	0.07	0.04	0.24	0.13
Others	3	2,927	1,753	+0.49 (-0.03, +0.13)	0.23	78.5	<0.01	
Study Region								
America	4	635	610	-0.02 (-0.04, +0.01)	0.17	0.02	0.21	0.36
Asia	6	3,986	2,323	+0.04 (-0.04, +0.11)	0.47	81.8	<0.01	
Follow-up Duration								
Average FU ≤ 2 years	4	2,804	1,770	+0.09 (+0.05, +0.13)	**<0.01**	<0.01	0.25	**0.04**
Average FU > 2 years	6	1,817	1,163	-0.02 (-0.04, +0.00)	0.06	0.03	0.41	
Measurement of Refractions								
Cycloplegia	5	1,737	1,082	-0.02 (-0.04, +0.01)	0.15	0.07	0.03	0.78
Non-Cycloplegia	5	2,884	1,851	+0.02 (-0.05, +0.08)	0.56	75.1	<0.01	
Baseline SER								
All Myopia or All with Negative SER	2	203	196	+0.03 (-0.09, +0.14)	0.67	74.0	0.05	0.33
All Hyperopia	1	1,063	451	-0.04 (-0.09, +0.02)	0.21	na.	na.	
Others	7	3,355	2,286	+0.02 (-0.03, +0.08)	0.40	81.2	<0.01	
Baseline Age								
Infancy	1	30	39	-0.01 (-0.06, +0.04)	0.73	na.	na.	0.49
Others	9	4,591	2,894	+0.02 (-0.03, +0.07)	0.44	78.9	<0.01	
Overall	**10**	**2,933**	**4,621**	**+0.01 (-0.03, +0.05)**	**0.51**	**74.8**	**<0.01**	**-**

Supplementary Table S2.4 Subgroup Analyses for the Impact of Astigmatic Magnitude on SER Progression

Note: Low, low magnitude of astigmatism. High, high magnitude of astigmatism. D, diopter. A WMD > 0 indicates lower astigmatism having more myopic progression than higher astigmatism.

[a] *P*-value for the comparisons of SER progression between WTR and ATR within each subgroup.

[b] *P*-value for the heterogeneity of SER across studies within the same subgroup.

[c] *P*-value for the comparisons of weighted mean differences between subgroups.

Chapter 3

Impact of Astigmatism on Axial Elongation

A Five-Year Population-based Study in Chinese School-aged Children

*(Note: This chapter has been published in "**Investigative Ophthalmology & Vision Science**, Dec 2024, Volume 65, Issue 13, Page 45. https://doi.org/10.1167/iovs.65.13.45"* (D. Liang et al., 2024). *The candidate contributed to the conceptualization, methodology, data analysis, writing, and visualization of this work. Permission to include the published material in this thesis has been granted by the corresponding author, who is also the supervisor of the candidate.)*

3.1 Introduction

Astigmatism, one of the most prevalent refractive errors globally, affects an estimated 14.9% of children and a significant 40.4% of adults (Hashemi et al., 2018). Astigmatism can be classified into three categories based on the axis orientation of the principal power meridians: WTR, ATR, and OBL. Despite the prevailing uncertainty surrounding the aetiology of astigmatism (Read et al., 2014), its clinical relevance is well-documented. Notably, significant astigmatism during early childhood is associated with various ocular and visual disorders, such as amblyopia (Dobson et al., 2003; Mitchell et al., 1973), strabismus (Cotter et al., 2011), abnormal retinal electrophysiology (Flitcroft, 2005), and decreased cognitive or behavioural performance (Orlansky et al., 2015; Harvey et al., 2017, 2018).

Astigmatism, which frequently coexists with myopia, has been linked to myopia development (Read et al., 2014; Kee, 2013), potentially serving as a visual cue to guide the process of emmetropization (Charman, 2011; Flitcroft, 2012; Howland, 1982). Conversely, the optical blur resulting from astigmatism may disrupt the normal emmetropization process, leading to the development of myopia (Fulton et al., 1982; Gwiazda et al., 2000). This hypothesis is supported by animal studies (Smith et al., 1998; Kee et al., 2003, 2004; Chu and Kee, 2015; Vyas and Kee, 2021), showing that early imposition of astigmatism using cylindrical lenses can alter the course of emmetropization. In human studies, a

higher magnitude of astigmatism (Fulton et al., 1982; Gwiazda et al., 2000; Fan et al., 2004; Twelker et al., 2013) or ATR astigmatism (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964) during early childhood has been associated with an increased progression of myopia. Our **meta-analysis** in **Chapter 2** further provides robust evidence supporting the association between baseline astigmatism and refractive development. In addition, astigmatism has also been linked to ocular structural changes, including choroidal thickness (Hoseini-Yazdi et al., 2020) and vascular density (Jung et al., 2020). Collectively, these findings underscore the potential role of astigmatism in influencing eye growth.

While numerous studies have investigated the association between astigmatism and refractive development (Fan et al., 2004; Fulton et al., 1982; Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964; Twelker et al., 2013), a substantial research gap persists concerning the impact of early astigmatism on ocular axial elongation. Furthermore, existing studies – often limited by small sample sizes – have reported controversial conclusions, highlighting the need for a larger-scale study to elucidate these relationships more comprehensively. Moreover, the interaction between astigmatism and spherical ametropia (*i.e.*, hyperopic *vs.* mixed *vs.* myopic astigmatism) on eye growth remains largely unexplored. To address these research gaps, we conducted a five-year study on a large cohort of school-aged children in Tianjin, China. This study aims to estimate and compare the progression rates of axial length (AXL) among children with different baseline astigmatism and spherical ametropia. This research marks a critical step towards a more comprehensive understanding of the role of astigmatism in ocular development, offering insights for improving personalized management and intervention strategies for paediatric refractive errors.

3.2 Methods

This longitudinal cohort study was conducted through annual vision screenings at seven primary and secondary schools in Tianjin, China, from 2018 to 2022. The screenings were carried out between September and December each year, targeting students from Grades 1 to 12. However, the COVID-19 pandemic interrupted the screening process in 2020 and 2022, leading to incomplete data collection in

these two years. The numbers of participants for each year were as follows: 12,683 in 2018; 13,583 in 2019; 5,466 in 2020; 16,026 in 2021; and 5,438 in 2022.

3.2.1 Measures and Outcomes

Vision screenings were performed by trained optometrists and ophthalmologists. AXL was measured using Lenstar 900 biometers (Haag-Streit, Switzerland) with three consecutive recordings averaged for accuracy (Rauscher et al., 2021). For non-cycloplegic autorefraction, the Spot Vision Screener (Welch Allyn, USA) was utilized from 2018 to 2020, and the KR-800 autorefractor (Topcon, Japan) was employed in 2021 and 2022. This change was prompted by our project's integration into a broader citywide vision screening initiative, requiring standardized equipment. Three consecutive readings of autorefraction were obtained and averaged for each eye, and those with discrepancies over 0.50 D in either spherical or cylindrical power were discarded and re-measured. Both biometers and autorefractors were calibrated before each screening session. Since data were acquired through non-cycloplegic measurements, the progression of AXL – an ocular biometric parameter less affected by ocular accommodation – was used as the primary outcome measure, with SER progression serving as a reference.

Due to the high correlations in AXL, SER, and astigmatism between the right and left eyes (Pearson's correlations, range = 0.88 to 0.97, all $P < 0.001$), only data from the right eyes were used for subsequent analyses. Individual annual progression rates for AXL and SER were calculated by fitting linear regression models to the longitudinal data for each eye. Missing data, attributed to COVID-19 disruptions, were not imputed to avoid introducing potential biases due to improperly addressing the complex patterns inherent in longitudinal data. To evaluate the effect of astigmatism on eye growth, mean AXL and SER progression rates were compared among groups categorized by magnitude and axis orientation of baseline astigmatism:

- Astigmatic Magnitude
    - None (Controls): cylindrical power > −0.50 D
    - Low: cylindrical power > −1.50 D and ≤ −0.50 D

    - High: cylindrical power ≤ −1.50 D
- Axis Orientation (for astigmatic eyes)
    - WTR: cylindrical axes between 0°–30° or 150°–180°
    - ATR: cylindrical axes between 60°–120°
    - OBL: cylindrical axes between 31°–59° or 121°–149°

In addition, sub-cohort analyses were conducted to investigate the impact of astigmatism within different spherical ametropia and sex sub-cohorts. Spherical ametropia was categorized by baseline spherical powers along two principal meridians (with zero dioptres serving as the reference):

- Spherical Ametropia
    - Compound Hyperopic: both principal meridians > 0.50 D
    - Compound Myopic: both principal meridians ≤ −0.75 D
    - Other Ametropic/Emmetropic: at least one meridian between > −0.75 D to ≤ 0.50 D

Acknowledging the potential influence of active accommodation on the measurements of spherical ametropia obtained through non-cycloplegic autorefraction in children (Sankaridurg et al., 2017), this study adopted a more conservative criterion for ametropia definition.

3.2.2 Study Population

This study included Chinese children aged 5 to 16 years at the time of examination, who had at least two vision screening records available for longitudinal analysis. Children who reported a history of contact lens wear, orthokeratology, or any form of myopia control interventions were excluded. To maintain consistency in assessing the effect of axis orientation of astigmatism on eye growth, children who demonstrated a change in the types of axis orientations during the follow-up period were excluded (**Figure 3.1**). To account for potential age-related differences in eye growth (Breslin et al., 2013; Hyman et al., 2005), study population was stratified into two age cohorts for further analyses: a younger (5 to 10 years at baseline) and an older (11 to 15 years at baseline) cohort.

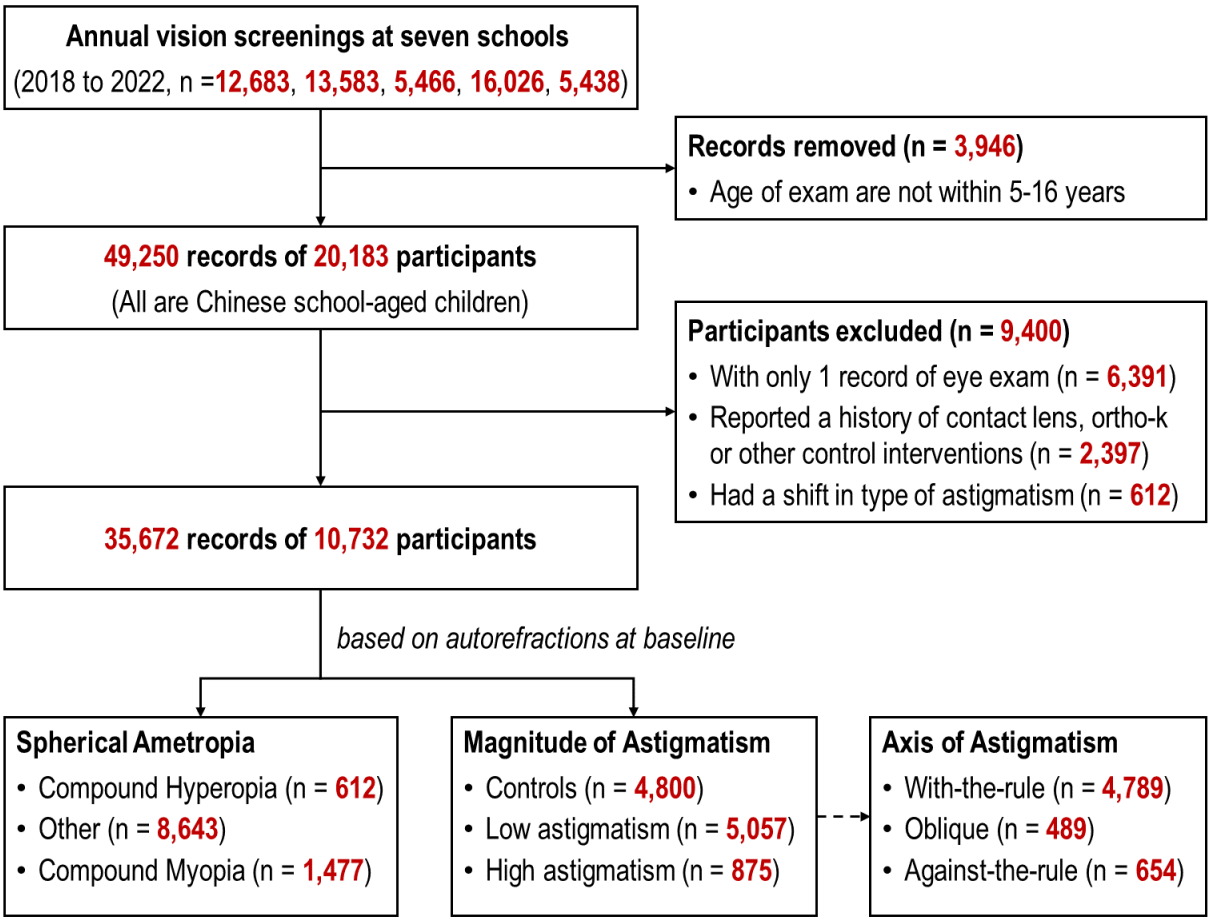

Figure 3.1 Flowchart for Inclusion and Exclusion of Study Cohort

Note: Ortho-k, orthokeratology.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Tianjin Medical University Eye Hospital and The Hong Kong Polytechnic University (HSEARS20230210006). Written informed consent was obtained from the parents or legal guardians of all participating children before the vision screenings.

3.2.3 Statistical Analysis

Statistical analyses were performed using SPSS Statistics (v27.0, IBM Corp., USA) and R (v4.0, https://www.r-project.org/). Data are presented as mean ± standard deviation (SD), 95% confidence interval (95% CI), or median (interquartile range [IQR]), unless specified otherwise. To test the effect of baseline astigmatism on eye growth, a two-way analysis of covariance (ANCOVA) with Bonferroni's *post-hoc* comparisons (Factor 1: astigmatic magnitude; Factor 2: astigmatic axis orientation) was employed to compare the AXL progression rates among the astigmatism subgroups, adjusted for baseline age, sex, follow-up duration, and baseline AXL as covariates. If a significant two-way interaction effect between the two factors was found, their simple main effects on AXL progression were reported; otherwise, their main effects were reported. The partial eta-squared (η^2) was calculated to indicate the effect size in ANCOVA tests: small effect, $\eta^2 = 0.01$ to 0.06; medium effect, $\eta^2 = 0.06$ to 0.14; and large effect, $\eta^2 > 0.14$ (Cohen, 1973). A two-tailed $P < 0.05$ was considered statistically significant for all statistical tests.

3.3 Results

3.3.1 Characteristics of Study Population

Longitudinal data from 10,732 children, comprising a total of 35,672 records, were analyzed. The younger cohort (n = 7,880) had a mean baseline age of 8.14 ± 1.39 years, with a mean follow-up period of 2.74 ± 0.98 years. The older cohort (n = 2,852) had a mean baseline age of 12.73 ± 1.09 years and a mean follow-up period of 2.34 ± 1.04 years.

	Full Cohort	Age Cohort #	
		Younger	Older
Numbers of participants	10,732	7,880	2,852
Baseline age, *year*	9.36 (2.42)	8.14 (1.39)	12.73 (1.09)
Follow-up duration, *year*	2.63 (1.01)	2.74 (0.98)	2.34 (1.04)
Sex, *n (%)*			
Boys	5,706 (53.2)	4,137 (52.5)	1,569 (55.0)
Girls	5,026 (46.8)	3,743 (47.5)	1,283 (45.0)
Education at baseline, *n (%)*			
Primary schools	8,946 (83.4)	7,880 (100)	1,066 (37.4)
Secondary schools	1,786 (16.6)	0 (-)	1,786 (62.6)
School types at baseline, *n (%)*			
Local schools	6,238 (58.1)	4,505 (57.2)	1,733 (60.8)
International schools	4,494 (41.9)	3,375 (42.8)	1,119 (39.2)
Biometry at Baseline			
Axial length, *mm*	23.51 (1.15)	23.23 (1.01)	24.30 (1.19)
Spherical equivalent, *D*	-0.50 (1.54)	-0.07 (1.05)	-1.69 (1.98)
Refractive astigmatism, *D*	-0.71 (0.62)	-0.67 (0.59)	-0.82 (0.66)
Biometry at Follow-up			
Axial length, *mm/year*	0.29 (0.50)	0.28 (0.44)	0.31 (0.46)
Spherical equivalent, *D/year*	-0.38 (0.55)	-0.39 (0.51)	-0.38 (0.57)
Refractive astigmatism, *D/year*	0.03 (0.28)	0.05 (0.25)	-0.01 (0.34)

Table 3.1 Demographic and Biometric Characteristics of Study Population at Baseline and During Follow-up

Note: Data are presented as mean (standard deviation) unless otherwise stated.

#, The full study cohort was divided into younger (5 to 10 years old) and older (11 to 16 years old) cohorts at baseline.

At baseline, 4,800 eyes (44.7%) in the full cohort had no astigmatism, serving as the control group; 5,057 eyes (47.1%) exhibited low astigmatism; and 875 eyes (8.2%) had high astigmatism. Among the astigmatic eyes, 4,789 (80.9%) were classified as WTR, 654 (11.0%) as ATR, and 489 (8.2%) as OBL astigmatism. Regarding baseline spherical ametropia, 612 eyes (5.7%) exhibited compound hyperopia, 1,477 (13.8%) exhibited compound myopia, and 8,643 (80.5%) were categorized as other ametropia/emmetropia (**Supplementary Table S3.1**).

Table 3.1 summarizes the demographic and biometric characteristics at baseline and during follow-up visits. The mean baseline AXL and SER were 23.23 ± 1.01 mm and −0.07 ± 1.05 D for the younger cohort, and 24.30 ± 1.19 mm and −1.69 ± 1.98 D for the older cohort, respectively. Over the follow-up period, the mean AXL and SER progression rates were 0.28 ± 0.39 mm/year and −0.39 ± 0.51 D/year for the younger cohort, and 0.31 ± 0.41 mm/year and −0.38 ± 0.57 D/year for the older cohort, indicating a prevailing trend towards axial elongation and myopia development. In contrast, changes in astigmatism over time were minimal, with a mean progression rate of 0.05 ± 0.25 D/year and −0.01 ± 0.37 D/year for both age cohorts, suggesting that refractive astigmatism remained relatively stable throughout the follow-up period.

Supplementary Table S3.2 provides more detailed demographic and biometric characteristics across different astigmatism groups at baseline. No significant differences were observed among the groups regarding baseline age, sex, follow-up duration, and ocular biometric measures (all $P \geq 0.10$).

3.3.2 AXL Progression across Different Astigmatism

The mean AXL progression rates across different astigmatism groups in the combined, younger, and older cohorts are presented in **Figure 3.2**. Two-way ANCOVA revealed no significant interaction effect between the magnitude and axis orientation of baseline astigmatism on AXL progression in any cohort (all $P \geq 0.224$), while controlling for baseline age, sex, follow-up duration, and baseline AXL. Therefore, an analysis of the main effects for astigmatic magnitude and axis orientation was performed, revealing two key findings.

First, axial elongation varied significantly with the axis orientation of astigmatism in the combined ($P < 0.001$; $\eta^2 = 0.037$) and younger cohorts ($P = 0.031$; $\eta^2 = 0.024$), with marginal significance observed in the older cohort ($P = 0.050$; $\eta^2 = 0.043$). *Post-hoc* analyses of the combined cohort revealed significantly faster axial elongation in eyes with ATR (0.415 mm/year; $P = 0.008$) and OBL astigmatism (0.373 mm/year; $P = 0.049$) compared to those with WTR astigmatism (0.285 mm/year). However, no significant difference was observed between ATR and OBL astigmatism ($P > 0.999$). A similar trend, as depicted in **Figure 3.2**, was observed in both the younger and older cohorts. In the younger cohort, only the difference between WTR (0.271 mm/year) and ATR (0.398 mm/year) reached statistical significance ($P = 0.045$). Neither the comparison between WTR and OBL (0.351 mm/year), nor between ATR and OBL, was statistically significant ($P \geq 0.614$). In the older cohort, *post-hoc* comparisons did not reveal any statistically significant differences, likely due to the smaller sample size (WTR, 0.314 mm/year; OBL, 0.389 mm/year; ATR, 0.439 mm/year; all $P \geq 0.164$).

Second, the magnitude of astigmatism at baseline significantly influenced AXL progression. In the combined cohort, eyes with high astigmatism (0.399 mm/year) exhibited significantly faster axial elongation compared to those with low astigmatism (0.316 mm/year; $P = 0.018$; $\eta^2 = 0.015$). A similar trend was observed in the older cohort (low astigmatism, 0.324 mm/year; high astigmatism, 0.427 mm/year; $P = 0.039$; $\eta^2 = 0.036$). However, this difference did not reach statistical significance in the younger cohort (low astigmatism, 0.309 mm/year; high astigmatism, 0.364 mm/year; $P = 0.302$).

In addition to axial elongation, SER progression rates were analyzed across astigmatism groups (**Figure 3.3**). Consistent with the AXL progression findings, both the magnitude and axis orientation of baseline astigmatism had significant main effects on SER progression in the combined and older cohorts (all $P \leq 0.017$; η^2 ranged from 0.029 to 0.150), whilst controlling for baseline age, sex, follow-up duration, and baseline SER. Similarly, high-magnitude and ATR astigmatism exhibited more myopic SER progression compared to low-magnitude and WTR astigmatism.

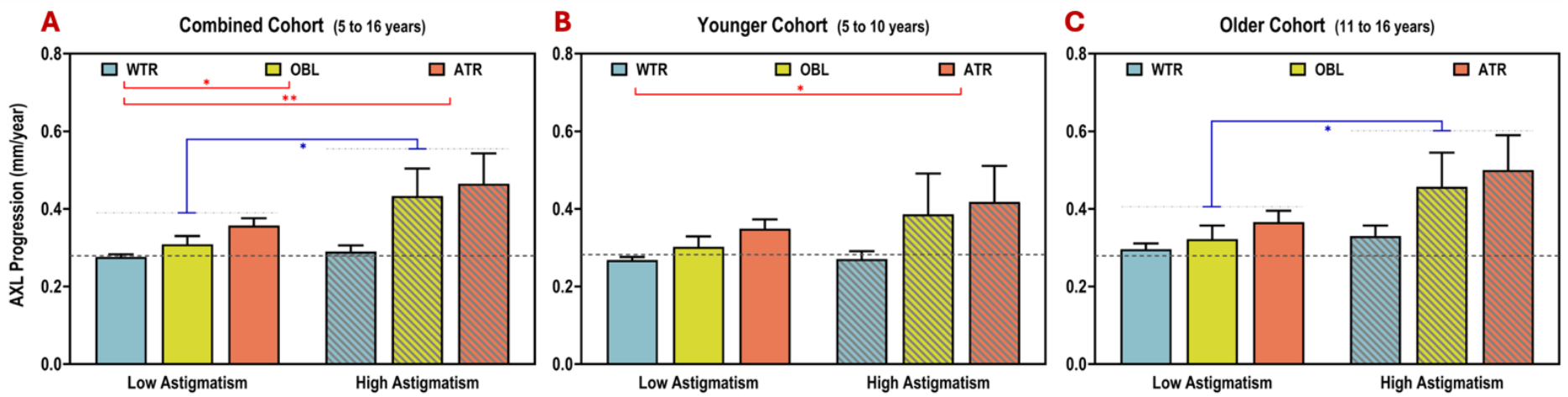

Figure 3.2 AXL Progression Rates across Different Astigmatism

Note: Figure shows the progression rates of axial length (AXL) stratified by astigmatic magnitude and axis orientation in the **(A)** combined, **(B)** younger, and **(C)** older cohorts. The dotted line represents Controls. Blue, yellow, and red bars represent with-the-rule (WTR), oblique (OBL), and against-the-rule (ATR) astigmatism, respectively. Solid bars indicate low astigmatism, while striped bars denote high astigmatism. Error bars represent standard errors. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration, and baseline AXL. *, $P < 0.05$. **, $P < 0.01$. Blue asterisks indicate comparisons between low and high astigmatism subgroups; red asterisks highlight differences between axis orientation subgroups.

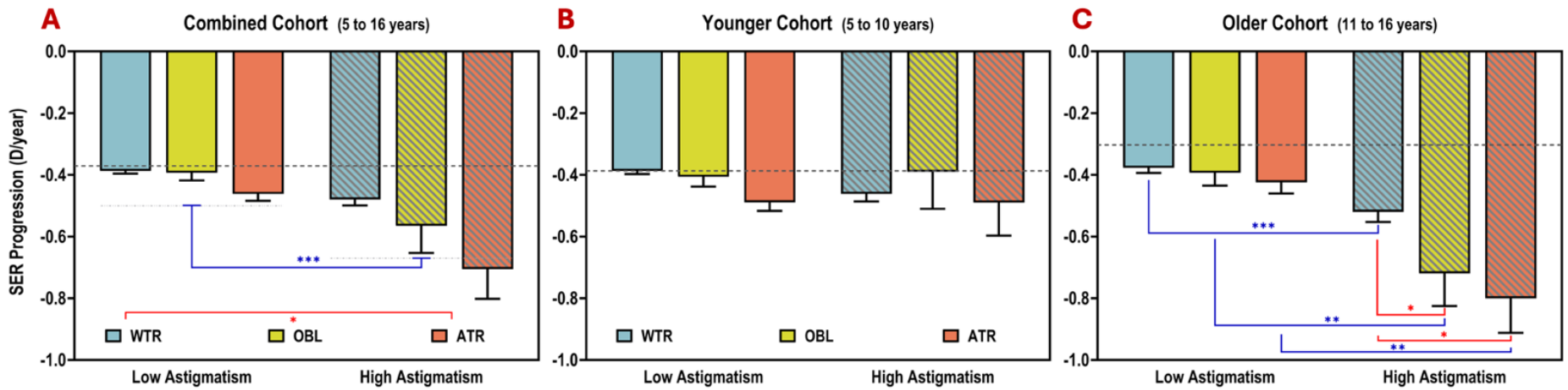

Figure 3.3 SER Progression Rates across Different Astigmatism

Note: Figure shows the progression rates of spherical-equivalent refraction (SER) stratified by astigmatic magnitude and axis orientation in the **(A)** combined, **(B)** younger, and **(C)** older cohorts. The dotted line represents Controls. Blue, yellow, and red bars represent with-the-rule (WTR), oblique (OBL), and against-the-rule (ATR) astigmatism, respectively. Solid bars indicate low astigmatism, while striped bars denote high astigmatism. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration, and baseline SER. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. Blue asterisks indicate comparisons between low and high astigmatism subgroups; red asterisks highlight differences between axis orientation subgroups.

3.3.3 AXL Progression across Different Astigmatism, Spherical Ametropia, and Sex

The impact of astigmatism on AXL progression was examined within sub-cohorts by baseline spherical ametropia subtypes (*i.e.*, compound hyperopia, compound myopia, other) and by sex (*i.e.*, female, male). However, due to the limited number of compound hyperopic eyes with high-OBL (n = 1) or high-ATR (n = 0) astigmatism, our sub-cohort analyses specifically compared AXL progression across different magnitudes of astigmatism within the WTR orientation (*i.e.,* Controls *vs.* low-WTR *vs.* high-WTR) and different axis orientations in those with a low magnitude of astigmatism (*i.e.,* low-WTR *vs.* low-OBL *vs.* low-ATR) in different spherical ametropia and sex sub-cohorts. This approach was employed to ensure the validity of our statistical analysis, considering the small sample size in some subgroups.

3.3.3.1 Impact of Astigmatic Magnitude across Spherical Ametropia Subtypes

Figure 3.4 illustrates the AXL progression rates among control eyes and those with low and high WTR astigmatism, stratified by baseline spherical ametropia subtypes – compound hyperopia, compound myopia, and other ametropia/emmetropia. A significant interaction between astigmatic magnitude and spherical ametropia subtypes was observed in the combined ($P = 0.001$; $\eta^2 = 0.027$) and younger cohorts ($P = 0.036$; $\eta^2 = 0.025$), indicating that the effect of astigmatism on AXL progression differed depending on the baseline refractive state. However, this interaction was not significant in the older cohort ($P = 0.319$).

As shown in **Figure 3.4A,** within the combined cohort, astigmatic magnitude significantly affected AXL progression in both compound hyperopic ($P = 0.017$; $\eta^2 = 0.016$) and compound myopic eyes ($P = 0.007$; $\eta^2 = 0.014$), but with opposite effects. In the compound hyperopic group, high WTR astigmatism (0.097 mm/year) was associated with significantly reduced AXL progression compared to non-astigmatic control eyes (0.254 mm/year; $P = 0.013$). Conversely, in the compound myopic group, high WTR astigmatism (0.508 mm/year) was associated with significantly increased AXL progression compared to control eyes (0.405 mm/year; $P = 0.024$).

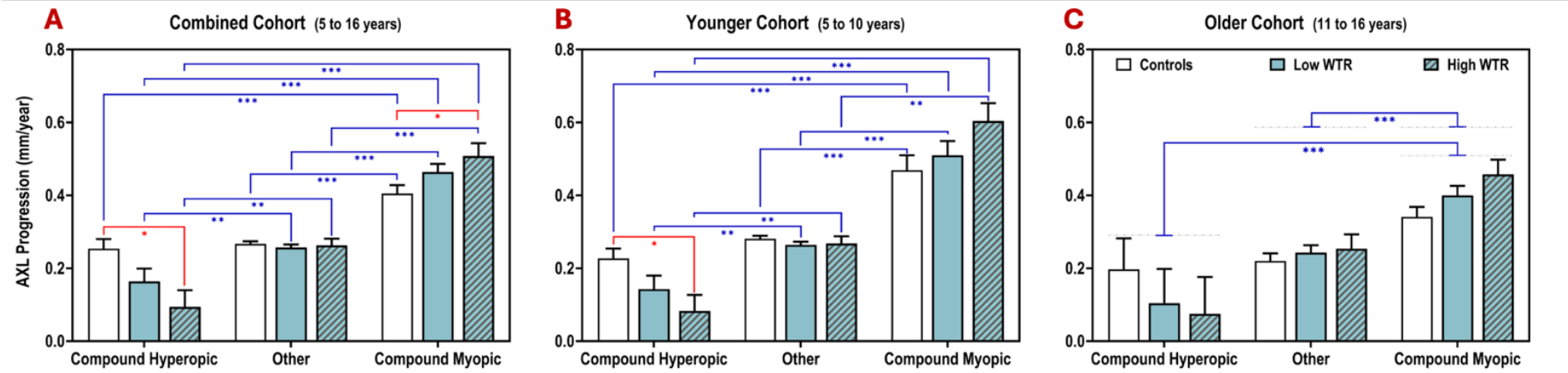

Figure 3.4 AXL Progression Rates across Different Magnitudes of WTR Astigmatism and Spherical Ametropia

Note: Figure shows the effect of the magnitude of with-the-rule (WTR) astigmatism on axial length (AXL) progression across different spherical ametropia in the **(A)** combined, **(B)** younger, and **(C)** older cohorts. White, solid-blue, and striped-blue bars represent the control, low, and high WTR astigmatism groups, respectively. Error bars represent standard errors. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration and baseline AXL. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. Blue asterisks indicate comparisons between spherical ametropia subtypes; red asterisks highlight differences between astigmatic magnitude subgroups.

A similar bi-directional trend was observed in the younger cohort (**Figure 3.4B**), with astigmatic magnitude significantly influencing AXL progression in compound hyperopic eyes (P = 0.012; η^2 = 0.015). Consistent with the combined cohort, high WTR astigmatism (0.085 mm/year) in younger group was associated with significantly less AXL progression compared to control eyes (0.227 mm/year; P = 0.027). While a similar trend of increased AXL progression with higher WTR astigmatism was also observed in compound myopic eyes, this difference did not reach statistical significance (Controls, 0.469 mm/year; Low, 0.508 mm/year; High, 0.600 mm/year; P = 0.293). The older cohort (**Figure 3.4C**) exhibited a similar bi-directional pattern, but the interaction between baseline astigmatic magnitude and spherical ametropia subtypes was not statistically significant.

Consistent with the AXL progression findings, the impact of astigmatic magnitude on SER progression rates was also modulated by baseline spherical ametropia subtypes. Higher WTR astigmatism was consistently associated with less myopic SER progression in compound hyperopic eyes but significantly more myopic progression in compound myopic eyes and the other ametropic/emmetropic group (**Figure 3.5A–C**).

To further quantify the effect of spherical ametropia magnitude on AXL progression and its potential interaction with astigmatic magnitude, the compound myopic sub-cohort – in which astigmatic magnitude demonstrated a significant effect on AXL progression – was further stratified into "*low-myopic*" (both meridians ≤ −0.75 D but not both ≤ −3.00 D) and "*medium-myopic*" (both meridians ≤ −3.00 D) groups. As shown in **Figure 3.6A–C**, a significant main effect of myopia magnitude was observed, with individuals classified as low myopic showing less AXL progression than those classified as medium myopic in both the combined cohort (0.326 *vs.* 0.400 mm/year; P < 0.001) and older cohort (0.303 *vs.* 0.397 mm/year; P < 0.001). This difference was not observed in the younger cohort (0.382 *vs*. 0.409 mm/year; P = 0.488). However, the interaction between myopic magnitude and astigmatic magnitude was not statistically significant in the combined, younger, and older cohorts (all $P \geq 0.498$).

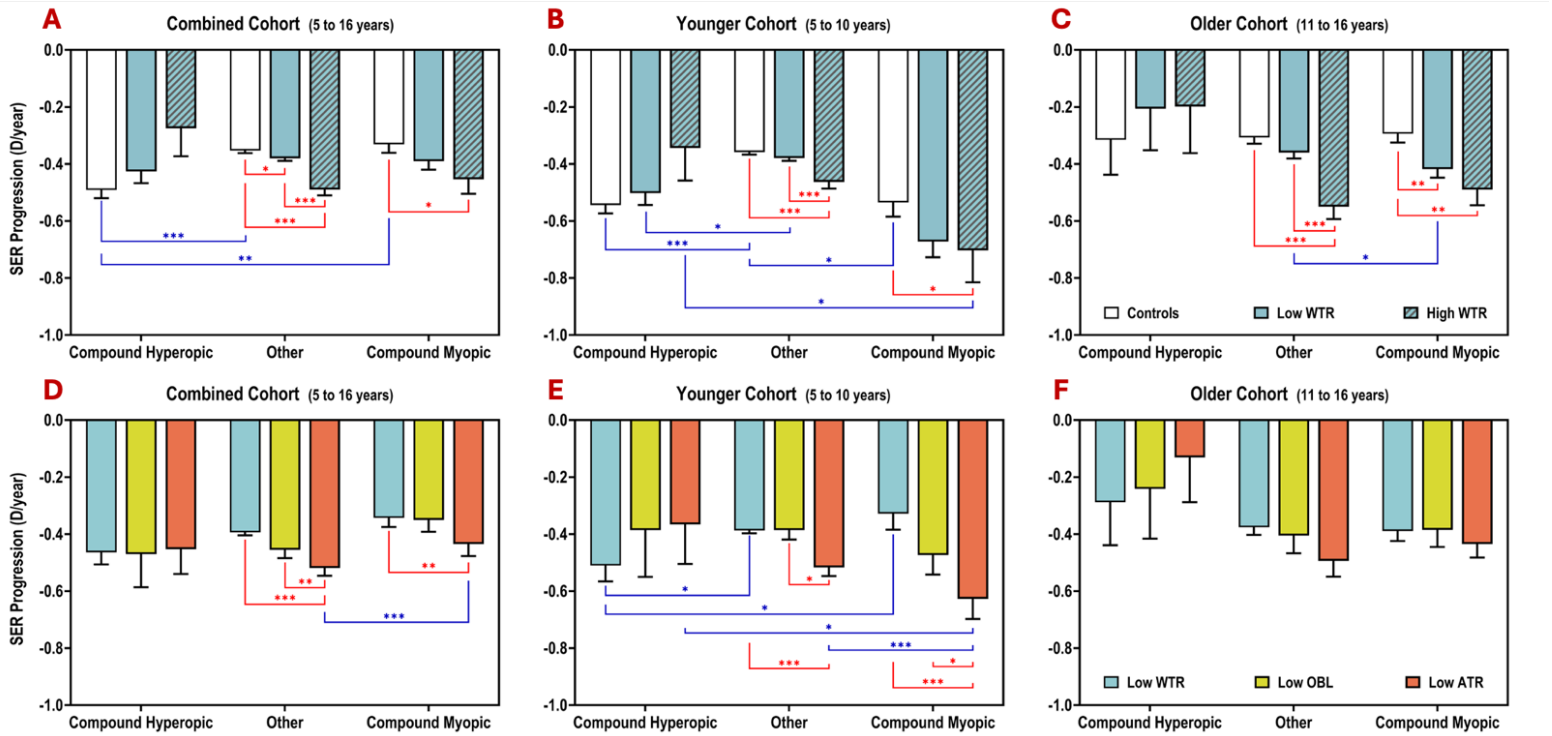

Figure 3.5 SER Progression Rates across Different Astigmatism and Spherical Ametropia

Note: Figure shows the effect of **(A–C)** WTR astigmatic magnitude and **(D–F)** axis orientation of low astigmatism on SER progression in different spherical ametropia (*i.e.*, compound hyperopia *vs.* other *vs.* compound myopia) and different age groups (*i.e.*, combined *vs.* younger *vs.* older), respectively. SER, spherical-equivalent refraction. WTR, with-the-rule. ATR, against-the-rule. OBL, oblique astigmatism. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration and baseline SER. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. Blue asterisks indicate comparisons between spherical ametropia subtypes; red asterisks highlight differences between astigmatism (magnitude or axis orientation) subgroups.

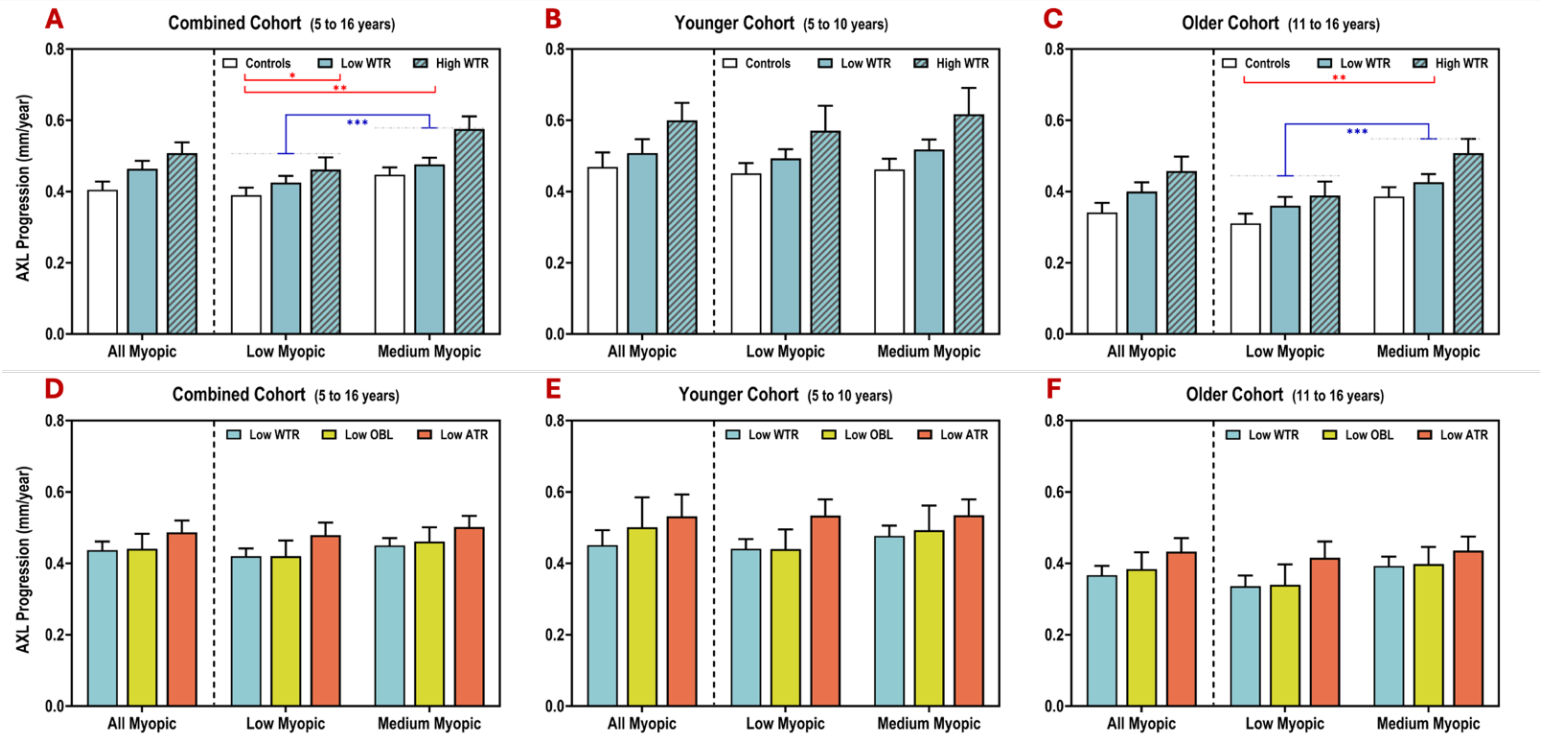

Figure 3.6 AXL Progression Rates across Different Astigmatism and Myopia Magnitudes

Note: Figure shows the effect of **(A–C)** WTR astigmatic magnitude and **(D–F)** axis orientation of low astigmatism on AXL progression in different myopia magnitudes (*i.e.*, low-myopic *vs.* medium-myopic) and different age groups (*i.e.*, combined *vs.* younger *vs.* older), respectively. The data of "all myopic" groups were presented for reference only. AXL, axial length. WTR, with-the-rule. ATR, against-the-rule. OBL, oblique astigmatism. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration and baseline AXL. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. Blue asterisks indicate comparisons between myopia magnitude subtypes; red asterisks highlight differences between astigmatism (magnitude or axis orientation) subgroups.

3.3.3.2 Impact of Astigmatic Axis Orientation across Spherical Ametropia Subtypes

Figure 3.7 illustrates the AXL progression rates across low-WTR, low-OBL, and low-ATR astigmatism groups, stratified by baseline spherical ametropia subtypes. Although a trend towards faster axial elongation in eyes with ATR and OBL astigmatism compared to WTR astigmatism was observed, particularly in the compound myopic and other ametropic/emmetropic groups, the interaction between astigmatic axis orientation and spherical ametropia on AXL progression was not statistically significant in the combined, younger, or older cohorts (all $P \geq 0.348$). Additionally, no significant main effect of axis orientation of astigmatism was found (all $P \geq 0.606$), potentially due to the reduced sample sizes. A similar effect of axis orientation of astigmatism on SER progression was also observed (**Figure 3.5 D–F**).

3.3.3.3 Impact of Astigmatism across Sex

No significant interaction effect was found between sex and either astigmatic magnitude or axis orientation on AXL progression in any of the age cohorts (all $P \geq 0.588$). However, a significant main effect of sex on AXL progression was observed. When stratifying participants by WTR astigmatic magnitude, males showed faster AXL progression than females in both the combined (0.306 *vs.* 0.253 mm/year; $P < 0.001$) and younger cohorts (0.309 *vs.* 0.231 mm/year; $P < 0.001$), but not in the older cohort (0.299 *vs.* 0.298 mm/year; $P = 0.968$; **Figure 3.8A–C**). Similarly, when stratifying by axis orientation of astigmatism, males in the younger cohort showed faster AXL progression than females (0.340 *vs.* 0.281 mm/year; $P = 0.023$), but this difference was not statistically significant in the combined (0.328 *vs.* 0.299 mm/year; $P = 0.163$) or older cohorts (0.316 *vs.* 0.315 mm/year; $P = 0.543$; **Figure 3.8D–F**).

Similar to the AXL progression findings, a significant difference in SER progression between males and females was observed in the combined and younger cohorts ($P \leq 0.002$), but not in the older cohort ($P = 0.302$), when stratifying by WTR astigmatic magnitude. No significant difference was found when stratifying by axis orientation of low astigmatism (all $P \geq 0.584$; **Figure 3.9**).

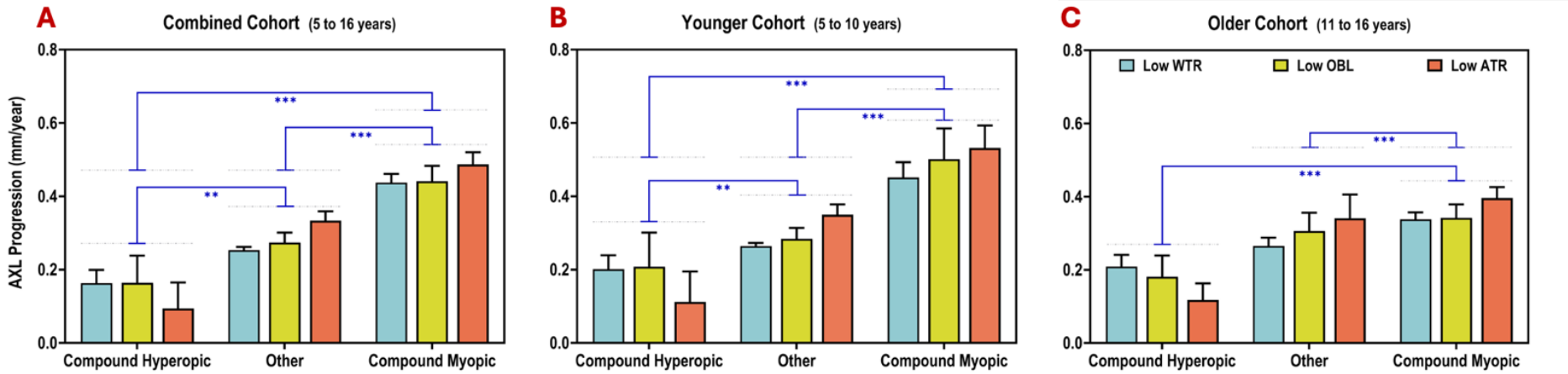

Figure 3.7 AXL Progression Rates across Different Axis Orientations of Low Astigmatism and Spherical Ametropia

Note: Figure shows the effect of the axis orientation of low astigmatism on axial length (AXL) progression across different spherical ametropia in the **(A)** combined, **(B)** younger, and **(C)** older cohorts. Blue, yellow, and red bars represent low with-the-rule (WTR), oblique (OBL), and against-the-rule (ATR) astigmatism, respectively. Error bars represent standard errors. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration, baseline AXL and astigmatic magnitude. **, $P < 0.01$; ***, $P < 0.001$. Blue asterisks indicate comparisons between spherical ametropia subtypes.

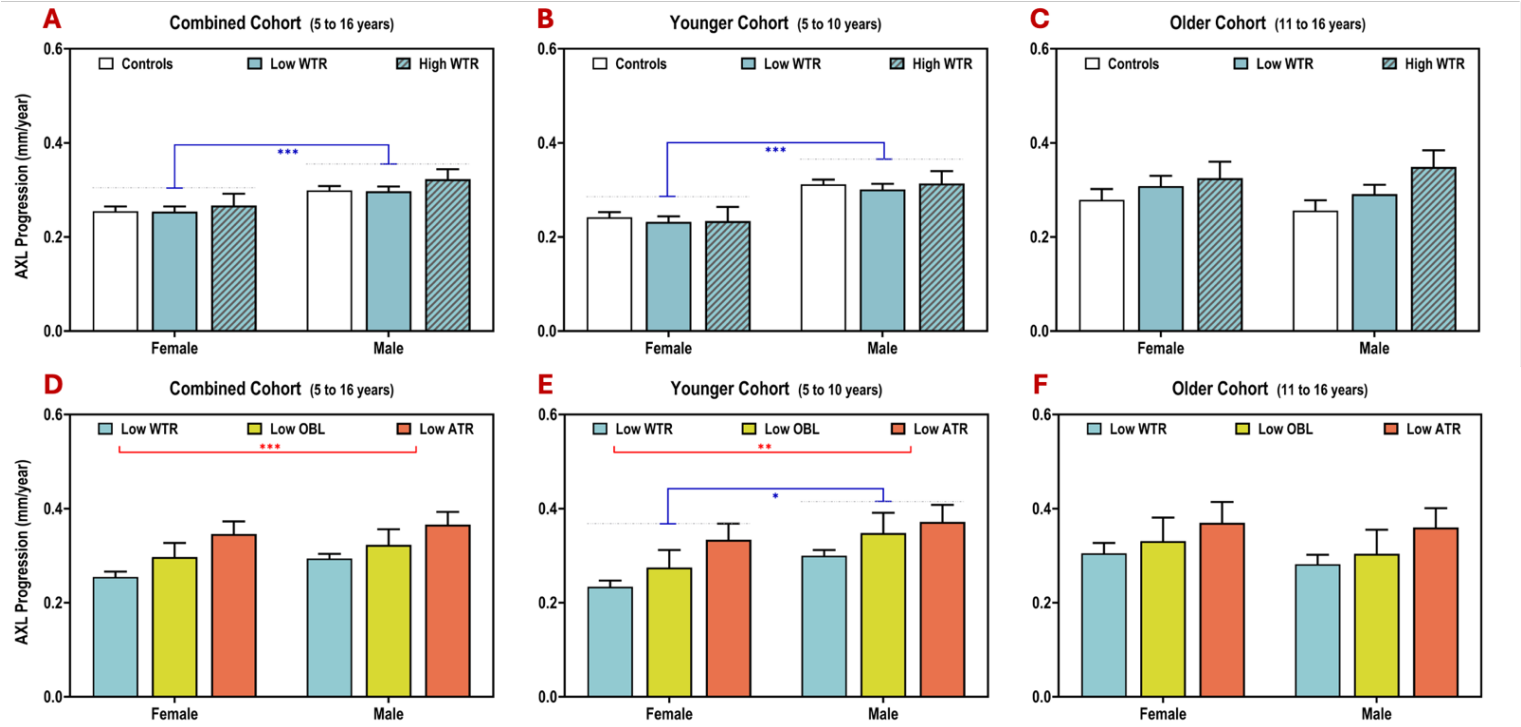

Figure 3.8 AXL Progression Rates across Different Astigmatism and Sex Groups

Note: Figure shows the effect of **(A–C)** WTR astigmatic magnitude and **(D–F)** axis orientation of low astigmatism, on AXL progression in different sex groups (*i.e.*, female *vs.* male) and different age groups (*i.e.*, combined *vs.* younger *vs.* older), respectively. Error bars represent standard errors. AXL, axial length. WTR, with-the-rule. ATR, against-the-rule. OBL, oblique astigmatism. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration and baseline AXL. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. Blue asterisks indicate comparisons between sexes; red asterisks highlight differences between astigmatism (magnitude or axis orientation) subgroups.

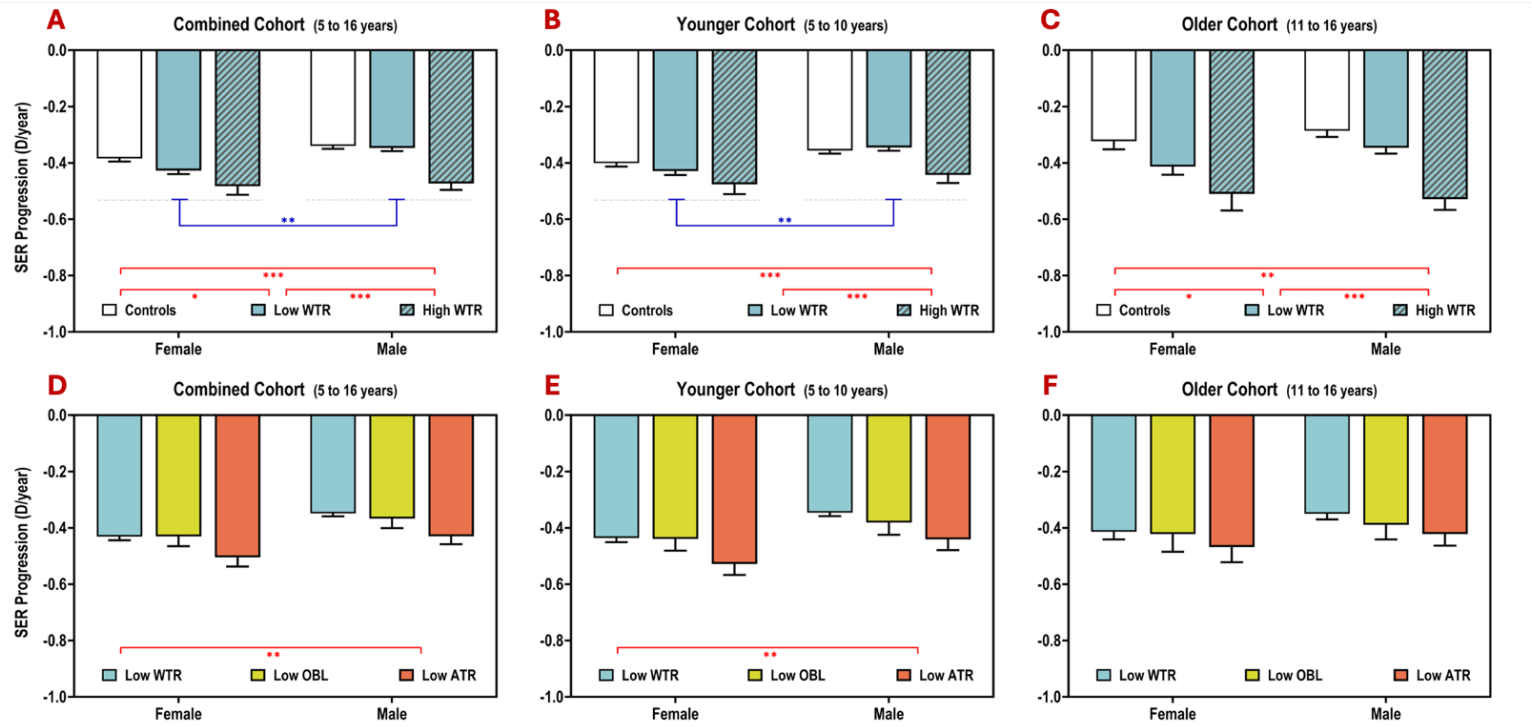

Figure 3.9 SER Progression Rates across Different Astigmatism and Sex Groups

Note: Figure shows the effect of **(A–C)** WTR astigmatic magnitude and **(D–F)** axis orientation of low astigmatism on SER progression in different sex groups (*i.e.*, female *vs.* male) and different age groups (*i.e.*, combined *vs.* younger *vs.* older), respectively. SER, spherical-equivalent refraction. WTR, with-the-rule. ATR, against-the-rule. OBL, oblique astigmatism. Statistical significance was determined by two-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for baseline age, sex, follow-up duration and baseline SER. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. Blue asterisks indicate comparisons between sexes; red asterisks highlight differences between astigmatism (magnitude or axis orientation) subgroups.

3.4 Discussion

In this five-year study of 10,732 Chinese school-aged children, we examined the impact of baseline astigmatism on axial elongation and myopia development. Our comprehensive analysis yielded two significant findings. First, baseline astigmatism was a significant factor in eye growth. Children with high magnitude and ATR astigmatism experienced greater axial elongation. Second, the impact of baseline astigmatism on axial elongation was modulated by baseline spherical ametropia. Specifically, higher astigmatism increased AXL progression in compound myopic eyes but decreased progression in compound hyperopic eyes. Moreover, greater AXL progression in ATR compared to WTR astigmatism was observed in the compound myopic and other ametropic/emmetropic groups, but not in compound hyperopic eyes. These findings underscore the significant and complex impacts of astigmatism on axial eye growth.

3.4.1 Impact of Astigmatism on Axial Elongation

Our study, distinguished by its large sample size and longitudinal design, offers a novel insight into how baseline astigmatism influences changes in axial length, the primary ocular biometry associated with myopia progression. Our findings suggest that both magnitude and axis orientation of baseline astigmatism affect axial elongation in the combined cohort, with similar patterns observed in both younger and older sub-cohorts (**Figure 3.2**). Specifically, eyes with ATR astigmatism exhibited the greatest axial elongation, followed by OBL and WTR astigmatism. In addition, a higher magnitude of astigmatism was associated with greater AXL progression compared to a lower magnitude.

To our knowledge, only one previous study involving 108 Chinese preschoolers (aged 2–6 years) documented increased axial growth associated with higher astigmatism (Fan et al., 2004). However, it did not observe a significant difference in AXL progression between WTR and ATR astigmatism, which contradicts our findings. This discrepancy could be due to the limited sample size of Fan et al.'s study, particularly for children with ATR astigmatism (n = 9). Furthermore, most eyes in this prior study were likely hyperopic astigmatism, with a mean SER of 0.89 D. It is noteworthy that in our study, increased

AXL progression associated with ATR astigmatism was identified in compound myopic or other ametropic/emmetropic eyes, but not in compound hyperopic eyes (**Figure 3.7**). Our study is the first to demonstrate a significant association between the axis orientation of baseline astigmatism and axial elongation in school-aged children.

While the impact of astigmatism on axial elongation is largely underexplored, its effect on refractive development has been extensively documented (see **Chapter 2** for details). For instance, previous studies have linked infantile astigmatism to increased progression of refractive myopia during infancy (Fulton et al., 1982) and a higher likelihood of developing myopia at school age (Edwards and Shing, 1999; Gwiazda et al., 2000). Additionally, higher baseline astigmatism in young children has been associated with a more pronounced myopic shift (Fan et al., 2004) and a steeper SER progression slope over the follow-up period (Twelker et al., 2013). These findings are supported by our observations on AXL progression, further emphasizing the significant role of astigmatism and its magnitude in eye growth.

Regarding the impact of axis orientation of astigmatism, previous studies also reported findings consistent with our results, where ATR astigmatism in infants and children was more likely to lead to subsequent myopia (Gwiazda et al., 2000; Hirsch, 1964) or greater myopic progression (Grosvenor et al., 1987). This is further supported by morphological analyses of the posterior eyeball, which have revealed significant differences in chorioretinal structure between WTR and ATR astigmatism (Hoseini-Yazdi et al., 2020). These structural variations suggest a potential role for the axis orientation of astigmatism in the development of the posterior eyeball.

However, while our findings align with the studies mentioned above, it is noteworthy that other research has not established a significant association between astigmatism – neither in terms of magnitude (Dobson et al., 2007; Pärssinen et al., 2015; Hu et al., 2016) nor axis orientation (Fan et al., 2004; Pärssinen, 1991; O'Donoghue et al., 2015; Goss and Shewey, 1990) – and myopia development. These discrepancies may arise from methodological differences, such as variations in sample sizes, definitions

of astigmatism, and age ranges of participants, factors known to affect the relationship between astigmatism and myopia development (Goss and Shewey, 1990; Pärssinen, 1991). For instance, astigmatic magnitude had a significant main effect on axial elongation in our study; therefore, using different definition criteria for astigmatism could lead to varying results. Similarly, axial elongation showed slight differences between younger and older cohorts, with the impact of baseline astigmatism appearing more pronounced in older ages (**Figure 3.2**). Notably, our study observed consistent patterns of associations between baseline astigmatism (both magnitude and axis orientation) and axial elongation across both younger and older ages, although some effects were not statistically significant, potentially due to the reduced sample sizes. As the largest longitudinal study to date, our research encompasses a broad spectrum of participant ages (*i.e.*, 5 to 16 years) and astigmatism characteristics (*i.e.*, varying magnitudes and axes), allowing for a more representative and comprehensive evaluation of astigmatism's role in eye growth.

In addition to baseline astigmatism, previous studies have identified that baseline spherical ametropia can also influence emmetropization (Saunders et al., 1995; Ehrlich et al., 1997; Schein et al., 2022) and myopia development (French et al., 2013; Hagen et al., 2019; Wu et al., 2015). This suggests that the impact of astigmatism on myopia development could be confounded by children's spherical ametropia. This complexity is further highlighted by studies showing that different subtypes of astigmatism – such as mixed, simple, or compound astigmatism – can affect myopia progression in distinct ways. For instance, mixed astigmatism does not exhibit significant myopia progression until it evolves into simple or compound myopic astigmatism (Goss, 1999). Additionally, infants with hyperopic-WTR or myopic-ATR astigmatism are prone to develop more myopia during childhood (Gwiazda et al., 1993). Our sub-cohort analysis also reveals that higher-magnitude astigmatism increased AXL progression in compound myopic eyes but decreased in compound hyperopic eyes across both younger and older ages (**Figure 3.4**). Similarly, greater AXL progression in ATR compared to WTR astigmatism was observed only in compound myopic and other ametropic/emmetropic eyes (**Figure 3.7**). These differential impacts underscore the importance of considering the baseline spherical ametropia when examining the effects of astigmatism on emmetropization and myopia development. Our study is the first to explore

how these complex interactions affect axial elongation and myopia development during school age.

3.4.2 Hypothetical Explanations

Our study contributes to the understanding of the impact of astigmatic magnitude on the emmetropization process. Previous research in monkeys (Kee et al., 2004; Smith et al., 1998) and chicks (Chu and Kee, 2015; Vyas and Kee, 2021) has shown that imposing astigmatism can alter the course of emmetropization, with the endpoints directed towards either the circle of least confusion or the least hyperopic focal plane associated with the imposed astigmatism (Troilo et al., 2019). In our sub-cohort analyses of spherical ametropia, compound hyperopic eyes with higher astigmatism showed significantly reduced axial elongation compared to those with lower astigmatism (**Figure 3.4**), suggesting that eye growth is directed towards the least hyperopic focal plane.

In humans, myopic eyes, which are more prolate in shape (Atchison et al., 2004; Logan et al., 2004; Atchison et al., 2005; Singh et al., 2006), tend to have relative peripheral hyperopic defocus (Tabernero et al., 2009; Lin et al., 2010), while hyperopic eyes are more oblate and show relatively peripheral myopic defocus (Mutti et al., 2000). This peripheral defocus could potentially serve as a signal to regulate myopia development (Smith, 2011). Therefore, in hyperopic eyes, higher astigmatism would bring the least hyperopic focal plane closer to the retina in the periphery compared to those with lower astigmatism, probably leading to reduced myopic progression and axial elongation. This observation aligns with findings from our recent chick study (Vyas and Kee, 2021), where hyperopic-astigmatic blur with higher astigmatic magnitude resulted in lower myopic error compared to similar hyperopic-astigmatic blur with lower astigmatic magnitude.

While the defocus mechanism explained above provides some insight, it does not fully explain the increased axial elongation in our compound myopic-astigmatic eyes (**Figure 3.4**). This could be due to several factors. For instance, myopic eyes tend to have a larger accommodative lag (Harb et al., 2006; Mutti et al., 2006) and higher ocular aberrations (He et al., 2002; Yazar et al., 2014) than emmetropic and hyperopic eyes. These deficiencies could impose a higher magnitude of hyperopic defocus and

degrade the quality of the retinal image (Logan et al., 2021), thereby complicating the effect of astigmatism on eye growth. Furthermore, the sensitivity of the focusing mechanism is reduced in myopic eyes (Swiatczak and Schaeffel, 2021, 2022b), making it more challenging for the myopic retina to determine the level of defocus. The chronic blur caused by significant astigmatism could further diminish the retina's ability to regulate emmetropization (Gwiazda et al., 2000; Kee, 2013), potentially confounding the endpoint for emmetropization.

Our study found that ATR astigmatism led to greater axial elongation than WTR astigmatism in compound myopic and other ametropic/emmetropic eyes (**Figure 3.7**). This suggests that horizontally oriented visual signals may be more potent in promoting axial elongation. Previous studies have reported varying effects of WTR and ATR astigmatism on refractive development (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964) and structural changes in the eyes (Chan et al., 2022; Hoseini-Yazdi et al., 2020), but the underlying mechanism is still unclear. One possible explanation is the orientation-selectivity of the retinal and neural processing pathways. For instance, the retinal circuits and cells of many vertebrates, such as ganglion and amacrine cells (Antinucci and Hindges, 2018), respond more robustly to stimuli aligned with their preferred orientation (Bloomfield, 1994; Schall et al., 1986). Given that relative hyperopic defocus predominantly occurs along the horizontal meridian (Atchison et al., 2006), eyes with myopic-ATR astigmatism (whose most hyperopic focal line is horizontally orientated) would receive stronger stimuli for axial elongation compared to myopic-WTR astigmatism. Supporting this hypothesis, studies in cats have shown that more neurons (Leventhal and Hirsch, 1980; Li et al., 2003) or a larger area of the cortical surface (Liu and Pettigrew, 2003) are tuned to horizontal than vertical stimuli. This suggests that horizontally oriented stimuli may play a critical role in directing eye growth. However, this hypothesis does not explain the insignificant but decreased axial elongation in hyperopic-ATR astigmatism compared to hyperopic-WTR astigmatism (**Figure 3.7**), possibly due to some astigmatism-related ocular biometric factors, such as compensated corneal astigmatism (Chan et al., 2022), which could confound the development and measurement of axial length.

3.4.3 Limitations

This study has several limitations. **First**, employing non-cycloplegic autorefraction using two different instruments in vision screenings might introduce biases in SER measurements. Studies in Chinese school-age children have reported a mean myopic shift ranging from −0.17 to −0.49 D with the same model of instruments (Qian et al., 2019; D. Wang et al., 2020). To address this, we adopted a more conservative criterion for myopia definition (*i.e.*, both principal meridians ≤ −0.75 D), and primarily focused on AXL progression rather than SER progression. The measurements of astigmatism and axial length are less influenced by non-cycloplegic examinations (Goyal et al., 2018; Huang et al., 2012), reinforcing the credibility of our findings. While these strategies minimize the influence of non-cycloplegic measurements, the potential for overestimating myopia and underestimating hyperopia cannot be entirely eliminated. Therefore, caution is warranted when interpreting findings related to SER. **Second**, without records of habitual spectacle prescriptions, this observational study cannot quantify the precise retinal image blur resulting from astigmatism during the follow-up period. Consequently, the observed AXL progression may stem from varying degrees of uncorrected astigmatism. Even with full optical correction, the relatively higher off-axis astigmatism in lenses with higher cylindrical power may also contribute to the progression (Jalie, 1972). Future studies that control for optical corrections are essential to validate our proposed mechanism. **Third**, our study included a limited sample size of high-OBL or high-ATR astigmatism, which may affect the robustness of our conclusions. This imbalanced distribution of astigmatism types may have limited our statistical power to detect a potential interaction effect between astigmatism magnitude and axis orientation on axial elongation. Future analyses with a more balanced sample size across different astigmatism and spherical ametropia are required. **Lastly**, ocular conditions that may affect astigmatism or AXL measurements, such as keratoconus and amblyopia, were not assessed during the vision screening, which may also introduce potential bias into our findings. Despite these limitations, the strength of our study lies in its novel findings and large sample size, which have the potential to guide future research in this field.

3.5 Conclusions

This five-year large-scale cohort study of 10,732 Chinese school-aged children has revealed that baseline magnitude and axis orientation of astigmatism are significantly associated with axial elongation. However, these associations may vary depending on the baseline spherical ametropia. Specifically, high-magnitude and ATR astigmatism are linked to increased axial elongation in compound myopic eyes, but with decreased progression in compound hyperopic eyes. These findings not only suggest the significant role of early astigmatism in eye growth but also provide valuable insights for developing personalized management and interventions for paediatric refractive errors.

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3.6 Supplementary Materials

Number of eyes	Full Cohort	Baseline Age #		Baseline Spherical Ametropia §		
		Younger	Older	Compound Hyperopia	Other	Compound Myopia
Overall	10,732	7,880	2,852	612	8,643	1,477
Controls	4,800	3,801	999	348	3,978	474
Low magnitude						
WTR	3,976	2,893	1,083	177	3,279	520
OBL	455	278	177	20	311	124
ATR	626	355	271	36	375	215
High magnitude						
WTR	813	524	289	30	654	129
OBL	34	13	21	1	24	9
ATR	28	16	12	0	22	6

Supplementary Table S3.1 Number of Studied Eyes with Different Astigmatism at Baseline

Note: WTR, with-the-rule. ATR, against-the-rule. OBL, oblique astigmatism.

#, The full cohort was divided into younger (aged 5-10 years) and older cohort (aged 11-16 years) at baseline.

§, Baseline spherical ametropia was defined as compound hyperopia (both meridians > 0.50 D), compound myopia (both meridians ≤ −0.75 D), and other ametropia/emmetropia (at least one meridian between > −0.75 D and ≤ 0.50 D).

Baseline Characteristics	Controls	Low astigmatism			High astigmatism			*P* #
		WTR	OBL	ATR	WTR	OBL	ATR	
Number of eyes, *n*	4,800	3976	455	626	813	34	28	
Baseline age, *year*	8.93 (2.28)	9.63 (2.40)	9.92 (2.70)	10.08 (2.62)	9.65 (2.64)	10.03 (2.90)	10.07 (2.33)	0.10
Follow-up duration, *year*	2.66 (1.00)	2.63 (1.02)	2.60 (0.97)	2.55 (1.03)	2.54 (1.05)	2.34 (1.10)	2.61 (1.13)	0.24
Sex, *n (%)*								0.63
Boys	2,509 (52.3)	2,163 (54.4)	203 (44.6)	311 (49.7)	485 (59.7)	17 (50.0)	18 (64.3)	
Girls	2,291 (47.7)	1,813 (45.6)	252 (55.4)	315 (50.3)	328 (40.3)	17 (50.0)	10 (35.7)	
Education, *n (%)*								0.19
Primary schools	4,212 (87.8)	3,310 (83.2)	327 (71.9)	439 (70.1)	619 (76.1)	17 (50.0)	22 (78.6)	
Secondary schools	588 (12.2)	666 (16.8)	128 (28.1)	187 (29.9)	194 (23.9)	17 (50.0)	6 (21.4)	
School types, *n (%)*								**<0.05**
Local schools	2,819 (58.7)	2,273 (57.2)	283 (62.2)	390 (62.3)	426 (52.4)	26 (76.5)	21 (75.0)	
International schools	1,981 (41.3)	1,703 (42.8)	172 (37.8)	236 (37.7)	387 (47.6)	8 (23.5)	7 (25.0)	
Ocular biometry at baseline								
Axial length, *mm*	23.43 (1.06)	23.52 (1.15)	23.75 (1.29)	23.75 (1.29)	23.54 (1.31)	23.59 (1.48)	23.89 (1.51)	0.15
Spherical equivalent, *D*	-0.37 (1.29)	-0.56 (1.50)	-0.73 (1.95)	-0.81 (1.94)	-0.66 (1.91)	-0.84 (2.02)	-0.98 (1.95)	0.55
Astigmatism, *D*	-0.29 (0.13)	-0.85 (0.26)	-0.79 (0.24)	-0.77 (0.23)	-2.29 (0.84)	-1.95 (0.55)	-1.95 (0.84)	**<0.05**

Supplementary Table S3.2 Demographic and Biometric Characteristics of Studied Eyes with Different Astigmatism at Baseline

Note: Data are presented as mean (standard deviation) unless otherwise stated. WTR, with-the-rule. OBL, oblique astigmatism. ATR, against-the-rule.

#, two-way ANOVA test across various astigmatism groups.

Chapter 4

Impact of Astigmatism on Retinal Thickness and Visual Acuity

A Case-Control Study in Chinese Adults

*(Note: This chapter has been published in "**Investigative Ophthalmology & Vision Science**, Jan 2023, Volume 64, Issue 1, Page 2. https://doi.org/10.1167/iovs.64.1.2"* (Liang et al., 2023). *The candidate contributed to the conceptualization, methodology, data acquisition, data analysis, writing, and visualization of this work. Permission to include the published material in this thesis has been granted by the corresponding author, who is also the supervisor of the candidate.)*

4.1 Introduction

Astigmatism, a common refractive error, is attributable to differential refractive powers across different meridians, and consequently, each point of an object is refracted into light spreading between two line foci with specific, typically orthogonal, orientations. Most infants are born with significant astigmatism, either WTR (Ehrlich et al., 1997; Mutti et al., 2004; Varughese et al., 2005) or ATR (Abrahamsson et al., 1988; Dobson et al., 1984; Friling et al., 2004; Gwiazda et al., 1984; Howland and Sayles, 1985). Several population-based studies have reported that the predominant type of astigmatism in Chinese infants is WTR, with the proportion of affected infants ranging from 72% to 97% (Edwards, 1991; Huo et al., 2021; S.-J. Yu et al., 2017). Astigmatism declines substantially throughout infancy and childhood (Atkinson et al., 1980; Harvey et al., 2015, 2013), but its prevalence increases during adolescence (Harvey et al., 2015; Kee, 2013). It then appears to stabilize during adulthood (Fledelius and Stubgaard, 1986; Leung et al., 2012) before rising again in old age (Leung et al., 2012; Liu et al., 2011).

It has been hypothesized that the degradation of retinal image quality produced by astigmatism disrupts defocus-guided emmetropization (Wallman and Winawer, 2004), and may potentially interfere with normal eye growth. This hypothesis is supported by studies in chicks (McLean and Wallman, 2003; Popa et al., 2020; Vyas and Kee, 2021) and monkeys (Smith et al., 1998; Kee et al., 2003, 2004) that

demonstrated an altered course of emmetropization with imposed astigmatism. In humans, significant associations between astigmatism and refractive development have been observed in several longitudinal studies (Fan et al., 2004; Fulton et al., 1982; Gwiazda et al., 2000; Twelker et al., 2013), as summarised in **Table 2.2**.

In addition, studies in chicks (Chu and Kee, 2015; Vyas and Kee, 2021) and monkeys (Kee et al., 2004) have demonstrated a significant impact of astigmatism on refractive development depending on its axis orientation. Notably, children with ATR astigmatism are more likely to develop myopia later in life (Gwiazda et al., 2000) or have a faster myopia progression (Grosvenor et al., 1987), which has been further confirmed by our **meta-analysis** (**Chapter 2**) and **Study I** (**Chapter 3**). Experimental studies in human eyes have shown that even 60 minutes of exposure to WTR and ATR astigmatic defocus using +3.00 DC cylindrical lenses can trigger bi-directional changes in choroidal thickness (Hoseini-Yazdi et al., 2020) and refractive astigmatism (Chan et al., 2022), suggesting that an orientation-dependent signalling pathway is in place.

Emerging evidence indicates that the retina plays an essential role in the development of astigmatism (Popa et al., 2020), probably through orientation-selective cells that decode the orientation-dependent visual signals (Antinucci and Hindges, 2018). While further investigation is required to fully understand astigmatism-related eye growth mechanisms, previous research has reported abnormal retinal electrophysiological responses in astigmatic eyes. For instance, Flitcroft recorded flash ERG signals from 123 children with reduced vision and found that children with high astigmatism (*i.e.*, > 1.50 DC) had abnormal ERG responses more frequently than those with low or no astigmatism (Flitcroft, 2005). Similarly, another study in chicks demonstrated a significant correlation between multifocal ERG responses and induced WTR or ATR astigmatism (Vyas et al., 2022). Specifically, in chicks that developed ATR astigmatism, the magnitude of induced astigmatism was inversely correlated with the amplitude of the IC of the multifocal ERG signal, which predominantly reflects inner retinal activity (Gupta et al., 2021). In contrast, the magnitude of induced WTR astigmatism was directly correlated with increased IC amplitude. While previous studies have heavily focused on functional measurements,

such as retinal electrophysiology, less is known about how retinal structures vary in eyes with different types of astigmatism.

In healthy myopic (Song et al., 2016; Wolsley et al., 2008) and highly myopic populations (Koh et al., 2014), flash and multifocal ERG responses have been shown to directly correlate with the retinal thickness measured by optical coherence tomography (OCT), with thinner retinas associated with lower amplitude and higher latency of ERG responses. However, despite previous studies reporting direct relationships between ERG responses and retinal thickness (Koh et al., 2014; Song et al., 2016; Wolsley et al., 2008), as well as between ERG responses and astigmatism (Flitcroft, 2005; Vyas et al., 2022), it remains unclear whether retinal thickness profiles differ between astigmatic and non-astigmatic eyes. Therefore, this study aims to characterize the OCT-measured retinal thickness in a Chinese adult population with either WTR or ATR astigmatism, and to compare it with non-astigmatic control eyes. Additionally, the study investigates whether variations in retinal thickness across different astigmatism groups are associated with best-corrected distance visual acuity (BCDVA). It is worth noting that OCT is a non-invasive and accurate method for measuring retinal thickness profiles, and is widely applied for detecting and managing various retinal abnormalities. By examining retinal thickness in eyes with different types of astigmatism, this study will provide insights into the orientation-dependent, visually guided optical defocus mechanisms in human eyes, and will highlight the importance of considering astigmatism when interpreting retinal OCT data in clinical settings.

4.2 Methods

This case-control study was approved by the Ethics Committee of Hong Kong Polytechnic University (HSEARS20201201003) and was conducted in accordance with the Declaration of Helsinki.

4.2.1 Study Population

This retrospective study analyzed OCT data and clinical records of Chinese adults in Hong Kong. Given that the majority of Chinese adults in Hong Kong exhibit WTR astigmatism (Leung et al., 2012), all

available participants with ATR astigmatism were first identified from records of patients attending the PolyU Optometry Clinic between January 2013 and January 2021, according to the inclusion criteria (see below). Study participants with WTR astigmatism and non-astigmats (Controls) were then identified by matching their age, sex, and SER with those of the ATR participants. Of the 3,611 records reviewed, 156 fulfilled the inclusion criteria and were categorized into WTR astigmatism, ATR astigmatism, and control groups.

Inclusion criteria for astigmatic participants were as follows: age between 18–45 years; SER ≥ −10.00 D; and CYL ≤ −0.75 DC with cylindrical axes of 0°–30° or 150°–180° for WTR and 60°–120° for ATR, as determined by subjective refraction. For the control group, inclusion criteria were age between 18–45 years; SER ≥ −10.00 D; and CYL ≥ −0.25 D. Because the prevalence of astigmatism, particularly ATR, increases after age forty-five (Leung et al., 2012), probably due to the aging effects on the cornea and crystalline lens, this study excluded older adults (*i.e.*, > 45 years) to prevent potential confounding factors from affecting the data interpretation. Additional exclusion criteria included: any coexisting or previous ocular disease, such as glaucoma and retinal anomalies, cataract and pre-cataractous lens changes, and keratoconus; and a history of ocular or retinal surgery. Study participants with BCDVA worse than 0.10 LogMAR and those with poor OCT imaging quality or unavailable clinical data were also excluded. The inclusion of young adults rather than children in this study was necessitated by the limited availability of OCT data for children, which made it challenging to collect a sufficient sample for meaningful analysis.

Of the 156 participants who fulfilled the inclusion criteria, 55 were excluded due to ocular disease (n = 24), history of ocular or retinal surgery (n = 7), BCDVA worse than 0.10 LogMAR (n = 1), or poor OCT imaging quality or unavailable data (n = 23). A total of 101 participants were included in the final analysis. None of the participants reported a history of myopia control interventions, particularly orthokeratology or rigid contact lenses that might affect corneal astigmatism. The flowchart illustrating the inclusion and exclusion of the study cohort is presented in **Figure 4.1**.

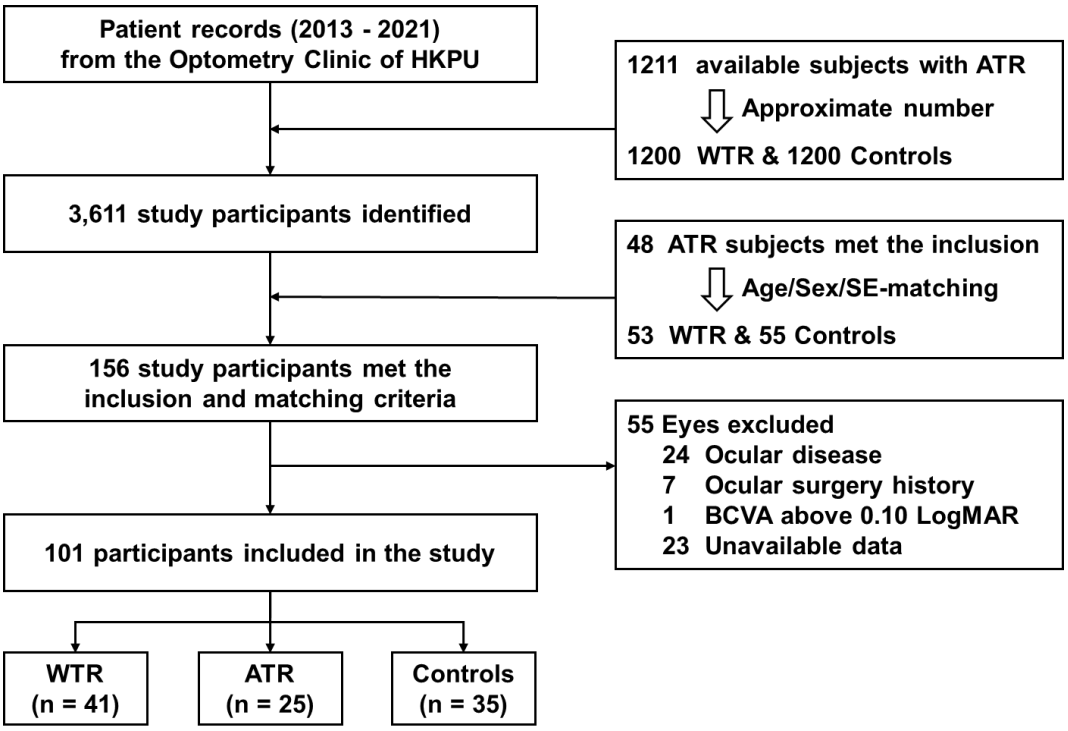

Figure 4.1 Flowchart for Inclusion and Exclusion of Study Cohort

WTR, With-The-Rule astigmatism; ATR, Against-The-Rule astigmatism; BCDVA, best-corrected distance visual acuity.

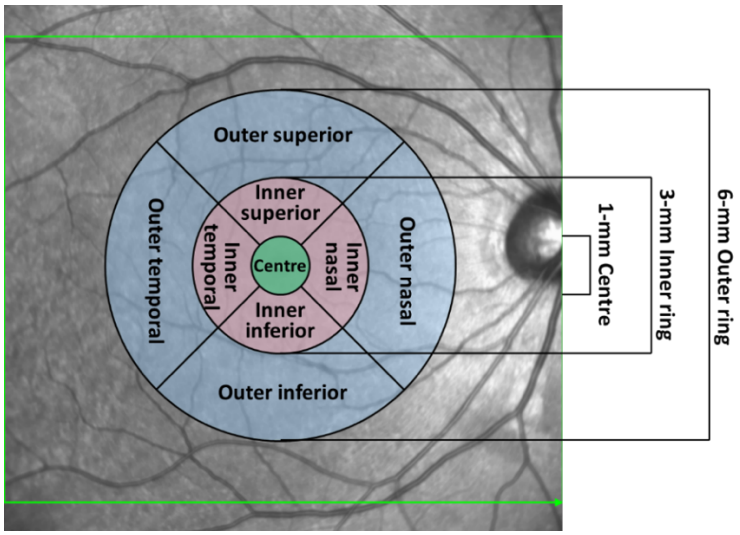

Figure 4.2 Demonstration of Early Treatment Diabetic Retinopathy Study (ETDRS) Grid

4.2.2 Measures and Outcomes

All study participants underwent a comprehensive eye examination performed by registered optometrists at the PolyU Optometry Clinic. Non-cycloplegic subjective refraction was conducted using the maximum plus with maximum visual acuity as the endpoint (Grosvenor, 2007), in which the sphere, cylinder, and axis were recorded. BCDVA was determined with Snellen visual acuity charts, and the results were converted into the logarithm of the minimal angle of resolution (LogMAR) for statistical analysis. AXL was obtained with a non-contact optical biometer (IOL Master, Carl Zeiss Meditec, Germany), with a minimum of three measurements taken for each participant, and the mean of these three measurements was used in the data analysis.

Refractive errors were converted into SER, J0, and J45 astigmatic components using the Fourier analysis (Thibos et al., 1997). The J0 and J45 astigmatic components represent astigmatism using power vectors, allowing the incorporation of both magnitude and axis orientation of all forms of astigmatism for statistical analysis. In the equations, SPH is spherical power, CYL is negative cylindrical power, and α is cylindrical axis orientation.

$$SER = SPH + CYL/2$$

$$J_0 = -CYL/2 \times \cos 2\alpha$$

$$J_{45} = -CYL/2 \times \sin 2\alpha$$

4.2.2.1 OCT Imaging

OCT images were obtained with a spectral-domain OCT (Spectralis OCT, Heidelberg Engineering Inc, Germany) using a macular volume scan, centred on the fovea formed by 49 horizontal B-scans (512 A-scans per B-scan). The OCT images were acquired by averaging at least 15 frames of B-scan images, with the eye movement tracked by the built-in TruTrack Active Eye Tracking technology to reduce speckle noise and minimize eye motion artefacts. Transverse ocular magnification was automatically adjusted by the Spectralis software based on the mean corneal radius of curvature and SER for each eye.

Only OCT images with a signal-to-noise ratio (SNR) of >15 dB and without significant blurring or artefacts affecting retinal layer segmentation were included for further analyses.

4.2.2.2 Retinal Thickness Measurements

Retinal thickness (RT) within the central 6-mm circle was automatically measured by the built-in Heidelberg segmentation software (Heidelberg Eye Explorer). The software delineated various retinal boundaries, including the Inner Limiting Membrane (ILM) and the Bruch's Membrane (BM), between which the distance represented the retinal thickness. The retinal segmentation of each B-scan and the grid alignment of each eye were checked, and segmentation errors were manually corrected by a masked imaging analyst. Manual corrections were performed only for apparent detectable errors visible on quick inspection, *e.g.*, ILM or BM delineation error. In total, OCT images from 9 eyes (8.9%) required manual correction, and no more than five B-scan frames were corrected per eye. The ICCs between retinal thickness measured by automatic segmentation with and without manual correction ranged from 0.917 to 0.977 (all $P < 0.001$), indicating good reliability of the retinal thickness measurements in this study.

A traditional macular grid, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), was used for retinal thickness analysis. The ETDRS grid divides the macula into nine sections, including a central 1-mm circle representing the foveal area, a 3-mm diameter inner ring, and a 6-mm diameter outer ring. Both the inner and outer rings were further divided into four quadrants: superior, nasal, inferior, and temporal. A demonstration of the ETDRS grid is presented in **Figure 4.2**.

4.2.3 Statistical Analysis

Statistical analyses were performed using SPSS Statistics (v26.0, IBM Corp, USA). Due to the high correlation of biometric parameters and OCT-measured RTs between the right and left eyes (Pearson's correlations, range = 0.76 to 0.98; all $P < 0.001$), only data from the right eyes were used for data analysis. Results were presented as mean (SD), median (range), or proportions, as appropriate. A one-way analysis of variance (ANOVA) test was performed to compare the demographic and biometric

characteristics among different types of astigmatism. A one-way ANCOVA test was performed to compare the retinal thickness across groups, with age, sex, and AXL adjusted as covariates. If a significant main effect was found in the ANOVA or ANCOVA, Bonferroni's *post-hoc* test was carried out to determine which pair was significantly different. The partial eta-squared (η^2) value was calculated to indicate the effect size in the ANOVA and ANCOVA tests: small effect, η^2 = 0.01–0.06; medium effect, η^2 = 0.06–0.14; and large effect, η^2 > 0.14 (Cohen, 1973). The associations between retinal thickness, BCDVA, and astigmatic components J0 and J45 were determined by Pearson's partial correlation analysis, with adjustment for age, sex, and AXL. A two-sided $P < 0.05$ was considered statistically significant.

4.3 Results

4.3.1 Characteristics of Study Population

In total, data from 101 right eyes of 101 study participants were analyzed in this study. Participants were grouped according to their astigmatic magnitude and axis orientation: WTR, n = 41; ATR, n = 25; and controls, n = 35. The demographic and biometric characteristics of the study groups are detailed in **Table 4.1**. No significant differences were observed across the groups in terms of age, sex, SER, AXL, corneal curvature, and intraocular pressure (all $P > 0.05$).

4.3.2 Visual Acuity across Different Astigmatism

BCDVA values were −0.015 ± 0.058, −0.034 ± 0.054, and −0.048 ± 0.060 LogMAR in the WTR, ATR, and control groups, respectively (**Table 4.1**). One-way ANOVA showed a significant difference in BCDVA among these three groups (P = 0.039; η^2 = 0.066), and Bonferroni's *post-hoc* test further revealed that the difference in BCDVA between WTR and control groups was significant (P = 0.041; η^2 = 0.065). Additionally, correlation analysis demonstrated that BCDVA was significantly associated with the magnitude of astigmatism (r = −0.233; P = 0.021) but not with the J0 or J45 astigmatic components (both $P > 0.05$) after adjusting for age, sex, and AXL.

	Astigmatism		Controls	*P* [a]
	WTR	**ATR**		
Number of eyes	41	25	35	
Age (years)	31.9 (8.1)	32.2 (8.2)	31.1 (7.5)	0.854
Sex (male/female)	18/23	7/18	13/22	0.331
Axial length (mm)	26.41 (1.14)	26.47 (0.98)	26.49 (1.18)	0.995
Corneal curvature (mm)	7.80 (0.30)	7.81 (0.34)	7.87 (0.32)	0.694
Spherical equivalent (D)	-4.49 (3.27)	-4.61 (3.52)	-4.13 (2.98)	0.830
Spherical power (D)				0.937
Mean (SD)	-3.88 (3.20)	-4.07 (3.54)	-4.08 (2.98)	
Median (Range)	-2.75 (-9.00, 0.00)	-3.00 (-9.50, 0.00)	-2.75 (-9.25, 0.25)	
Cylindrical power (D)				**<0.001**
Mean (SD)	-1.22 (0.38)	-1.07 (0.32)	-0.11 (0.13)	
Median (Range)	-1.25 (-2.00, −0.75)	-1.00 (-1.75, −0.75)	0.00 (-0.25, 0.00)	
Component J_0	-0.60 (0.20)	0.42 (0.16)	0.01 (0.06)	**<0.001**
Component J_{45}	0.03 (0.22)	0.16 (0.27)	0.01 (0.05)	**0.013**
BCDVA (LogMAR)	-0.015 (0.058)	-0.034 (0.054)	-0.048 (0.060)	**0.039**
IOP (mmHg)	14.42 (2.68)	14.89 (3.06)	15.60 (2.72)	0.250

Table 4.1 Demographic and Biometric Characteristics of Study Population

Note: All data were expressed as mean (SD) for continuous variables or proportions for categorical variables unless stated otherwise. WTR, with-the-rule astigmatism; ATR, against-the-rule astigmatism; D, dioptre; BCDVA, best-corrected distance visual acuity; IOP, intraocular pressure.

[a] The *P* value was calculated using a one-way ANOVA test among three groups.

4.3.3 Retinal Thickness across Different Astigmatism

The whole macular and subfield retinal thicknesses (RTs) across eyes with different types of astigmatism are shown in **Figure 4.3**. The mean (SD) of whole macular RTs were 307.54 ± 11.57 μm, 301.60 ± 7.90 μm, and 302.12 ± 10.46 μm in WTR, ATR, and control groups, respectively. For the central subfield (fovea), the mean (SD) of RTs were 269.59 ± 17.21 μm, 262.36 ± 17.92 μm, and 265.80 ± 21.56 μm in WTR, ATR, and control groups, respectively.

The WTR group showed a thicker retina in all sectors compared to the ATR and control groups, with statistically significant differences observed in the whole macula ($P = 0.028$; $\eta^2 = 0.073$), inner-superior ($P = 0.042$; $\eta^2 = 0.065$), inner-nasal ($P = 0.036$; $\eta^2 = 0.067$) and outer-temporal ($P = 0.026$; $\eta^2 = 0.074$) subfields, after adjusting for age, sex and AXL. Bonferroni's *post-hoc* tests further showed that the between-group differences in RT at the inner-nasal (WTR *vs.* ATR, $P = 0.034$; $\eta^2 = 0.068$) and outer-temporal (WTR *vs.* Control, $P = 0.042$; $\eta^2 = 0.070$) subfields were statistically significant.

In these 101 eyes analyzed, retinal thickness was negatively associated with the J0 astigmatic component, reaching statistical significance in the whole macular region ($r = -0.267$; $P = 0.037$), inner-superior ($r = -0.268$; $P = 0.037$), and inner-nasal subfields ($r = -0.347$; $P = 0.006$) after adjusting for age, sex, and AXL. No significant correlation was found between RT and either astigmatic magnitude or the J45 astigmatic component in any sector (all $P > 0.050$). The correlations between retinal thickness and J0 and J45 astigmatic components are detailed in **Table 4.2**.

4.3.4 Correlations between Visual Acuity and Retinal Thickness

BCDVA was positively associated with RT in all sectors, reaching statistical significance in the whole macular region ($r = 0.206$; $P = 0.041$) and the four quadrants in the outer ring of the ETDRS grid ($r = 0.199$ to 0.243; $P = 0.016$ to 0.049), after adjusting for age, sex, and AXL. Correlations between BCDVA and RTs in the whole cohort are shown in **Figure 4.4**.

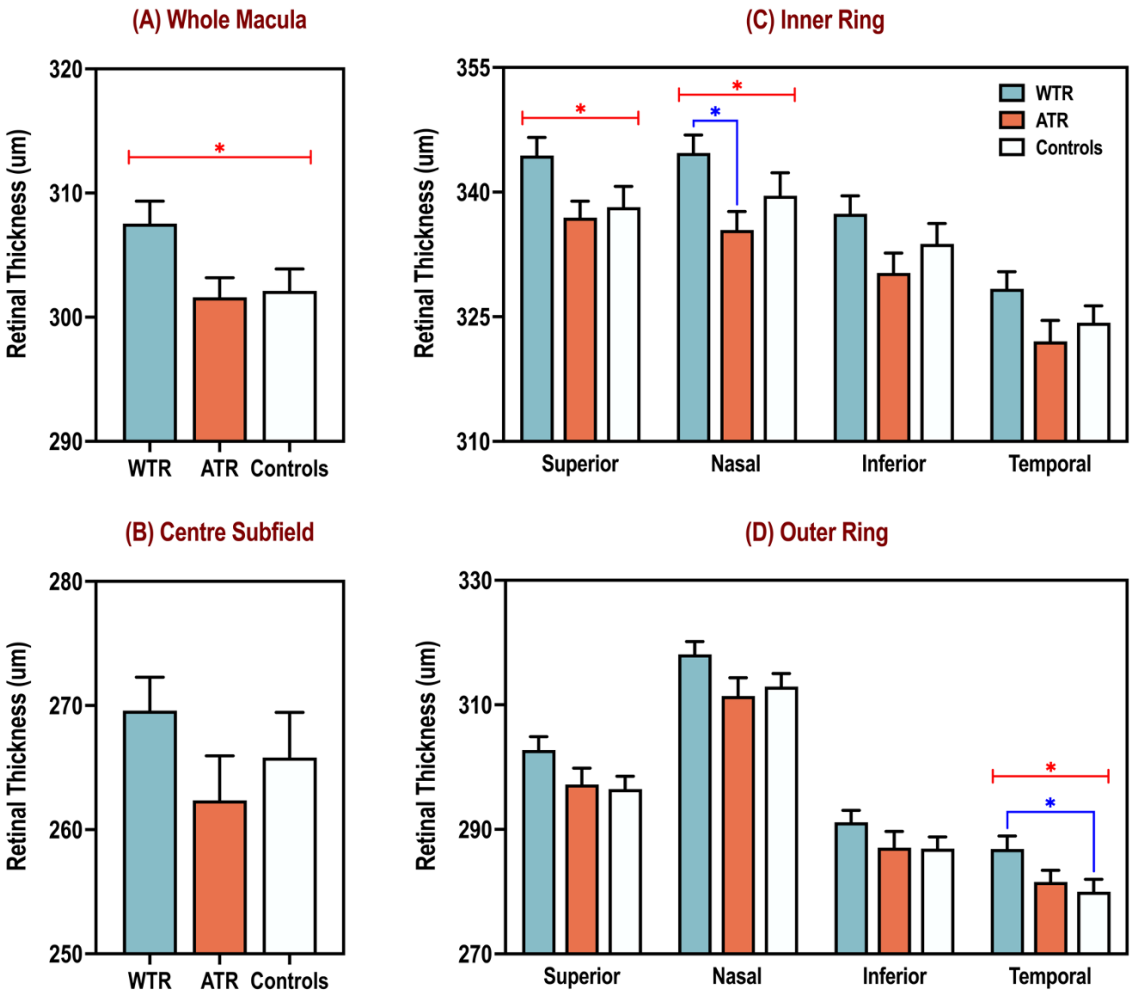

Figure 4.3 Retinal Thickness across Different Astigmatism (WTR *vs.* ATR *vs.* Controls)

Note: OCT-measured retinal thickness at **(A)** the whole macula, **(B)** the centre subfield, **(C)** the inner, and **(D)** the outer ring of the measured region in eyes with different types of astigmatism. WTR, with-the-rule. ATR, against-the-rule. Statistical significance was determined by one-way ANCOVAs with Bonferroni's *post-hoc* test after adjusting for age, sex, and axial length. *, $P < 0.05$. Red asterisks indicate comparisons across three groups; blue asterisks highlight *post-hoc* pair-wise comparisons between groups.

	BCDVA [a]		J0 [b]		J45 [c]	
	r	*P*	*r*	*P*	*r*	*P*
Retinal Thickness (um, in ETDRS grid)						
Whole macula	0.206	**0.041**	-0.267	**0.037**	-0.032	0.807
Centre subfield	0.036	0.716	-0.226	0.079	-0.120	0.357
Inner-Nasal	0.148	0.145	-0.347	**0.006**	-0.093	0.478
Outer-Nasal	0.243	**0.016**	-0.245	0.057	-0.045	0.732
Inner-Superior	0.135	0.185	-0.268	**0.037**	0.054	0.680
Outer-Superior	0.214	**0.034**	-0.202	0.118	0.002	0.989
Inner-Temporal	0.082	0.423	-0.232	0.071	0.006	0.962
Outer-Temporal	0.224	**0.027**	-0.160	0.218	0.001	0.999
Inner-Inferior	0.109	0.284	-0.227	0.078	-0.030	0.817
Outer-Inferior	0.199	**0.049**	-0.123	0.344	-0.016	0.905

Table 4.2 Correlations between Retinal Thickness, BCDVA, and Astigmatic Components

Note: [a] Correlations between BCDVA and retinal thickness, adjusted for age, sex, and axial length.

[b] Correlations between J0 astigmatic component and retinal thickness, adjusted for age, sex, and axial length.

[c] Correlations between J45 astigmatic component and retinal thickness, adjusted for age, sex, and axial length.

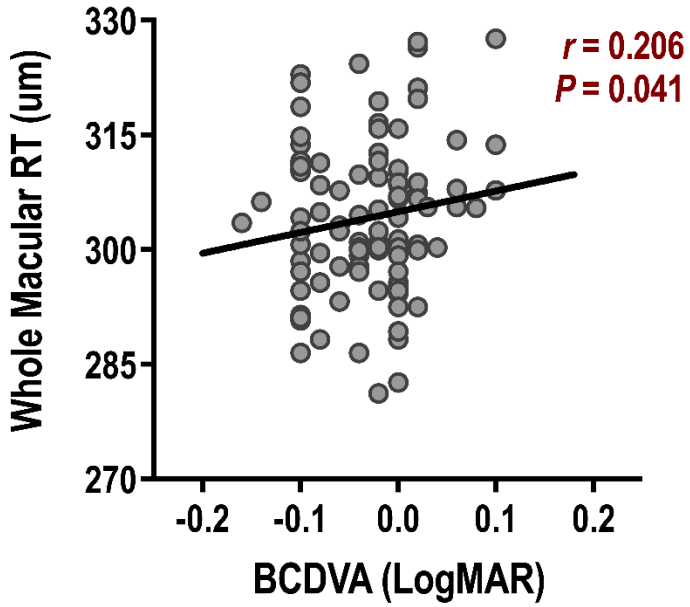

Figure 4.4 Correlation between BCDVA and Macular Retinal Thickness in the Whole Cohort

Note: Pearson's partial correlation analysis after adjusting for age, sex, and axial length. RT, retinal thickness; BCDVA, best-corrected distance visual acuity.

The association between BCDVA and RT was further investigated in eyes with different types of astigmatism through stratification analysis. Within the WTR group, BCDVA was positively correlated with RT for the whole macular region (r = 0.338; P = 0.038) and four quadrants in the outer ring of the ETDRS grid (r = 0.340 to 0.485; P = 0.002 to 0.041), after adjusting for age, sex, and AXL. However, no significant correlations were found between BCDVA and RTs in either the whole macular region or individual subfields within the ATR and control groups. Stratification analyses for correlations between BCDVA and RTs are shown in **Supplementary Table S4.2**.

4.4 Discussion

This study reports, for the first time, the influence of different types of astigmatism on retinal thickness and its relationship with visual acuity in a Chinese adult population. Our results demonstrate significant differences in retinal thickness and BCDVA across different types of astigmatism, with the thickest retinas and poorest BCDVA found in eyes with WTR astigmatism. In addition, a significant correlation between increased retinal thickness and poorer BCDVA was observed. However, stratification analysis revealed that this significant correlation was only observed in the WTR group. Our findings suggest that the impact of astigmatism on retinal thickness and BCDVA may vary depending not only on the magnitude but also on the axis orientation of astigmatism.

4.4.1 Impact of Astigmatism on Retinal Thickness

Orientation-dependent optical cues associated with astigmatism may play a critical role in ocular growth, affecting not only refractive development and axial elongation (Grosvenor et al., 1987; Gwiazda et al., 2000; Kee et al., 2004), but also changes in chorioretinal structure (Hoseini-Yazdi et al., 2020; Vyas and Kee, 2021). For instance, Hoseini-Yazdi et al. observed that imposing 60 minutes of WTR and ATR astigmatic blurs using +3.00 DC cylindrical lenses on healthy young adults led to bi-directional changes in choroidal thickness, with significant thickening in the WTR condition and thinning in ATR condition (Hoseini-Yazdi et al., 2020). In contrast, after imposing WTR and ATR astigmatic blurs on chicks using sphero-cylindrical lenses for a week, Vyas and Kee found significant choroidal thickening in chicks

with ATR treatment but not in the WTR treatment group (Vyas and Kee, 2021). In a recent study, Chan et al. reported bi-directional changes in refractive astigmatism in young adults (n = 19) exposed to only 60 minutes of either WTR or ATR astigmatic blur using +3.00 DC cylindrical lenses. The J0 astigmatism became less positive (from +1.53 DC to +1.28 DC) in the WTR condition and less negative (from −1.33 DC to −0.94 DC) in the ATR condition, suggesting compensatory responses to minimize the astigmatic blur at the outset of the experiment (Chan et al., 2022). Taken together, these findings are consistent with orientation-dependent modulation of astigmatic errors as a component of refractive development.

In our study, when the retinal thickness was obtained by SD-OCT and compared across eyes with different types of astigmatism, WTR astigmats showed a significantly thicker retina in the macula compared to ATR astigmats and the control group. This finding has not been previously reported. In Vyas and Kee's study, no significant difference in retinal thickness measured by A-scan ultrasonography was found between chicks with induced WTR and ATR astigmatism, which agreed with our findings on foveal retinal thickness ($P > 0.05$). However, perifoveal retinal thicknesses were not measured in that chick study (Vyas and Kee, 2021).

4.4.2 Hypothetical Explanations

When examining the regional retinal thickness, *post-hoc* analyses revealed that WTR astigmats had a thicker retina along the horizontal meridian than ATR astigmats and the control group, reaching statistical significance in the inner nasal and outer temporal regions. In this study, all astigmatic subjects were myopic, which tended to have relative peripheral hyperopic defocus (Tabernero et al., 2009; Lin et al., 2010). In a myopic eye with WTR astigmatism, the horizontal line focus is formed closer to the peripheral retina than the vertical line focus, creating a horizontally oriented blur signal at the retinal plane, *i.e.*, each point object becomes an ellipse with a horizontal major axis. Regarding the retinal neural processing pathway, it is well-documented that ganglion and amacrine cells in many vertebrates are orientation-selective, responding more robustly to stimuli with specific orientations (Antinucci and Hindges, 2018; Hubel and Wiesel, 1962). In the peripheral retina, the preferred orientation of these orientation-selective cells appears to lie in parallel to the radial orientation, *e.g.*, cells in the nasal and

temporal retina prefer horizontally oriented stimuli (Bloomfield, 1994; Leventhal and Schall, 1983; Schall et al., 1986). Thus, under conditions of myopic WTR astigmatism, these cells in the peripheral nasal and temporal retina are more likely to receive optical signals of their preferred orientation compared to those in the superior and inferior retina. This orientation-dependent optical blur induced by astigmatism could influence retinal structural changes and lead to meridional differences in retinal thickness.

However, it is worth noting that this hypothesis does not fully explain the lack of significant differences in regional retinal thickness between the ATR and control groups, and the current retrospective study did not track retinal structural changes over time. Therefore, further longitudinal clinical studies or animal research are required to validate the proposed speculation about the effects of astigmatism on retinal thickness. In addition, while on-axis astigmatism dominates in the central visual field, off-axis astigmatism increases in the mid-to-far peripheral regions (Atchison et al., 2006) and largely determines the characteristics of peripheral retinal defocus, consequently affecting peripheral retinal thickness and local eye growth in those regions. However, this study focused solely on on-axis astigmatism and the retinal thickness in the macular region (central 6-mm diameter, ~20˚ of the central visual field). Although peripheral refraction data were not available in the current study, the off-axis astigmatism – which was calculated using data from the study by Atchison et al. (Atchison et al., 2006) – appears to be negligible across the 6-mm central retina (within −0.476 DC for off-axis astigmatism, and within −0.302 DC for relative off-axis astigmatism, see **Supplementary Table S4.1** for details). Thus, off-axis astigmatism likely had a limited impact on the retinal thickness data reported here. Nevertheless, further investigation would be worthwhile to determine whether and how off-axis astigmatism – in terms of its magnitude, axis orientation, and asymmetry – influences the retinal defocus pattern in mid to far peripheral regions and contributes to subsequent retinal structural development. Future studies should incorporate peripheral refractions and would also benefit from wide-field OCT measurements. They would also benefit from a more detailed analysis of retinal images and the inclusion of choroidal thickness data.

Due to the limitations of the cross-sectional design, the causal relationship between astigmatism and retinal thickness cannot be addressed in this study. Given that a thicker retina was also found to be associated with poorer BCDVA, it is possible that participants in different astigmatism groups had different early visual experiences, which may have affected retinal structures and function, and subsequently, the course of emmetropization, resulting in different amounts and types of astigmatism later in life. Supporting this, Popa et al. demonstrated that while chicks could develop astigmatism to partially compensate for the optically imposed cylindrical errors by +4.00DS/-8.00DC lenses, this compensatory astigmatism could not be induced when the retinal circuit was destroyed by intravitreal injection of 20 µL excitotoxin mixture (2 µmol N-methyl-D-aspartate, 0.2 µmol quisqualic acid, 0.2 µmol kainic acid; known to destroy most retinal interneurons, mainly amacrine cells), indicating the necessity of a healthy retina for normal astigmatic compensation (Popa et al., 2020). Further clinical and laboratory studies are required to verify our speculation and to better understand the mechanisms controlling retinal structural changes in astigmatic eyes.

Several studies have reported that astigmatism can influence the optical measurements obtained by OCT (Hwang et al., 2012; Liu et al., 2012), likely due to an ocular magnification effect caused by corneal astigmatism. This optical distortion, due to the magnification factor, may alter scan distance and lead to changes in retinal thickness measurements. Therefore, in the current study, both corneal curvature and refraction were first matched across groups (**Table 4.1**), and were entered into the Spectralis software to minimize the influence of any astigmatism-related magnification factor on OCT measurements. According to the Spectralis technical guidelines, a 0.1 mm difference in corneal radius of curvature would induce only a 0.8% error in lateral measurement (Ctori et al., 2015). Based on the corneal curvature for individual groups in this study, the deviation of transverse magnification – calculated from the mean corneal radius of curvature and from each power meridian – should be less than 1%. Notably, a previous study found only negligible changes (<1 um) in macular thickness measured by OCT immediately after participants wore −3.25 DC astigmatic soft contact lenses to induce WTR and ATR astigmatism (Hwang et al., 2012). Taken together, the potential optical magnification effects of corneal astigmatism on OCT measurements cannot explain the increased retinal thickness in the WTR group of

the current study.

4.4.3 Impact of Astigmatism on Visual Acuity

In this study, BCDVA differed significantly among the WTR, ATR, and control groups, with WTR astigmatic eyes having the poorest BCDVA. In this regard, many studies have reported a reduction in visual acuity with increasing magnitude of astigmatism (Casagrande et al., 2014; Wang et al., 2018); however, the influence of astigmatic axis orientation on visual acuity remains controversial (Casagrande et al., 2014; Remón et al., 2017; Trindade et al., 1997; Mimouni et al., 2017; Ohlendorf et al., 2011; Remón et al., 2014). In contrast to the current study, astigmatism in most previous studies was optically induced by cylindrical lenses (Casagrande et al., 2014; Remón et al., 2017), refractive surgery (Mimouni et al., 2017; Trindade et al., 1997), or computer simulations (Ohlendorf et al., 2011; Remón et al., 2014), and these varying study methodologies may have led to varying findings. For instance, the neural response to astigmatic blur could be influenced by the magnitude and axis orientation of the imposed blur or the subjects' natural astigmatism, as well as the types of stimuli (*e.g.*, optical defocus *vs.* simulated blur) (Read et al., 2014). Notably, a population-based study in China (Wang et al., 2018) observed a higher prevalence of visual impairment (defined as BCDVA $\leq$ 0.7) in children with WTR astigmatism when the astigmatism was $\geq$ 0.75 D, which is in agreement with our findings in a similar study population (*i.e.*, Chinese with naturally occurring astigmatism).

Astigmatism during childhood may result in a form of meridian-specific visual impairment, termed "*meridional amblyopia*" (Dobson et al., 2003; Mitchell et al., 1973), which arises from abnormal development in the primary visual cortex and can lead to visual deficits across a range of visual functions (Freeman et al., 1972; Harvey et al., 2007; Mitchell et al., 1973). Several studies have suggested subtle increases in the retinal thickness of amblyopic eyes (BCDVA > 0.3 LogMAR) (Huynh et al., 2009; Li et al., 2015). Indeed, children born with WTR astigmatism – the predominant form in Chinese infants (Edwards, 1991; Huo et al., 2021; S.-J. Yu et al., 2017) – are prone to developing amblyopia if it is not corrected during childhood (Harvey et al., 2007). Although none of the participants in the current study reported amblyopia, whether the increased retinal thickness and poorer BCDVA

observed in our WTR group were by-products of amblyopia remains unanswered. Notably, despite the significant differences in BCDVA across groups, all participants had BCDVA better than 0.10 LogMAR, and the difference across groups ranged only from 1 to 2 letters, which may not be clinically significant.

Correlation analysis revealed that BCDVA was positively associated with retinal thickness after adjusting for age, sex, and AXL, with statistical significance reached in the whole macular and the outer rings of the measured regions. In this context, several studies have reported associations between macular retinal thickness and visual acuity, but the direction of these associations has varied (Flores-Moreno et al., 2013; Lee et al., 2021; Poh et al., 2020; Sandberg et al., 2005; Scott et al., 2009). In amblyopic eyes, increased macular thickness has been associated with poorer visual acuity (Huynh et al., 2009). Yen et al. (Yen et al., 2004) suggested that amblyopia might disrupt the postnatal development of the macula, including the normal decline in the number of retinal ganglion cells (Provis et al., 1985a) and axons (Provis et al., 1985b), resulting in a thicker macula compared to non-amblyopic eyes. However, other studies have observed a reverse association in normal emmetropic (Lee et al., 2021; Poh et al., 2020) and myopic (Flores-Moreno et al., 2013) eyes, with a thicker retina corresponding to better visual acuity. Presumably, a thicker macula might reflect more densely packed retinal neurons (*e.g.*, photoreceptors, ganglion cells), which could increase the Nyquist frequency and thereby improve visual acuity. However, neither of these explanations can fully explain the findings of the current study.

A noticeable difference in this study, compared to previous reports, is that we stratified participants into WTR, ATR, and non-astigmatic control groups. It should be noted that the inverse relationship between retinal thickness and BCDVA only existed in the WTR group, but not in the ATR or control groups in the stratification analyses (**Supplementary Table S4.2**), suggesting that the relationship between RTs and BCDVA may be modulated by astigmatism. Further studies, incorporating a more detailed analysis of individual retinal layers and multifocal electrophysiological recordings, are needed to investigate the origin of observed retinal thickness changes and their association with functional changes. Additionally, this study only included participants with BCDVA better than 0.1 LogMAR, whereas other studies (Flores-Moreno et al., 2013; Lee et al., 2021; Poh et al., 2020) recruited participants with a broader

range of BCDVA (up to 1.0 LogMAR). Thus, the insignificant correlations in the ATR and control groups may be due to the restricted BCDVA range in this study.

4.4.4 Limitations

This is the first study to compare retinal thickness and BCDVA among different types of astigmatism (WTR, ATR, and Controls) while closely matching participants' other characteristics in a Chinese adult population. Our findings suggest that both the magnitude and axis orientation of astigmatism may influence retinal development, highlighting the importance of considering astigmatism in the clinical management of refractive errors and ocular diseases related to retinal abnormalities, as well as in the interpretation of OCT data.

However, this study has several limitations. **First**, this is not a population-based study, as participants were drawn from an existing clinical patient base retrospectively, potentially limiting the generalizability of the findings. The relatively limited sample size within each group may have reduced the study's power to detect the differences in RT and BCDVA among the three types of astigmatism. The limited number of participants, particularly in the ATR (n = 25) and control groups (n = 35), may partly explain why a significant correlation between retinal thickness and BCDVA was only found in the WTR group (n = 41). **Second**, the cross-sectional design of this study did not establish a causal relationship between astigmatism and retinal thickness changes. Longitudinal studies are necessary to explore how axis orientation of astigmatism influences the development of retinal structures and visual acuity over time. **Third**, the manual correction for automatic segmentation may introduce some bias in retinal thickness measurements. Although the ICCs between RT measurements with and without manual correction indicated good reliability, future studies should consider employing a second independent evaluator or a more robust automatic segmentation approach to minimize measurement bias. **Lastly**, the participants' history of refractive correction during childhood was unavailable in this retrospective study, and we cannot rule out the possibility that the reduced visual acuity could be due to abnormal visual development during childhood. A pinhole visual acuity test, which could help distinguish between optical and neural contributions to the reduced visual acuity, was not conducted in this study.

Including higher-order aberration measurements could have also provided additional insights into the underlying causes of the reduced visual acuity observed in eyes with WTR astigmatism.

4.5 Conclusions

Greater retinal thickness and poorer best-corrected distance visual acuity were found in eyes with WTR astigmatism, compared to those with ATR astigmatism and non-astigmatic control groups in Chinese adults. These findings suggest that both the magnitude and axis orientation of astigmatism can significantly influence retinal structure and function. However, the underlying mechanism has yet to be investigated. Further longitudinal studies are particularly needed to explore retinal structural and functional changes in astigmatic children, which may provide insights for improving the clinical management of refractive errors and retinal abnormalities.

4.6 Supplementary Materials

Supplementary Table S4.1 Estimation of Off-Axis Astigmatism and Its Asymmetry along the Horizontal Visual Field

In this study, retinal thickness was measured using the ETDRS grid, which includes a 6-mm-diameter (~20°×20°) scan field. However, peripheral refraction was not measured, limiting our direct assessment of how peripheral retinal defocus may influence the retinal thickness along the horizontal visual field. To estimate the potential influence of off-axis astigmatism on retinal defocus, we utilized data from a comparable group of −4 D myopic adults reported by Atchison, Pritchard, and Schmid (Atchison et al., 2006). Using the formulae provided for changes in the J0 and J45 astigmatic components, we calculated the relative off-axis astigmatism across the visual field.

The table below provides the relative off-axis astigmatism data specifically along the horizontal visual field, as our study showed significant retinal thickness asymmetry only along this meridian. As shown, the relative off-axis astigmatism were −0.105 DC and 0.008 DC at ±5° eccentricity of nasal and temporal fields, respectively, and −0.302 DC and −0.054 DC at ±10° eccentricity of nasal and temporal fields, respectively. These calculations suggest minimal off-axis astigmatism within the central 6-mm diameter of the retina, supporting that off-axis astigmatism likely had a limited impact on our findings.

Visual Field	*Temporal*					*Nasal*			
	-30°	*-20°*	*-10°*	*-5°*	*0°*	*5°*	*10°*	*20°*	*30°*
J0 (D)*	-0.570	-0.247	-0.084	-0.062	-0.081	-0.139	-0.238	-0.555	-1.032
J45 (D)*	-0.167	-0.122	-0.077	-0.055	-0.032	-0.010	0.013	0.058	0.103
Astigmatism (D)*	-1.187	-0.550	-0.227	-0.165	-0.173	-0.279	-0.476	-1.115	-2.073
Relative off-axis astigmatism (D)	-1.014	-0.377	-0.054	0.008	-	-0.105	-0.302	-0.942	-1.900

* Estimated astigmatism along the horizontal field of subjects with around −4D spherical equivalence refraction and low astigmatism (Atchison et al., 2006).

$$J0_{Eccentricity} = -0.0008 \times (Eccentricity + 4.812)^2 - 0.062 \quad \text{..... (Eq.1)}$$

$$J45_{Eccentricity} = 0.0045 \times Eccentricity - 0.032 \quad \text{..... (Eq.2)}$$

$$CYL_{Eccentricity} = -2 \times \sqrt{J0^2_{Eccentricity} + J45^2_{Eccentricity}} \quad \text{..... (Eq.3)}$$

$$CYL_{relative} = CYL_{Eccentricity} - CYL_{0^\circ} \quad \text{..... (Eq.4)}$$

where *Eccentricity* refers to the angle of the horizontal visual field. Eq.1 and Eq.2 are the polynomial equations derived for J0 and J45 astigmatic components in the −4D myopic group. Eq.3 converts astigmatism from J0 and J45 astigmatic components back to negative-cylinder form, according to Thibos, Wheeler and Horner (Thibos et al., 1997). The relative off-axis astigmatism is calculated by subtracting on-axis astigmatism from off-axis astigmatism at different eccentricities, where a minus value indicates a greater cylindrical power in off-axis astigmatism than in on-axis astigmatism.

	WTR (n = 41)		ATR (n = 25)		Controls (n = 35)	
	r	*P*	*r*	*P*	*r*	*P*
Retinal Thickness (um, in ETDRS grid)						
Whole Macula	**0.338**	**0.038**	-0.101	0.655	0.116	0.528
Centre-subfield	0.055	0.741	0.041	0.856	0.050	0.788
Inner-Nasal	0.276	0.094	-0.005	0.985	0.074	0.687
Outer-Nasal	**0.485**	**0.002**	-0.041	0.857	0.050	0.787
Inner-Superior	0.291	0.076	-0.244	0.274	0.070	0.705
Outer-Superior	**0.346**	**0.033**	-0.126	0.576	0.189	0.299
Inner-Temporal	0.266	0.107	-0.094	0.678	-0.016	0.932
Outer-Temporal	**0.340**	**0.041**	0.030	0.896	0.147	0.423
Inner-Inferior	0.285	0.083	-0.077	0.734	0.026	0.890
Outer-Inferior	**0.369**	**0.023**	-0.079	0.727	0.106	0.564

Supplementary Table S4.2 Stratification Analyses for the Correlation between Retinal Thickness and BCDVA in WTR, ATR, and Control Groups

Note: The *P* value was calculated using partial correlation analyses between BCDVA and retinal thickness, after adjusting for age, sex, and axial length. A $P < 0.05$ indicates a statistically significant correlation. WTR, with-the-rule. ATR, against-the-rule.

Chapter 5

Impact of Astigmatism on Predicting Axial Elongation

A Two-Centre Machine-Learning Study in School-age Children

5.1 Introduction

Myopia has become a global concern for public health, with its growing prevalence and increased risk of ocular disease (Holden et al., 2016; Baird et al., 2020). This concern is particularly pressing in school-age children due to its early onset (Chen et al., 2023) and progressive nature (Breslin et al., 2013; Chua et al., 2016). Axial length (AXL) is a critical biometric parameter closely related to the development of myopia and associated pathologies (Brennan et al., 2021). Studies have shown that children who become myopic exhibit significantly more axial elongation before and after the onset of myopia (Mutti et al., 2007; Rozema et al., 2019). The excessive axial elongation in myopic eyes further promotes mechanical stretching and distortion of the ocular posterior globe (Ohno-Matsui et al., 2021), potentially leading to irreversible visual impairment and even blindness (World Health Organization, 2015; Yan et al., 2023, 2024). Therefore, it is vital to assess and monitor axial elongation in the management of myopia, particularly for school-age children (Gifford et al., 2019).

However, accurately predicting individual axial elongation remains challenging in clinical practice, possibly due to nonlinear growth trajectories and significant inter-individual variability in ocular structural growth (Chamberlain et al., 2021; Cruickshank and Logan, 2018; Tideman et al., 2018). Numerous studies have highlighted various factors associated with axial elongation, including age (Breslin et al., 2013; S. Zhang et al., 2023), sex (Rozema et al., 2019), ethnicity (Tideman et al., 2019; Truckenbrod et al., 2021), body height (Kearney et al., 2020; Wang et al., 2011), baseline AXL (Lee et al., 2020; Du et al., 2021), baseline SER (Breslin et al., 2013; Jiang et al., 2023; Rozema et al., 2019), corneal curvature (Scheiman et al., 2016), and some environmental factors (Tideman et al., 2019; Ulaganathan et al., 2019). These variables underscore the complexity of predicting axial elongation.

In this context, machine learning (ML) offers a robust approach to navigating the complexities of nonlinear data and individual heterogeneity, by analyzing high-dimensional data in a nonlinear and highly interactive manner (Obermeyer and Emanuel, 2016). ML refers to a subset of artificial intelligence that enables computer systems to learn patterns from input data and make predictions or decisions without being explicitly programmed (El Naqa and Murphy, 2015). ML is an ideal tool for developing prediction models for axial elongation, and its capacity and feasibility have been supported by previous ML-based models for predicting refractive development (Guo et al., 2022; Li et al., 2022; Lin et al., 2018).

Regarding axial elongation, most existing models are developed from cross-sectional studies and are primarily designed to estimate current AXL based on other ocular variables, thus serving as an alternative to direct axial measurement (Kim et al., 2019; Morgan et al., 2020; Tang et al., 2020; Dutt et al., 2022; Queirós et al., 2022; Lingham et al., 2024). However, these models cannot forecast future axial measurements. To our knowledge, only one study has developed a prediction model for longitudinal axial elongation in a general population; however, it was limited by a small sample size (n = 179) and lacked external validation (Zhu et al., 2023). Therefore, a significant research gap remains in developing reliable prediction models for longitudinal axial elongation in a representative cohort, as well as in determining the key factors influencing the prediction of axial elongation.

To address this research gap, we conducted a machine-learning study using a large longitudinal cohort of Chinese school-age children from Hong Kong and Tianjin, China. The objectives of this study include: **1)** to develop machine-learning algorithms using baseline variables to predict future axial elongation in children; and **2)** to evaluate the influential factors for predicting axial elongation, in particular astigmatic characteristics (magnitude and axis orientation). This research can develop advanced prediction models for the early identification of children at high risk for progressive axial myopia, and deepen our understanding of the factors associated with axial elongation.

5.2 Methods

5.2.1 Study Population and Dataset Preparation

The overall study design is illustrated in **Figure 5.1**. This study utilized data from the ***Tianjin and Hong Kong Research in Vision and Eye (THRiVE)*** database, which comprises a two-centre longitudinal cohort of school-age children from Tianjin (northern China) and Hong Kong (southern China). This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Tianjin Medical University Eye Hospital and The Hong Kong Polytechnic University. Written informed consent was obtained from the parents or legal guardians of all participating children.

Data from Tianjin (***Centre 1***) were collected as part of a school-based cohort study involving annual vision screenings conducted at seven primary and secondary schools in Tianjin, China, from 2018 to 2022. All participating children underwent non-cycloplegic autorefraction and AXL measurements performed by licensed optometrists and ophthalmologists. The detailed methodology of the vision screening is previously described in the **Study I** (**Chapter 3**). In brief, AXL was measured using Lenstar 900 biometers (Haag-Streit, Switzerland), and autorefraction was measured using either Spot Vision Screener (Welch Allyn, USA) or KR-800 autorefractor (Topcon, Japan).

Data from Hong Kong (***Centre 2***) were obtained from a clinic-based cohort study at the PolyU Optometry Clinic, involving subjects who attended the clinic between 2010 and 2021, with longitudinal history records. Non-cycloplegic autorefraction and AXL measurements were performed according to the standard clinic protocols by registered optometrists or ophthalmologists. In brief, AXL was measured using an IOL Master (Zeiss, Germany) or AL-Scan (Nidek, Japan), and autorefraction was carried out using either ARK-510A (Nidek, Japan) or KR-800 (Topcon, Japan).

Longitudinal data were obtained from the ***THRiVE*** database, focusing on children aged 5 to 16 years at the time of their first examination, with at least three visit records. The interval between the first two visits was flexible, as these data were used to calculate the previous progression rates of axial elongation

(***PRAXL***, calculated as follows), which served as one of the predictors in the models. In contrast, the follow-up intervals between the second and subsequent visits were standardized to one, two, or three years. Participants who reported a history of orthokeratology, atropine use, or other myopia control interventions were excluded. Only data from the right eye were analyzed.

$$\boldsymbol{PRAXL} = {}^{\Delta AXL_{(2nd-1st)}}\Big/_{\Delta Age_{(2nd-1st)}}$$

In the equations, $\Delta AXL_{(2nd-1st)}$ represents the change in axial length between the first and second visits, while $\Delta Age_{(2nd-1st)}$ refers to the age interval (in years) between the first and second visits. The calculation provides a standardized measure of axial elongation per year across individuals with different intervals between visits before the prediction time points.

5.2.2 Model Development

Baseline variables, including age, sex, SER, AXL, refractive astigmatism, and the previous progression rate of AXL (***PRAXL***), were used as predictor variables for modelling. The calculation of PRAXL is detailed in **Figure 5.1**. Based on these predictors, two predictive models were developed: 1) **AXL-Estimator**: to predict future axial length; and 2) **AXL-Classifier**: to identify children at risk of progressive myopia, over the next three years (with each year as a predictive time point). Progressive myopia was defined as axial elongation over 0.30 mm/year (Lingham et al., 2022).

ML Algorithm. The random forest algorithm was employed to develop the predictive models (both AXL-Estimator and AXL-Classifier). Random forest is an ensemble learning method that constructs multiple decision trees and can be applied to both classification and regression tasks. Studies have shown that the random forest algorithm performs comparably or even better than other ML algorithms in most tasks (Fernández-Delgado et al., 2014; Grinsztajn et al., 2022; Huang et al., 2021).

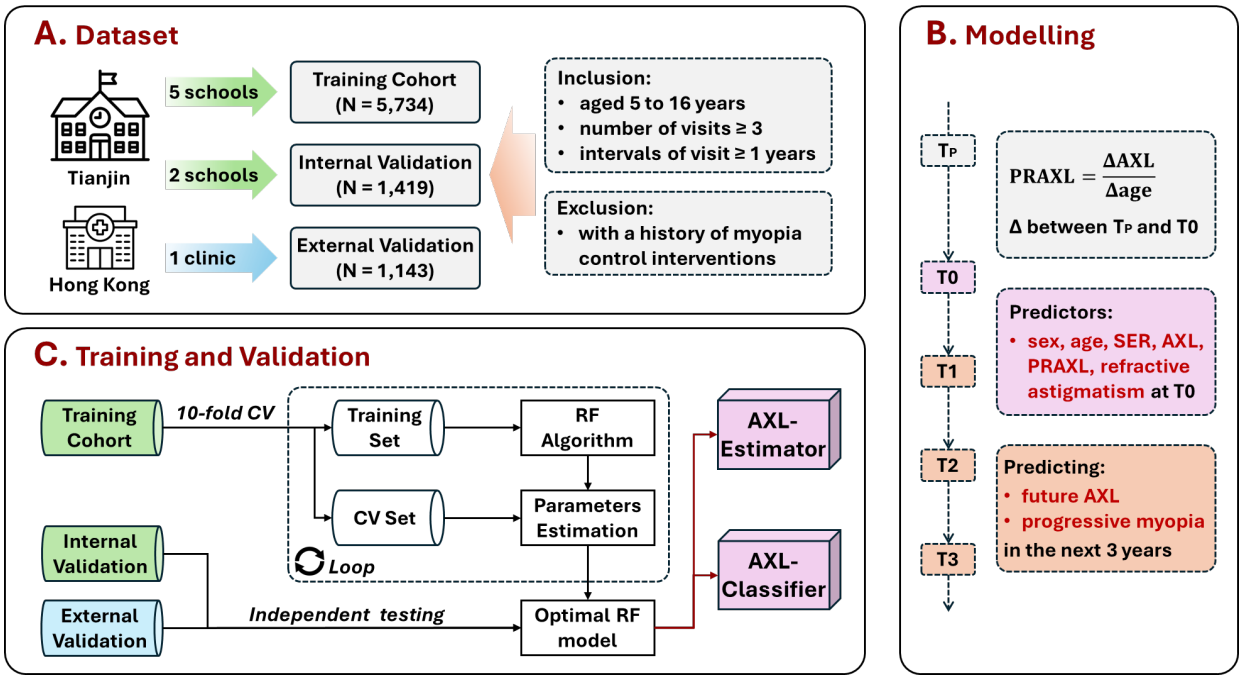

Figure 5.1 Study Design of This Machine-Learning Study

Note: SER, spherical-equivalent refraction. AXL, axial length. CV, cross-validation. RF, random forest.

(**A**) Two-centre longitudinal cohorts of school-age children were collected from Tianjin and Hong Kong. Only individuals aged from 5 to 16 years, with at least 3 visits and over 1-year intervals, were included. **(B)** Baseline variables, including age, sex, SER, astigmatism, AXL, and previous progression rate of AXL (PRAXL), were used as predictor variables for modelling to predict the future AXL ("AXL-Estimator") and to identify children at risk of progressive myopia ("AXL-Classifier") in the subsequent three years. **(C)** Ten-fold CV and RF methods were used to develop prediction algorithms. Seven schools participated in the Tianjin Centre, and data from five of them were used as the training dataset. Data from five schools in Tianjin were used as the training cohort, while data from the two remaining schools in Tianjin were used for internal validation. All data from Hong Kong served as external validation.

Training Process. Seven schools participated in the Tianjin Centre of the *THRiVE* database. Among these, data from five schools were used as the training dataset (n = 5,734), while data from the remaining two schools were used for internal validation (n = 1,419). All available data from the Hong Kong Centre served as external validation (n = 1,143).

Ten-fold cross-validation was performed on the training cohort, and a grid-search strategy was used to determine the optimal hyperparameters, including *n-estimators* (the number of trees in forest model), *min_sample_leaf* (the minimum number of samples in a terminal node), *max_depth* (the maximum depth of the trees), and *criterion* (categorical hyperparameter, the splitting rule).

The model's performance in the training cohort was assessed based on all predictions from testing samples in each fold during the cross-validation. The final predictive models (AXL-Estimator and AXL-Classifier) were then trained on the entire training dataset using the best hyperparameters, and tested on the internal and external validation datasets, respectively. Model development was conducted using Python (v3.7; https://www.python.org/) with the Scikit-learn package (v1.3; https://www.scikit-learn.org/).

Evaluation Metrics. The performance of the AXL-Estimator was evaluated using mean absolute error (MAE), root mean square error (RMSE), and the coefficient of determination (R^2) between actual AXL and predicted AXL values. Additionally, a Bland-Altman plot was used to evaluate whether the ML-based AXL prediction are sufficiently accurate and unbiased.

The performance of the AXL-Classifier was evaluated using the area under the receiver operating characteristic (ROC) curve (AUROC). An AUROC of 0.50–0.69 was considered mild, 0.70–0.89 was moderate, and 0.90–1.00 was good performance (Li et al., 2021). The accuracy, sensitivity, and specificity were further calculated from the ROC curve according to the cut-off value that maximizes the Youden index.

5.2.3 Evaluation of Influential Factors

Feature Importance. The contribution of predictor variables in the AXL-Estimator and AXL-Classifier models was evaluated using the Gini importance measure, which was calculated as the total reduction in the criterion brought by each predictor variable (Kuhn and Johnson, 2013). While the Gini importance cannot be interpreted in absolute terms, it provides a relative comparison and ranking of the contribution of each predictor variable.

Stratification Analysis. To further explore the influence of demographic and biometric factors on predicting axial elongation, the prediction performance of our models was separately evaluated across different sub-cohorts. If a significant reduction in predictive performance was observed in specific sub-cohorts, it may suggest that these factors have a considerable influence on the prediction of axial elongation. The sub-cohorts were stratified based on:

- Baseline Age
    - Younger: aged 5–10 years
    - Older: aged 11–16 years
- Baseline SER
    - Hyperopia: SER > +0.75 D
    - Emmetropia (Pre-myopia): SER ≤ +0.75 D and > −0.50 D
    - Low Myopia: SER ≤ −0.50 D and > −6.00 D
    - High Myopia: SER ≤ −6.00 D
- Baseline Magnitude of Astigmatism
    - None: cylindrical power > −0.50 DC
    - Low: cylindrical power ≤ −0.50 DC and > −1.50 DC
    - Medium: cylindrical power ≤ −1.50 DC and > −3.00 DC
    - High: cylindrical power ≤ −3.00 DC
- Baseline Axis Orientation of Astigmatism (for astigmatic eyes)
    - WTR: cylindrical axes between 0°–30° or 150°–180°

- OBL: cylindrical axes between 31°–59° or 121°–149°
- ATR: cylindrical axes between 60°–120°

5.2.4 Statistical Analysis

Statistical analyses were performed using SPSS Statistics (v27.0, IBM Corp., USA) and R (v4.3, http://www.R-project.org). Continuous variables were expressed as mean ± SD or median [IQR], and categorical variables were presented as counts and percentages. Differences in demographic and biometric variables across training and validation datasets, as well as the predictive performance of AXL-Estimator across stratified sub-cohorts, were compared using the ANOVA test. For the AXL-Classifier, paired and unpaired ROC curves across stratified sub-cohorts were compared using the DeLong method (DeLong et al., 1988). A two-tailed $P < 0.05$ was considered statistically significant.

5.3 Results

5.3.1 Characteristics of Study Population

The demographics and biometric characteristics of the study population are detailed in **Table 5.1**. A total of 31,380 longitudinal eye examination records from 8,296 children in the ***THRiVE*** database were included. Of these, 5,734 children from Centre 1 were used as the training cohort, 1,419 remaining children from Centre 1 were used for internal validation, and 1,143 children from Centre 2 were used for external validation.

The average age at the first visit was 11.6 ± 2.2 years (range, 6.51 to 15.99 years) for the internal validation cohort and 10.41 ± 2.4 years (range, 6.00 to 15.95 years) for the external validation cohort. In the internal validation cohort, the SER and AXL at the first visit were −1.30 ± 1.79 D (range, −8.25 to 5.37 D) and 24.23 ± 1.13 mm (range, 21.12 to 28.36 mm), respectively. As for the external validation cohort, the SER was −0.53 ± 1.99 D (range, −8.25 to 6.12 D), and AXL was 23.58 ± 1.18 mm (range, 19.91 to 28.12 mm). These broad ranges of study characteristics for internal and external validations allowed for a comprehensive evaluation of our models.

Characteristics	Training Cohort	Internal Validation	External Validation
Data source	Tianjin	Tianjin	Hong Kong
Number of children, n	5,734	1,419	1,143
Number of records, n	21,789	5,734	3,857
Sex			
Female, n (%)	2,664 (46.5)	680 (47.9)	595 (52.1)
Male, n (%)	3,070 (53.5)	739 (52.1)	548 (47.9)
Follow-up, year	3.20±0.70 (2.00, 4.00)	3.02±0.58 (2.00, 4.00)	3.46±0.53 (1.12, 4.09)
Age at first visit, year	10.49±2.39 (6.06, 16.00)	11.6±2.2 (6.51, 15.99)	10.41±2.4 (6.00, 15.95)
SER at first visit, D	-0.55±2.00 (-8.50, 6.00)	-1.30±1.79 (-8.25, 5.37)	-0.53±1.99 (-8.25, 6.12)
AXL at first visit, mm	23.62±1.25 (20.19, 27.99)	24.23±1.13 (21.12, 28.36)	23.58±1.18 (19.91, 28.12)
CYL at first visit, D	-0.87±0.76 (-5.51, 0.00)	-0.79±0.64 (-6.50, 0.00)	-0.86±0.75 (-7.50, 0.00)
Spherical equivalent refraction at first visit			
Hyperopia, n (%)	1,325 (23.1)	283 (20.0)	249 (21.8)
Emmetropia, n (%)	1,947 (33.9)	452 (31.9)	386 (33.8)
Myopia, n (%)	2,462 (42.9)	684 (48.2)	508 (44.4)
Astigmatic magnitude at first visit			
None, n (%)	1,876 (32.7)	452 (31.8)	363 (31.7)
Low, n (%)	2,649 (46.2)	793 (55.9)	566 (49.5)
High, n (%)	1,209 (21.1)	174 (12.2)	214 (18.8)
Astigmatic axis orientation at first visit			
With-the-rule, n (%)	3,303 (85.6)	789 (81.6)	658 (84.4)
Oblique, n (%)	280 (7.3)	91 (9.4)	60 (7.7)
Against-the-rule, n (%)	275 (7.1)	87 (9.0)	62 (8.0)

Table 5.1 Demographic and Biometric Characteristics of Study Population

Note: SER, spherical-equivalent refraction. AXL, axial length. CYL, cylindrical power.

5.3.2 Model Performance

AXL-Estimator. The predictive performance of the AXL-Estimator is shown in **Figure 5.2** and **Table 5.2**. Our algorithm achieved high accuracy in predicting future AXL over the following three years. In the training cohort with ten-fold cross-validation, the AXL-Estimator achieved MAEs of 0.126 mm, 0.222 mm, and 0.292 mm for one-, two-, and three-year predictions, respectively.

For internal and external validations, the AXL-Estimator exhibited excellent performance and remarkable robustness, with one-year MAEs ranging from 0.136 to 0.146 mm, two-year MAEs from 0.232 to 0.277 mm, and three-year MAEs from 0.299 to 0.310 mm. The corresponding R^2 values for these AXL estimations ranged from 0.884 to 0.985, indicating a good fit of the AXL-Estimator. The Bland-Altman plot between the actual and predicted AXL in the validation cohorts (internal + external) suggested a good agreement, with a low mean difference (one-year prediction, −0.079 mm; two-year prediction, −0.011 mm; three-year prediction, 0.049 mm) and narrow 95% limits of agreement (**Figure 5.2**).

AXL-Classifier. The predictive performance of the AXL-Classifier is shown in **Figure 5.3** and **Table 5.3**. Our algorithm yielded significant diagnostic performance in predicting children at risk of progressive myopia across all datasets at each predictive time point. In the training cohort with ten-fold cross-validation, the AXL-Classifier achieved AUROCs of 0.914 (95%CI, 0.905 to 0.923), 0.949 (95%CI, 0.943 to 0.955), and 0.943 (95%CI, 0.928 to 0.956) for one-, two-, and three-year predictions, respectively.

For internal and external validations, the AUROCs for one-year predictions ranged from 0.893 to 0.895, for two-year predictions from 0.938 to 0.974, and for three-year predictions from 0.926 to 0.959 (all $P < 0.001$). No significant difference in AUROCs was observed across the training and validation cohorts over all prediction time points (all $P \geq 0.145$), suggesting the considerable robustness of the AXL-Classifier.

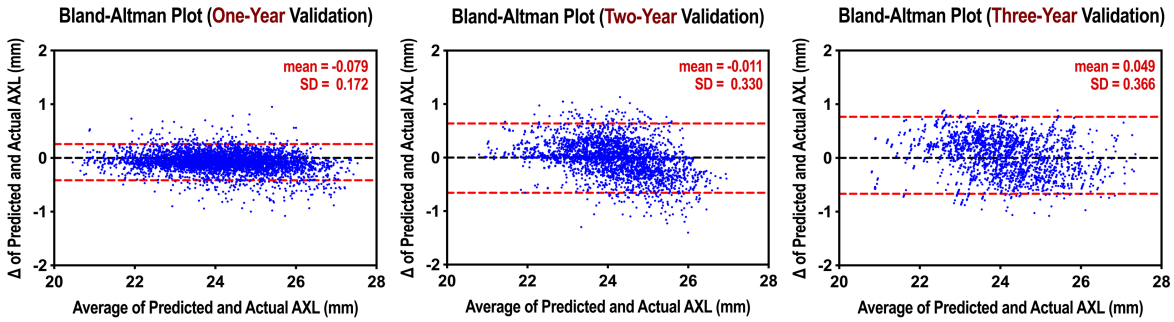

Figure 5.2 Prediction Performance of AXL-Estimator

Note: The performance of the AXL-Estimator was evaluated using a Bland-Altman plot between actual and predicted AXL over up-to-3-year validations (internal + external).

	Metric	Prediction at Given Time Points, year(s)		
		1-year	2-year	3-year
Cross-validation on the training cohort	R^2	0.985	0.946	0.914
	MAE	0.126	0.222	0.292
	RMSE	0.156	0.263	0.344
Internal validation	R^2	0.964	0.894	0.884
	MAE	0.146	0.277	0.299
	RMSE	0.210	0.326	0.367
External validation	R^2	0.977	0.909	0.901
	MAE	0.136	0.232	0.310
	RMSE	0.185	0.341	0.369

Table 5.2 Prediction Performance of AXL-Estimator

Note: The predictive performance for AXL-Estimator was evaluated by comparing the actual and predicted future AXL values at given time points. R^2, coefficient of determination. MAE, mean absolute error. RMSE, root mean square error.

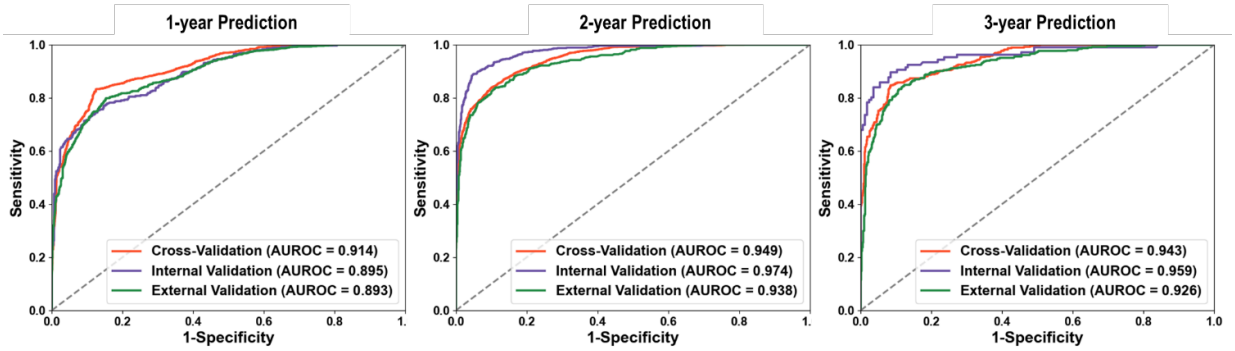

Figure 5.3 Prediction Performance of AXL-Classifier

Note: The performance of the AXL-Classifier was evaluated using the area under the receiver operating characteristic (ROC) curve (AUROC).

	Metric	Prediction at Given Time Points, year(s)		
		1-year	2-year	3-year
Cross-validation on the training cohort	AUROC	0.914 (0.905, 0.923)	0.949 (0.943, 0.955)	0.943 (0.928, 0.956)
	Sensitivity	0.833 (0.812, 0.852)	0.837 (0.821, 0.852)	0.848 (0.808, 0.882)
	Specificity	0.875 (0.861, 0.887)	0.901 (0.890, 0.911)	0.915 (0.892, 0.935)
Internal validation	AUROC	0.895 (0.874, 0.913)	0.974 (0.965, 0.982)	0.959 (0.928, 0.979)
	Sensitivity	0.772 (0.723, 0.813)	0.891 (0.862, 0.915)	0.840 (0.756, 0.904)
	Specificity	0.853 (0.823, 0.880)	0.949 (0.932, 0.963)	0.964 (0.923, 0.987)
External validation	AUROC	0.893 (0.880, 0.906)	0.938 (0.925, 0.950)	0.926 (0.909, 0.941)
	Sensitivity	0.780 (0.748, 0.809)	0.830 (0.797, 0.860)	0.833 (0.792, 0.869)
	Specificity	0.856 (0.837, 0.874)	0.894 (0.874, 0.913)	0.886 (0.860, 0.909)

Table 5.3 Prediction Performance of AXL-Classifier

Note: The sensitivity and specificity of prediction models were calculated from the receiver operating characteristic (ROC) curve according to the cut-off value that maximizes the Youden index.

5.3.3 Feature Importance

AXL-Estimator. Figure 5.4A illustrates the predictive importance of each predictor variable for the AXL-Estimator at each time point. Overall, the baseline AXL, PRAXL, and SER were the top three most influential variables for predicting future axial elongation. For one-year prediction, baseline AXL had the highest importance (43.88%), followed by SER (19.66%) and PRAXL (18.21%). In contrast, for two- and three-year predictions, baseline PRAXL became the most important predictor (27.76% and 28.23%, respectively), closely followed by SER (26.57% and 22.86%) and AXL (21.32% and 19.95%). Interestingly, the importance of baseline age increased with the longer predictive time frames, rising from 7.97% for one-year, to 12.07% for two-year, and 15.40% for three-year predictions. However, the importance of astigmatic magnitude (range, 6.66% to 8.32%), astigmatic axis orientation (range, 1.87% to 2.34%), and sex (range, 1.41% to 2.89%) remained relatively low throughout the three years.

AXL-Classifier. Figure 5.4B shows the importance of predictor variables for the AXL-Classifier at each time point. For one-year prediction, baseline age (22.36%), PRAXL (21.11%), AXL (19.73%), and SER (18.01%) were the most important predictors for differentiating children at high risk of progressive myopia. For two- and three-year predictions, PRAXL's contribution significantly increased (40.76% and 39.43%, respectively), followed by age (18.63% and 16.41%), AXL (15.66% and 15.75%), and SER (12.52% and 12.77%). Notably, baseline age had a greater impact on the AXL-Classifier than on the AXL-Estimator. This trend was also observed for astigmatic magnitude, which had a higher influence on the AXL-Classifier (range, 9.53% to 13.10%) than on the AXL-Estimator.

5.3.4 Stratification Analysis

Figure 5.5 shows the stratification analysis results for the AXL-Estimator and AXL-Classifier, categorized by baseline age, SER, astigmatic magnitude, and axis orientation.

Baseline Age. There was no significant difference in the predictive performance of both the AXL-Estimator and AXL-Classifier between younger and older children (all $P \geq 0.131$).

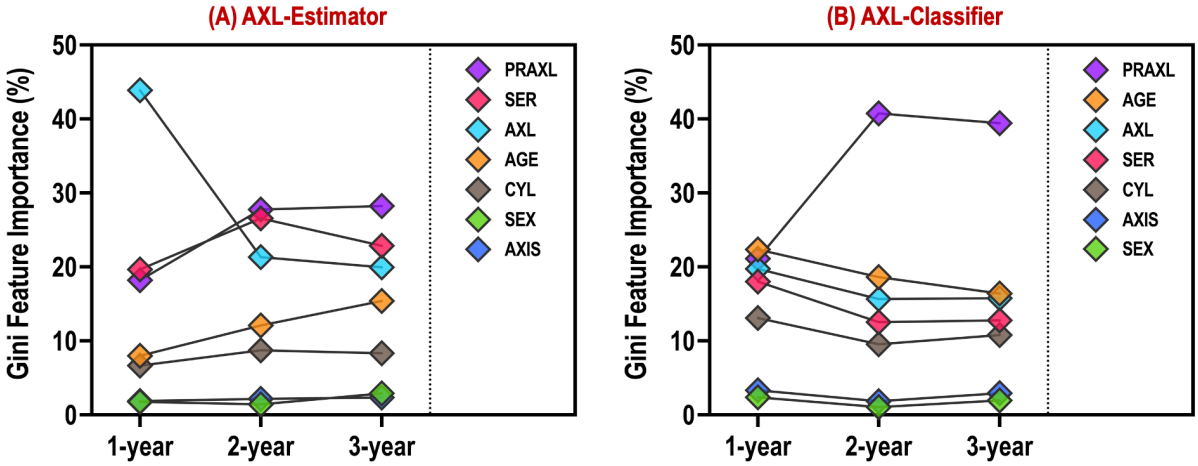

Figure 5.4 Feature Importance of Predictor Variables in AXL-Estimator and AXL-Classifier

Note. The feature importance of **(A)** AXL-Estimator and **(B)** AXL-Classifier over up to three-year predictions. Feature importance was calculated using Gini criteria in the random forest models.

PRAXL, the previous progression rate of axial length. SER, spherical-equivalent refraction. AXL, axial length. CYL, magnitude of refractive astigmatism. AXIS, axis orientation of refractive astigmatism.

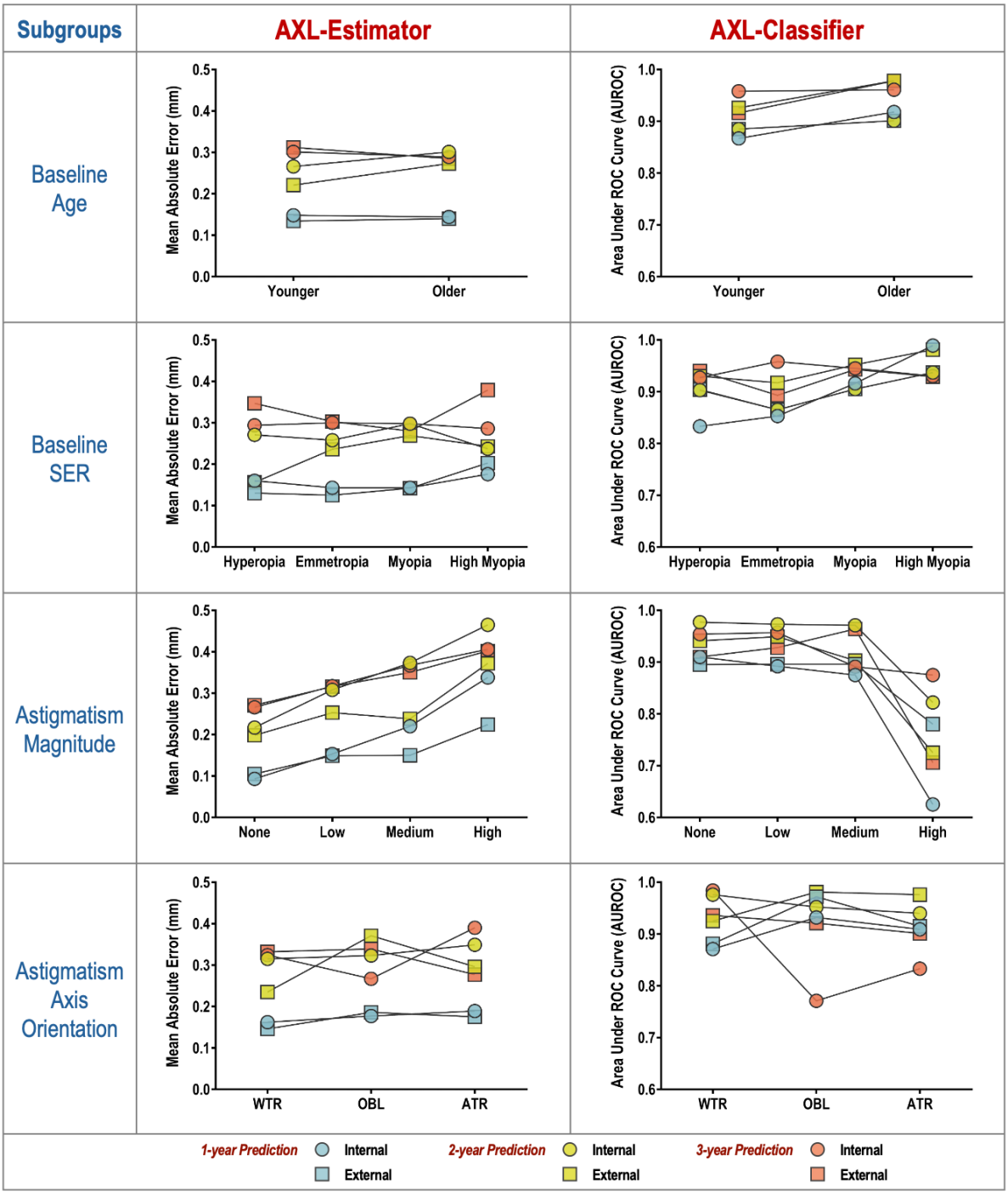

Figure 5.5 Stratification Analyses of AXL-Estimator and AXL-Classifier

Note: The prediction performance of AXL-Estimator (*left*) and AXL-Classifier (*right*) was separately evaluated in different sub-cohorts stratified by baseline age (*first row*), SER (*second row*), astigmatic magnitude (*third row*) and axis orientation (*fourth row*).

Baseline SER. The AXL-Estimator demonstrated stable predictive performance across different SER categories (*i.e.*, hyperopia *vs.* emmetropia *vs.* low myopia *vs.* high myopia), with no statistically significant differences in MAEs (all $P \geq 0.352$). Similarly, the AXL-Classifier achieved significant diagnostic performance across all SER sub-cohorts (AUROCs = 0.833 to 0.989; all $P < 0.001$), suggesting that our models' performance is robust across varying baseline SER.

Baseline Magnitude of Astigmatism. The AXL-Estimator showed a consistently increased MAE when predicting children with a higher magnitude of astigmatism in both internal and external validations, indicating that the presence of astigmatism, particularly at higher magnitudes, may negatively affect the accuracy of predicting future AXL. A similar trend was observed in the AXL-Classifier, where the AUROC significantly decreased in the sub-cohort of high astigmatism, leading to insignificant diagnostic efficacy in both internal validation (one-year AUROC = 0.625; $P = 0.482$) and external validation (two-year AUROC = 0.725, $P = 0.294$; three-year AUROC = 0.706, $P = 0.141$).

Baseline Axis Orientation of Astigmatism. The predictive performance of the AXL-Estimator remained relatively stable across eyes with different axis orientations of astigmatism, with no statistically significant differences in MAEs across these sub-cohorts (all $P \geq 0.156$). However, for the AXL-Classifier, predictive performance may vary by astigmatic axis orientation, particularly when predicting long-term axial elongation. While the AUROC for differentiating progressive myopia was statistically significant across all axis orientation sub-cohorts at all time points (AUROCs = 0.833 to 0.984; all $P < 0.05$), it was not significant in eyes with OBL astigmatism for the three-year prediction (AUROC = 0.771; $P = 0.194$).

5.4 Discussion

This study, to our knowledge, presents the largest longitudinal analysis to date for predicting axial elongation among Chinese school-age children. We developed and validated two machine-learning algorithms – the AXL-Estimator and AXL-Classifier – both of which exhibited high accuracy and

remarkable robustness in predicting future axial length and identifying children at risk of progressive myopia over up to three years. Furthermore, we examined the influential factors in predicting axial elongation using Gini importance and stratification analyses. We found that, although baseline astigmatism (both magnitude and axis orientation) was not a significant influential factor in these models, the presence and higher magnitude of astigmatism did negatively affect the predictive performance of our models. These findings not only provide compelling evidence of the capacity of ML techniques for predicting axial elongation in school-age children, but also expand our understanding of the various factors contributing to axial elongation and its prediction.

5.4.1 Model Performance

Excessive axial elongation in school-age children is a significant concern due to its close association with ocular pathologies and irreversible visual impairments (Holden et al., 2016; Morgan et al., 2012; Ohno-Matsui et al., 2021). Therefore, accurate prediction of axial elongation in childhood and early identification of children at high risk for rapid axial elongation is crucial for enabling personalized and targeted interventions (Gifford et al., 2019). Although several models have been developed for predicting refractive development (*i.e.*, SER, an optical factor highly related to axial length), there is limited research on prediction models specifically designed to predict AXL elongation. For instance, Morgan et al. (Morgan et al., 2020) and Lingham et al. (Lingham et al., 2024) have proposed cross-sectional methods to estimate AXL for other ocular biometry; however, they lack the capability to predict future trajectories of axial elongation.

To the best of our knowledge, only one study has developed a model for predicting AXL elongation over time, but it was limited by a small sample size (n = 179) and the absence of external validation. Our study filled these gaps by presenting the largest longitudinal, two-centre analysis of AXL prediction models in Chinese school-age children. Our models, the AXL-Estimator and AXL-Classifier, achieved high accuracy in predicting future axial length and identifying children with rapid axial elongation over up to three years, demonstrating better performance compared to the prediction model proposed in the previous study (Zhu et al., 2023), likely due to the larger sample size and the inclusion of additional

predictors that are potentially relevant to axial elongation, such as PRAXL and astigmatic characteristics.

Our proposed models were independently validated using both internal and external validation cohorts, and demonstrated remarkable robustness at each prediction time point (**Figure 5.2** and **Figure 5.3**). Interestingly, our models performed better in the external validation compared to the internal validation, though the exact reason was unclear. One possible explanation could be related to the differences in data characteristics, such as baseline age and SER, between the two validation cohorts. In addition, it is worth noting that the external validation cohort was derived from a clinic dataset, where children exhibiting excessive axial elongation might have had a higher chance of receiving myopia control interventions during follow-up. This could have introduced potential bias, contributing to better prediction performance. Nevertheless, our models showed remarkable predictive performance and significant potential in both clinical settings and population-based screenings.

5.4.2 Feature Importance

In this study, the feature importance of the prediction models was assessed using the Gini importance in the random forest algorithm. For the AXL-Estimator, baseline AXL, SER, and PRAXL were the top three most influential factors throughout three-year predictions, collectively accounting for over 70% of the total importance weight (**Figure 5.4A**). Specifically, baseline AXL was the most weighted predictor for one-year AXL prediction, but its importance gradually declined over longer prediction periods (from 43.88% to 19.95%). Conversely, the importance of PRAXL increased with longer prediction periods (from 18.21% to 28.23%). A similar trend was observed in the AXL-Classifier, where PRAXL's feature importance significantly increased from 21.11% to 39.43% (**Figure 5.4B**). These findings suggested significant associations between previous AXL progression and future axial elongation during school age, emphasizing the need to consider previous AXL progression rates in the monitoring and management of myopia (Brennan et al., 2021).

Furthermore, our findings aligned with previous studies that had linked past myopia progression with future myopia development. For instance, a survey covering 794 paediatric ophthalmologists worldwide

reported that the most favoured criterion for initiating myopia treatment was the previous progression rate of myopia (Leshno et al., 2020). Similarly, Matsumura et al. analyzed three-year longitudinal data from 618 myopic Singaporean children and found that the first year's myopia progression achieved an AUROC of 0.77 for predicting myopia progression in the next two years. However, the correlation between previous and future myopia progression appeared to be weak, with a regression coefficient of 0.28 (Matsumura et al., 2020). A more recent study re-analyzing CLEERE data also reported a weak correlation between previous and future myopia progression (R^2 = 0.015) and found no significant improvement in performance when incorporating previous AXL progression into the prediction models (Mutti et al., 2022), which somewhat contradicted our findings on feature importance. These discrepancies may be caused by differences in study population (*e.g.,* age, ethnicity), AXL measurement techniques (*e.g.,* A-scan ultrasound *vs.* biometers), or modelling methodologies (*e.g.,* different predictors and labels used).

Regarding the feature importance of astigmatism, both its magnitude and axis orientation had relatively low but stable importance in the AXL-Estimator and AXL-Classifier throughout the three-year predictions. This suggested that astigmatism may not be a significant contributor to predicting axial elongation, although it had been reported as a potential factor guiding emmetropization and axial eye growth. One possible explanation is that, as observed in our previous study (**Study I**), the impact of astigmatism on axial elongation appears to be the opposite between myopic and hyperopic eyes. This opposing influence could introduce a confounding effect in the prediction models, leading to the relatively low contribution of astigmatism.

Additionally, findings from **Study I** revealed a significant association between baseline astigmatism and future AXL progression rate. This may partially explain the relatively higher importance of astigmatic characteristics in the AXL-Classifier, which directly relates to future AXL progression rate, compared to their importance in the AXL-Estimator, which focuses more on future AXL (**Figure 5.4**). It is important to note that Gini importance measures each predictor's contribution to overall model accuracy based on the purity of decision tree nodes, and several factors, including feature selection,

dataset characteristics, and overall model performance, can influence this metric (Strobl et al., 2007). Therefore, interpretations of feature importance should be approached with caution.

5.4.3 Stratification Analysis

Given that axial elongation is associated with various risk factors, such as baseline age and refractive states (Hyman et al., 2005; Morgan et al., 2021), it is essential to evaluate our models' ability across different sub-cohorts stratified by these associated factors. In stratification analyses, both the AXL-Estimator and AXL-Classifier achieved stable performance across sub-cohorts with different ages and SER categories, highlighting the promising generalizability of our models across diverse populations. However, a consistent decrease in the AXL-Estimator's performance was observed with increasing magnitude of astigmatism (**Figure 5.5**). Similarly, the AXL-Classifier's performance also notably decreased in children with high astigmatism, resulting in insignificant AUROCs at all prediction time points. These findings suggest that the presence and magnitude of baseline astigmatism may negatively affect the accuracy of predicting axial elongation.

Regarding the stratification analysis of the axis orientation of astigmatism, while the AXL-Estimator remained relatively stable in terms of performance, the AXL-Classifier showed notably decreased performance in three-year prediction for eyes with OBL and ATR astigmatism (**Figure 5.5**). This indicated that the impact of astigmatic axis orientation on the AXL-Classifier was likely more pronounced over a longer follow-up period rather than a shorter one. This finding may explain why some previous studies have reported no significant effect of the axis orientation of astigmatism on myopia development over short follow-up periods, such as one year (Chan et al., 2018).

The reason our models failed to effectively learn the inherent pattern of axial elongation in eyes with astigmatism, particularly high astigmatism, remains unknown. One possible explanation could be the relatively small sample size of high astigmatism, which may have limited the information available to train our models. However, this explanation is challenged by the fact that a similarly small sample size of high myopia did not result in a significant decrease in prediction performance. Another possibility is

that the trajectory of eye growth is more diverse or complex in high astigmats compared to other sub-cohorts, making it more challenging to learn, and thereby resulting in poorer performance. For instance, Flitcroft et al. found that highly astigmatic children had abnormal flash ERG responses more frequently than low- or non-astigmatic children (Flitcroft, 2005). Our previous study (**Study II**) also reported a significant difference in retinal thickness between WTR-astigmatic and non-astigmatic eyes. These findings suggest that a high magnitude of astigmatism may be associated with abnormal retinal characteristics, which could complicate the accurate prediction of axial elongation. Future research should consider incorporating more training data from children with high astigmatism to address these challenges.

Nonetheless, our results highlight a significant finding: machine-learning models for predicting axial elongation – and possibly other existing models for predicting refractive development – may experience unexpected decreases in performance when predicting for subjects with astigmatism. However, few studies have investigated the robustness of these predictive models across eyes with different astigmatism by performing additional stratification or sensitivity analyses. As machine learning increasingly becomes an essential tool in assisting clinical decision-making (Foo et al., 2021), recognizing this potential limitation is crucial for the evaluation and application of AXL or SER prediction models in both research and clinical settings.

5.4.4 Limitations

This study has several limitations. **First**, only Chinese children were included in this study, raising uncertainty about the robustness of our findings across other ethnic groups. Previous studies have shown significant variations in axial elongation across different ethnicities (Tideman et al., 2019; Truckenbrod et al., 2021; Hyman et al., 2005). **Second**, as a retrospective study, we did not include other factors that have been proven to influence axial elongation or myopia development, such as corneal biometrics (Lee et al., 2020; Scheiman et al., 2016) and behaviour or environmental factors (Tideman et al., 2019; Ulaganathan et al., 2019). It remains unclear whether the models' performance would improve by including these associated predictors, and if these predictors would hold greater feature importance.

Additionally, the retrospective design may introduce selection bias, particularly since children who underwent myopia control interventions were excluded. These excluded children could have originally exhibited higher rates of myopia development and axial elongation, potentially skewing our results. Future prospective studies that incorporate intervention details and additional predictors are needed to validate our findings. **Third**, while our study observed that astigmatism significantly affects the predictive performance of both the AXL-Estimator and AXL-Classifier, we did not explore the underlying mechanisms behind this effect. Future research focusing on model interpretability may offer insights into the association between astigmatism and AXL prediction. Nevertheless, the strengths of this study include the use of a large longitudinal two-centre dataset, the high accuracy and robustness of our prediction models, and the comprehensive assessment of influential factors.

5.5 Conclusions

This study presents the largest longitudinal analysis for predicting axial elongation among Chinese school-age children. Our proposed machine-learning models exhibited high accuracy in predicting future axial length and identifying children at risk of progressive myopia, showing remarkable robustness across independent two-centre validations and among sub-cohorts stratified by age or SER. However, significant decreases in the models' performance were observed in eyes with astigmatism, particularly high astigmatism. This suggests that baseline astigmatism may influence the accuracy of axial elongation predictions, and caution should be taken when applying these models to children with high astigmatism. Overall, this study not only highlights the potential of machine-learning techniques in predicting axial elongation in school-age children, but also expands our understanding of the factors contributing to axial elongation and its prediction.

Chapter 6

General Conclusions

6.1 Discussion

The degradation of retinal image quality caused by astigmatism has been hypothesized to serve as a visual cue that guides the emmetropization process (Charman, 2011; Flitcroft, 2012; Howland, 1982). Conversely, the optical blur resulting from astigmatism could disrupt the normal process of emmetropization, thereby leading to myopia development (Fulton et al., 1982; Gwiazda et al., 2000). Ample evidence suggests that the presence of astigmatism can alter refractive development, as demonstrated in both chicks (Irving et al., 1995; Chu and Kee, 2015; Popa et al., 2020; Vyas and Kee, 2021; McLean and Wallman, 2003; Schmid and Wildsoet, 1997) and monkeys (Kee et al., 2003; Smith et al., 1998; Kee et al., 2004).

In contrast to experimental animal models, human studies – which are mostly observational – have reported varying findings on the impact of astigmatism on emmetropization. Some studies have identified significant associations between baseline astigmatism, either its magnitude (Gwiazda et al., 2000; Fulton et al., 1982; Fan et al., 2004; Twelker et al., 2013) or axis orientation (Grosvenor et al., 1987; Gwiazda et al., 2000; Hirsch, 1964), with myopia development in children. However, other studies have not found such associations (Chan et al., 2018; Ehrlich et al., 1995; Fan et al., 2004; Goss and Shewey, 1990; Hu et al., 2016, 2019; Mutti et al., 2004; O'Donoghue et al., 2015; Pärssinen, 1991). These discrepancies, which may arise from methodological differences, have greatly affected the reliability of the conclusions drawn from these studies. Therefore, conducting a systematic review and meta-analysis to comprehensively evaluate the progression rates of refractive myopia in eyes with different astigmatism is necessary.

Using data from 3,021 WTR and 943 ATR astigmatic eyes across eight longitudinal studies worldwide, our **meta-analysis** in Chapter 2 revealed that ATR astigmatism exhibits significantly more myopic

SER progression than WTR astigmatism (−0.44 *vs.* −0.36 D/year, **Figure 2.2**). This finding is consistent with our hypothesis that the axis orientation of astigmatism can alter the course of refractive development. By including a significant number of subjects from multiple original studies, our meta-analysis likely offers greater statistical power and more robust conclusions than those drawn from individual studies alone.

Our meta-analysis also provides valuable insights for shaping future research. For instance, we found that ATR astigmatism is associated with higher myopia progression across all subgroups, except in those with baseline hyperopia (**Supplementary Table S2.3**). This finding highlights a potentially complex interaction between astigmatism and refractive states in guiding emmetropization (Goss, 1999), and further informs the design of our **Study I** in **Chapter 3**, where we explored the impact of astigmatism on axial elongation across different spherical ametropia subtypes.

However, our meta-analysis did not find a statistically significant difference in myopia progression between different magnitudes of astigmatism (**Figure 2.4**), which may be attributed to significant methodological heterogeneity. Our subgroup analysis further identified that the high heterogeneity was likely due to variations in follow-up duration across the included studies (**Supplementary Table S2.4**). Therefore, future research employing standardized methodologies is needed to minimize the potential bias and to validate the generalizability of our observations.

While our **meta-analysis** (**Chapter 2**) confirmed the significant role of astigmatism in refractive development in children, its impact on ocular structural changes remains underexplored. Axial length – the primary ocular parameter that is associated with refractive error (Flitcroft et al., 2019) – plays a crucial role in emmetropization by aligning the ocular axial length with the focal lengths of the cornea and crystalline lens combined (Wildsoet, 1997). Therefore, in **Study I** of this thesis, we investigated axial elongation across different magnitudes and axis orientations of baseline astigmatism, aiming to offer a more comprehensive understanding of how ocular structural growth responds to astigmatism.

Our **Study I**, distinguished by its large sample size (10,732 children) and longitudinal design (five-year follow-up), offers a novel finding: both the baseline magnitude and axis orientation of astigmatism significantly affect axial elongation (**Figure 3.2**). Specifically, across all age groups (younger and older) and astigmatic magnitudes (low and high), eyes with ATR astigmatism exhibited the most rapid AXL progression, followed by those with OBL and WTR astigmatism. This study is the first to demonstrate a significant association between the axis orientation of astigmatism and axial elongation in school-age children, aligning with the findings from our **meta-analysis** (**Chapter 2**) and previous research on refractive development (Fulton et al., 1982; Gwiazda et al., 2000; Fan et al., 2004; Twelker et al., 2013; Grosvenor et al., 1987; Hirsch, 1964).

Another key finding from **Study I** is that the impact of baseline astigmatism on axial elongation is modulated by baseline spherical ametropia. Specifically, higher astigmatism increased AXL progression in compound myopic eyes but decreased progression in compound hyperopic eyes (**Figure 3.4**). Moreover, greater AXL progression in ATR astigmatism compared to WTR astigmatism was observed in the compound myopic and other ametropic/emmetropic groups, but not in compound hyperopic eyes (**Figure 3.7**). These results indicate a significant and complex interaction between astigmatism and spherical ametropia in guiding ocular growth during school age, as highlighted in our **meta-analysis**. This interaction is further supported by previous studies that have reported different types of astigmatism can affect refractive development in distinctive ways. For instance, mixed astigmatism does not exhibit significant myopia progression until it evolves into simple or compound myopic astigmatism (Goss, 1999). Additionally, infants with hyperopic-WTR or myopic-ATR astigmatism are prone to developing more myopia during childhood (Gwiazda et al., 1993).

In addition to axial elongation, our **Study II** reports, for the first time, the significant impact of astigmatism on retinal characteristics in a young Chinese adult population. We found significant differences in both retinal thickness and BCDVA across different types of astigmatism, with the thickest retina and poorest BCDVA observed in eyes with WTR astigmatism (**Figure 4.3**). These findings confirm that the impact of astigmatism on retinal thickness and visual acuity may vary depending not

only on the magnitude but also on the axis orientation.

The impact of astigmatism on retinal thickness has not been previously reported; however, relevant findings on choroidal thickness have been documented. Hoseini-Yazdi et al. imposed 60 minutes of WTR and ATR astigmatic blurs on 18 healthy young adults using +3.00 DC cylindrical lenses and observed bi-directional changes in choroidal thickness – significant thickening in WTR and thinning in ATR astigmatism (Hoseini-Yazdi et al., 2020). This finding, along with those from our studies in this thesis, supports the hypothesis that refractive development and structural growth in human eyes are modulated through an orientation-dependent mechanism. Taken together, ATR astigmatism has been associated with more myopic refractive development (**meta-analysis**), faster axial elongation (**Study I**), thinner retinal thickness (**Study II**), and decreased choroidal thickness (Hoseini-Yazdi et al., 2020).

Our studies also contribute to understanding how astigmatism, both its magnitude and axis orientation, influences ocular structural growth in humans:

6.1.1 Impact of Astigmatic Magnitude on Ocular Structures

Previous animal research has shown that imposing astigmatism can direct the course of emmetropization towards specific endpoints, either the circle of least confusion (Chu and Kee, 2015; Irving et al., 1995) or the least hyperopic focal plane associated with the imposed astigmatism (Kee et al., 2004; McLean and Wallman, 2003; Schmid and Wildsoet, 1997; Vyas and Kee, 2021). These hypotheses provide a crucial framework for interpreting the results presented in this thesis.

In **Study I**, our sub-cohort analyses revealed that compound hyperopic eyes with higher astigmatism showed significantly reduced axial elongation compared to those with lower astigmatism (**Figure 3.4**), suggesting that eye growth may be directed towards the least hyperopic focal plane associated with astigmatism. In humans, myopic eyes are more prolate in shape (Atchison et al., 2004; Logan et al., 2004; Atchison et al., 2005; Singh et al., 2006) and tend to have relative peripheral hyperopic defocus (Tabernero et al., 2009; Lin et al., 2010), while hyperopic eyes are more oblate and show relatively

peripheral myopic defocus (Mutti et al., 2000). This peripheral defocus could potentially serve as a signal to regulate refractive development and eye growth (Smith, 2011). Therefore, in compound hyperopic eyes, higher astigmatism could bring the least hyperopic focal plane closer to the retina in the periphery compared to those with lower astigmatism, potentially leading to reduced myopia progression and axial elongation. Following this hypothesis, our **Study II** – in which most eyes were myopic – found that WTR astigmatism was associated with a thicker retina compared to non-astigmatic control eyes (**Figure 4.3**).

However, this defocus mechanism does not fully explain the increased AXL progression in compound myopic-astigmatic eyes in **Study I** (**Figure 3.4**). This could be due to several factors. For instance, myopic eyes tend to have a larger accommodative lag (Harb et al., 2006; Mutti et al., 2006) and higher ocular aberrations (He et al., 2002; Yazar et al., 2014) than emmetropic and hyperopic eyes. These deficiencies could impose a higher magnitude of hyperopic defocus and degrade the quality of the retinal image (Logan et al., 2021), thereby complicating the effect of astigmatism on ocular growth. Furthermore, the sensitivity of the focusing mechanism is reduced in myopic eyes (Swiatczak and Schaeffel, 2021, 2022b), making it more challenging for the myopic retina to accurately determine the level of defocus. The chronic blur caused by significant astigmatism could further diminish the retina's ability to regulate emmetropization (Gwiazda et al., 2000; Kee, 2013), potentially confounding the end point of refractive development and ocular growth.

6.1.2 Impact of Astigmatic Axis Orientation on Ocular Structures

Our **Study I** also revealed that in compound myopic and other ametropic/emmetropic eyes, ATR astigmatism led to greater axial elongation compared to WTR astigmatism (**Figure 3.7**), suggesting that horizontally oriented visual signals may be more potent in promoting eye growth. This observation could be explained by the orientation-selectivity of the retinal and neural processing pathways. For instance, the retinal circuits and cells of many vertebrates, such as ganglion and amacrine cells (Antinucci and Hindges, 2018), respond more robustly to stimuli that align with their preferred orientation, which tends to be parallel to the radial orientation (Bloomfield, 1994; Schall et al., 1986).

Given that relative hyperopic defocus predominantly occurs along the horizontal meridian (Atchison et al., 2006), and that peripheral ganglion cell density is higher in horizontal than vertical meridians (Curcio and Allen, 1990; Provis et al., 1985a), eyes with myopic-ATR astigmatism – where the most hyperopic focal line is horizontally orientated – would receive stronger stimuli for axial elongation compared to myopic-WTR astigmatism. Supporting this hypothesis, studies in cats have shown that more neurons (Leventhal and Hirsch, 1980; Li et al., 2003) or a larger area of the cortical surface (Liu and Pettigrew, 2003) are tuned to horizontal rather than vertical stimuli.

Similarly, our **Study II** found that WTR astigmatic eyes had a significantly thicker retina compared to the ATR and control groups, particularly along the horizontal meridian (**Figure 4.3**), further supporting the hypothesis of orientation-dependent modulation in eye growth. In **Study II**, all astigmatic subjects had myopic eyes, which tend to have relative peripheral hyperopic defocus (Tabernero et al., 2009; Lin et al., 2010). Therefore, in those myopic eyes with WTR astigmatism, the horizontal line focus is formed closer to the peripheral retina than the vertical line focus, creating a horizontally oriented blur visual signal at the retinal plane. Under this condition, cells in the peripheral nasal and temporal retina are more likely to receive optical signals of their preferred orientation compared to those in the superior and inferior retina, thereby leading to a significantly thicker retina along the horizontal meridian.

However, this hypothesis does not fully explain the slightly decreased axial elongation in hyperopic-ATR astigmatism compared to hyperopic-WTR astigmatism observed in **Study I** (**Figure 3.7**). This could be due to the relatively smaller sample sizes, or some astigmatism-related ocular biometric factors, such as compensated corneal astigmatism, which might confound axial elongation. Despite these limitations, the strength of our studies presented in this thesis lies in their novel findings on astigmatism's impact on ocular structures, particularly in relation to axial length and retinal thickness, which could guide future research in this field.

6.1.3 Impact of Astigmatism on Predicting Ocular Structures

Given the significant impact of both the magnitude and axis orientation of astigmatism on axial

elongation observed in **Study I**, we further investigated how astigmatism influences the prediction of axial elongation. Specifically, based on the largest-to-date, two-centre longitudinal cohort of Chinese children, we developed two random forest algorithms – AXL-Estimator and AXL-Classifier – to predict the future axial length and identify children at risk of progressive myopia over three years in **Study III**. Both algorithms exhibited high accuracy and remarkable robustness across independent validations from two centres (**Figure 5.2–5.3**), as well as across sub-cohorts stratified by factors such as age and SER (**Figure 5.5**). These findings provide compelling evidence of the capacity of machine learning techniques to predict axial elongation in school-age children.

The feature importance of the prediction models was assessed using Gini importance (Kuhn and Johnson, 2013). Both the baseline magnitude and axis orientation of astigmatism had relatively low feature importance in the AXL-Estimator and AXL-Classifier throughout the three-year predictions (**Figure 5.4**). This suggests that refractive astigmatism might not be a significant contributor to predicting axial elongation, even though it has been reported as a significant factor affecting axial elongation in **Study I**. However, the interpretation of Gini feature importance should be approached with caution, as they can be influenced by factors such as training dataset, feature selection, and model performance (Strobl et al., 2007).

Moreover, the models' performance was evaluated across sub-cohorts stratified by magnitude and axis orientation of astigmatism. A consistent decrease in the predictive performance of the AXL-Estimator and AXL-Classifier was observed in sub-cohorts with higher astigmatism (**Figure 5.5**), suggesting that the baseline magnitude of astigmatism may negatively affect the accuracy of axial elongation predictions. However, the underlying reasons on why our models failed to learn the patterns of axial elongation in high astigmatism remain unclear. One possible explanation could be the relatively small sample size for high astigmatism, leading to insufficient data to train the models effectively. However, this is challenged by the observation that a similarly small sample size for high myopia did not result in a significant decrease in the models' performance. Another possibility is that the trajectory of axial elongation may be more diverse or complex in highly astigmatic eyes compared to other sub-cohorts,

making it more challenging for our models to accurately learn and predict, thereby resulting in poorer performance.

The performance of the AXL-Estimator remained relatively stable across all axis orientations of astigmatism throughout all prediction time points. However, the AXL-Classifier exhibited notably decreased performance in three-year predictions for eyes with OBL and ATR astigmatism (**Figure 5.5**), indicating that the impact of axis orientation of astigmatism on classifying progressive axial elongation is more pronounced over longer periods (*i.e.*, 3 years) than over shorter terms (*i.e.*, 1–2 years). This finding may help explain why some previous studies, such as Chan et al. (Chan et al., 2018), reported no significant effects of the axis orientation of astigmatism on myopia development when follow-up periods were relatively short (*e.g.*, 1 year). Furthermore, this finding aligns with our **meta-analysis** in **Chapter 2**, where the follow-up duration was identified as a significant factor contributing to the high heterogeneity among the included studies (**Supplementary Table S2.4**).

Our machine-learning results revealed a critical finding: our models for predicting axial elongation – and possibly other existing models designed for predicting refractive development – may experience unexpected decreases in performance and should be applied with caution when used for patients with astigmatism. Since machine learning is becoming an essential tool for assisting clinical decision-making (Foo et al., 2021), understanding this potential limitation is crucial for both the development and application of prediction models for refractive development and axial elongation.

6.2 Future Studies and Directions

6.2.1 Off-axis Astigmatism and Its Role in Emmetropization

While ample evidence, including findings from this thesis, has suggested that on-axis astigmatism can influence ocular growth and refractive development, the role of off-axis astigmatism remains underexplored. Studies in animals have shown that the vision-dependent mechanisms regulating eye growth are mediated by the local retina (Popa et al., 2020; Smith et al., 2010; Wallman et al., 1987).

Notably, the peripheral retina can independently regulate ocular growth without signals from the fovea (Huang et al., 2011; Smith et al., 2007, 2005). Moreover, when there is a conflict between signals from the central and peripheral retina, visual cues from the periphery appear to override those from the fovea (Smith, 2011; Smith et al., 2005), ultimately influencing central ocular growth and refractive development (Smith et al., 2009; Wallman and Winawer, 2004). These findings highlight the potential significance of peripheral defocus, including off-axis astigmatism, in the process of emmetropization.

In human eyes, regardless of their on-axis refraction, a considerable amount of off-axis astigmatism remains uncorrected, which could have significant implications for central ocular development (Gustafsson et al., 2001; Williams et al., 1996). While there is no direct research linking off-axis astigmatism with central refractive development, studies have reported increased off-axis astigmatism in the far periphery during accommodation for near targets (Whatham et al., 2009). This raises important questions about the potential impact of off-axis astigmatism on central refractive development and ocular structural growth. Understanding this relationship could provide new insights into the mechanisms of emmetropization and potentially inform more targeted strategies for myopia control.

6.2.2 Dynamic and Regional Changes in Ocular Structures Related to Astigmatism

Significant associations between astigmatism and retinal thickness have been reported in our cross-sectional **Study II**, indicating that both the magnitude and axis orientation of astigmatism influence retinal structural changes. However, the causal relationships have yet to be fully investigated. To uncover the underlying mechanisms, future studies should employ a longitudinal cohort design in children to explore the dynamic association between baseline astigmatism and subsequent changes in retinal structures over time.

In addition to the retinal thickness profile, future research should also consider additional ocular biometric parameters, such as the changes in individual retinal layers, retinal curvature, choroidal thickness, and microvasculature assessed by OCT Angiography (OCT-A). Furthermore, investigating regional variations in these parameters could provide a more comprehensive understanding of how

different regions of the retina and choroid respond to astigmatism over time. Such studies could also elucidate how the peripheral retina contributes to central ocular growth that is related to astigmatism.

6.2.3 Validations across Ethnic and Age Groups

All studies presented in this thesis were conducted on Chinese population. Whether our findings are generalizable across other ethnic and age groups remains unknown. This concern is particularly significant given the considerable variations in eye size (Tariq et al., 2010; Lim et al., 2020) and axial elongation patterns (Tideman et al., 2019; Truckenbrod et al., 2021; Hyman et al., 2005) observed in different populations. In addition, it is suggested to validate our findings using varied measurement techniques for axial length and OCT imaging. Such validations are crucial for confirming the reliability and applicability of our conclusions across diverse demographic groups and clinical settings.

6.3 Conclusions

This thesis highlights the significant impact of astigmatism on refractive development (**meta-analysis**) and ocular axial length in humans. Both the magnitude and axis orientation of baseline astigmatism significantly influence axial elongation in school-age children (**Study I**), potentially leading to significant alterations in retinal thickness and visual acuity (**Study II**). Furthermore, while our machine learning models can accurately predict axial elongation, their performance may decrease in children with significant astigmatism (**Study III**). These findings not only enhance our understanding of how astigmatism regulates ocular structural growth but also provide valuable insights for personalized management and interventions for refractive errors.

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