Interocular Symmetry in Retinal Nerve Fiber Layer Thickness in Children: The Hong Kong Children Eye Study

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ABSTRACT

Introduction: The aim of this work is to determine the interocular differences in peripapillary retinal nerve fiber layer (p-RNFL) thickness and its associations among school children in Hong Kong.

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Methods: We conducted a population-based study including 4034 children aged 6–8 years from the Hong Kong Children Eye Study (HKCES). All participants received comprehensive ocular examinations where p-RNFL thickness was measured using spectral-domain optical coherence tomography (SD-OCT). The degree of symmetry between both eyes was analyzed and represented by intraclass correlation coefficient (ICC) values. Multivariable linear regression analysis was used to investigate the associations between ocular and systemic factors with p-RNFL thickness difference.

Results: The study included 4034 children with a mean age of 7.61 ± 0.98 years. The mean

global p-RNFL thickness was 106.60 ± 9.41 μm in right eyes and 105.99 ± 9.30 μm in left eyes. The ICC for global p-RNFL difference was 0.866 (95% CI 0.858–0.873, $p < 0.001$). The symmetry displayed the largest values in nasal inferior quadrant with the ICC value of 0.736 (95% CI 0.721–0.749); and the smallest degree of symmetry was found to be in the superior temporal quadrant with the ICC value of 0.567 (95% CI 0.546–0.588). Axial length (AL) difference was found to have more pronounced correlation to interocular symmetry in p-RNFL thickness with the coefficient of 0.514 ($p < 0.001$).

Conclusions: Normal variation in interocular symmetry exists in children. Our results can contribute to the establishment of a standard reference for interocular differences in OCT parameters in children. The interocular differences in AL should be considered in the interpretation of RNFL symmetry, in terms of identifying children at risk of developing glaucoma or other ocular disorders.

Keywords: Peripapillary retinal nerve fiber layer (p-RNFL) thickness; Interocular symmetry; Retinal parameters; Optical coherence tomography (OCT); Pediatric ophthalmology

Key Summary Points

There is currently limited research on interocular symmetry specifically in the thickness of the retinal nerve fiber layer (RNFL) among Chinese children. Therefore, it is crucial to assess the normal range of interocular variation and its potential associations. This information will aid eye care professionals in enhancing diagnostic accuracy in pediatric populations.

The aim of this study was to determine the interocular differences in p-RNFL thickness and its associated factors among school children in Hong Kong.

Our study findings demonstrate the presence of normal variation in interocular symmetry among children. These results have significant implications for establishing a standard reference for interocular differences in optical coherence tomography (OCT) parameters in this population. It is crucial to consider the interocular differences in axial length (AL) when interpreting RNFL symmetry, as this has important implications for assessing ocular health and diagnosing various ocular conditions.

Our study contributes valuable insights to enhance the accuracy and interpretation of OCT measurements in children, further advancing ocular health assessment and disease diagnosis.

INTRODUCTION

Interocular asymmetry could be an abnormal sign necessitating further investigation [1–3]. In addition, some disease entities preferentially affect one eye [4]. While our vital organs are not perfectly symmetrical due to inherent physiological asymmetries, it is important to note that a certain degree of asymmetry can be a typical variation in healthy eyes. Hence, understanding the range of this asymmetry in normal eyes is crucial.

Optical coherence tomography (OCT) is firmly established as a vital tool for structural imaging in the diagnosis and management of ophthalmic diseases [5]. Its rapid, non-invasive, and non-contact nature makes it particularly valuable in evaluating children with various ocular pathologies. However, interpreting pediatric tomograms presents unique challenges compared to those of adults, given the growth of the eyeball, changes in axial lengths, and the continuous development of the retina and optic nerve. As such, additional adjustments are essential for the precise interpretation of pediatric tomograms.

To date, in adult populations, the peripapillary retinal nerve fiber layer (p-RNFL) thickness has been well documented, with several studies establishing norms for interocular symmetry [6, 7]. However, there remain limited data specific to pediatric populations. Notably, while previous studies have examined RNFL asymmetry in children, the majority have focused on non-Asian cohorts [8, 9], leaving a noticeable gap in data specific to Chinese children. Moreover, there has been a marked increase in myopia in East Asian regions such as Hong Kong and an elongated axial length (AL) associated with myopia can influence the RNFL thickness. Given the heightened prevalence of myopia in this demographic, understanding the variations of AL and asymmetries in RNFL thickness becomes even more vital. Recognizing the normal variations and asymmetries in RNFL thickness among children can guide clinicians in distinguishing between physiological variations and pathological changes. This study aims to fill the knowledge gap by investigating the interocular symmetry of RNFL thickness and the associated factors in Chinese children, providing a foundation for future clinical and research applications in this demographic.

METHODS

Study Design and Population

The Hong Kong Children Eye Study (HKCES) is a population-based cross-sectional study targeting primary school children from 6 to 8 years old in Hong Kong who were invited to visit the Hong Kong Eye Centre for comprehensive ophthalmological examinations [10–16]. It aims to evaluate various eye conditions among children in this age group and to determine the prevalence of different eye diseases. The sample selection was based on a stratified and clustered randomized sampling frame. Further details on sample size calculation and the study protocol were mentioned in previous reports. The participants were invited to attend in comprehensive ophthalmic examinations, physical examinations, and standardized interviews [10]. This study excluded children with congenital

malformations, previous ocular trauma, a history of ocular surgery, or any ocular disorders other than refractive errors. Additionally, children with systemic diseases, except for obesity, or those who were unable to cooperate were also excluded from the study. The project adhered strictly to the Declaration of Helsinki, and approval was obtained from the Ethics Committee Board of the Chinese University of Hong Kong. Participating children and their parents gave informed consent prior to their participation in the study. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

OCT Imaging

OCT imaging was performed with the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) system by a well-trained ophthalmic photographer. All the averaged B-scans in this study had a signal quality of at least 15 dB [15]. Imaging of the peripapillary retinal nerve fiber layer (p-RNFL) was performed at a central wavelength of 870 nm. For each participant, a scan circle with a diameter of approximately 3.45 mm (consisting of 1536 A-scans) was manually positioned at the center of the optic disc, with the eye-tracking system activated. Fifteen B-scans were captured at the same location and automatically averaged using the built-in software (Heidelberg Eye Explorer, version 1.6.1.0; Heidelberg Engineering) to enhance the signal-to-noise ratio of the images. The software's automatic segmentation feature was employed to delineate the p-RNFL on each averaged B-scan. The measurements obtained from the SD-OCT scans included the mean circumpapillary p-RNFL thickness as well as the sectorial peripapillary p-RNFL thickness in six specific regions: nasal, temporal, superonasal, inferonasal, inferotemporal, and supratemporal. These measurements were derived from the segmented p-RNFL using the aforementioned built-in software. To ensure high-quality scans, all averaged B-scans included in this study had a signal quality of $\geq$ 15 dB, as per the manufacturer's recommendation.

Ocular Examinations

Visual acuity was measured by using a logarithm of the minimum angle of resolution (logMAR) chart (Nidek Inc., Gamagori, Aichi, Japan). Cycloplegic autorefraction was performed using an autorefractor (ARK-510A, Nidek, Gamagori, Japan) after a cycloplegic regime, which consisted of at least two cycles of eye drops. At the first cycle, two separate eye drops, cyclopentolate 1% (Cyclogyl, Alcon-Convreur, Rijksweg, Belgium) and tropicamide 1% (Santen, Osaka, Japan), were administered to both eyes 5 min apart. A second cycle of the same cycloplegic drops would be administered 10 min after the first cycle. A third cycle of the same cycloplegic eye drops would be given 30 min after the second cycle if pupillary light reflex was still present or the pupil size was less than 6.0 mm. Further cycles of cycloplegic eye drops would be administered if necessary to ensure the pupils are well dilated. Five readings, all of which had to be less than 0.25 D apart, were obtained and averaged. Ocular axial length (AL) was measured on a Zeiss IOL Master unit (Carl Zeiss Meditec Inc., Dublin, CA, USA) using noncontact partial coherence interferometry. A non-contact tonometer, Corvis ST (Corvis ST; Oculus, Arlington, WA, USA) was used to measure the subjects' intro-ocular pressure (IOP) and central corneal thickness. Trained ophthalmologists conducted complete ocular examinations for each participant, including examinations of the anterior segment, posterior segment, and ocular motility [13–16]. Spherical equivalent refraction (SER) was defined as spherical diopters (D) plus one-half of the value for cylindrical diopters.

Other Examinations

Blood pressure (BP) was measured in the seated position after a 5-min rest using a digital autonomic BP monitor (Vital Signs Monitor; Heal Force Bio-Meditech, Shanghai, China). Body height and weight were measured using a professional integrated set (seca; Hamburg, Germany). A tape measure was used to measure the child's waist and head circumference, the most prominent part of the forehead-1 to 2 fingers above the eyebrows and to the widest part of the back of the head. Three measurements were taken, with the average result taken for subsequent analysis. Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of body height (in meters).

Statistical Analysis

Stata Version 14.0 (StataCorp LLC, College Station, TX, USA) was used for all statistical analyses. Confidence intervals (CIs) and p values (significant at the < 0.05 level) were derived for difference estimates. Mean differences for all parameters were calculated by subtracting the left eye parameters from the right eye parameters, and their respective p values were reported using the paired sample t test. Therefore, mean differences were stated as positive when right eyes had higher values than left eyes, and vice versa. To measure interocular correlation, intraclass correlation coefficients (ICCs) were computed. Absolute interocular differences were log-transformed due to the skewed distribution. Univariable and multiple linear regression analyses were conducted to determine associations, if any, between systemic, demographic, and ocular variables (as independent variables) with log-transformed absolute interocular p-RNFL thickness differences (as dependent variables). We interpreted the effect of each independent variable on the outcome and reported the result as the unstandardized correlation coefficients (β). We also calculated the standardized regression coefficients ($s\beta$) for each independent variable. The dataset utilized in the current study was sourced from the same dataset as our previous studies [15], emphasizing different research questions. Any data with a p value < 0.05 were considered as statistically significant.

RESULTS

Study Population

Among the 4273 children who participated in the study, 159 either declined later or were not able to complete the OCT examination, and another 80 children were also excluded due to suboptimal imaging quality. Consequently, 8068 eyes from 4034 children were included in the final analysis, including 2067 boys (51.2%) and 1967 girls (48.8%), with a mean age of 7.61 ± 0.98 years. Among them, 1009 had myopia with the mean SER of -1.95 ± 1.33 D (Table 1).

Interocular Symmetry of p-RNFL Thickness

The means for global p-RNFL thickness of right and left eyes were, respectively, 106.60 ± 9.41 μm and 105.99 ± 9.30 μm, with ICC 0.866 (95% CI 0.858 to 0.873, $p < 0.001$) (Table 2). The absolute difference of global p-RNFL thickness was difference was 3.58 ± 3.84 μm (Table 3).

Among the differences of p-RNFL in various quadrants, the temporal superior quadrant had the largest degree of asymmetry, with an ICC value of 0.567 (95% CI 0.546–0.588) and an absolute mean difference of 13.30 μm; while the least asymmetry was found to be in the nasal inferior quadrant, with a ICC being 0.736 (95% CI 0.721–0.750) and an absolute mean difference of 12.89 μm (Tables 2, 3).

Associations of p-RNFL Thickness Differences with AL

After adjusting for confounders such as age, sex, BMI, systolic and diastolic BP, waist and head circumference, VA, IOP, CCT, and central macular thickness, we found greater axial length differences was significantly associated with increased absolute global p-RNFL thickness difference ($\beta = 0.514$; 95% CI = [0.342, 0.687]; $p < 0.001$). This association with AL was significant across all subfields except temporal superior region (β from 0.051 to 0.649; $p < 0.001$ to

0.039) (Table 4). The univariable analysis echoed these observations, pinpointing axial length and SE differences as the predominant factors influencing the absolute global p-RNFL thickness difference, whereas variables such as age, sex, and IOP did not exhibit significant associations (Supplementary Table 1).

Table 1 Baseline characteristics of participants

Gender	
Male, N (%)	2067 (51.2%)
Female, N (%)	1967 (48.8%)
Myopia, N (%)	1009 (25.0%)
SER (right eye, mean $\pm$ SD), D	0.13 ± 1.56
SER (left eye, mean $\pm$ SD), D	0.17 ± 1.57
SE difference[a], D	-0.04 ± 0.57
Body mass index (mean $\pm$ SD), kg/m²	16.14 ± 2.88
Waist circumference (mean $\pm$ SD), cm	57.8 ± 6.84
Head circumference (mean $\pm$ SD), cm	57.86 ± 1.98
Systolic blood pressure (mean $\pm$ SD), mmHg	101.51 ± 11.13
Diastolic blood pressure (mean $\pm$ SD), mmHg	64.50 ± 9.03
Visual acuity difference[a], logMAR unit	-0.01 ± 0.04
Axial length difference[a], mm	0.01 ± 0.22
Spherical equivalent difference[a], D	-0.04 ± 0.57
Central corneal thickness difference[a], μm	-1.60 ± 14.49
Astigmatism difference[a], D	0.05 ± 0.42
Central macular thickness difference[a], μm	-0.90 ± 15.23
Intraocular pressure (mean $\pm$ SD)[a], mmHg	-0.029 ± 2.26

logMAR logarithm of the minimum angle of resolution, *D* diopter

[a]Right eye minus left eye

Table 2 RNFL thickness and ICC of interocular differences (right eye minus left eye) in RNFL thickness for right and left eyes

RNFL thickness, μm	Right eyes		Left eyes		p values	ICC	95% CI		p values
	Mean	SD	Mean	SD					
Global	106.60	9.41	105.99	9.30	0.011	0.866	0.858	0.873	< 0.001
Temporal superior	154.22	20.53	155.12	19.42	0.002	0.567	0.546	0.588	< 0.001
Temporal	83.98	13.13	81.99	12.40	< 0.001	0.685	0.668	0.701	< 0.001
Temporal inferior	155.65	19.11	154.60	19.72	< 0.001	0.662	0.645	0.679	< 0.001
Nasal inferior	117.26	23.69	115.83	23.45	< 0.001	0.736	0.721	0.750	< 0.001
Nasal	68.34	14.15	63.88	13.73	< 0.001	0.624	0.605	0.643	< 0.001
Nasal superior	121.14	20.75	130.46	22.45	< 0.001	0.703	0.687	0.718	< 0.001

RNFL retinal nerve fiber layer

Table 3 Percentile distribution in retinal nerve fiber layer thickness (μm)

RNFL	Absolute differences			Percentiles		Differences[a]			Percentiles	
	Mean	SD	Median	5th	95th	Mean	SD	Median	5th	95th
Global	3.85	3.84	2.83	0.17	11.00	0.60	4.88	− 0.17	− 6.00	7.75
Temporal superior	13.30	13.01	10.00	1.00	38.00	− 0.90	18.59	0.00	− 30.00	26.00
Temporal	7.43	7.17	6.00	1.00	20.00	1.98	10.14	2.00	− 13.00	18.00
Temporal inferior	11.68	10.93	9.00	1.00	31.00	1.04	15.96	1.00	− 22.00	26.00
Nasal inferior	12.89	11.26	10.00	1.00	33.25	1.43	17.23	1.50	− 25.00	29.00
Nasal	9.06	9.16	7.00	1.00	23.00	4.45	12.09	4.00	− 12.00	22.00
Nasal superior	14.82	11.89	12.00	1.00	37.00	− 9.32	16.72	− 9.00	− 36.00	17.00

RNFL retinal nerve fiber layer

[a]Right eye minus left eye

DISCUSSION

In this population-based study, we established a normative database of p-RNFL thickness difference among Chinese children aged 6–8 years old in Hong Kong. We observed the differences in global and all six quadrants of the p-RNFL thickness between two eyes, indicating a discernible level of asymmetry. Notably, the disparity in axial length demonstrated a robust association with p-RNFL thickness difference: a greater variation in axial length corresponded to increased p-RNFL symmetry between eyes.

Our study has clinical implications that when evaluating the nature of p-RNFL asymmetry—whether it is physiological or pathological—it is imperative to factor in the influence of axial length differences. This insight can refine diagnostic precision in pediatric patients.

We found that the ICC value of the global p-RNFL thickness was 0.872. In line with our findings, prior studies also observed the asymmetry in p-RNFL thickness between eyes [8, 9, 17]. In the Sydney Childhood Eye Study, which involved 1765 children aged 6 years, an interocular correlation of 0.7 was observed for

Table 4 Multiple regression models of interocular absolute difference of RNFL thickness with systemic and ocular determinants

	β	95% CI		Standardized β	p values
(A) Global					
Axial length difference, mm	0.514	0.342	0.687	0.096	< 0.001
CCT difference, μm	0.030	0.002	0.054	0.040	0.001
(B) Temporal superior					
CCT difference, μm	0.051	0.017	0.084	0.050	0.003
(C) Temporal					
Axial length difference, mm	0.228	0.016	0.440	0.035	0.035
(C) Temporal inferior					
Axial length difference, mm	0.356	0.122	0.591	0.049	0.003
(D) Nasal inferior					
Axial length difference, mm	0.649	0.427	0.871	0.091	< 0.001
Age	− 0.016	− 0.028	− 0.004	− 0.040	0.011
(E) Nasal superior					
Axial length difference, mm	0.226	0.011	0.442	0.032	0.039

Refers to log-transformed absolute difference between the right and left eye
RNFL retinal nerve fiber layer, *CCT* central corneal thickness

average RNFL thickness [8]. Another study, which focused on the degree of symmetry among healthy adults of different ethnicities, showed a symmetry value of 86.7% in the mean p-RNFL thickness among Chinese [18]. This supported our data in terms of the representativeness of the ethnic Chinese populations.

We established a normative database of p-RNFL thickness in Hong Kong. In our study, the observed mean and median differences in global p-RNFL thickness were 3.85 and 2.83 μm, respectively, with the 95th percentile marked at 11 μm. This falls within the interocular differences range observed in prior studies on healthy populations. A study involving 357 healthy children determined that the typical interocular disparity in average RNFL should not surpass 13 μm for normal individuals [9]. Similarly, research conducted among adults highlighted that standard variations between the two eyes generally stay within the limits of 9–12 μm [17].

It was further posited that variations exceeding these identified thresholds could potentially be indicative of the early stages of optic neuropathy, such as glaucoma [17]. Given our findings, the majority of the studied children remains within these established norms. This emphasizes the importance of understanding these baseline variations for pediatric eye care practitioners, as discerning physiological variances from potential pathological markers is crucial. Therefore, in a clinical setting, when children present with interocular differences beyond the recognized range, further in-depth evaluation might be warranted to rule out potential pathological conditions.

Prior research has consistently indicated an inverse relationship between axial length and p-RNFL thickness, suggesting that eyes with longer axial lengths tend to have thinner p-RNFLs and vice versa [7, 19, 20]. However, few studies established the correlation of differences

in axial length with variations in p-RNFL thickness. Our study is pioneering in highlighting this significant association between variances in axial length and p-RNFL thickness symmetry between the eyes. These findings carry substantial implications for interpreting axial length and p-RNFL thickness symmetry in the pediatric population, especially in the context of Hong Kong. Furthermore, when differentiating physiological from pathological asymmetry, clinicians should consider the influence of axial length differences.

In our study, the variation in p-RNFL thickness across different quadrants appeared more pronounced than that in global p-RNFL thickness. The ICC for the six quadrants ranged from 0.567 to 0.736, and the mean absolute differences extended from 7.43 to 14.82 μm. Moreover, the disparity in AL influenced p-RNFL thickness across most quadrants in varying degrees. It remains unclear how AL differences might distinctly impact different p-RNFL quadrants. Historical research observed AL correlated negatively with sectoral p-RNFL thickness in all non-temporal quadrants, but correlated positively with the temporal quadrant in both adults and children [21, 22]. There is likely redistribution of retinal nerve fiber with increasing AL, in which the retinal thickness in the most central area—the temporal sector of the RNFL—is preserved, but the peripheral retina becomes thinner since it is less resistant to traction and stretch [23]. As axial length increases, the retina is dragged towards the temporal horizon, and consequently the RNFL thickens in the temporal quadrant [24]. Although this theory provides insights, it does not entirely elucidate the phenomenon our study observed—where AL differences exert varying impacts on distinct p-RNFL quadrants. Nonetheless, it highlights the intricacy underlying the influence of AL on the quadrants of p-RNFL thickness.

The strength of this study includes its large-scale population-based setting, with its standardized random sampling method. In addition, the study had well-experienced ophthalmologists and optometrists who carried out comprehensive ophthalmoscopic examinations for the subject group in a well-equipped eye center. Meanwhile, several limitations of the study were noted. First, we did not include the optic disc parameters such as cup disk ratio (CDR) value. Second, we did not evaluate tilted disc. Also, the cyclotorsion in the tilted disc might influence the RNFL symmetry measurement, potentially resulting in under or overestimation. Third, the causal relationship between symmetry and its associated factors cannot be inferred because of the cross-sectional nature of our data. Fourth, this study included a narrow age range, from 6 to 8 years. As a result, the findings might not extend to a more diverse age group. Future studies including a broader age spectrum could provide more information on the asymmetry of p-RNFL thickness and will be warranted.

CONCLUSIONS

In conclusion, we established a normative database of p-RNFL thickness difference among Chinese children aged 6–8 years old in Hong Kong. Asymmetry in p-RNFL thickness was observed among children, with a notable association between this asymmetry and the difference in axial length between the two eyes. Our study highlights the importance of considering axial length differences when assessing the nature of p-RNFL asymmetry, whether physiological or pathological. Incorporating this understanding can enhance diagnostic accuracy in pediatric populations.

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Data Availability. Deidentified participant data are available upon reasonable request from JCSY, ORCID: 0000-0002-5835-208X.

Declarations

Conflict of Interest. All named authors confirm they have no conflicts of interest to declare.

Ethical Approval. The project adhered strictly to the Declaration of Helsinki, and approval was obtained from the Ethics Committee Board of the Chinese University of Hong Kong. Participating children and their parents gave informed consent prior to their participation in the study. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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