



# Evaluation of the association of macular ganglion cell–inner plexiform layer thickness and myopia in Chinese young adults

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Received: 1 October 2019 / Revised: 20 February 2020 / Accepted: 17 March 2020 / Published online: 14 April 2020  
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## Abstract

**Purpose** To describe the distribution of ganglion cell–inner plexiform layer (GCIPL) thickness among Chinese young adults and report whether the decreased GCIPL thickness is associated with myopia.

**Methods** In this study, we included Chinese young adults who underwent Cirrus spectral domain-optical coherence tomography (SD-OCT). SD-OCT was used to measure average and minimum GCIPL thickness, and GCIPL thickness at all sectors. Subfoveal choroidal thickness (CT), axial length (AL), and spherical equivalents (SE) were also measured.

**Results** A total of 348 eyes were included in the analysis. Average GCIPL thickness showed a significant difference between myopes and emmetropes, with  $87.89 \pm 3.65 \mu\text{m}$  for emmetropic groups and  $82.65 \pm 4.96 \mu\text{m}$  for myopic groups. The GCIPL thickness was significantly thinner in myopia than in emmetropia at all locations ( $P < 0.05$ ), affirming that myopia was associated with thinner GCIPL thickness ( $P = 0.001$ ). The mean subfoveal CT also showed a significant difference between myopes and emmetropes, with  $330.57 \pm 9.43 \mu\text{m}$  for emmetropic groups and  $265.98 \pm 4.12 \mu\text{m}$  for myopic groups. GCIPL (OR 0.863, 95% CI, 0.785–0.949), AL (OR 2.499, 95% CI, 1.532–4.075) and intraocular pressure (IOP) (OR 1.250, 95% CI, 1.086–1.438) revealed significant associations with myopia. When adjusting for AL, IOP, and anterior chamber depth (ACD) in the myopia subgroup, the GCIPL thickness remained positively associated.

**Conclusions** In a specific Chinese young population, myopic eyes have measurably less macular GCIPL thickness than normal eyes. Decreasing GCIPL thickness may be associated with the progression of myopia.

## Introduction

High myopia or pathologic myopia is associated with a progressive elongation of the globe which may result in

many fundal changes and lead to visual impairment. The prevalence of myopia has increased rapidly in the Asian population in recent decades, especially among young adults [1–3]. In a population of Chinese college students, its prevalence ran as high as 95.5% [4]. It is estimated that by 2050 the prevalence of myopia worldwide will reach 50% and high myopia may reach 10% [5]. Longer axial length (AL) [6], and thinning of the retina [7] and choroid [8] are thought to be the key processes involved in the development of myopia.

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**Supplementary information** The online version of this article (<https://doi.org/10.1038/s41433-020-0847-7>) contains supplementary material, which is available to authorized users.

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Recent interest has focused on the structure of the retinal layer in the pathophysiology of myopia. The macular ganglion cell–inner plexiform layer (GCIPL) thickness, the combination of the thickness of the ganglion cell layer (GCL) and the inner plexiform layer, is less influenced by variations of the retinal nerve fibre layer thickness than by the ganglion cell complex thickness [9]. It has proven to be a good diagnostic indicator of retinal ganglion cell damage or loss and can be used for early detection of glaucoma [10]. Deng et al. found that the change in asymmetry was obvious in the GCL and neural retina in myopic children [11], but they were unable to determine the change in the GCIPL in different sectors and whether the change in asymmetry contributes to myopia.

The widespread use of spectral domain-optical coherence tomography (SD-OCT) enables the evaluation of the GCIPL thickness and provides important information about the role of the inner retinal layer in human myopia [12–14]. However, variations of GCIPL thickness and their association with myopia have not yet been fully elucidated; only a few studies have investigated the association of GCIPL thickness and refractive errors, reporting thinner GCIPL in myopic eyes of patients with glaucoma [10, 15, 16]. Sam [17] found that the average GCIPL was significantly thinner in high myopia, but their study did not compare myopic patients with normal controls.

To investigate whether the GCIPL thickness in all degrees of myopia is thinner than that of normal eyes and whether decreased GCIPL thickness is associated with myopia, we used a Cirrus SD-OCT to examine the GCIPL thickness at different sectors around the macula of myopic young adults selected from the Chinese population. The data were compared with those of controls obtained from the same source, and risk factors for myopia were analysed.

## Materials and methods

### Study subjects

This prospective study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki and with the approval of the Ethical Review Committee of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine. One hundred and seventy-six healthy subjects of Chinese ethnicity (age between 18 and 32 years old) underwent comprehensive ophthalmologic examinations and written informed consent was obtained from each participant in the study, which took place from June 2015 to July 2016 in Shanghai General Hospital.

The ophthalmic assessment included slit-lamp examination, IOP measurement (by Goldmann applanation tonometry), noncycloplegic refraction (Nidek AR-310A, Japan),

AL, anterior chamber depth (by IOL Master, Carl Zeiss), cornea endothelium counter, corneal thickness, fundus examination, an SD-OCT B-scan (Carl Zeiss Meditec) and an enhanced depth imaging optical coherence tomography B-scan (Optovue RTVue). Refraction data were converted to spherical equivalents (SE) using the spherical dioptre (D) plus one half of the cylindrical dioptric power [18]. Participants with any systematic disease, IOP of 22 mm Hg or more in either eye, hyperopia (SE > 0.5 D), previous ocular trauma or surgery, poor OCT image quality, best corrected visual acuity (BCVA) less than 20/20, and those with other clinically significant ocular comorbidity were excluded.

### OCT measurements

All imaging procedures were obtained using Cirrus Spectral domain-OCT (Carl Zeiss Meditec) with version 6.0 software and Optovue RTVue OCT (Optovue Inc., Fremont, Calif., USA). By SD-OCT, two scan patterns, including one macular scan centred on the fovea (macula cube 512 × 218 protocols) and one peripapillary scan centred on the optic disc (optic disc cube 200 × 200 protocols), were acquired from both eyes of each subject. Only images with a signal strength of 6 or greater [15] and well-centred on the fovea or optic disc were included [19]. By Optovue RTVue OCT, choroidal thickness was measured with horizontal B-scans on vertical lines running towards the choriocleral junction, at the subfoveal region and 1.5 temporal and 1.5 mm nasal to the fovea [20].

The ganglion cell analysis (GCA) algorithm in the SD-OCT device software was used to measure macular GCIPL thickness within a 6 × 6 × 2 mm cube centred on the fovea. The sectoral thicknesses of the GCIPL were measured in an elliptical annulus (diameters: inner vertical diameter of 1 mm, outer diameter of 4 mm, inner horizontal diameter of 1.2 mm, and outer diameter of 4.8 mm) [15, 21]. The average, minimum, and six sectoral GCIPL thickness parameters (superotemporal, superior, superonasal, inferonasal, inferior and inferotemporal) were used for analysis.

### Statistical analyses

Statistical analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL). The ocular parameters and demographics of emmetropic and myopic eyes were compared using independent *t*-tests.

According to the SE, the myopic eyes were divided into three groups: low myopia (less than −0.50 D to −3.0 D), moderate myopia (less than −3.00 D to −6.00 D), and high myopia (greater than −6.00 D).

Univariate and multiple linear regression analyses were performed to determine the association of ocular and systemic factors (independent variables) with GCIPL thickness

measurements (dependent variables). The association between the GCIPL thickness and the presence of myopia was evaluated using logistic regression models to determine the odds ratio (OR) and a 95% confidence interval (CI). Multivariate-adjusted ORs were obtained after adjustment for the ACD, IOP, and AL. Receiver operator characteristic curves were generated, and the area under the curve (AUC) was used to assess the performance of the ocular parameters in developing myopia. *P* values < 0.05 were considered statistically significant.

## Results

Of all the recruited subjects for this study, one was excluded because of the diagnosis of glaucoma and another was excluded after a finding of choroidal neovascularization by SD-OCT. A total of 348 eyes (174 subjects) were included in the analysis. The mean age of subjects was  $25.97 \pm 1.79$  years. The subjects, as stated above, were divided into two groups, emmetropic ( $n = 36$ ) and myopic ( $n = 312$ ). The mean SE was  $-4.43 \pm 2.27$  D (ranging,  $-6$  to  $-11.63$  D) for the myopic group and  $-0.09 \pm 0.33$  D (ranging,  $0.50$  to  $-0.50$  D) for the emmetropic group. The detailed demographics and baseline characteristics are shown in Table 1. In comparing the myopes and emmetropes, no statistically significant differences were observed in age, central corneal thickness, systolic blood pressure (SBP), diastolic blood pressure (DBP), or systolic ocular perfusion pressure (OPP). SE, AL, intraocular pressure (IOP), anterior chamber depth, central subfoveal choroidal thickness (SFCT), diastolic OPP, and mean OPP showed statistically significant differences between myopes and emmetropes.

Average GCIPL thickness showed a significant difference between myopes and emmetropes, with  $87.89 \pm 3.65$   $\mu\text{m}$  for emmetropic groups and  $82.65 \pm 4.96$   $\mu\text{m}$  for myopic groups. The mean SFCT also showed a significant difference between myopes and emmetropes, with  $330.57 \pm 9.43$   $\mu\text{m}$  for emmetropic groups and  $265.98 \pm 4.12$   $\mu\text{m}$  for myopic groups. The average, and the minimum GCIPL thickness, and the GCIPL thicknesses at different sectors in emmetropic and myopic subgroups are shown in e-Table 1 of the online supplement. The GCIPL thickness was significantly thinner in myopia than in emmetropia at all locations ( $P < 0.05$ ). Average GCIPL thickness in high myopes was significantly thinner than that in moderate myopes, and moderate myopes had thinner average GCIPL thicknesses than low myopes. Overall, GCIPL thickness varied across the six locations. The pattern of distribution in different myopic subgroups was similar to emmetropes (Fig. 1). Among the myopic subgroups, the GCIPL was thickest at the superonasal location ( $85.04 \pm 5.77$   $\mu\text{m}$ ), which was consistent with that in the emmetropic group

**Table 1** Clinical characteristics in study subjects.

|  | Myopes<br><i>N</i> = 312 | Emmetropes<br><i>N</i> = 36 | <i>P</i> Value      |
|--|--------------------------|-----------------------------|---------------------|
| Age, years   | 25.99 (1.73)             | 25.78 (2.27)                | 0.595 <sup>a</sup>  |
| Sex, female, %                                       | 194 (62.2)               | 14 (38.9)                   | 0.011 <sup>b</sup>  |
| Axial length(AL), mm                                 | 25.16 (1.14)             | 23.78 (0.90)                | <0.001 <sup>a</sup> |
| Spherical equivalent (SE), D                         | -4.43 (2.27)             | -0.09 (0.33)                | <0.001 <sup>a</sup> |
| IOP, mm Hg   | 16.93 (3.10)             | 15.21 (2.91)                | 0.002 <sup>a</sup>  |
| Central corneal thickness, $\mu\text{m}$             | 540.41 (34.67)           | 542.31 (32.24)              | 0.755 <sup>a</sup>  |
| ACD, mm  | 3.65 (0.27)              | 3.50 (0.25)                 | 0.002 <sup>a</sup>  |
| Average GCIPL thickness, $\mu\text{m}$               | 82.65 (4.96)             | 87.89 (3.65)                | <0.001 <sup>a</sup> |
| Central subfoveal choroidal thickness, $\mu\text{m}$ | 265.98 (4.12)            | 330.57 (9.43)               | <0.001 <sup>a</sup> |
| SBP, mmHg  | 114.92 (12.22)           | 116.58 (10.42)              | 0.433 <sup>a</sup>  |
| DBP, mmHg  | 68.31 (7.67)             | 69.72 (10.04)               | 0.312 <sup>a</sup>  |
| Systolic OPP, mmHg <sup>c</sup>                      | 97.99 (12.42)            | 101.37 (9.38)               | 0.115 <sup>a</sup>  |
| Diastolic OPP, mmHg <sup>d</sup>                     | 51.38 (8.18)             | 54.51 (9.79)                | 0.034 <sup>a</sup>  |
| Mean OPP, mmHg <sup>e</sup>                          | 66.92 (8.56)             | 70.14 (8.49)                | 0.033 <sup>a</sup>  |

*SD* standard deviation, *IOP* intraocular pressure, *D* dioptre, *AL* axial length, *ACD* anterior chamber depth, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *OPP* ocular perfusion pressure.

<sup>a</sup>Independent sample *t* test.

<sup>b</sup>Fisher's exact test.

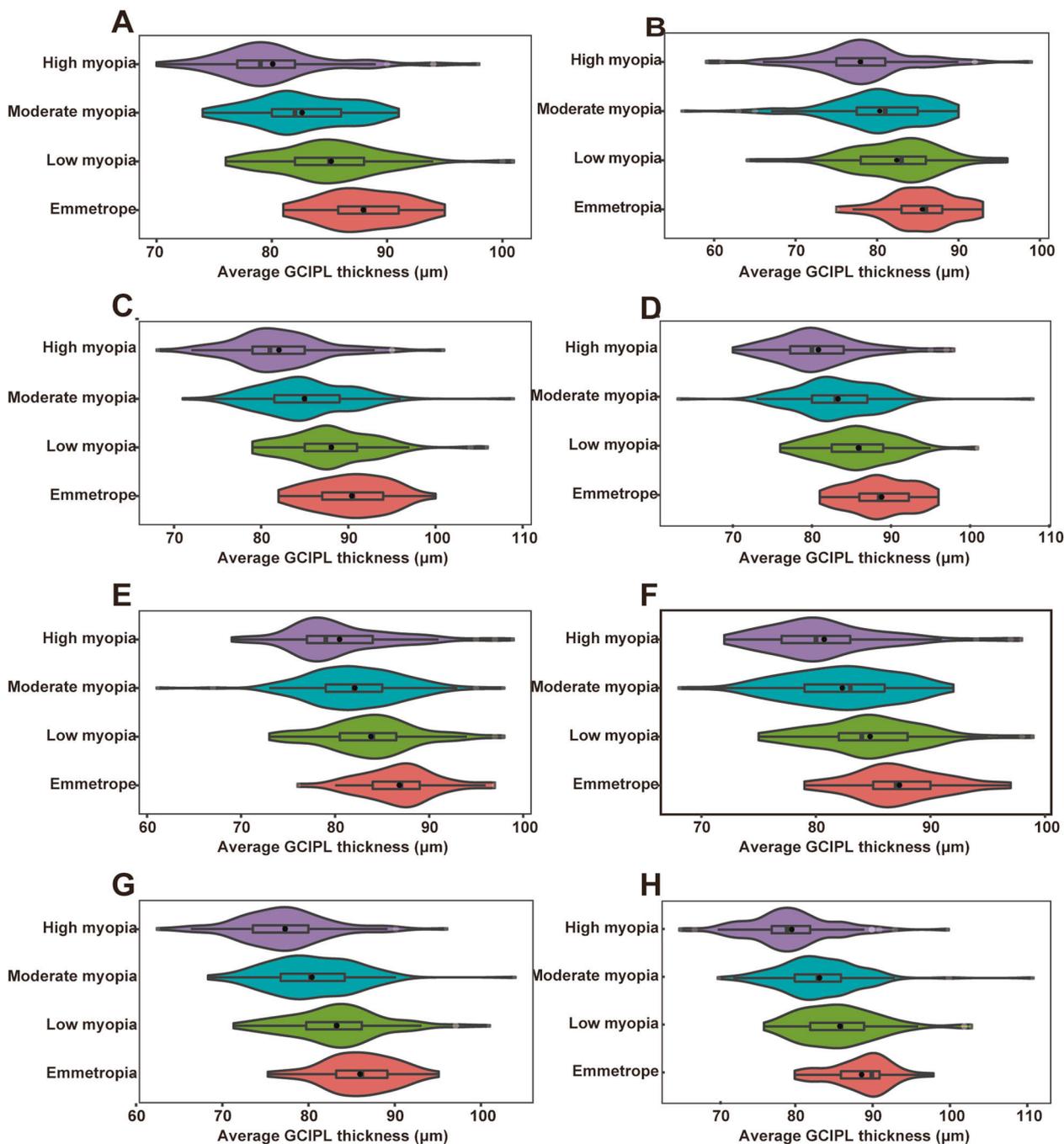
<sup>c,d</sup>Calculated as the differential pressure between Diastolic or Systolic Blood Pressure and IOP.

<sup>e</sup>Calculated as the differential pressure between mean BP and IOP (mean BP = DBP + 1/3 × (SBP - DBP)).

( $90.33 \pm 4.28$   $\mu\text{m}$ ). The GCIPL was thinnest in both myopic ( $80.00 \pm 6.60$   $\mu\text{m}$ ) and emmetropic eyes ( $85.72 \pm 4.28$   $\mu\text{m}$ ) at the inferior location.

In the univariate analysis, SE, AL, SFCT, and systolic BP, were significantly associated with average GCIPL thickness. Stepwise analysis was performed to determine factors associated with the GCIPL thickness. The model included the group of myopia (categorised by SE), AL, SFCT, and systolic BP. After adjusting for the AL, SFCT, and systolic BP by multivariate linear regression analysis, myopic eyes (which had a GCIPL that was, on average,  $3.254$   $\mu\text{m}$  thinner than that of emmetropic eyes) were associated with the GCIPL thickness ( $P < 0.001$ ) (Table 2). When the confounding factors of AL and systolic BP were controlled at all macular locations, the differences in the minimum GCIPL and GCIPL thickness at all sectors still remained statistically significant ( $P < 0.05$ ) (e-Table 2 of the online supplement).

Table 3 summarises the OR of the ocular characteristics for myopia. There was a significant association between increased AL, increased IOP, increased ACD, and



**Fig. 1** The Box+Violin plot in distribution of the GCIPL thickness in different myopic subgroups. Box + Violin plot showing the GCIPL thickness of the emmetropia group, low myopia, moderate myopia, and high myopia groups, as to: **a** Average GCIPL thickness of emmetropia group and different myopia subgroups. **b** Minimum GCIPL thickness of emmetropia group and different myopia subgroups. **c** Superonasal GCIPL thickness of emmetropia group and

different myopia subgroups. **d** Superior GCIPL thickness of emmetropia group and different myopia subgroups. **e** Superotemporal GCIPL thickness of emmetropia group and different myopia subgroups. **f** Inferotemporal GCIPL thickness of emmetropia group and different myopia subgroups. **g** Inferior GCIPL thickness of emmetropia group and different myopia subgroups. **h** Inferonasal GCIPL thickness of emmetropia group and different myopia subgroups.

decreased GCIPL thickness and greater odds of association with myopia in the univariate analysis. GCIPL (OR 0.863, 95% CI 0.785–0.949), AL (OR 2.499, 95% CI 1.532–4.075), and IOP (OR 1.250, 95% CI 1.086–1.438) remained significant in the multivariate analysis.

The relation between the GCIPL thickness at all sectors and myopia is shown in e-Table 3 of the online supplement. The univariate analysis showed that the GCIPL thickness at each sector was significantly associated with myopia. After adjusting for AL, IOP, and ACD in the multivariate logistic

analysis, the adjusted ORs of each sector (95% CI) for myopia, as compared with emmetropia, were all <1.

Multivariable models of myopic subgroups with different degrees of myopia is shown in e-Table 4 of the online supplement. When adjusting for AL, IOP, and ACD in the myopia subgroup, the GCIPL thickness of each sector remained positively associated. Similar associations were present in the moderate and high myopia subgroups in the multivariate analysis.

We calculated the AUC, sensitivity, and specificity in Table 4. The greatest AUC was obtained for AL (AUC = 0.830). The next best performance was obtained for average GCIPL thickness (AUC = 0.804), followed by ACD and AL.

## Discussion

The current study investigated the ocular associations for myopia. Previous studies have reported significant relationships between myopia and several factors, such as AL [6], choroid thickness [8], retinal thickness, and macular vessel density [7]. Among these, the elongation of the globe, which leads to the thinning of macular retinal thickness in myopic eyes, is well confirmed. Although understanding the characteristics of the inner retinal layer has increased substantially in recent years, only a few studies have assessed the relationship between the GCIPL thickness and varying degrees of myopia.

In our study, we found that the mean GCIPL thickness in the myopic group was significantly thinner than that in the

emmetropic group. The mean GCIPL thickness in the myopic group was 82.65  $\mu\text{m}$ , which is much thicker than those reported in previous studies showing a mean GCIPL thickness of 72.86  $\mu\text{m}$  [10, 19]. The differences may be due to differences in subjects' characteristics, such as age, ethnicity, and refractive error [22]. Compared with other studies, the age of our participants is about half, with a mean age of 25.97 years [19]. We speculated that the GCIPL may undergo further age-related attenuation with advancing age.

When comparing the GCIPL thickness at different sectors between the emmetropic group and groups with different degrees of myopia, the thinnest and thickest sectors were the inferior and superonasal sectors, respectively. Our result is in accordance with Mwanza's study [15], which showed superonasal GCIPL as the thickest sector and the inferior GCIPL as the thinnest sector. In a study among myopic Chinese children, Deng et al. also found a change in asymmetry in the GCL + layer [11]. Moreover, a histologic study by Curcio and Allen [23] showed greater ganglion cell density in the nasal and superior retinal regions and the lowest density in the inferior sector. These findings, in line with our study, may indicate that the distribution of GCIPL varies in different sectors.

Our study revealed that, among the range of ocular factors, AL, degree of myopia, central subfield choroidal thickness (SFCT), and SBP were the independent correlative factors of GCIPL thickness. After adjusting for the AL, SFCT, and SBP by multivariate linear regression analysis, the average GCIPL thickness of the myopic group remained significantly thinner than that of the emmetropic group. These predictors of GCIPL thickness were somewhat similar to Koh's study on emmetropic GCIPL thickness [19]. The reason for the thinning of the GCIPL thickness in myopia can be explained by the stretching effect from an elongated eye and the lower ganglion cell density resulting from the larger retinal surface area in myopic eyes. It is possible that the lower superficial parapapillary microvascular density in myopia [24] to satisfy the metabolic demands of the neuroretina also may lead to ocular structural changes.

Unexpectedly, our study first found that SBP was the independent factor associated with mean GCIPL thickness

**Table 2** Mean GCIPL thickness and stepwise model multivariable associations.

| Factors   | Beta (95% CI)             | P value |
|---|---------------------------|---------|
| Myopia (versus emmetropia)                          | -3.254 (-5.001 to -1.507) | <0.001  |
| AL, mm  | -1.441 (-1.924 to -0.958) | <0.001  |
| Systolic BP, mmHg                                   | 0.067 (0.028–0.105)       | 0.001   |
| Central subfield choroidal thickness, $\mu\text{m}$ | 0.006 (-0.002 to 0.013)   | 0.133   |

AL axial length.

**Table 3** Univariate and multivariate analysis of risk factors associated with myopia.

| Factors                                | Unadjusted OR (95% CI) | P value | Multivariate-adjusted OR (95% CI) | P value |
|--|------------------------|---------|-----------------------------------|---------|
| Average GCIPL thickness, $\mu\text{m}$ | 0.809 (0.747–0.875)    | <0.001  | 0.863 (0.785–0.949)               | 0.002   |
| AL, mm                                 | 3.417 (2.275–5.132)    | <0.001  | 2.499 (1.532–4.075)               | <0.001  |
| IOP, mm Hg                             | 1.215 (1.074–1.375)    | 0.002   | 1.250 (1.086–1.438)               | 0.002   |
| ACD, mm                                | 6.515 (1.897–22.371)   | 0.003   | 1.932 (0.351–10.631)              | 0.449   |

OR odds ratio, CI confidence interval, AL axial length, IOP intraocular pressure, ACD anterior chamber depth.

**Table 4** AUC, sensitivity and specificity of mean GCIPL, ACD, AL and IOP for detecting myopia.

| Factor                                 | Sensitivity (%) | Specificity (%) | AUC (95% CI)        | <i>P</i> value |
|--|-----------------|-----------------|---------------------|----------------|
| Average GCIPL thickness, $\mu\text{m}$ | 83.3            | 66.7            | 0.804 (0.742–0.865) | <0.001         |
| AL, mm                                 | 77.2            | 75.0            | 0.830 (0.769–0.892) | <0.001         |
| IOP, mm Hg                             | 84.9            | 38.9            | 0.654 (0.561–0.747) | 0.002          |
| ACD, mm                                | 62.8            | 63.9            | 0.662 (0.572–0.753) | 0.001          |

AUC area under the curve, CI confidence interval, AL axial length, IOP intraocular pressure, ACD anterior chamber depth.

among young adults. The inner retinal layer, where blood flow is autoregulated [25], is metabolically controlled and nourished by the retinal vasculature through Müller cells [26]. The relation between blood pressure and retinal susceptibility to an elevation of IOP has been clarified in a rat model by He et al. [27]. That study indicated that the GCIPL thickness might be sensitive to the SBP. Since our study did not find an association of GCIPL thickness with retinal arterial or venous vessels in myopia, further investigations into the precise mechanisms of GCIPL thickness influenced by SBP and the correlation between ocular vascular changes and myopia are warranted in the future.

It is noteworthy that we found that decreased GCIPL thickness was independently associated with myopia after adjusting for other known associated biometric parameters, including AL. The myopic subgroup analysis further ascertained that GCIPL thickness in all sectors could predict the progression of myopia. Choroidal thickness has been considered a higher predictor than retinal thickness of posterior staphyloma height in myopic eyes, and hypoxia in scleral extracellular matrix plays an essential role in myopia [28, 29]. Thinner GCIPL thickness leads to decreased blood flow in the inner retinal layer that partially nourishes the inner retina, thus making it more susceptible to hypoxia, and this may aggravate the development of myopia. This identification was a novel finding among young adults and might help develop an imaging biomarker to detect early onset of myopia-related retinopathy. Further longitudinal studies are needed to reveal which event occurs first.

In this study, we also found that IOP was independently associated with myopia. Under elevated IOP, there may be biomechanical traction of the sclera, which will elongate the eyeball. Myopia is a well-known risk factor for primary open-angle glaucoma [30], and our research also confirmed that the myopic group had relatively higher IOP than the emmetropic group. These suggest that more attention should be paid to an increase in IOP in myopia, especially in high myopia.

The present study has its strengths as well as certain limitations. It is strengthened by its large, young myopic population with a range of myopia and thus free of confounding factors. Findings from this population have clinical implications and may help us to better understand the role of the GCIPL in myopia development and progression.

However, this may limit the application of these data to subjects of different ages or ethnicities. Further studies in other ethnic groups and different age ranges are needed to confirm the results. Another limitation is the small number of normal controls. Further large-cohort studies comparing the characteristic of GCIPL between myopic eyes and nonmyopic eyes will be valuable to validate our findings.

In conclusion, our study showed that in a specific young Chinese population, myopic eyes have a lower macular GCIPL thickness than normal eyes. Decreasing GCIPL thickness may be associated with the progression of myopia. Findings from this study may help us better understand the role of the inner retinal layer in the development and progression of myopia. Further investigations into the precise mechanisms of how decreasing GCIPL thickness affects the progression of myopia and glaucoma are needed.

## Summary

### What was known before

- A longer axial length (AL), thinning of the retina, and choroid are thought to be the key processes in the development of myopia.

### What this study adds

- To describe the distribution of GCIPL thickness among Chinese young adults and report whether the decreased GCIPL thickness is association with myopia.

**Funding** This work was supported by National Nature Science Foundation of China (81730026), National Science and Technology Major Project for Drug Discovery of the Ministry of Science and Technology of China (2018ZX09301029-001), Frontier Project of Hospital Development Center (SHDC12016105), Clinical Research Innovation Team Project of Shanghai General Hospital (CTCCR-2016A02), Cross Funding of Shanghai Jiao Tong University (YG2017QN31), and Shanghai Natural Science Foundation (19ZR1440900).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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