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Sympathetic nervous system activity is associated with choroidal thickness and axial length in school-aged children

Senlin Lin ,¹ Bijun Zhu,² Ting Wang,³ Hong Wang,³ Xian Xu ,² Shanshan Wang,² Yao Yin,⁴ Zhaoyu Xiang,² Yu Qian,² Zhang Zhang,² Lipu Cui ,² Haidong Zou,^{1,2} Xiangui He ,¹ Jianfeng Zhu ,¹ Yingyan Ma ^{1,2}

¹Shanghai Eye Disease Prevention and Treatment Center, Shanghai Eye Hospital, Shanghai, China

²Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Fundus Diseases, National Clinical Research Center for Eye Diseases, Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai, China

³Department of Preventive Ophthalmology, Yangpu District Kongjiang Hospital, Shanghai, China

⁴Department of Ophthalmology, Fengcheng Hospital, Shanghai, China

Correspondence to

Dr Yingyan Ma, Dr Jianfeng Zhu, Dr Xiangui He and Dr Haidong Zou, Shanghai, People's Republic of China; mYy_29@163.com, jfzhu1974@hotmail.com, xianhezi@163.com, zouhaidong@sjtu.edu.cn

SL and BZ contributed equally.

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ABSTRACT

Background/aims We aim to explore the effect of sympathetic nervous system (SNS) on choroid thickness (ChT) and axial length (AL).

Methods Students of grade 2 and 3 from a primary school were included and followed for 1 year. Visual acuity, refraction, AL and ChT were measured. Morning urine samples were collected for determining SNS activity by analysing concentrations of epinephrine, norepinephrine and dopamine using the liquid chromatography-tandem mass spectrometry. The most important factor (factor 1) was calculated using factor analysis to comprehensively indicate the SNS activity.

Results A total of 273 students were included, with an average age of 7.77±0.69 years, and 150 (54.95%) were boys. Every 1 µg/L increase in epinephrine is associated with 1.60 µm (95% CI 0.30 to 2.90, p=0.02) decrease in average ChT. Every 1 µg/L increase in norepinephrine is associated with 0.53 µm (95% CI 0.08 to 0.98, p=0.02) decrease in the ChT in inner-superior region. The factor 1 was negatively correlated with the ChT in the superior regions. Every 1 µg/L increase in norepinephrine was associated with 0.002 mm (95% CI 0.0004 to 0.004, p=0.016) quicker AL elongation. The factor 1 was positively correlated with AL elongation (coefficient=0.037, 95% CI 0.005 to 0.070, p=0.023).

Conclusions We hypothesised that chronic stress characterised by elevated level of the SNS, was associated with significant increase in AL elongation, probably through thinning of the choroid.

INTRODUCTION

Myopia is one of the most common eye diseases in school-aged children, with a prevalence of 69% at 15 years of age in East-Asia.¹ The visual impairment caused by uncorrected myopia and pathological myopia could lead to a huge disease burden on a global scale.^{2,3} Education is an important risk factor of myopia.⁴ Prevalence of myopia increases dramatically after children enter primary school, and more years of education are associated with increased prevalence of myopia, and the causal relationship has been verified by Mendelian randomisation.^{4–6} Moreover, children studying in academically oriented classes or schools tend to be more myopic.^{4,6} However, the mechanism by which

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Education is a well-known risk factor for myopia. Whether stress response caused by education could lead to myopia is unclear.

WHAT THIS STUDY ADDS

⇒ This longitudinal study of 273 school children found that activity of sympathetic nervous system (SNS) measured by urine catecholamine concentrations was associated with longer axial length (AL) and quicker axial length elongation. Mediation analyses found that the effect was through the thinning of the choroid.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study proposed that chronic stress resulting from stressful education environment characterised by the elevated level of the SNS, was associated with significant increase in the AL elongation, which could explain how education leads to myopia.

education causes myopia is unclear.⁴ Although it may be related to too much near work activity, the current studies suggested the association is weak and inconsistent, and the mechanism is still controversial.⁴ The unknown mechanisms by which education leads to myopia hinder effective interventions to control the prevalence.

Biopsychological social medicine believes that socialpsychological factors can act on the body and cause various physiological or pathological changes.⁷ The modern education environment, especially in East-Asia, is full of pressure, for example, pressure from various kinds of examinations, pressure from competition among classmates, and pressure from schools, teachers and parents' expectations. The intensive and highly stressful education environment, along with little physical activity, may cause a heavy and long-lasting mental and psychological burden on children.^{8,9} Chronic stress response characterised by activation of the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal axis can be generated.¹⁰ The activation of the SNS under stress response is

associated with the activation of the preganglionic sympathetic nerves, located in the locus coeruleus of the brain stem, which trigger the release of catecholamines from the adrenal medulla.¹¹ These catecholamines help facilitate the immediate physical reactions characteristic of SNS activity, such as elevated heart rate (HR) and breathing, and vasoconstriction or vasodilation in different organs.¹¹

The activation of SNS can also act on the fundus tissues, especially the choroid. In a variety of mammals, including primates, unilateral sympathetic nerve stimulation causes a substantial reduction in choroidal blood flow, mediated through α -adrenoreceptors, likely via α_1 -adrenoreceptors.¹² In rats, sympathetic denervation can increase the blood flow and thicken the choroid.^{13–14} In human eyes, systemic use of adrenergic receptor agonists or blockers can correspondingly thin or thicken the choroid.^{15–17} The sympathetic nerves innervate the choroidal blood vessels of the eye and the non-vascular smooth muscle cells in the suprachoroidal space and directly regulate the contraction and dilation of the choroidal blood vessels and the non-vascular smooth muscle cells in the suprachoroidal space, which could be the reason for changes in choroidal blood flow and thickness.^{12–18}

Current researches suggest that choroid plays an important role in the development and progression of myopia and the regulation of axial length (AL) elongation.^{18–19} The thickening of the choroid was usually associated with inhibition of AL elongation, while, the thinning of the choroid was usually associated with promotion of AL elongation.^{18–19} Therefore, we speculate that activation of SNS in school-aged children can lead to choroidal thinning and promote the growth of the AL, which could be the reason for the incidence or progression of myopia. To verify this hypothesis, we conducted a longitudinal study investigating 273 school-aged children in Yangpu District, Shanghai. First, we explored the relationship between SNS activity, measured by the urine epinephrine (E), norepinephrine (NE) and dopamine (DA) concentration, and the choroid thickness (ChT). Then, we analysed the association between the activity of the SNS and AL elongation.

METHODS

Participants and study design

A primary school in Yangpu District, Shanghai, China was randomly selected, and students from second grade to third grade were all included. Children with pre-existing serious systemic diseases or eye diseases (except for refractive error) were excluded from the study. The first investigation was carried out in September 2019, and the second was carried out in September 2020.

Ocular examinations

Students underwent an uncorrected distant visual acuity test and best-corrected visual acuity test using the Early-Treatment Diabetic Retinopathy Study (ETDRS) chart. Axial length were measured using IOL-Master (version 5.02, Carl Zeiss, Jena, Germany), and were determined by the mean of three consecutive measurements, which represented the length between the tear film and the retinal pigment epithelial layer. To test the repeatability of AL, we did the measurement twice for another 14 children apart for 1 hour, and the difference between the two measurements ranged from -0.01 mm to $+0.01$ mm, with the average difference of -0.0007 ± 0.007 mm. Refraction was measured as the mean of three consecutive auto-refractor measurements (KR-8900, Topcon, Tokyo, Japan). This gave

values for spherical dioptres (DS) and cylinder dioptres (DC). Spherical equivalent refraction (SE) = $DS + 0.5 * DC$.

An swept-source OCT (SS-OCT) (DRI OCT Triton-1, Topcon, Tokyo, Japan) was used to measure the choroidal thickness. Before scanning, AL (mm) was input to the OCT system to perform calibration. The ETDRS grid was applied once the tomography map was obtained, which divided the macula into three concentric circles centred in the fovea: 1 mm (centre), 3 mm (inner) and 6 mm (outer). The inner and outer rings were further divided into four quadrants: temporal, superior, nasal and inferior. Average choroidal thickness was directly output by the SS-OCT, which represents the average choroidal thickness over a diameter range of 6 mm centred on the fovea. The measurement was carried out between 9:00 and 11:00 hours, and the average of three consecutive measurements was determined as the ChT. The repeatability of the measurement of the choroidal thickness was presented in our previous study.²⁰

Urine catecholamine collection and measurement

The participants were informed to avoid eating bananas, vanillin-containing foods, coffee and tea within 2 days before the test, since these diets could influence the accuracy of urinary catecholamine measurement. One day before the test, test tubes with names numbered labels, and preservatives were distributed to the participants. Children were asked to collect their first urination in the morning with the assistance of their parents and bring them back to school the same day in the morning. The researcher of the study collected the urine samples and transported them to the laboratory in time in an environment protected from light and under the temperature of 4°C.

After the solid phase extraction technology for sample clean-up, the liquid chromatography-tandem mass spectrometry is used to determine the urine concentrations of E, NE and DA in the multireaction detection mode, and the internal standard method is used for quantification.

Table 1 Basic characteristics of the study population

Variables	All (n=273)
Age, years, mean \pm SD	7.77 \pm 0.69
Gender, male no (%)	150 (54.95)
Grade 2, no (%)	141 (51.65)
LogMAR VA, mean \pm SD	0.13 \pm 0.25
Spherical equivalent refraction in 2019, D, mean \pm SD	-0.2 \pm 0.98
Axial length in 2019, mm, mean \pm SD	23.26 \pm 0.87
Spherical equivalent refraction in 2020, D, mean \pm SD	-0.78 \pm 1.23
Axial length in 2020, mm, mean \pm SD	23.71 \pm 0.96
Average choroidal thickness, μ m, mean \pm SD	242.67 \pm 45.57
Central choroidal thickness, μ m, mean \pm SD	267.2 \pm 59.13
Inner temporal choroidal thickness, μ m, mean \pm SD	280.53 \pm 58.06
Inner superior choroidal thickness, μ m, mean \pm SD	261.02 \pm 55.9
Inner nasal choroidal thickness, μ m, mean \pm SD	228.91 \pm 54.21
Inner inferior choroidal thickness, μ m, mean \pm SD	270.49 \pm 58.39
Outer temporal choroidal thickness, μ m, mean \pm SD	277.28 \pm 50.45
Outer superior choroidal thickness, μ m, mean \pm SD	248.04 \pm 49.73
Outer nasal choroidal thickness, μ m, mean \pm SD	171.76 \pm 46.29
Outer inferior choroidal thickness, μ m, mean \pm SD	249.95 \pm 50.48
DA, μ g/L, mean \pm SD	287.62 \pm 140
NE, μ g/L, mean \pm SD	20.03 \pm 15.44
E, μ g/L, mean \pm SD	2.76 \pm 4.31
DA, dopamine; E, epinephrine; NE, norepinephrine; VA, visual acuity.	

Statistical analyses

Since the concentrations of E, NE and DA were affected by the activity of SNS, factor analysis was performed to accurately estimate the activity of SNS. Factor analysis is a method for modelling observed variables, and their covariance structure, in terms of a smaller number of underlying unobservable factors. In factor analysis, the observed variables were modelled as linear functions of the factors. Factor rotation is employed.²¹ In our study, the most important factor (factor 1) was calculated and used as the measurement of SNS activity (eigenvalue=1.65). Therefore, E, NE, DA and Factor 1 were all analysed, respectively, for exploring associations between SNS activity and ChT and AL.

The data from the right eye were used for analyses. Myopia was defined as SE \leq -0.5 and uncorrected visual acuity \leq 20/25. The influence of E, NE, DA and factor 1 on the baseline AL, 1-year change in AL, baseline SE, 1-year change in SE and ChT were analysed, respectively, using robust regression. The 1-year change in AL/SE was calculated as the AL/SE at the second visit minus the AL/SE at the first visit. Furthermore, the influence of ChT on the baseline AL and the 1-year change in AL were also analysed using robust regression. We used mediation analysis to test whether the thickness of ChT was a potential mediator of the association between catecholamine concentrations and AL, after adjusting the confounders including sex, age and refractive status. All statistics were performed using SAS V.9.4 (SAS).

RESULTS

Basic characteristics

Fourteen students were excluded from the study because of missing items from the ocular examinations or urine samples. Therefore, the study finally included 273 students, with an average age of 7.77 ± 0.69 years, and 150 (54.95%) were boys. Baseline characteristics of ocular examinations, ChT and urine catecholamine concentration were presented in table 1.

Correlations between catecholamine and ChT

The multivariate regression analyses suggested that E concentration was negatively associated with the ChT in almost all the regions, except for the outer ring of the superior and nasal quadrant. Every 1 $\mu\text{g/L}$ increase in E is associated with a 1.60 (95% CI 0.30 to 2.90) μm decrease in average ChT. The NE concentration was negatively associated with the ChT in the inner superior region, and every 1 $\mu\text{g/L}$ increase in NE is associated with a 0.53

(95% CI 0.08 to 0.98) μm decrease in the ChT. The factor 1 was negatively associated with the ChT in the inner superior and outer superior region (table 2).

Correlations between catecholamine, AL and refraction

The multivariate regression analyses suggested that NE concentration was positively correlated with the baseline AL, and every 1 $\mu\text{g/L}$ increase in NE was associated with a 0.008 mm increase in the baseline AL (table 3). The factor 1 was positively correlated with the baseline AL ($p=0.022$). For all children, NE concentration was positively correlated with AL elongation, and every 1 $\mu\text{g/L}$ increase in NE was associated with 0.002 mm (95% CI 0.0004 to 0.004, $p=0.016$) greater elongation of AL in 1 year. The factor 1 was positively correlated with AL elongation (coefficient=0.037, 95% CI 0.005 to 0.070, $p=0.023$). Negative associations were found between baseline SE and NE, DA and factor 1, and the relationship remained significant for change in SE and NE, factor 1 (table 3).

Correlations between ChT and AL

The multivariate regression analyses suggested that ChT in all the regions were negatively associated with the baseline AL (table 4). In addition, the average ChT, inner superior ChT, inner inferior ChT, outer superior ChT, outer nasal ChT and outer inferior ChT were negatively associated with AL elongation. Every 1 μm decrease in the average ChT was associated with 0.0009 (0.0002–0.0015) mm quicker elongation of AL.

Furthermore, through mediation analysis, we found that the thickness of inner superior ($p=0.35$, root-mean-square error of approximation (RMSEA)=0.02, goodness-of-fit index (GFI)=0.99, adjusted goodness-of-fit index (AGFI)=0.98, comparative fit index (CFI)=1.00, normed fit index (NFI)=0.96) ChT significantly mediated the association between factor 1 and the change of AL and SE (figure 1).

DISCUSSION

This is the first study to explore the relationship between the activity of SNS, measured by children's urinary catecholamines and myopia. We found that children with higher activity of SNS had thinner ChT, longer AL and quicker AL elongation. Therefore, we speculate that a higher level of SNS activity was

Table 2 Correlations between catecholamine concentrations and choroidal thickness

ChT region	Avg	Centre	InT	InS	InN	InI	OutT	OutS	OutN	OutI
E										
Coefficient*	-1.60	-1.88	-1.97	-1.97	-1.84	-1.83	-1.66	-1.29	-1.16	-1.67
P value	0.02	0.03	0.02	0.01	0.02	0.03	0.03	0.07	0.10	0.02
NE										
Coefficient*	-0.31	-0.37	-0.39	-0.53	-0.31	-0.30	-0.35	-0.38	-0.08	-0.29
P value	0.12	0.14	0.12	0.02	0.18	0.24	0.11	0.07	0.68	0.18
DA										
Coefficient*	-0.02	-0.03	-0.03	-0.04	-0.02	-0.02	-0.03	-0.04	0.00	-0.02
P value	0.29	0.32	0.22	0.16	0.34	0.56	0.23	0.10	0.96	0.31
Factor 1										
Coefficient*	-5.63	-6.74	-7.37	-9.12	-5.83	-5.44	-6.48	-6.96	-1.65	-5.65
P value	0.09	0.11	0.08	0.02	0.14	0.20	0.08	0.047	0.63	0.12

*Effects of E, NE, DA and factor 1 on the choroidal thickness of various regions were analysed using robust regression, adjusted for age, gender and baseline refractive status. Avg, average; ChT, choroidal thickness; DA, dopamine; E, epinephrine; InI, inner inferior; InN, inner nasal; InS, inner superior; InT, inner temporal; NE, norepinephrine; OutI, outer inferior; OutN, outer nasal; OutS, outer superior; OutT, outer temporal.

Table 3 Correlations between catecholamine concentrations, AL and refraction

	Baseline AL		1 year change in AL		Baseline SE		1 year change in SE	
	Coefficient*	P value	Coefficient*	P value	Coefficient*	P value	Coefficient*	P value
E	0.0015	0.894	0.0018	0.604	-0.0047	0.563	-0.0048	0.591
NE	0.0082	0.013	0.0024	0.016	-0.0046	0.045	-0.0057	0.025
DA	0.0006	0.066	0.0002	0.073	-0.0006	0.017	-0.0004	0.189
Factor 1	0.1274	0.022	0.0373	0.023	-0.0855	0.028	-0.0866	0.045

*Effects of E, NE, DA and Factor 1 on the baseline AL, 1-year change in AL, baseline SE and 1-year change in SE were analysed using robust regression, adjusted for age, gender and baseline refractive status.
AL, axial length; DA, dopamine; E, epinephrine; NE, norepinephrine; SE, spherical equivalent refraction.

Table 4 Correlations between choroidal thickness and axial length

ChT region	Avg	Centre	InT	InS	InN	InI	OutT	OutS	OutN	OutI
Baseline AL										
Coefficient*	-0.0036	-0.0031	-0.003	-0.002	-0.0034	-0.0037	-0.0019	-0.002	-0.0033	-0.0035
P value	0.001	0.0003	0.0003	0.0275	0.0002	<0.0001	0.0477	0.0506	0.002	0.0004
Change in AL										
Coefficient*	-0.0009	-0.0004	-0.0004	-0.0007	-0.0005	-0.0005	-0.0006	-0.0007	-0.0007	-0.0007
P value	0.012	0.1132	0.1328	0.0075	0.0542	0.0365	0.0504	0.0166	0.0266	0.0142

*Effect of choroidal thickness on the axial length were analysed using robust regression, adjusted for age, gender and baseline refractive status.
AL, axial length; Avg, average; ChT, choroidal thickness; InI, inner inferior; InN, inner nasal; InS, inner superior; InT, inner temporal; OutI, outer inferior; OutN, outer nasal; OutS, outer superior; OutT, outer temporal.

associated with AL elongation probably through thinning of the choroid (figure 1).

The results of the present study were in accordance with previous studies. Topical use of 2.5% phenylephrine hydrochloride in the eye did not show any effect on the ChT in healthy adults.²² However, after 1-hour oral administration of pseudoephedrine, the choroid thinned about 13 µm but recovered after 3 hours.¹⁵ Using α1A-adrenoceptor antagonist tamsulosin hydrochloride for 3 months can increase ChT by 12–16 µm.¹⁶ In

addition, taking 100 mL Turkish coffee (57 mg caffeine/100 mL), an SNS stimulator, can lead to a significant thinning of the human choroid (up to 50 µm) and last for more than 4 hours.²³ The present study is the first to report the positive association between sympathetic excitation and ChT in children under natural conditions.

We also find a significant association between urine catecholamine concentrations and AL, that is, higher the urine catecholamine concentrations, longer the AL and quicker elongation. We

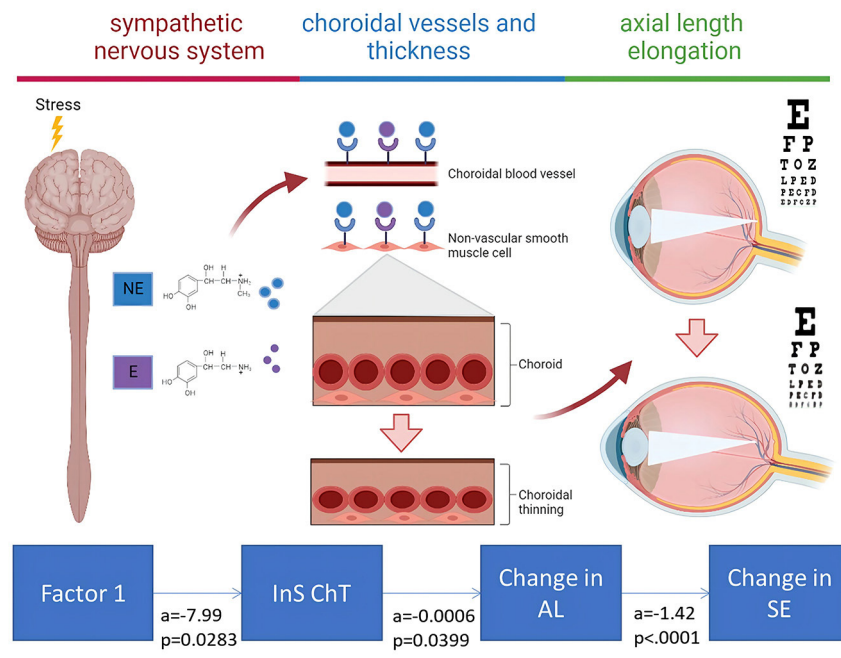


Figure 1 Mediation analyses and schematic diagram of the research hypothesis. The results of the mediation analyses and the schematic diagram of the research hypothesis are shown in figure 1. AL, axial length; ChT, choroidal thickness; InS, inner superior; SE, spherical equivalent refraction.

proved that this effect is caused by the thinning of the choroid through mediation analyses. The choroid is a highly vascular structure. Animal studies found that the choroid thins during myopia development and thickens during recovery in various kinds of animals, including chicks, guinea pigs and marmosets.^{18,19} The thinning in ChT was associated with a decrease in choroidal blood perfusion, thus leading to hypoxia in the nearby scleral tissue.²⁴ Scleral hypoxia would enable transdifferentiation of fibroblasts into myofibroblasts, causing extracellular matrix remodelling and axial elongation.²⁴ Although the present study did not measure choroidal blood perfusion, Jendzjowsky *et al* found that choroid vascular perfusion density (VPD), but not retina VPD, was negatively associated with muscle sympathetic nerve activity assessed using microneurography ($R = -0.76$; $p < 0.0001$), and the correlation is even stronger than HR variability,¹⁷ which also proved our assumption. Additionally, thicker choroids may function to slow the AL elongation by acting as a barrier to the diffusion of growth factors or as a mechanical buffer for the sclera as suggested by Troilo *et al*.²⁵ In contrast, thinner choroids may promote the access of molecules to the sclera, accelerate the scleral extracellular matrix remodelling and eventually facilitate AL elongation.^{18,24,25}

Stress is generally believed to lead to elevated levels of the SNS, which is characterised by increased catecholamines excretion.^{10,11,26} Our results suggested a possible mechanism of how education leads to myopia: the education-related stress, could increase the sympathetic nervous activation, which is associated with decreased choroidal thickness and increased AL, leading to myopia incidence or progression. Literature about stress and myopia is scarce. Angi and associates conducted a prospective study on 57 university students, and they did not find a causal relationship between psychophysical stress and myopia, despite that the anxiety scores were higher in myopic students at baseline.²⁷ Some later researches also confirmed that myopic people usually have higher anxiety levels compared with non-myopic people.^{28–30} Anxiety could also lead to an elevated level of SNS activity, similar to that proposed for chronic stress, characterised by increased release of peripheral catecholamines.³¹ Meanwhile, other environmental risk factors which could cause chronic elevated SNS activity, such as excessive use of electronic devices, less time for physical activity and air pollution also need our attention.^{9,32–34} Future studies were needed to clarify how environmental risk factors affect the activity of SNS, and potential prevention methods could be achieved.

There are some limitations of this study. First, the refraction and refractive status were not measured after cycloplegia. The present study used non-cycloplegic $SE \leq -0.5$ and uncorrected visual acuity $\leq 20/25$ to classify myopia and non-myopia children. Using a combination of the two tests in serial order was verified to increase specificity without significantly reducing sensitivity.³⁵ Second, the measurement of urine catecholamine concentrations without creatinine correction might affect the accuracy of the concentrations. Since the participants in the present study were all grade 2 and 3 students without renal diseases or other systemic diseases, and without history of medication, taking the morning urine can also avoid the influence of strenuous exercise, food and drink on the measurement, which has been widely used in previous researches, and proved to be comparable to 24-hour urine collection.^{36,37} Third, the activity of the SNS was only based on the urine catecholamine concentrations, without other examinations to verify the accuracy. Methods for assessing sympathetic activity vary and include cardiovascular measures such as HR, blood pressure, the muscle sympathetic nerve microneurography and urinary catecholamine

concentrations.³⁸ Urinary catecholamine levels could serve as an approximation of the activity of the SNS and can be useful as measures of chronic stress.²⁶ Unlike measuring circulating catecholamines, they represent the sum of events occurring over a long run including central sympathetic outflow as well as the release and reuptake into nerve terminals and overflow from various vascular beds by peripheral mechanisms.³⁹ Future studies are needed to determine the activity of the SNS using different measurements to comprehensively verify the present results and hypothesis. Last but not the least, the coefficients between choroidal thickness and change in AL were relatively small, despite the p values were significant. The results were in accordance with previous studies,^{40–42} however, we also need to be cautious that the relationship between choroidal thinning and AL elongation is not absolute, and can be dissociated under some certain conditions such as brief episodes of lens wear.^{43–45}

CONCLUSIONS

Elevated level of the SNS is associated with a significant decrease in choroidal thickness and increase in the AL elongation. According to the results, we proposed a hypothesis that chronic stress characterised by the elevated level of the SNS, was associated with significant increase in the AL elongation, probably through the thinning of the choroid, which provides cues for explaining the mechanisms by which education causes myopia.

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ORCID iDs

Senlin Lin <http://orcid.org/0000-0002-0166-1308>
 Xian Xu <http://orcid.org/0000-0002-5845-107X>
 Lipu Cui <http://orcid.org/0000-0002-6629-1272>
 Xiangui He <http://orcid.org/0000-0002-8938-1879>
 Jianfeng Zhu <http://orcid.org/0000-0002-4453-611X>
 Yingyan Ma <http://orcid.org/0000-0003-4250-0356>

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