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Population-based associations between progression of normal-tension glaucoma and Yang-deficient constitution among Chinese persons

Lewei Tang,[1,2] Liang Chen,[3] Cong Ye,[1,2] Jingwei Zheng,[1,2] Yi Zhou,[4] Yan Tao,[1,2] Qiangjie Huang,[1,2] Xiaoyan Wang,[1,2] Xiao Shang ,[1,2] Xiafei Pan,[1,2] Nathan Congdon ,[5,6] Yuanbo Liang [1,2]

[1]Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China
[2]National Clinical Research Center for Ocular Diseases, Wenzhou, China
[3]Wenzhou Medical University Second Affiliated Hospital, Wenzhou, China
[4]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[5]Centre for Public Health, Queen's University Belfast, Belfast, UK
[6]ORBIS International, New York, New York, USA

Correspondence to
Dr Yuanbo Liang, Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, Zhejiang, China; yuanboliang@126.com

Received 25 March 2021
Accepted 23 July 2021
Published Online First 6 August 2021

ABSTRACT

Purpose To explore the association between constitution types as defined by traditional Chinese medicine (TCM) and risk for normal-tension glaucoma (NTG).

Design Population-based cohort study.

Methods Persons were identified in a population cohort aged ≥30 years with NTG, defined as having an untreated mean intraocular pressure measurement ≤21 mm Hg over six separate occasions, with no single reading >24 mm Hg (as in the Collaborative Normal Tension Glaucoma Study). The Body Constitution in Traditional Chinese Medicine Questionnaire was used to assess each participant's TCM constitution types. The association between various constitutions and visual field progression according to Early Manifest Glaucoma Trial criteria was assessed using Cox regression HR models.

Results Among 142 participants (245 eyes), 23 persons (17.6%) and 25 eyes (10.2%) progressed, over a mean (SD) follow-up duration of 3.49 (0.99) years. Progression rates were highest in participants with Yang-deficient constitution (n=19, 13.4%), among whom 7 (36.8%) exhibited worsening fields. After adjusting for sex, age, central corneal thickness, retinal nerve fibre layer thickness and mean deviation on visual field testing, Yang-deficient constitution (HR 4.63, 95% CI 1.77 to 12.1, p=0.002) and higher mean intraocular pressure during follow-up (HR 1.25, 95% CI 1.01 to 1.56, p=0.044) were associated with field progression.

Conclusions Yang-deficient constitution and higher intraocular pressure are risk factors for visual field progression in NTG patients. Yang deficiency is characterised by abnormal vasoregulation, and these results may be consistent with prior studies linking NTG progression to Raynaud's phenomenon and migraine.

INTRODUCTION

Glaucoma is the most common global cause of irreversible blindness.[1] It is estimated that in 2020 there were 79.6 million persons with glaucoma globally, among whom 11 million were blind, 20% dwelling in China.[2 3] Recently, population-based surveys in Beijing and Guangzhou have shown that the prevalence of primary open angle glaucoma (POAG) in urban populations over 40 years old in China is as high as 2%–2.6%.[4 5] A population study in rural Handan, Hebei Province, reported a POAG prevalence among those ≥50 years of 1.5%,[6 7] twice the rate of primary angle-closure glaucoma.[8]

Normal-tension glaucoma (NTG) is characterised by typical optic disc changes and corresponding glaucomatous visual field defects, with intraocular pressure (IOP) in the normal range.[9] In the Handan eye study, approximately 91% of patients with POAG had an IOP <21 mm Hg (that is, in the normal range) at initial screening.[6 7] Subsequently, 24-hour IOP monitoring showed that 83% of participants had a peak IOP <21 mm Hg,[10] suggesting that NTG accounts for a high proportion of POAG in China. Consistent with this, in population surveys from Beijing[4] and Guangzhou,[5] 60%–85% of persons with glaucoma had IOP <21 mm Hg. As a lifelong illness, glaucoma requires long-term treatment and monitoring. Given its high prevalence in China and globally, developing proven models to detect and treat NTG has become is an urgent public health problem.

The rate of progression of NTG optic nerve damage is highly variable in the population. In the Early Manifest Glaucoma Trial (EMGT), NTG progressed at a rate of −0.36 dB per year, while high-tension glaucoma progressed by −1.31 dB per year.[11] In the Collaborative Normal Tension Glaucoma Study (CNTGS), untreated patients had an annual progression between −0.2 and −2 dB over more than 3 years.[12] In a study of Hong Kong patients with NTG (mean IOP <21 mm Hg), the 3-year incidence of visual field damage was 44%.[13] In the EMGT study, the visual field progression rate for NTG over 6 years was approximately 56%. Aggressive management of all persons with NTG would lead to significant overtreatment, with attendant waste and unnecessary side effects. Proven models to identify persons with a particularly high risk of progression, in order to focus treatment resources efficiently, is a high public health priority for China.

The Body Constitution in Traditional Chinese Medicine Questionnaire (BCTCMQ) has been developed by the China Association of Chinese Medicine, and has been verified and widely used among Asian and North American populations.[14–16] According to traditional Chinese medicine (TCM), the body constitution is divided into nine basic categories based on inherited and acquired influences, including gender, age, mental state and living environment. Except for the balanced constitution,

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To cite: Tang L, Chen L, Ye C, *et al*. *Br J Ophthalmol* 2023;**107**:37–42.

the other eight types are regarded as biased constitutions, indicating that although they do not constitute definite diseases, they reflect imbalance of Yin and Yang, Qi and blood and/or fluid and humour.

We have used the BCTCMQ to characterise a large population-based cohort, aiming to identify factors associated with more rapid disease progression among high risk NTG patients.

METHODS

This population-based cohort study examined an adult urban population from Wenzhou City in eastern China.[17] After completing community screening, patients who met inclusion criteria provided written informed consent and entered the study cohort for follow-up.

PARTICIPANTS

Community screening using non-contact tonometry, non-mydriatic fundus photography and portable slit lamps was conducted on approximately 30 000 community members in Wenzhou. If one or more of the following characteristics were present in either eye, a participant was considered to be a glaucoma suspect: (1) Any of these abnormalities of the optic disc cup: cup-disc ratio (CDR) ≥0.65, CDR asymmetry ≥0.2 or neural rim tissue ≤0.1; (2) Optic disc haemorrhage on either disc photography or clinical examination; (3) Localised or diffuse retinal nerve fibre layer (RNFL) defects on fundus photography.[18] All suspected POAG patients were then invited to the Clinical Research Centre of the Eye Hospital of Wenzhou Medical University (EHWMU) for further examination, including assessment of habitual visual acuity, refraction, Goldmann applanation tonometry (GAT), central corneal thickness (CCT), standard automated perimetry (Humphrey 750i, Zeiss, Oberkochen, Germany), fundus photography and spectral domain optical coherence tomography (SD-OCT, Zeiss Cirrus HD-OCT 4000, Oberkochen, Germany.)

NTG was defined as open-angle glaucoma (repeatable glaucomatous visual field damage corresponding to glaucomatous optic neuropathy (optic disc haemorrhage, RNFL defect, CDR >0.7, asymmetry >0.2 or neuroretinal rim width <0.1) and a gonioscopically open angle[18]) with untreated IOP measuring ≤21 mm Hg on six separate occasions, with no single reading >24 mm Hg, as described by the CNTGS.[19] Participants with NTG were eligible for the current study if they were ≥30 years of age, without history of glaucoma surgery, other intraocular surgery or other eye diseases affecting the fundus, such as high myopia.

Assessment of TCM body constitution

Participants completed the BCTCMQ with the assistance of a physician trained in TCM, as has been previously described according to the 2009 'Classification and Judgment of Body Constitution in TCM'.[20] The BCTCMQ is divided into nine subscales, one for each body constitution type and consisting of 7–8 questions, for a total of 67 questions. Each question is scored on a 5-point scale, depending on the degree to which the symptom is present. The entire questionnaire requires some 2 min to complete. The final score is transformed to a maximum of 100, and the type of constitution determined, with the cut-off for a particular body constitution being 30 points on the transformed scale, with the exception of the pinghe ('balanced') constitution, with a cut-off of 60 points. The reproducibility correlation coefficients of the scores of the nine subscales ranged from 0.76 to 0.9. Internal consistency Cronbach'α was achieved for each of the nine subscales with 0.72–0.8.[14]

Examinations

Participants were evaluated every 3 months to monitor visual field progression (Humphrey 750i, Zeiss, Oberkochen, Germany). At each visit, participants underwent ophthalmic evaluation including assessment of habitual visual acuity, refraction, measurement of corneal thickness (Lenstar 900, Haag-Streit, Kloniz, Switzerland), GAT, fundus photography (Visucam 200, Zeiss, Oberkochen, Germany), SD-OCT (Cirrus HD-OCT 4000, Zeiss, Oberkochen, Germany) and standard automated perimetry (Humphrey750i, SITA 24–2 Standard, Zeiss, Germany). Fundus photographs were reviewed by the Digital Image Reading Department to assess the presence of glaucoma, according to the above definition, and of optic disc haemorrhages. Additional measurements included assessment of height, weight, waist and hip circumference, blood pressure and pulse rate. Blood pressure and pulse rate were measured using an automatic sphygmomanometer (HEM-7136, Omron, Tokyo, Japan). Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg, or prior diagnosis or current use of hypertensive medications.

A participant was considered to have visual field defect progression if she/he had three consecutive visual field examinations showing ≥3 points which had deteriorated compared with baseline, as per the Guided Progression Analysis criteria from the EGMT.[21]

Sample size

According to the guidelines for estimating the sample size for Cox regression modelling, 10 positive events are needed per variable for adequately powered statistical analysis.[22] For the five prognostic factors previously linked with risk of visual field damage progression in NTG (age, disc haemorrhages, baseline visual field loss, baseline IOP, and exfoliation syndrome),[23] a minimum of 50 positive events are therefore required. In order to observe 50 positive events with an assumed NTG progression rate of 50% over 3 years,[22] a sample size of 100 participants was needed, which was expanded to 120 in order to allow for a 15% drop-out rate.

Statistical methods

Cross-sectional data on the baseline distribution of TCM body constitution type among participants were analysed using non-parametric testing. Comparisons of fast and slow progression were carried out using Student's t-tests, while the associations between hypertension or optic disc haemorrhage and fast or slow progression were analysed using Fisher tests. Cox regression HR modelling was used to analyse the association between potential prognostic factors and the progression of participants' visual field damage, and to compare differences in visual field damage progression rates of participants with different body constitution types. The ID variable was added to the Cox regression analysis in order to correct for the correlation between eyes in the same individual. Potential factors significant at the $p<0.05$ level in univariate analyses were included in multivariate models.

All statistical analyses were performed with R V.3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) with survival and survminer packages. Values of $p<0.05$ were considered statistically significant.

RESULTS

By 31 May 2019, a total of 181 NTG patients who met the inclusion criteria had been identified as provisionally eligible, among whom 2 patients (1.10%) were excluded due to unwillingness to

Table 1 Baseline demographic and clinical information for participants

Category	Mean±SD or no (%)
Age (years)	63.2±11.2
Sex (male/female)	67/75
Follow-up duration (years)	3.49±0.99
Baseline Intraocular pressure (IOP, mm Hg)	15.1±3.17
Follow-up IOP (mm Hg)	14.9±2.37
Central corneal thickness (µm)	535±29.3
Vertical cup-disc ratio	0.71±0.13
Retinal nerve fibre layer thickness (µm)	77.9±13.1
Mean deviation (MD, dB)	−5.82±4.61
MD slope (dB/year)	0.24±0.93
Self-report of hypertension	62 (43.7)
Optic disc haemorrhage on fundus photography	45 (18.4)

IOP, intraocular pressure; MD, mean deviation.

Table 3 Body constitution types of participants and rates of field progression by type

	Total		Progressed		
Body constitution type	No	%	No	%	P value*
Balanced constitution	95	66.9	13	13.7	
Yang-deficient constitution	19	13.4	7	36.8	0.016
Qi-deficient constitution	4	2.82	0	0	
Yin-deficient constitution	3	2.11	0	0	
Phlegm-dampness constitution	1	0.70	0	0	
Damp-heat constitution	3	2.11	0	0	
Stagnant blood constitution	2	1.41	0	0	
Stagnant qi constitution	3	2.11	0	0	
Inherited special constitution	0	0	0	0	
Concurrent constitution	12	8.45	3	25.0	

*Fisher's exact test comparing the risk of progression between participants with and without Yang-deficient body constitution.

complete the BCTCMQ and 4 (2.20%) were excluded because their mean IOP was >21 mm Hg over the first six follow-up visits. Additionally, 15 patients (8.29%) did not follow up at scheduled intervals and 18 (9.94%) completed <1.5 years of follow-up; these patients were excluded from the longitudinal analysis. Thus, the final analysis included 142 participants (78.5%, 245 eyes affected with NTG).

Demographic characteristics

Participants had a mean age of 63.2±11.2 years, with 75 (52.8%) being female. Among them, 39 patients (27.5%) had unilateral NTG while 103 (72.5%) were bilaterally affected. The mean IOP at baseline and during follow-up were 15.1±3.17 mm Hg and 14.9±2.37 mm Hg, respectively. Table 1 summarises participant data for CCT, vertical CDR (VCDR), RNFL and mean deviation (MD) on visual field testing. Over a mean follow-up period of 3.49±0.99 years, the MD progressed at a rate of 0.24±0.93 dB/year. Visual field progression was identified in 23 of 142 participants (16.2%) and 25 of 245 eyes (10.2%), with a mean progression rate of −1.27±1.23 dB/year. A total of 11 (47.8%) participants experienced rapid progression, defined as an MD slope of ≥−1.50 dB (mean −2.40±0.49 db/year), while 12 (52.2%) participants progressed more slowly (≤1.50 db/year, mean 0.21±0.51 dB/year) (table 1).

Table 2 describes differences between the slow and fast-progressing participants. Fast progressors had a significantly larger mean VCDR (p<0.001) at baseline, and were significantly younger (p=0.019), but the two groups did not differ in baseline CCT, baseline RNFL or baseline or mean follow-up IOP.

Distribution of body constitution and association with field progression

Table 3 gives the distribution of body constitution types among the 142 participants. Over two-thirds of participants (n=95, 66.9%) had a balanced constitution, among whom visual field progression occurred in 13 (13.7%), while 7 of 19 with Yang-deficient constitution (36.8%), and 3 of 12 patients with jianjia ('concurrent') constitution (25%) experienced field progression. Patients with none of the other body constitution types experienced visual field progression (p=0.016, Fisher's exact test; table 3). Additionally, patients with Yang-deficient constitution comprised 4 of the 11 cases (36.4%) with rapid progression. In Cox hazard univariate analyses, the following factors were significantly associated with greater risk of field progression: older age (HR 1.05, 95% CI 1.01 to 1.08, p=0.015), higher mean IOP during follow-up (HR 1.22, 95% CI 1.02 to 1.45, p=0.027), Yang-deficient body constitution (HR 3.45, 95% CI 1.29 to 9.26, p=0.014) and presence of optic disc

Table 2 Comparison between participants with slow and rapid progression

Category	Rapid progression (n=12)	Slow progression (n=13)	P value (comparing rapid vs slow)
Age (years)	65.1±6.73	70.7±4.25	0.019
Sex (male/female)	4/8	5/8	1
Baseline intraocular pressure (IOP, mm Hg)	16.0±3.77	16.9±3.68	0.572
Follow-up IOP (mm Hg)	15.8±2.57	16.3±2.89	0.652
Baseline central corneal thickness (µm)	533±29.8	542±31.3	0.465
Baseline vertical cup-disc ratio	0.78±0.04	0.68±0.07	<0.001
Baseline retinal nerve fibre layer thickness (µm)	71.2±13.20	78.0±8.70	0.137
Baseline mean deviation (MD, dB)	−6.24±5.07	−5.48±4.06	0.682
Time to progression (y)	1.70±0.78	2.91±1.19	0.007
MD slope (dB/year)	−2.40±0.49	−0.21±0.51	<0.0001
Self-reported hypertension	6/12	9/13	0.428
Optic disc haemorrhage during follow-up	4/12	5/13	1

IOP, intraocular pressure; MD, mean deviation.

Table 4 Regression model of factors associated with visual field progression (rows in bold are significant at the p<0.05 level)

	Univariate model		Multivariate model	
Potential predictors	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age (y)	1.05 (1.01 to 1.08)	0.015	0.89 (0.40 to 2.00)	0.781
Male sex	0.58 (0.24 to 1.41)	0.228	0.46 (0.17 to 1.26)	0.129
Yang-deficient constitution	**3.45 (1.29 to 9.26)**	**0.014**	**4.63 (1.77 to 12.1)**	**0.002**
Self-reported hypertension	1.67 (0.69 to 4.03)	0.252	2.71 (0.97 to 7.58)	0.058
Baseline intra-ocular pressure (IOP, mm Hg)	1.13 (0.99 to 1.29)	0.069	–	–
IOP fluctuation (mm Hg)	1.21 (0.71 to 2.05)	0.48	–	–
Follow-up IOP (mm Hg)	**1.22 (1.02 to 1.45)**	**0.027**	**1.25 (1.01 to 1.56)**	**0.044**
Central corneal thickness (um)	1.00 (0.99 to 1.02)	0.895	1.00 (0.99 to 1.02)	0.976
Bseline vertical cup-disc ratio	5.60 (0.43 to 72.6)	0.188	29.9 (0.70 to 1291)	0.077
Baseline retinal nerve fibre thickness (μm)	0.98 (0.95 to 1.01)	0.136	1.00 (0.95 to 1.04)	0.896
Baseline mean deviation (MD, dB)	1.00 (0.92 to 1.08)	0.916	1.05 (0.95 to 1.16)	0.339
Optic disc haemorrhage during follow-up	2.49 (1.08 to 5.76)	0.03	1.91 (0.82 to 4.47)	0.14
β-PPA	1.18 (0.34 to 4.11)	0.79	–	–

Bold values indicate p<0.05 in both univariate and multivariate models.
IOP, intraocular pressure; MD, mean deviation; β-PPA, β-zone parapapillary atrophy.

haemorrhage during the follow-up (HR 2.49, 95% CI 1.08 to 5.76, p=0.033). In multivariate models, Yang-deficient body type (HR 4.63, 95% CI 1.77 to 12.1, p=0.002) and mean follow-up IOP (HR 1.25, 95% CI 1.01 to 1.56, p=0.044) remained significantly associated (table 4, figure 1).

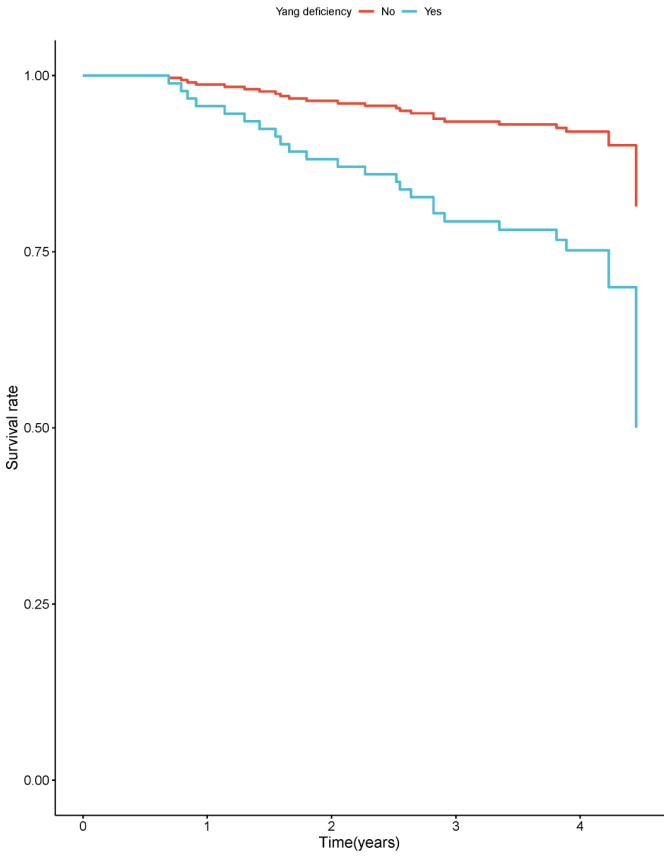

Figure 1 Survival analysis of NTG patients with Yang-deficient constitution. The blue line ('Yang deficiency') represents NTG patients with Yang deficiency constitution; the red line ('non-Yang deficiency') represents NTG patients with the other constitution. NTG, normal-tension glaucoma.

We also analysed the MD slope for the different constitution population. MD-slope of patients with non-Yang-deficient constitution type was 0.23±0.89, while with Yang-deficient constitution type was −0.036±1.15. In the Yang-deficient constitution type cohort, the MD-slope of patients with field progression was −1.29±1.24, while for those without progression, it was 0.38±0.78.

DISCUSSION

Our finding that elevated IOP was associated with increased risk of NTG progression is consistent with other studies. The EMGT[24] reported that follow-up IOP continued to have a significant influence on progression (HR 1.12, 95% CI 1.07 to 1.16), regardless of baseline IOP. Some studies had reported that the IOP variation during follow-up rather its mean during follow-up was a more important risk factor for progression in NTG. However, we performed a correlation analysis and the presence or absence of IOP fluctuation (It was defined as the SD of IOP measurements during follow-up) was not statistically significantly associated with NTG field progression in our cohort (Univariate model: HR 1.21, p=0.48, 95% CI 0.71 to 2.05). So, we included mean IOP during follow-up rather than IOP fluctuation during follow-up in our multivariate models. In the Collaborative Initial Glaucoma Treatment Study,[25] various measures of better IOP control during treatment were significantly predictive of visual field preservation, including a lower mean IOP (OR 1.30, 95% CI 1.10 to 1.54), a lower minimum IOP (OR 1.21, 95% CI 1.04 to 1.41), and lower sustained levels of IOP over follow-up (All IOP <20 mm Hg, OR:1.93, 95% CI 1.34 to 2.78). Patients with NTG benefit from lowering of IOP,[26] this suggesting that IOP is an important risk factor for glaucoma progression and that follow-up IOP is particularly important, as we found.

Adding β-Zone Parapapillary Atrophy (β-PPA) to our multivariate analysis does not affect the significant association with a Yang-deficient constitution (HR 4.63, p=0.002, 95% CI 1.73 to 12.4). However, the previous finding of an association between progression and mean IOP during follow-up (HR 1.25, p=0.044, 95% CI 0.94 to 1.70) became statistically insignificant when β-PPA was added to the model (HR 1.26, p=0.12, 95% CI 0.94 to 1.70). Considering the potential for

multicollinearity between these two variables, we elected not to include β-PPA in the multivariate analysis.

We also found that Yang-deficient constitution was an important independent risk factor for NTG progression. Yang-deficient constitution is a concept based on Chinese medical theory.

The determination of Yang-deficient constitution is made on the basis of a number of questions relating to fear of cold, including: Do your hands or feet feel cold or clammy? Do you commonly feel cold in your abdomen, back, lower back or knees? Are you sensitive to cold and tend to wear more clothes than others? Do you feel unusually affected by air conditioners, fans, etc.? In summary, people with Yang-deficient constitution are mainly characterised by decreased temperature of the extremities, chills, or cold-induced discomfort.

Genetic factors are thought to play a role in the formation of a Yang-deficient constitution. An individual's body constitution is relatively stable due to their genetic makeup. Lu *et al*[27] studied a family with Yang-deficient constitution and found that all of the children and 10 out of 14 grandchildren (71.4%) of two Yang-deficient individuals were also Yang-deficient. Zhou *et al*[28] showed further evidence for the genetic basis of this constitution by finding genomic variations in DCDC5 associated with Yang-deficiency through linkage disequilibrium single nucleotide polymorphism gene sequencing on 12 family members and three spouses with Yang-deficiency syndrome. A genome-wide association study on Yang-deficient constitution by Yao *et al*[29] showed that Yang-deficient constitution had polygenic genetic characteristics, and found that polymorphism of RGS6, mGluR5, GAPDHL19 and IKZF1 genes were related to changes in cyclic AMP and cyclic guanosine monophosphate levels, memory, metabolic energy state and immune function respectively in Yang-deficient cohorts.

Environment, however, may also play a role in the development of a Yang-deficient constitution. One study[30] that surveyed 1121 patients about their life, work environment and TCM body constitution type found that significant risk factors for Yang-deficiency included: lack of sun exposure, living around fewer other persons, setting the home air conditioner temperature <25°C in summer, not often staying in warm environments in winter and not adding warmer clothes when the temperature is low. Avoiding the aforementioned environmental factors may help avoid or improve a Yang-deficient constitution.

Cold hands and feet, as an over-reaction to cold or stress, are suggestive of defective vasoregulation. Abnormal vasoregulation, such as Raynaud's phenomenon and migraine, have been reported to be associated with NTG,[31] but this conclusion is also controversial. Several studies have found vasoregulation to be associated with visual field progression in NTG. Kang *et al*[32] reported hypotension, migraine and Raynaud's phenomenon were found in significantly higher frequency among NTG patients with initial central scotoma (ICS) as opposed to initial peripheral scotoma (IPS). Another study in NTG patients[33] found that most migraine occurred in women, but that gender and presence of migraine contributed independently to the overall risk of progression. However, other studies have reported no correlation between Raynaud's phenomenon or migraine and NTG visual field progression. Cho *et al*[34] concluded that there were no differences in clinical characteristics between NTG patients with initial ICS versus IPS, except for the initial VF index and occurrence of superior hemi field defects. Prevalence of disc haemorrhage, hypotension, migraine or Raynaud's phenomenon were not significantly different between the two groups. Park *et al*[35] also found that migraine, Raynaud's phenomenon, systemic hypertension or diabetes mellitus showed no significant association with a diagnosis of NTG.

Current research on conditions associated with defective vasoregulation, such as Raynaud's phenomenon and migraine, depends on strict diagnostic criteria and some patients may not meet the precise criteria for these diseases despite the presence of defective vasoregulation, and therefore may be missed. Furthermore, the pathogenesis of Raynaud's phenomenon and migraine headaches is unclear. Migraines are not directly related to exposure to cold and so may have little to do with Yang-deficient constitution. Although the cause of Raynaud's phenomenon is also not fully understood, exposure to cold appears to be its main trigger, thus, it appears similar in pathogenesis to Yang-deficient constitution. However, Raynaud's phenomenon only manifests itself in localised disorders of blood flow at the distal end of the limbs and does not affect the entire body, as Yang-deficient constitution does. The cold which characterises Yang-deficient constitution is associated with more than just defective vasoregulation, as it encompasses physical, physiological, and psychological aspects as well.

Physically,[36 37] there is no sensation of hot or cold at a body surface temperature of 30°C–34°C, and awareness of cold is only induced when the surface temperature is below 30°C. Physiologically, the sensation of cold is related to the corresponding temperature receptors. The temperature sensory pathway is mainly transmitted by the TRP family.[38] In turn, TRP is a codomain with TREK, a potassium ion channel subclass.[39–41] Numerous studies have shown that TREK-1 is a key molecule in determining trabecular meshwork potential, pressure sensitivity, calcium homeostasis and cell permeability. TREK-1 has an important role in maintaining IOP homeostasis, which could suggest a potential common pathway between cold sensitivity and NTG progression.[42]

Psychologically, studies have shown that lonely and depressed patients have a marked fear of cold,[43] which is manifested in two ways: first, they have a fear of cold when their body surface temperature decreases and second, they are inaccurate in their temperature determination, which leads to an exaggerated sense of cold. Recent studies have identified depression as a risk factor for progression of glaucomatous optic nerve damage.[44 45]

Strengths of the current study include large sample size, high follow-up rate and the NTG diagnostic criteria used in the study refer to large studies such as CNGTS. The assessment of TCM constitution was based on Chinese national standards, which were applied consistently. Limitations must be acknowledged as well. This study suggests a potential role of Yang-deficient constitution in predicting NTG visual field progression, but further research is needed to determine whether this schema can be helpful in diagnosis of NTG, or in formulating novel treatments. Based on the results of this study, we plan to develop a predictive model of NTG visual field progression, validate its accuracy prospectively, and see if we can identify high-risk patients by screening through the assessment of Yang-deficient constitution.

Acknowledgements The authors thank Dr. Ji Wang for her support and assistance in the use of the BCTCMQ, thank Dr. Kemi Feng and Dr. Xiang Xu for their help in data analysis and thank all the staff at the Clinical Research Centre for examining and collecting relevant data from the subjects.

Contributors LT and YL were involved in the study concept and design. JZ performed statistical analysis. LT and LC interpreted data and drafted the manuscript. All authors provided critical input to the analysis and interpretation of the data and revised the manuscript critically. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. YL is the guarantor.

Funding Zhejiang Traditional Chinese Medicine Science and Technology Project , Grant/Award Number: 2017ZB069. Scientific Research Foundation of the Eye Hospital, School of Ophthalmology and Optometry, Wenzhou Medical University, Grant/Award Number: KYQD20180305.

Disclaimer None of the funding sources had any role in study design, writing of the report and decision to submit this article for publication.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the institutional review board at Eye Hospital, Wenzhou Medical University (KYK (2013) 12). Consent from participants was indicated by the completion and return of the questionnaires.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data are at the Clinical Research Centre of the Eye Hospital of WMU.

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ORCID iDs
Xiao Shang http://orcid.org/0000-0002-2381-4598
Nathan Congdon http://orcid.org/0000-0001-9866-3416
Yuanbo Liang http://orcid.org/0000-0001-9685-7356

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