• Investigation •

Analysis of risk and protective factors associated with retinal nerve fiber layer defect in a Chinese adult population

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Abstract

● **AIM:** To investigate the risk and protective factors associated with the retinal nerve fiber layer defect (RNFLD) in a Chinese adult population.

● **METHODS:** This study was a cross-sectional population-based investigation including employees and retirees of a coal mining company in Kailuan City, Hebei Province. All the study participants underwent a comprehensive systemic and ophthalmic examination. RNFLD was diagnosed on fundus photographs. Binary logistic regression was used to investigate the risk and protective factors associated with the RNFLD.

● **RESULTS:** The community-based study included 14 440 participants. There were 10 473 participants in our study, including 7120 males (68.0%) and 3353 females (32.0%). The age range was 45-108y, averaging 59.56±8.66y. Totally 568 participants had RNFLD and the prevalence rate was 5.42%. A higher prevalence of RNFLD was associated with older age [*P*<0.001, odds ratio (OR): 1.032; 95% confidence interval (CI): 1.018-1.046], longer axial length (*P*=0.010, OR: 1.190; 95%CI: 1.042-1.359), hypertension (*P*=0.007, OR: 0.639; 95%CI: 0.460-0.887), and diabetes mellitus (*P*=0.019, OR: 0.684; 95%CI: 0.499-0.939). The protective factors of RNFLD were visual acuity (*P*=0.038, OR: 0.617; 95%CI: 0.391-0.975), and central anterior chamber depth (*P*=0.046, OR: 0.595; 95%CI: 0.358-0.990).

● **CONCLUSION:** In our cross-sectional community-based study, with an age range of 45-108y, RNFLD is associated with older age, longer axial length, hypertension, and diabetes mellitus. The protective factors of RNFLD are visual acuity and central anterior chamber depth. These can help to predict and evaluate RNFLD related diseases and identify high-risk populations early.

● **KEYWORDS:** retinal nerve fiber layer defect; retinal nerve fiber layer; age; axial length; hypertension; diabetes mellitus; visual acuity; central anterior chamber depth

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INTRODUCTION

The retinal nerve fiber layer (RNFL) consists of the axons of the retinal ganglion cells. Most of the nerve fibers terminate in the lateral geniculate body. Therefore, the RNFL is contiguous with the intracranial optic nerve. Many diseases can damage this neural pathway, leading to retinal nerve fiber layer defect (RNFLD). RNFLD can be found in eyes with ischemic optic neuropathy, glaucomatous optic neuropathy, optic disc drusen, retinitis pigmentosa, retinal artery occlusion, contusion of the optic nerve, compression of pituitary tumor, visual pathway impairment, toxic optic neuropathy, and as a sequela of long-standing papilledema, optic neuritis, *etc*[1-8].

In addition, many risk factors, such as age, race, gender, blood pressure, blood glucose, smoke, *etc*., are known to increase an individual's chance of developing RNFLD[9-11]. RNFLD may result in vision loss. The majority of people do not lose their vision during the initial stages of RNFLD, since it frequently happens earlier than vision impairment. Most of the studies used color fundus photographs to diagnose RNFLD. Previous research suggested that RNFLD play a significant role in the detection of various abnormal physical condition and diseases, such as diabetic mellitus, stroke, hypertension, Alzheimer's disease, multiple sclerosis, Parkinson's disease, pathologic myopia, *etc*[9,12-16]. Some studies indicated that the prevalence of RNFLD in health examination participants is about 4.7%-5.4%[16-17]. Other studies have found that the prevalence of RNFLD in the age group over 50y can reach 14.8%, the prevalence of RNFLD in the age groups of 50-59, 60-69, and 70 and above is about 7.0%, 8.5%, and 10.4%, respectively[16-19]. Population-based researches showed significant differences between regions and ethnic groups[20-21].

Previous studies had identified several risks and protective factors associated with RNFLD, however, some controversies and limitations still exist: 1) The risk and protective factors reported varied across studies, with significant differences in some studies; 2) Previous studies focused on Caucasians or Mexicans, while few epidemiological surveys were conducted in China; 3) Previous studies have had small sample sizes. Therefore, we conducted this large community-based study in a Chinese population, hoping to clarify the risk and protective factors of RNFLD in the Chinese population based on large sample data. To date, our study has the largest sample size of RNFLD in a Chinese population.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Medical Ethics Committee of Beijing Tongren Hospital and followed the tenets of the Declaration of Helsinki. All the participants signed a written informed consent form after an explanation of the nature and possible consequences of the study.

This study was a cross-sectional population-based study. The study population included employees and retirees of a coal mining company (Kailuan Group Company). At baseline, the study population consisted of 101 510 individuals with an age ranging between 21y and 110y. The participants were followed with repeated questionnaires and medical examinations *via* face-to-face interviews with medical staff and trained research nurses at 2-year intervals[22-23]. All participants underwent an interview with standardized questions about their socioeconomic background, educational level, physical activity, psychic depression, known major systemic diseases such as coronary heart disease, arterial hypertension, and diabetes mellitus, medical treatment status, lifestyle parameters (including alcohol consumption, sleep patterns, and smoking status). We randomly selected a sample of 14 440 subjects out of the cohort, using an examination unit-based cluster random sampling method. We conducted research and analysis on adults aged 45 and older.

All the study participants underwent a comprehensive ophthalmic examination. Visual acuity was measured. Color fundus photographs centered on the macular and the optic disc were obtained by a digital 45° non-mydriatic retinal camera (Type CR6-45NM, Canon Inc. Tokyo, Japan). Ocular biological parameters were collected by using optical low-coherence reflectometry (Lenstar 900 Optical Biometer, Haag-Streit, Koeniz, Switzerland), including axial length, central anterior chamber depth, lens thickness, central cornea thickness, *etc*. The operators and photographers of the retinal camera and Lenstar device were trained and certified by retinal specialists and experienced ophthalmic examiners in Beijing Tongren Hospital, and Beijing Tongren Eye Center.

The heart rate and blood pressure were assessed with the participants sitting for at least 5min. Body weight and body height were measured using a standard technique and body mass index (BMI) was calculated. BMI less than 18 kg/m^2 was lower than normal, 18-24 kg/m^2 was normal, and more than 24 kg/m^2 was overweight. Under fasting conditions, blood samples were collected to determine the concentrations of blood glucose and triglyceride. Urine samples were collected to determine the urine protein. Smoking was defined as smoking at least one cigarette per day for more than a year. Hypertensive patients were defined as subjects with a history of hypertension, a history of hypertension medication, systolic blood pressure greater than or equal to 130 mm Hg, or diastolic blood pressure greater than or equal to 80 mm Hg. Subjects with a history of diabetes mellitus, a history of glucose-lowering medication, or fasting glucose greater than or equal to 7.0 mmol/L were defined as diabetic. We also accurately

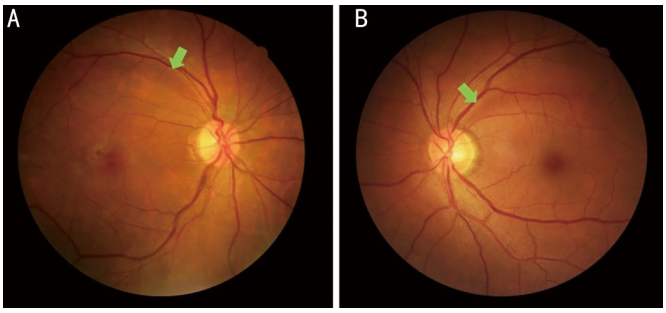

Figure 1 Color fundus photographs of localized retinal nerve fiber layer defect (RNFLD) A: Color fundus photograph revealed a bundle of RNFLD (green arrow) under the arch of the superior temporal vessel with dilated retinal veins in the right eye; B: Color fundus photograph indicated a bundle of RNFLD (green arrow) under the arch of the superior temporal vessel in the left eye.

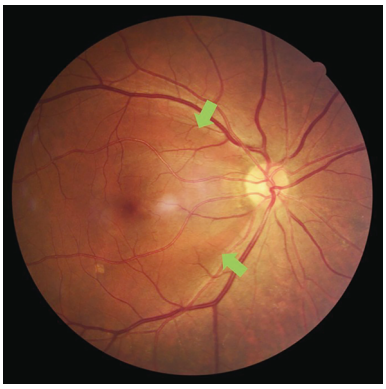

Figure 2 Color fundus photograph of diffuse retinal nerve fiber layer defect (RNFLD) in the right eye Color fundus photograph of the right eye shows a bundle of RNFLD (green arrow) near the superior and inferior temporal vascular arch at the posterior pole.

recorded whether the subjects had a history of atrial fibrillation and stroke. RNFLD in our study included both localized RNFLD and diffuse atrophy of RNFL. Localized RNFLD was defined as a wedge-shaped, not a spindle-like defect, running toward or touching the optic disc border (Figure 1). Diffuse atrophy of RNFL was defined as a diffuse thinning or absence of RNFL (Figure 2). The presence of any of these was defined as RNFLD[24-25]. Image enhancement tools were not used and any manipulation of the images was not allowed for the detail.

Statistical Analysis The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 26.0, IBM-SPSS, Chicago, IL, USA). In this study mean±standard deviation was used to describe the quantitative data, such as age, best visual acuity, BMI, various laboratory indicators, *etc*. Test the normal distribution and homogeneity of variance of each index and select the appropriate test methods (parametric or nonparametric tests). Logistic regression was used to investigate the associated factors with the RNFLD. Univariate analyses were used to assess the associations between the prevalence of RNFLD and other systemic and ocular parameters. Logistic regression models were subsequently calculated with variables such as age and gender as independent variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All *P* values were 2-sided and were considered statistically significant when the values were <0.05. The indicators enrolled in this study were: age, gender, triglycerides, smoking history (never smoked, had smoked and quit, continuous smoking), urine protein, diabetes mellitus, atrial fibrillation, stroke, hypertension, BMI, visual acuity, central anterior chamber depth, lens thickness, and axial length.

Table 1 Baseline demographics and clinical characteristics of participants

n (%)

Parameters	Mean±SD (range)
Age (y)	59.56±8.66 (45-108)
Triglyceride (mmol/L)	2.30±1.75 (0.21-15.89)
Central anterior chamber depth (mm)	2.63±0.42 (1.51-5.47)
Lens thickness (mm)	4.50±0.36 (2.78-6.01)
Axial length (mm)	23.47±1.12 (18.90-31.76)
Gender	
Men	7120 (68.0)
Women	3353 (32.0)
Smoking history	
Never smoked	6296 (60.1)
Had smoked and quit	670 (6.4)
Continuous smoking	3507 (33.5)
Urea protein (+)	297 (2.8)
Stroke	735 (7.0)
Hypertension	1262 (12.1)
Diabetic mellitus	1577 (15.1)
Atrial fibrillation	32 (0.3)
BMI (kg/m^2)	
<18	94 (0.8)
18-24	3701 (35.3)
>24	6678 (63.8)
RNFLD	568 (5.42)

BMI: Body mass index; RNFLD: Retinal nerve fiber layer defect.

RESULTS

There were 10 473 cases in this group, including 7120 males (68.0%) and 3353 females (32.0%). The age range was 45-108y, with an average age of 59.56±8.66y. The baseline demographics and clinical characteristics of participants were shown in Table 1. The results showed that 568 participants had RNFLD, and the prevalence rate was 5.42%. Among them, there were 5300 participants aged 40-59 years old, of which 238 had RNFLD, with a prevalence rate of 4.49%. A total of 4951 participants were aged 60-79 years old, 303 of whom had RNFLD, with a prevalence rate of 6.12%. The 222 participants aged 80 years old and above, 27 of whom had RNFLD, with a prevalence rate of 12.16%. The right eyes were selected for statistical analysis. The associated factors of RNFLD were analyzed by binary logistic regression.

The Hosmer test showed that the curve fit was 0.940. The variables included in the logistic regression were as follows: 1) continuous variables: age, blood triglyceride, visual acuity, central anterior chamber depth, lens thickness, axial length; 2) categorical variables: gender (male, female), smoking history (never smoked, had smoked and quit, continuous smoking), urine protein (positive urine protein, negative urine protein), stroke (history of any kind of stroke, no history of stroke), hypertension (hypertension, no history of hypertension), atrial fibrillation (with atrial fibrillation, without atrial fibrillation), diabetes mellitus (with diabetes mellitus, no diabetes mellitus), BMI (low, normal, overweight).

Statistical results showed that the risk factors for RNFLD were age, axial length, hypertension, and diabetes mellitus. The risk of RNFLD increased by 1.032 times every year (95%CI: 1.018-1.046, *P*<0.001). The RNFLD risk increased 1.190-fold for each 0.01 mm increase in axial length (95%CI: 1.042-1.359, *P*=0.010). People with hypertension had an increased risk of RNFLD compared with people without hypertension, OR=0.639 (95%CI: 0.460-0.887, *P*=0.007). People with diabetes mellitus were at an increased risk of developing a defect in the RNFL compared to people without diabetes mellitus, OR=0.684 (95%CI: 0.499-0.939, *P*=0.019). The protective factors of RNFLD were visual acuity and central anterior chamber depth. For every 0.1 increase in visual acuity, the risk of RNFLD was reduced by 0.617 times (95%CI: 0.391-0.975, *P*=0.038). For each 0.01 mm increase in central anterior chamber depth, the risk of RNFLD was reduced by 0.595 times (95%CI: 0.358, 0.990, *P*=0.046; Table 2).

Table2 Results of binary logistic regression analysis of factors associated with RNFLD

Parameters	Odds ratio	95%CI	*P*
Age (y)	1.032	1.018-1.046	<0.001
Gender	0.862	0.612-1.214	0.395
Triglyceride (mmol/L)	0.928	0.839-1.027	0.148
Presenting visual acuity	0.617	0.391-0.975	0.038
Smoking history			
Never smoked			0.302
Had smoked and quit	1.265	0.937-1.707	0.124
Continuous smoking	1.112	0.664-1.863	0.687
Central anterior chamber depth (mm)	0.595	0.358-0.990	0.046
Length thickness (mm)	0.655	0.405-1.058	0.084
Axial length (mm)	1.190	1.042-1.359	0.010
Urea protein (+)	0.602	0.337-1.074	0.086
Stroke	0.760	0.468-1.236	0.269
Hypertension	0.639	0.460-0.887	0.007
Diabetic mellitus	0.684	0.499-0.939	0.019
Atrial fibrillation	<0.001	<0.001	0.999
BMI<18 (kg/m^2)			0.440
BMI 18-24 (kg/m^2)	0.403	0.053-3.038	0.378
BMI>24 (kg/m^2)	0.871	0.662-1.148	0.327

CI: Confidence interval; BMI: Body mass index; RNFLD: Retinal nerve fiber layer defect.

DISCUSSION

The RNFL is mainly composed of the axons of ganglion cells, in addition to efferent fibers, Müller cells, glial cells, and retinal blood vessels. The RNFL thickness is a reliable index for the diagnosis and evaluation of treatment effects in many ocular and systemic diseases. It is necessary to fully understand the RNFL thickness and its influencing factors in the normal population. This study found that age, axial length, hypertension, and diabetes mellitus were negatively correlated with RNFL thickness, and visual acuity and central anterior chamber depth were positively correlated with it.

The conclusion that RNFL thickness decreases with age has been confirmed by many studies domestically and abroad. There were significant differences between all age groups before and after 44 years old. Although the mean value of RNFL decreased with age before 44 years old, the difference was not statistically significant. The results suggest that the degeneration of RNFL is more rapid in the aged than in the young. The prevalence of RNFLD is significantly higher in middle-aged and older adults[17,19,26-27]. In our study, logistic regression analysis showed a significant association between the prevalence of RNFLD and increasing age in people aged 45y and older (*P*<0.001), 95%CI: 1.018-1.046. The prevalence of RNFLD increased with age, and the risk of RNFLD increased by 1.032 times when age increased by 1y. This might be explained by the increased apoptosis of retinal ganglion cells brought on by aging[27-28]. Previous histological studies have reported that the human RNFL loses an average of 2500 ganglion cell axons per year before 50 years of age. After 50 years of age, an average of 4000 to 5000 ganglion cell axons are lost per year[27]. The ganglion cell layer loss rate is about 0.8% to 4.5% per decade[29]. Age-related loss of thickness in the primary visual cortex is significantly associated with global and multilamellar retinal thickness reduction. The atrophy of both structures may together explain the decline in various visual functions that accompany the aging process. In addition, the retinal status may reflect cortical integrity in general[30]. Therefore, the thinning of the RNFL, not necessarily the result of disease progression alone, may also be caused by an age-related natural loss of optic nerve fibers. Therefore, the effect of age on RNFL should be taken into account in the diagnosis and evaluation of the disease.

We found that axial length was significantly associated with RNFLD (*P*=0.010, 95%CI: 1.042-1.359). The longer the axial length, the higher the risk of RNFLD. With each 0.01 mm increase in axial length, the risk of RNFLD increased by 1.190 times, and the thickness of RNFL decreased with the increase in axial length. The negative correlation between axial length and RNFL can be explained by the overall thinning of the

retina in eyes with longer axial length. This is also consistent with previous literature. Previous studies have suggested that axial elongation is one of the important determinants of RNFL thinning in axial myopia[31], and Bedggood *et al*[32] confirmed that axial elongation in myopic patients is mainly in the equatorial region and posterior pole. Axial length is one of the important factors affecting refractive status. The prolongation of axial length can directly lead to myopia. It is believed that when the axial length of the eye is prolonged, the retinal and scleral extension becomes thinner, the retinal blood flow is reduced due to the dilation of the eye wall, the retinal ganglion cell axons become degenerated and the number of axons is reduced, so that a certain number of retinal ganglion cell axons are arranged over a larger area, leading to the thinning of the RNFL.

People with hypertension have an increased risk of RNFLD relative to people without hypertension, and hypertension is positively associated with RNFLD (P=0.007); 95%CI: 0.460-0.887. Reduced RNFL thickness is a reflection of reduced axons of unmyelinated retinal ganglion cells and is an ocular manifestation of target organ damage in hypertension. In hypertension, vascular resistance increases over time, which can lead to microvascular damage and atherosclerosis. Atherosclerosis caused by hypertension can cause self-regulation disorders of the vascular bed, and a series of pathological changes such as arteriolar endothelial damage, media thickening, and luminal stenosis occurs, leading to perfusion disorders of the posterior ciliary artery[33]. Retinal tissue is one of the most metabolically active tissues in the whole body. Ischemia and hypoxia of the retinal tissue caused by hypertension cause changes in the activities of glucose and energy metabolism enzymes in the retinal tissue, which directly affects the metabolism of glucose and energy in the retinal tissue, leading to the damage of retinal structure and function. The apoptosis of retinal ganglion cells leads to the thinning of RNFL thickness and damage to its axon structure. It can even cause permanent damage. Lim *et al*[34] found that RNFLD was significantly higher in the hypertensive group than in the healthy group. Studies have shown that the thinning of RNFL thickness is associated with a long-term state of uncontrolled hypertension state[13,35]. Therefore, more active antihypertensive treatment measures for people with significantly reduced RNFLD or thickness may be beneficial to protect the RNFL and thereby protect the patients' visual function.

The risk of RNFLD was increased in people with diabetes mellitus compared with people without diabetes mellitus (P=0.019) OR=0.684; 95%CI: 0.499-0.939. More and more studies have shown that diabetic retinopathy is not only a microvascular disease but also a neuronal disease[36-37]. Diabetes mellitus can lead to structural and functional abnormalities in almost all types of retinal nerve cells. In addition to affecting retinal microvessels, it also affects the optic nerve, various types of retinal nerve cells, glial cells, and retinal pigment epithelial cells, including the entire neurocyte-glial network and the neurovascular unit[37-38]. Cotton-wool spots, a common pattern in diabetic retinopathy, are infarcts of the RNFL. They occur in regions with dense nerve fibers due to terminal swelling caused by axoplasmic flow interruption and accumulation of transport materials. Functional and anatomical RNFL changes can occur before the development of retinal microangiopathy[36-38], and retinal neurodegenerative changes may be independent of retinal microangiopathy[36-37]. Studies have found that RNFL thickness may be reduced or even defective in diabetic patients without diabetic retinopathy detected by fundus mydriasis and fluorescence angiography[37-38]. It suggested that there is degeneration and reduction of retinal nerve cells and their axons in diabetic patients without diabetic retinopathy, and the thickness of some RNFL has begun to become thinner. Therefore, early observation of changes in the thickness of the RNFL in diabetic patients can help predict the occurrence of early diabetic retinopathy. This study suggests that understanding the changes of RNFL may help us to predict and prevent the occurrence of diabetic peripheral neuropathy. Timely treatment of retinal nerve protection and improvement of microcirculation disorders are equally important for the prevention and delay of diabetic retinopathy.

We found a significant correlation between RNFLD and visual acuity, P=0.046, 95%CI: 0.391-0.975. For every 0.1 improvement in visual acuity, the risk of RNFLD decreased by 0.617 times. RNFL thickness was positively correlated with visual acuity. Retinal ganglion cells are mainly found in the inner plexiform layer, ganglion cell layer, and RNFL. The RNFL is located in the ganglion cell complex in the three-layer structure. The RNFL is mainly composed of the axons of retinal ganglion cells. The thinning of RNFL thickness will lead to the reduction of nutrition and oxygen supply to the retina, the loss of retinal ganglion cells, and the loss of vision. The preservation of visual acuity depends mainly on the surviving number of retinal ganglion cells. Therefore, RNFL thickness can reflect the status of visual function to a certain extent[39]. The decrease in visual acuity and the thickness of RNFL were found in healthy people. We think that the decrease in the nutritional status of retinal nerve cells may be related to the decrease in visual acuity and the thickness of RNFL. We speculate that people with vision loss may have retinal microcirculation disorders caused by various reasons, and the thinning or loss of RNFL thickness in this population can reflect the reduction and damage of retinal ganglion cells caused by the decrease of retinal nutritional status and oxygen

content. People with RNFL thinning or defect may already have nutrient metabolism disorders of retinal nerve cells, which also suggests that multiple ocular diseases, or even systemic diseases, may be responsible for vision loss. It can be used as an early warning to remind such people to carry out targeted screening of related diseases as soon as possible.

Central anterior chamber depth was significantly correlated with RNFLD (P=0.046), and OR=0.595 (95%CI: 0.358-0.990) was a protective factor for RNFLD. For every 0.01 mm increase in central anterior chamber depth, the risk of RNFLD decreased by 0.595 times. Conversely, the shallower the central anterior chamber depth, the more likely the RNFLD was. The thickness and volume of the lens gradually increase with age. Moving the iris forward can cause the anterior chamber to become shallower. The shallow anterior chamber may lead to narrowing or even closure of the chamber angle, causing abnormal elevation of intraocular pressure. High intraocular pressure changes the ocular blood circulation and perfusion, which can lead to the interruption of the axoplasmic flow of retinal nerve fibers, axonal disintegration, apoptosis of retinal ganglion cells, and thinning or even defect of RNFL. Abnormal blood flow in the eye leads to the reduced blood supply to the eye, leading to chronic ischemia and hypoxia, which in turn can cause RNFL thinning or even defect[40].

In conclusion, these data and findings contribute to the assessment of factors associated with RNFLD, and to predict and evaluate diseases related to RNFLD. This study has been the largest sample size community-based cross-sectional RNFLD study of the Chinese population. The advantage is that the sample size is maximized, but it also has regional limitations. In addition, we could not assess all the potential factors associated with RNFLD, and missing variables may lead to bias in estimating relevant factors.

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