·Investigation·

Retinal nerve fiber layer thickness and retinal vascular caliber alterations in coal miners in northern China: a community-based observational study

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Abstract
● **AIM:** To evaluate retinal nerve fiber layer thickness and retinal vascular caliber alterations in coal mine workers.
● **METHODS:** The community-based observational cross-sectional study included 4004 participants of a sub-population of the Kailuan Study. All the study participants underwent structured interviews with a standardized questionnaire, fundus photography and spectral-domain optical coherence tomography (OCT) examinations performed by trained doctors.
● **RESULTS:** The retinal nerve fiber layer thickness was significantly higher (P=0.006) and the central macular thickness was lower in coal miners (n=659, 51.0±7.8y) as compared to the control (working above the ground; n=477, 51.8±7.5y; P=0.032). Additionally, the downhole workers showed a significantly thicker retinal artery (P=0.012) and vein diameters (P<0.001). In multivariable regression, a thicker retinal nerve fiber layer was associated with a higher cumulative silica dust exposure (P=0.005) after adjusting for younger age and larger spherical equivalent. In a reverse pattern, a higher cumulative silica dust exposure (P=0.004) was significantly associated with a thicker retinal nerve fiber layer after adjusting for age, high-density lipoproteins and uric acid. Wider retinal vein diameters were associated with higher cumulative silica dust exposure (P=0.036) after adjusting for younger age and larger spherical equivalent.
● **CONCLUSION:** The retinal vessels diameters and retinal nerve fiber layer thickness are significantly thicker in long term of coal mining. The results of our study indicate that underground working environment may lead to retinal vessel dilation and inflammation. Thus, ocular examination might be needed within coal miners in order to monitor the occupational eye health as well as the incidence and progression of eye diseases.
● **KEYWORDS:** retinal vessels diameter; retinal nerve fiber layer thickness; cumulative silica dust exposure
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INTRODUCTION
Nowadays, coal is still one of the most important energy sources providing energy and electricity worldwide. Work-place exposure to coal mine dust during coal mining remains a significant hazard worldwide. The occupational exposure to crystalline silica may cause progressive lung inflammation culminating in forming of pneumoconiosis[1]. Coal mine dust may lead to systemic silica-associated inflammatory response triggered by cytokines released from macrophages, lymphocytes and epithelial cells[2-5]. Such cytotoxic effect of inhaled silica dusts may cause alterations of various organs throughout the body, including inner structures of the eye such as choroid and retinal tissue[6]. Previous investigations revealed that active inflammation led to a significantly thickened retinal nerve fiber layer (RNFL), which can be clearly detected by optical coherence tomography (OCT), a high-resolution imaging technique suitable for

evaluating the RNFL at and around the optic nerve head (ONH)[7-9].

The metabolism in the outer retina and retinal blood flow had been demonstrated to be increased in darkness, such alterations may affect the progression of retinal disease during coal mining[10-11]. However, studies on the retinal thickness changes in long-term effects of working underground by means of OCT have been scarce so far. Besides, our group also would like to explore the retinal vessel caliber alterations in the dark working environment, since the retinal hemodynamics and oxygen saturation can be different in the dark[12].

The aim of this study was to explore the potential alterations of retinal thickness and retinal vessel calibers in coal mine workers. In attempt to reduce the risk of a referral bias, we chose the design of a relatively community-based study population.

SUBJECTS AND METHODS

Ethical Approval This research conducted in accordance with the ethical standards of the Helsinki Declaration and the study protocol was approved by the Institutional Ethics Committee of the Beijing Tongren Hospital. All participants in our study gave their written informed consent before enrolment.

Study The community-based observational study was a subgroup of the longitudinal Kailuan Study which included 101 510 employees and retirees of a coal mining company (Kailuan Group Company), as described in our previous studies[13-14]. From 2012 to 2013, randomly selected participants completed baseline data collection, out of whom 4004 individuals eventually met the inclusion criteria and underwent fundus photography and OCT from 2013 to 2014. Exclusion criteria were history of any ocular diseases and ocular surgeries, or any use of medications that affect the eyes. Cataract and pseudophakia not affecting the quality of OCT and fundus photography images were not exclusion criteria. Among them, individuals that worked underground were included as study group, and participants working above the ground were defined as control group.

Methods Structured interviews with standardized questions included information on the working areas, history of occupational exposure, level of education, history of systemic medical disorders such as diabetes and hyperlipidemia, alcohol consumption and smoking, were performed by trained investigators, as described in our previous study[13]. The working areas in the Kailuan Colliery Group were defined as above the ground and underground. We also measured height and weight and calculated body mass index (BMI). Systolic blood pressure and diastolic blood pressure were measured twice with the participant sitting for at least 5min using a mercury sphygmomanometer. For all study participants, we collected blood samples under fasting conditions and transfused into vacuum tubes containing ethylene diamine tetraacetic acid (EDTA). All blood samples were analyzed using an auto-analyzer and underwent a biochemical analysis of the serum concentration of glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol and uric acid.

Estimates of cumulative silica dust exposure (CDE), presented in milligrams/cubic meter-years, was calculated as follow: the duration of exposure in years multiplied by the dust concentration during the same time of employment period for each coal worker[15]. Given by the department of dust detection and monitoring of the Kailuan Colliery Company, dust concentration and free silica content were measured using national standard methods in order to calculate the geometric means yearly. These numerical data were collected by gravimetric method, and then used to calculate the CDE for each subject.

We applied a non-mydriatic approach in a dimly lit room by using a digital fundus camera (Type CR6-45NM; Canon, Ōta, Tokyo, Japan) to obtain retinal photographs. Two 45° color fundus photographs of each participant were obtained, centered on optic disc and fovea. The retinal vessel diameters were measured using a semiautomated algorithm interactive vessel analysis software (IVAN; Vasculomatic ala Nicola, University of Wisconsin-Madison, WI, USA), as described in our previous studies[16]. Central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) diameters were measured through an area of 0.5 to 1 disc diameter surrounding the optic disc margin, estimated by means of the Big-6 formula on the infrared fundus photographs. The arteriovenous ratio (AVR) was calculated as CRAE divided by CRVE.

All the study participants underwent a spectral-domain OCT (iVue SD-OCT; Optovue Inc, Fremont, California, USA) examination obtaining images of the ONH, macula and adjacent retina. A 6×6 mm^2 raster scan was centered on the optic disc and macula. The mean temporal, nasal, inferior, superior quadrant peripapillary RNFL thicknesses and central macular thickness (CMT) were assessed from high resolution images. RNFL segmentation was checked for every OCT image. Images not centered, or a signal strength index less than 40, any algorithm failures, motion artifacts, poor focusing were excluded from the assessment. As described in our previous study, two experienced ophthalmologists scanned all subjects[13].

Statistical Analysis The statistical analysis of this study was applied using a commercially available statistical package (SPSS for Mac, version 25.0; IBM/SPSS, Chicago, Illinois, USA). For the first analysis, we described the mean values (presented as mean standard deviation) of the participants' characteristics. Then the Student *t* test for un-paired samples

Table 1 Clinical characteristics of the study group and control group *n* (%)

Parameters	Study group	Control group	*P*
Participants (*n*)	659	477	-
Age (y)	51.0±7.8	51.8±7.5	0.077
Men/women	650:9	473:4	0.410
Diabetes	25 (3.99)	29 (6.26)	0.105
Alcohol consumption	377 (58.17)	267 (55.97)	0.242
Smoking history	432 (67.19)	307 (64.36)	0.714
Systolic blood pressure (mm Hg)	131.8±17.8	133.9±16.2	0.045
Diastolic blood pressure (mm Hg)	84±11.1	85±10.7	0.145
Body mass index	25.2±3.3	25.3±3.3	0.427
Spherical equivalent	-0.06±1.62	-0.32±1.52	0.056
High-density lipoproteins (mmoL)	1.42±0.59	1.33±0.6	0.016
Uric acid (mmoL)	313.3±97	334.4±97.1	<0.001
Cumulative silica dust exposure (mg/m^3 per year)	744.4±594.2	-	-

Table 2 Ocular findings in patients with downhole workers and control group

Parameters	Study group	Control group	*P*
Retinal artery diameter (μm)	154.52±19	151.56±19.8	0.012
Retinal venular diameter (μm)	236.27±27.3	230.35±27.75	<0.001
Arterio-venous ratio	0.66±0.12	0.67±0.11	0.687
CMT (μm)	246.17±22.1	249.06±19.61	0.032
Mean RNFL thickness (μm)	103.11±9.23	101.36±10.56	0.006
RNFL thickness superior quadrant (μm)	124.15±14.93	121.66±16.76	0.012
RNFL thickness temporal quadrant (μm)	81.59±14.14	79.02±12.21	0.002
RNFL thickness inferior quadrant (μm)	129.9±14.17	128.23±15.25	0.075
RNFL thickness nasal quadrant (μm)	77.4±10.17	77.59±10.87	0.774

RNFL: Retinal nerve fiber layer; CMT: Central macular thickness.

was to evaluate the statistical significance of differences between the coal workers and the controls. Multiple linear regression analysis was applied to evaluate the potential associations between ocular and systematic risk factors. The 95% confidence intervals of each risk factor were presented. Two-tailed *P*-values were considered to be statistically significant if lower than 0.05.

RESULTS

A total of 4004 participants [1720 women (43.0%)] with a mean age of 59.7±11.0y were included into the present investigation. After matched with age (±1y), spherical equivalent and gender, we included 659 coal workers (working underground) as study group, and 477 participants (working above the ground) as control group. There is no significant difference between study and control group in gender (*P*=0.41), age (51.0±7.8y *vs* 51.8±7.5y; *P*=0.077), diabetes status (*P*=0.105), alcohol consumption (*P*=0.242) or smoking history (*P*=0.714; Table 1).

As compared to the control group, the study group showed a significantly thicker retinal artery (154.52±19 *vs* 151.56±19.8 μm; *P*=0.012) and vein diameters (236.27±27.3 *vs* 230.35±27.75 μm; *P*<0.001), while the AVR did not differ significantly (0.66±0.12 *vs* 0.67±0.11; *P*=0.687) between both groups (Table 2). Additionally, the RNFL thickness was significantly higher in the study group than the control in superior and temporal quadrants (124.15±14.93 *vs* 121.66±16.76 μm, *P*=0.012; 81.59±14.14 *vs* 79.02±12.21 μm, *P*=0.002, respectively), while the CMT was lower in the downhole workers as compared to the control (246.17±22.1 *vs* 249.06±19.61 μm; *P*=0.032; Table 2).

In multivariable linear regression analysis (regression coefficient *r*=0.42), a thicker RNFL was associated with a higher CDE (*P*=0.005, *B*=0.002, 95%CI: 0.001, 0.003) after adjusting for younger age (*P*<0.001, *B*=-0.339, 95%CI: -0.437, -0.241), smaller cup-to-disc ratio (*P*<0.001, *B*=-6.315, 95%CI: -9.75, -2.879) and larger spherical equivalent (*P*<0.001, *B*=1.863, 95%CI: 1.324, 2.403). In a reverse pattern (regression coefficient *r*=0.19), a higher CDE was significantly associated with a thicker RNFL (P=0.004, B=5.194, 95%CI: 1.624, 8.763) after adjusting for age (P=0.003, B=0.094, 95%CI: 2.389, 11.955), high-density lipoproteins (P=0.009, B=0.082, 95%CI: 18.897, 134.474) and uric acid (P<0.001, B=-0.118, 95%CI: -1.026, -0.322). Wider retinal vein diameters were associated with higher CDE (P=0.036, B=0.004, 95%CI: 0, 0.009) after adjusting for younger age (P<0.001, B=-1.056, 95%CI: -1.367, -0.744) and larger spherical equivalent (P=0.027, B=1.876, 95%CI: 0.211, 3.541).

DISCUSSION

This community based study found that the retinal vessels diameters was significantly thicker in coal workers than in the control group. In addition, the RNFL thickness was significantly higher in the study group while the CMT was lower in the underground coal workers as compared to the controls. As a corollary, thicker RNFL was significantly associated with higher CDE, and wider retinal veins were also significantly correlated to higher CDE after adjustment for age. A higher CDE was significantly associated with a thicker RNFL in multivariable analysis.

The results of our study indicated that long-term working underground may lead to vessel dilation, which supported by Kappelgaard *et al*[17] that dark adaptation was associated with wider retinal vessel. Previous study has demonstrated that increased flow velocity in the central retinal artery in dark may relate to the square of the vascular caliber[10]. In addition, increased metabolic activity of the retina induced by dark adaptation may also lead to retinal vasodilation[17]. However, there had apparently contradictory findings. Barcsay *et al*[18] reported results with a venular constriction of 1.5% in 11 healthy young adults during dark and light adaptation by near-infrared laser light of 785 nm wavelength. Similarly, von Hanno *et al*[12] observed a slightly venular constriction (2.8%) after dark exposure, while no difference was observed in retinal artery diameter. Reasons for this discrepancy may have been the differences in study population and methodology. Our results may help explain how long-term changing of light conditions affect retinal vessels.

The retinal vein diameter was correlated with the CDE in both univariate and multivariable analysis. Nemmar *et al*[19] measured the distribution of radioactivity after the inhalation of pollutant particles and found that inhaled pollutant particles can cross the pulmonary epithelium into the cardiovascular system and thus exert direct effects on the cardiovascular system or the indirect effects mediated by the inflammatory response on the heart and vessels. With the central retinal artery as branch of the ophthalmic artery and internal carotid artery, the microvascular system of the retina can be assumed as part of the cardiovascular system. In addition, Nagaoka and Yoshida[20] detected that the stage of chronic kidney disease was a significant variable for the serum concentration of low-density lipoprotein and retinal blood flow. Both retina and kidney are low-resistance end organs that are supplied by small blood vessels, which are vulnerable to fluctuations in blood flow. The anatomical similarities in the vascularization of the retina and kidney may lead to similar aspects in the pathogenesis of cellular apoptosis and upregulation of pro-inflammatory markers in both organs. Therefore, it is reasonable to assume that long-term silica dust exposure can initiate the inflammation response on vascular endothelial cells which may influence ocular structures.

In our study, the RNFL thickness was significantly higher in the study group than the control in superior and temporal quadrants and the RNFL thickness was significantly associated with a higher CDE in multivariable analysis. The result of our study was in agreement with previous ophthalmological studies that active inflammation may lead to a significantly thickened RNFL[7,21]. The finding may be explained by the theory that the breakdown in the blood-retinal barriers and increased production of prostaglandins, inflammatory cytokines, and vascular permeability factor may be related to increased RNFL thickness[9]. Since exposure to silica dust may induce the accumulation of inflammatory cells, our result could go along with the similar mechanism. With the increased RNFL thickness as a sign of optic disc edema, the correlation between glaucoma severity and CDE is worth investigating further.

Interestingly, CMT was slightly thinner in study group compared with the control in our results. Former studies have indicated that cytokines (such as IL-1β, TNF-α, MMPs and TGF-β) induced by the inflammatory reactions occurred within the uveal tissue or the retinal pigment epithelium might give rise to retinal pathophysiologic changes[22-23]. Han *et al*[24] reported that the CMT in the eyes of the Vogt-Koyanagi-Harada (VKH) patients was significantly lower at 12 and 24mo, while the RNFL thickness was significantly higher in VKH eyes at the initial visit and at the 6- and 12-mo follow-up visits. They suggested that the degeneration of choriocapillaris layer might have a correlation with the disruption of photoreceptor or external limiting membrane. Such results indicate that long-term accumulation of trace elements and chronic inflammation might result in decrease of retinal thickness in macular area, however, assessing the thickness of the RNFL. Ayar *et al*[6] evaluated ocular findings in 46 coal mine workers who diagnosed with pneumoconiosis. Their results showed that CMT values were slightly thinner in coal miners than the controls. However, the difference did not reach a significant level. Reasons for the discrepancy between the results of Ayar *et al*'s[6] study and ours may have been differences in the recruitment of study population (pneumoconiosis patients *vs* population-based investigation).

In additon, various systemic medical disorders (neurologic, cardiovascular, endocrinological, metabolic, inflammatory and rheumatologic) may affect the measurement of CMT. In our study, there was no significantly association between CDE and CMT after adjusted systemic parameters in multivariable analysis. To determine this more clearly, future studies may explore the pathology and longitudinal changes in retinal thickness affected by the respirable silica particles in coal miners.

The main strengths of this study include a population-based cohort, quantitative measurements of retinal alterations and detailed information on systemic parameters. Nevertheless, potential limitations of our study should be considered. First, the recruitment of the study population was a randomly selected sub-group of the large Kailuan Study which was not representative for the Chinese population. The large sample size of our study however allows forming subgroups of coal miners. The study design may therefore enable to compare the study parameters within the influence of different working conditions. Second, we did not investigate the HbA1c level, which may better present the average level of glucose. Third, the changes of CMT and retinal vessel diameter were not analyzed in different layers or areas, which may better help us understand the pathological changes in the retina affected by the respirable silica particles. In addition, our study was a community-based observational cross-sectional investigation, the design of which did not allow drawing longitudinal conclusions.

In conclusion, the retinal vessels diameters and RNFL were significantly thicker in underground coal worker than the controls. The results of our study indicated that long-term coal mining may lead to retinal vessel dilation and inflammation. We therefore recommend that OCT and fundus photography examination might be needed within coal workers in order to monitor the occupational eye health as well as the incidence and progression of eye diseases.

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