

Prevalence and Association of Retinal Vascular Abnormalities: a study among the Elderly in Rural Southwestern Harbin, China

Ping Liu (✉ pingliu2598@163.com)

First Affiliated Hospital of Harbin Medical University

Junwei Wang

First Affiliated Hospital of Harbin Medical University

Fei Leng

First Affiliated Hospital of Harbin Medical University

Zhijian Li

First Affiliated Hospital of Harbin Medical University

Xianling Tang

First Affiliated Hospital of Harbin Medical University

Hua Qian

Harbin Medical University

Xiaoguang Li

Harbin Medical University

Yi Zhang

First Affiliated Hospital of Harbin Medical University

Xuedong Chen

First Affiliated Hospital of Harbin Medical University

Haitao Du

First Affiliated Hospital of Harbin Medical University

Research article

Keywords: Retinal vascular abnormalities; risk factors; cross-sectional study; prevalence; rural population; cardiovascular and cerebrovascular diseases.

Posted Date: May 9th, 2019

DOI: <https://doi.org/10.21203/rs.2.9522/v1>

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Version of Record: A version of this preprint was published at BMC Ophthalmology on April 6th, 2020. See the published version at <https://doi.org/10.1186/s12886-020-01407-y>.

Abstract

Background: Data on the retinal vessel morphology in the north China are still scarce so far. The study aimed to evaluate retinal vascular abnormalities and their associations with self-reported diagnosis of cardiovascular and cerebrovascular diseases in a rural adult population of northeast China. **Methods:** A population-based, cross-sectional study was conducted, using the cluster random sampling method. two 40° non-mydratic retinal photographs of one eye from each participant was taken using a fundus camera. The main Outcome measures: the prevalence of focal and general arteriolar narrowing, arteriovenous nicking, arteriolar sheathing, and retinopathy. Clinical data including general parameters and system diseases were collected by physical and laboratory examination and standard questionnaires. The association between retinal vascular abnormalities and cardiovascular and cerebrovascular diseases and their risk factors was determined using logistic regressions. **Results:** Among 6 267 participants with an age ≥ 50 years, photographs were obtained of 99.2%, with quality sufficient to perform retinal evaluations in 82.5% (from 5172 participants). Among them, 432 subjects had diabetes. The average age was 61.25 ± 7.37 years. The prevalence of focal arteriolar narrowing, arteriovenous nicking, arteriolar sheathing, retinopathy and general arteriolar narrowing were 9.1%, 8.9 %, 5.0 %, 6.6 % and 6.2% respectively. All the retinal lesions were associated with hypertension (all $P < 0.01$). No significant associations were found between the subjects with or without the presence of diabetes mellitus ($P > 0.05$). After adjusting for age, gender and left/right eyes, hypertension, hyperlipidemia, diabetes mellitus, habits of past or current smoking and alcohol drinking, arteriovenous nicking was strongly associated with the self-reported histories of coronary heart diseases (OR, 1.44; 95% CI, 1.09, 1.89) and retinopathy was significantly associated with self-reported histories of stroke (OR, 2.05; 95% CI, 1.18, 3.57). **Conclusions:** Retinopathy is associated with self-reported diagnosis stroke while arteriovenous nicking is associated with the self-reported diagnosis of coronary heart diseases, but the rest retinal lesions are not consistently related to the self-reported diagnosis of coronary heart diseases. Thus, an examination of retinal microvascular characteristics may offer clues to the cardiovascular and cerebrovascular diseases and could be a potentially novel risk marker.

Introduction

Cardiovascular and cerebrovascular diseases (CCVDs) are a leading cause of death worldwide. A large proportion of CCVDs could not be explained by traditional risk factors alone. Current cardiovascular biomarkers (eg, C-reactive protein) and risk assessment methods (eg, Framingham risk score model) can provide only modest improvements in predictive accuracy [1,2]. Although substantial epidemiological studies reporting the association between retinal vascular changes and risk of CCVDs [3-13], nevertheless, specialized computer software and trained technicians are required for such measurements and, thus, is only used as a research tool and not yet widely available for clinical use. Therefore, how to convert retinal vascular imaging into a clinical tool of the daily routine in assessing CCVDs risk prediction is an urgent problem to be solved.

Retinal vascular abnormalities (RVAs, a general term for retinal lesions such as focal and general retinal arteriolar narrowing, arteriovenous nicking, arteriolar sheathing, and retinopathy [14-17], have increasingly been taken into account to assess the risk of CCVDs [17]. Previous population-based studies have reported the strong link between RVAs and clinical stroke [7,9,12,13,18-20], and there is also evidence that RVAs are predictive of clinical coronary artery disease events [21,22]. However, most of the previous studies were conducted in white populations. One study in Beijing (China) [23] reported that RVAs are not related to the self-reported diagnosis of coronary heart disease (CHD) or previous cerebrovascular events such as stroke.

In consideration of the importance retinal vascular changes may have for the early detection of CCVDs and because data on the retinal vessel morphology in adult Asia are still scarce so far, we conducted the present study to assess the retinal vascular abnormalities in Northeastern China. The focus is on the prevalence of retinal vascular abnormalities and their associations with cardiovascular and cerebrovascular diseases among subjects aged 50 years or more. We try to find a simple and effective assessment method which will allow the translation of retinal vascular imaging as a tool to improve the screening of CCVDs in clinical practice.

Methods

2.1 Population and Sample ascertainment

Shuangcheng (Figure 1), a specific region of southwestern Harbin, northeast China, was selected to be the survey area. The population of the region is approximately 830,000, with 650,000 people living in rural areas (18 Xiang, 256 villages).

Geographically-defined clusters based on village register census data were used as the study sampling frame within each county/district. The sampling design was similar to that used for the study in Doumen[24], sample size was determined by retinal microvascular abnormalities prevalence (age \geq 40 years, 0.043)[23] within the allowable error bound of 20% with a 95% confidence interval (CI)[25] along with assuming an examination response rate of 85% and a design effect of 1.5 to account for inefficiencies associated with the cluster sampling design. A method of cluster random sampling was employed in this study. Briefly, the sample design used village-based clusters of almost the same size (around 1000 people). Using the street as dividing lines, villages with a population of more than 1500 people were separated into two units, and villages with a population of fewer than 500 people were merged with the neighboring village with a population of fewer than 800 people[26]. Then, 582 sampling units were obtained, from which 35 units were randomly selected. This study mainly aimed at individuals over 50 years old, who made up about 20% of the total population[27]. Finally, 6849 people were eligible for this study.

2.2 Survey methods

The research protocol was approved by the Medical Ethics Committee (The First Affiliated Hospital of Harbin Medical University No:201532) and all the subjects were given informed consents, according to the Helsinki Declaration. Listing of households with the names of residents \geq 50 years of age were obtained from the village registers, followed by door-to-door visits conducted by the enumeration team. Individuals temporarily absent at the time of the household visit were included in the enumeration. Unregistered adults \geq 50 years of age were enumerated and included in the study sample if they had been living in the household for at least six months. All the subjects were invited for eye examination (including visual acuity test, intraocular pressure measurement, slit lamp examination, and fundus examination). All examinations were carried out in the villages, either in clinics or in houses of the village committee. Those who did not appear at the examination site were revisited, repeatedly if necessary, by a member of the enumeration team to encourage participation. The inspections also included a variety of standardized assessments, including demographic characteristics, medical histories (hypertension, hyperlipemia, diabetes, stroke, cardiovascular and cerebrovascular diseases, smoking and alcohol drinking), blood pressure measurements, fasting blood glucose measurement and blood lipid measurements. Blood samples were collected between 7:00 and 9:00 a.m. after at least an 8-h overnight fast. Sterile vacuum tubes with and without ethylenediaminetetraacetic acid were used, and centrifugation was done within 3-h of blood collection. Serum analysis was performed in the laboratory of the First Affiliated Hospital of Harbin Medical University (quality control of the laboratory was certified and monitored yearly by the Ministry of Health, China).

2.3 Assessment of Hypertension, Hyperlipemia, CVDs and their Risk Factors

The methods of assessment of hypertension, CVDs, and their risk factors are highlighted here. Self-reported histories of CVDs and habits of smoking and alcohol drinking were obtained from a standardized questionnaire. Sitting brachial blood pressure was measured three times with a random-zero sphygmomanometer after 5 minutes of rest by trained technicians. Hypertension is diagnosed, if the Systolic blood pressure \geq 140mmHg or Diastolic blood pressure \geq 90mmHg, or self-reported history of hypertension and antihypertensive therapy. Hyperlipemia is diagnosed, if Triglyceride \geq 2.0mmol/L and high-density lipoprotein \leq 1.0mmol/L, or self-reported history of hyperlipemia and lipid-lowering therapy. Diabetes mellitus was diagnosed, if the fasting glucose \geq 7.0 mmol/ L (\geq 126 mg/dl) or use of insulin or oral hypoglycemic medication[28].

2.4 Assessment of retinal vascular abnormalities

In order to evaluate RVAs, two 40° non-mydratic retinal photographs of one eye from each participant was taken using a fundus camera (Type. Classic, 3nethra, Indian). One centered on optic disc and another on the fovea center (Figure 2 was followed the standard Field 1 and 2 in Early Treatment of Diabetic Retinopathy Study(ETDRS))[28]. To achieve the balance, if the identification numbers were even, the right eye was chosen, on the contrary, if the identification numbers were uneven, the left eye was chosen. Above methods of taking retinal photographs were principally followed the ARIC protocol[3].

Inclusion criteria for the study population: subjects who had clear fundus photographs and could be evaluated were included. Exclusion criteria of this study population: subjects whose fundus photographs are not clear and can not be evaluated; those who lack relevant data; Refusal to sign informed consent was as an exclusion criterion.

The color photographs (Image Resolution: 2048*1536 24 bits per pixel, JPG) of each subject were evaluated, according to the evaluation agreement of the ARIC[3] and ETDRS[28] study. The photographs were assessed by two assessors who were trained at the

Retinal Vascular Imaging Centre, the University of Melbourne (blind to participant characteristics) using a semi-quantitative manual grading approach on digital images.

For the evaluation of RVAs, the focal arteriolar narrowing (FAN), arteriovenous nicking (AVN), arteriolar sheathing (AS), retinopathy and generalized arteriolar narrowing (GAN) were assessed. The grader compared possible abnormalities with standard and example photographs to help determine their presence and severity. The ARIC grid[3](described in Figure 2) was applied to divide the retina into standard regions. Outside Zone A region (zone B and distally), FAN, AVN, AS, GAN in each quadrant was graded. Standard photographs for retinal microvascular signs were selected by a retinal specialist from the standard photographic set developed for the Modified Airlie House Classification of Diabetic Retinopathy[28].

FAN[3] was diagnosed if the artery of which the diameter should be greater than or equal to 50- μ m appeared a narrow area which diameter is equal to or smaller than 2/3 of its distal and proximal vessel segments. According to the total length of vascular stenosis in the quadrant, less than 1/2 DD, between 1/2DD and 2 DD, and 2 DD or more, respectively, the different severity levels including mild, moderate and severe were delineated; AVN[3] was diagnosed if both sides of the venous blood column were gradually narrowed at the intersection of the arteries and veins. If the narrowing approaching approximately 1/2 of the blood column, AVN was graded as "mild/moderate." If the narrowing was equaling or less than 1/2 of the blood column, AVN was considered as "severe." AS[3] was considered definite if white sheathing was observed on one side or both sides of retinal vessels. For the assessment of generalized narrowing of the retinal arterioles, the arterial diameter was compared with the corresponding veins, unless the veins were engorged and tortuous. If the arterioles appeared to be narrow in comparison with the veins, GAN was graded as "questionable." If some arterioles in the eye were markedly narrowed or thready but appeared normal in other quadrants of the fundus, GAN was graded as "definite." If the arterioles were small threads throughout the entire eye, GAN was graded as "severe"[23].

For retinopathy, the following lesions were evaluated in each of the four quadrants of the retina: microaneurysms, hemorrhages, soft exudates or cotton wool spots, hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, and vitreous hemorrhage. Retinopathy was diagnosed if any of these lesions were definite or probable in any of the four quadrants. The severity of retinopathy was summarized according to the ETDRS severity scale. [28]

2.5 Quality control

To examine the reproducibility of the assessment of retinal vascular abnormalities, 100 pictures were randomly selected and evaluated by two ophthalmologists respectively. Every observer repeated the work two weeks later.

2.6 Statistical analysis

The statistical analysis was carried out using SPSS 19.0 (Chicago, IL, USA). The five primary endpoints in the study were focal arteriolar narrowing(FAN), arteriovenous nicking(AVN), arteriolar sheathing (AS), retinopathy and generalized arteriolar narrowing(GAN), We calculated the prevalence of each retinal outcome, according to gender and age group. The association between retinal vascular abnormalities (FAN, AVN, AS, retinopathy and GAN) and CCVDs and their risk factors was determined using logistic regressions. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All the p values were using a 2-sided test and were regarded as significant when were less than 0.05.

Results

3.1 Participants

A total of 6 267 participants received examinations, the response rate was 91.5%. Fundus photographs were obtained from 99.2% of responding participants and 82.5% of photographs (from 5172 participants) were able to be used for retinal evaluations. There was no difference in age ($P = 0.38$) and gender ($P = 0.63$) between participants with evaluable photographs (5172) and those with unevaluated photographs (1095) (Table 1).The 5172 participants with evaluable photographs were finally employed for all the following analyses. Of the 5172 participants, 2043 were males and 3129 were females. The average age was 61.25 \pm 7.37 years. Among them, 432 subjects had diabetes.

3.2 Prevalence of Retinal Vascular Abnormalities

For the entire study population, prevalence of focal arteriolar narrowing(FAN), arteriovenous nicking(AVN), arteriolar sheathing(AS), retinopathy and generalized arteriolar narrowing(GAN), respectively, were 9.1%, 8.9 %, 5.0 % ,6.6 % and 6.2 % (Table 2). In general, the prevalence of AS, retinopathy, and GAN increased significantly with age, even after adjusting for gender. After adjusting for age, FAN, AS, and retinopathy was significantly more frequently in males than in females. For all types of retinal vessel abnormalities, no significant differences in the frequencies were found between left and right eyes($P > 0.05$, Table 2).

3.3 Association of RVAs with CCVDs and their risk factors

Logistic regression models were constructed to determine the association between each retinal outcome and CCVDs and their risk factors. All types of RVAs were more frequently in persons with hypertension than in those without, the age, gender and eye-adjusted OR ranged from 1.81 for retinopathy to 2.22 for focal arteriolar narrowing (Table 3).

After adjusting for age, gender and left/right eyes, FAN and AVN were associated with self-reported histories of coronary heart diseases(CHD), hyperlipidemia, and habits of past or current smoking and alcohol drinking(all $P < 0.01$). But the above two types of retinal lesions was not significantly associated with self-reported history of stroke(Table 3). After further adjusting for hypertension, hyperlipidemia, diabetes mellitus, habits of past or current smoking and alcohol drinking, the FAN association with self-reported histories of CHD was no longer were statistically significant (OR, 1.27; 95% CI, 0.95, 1.68). Only AVN was strongly associated with the self-reported histories of CHD (OR, 1.44; 95% CI, 1.09, 1.89)(Table 4).

Also after controlling for age, gender, and left/right eyes, retinopathy was associated with self-reported history of stroke, and with hyperlipidemia and habits of past or current smoking and alcohol drinking(all $P < 0.01$)(Table 3). After additional adjustment for hypertension, hyperlipidemia, diabetes mellitus, habits of past or current smoking and alcohol drinking, the association for stroke persisted (OR, 2.05; 95% CI, 1.18, 3.57). Retinopathy was not significantly associated with self-reported histories of CHD (OR, 0.89; 95% CI, 0.63, 1.26)(Table 4).

AS and GAN was not related to the self-reported diagnosis of CHD and stroke but were independently associated with hyperlipidemia, habits of past or current smoking and alcohol drinking. For all types of retinal lesions, no significant associations were found between the subjects with or without the presence of diabetes mellitus ($P > 0.05$).

Discussion

The county of Shuangcheng, northeast China, was selected for study to represent the typical environmental region (characterized by cold weather, low elevation, farming communities, and plains). This study provides vital epidemiological data on the prevalence of retinal microvascular abnormalities and their associations with CCVDs in this environment. Each retinal outcome was determined by the assessment of retinal digital images. First, we found that the overall prevalence of retinal microvascular abnormalities in the present population is relatively higher than that reported in other regions of the world, but the prevalence of retinopathy is lower. Second, we showed that retinopathy is associated with the self-reported diagnosis of a stroke while arteriovenous nicking is associated with a self-reported diagnosis of coronary heart diseases, but focal and generalized arteriolar narrowing and arteriolar sheathing are not consistently related to the self-reported diagnosis of coronary heart diseases or previous cerebrovascular events such as stroke. Thus, an examination of retinal microvascular characteristics may offer clues to CCVDs and could be a potentially novel biomarker of CCVDs risk.

In the present study, of the total sample, the prevalence of FAN, AVN, AS, retinopathy, and GAN were 9.1%, 8.9%, 6.6%, and 6.2%, respectively. In comparison, using almost the same methods of assessment, the prevalence for FAN, AVN, AS and GAN was 6.3%, 6.6%, 4.8%, and 4.3% respectively, in the Beijing Eye Study[23] (Chinese population: 40-101 years of age, including those with diabetes). Apparently, the prevalence of RVAs in the present study was relatively higher than those of the Beijing Eye Study. The prevalence of FAN, AVN, AS and retinopathy in persons without diabetes was 9.0%, 8.9%, 5.0%, and 6.8% respectively in the present study. In comparison, the ARIC study[3], which examined a non-diabetic study population aged 48 to 73 years, found that the prevalence was 7.3% for FAN, 6.0% for AVN, and 4.0% for retinopathy; And the CHS study[29], also with a non-diabetic population aged 69 to 97 years found that the prevalence was 9.6 % for FAN, 7.7% for AVN, and 8.3% for retinopathy. Obviously, the prevalence of RVAs in the present study was roughly equivalent to the data of CHS study but was relatively higher than that of the ARIC study. These differences might result from: first, sample selection and population characteristics (e.g., the average age[3,29,30], the frequency of

hypertension[30-34] between these studies). Second, the average latitude of the survey area is relatively high(Figure 1), and the average annual temperature is about 4.5 degrees. The stimulation of cold air is a precipitating factor for CCVDs[35,36]. Presumably, it may be related to the high frequency of RVA in this area. Third, the unique habits of the current sample (e.g. high salt diet, and high rates of smoking and alcohol drinking, which are already well-known risk factors for CCVDs, and correlation with RVAs will be discussed later). In addition, our study employed a 40° non-mydratic camera to obtain fundus images and used digital images to grade retinal lesions in the present study. These methods differ from those used in previous studies and thus may have also contributed to the difference in our results and previous findings.

It's also worth mentioning that the prevalence of retinopathy (5.1%) in persons with diabetes was lower than that of Chinese in Beijing (27.9%, ≥45 years)[37], Koreans (15.8%, ≥40 years)[38], and Chinese in rural Handan (43.1%, ≥30 years)[39]. The specific reasons for the low prevalence were not clear, in addition to different examination techniques and the grading system, presumably associated with a still lower living standard, mainly physical labor and high salt diet. And interestingly, for all types of retinal lesions, no significant differences were detected between the subjects with and without diabetes of the whole sample, which is consistent with the Beijing study. That is to say, although retinopathy(e.g., microaneurysms, hemorrhages, soft exudates or cotton wool spots, hard exudates, and etc.) is a landmark of diabetic retinopathy, it is still common in nondiabetic subjects over 50 years old. We should be cautious about the diagnosis of diabetic retinopathy, especially for elderly subjects.

Stratifying the population by age and gender (Table 2), males and older subjects tended to have more frequent RVAs of all types than their counterparts. These findings are consistent with previous reports such as those from the ARIC study[3] and the National Health and Nutrition Examination Survey (NHANES)[40] but different from the Beijing Eye study[23] which even showed that the AS was more frequently found in females than in males.

The focus of the present study was the correlation between RVAs and CCVDs, which was discussed respectively. In general, after adjusting for age, gender and left/right eyes, FAN, and AVN was found to be associated with self-reported histories of CHD (OR, 1.72; 95% CI, 1.31, 2.25; and OR, 1.89; 95% CI, 1.45, 2.46, respectively), and their risk factors (e.g., hypertension, hyperlipidemia, and habits of past /current smoking or drinking), and when we further adjusted for these above risk factors, the FAN association for CHD disappeared, suggesting that FAN was only related to the risk factors of CHD, but was not related to CHD at all; And the AVN-CHD association attenuated but still existed (OR, from 1.89 to 1.44) (Table 3, 4), suggesting that the changes of AVN could partly reflect the changes of cardiac-macrovascular, not only be restricted to the changes of microvascular. In the same way for retinopathy, when adjusting for age, gender and left/right eyes, retinopathy was associated with self-reported history of stroke(OR, 3.27; 95% CI, 1.93,5.54) and its risk factors(hypertension, hyperlipidemia, habits of past or current smoking, habits of past or current drinking), and when further adjusted for these above risk factors, the retinopathy–stroke association also weaken (OR, from 3.27 to 2.05) but still existed. Thus, these data suggest that point to point association may exist between retinal vascular changes and CCVDs(eg, the AVN-CHD association or retinopathy–stroke association). A multicenter study even demonstrated that different retinopathy signs were associated with specific stroke subtypes:[20] for example, retinal arteriolar narrowing was associated with lacunar stroke, whereas retinal hemorrhages were linked with cerebral hemorrhages[9,13,20,41,42]. But the results of the CHS study[29] claim that only retinopathy was associated with prevalent CHD and stroke and the results of the Beijing eye study[23] which claim that RVAs are not related to the self-reported diagnosis of CHD or previous cerebrovascular events such as stroke. These inconsistent results might be caused by the different assessment methods and grading thresholds between these studies.

The rest, except for retinopathy, the other four types of RVA are not related to the self-reported diagnosis history of stroke, but are associated with its risk factors; AS, retinopathy and generalized arteriolar narrowing are not related to the self-reported history of CHD, but are associated with the risk factors of CHD (Table 3). Although RVA and CVDs share some of the same risk factors, they are different in structure. Certain types of retinal microvascular abnormalities appear to be associated with systemic processes but still different from macrovascular changes(e.g., structure, and pathological features), supporting the ARIC[3] and CHS study[29] findings in middle-aged people.

This survey was performed in the rural areas of northern China. Due to the low standard of living, lower health awareness of residents, and poor medical and health conditions, many chronic diseases, such as cardiovascular diseases and cerebrovascular diseases were allowed to follow their natural course without manual intervention. The assessment of each outcome for individuals is closely performed in untreated conditions, which is also one important reason that this survey was conducted in rural areas. However, some factors may influence our evaluation of the prevalence of RVAs and their possible correlation with CCVDs. Firstly, images were not

obtained in some of the participants; some photos could not be evaluated due to refractive interstitial opacity; and a higher proportion of these images were obtained from elderly patients, who generally have more RVAs. Secondly, the evaluation of retinal abnormalities was performed manually, which may lead to the relative low κ values, for intraobserver and interobserver variation. Lastly, due to the use of a cross-sectional study rather than a cohort study, the current study could not elucidate the evolution of RVAs and their real-time relationship to systemic diseases.

Then what is the clinical significance of the present study? First, previous studies show that retinal vascular changes could predict CCVds risk[7,9,12,13,18-22,40,43,44] independently of traditional risk factors(e.g., hypertension, hyperlipidemia, and smoking). The present study may further refinement the association between retinal vascular changes and CCVds. If such an association could be proved stable, we may need to pay more attention to the correlation between the specific type of RVAs and CCVds(e.g., the retinopathy–stroke association). Thus, the prediction of CCVds may become more targeted, especially in rural primary hospitals where medical equipment is relatively scarce. Second, the purpose of the present study is how to convert retinal vascular imaging into a clinical tool of the daily routine in assessing cardiovascular risk prediction. The semi-quantitative classification method of retinal vascular abnormalities was used in this study. Due to the use of digital fundus photographs and standard evaluation system(ARIC and Beijing), the variability among observers is significantly lower than that of using only a direct fundoscopic examination. Moreover, because it is low-cost and efficient and it does not need professional technicians and expensive professional software. It could be popularized and implemented in primary hospitals among undeveloped regions. Subjects with CCVds or at high CCVds risks can be detected earlier and treated earlier, which can greatly save the cost of medical treatment. However, due to the relatively limited geographical scope of this study, future studies need a large sample and multi-regional clinical study to clarify the stability of this correlation.

In summary, the study details retinal microvascular abnormalities in a rural population of northeast Chian at low altitude with a cold climate. The overall prevalence of retinal microvascular abnormalities in this population is relatively higher than that reported in other regions of the world. But the prevalence of retinopathy is lower, which may be associated with cold climate, high salt diets, and still lower living standards. Retinal microvascular abnormalities are common in older persons and are related to hypertension. Retinopathy is associated with a self-reported diagnosis of stroke history and arteriovenous nicking is associated with the self-reported diagnosis of coronary heart diseases history, but focal and generalized arteriolar narrowing and arteriolar sheathing are not consistently related to the self-reported diagnosis of coronary heart disease or previous cerebrovascular events such as stroke. Thus, an examination of retinal microvascular characteristics may offer clues to the cardiovascular and cerebrovascular diseases and could be a potentially novel biomarker of cardiovascular and cerebrovascular diseases risk.

Abbreviations

Abbreviation	Full Word
RVAs	Retinal vascular abnormalities
GAN	Generalized arteriolar narrowing
FAN	Focal arteriolar narrowing
AVN	arteriovenous nicking
AS	Arteriolar sheathing
CCVds	Cardiovascular and Cerebrovascsular diseases
ARIC	Atherosclerosis Risk in Communities study
CHS	the Cardiovascular Health Study
DM	Diabetes mellitus
HP	Hypertension
OR	Odds Ratio

Declarations

- Ethics approval and consent to participate

The research protocol was approved by the Medical Ethics Committee (The First Affiliated Hospital of Harbin Medical University No:201532) and all the subjects were given informed consents, according to the Helsinki Declaration.

- Consent for publication

Not applicable

- Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests"

- Funding

This study was supported by grants from the National Natural Science Foundation,China (81470618), the Scientific Research Fund of Heilongjiang Provincial Education Department,China (12521262)

- Authors' contributions

All authors listed were involved in the implementation of the survey and data collection. In addition, JW Wang and HT Du were responsible for data statistics and analysis and was a major contributor in writing the manuscript. All the authors listed have approved the manuscript that is enclosed.

- Acknowledgements

The authors would like to acknowledge the Government and Hospital of Mingshui County for their organizational support, associate professor Qiuju Zhang and the volunteers at the First Affiliated Hospital of Harbin Medical University for their kind help and cooperation.

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Tables

Table 1. Characteristics of survey population (N,%)

	Total N(%)	Participants with evaluable photographs N(%)	Non-participants or participants with non-evaluable photographs N(%)	p value
*Age(Yrs)				
50-59	2763(44.1)	2281(44.1)	482(44.0)	0.38
60-69	2649(42.3)	2198(42.5)	451(41.2)	
70-79	757(12.1)	618(11.9)	139(12.7)	
80-91	98(1.6)	75(1.5)	23(2.1)	
**Gender				
Male	2467(37.5)	2043(39.5)	424(38.7)	0.63
Female	3800(62.5)	3129(60.5)	671(61.3)	

Chi-square test;

* $\chi^2 = 0.75$, $P = 0.38$, Participants with evaluable photographs versus nonparticipants(or participants with unvaluable photographs) in age;

** $\chi^2 = 0.23$, $P = 0.63$, Participants with evaluable photographs versus nonparticipants (or participants with unvaluable photographs) in gender

Table 2. Prevalence of Retinal Vascular Abnormalities in elderly Chinese in Rural Southwestern Harbin (%)

		Focal Retinal Vascular Abnormalities				Generalized Narrowing
		Focal arteriolar narrowing	AV nicking	Arteriolar sheathing	Retinopathy	
Total		9.1	8.9	5.0	6.6	6.2
Age(Yrs)†	50-59	8.2	8.2	3.9	5.6	5.7
	60-69	9.7	8.8	5.4	6.5	5.7
	70-79	9.7	12.3	6.6	10.4	9.1
	80-91	13.3	6.7	10.7	13.3	10.7
P value		0.626	0.096	0.034	<0.001	0.036
Gender‡	Male	11.3	9.9	6.8	6.3	7.1
	Female	7.7	8.3	3.8	6.9	5.6
P value		<0.001	0.183	<0.001	0.017	0.161
Eye	Left	8.7	9.6	5.2	7.2	6.5
	Right	9.5	8.3	4.7	6.1	5.9
P value		0.339	0.117	0.370	0.122	0.829

Test of trend, comparing % between groups.
 †,comparing adjusted % age groups.

‡Adjusted to age , comparing adjusted % between male and female.

†Adjusted to gender

Table 3. Association between Retinal vascular abnormalities and risk factors in elderly Chinese in Rural Southwestern Harbin

		Focal Retinal Vascular Abnormalities								Generalized Narrowing		
		Focal arteriolar narrowing		AV nicking		Arteriolar sheathing		Retinopathy				
	NO.at risk	%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†	
Hypertension	<i>No</i>	2801	6.2	1	5.9	1	3.4	1	4.8	1	4.3	1
	<i>YES</i>	2371	12.6	2.15(1.77,2.62)**	12.5	2.22(1.82,2.71)**	6.8	1.95(1.51,2.54)**	8.8	1.81(1.44,2.26)**	8.4	1.98(1.57,2.50)**
Hyperlipidemia	<i>No</i>	4113	8.0	1	8.6	1	4.6	1	6.1	1	4.9	1
	<i>YES</i>	1059	13.4	2.60(2.03,3.33)**	10.2	1.51(1.17,1.95)**	6.5	2.51(1.80,3.50)**	8.8	2.16(1.62,2.88)**	11.1	4.21(3.15,5.62)**
Diabetes Mellitus	<i>No</i>	4740	9.0	1	8.9	1	5.0	1	6.8	1	6.1	1
	<i>YES</i>	432	10.2	1.09(0.79,1.52)	9.7	1.08(0.77,1.51)	4.2	0.76(0.46,1.24)	5.1	0.75(0.48,1.17)	7.4	1.19(0.82,1.75)
Stroke History	<i>No</i>	5075	9.0	1	8.9	1	4.9	1	6.4	1	6.2	1
	<i>YES</i>	97	13.4	1.56(0.86,2.82)	12.4	1.43(0.78,2.64)	6.2	1.04(0.69,1.56)	18.6	3.27(1.93,5.54)**	8.2	1.35(0.65,2.80)
CHD	<i>No</i>	4652	8.6	1	8.3	1	4.9	1	6.4	1	6.1	1
	<i>YES</i>	520	14.0	1.72(1.31,2.25)**	14.8	1.89(1.45,2.46)**	5.4	1.24(0.54,2.87)	8.5	1.26(0.91,1.76)	7.1	1.13(0.79,1.62)
Smoking Status	<i>never</i>	2860	7.1	1	6.3	1	4.1	1	5.8	1	3.1	1
	<i>past</i>	1103	11.4	1.77(1.40,2.23)**	15.2	2.71(2.17,3.38)**	7.0	1.75(1.31,2.34)**	10.0	1.60(1.25,2.06)**	9.4	3.24(2.43,4.32)**
	<i>current</i>	891	12.7	2.17(1.70,2.77)**	9.1	1.56(1.19,2.05)**	5.1	1.50(1.05,2.13)*	5.1	0.90(0.65,1.27)	12.2	5.13(3.82,6.90)**
Alcohol Drinking Status	<i>never</i>	3528	7.2	1	7.3	1	4.3	1	5.5	1	4.3	1
	<i>past</i>	826	16.4	3.30(2.63,4.14)**	15.1	2.60(2.06,3.27)**	7.0	2.23(1.63,3.05)**	9.8	1.77(1.35,2.32)**	10.3	3.16(2.39,4.19)**
	<i>current</i>	500	9.4	1.71(1.23,2.38)**	9.2	1.51(1.08,2.10)*	6.2	2.03(1.35,3.05)**	8.7	1.79(1.27,2.54)**	12.3	4.09(2.96,5.65)**

The association between retinal vascular abnormalities and risk factors was determined using logistic regressions. *P<0.05;**P<0.01
 †OR(95%CI)=Odds ratio and 95% confidence interval, adjusted for age, gender and left/right eyes.

CHD:Coronary Heart Diseases History

Table 4 Logistic Regression of the Association between Retinal vascular abnormalities and Cardiovascular and Cerebrovascular Diseases in elderly Chinese in Rural Southwestern Harbin

		NO.at risk	Focal Retinal Vascular Abnormalities								Generalized Narrowing	
			Focal arteriolar narrowing		AV nicking		Arteriolar sheathing		Retinopathy		%	OR(95%CI)†
			%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†	%	OR(95%CI)†
Stroke History	No	5075	9.0	1	8.9	1	4.9	1	6.4	1	6.2	1
	YES	97	13.4	1.02(0.55,1.90)	12.4	0.99(0.53,1.84)	6.2	0.74(0.31,1.76)	18.6	2.05(1.18,3.57)**	8.2	0.91(0.41,1.99)
CHD	No	4652	8.6	1	8.3	1	4.9	1	6.4	1	6.1	1
	YES	520	14.0	1.27(0.95,1.68)	14.8	1.44(1.09,1.89)*	5.4	0.72(0.47,1.10)	8.5	0.89(0.63,1.26)	7.1	0.79(0.54,1.17)

*P<0.05;**P<0.01

†OR(95%CI)=Odds ratio and 95% confidence interval, CHD=Coronary Heart Diseases History;

Adjusted for age, gender, left/right eyes,Hypertension,Hyperlipidemia,Diabetes Mellitus,smoking status and alcohol drinking Status.

Figures

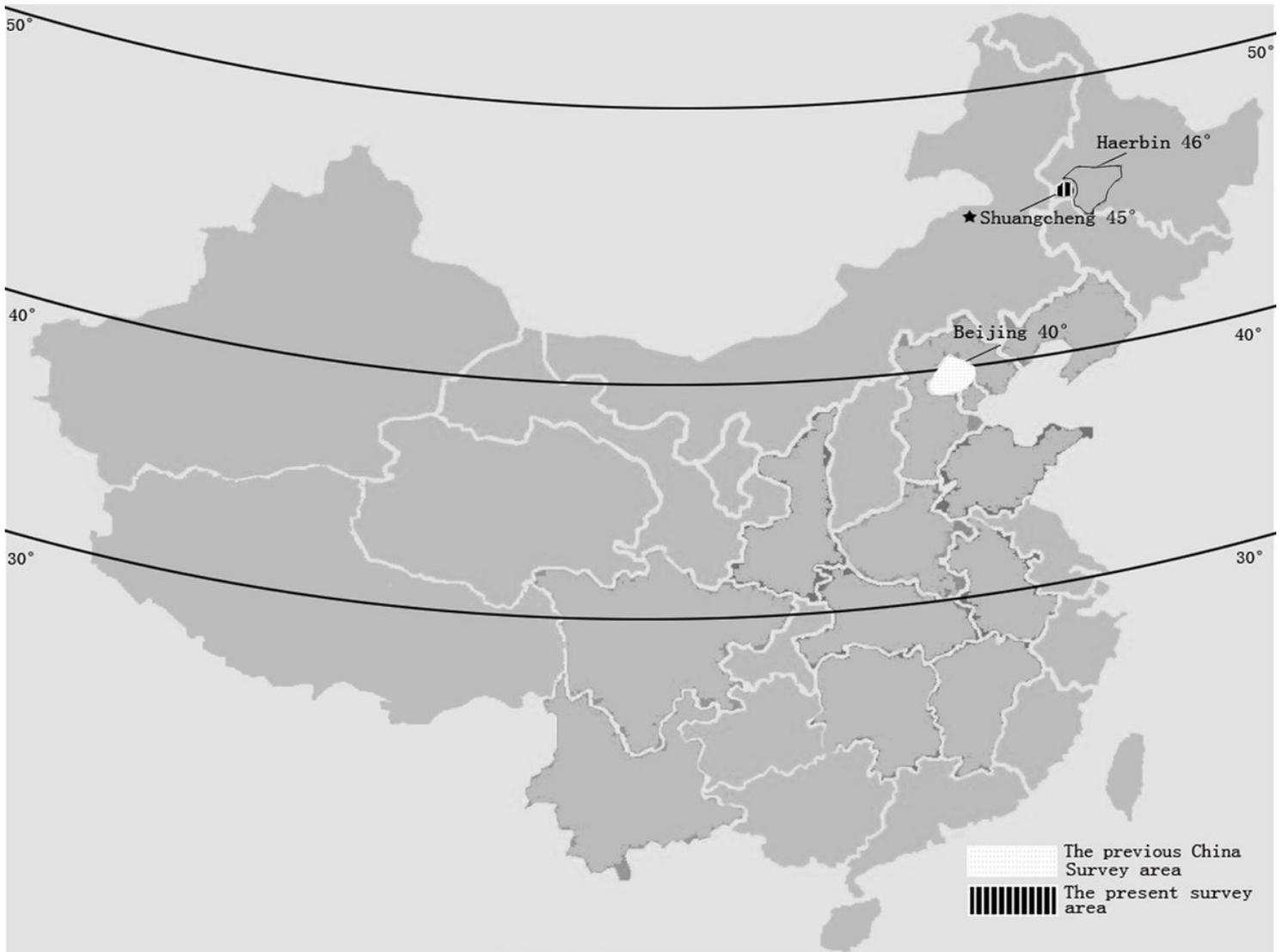


Figure 1

The map shows part of previous survey areas in China and the present survey area. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

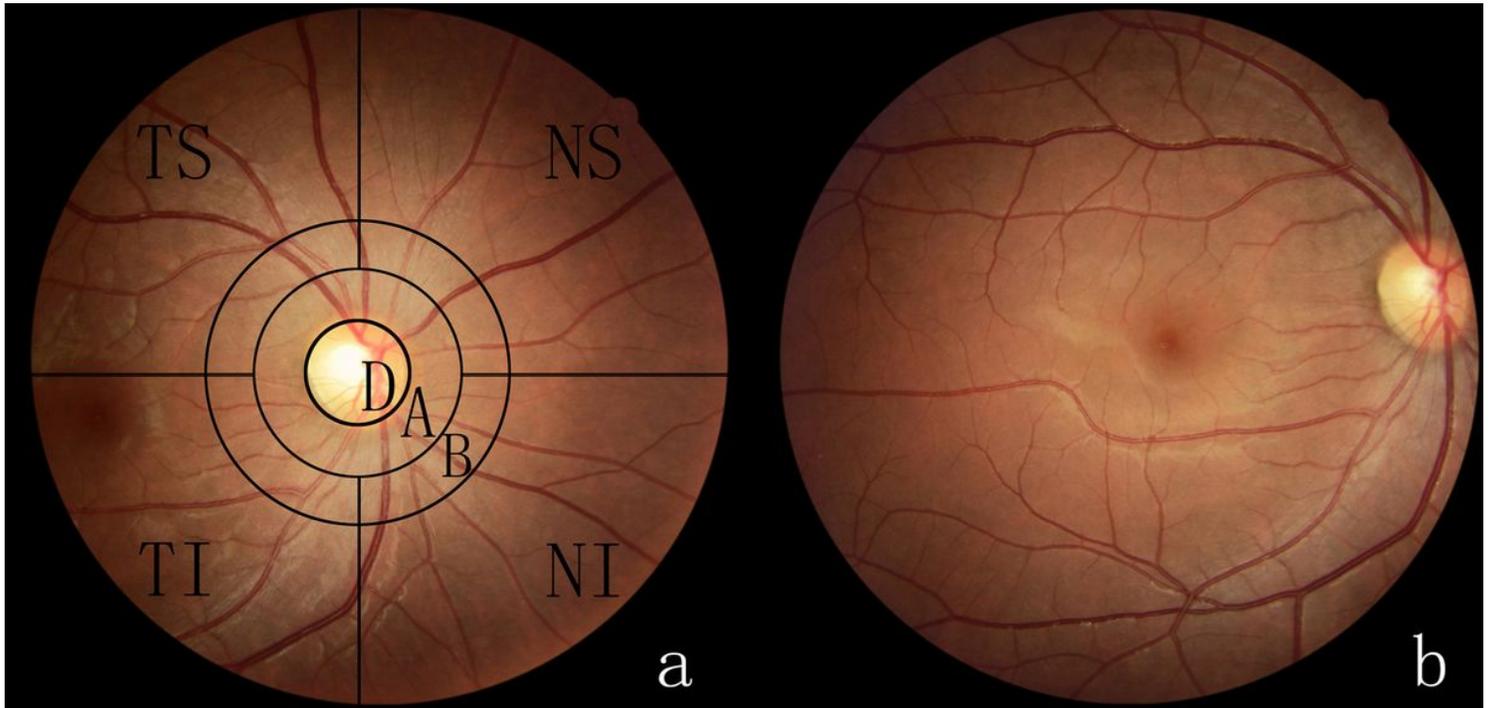


Figure 2

a. The color fundus photograph of the right eye of a participant, centered on optic disk, shows the photographic field definition and the superimposed grid. The grid is composed of three circles concentric with the optic disc: the innermost circumscribing the average disc, the middle one bounding the annulus from the disc margin to $\frac{1}{2}$ disc diameter (DD) from the margin (zone A), and the outer one bounding the annulus from $\frac{1}{2}$ DD to 1 DD from the disc margin (zone B). The four lines radiating from the central circle divide the photograph into four quadrants in relation to the disc: superior temporal (TS), superior nasal (TN), inferior nasal (NI), and inferior temporal (TI). b. The color fundus photograph of the right eye of a participant, centered on macula.