

Atherosclerosis

Association of retinal microvascular density and complexity with incident coronary heart disease

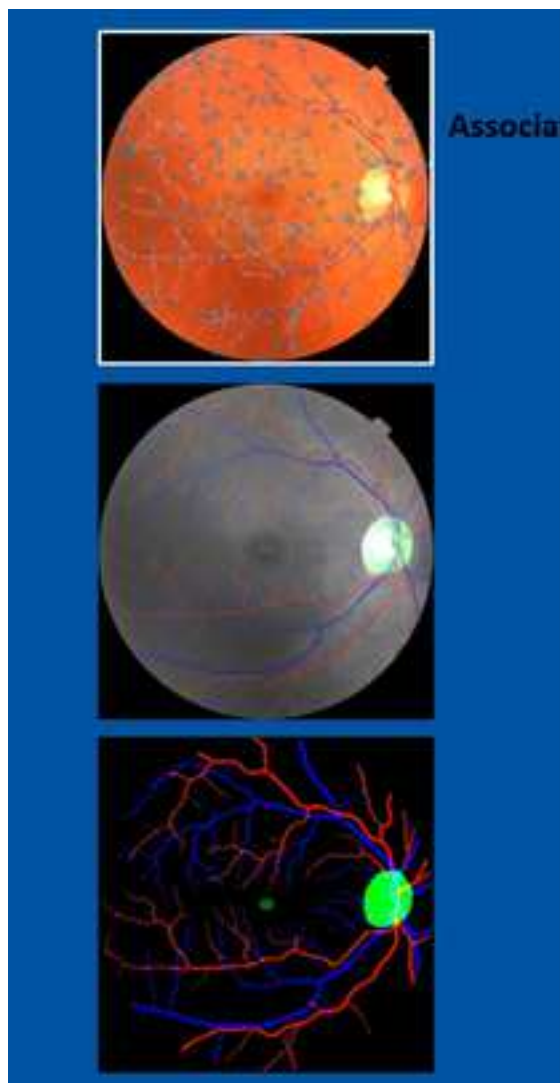
--Manuscript Draft--

Manuscript Number:	ATH-D-23-00382R1
Article Type:	Research paper
Section/Category:	Clinical & Population Research
Keywords:	coronary heart disease; deep learning; retinal microvascular density; retinal microvascular complexity
Corresponding Author:	Danli Shi CHINA
First Author:	Yuechuan Fu
Order of Authors:	Yuechuan Fu Mayinuer Yusufu Yueye Wang, MD Danli Shi Mingguang He, MD, PhD Ruobing Wang, MD, PhD
Abstract:	<p>Background</p> <p>The high mortality rate and huge disease burden of coronary heart disease (CHD) highlight the importance of its early detection and timely intervention. Given the non-invasive nature of fundus photography and recent development in the quantification of retinal microvascular parameters with deep learning techniques, our study aims to investigate the association between incident CHD and retinal microvascular parameters.</p> <p>Methods</p> <p>UK Biobanks participants with gradable fundus images and without a history of diagnosed CHD at recruitment were included for analysis. A fully automated artificial intelligence system was used to extract quantitative measurements that represent the density and complexity of the retinal microvasculature, including fractal dimension (Df), number of vascular segments (NS), vascular skeleton density (VSD) and vascular area density (VAD).</p> <p>Results</p> <p>A total of 57,947 participants (mean age 55.6±8.1 years; 56% female) without a history of diagnosed CHD were included. During a median follow-up of 11.0 (interquartile range, 10.88 to 11.19) years, 3,211 incident CHD events occurred. In multivariable Cox proportional hazards models, we found decreasing Df (adjusted HR= 0.80, 95% CI, 0.65-0.98, P=0.033), lower NS of arteries (adjusted HR= 0.69, 95% CI, 0.54-0.88, P=0.002) and venules (adjusted HR= 0.77, 95% CI, 0.61-0.97, P=0.024), and reduced arterial VSD (adjusted HR= 0.72, 95% CI, 0.57-0.91, P=0.007) and venous VSD (adjusted HR= 0.78, 95% CI, 0.62-0.98, P=0.034) were related to an increased risk of incident CHD.</p> <p>Conclusions</p> <p>Our study revealed a significant association between retinal microvascular parameters and incident CHD. As the lower complexity and density of the retinal vascular network may indicate an increased risk of incident CHD, this may empower its prediction with</p>

	the quantitative measurements of retinal structure.
--	-----------------------------------------------------

Highlights

- Coronary heart disease (CHD) is one of leading causes of morbidity and death around world, and the disease burden remains increasing.
- Current assessment methods of coronary microvasculature are unsuitable to be a screening tool for CHD, due to technically challenging and operating hardly.
- Retinal fundus images can be obtained noninvasively and conveniently, while the accuracy and efficacy of retinal feature measurements from fundus images has significantly been improved with the constant development of deep learning (DL).
- we integrated the clinical data from the UK Biobank, a large cohort of 57,947 individuals with gradable retinal fundus images, to reduce the limitation of small samples.
- A significant association between quantitative density and complexity of retinal microvasculature and incident CHD was revealed, supporting the potential of the quantitative retinal structure measurements in predicting individuals with a high risk of incident CHD.



Association of retinal microvascular density and complexity with incident coronary heart disease

UK Biobanks

a large community-based database of UK residents, including more than 500,000 people

RMHAS

an artificial intelligence system, enables automated microvasculature segmentation and quantification of the retinal vessels

prediction



Increased risk of CHD events

Association of retinal microvascular density and complexity with incident coronary heart disease

Yuechuan Fu¹; Mayinuer Yusufu^{2,3#}; Yueye Wang⁴; Mingguang He^{2,3,4*};
Danli Shi^{2*}; Ruobing Wang^{1*}

1. Department of Ophthalmology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China
2. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia
3. Department of Surgery (Ophthalmology), The University of Melbourne, Melbourne, Australia.
4. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, 510060, China

Correspondence

* Mingguang He, Centre for Eye Research Australia, University of Melbourne, VIC 3002, Melbourne.

E-mail: mingguang.he@unimelb.edu.au

* Danli Shi, Centre for Eye and Vision Research (CEVR), 17W Hong Kong Science Park; School of Optometry, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China

E-mail: sdlmed@163.com

* Ruobing Wang, Department of Ophthalmology, Renji Hospital, School of

Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China

E-mail: adawrb@126.com

These authors contributed equally to this work

Abstract

Background and aims: The high mortality rate and huge disease burden of coronary heart disease (CHD) highlight the importance of its early detection and timely intervention. Given the non-invasive nature of fundus photography and recent development in the quantification of retinal microvascular parameters with deep learning techniques, our study aims to investigate the association between incident CHD and retinal microvascular parameters.

Methods: UK Biobanks participants with gradable fundus images and without a history of diagnosed CHD at recruitment were included for analysis. A fully automated artificial intelligence system was used to extract quantitative measurements that represent the density and complexity of the retinal microvasculature, including fractal dimension (Df), number of vascular segments (NS), vascular skeleton density (VSD) and vascular area density (VAD).

Results: A total of 57,947 participants (mean age 55.6 ± 8.1 years; 56% female) without a history of diagnosed CHD were included. During a median follow-up of 11.0 (interquartile range, 10.88 to 11.19) years, 3,211 incident CHD events occurred. In multivariable Cox proportional hazards models, we found decreasing Df (adjusted HR= 0.80, 95% CI, 0.65-0.98, $p=0.033$), lower NS of arteries (adjusted HR= 0.69, 95% CI, 0.54-0.88,

$p=0.002$) and venules (adjusted HR= 0.77, 95% CI, 0.61-0.97, $p=0.024$), and reduced arterial VSD (adjusted HR= 0.72, 95% CI, 0.57-0.91, $p=0.007$) and venous VSD (adjusted HR= 0.78, 95% CI, 0.62-0.98, $p=0.034$) were related to an increased risk of incident CHD.

Conclusions: Our study revealed a significant association between retinal microvascular parameters and incident CHD. As the lower complexity and density of the retinal vascular network may indicate an increased risk of incident CHD, this may empower its prediction with the quantitative measurements of retinal structure.

Key words: coronary heart disease, deep learning, retinal microvascular density, retinal microvascular complexity

1. Introduction

Coronary heart disease (CHD), as one of the major causes of death worldwide, led to 20% of all death in Europe, and the burden of CHD tends to increase further[1]. Currently, the assessment of coronary microvasculature with invasive coronary angiography is the gold standard for the diagnosis of CHD. While those imaging modalities exhibit a high degree of specificity and sensitivity in determining the presence and severity of CHD, it is not a suitable screening tool for CHD, due to technical

1 challenges, complex procedures, and its invasiveness. Without regular
2
3 screening, patients would present to cardiologists only when serious
4
5 events have already occurred, such as myocardial infarction. To empower
6
7 early detection and preventative healthcare, a noninvasive and cost-
8
9 efficient diagnostic screening tool for CHD is urgently needed.
10
11
12
13

14 The retinal microvasculature is the only vascular tissue in the human body
15
16 that can be observed directly, and it possesses common physiologic and
17
18 anatomic characteristics with the vasculature of the coronary vascular
19
20 tree. The retinal microvasculature abnormalities could reflect chronic
21
22 vascular damage from various cardiovascular risk factors including
23
24 ageing[2], diabetes mellitus[3], hypertension[4], and other vascular
25
26 diseases[5]. Atherosclerosis, the main cause of cardiovascular disease, is
27
28 a chronic inflammatory condition that impacts blood vessels all over the
29
30 human body. Hence, non-invasive visualization of retinal microvasculature
31
32 shows the potential to reveal significant dysfunction of vessels and to
33
34 assist in predicting incident cardiovascular events in the general
35
36 population.
37
38
39
40
41
42
43
44
45
46
47

48 The development of fundus photography and image-processing software
49
50 in the last decade greatly facilitated the progress in the assessment of
51
52 retinal microvasculature. The constant advancement in deep learning (DL)
53
54 has significantly improved the accuracy and efficacy of retinal feature
55
56 measurements from fundus images. Retina-based Microvascular Health
57
58
59
60
61
62
63
64
65

1 Assessment System (RMHAS), an artificial intelligence system, enables
2
3 automated microvasculature segmentation and quantification of the
4
5 retinal vessels. Various features in the retina can be non-invasively
6
7 visualized from retinal fundus images, including vessel calibre, bifurcation,
8
9 tortuosity, the number of vascular segments (NS), vascular density and
10
11 fractal dimensions (Df). Retinal vasculature complexity is a complex
12
13 branching pattern of vascular network as measured with NS and Df. Lower
14
15 branching complexity of retinal vessels was observed associated with
16
17 higher risk of cardiometabolic[6]. Vessel density referred to the
18
19 percentage of area with bloodstream over the total measured area.
20
21 RMHAS achieves good segmentation accuracy and repeatability of vessel
22
23 measurements across various datasets with diverse eye status and retinal
24
25 photograph resolutions[7].
26
27

28
29 The changes in retinal vessels, including vascular calibre, arteriovenous
30
31 crossing points, and occlusions, have been assessed as biomarkers of
32
33 severity, prognosis, longevity, and therapeutic response in clinical
34
35 conditions[8-10]. Previous studies have demonstrated that various retinal
36
37 vascular features can reflect the status of the cardiovascular system, such
38
39 as vessel calibre [11], bifurcation or tortuosity[12] and vascular fractal
40
41 dimensions[13]. However, no consensus has emerged on the association
42
43 between retinal vessel parameters and CHD risk, and previous studies
44
45 have relatively small sample sizes. Therefore, further investigation of the
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

clinical implications of retinal vascular features is required

To better understand the potential application of retinal vascular traits as biomarkers for predicting incident CHD, we integrated the clinical data from the UK Biobank, a large community-based database, to assess the association between quantitative density and complexity of retinal microvasculature and CHD development.

2. Patients and methods

2.1 Study population

The UK Biobank is a large community-based database of UK residents. At baseline, the UK Biobank recruited more than 500,000 people aged 40 to 70 years between 2006 and 2010 at 22 study assessment centres. Participants underwent physical measurements, such as blood pressure, height, and weight, and finished a wide-ranging detailed questionnaire containing information on social economics, demographics, health, and lifestyle. The identification of hypertension, diabetes mellitus, and smoking was based on self-reported data. Biochemical measurements, including high-density lipoprotein (HDL) cholesterol and HbA1c, were performed. Retinal fundus images were collected from 66,487 participants.

2.2 CHD ascertainment

CHD diagnosis was ascertained using the International Classification of

1 Diseases (ICD), Ninth and Tenth editions, and participants' self-reported
2 previous diagnoses. We defined CHD as non-fatal myocardial infarction
3 and fatal ischemic heart disease by diagnosis codes 410-414 of the ICD-9
4 and codes I20-I25 of the ICD-10. The history of CHD was defined as the
5 emergence of CHD events before recruitment, while incident CHD was
6 defined as the emergence of CHD events after recruitment and during the
7 follow-up period. We calculated the follow-up time from the date of
8 recruitment to the earliest recorded date of CHD diagnosis, lost to follow-
9 up, or death, whichever occurred first. Participants with a history of CHD
10 were excluded from the analysis.

2.3 Quantitative retinal microvascular parameters

11 Retinal images were obtained from 66,487 participants using a 45°
12 primary field and non-mydratic fundus camera (Topcon 3D OCT-1000
13 Mk2, Japan) at baseline. Quantitative analysis of the retinal vascular size
14 and topology was performed with RMHAS, an artificial intelligence system.
15 Custom region-specific summarization and global physical/geometric
16 parameters were used to measure the retinal vascular morphology. The
17 retinal vessels were transformed into segments separated by breaks at the
18 crossing or branching points and the following retinal parameters were
19 measured: Df, NS, vascular skeleton density (VSD), and vascular area
20 density (VAD). Images with poor quality were excluded. Measurements
21 from the image of the right eye were used for analysis, and when retinal

1 images of the right eye were not available or gradable, measurements
2
3 from the image of the left eye were used.
4
5

6
7 Quantitative measurements of VSD and VAD were analyzed and compared
8
9 between those with incident CHD and the healthy control. VSD was
10 defined as the ratio of the total length of vessels to the total area of the
11 image at 1 pixel, a measure of overall vessel length within a fundus image.
12
13 VAD was used to evaluate the ratio of the area occupied by vessels divided
14 by the total area. In addition to vascular density, Df was calculated using
15 the box-counting method, expressing the density and overall complexity
16 of retinal vasculature. Df and NS indicate the extent of branching
17 complexity of retinal blood vessels, depending on the angles of
18 bifurcations, the number of bifurcations, and the length of vessels
19 between two successive bifurcations[14].
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 **2.4 Covariates**

38
39
40

41 In the UK Biobank, covariate data were obtained from baseline
42 questionnaires and physical and biochemical measurements. We assessed
43 covariates, including baseline age, sex, ethnicity (recorded as white or
44 nonwhite), smoking condition (current/ever or never), education degree
45 (college/university degree, or others), Townsend deprivation index (an
46 area-based proxy measure for socioeconomic status), systolic blood
47 pressure (SBP), Body mass index (BMI), HDL cholesterol, total cholesterol,
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

HbA1c, triglyceride (TG), and presence of diabetes mellitus, hypertension, stroke, diabetic retinopathy (DR), rein vascular occlusion, age-related macular degeneration (AMD) and glaucoma.

2.5 Statistical analysis

The statistical analysis was performed using Stata 17.0. Descriptive statistics were carried out to describe the characteristics of participants at baseline. For quantitative variables, the characteristics were reported as mean \pm standard deviation (SD) and interquartile range (IQR). For qualitative variables, the absolute and relative frequencies were presented. Baseline characteristics were compared by one-way analysis of variance (ANOVA). The hazard ratios (HRs) with 95% confidence intervals (CIs) were utilized to assess the association between incident CHD and retinal microvascular parameters (continuous and quartiles) by Cox proportional hazards regression models.

Four multivariable Cox proportional hazards regression models were fitted. Model 1 adjusted for age at recruitment and sex. Model 2 extended model 1 with further adjustment for physical measurements, including total cholesterol, HbA1c, HDL, TG, SBP, and BMI. Model 3 further adjusted model 2 for hypertension, diabetes mellitus, smoking, and prior stroke. Model 4 added four potential ophthalmic confounders to model 3, including DR, AMD, rein vascular occlusion, and glaucoma. The

proportional hazards assumption was evaluated graphically for each variable included in the Multivariable Cox proportional hazards models. To investigate the effect-response association between retinal microvascular parameters and incident CHD, values were transferred into a categorical variable by quartile. The highest quartile of retinal microvascular parameters (fourth quartile) was used as the reference. We additionally performed a sensitivity analysis in participants without missing covariates. A p-value less than 0.05 was regarded as statistically significant.

3. Results

3.1 Participants characteristics

Among 57,947 participants, 56% were female and the mean age at recruitment was 55.6 ± 8.1 years. The median follow-up time was 11.0 (interquartile range [IQR], 10.88-11.19) years. During the follow-up, 3,211 participants experienced incident CHD. The incident CHD were related to the male gender, older age, smoking status (current or previous smoker), a lower level of education, higher BMI, lower HDL and total cholesterol levels, higher SBP, and elevated HbA1c and TG levels at baseline. Among participants with incident CHD, the proportions of diabetes mellitus, hypertension, stroke, DR, glaucoma, and AMD were also higher. Table 1 shows the detailed characteristics of participants at baseline.

3.2 Retinal microvascular parameters measurements and incident CHD

Quantitative measurements of the retinal vessels were analyzed, including Df, NS, VSD, and VAD. The incident CHD was associated with all four parameters in the unadjusted model. After multivariate adjustments, the CHD outcomes were still significantly associated with Df, NS, and VSD. However, the relationship between CHD outcomes and VAD of retinal arteries and venules was nonsignificant in the fully adjusted model. The associations between the retinal microvascular parameters and incident CHD using univariate and multivariable Cox regression models are listed in Table 2 and Table 3. Similar associations were observed after excluding participants with missing covariates in the sensitivity analysis.

In the univariable Cox proportional hazards regression model, the incident CHD showed a significantly negative correlation with Df (unadjusted HR=0.38, 95% CI, 0.32-0.45, $p<0.001$), arterial NS (unadjusted HR=0.23, 95% CI, 0.19-0.27, $p<0.001$), venous NS (unadjusted HR=0.41, 95% CI, 0.34-0.50, $p<0.001$), arterial VSD (unadjusted HR=0.24, 95% CI, 0.20-0.29, $p<0.001$), venous VSD (unadjusted HR=0.43, 95% CI, 0.35-0.52, $p<0.001$), arterial VAD (unadjusted HR=0.26, 95% CI, 0.22-0.32, $p<0.001$) and venous VAD (unadjusted HR=0.66, 95% CI, 0.54-0.80, $p<0.001$). There was no violation of the proportional hazards assumption.

After adjusting for age, sex, BMI, the measurement of cholesterol, HbA1c,

1 HDL, TG and SBP and the history of diabetes mellitus, smoking, stroke,
2
3 hypertension, DR, rein vascular occlusion, AMD and glaucoma, the
4
5 association between Df and incident CHD remained significant (adjusted
6
7 HR= 0.80, 95% CI, 0.65-0.98, $p=0.033$, model 4 in Table 2). When the
8
9 parameter was transformed into a categorical variable by quartile,
10
11 participants with Df in the second (adjusted HR= 1.00, 95% CI, 0.88-1.13,
12
13 $p=0.940$, model 4 in Table 3) and third (adjusted HR= 1.04, 95% CI, 0.92-
14
15 1.18, $p=0.494$, model 4 in Table 3) quartiles had similar risks of incident
16
17 CHD event compared with those with Df in the fourth quartile, while the
18
19 risk was significantly higher for those with Df in the first quartile after full
20
21 adjustments (adjusted HR= 1.15, 95% CI, 1.02-1.18, $p=0.020$, model 4 in
22
23 Table 3).
24
25
26
27
28
29
30
31
32
33

34 The increased risk of incident CHD was observed in participants with lower
35
36 NS of retinal arteries (adjusted HR= 0.69, 95% CI, 0.54-0.88, $p=0.002$,
37
38 mode 4 in Table 2) and venules (adjusted HR= 0.77, 95% CI, 0.61-0.97,
39
40 $p=0.024$, model 4 in Table 2). In the fully adjusted model, participants with
41
42 the lowest quartile of arterial (adjusted HR= 1.16, 95% CI, 1.02-1.31,
43
44 $p=0.020$, model 4 in Table 3) and venous (adjusted HR= 1.14, 95% CI, 1.02-
45
46 1.29, $p=0.026$, model 4 in Table 3) NS had 16% and 14% higher risks of
47
48 incident CHD, compared with the fourth quartile.
49
50
51
52
53
54
55
56

57 The VSD of both retinal arterioles and venules was markedly negatively
58
59 associated with incident CHD in multivariable analysis. In model 4, the
60
61
62
63
64
65

1 increase in one standard deviation unit in VSD of arterioles and venules
2
3 was associated with a 28% and 22% decreased risk of incident CHD
4
5 (adjusted HR= 0.72, 95% CI, 0.57-0.91, $p=0.007$; adjusted HR= 0.78, 95%
6
7 CI, 0.62-0.98, $p=0.034$, model 4 in Table 2). Participants with arterial VSD
8
9 in the fourth quartile (adjusted HR= 1.17, 95% CI, 1.03-1.32, $p=0.014$,
10
11 model 4 in Table 3) had a distinctly increased risk of incident CHD events,
12
13 compared with the fourth quartile. There was no significant difference
14
15 across 4 venous VSD quartiles regarding the risk of incident CHD.
16
17
18
19
20
21
22

23 **4. Discussion**

24
25
26 In this study, we investigated the association of the retinal microvascular
27
28 parameters in a large cohort of 57,947 participants from the UK Biobank.
29
30 The results showed that the risk of incident CHD was significantly
31
32 associated with Df, NS, and VSD when analyzed as both continuous and
33
34 categorical variables after multiple adjustments (Fig. 3). This revealed the
35
36 potential predictive value of retinal microvascular parameters and the
37
38 possibility of developing a DL prediction model with retinal fundus images
39
40 for the risk of cardiovascular events.
41
42
43
44
45
46
47
48

49
50 Previous studies have reported on the relationship between retinal
51
52 characteristics and the incidence, risk factors, and prognosis of CHD. The
53
54 study by Qu Y et al. showed significantly increased tortuosity (average
55
56 tortuosity, arteriole tortuosity and venule tortuosity) in patients with CHD
57
58
59
60
61
62
63
64
65

[15]. The higher platelet activation rate and occurrence of mural thrombi are observed in the arteries, which could result from the restriction or complete occlusion of the blood perfusion by increased vessel tortuosity, leading to cardiovascular events or stroke[16]. Previous studies have revealed connection between retinal microvascular features, retinal diseases, and cardiovascular diseases[17-19]. While the underlying mechanism remains unclear, the similarities and interactions between the vascular structure of the heart and the eye may be the key to understand their association [20]. Multiple risk factors of cardiovascular diseases may contribute to the changes in retinal traits, including hemodynamic changes, structural changes, and genetic alterations. In addition, various chronic diseases, such as diabetes mellitus, atherosclerosis, and hypertension, were reported as risk factors for both vascular changes in the retina and cardiovascular diseases [21]. More importantly, previous studies have demonstrated retinal vascular features may be a potential novel biomarker for the risk of future cardiovascular events, such as coronary artery calcification and carotid intima-media thickness[22, 23]. Compared with invasive coronary angiography, fundus photography offers considerable advantages for efficient risk assessment for cardiovascular diseases as a safe, convenient, and cost-effective approach.

With the utilization of DL technologies, retinal vascular characteristics could be automatically derived from retinal fundus images and analyzed

with high efficiency. The complexity microvascular indicates the intricate network of retinal vessels. Our study found complexity of retinal microvasculature (Df and NS) to be potential biomarkers for future incident CHD events, and the association remained statistically significant even after adjustment for demographic and vascular factors. Several studies have revealed the relation of retinal vascular Df with hypertension, diabetes mellitus, and CHD[24, 25]. Sarah B et al. obtained a range of quantified retinal vessel geometric measurements from retinal photographs using semi-automated software and reported that lower Df of retinal vessels is associated with the greater extent and severity of coronary artery disease[26]. Retinal arteriolar endothelial dysfunction is an effective predictor of major adverse events in patients with cardiovascular risk factors[18], and it's reported that retinal vessel atherosclerosis correlates strongly with the risk factors and severity of cardiovascular diseases[19]. As the common risk factor for both dysregulation of retinal blood perfusion and cardiovascular diseases, endothelial dysfunction can be caused by lipid accumulation, excessive oxidative stress, and chronic inflammation[27], which indicates the presence of systemic pathological changes.

In addition to measurements of retinal vascular complexity, the risk of incident CHD was also significantly associated with density of retinal vessels. Compared to venous VSD, the negative correlation was stronger

1 between arterial VSD and CHD events. This may reflect arterial-venous
2
3 distinction after hypoxia, due to their respective functions in the retinal
4
5 vascular network. The association between CHD and retinal blood flow
6
7 perfusion remains controversial. Arbel Y et al. reported elevated retinal
8
9 arteriolar blood perfusion in patients with slow coronary blood flow,
10
11 resulting from endothelial and microvascular dysfunction[28]. The
12
13 presence of endothelium dysfunction may lead to the dysregulation of
14
15 vascular bifurcation and consequently result in decreased VSD, which
16
17 could compromise the efficiency of vascular networks and reduce blood
18
19 (including oxygen and nutrient) supply[29]. This could explain the
20
21 increased risk of incident CHD in participants with decreased retinal VSD.
22
23
24
25
26
27
28
29
30

31 Our study also found a significant association between VAD and incident
32
33 CHD. The previous study reported that decreased VAD is related to the
34
35 increased severity of diabetic retinopathy and significantly correlated with
36
37 diabetic macular oedema[30]. Cheng L et al. examined the relevance of
38
39 retinal microvascular features to coronary artery abnormalities and found
40
41 that retinal hemorrhage, moderate microvascular retinopathy, and
42
43 diabetic retinopathy are correlated with more severe coronary artery
44
45 disease with angiograms[17]. Li J et al. demonstrated that mild
46
47 hypertensive retinopathy is positively related to the likelihood of stroke
48
49 and cardiovascular disease, but not to the risk of CHD [31], while the data
50
51 from the ARIC Study showed the positive relevance of arteriolar narrowing
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 to the risk of CHD [32]. Therefore, decreased VAD may be the common
2
3 mechanism of retinopathy and cardiovascular disease and, to some extent,
4
5 explains the association between the presence of retinopathy and the risk
6
7 of cardiovascular events.
8
9

10
11 The previous study illustrated the incremental value of retinal vessel
12
13 examination in predicting atherosclerotic cardiovascular disease events,
14
15 by demonstrating that wider retinal venules and narrower retinal
16
17 arterioles indicated the long-term risk of CHD in women[33]. Our study
18
19 further revealed that the microvascular parameters that represent the
20
21 complexity and density of retinal vascular network were significantly
22
23 associated with the risk of CHD in general population. Hence, early non-
24
25 invasive observation of retinal microvasculature may assist in identifying
26
27 individuals at increased risk of developing CHD, thereby empowering early
28
29 preventive treatments.
30
31
32
33
34
35
36
37
38
39

40 **4.1 Strengths and limitations**

41
42 This study benefitted from the large sample size and the standardized,
43
44 systematic methods of data collection. In addition, our study used RMHAS,
45
46 an artificial intelligence system that performs fully automated vessel
47
48 segmentation and provides precise quantitative measurements of the
49
50 retinal vessels. Its accuracy and efficiency warrant the potential
51
52 application of quantitative measurement-based models in real-world
53
54
55
56
57
58
59
60
61
62
63
64
65

settings.

However, our study also has several limitations. The participants are more likely to be healthy, on account of a volunteer cohort,[34] and a high proportion of volunteers did not have data on fundus images. In addition, the diagnosis of CHD and other conditions was based on self-report, which may cause recall bias, especially when it comes to the disease classifications or diagnosis date. The majority of the participants in the UK Biobank were white, which may limit the generalizability of results in other ethnic populations.

4.2 Conclusions

Our results suggested that reduced Df, NS and VSD of retinal microvasculature were associated with an increased risk of incident CHD. Further research should explore the potential clinical application of the DL model based on retinal microvascular parameters, which may facilitate the efficient assessment of systemic vascular health status, as well as the screening and prediction of cardiovascular diseases.

Author contributions

Danli Shi and Mingguang He contributed to the conception and design of the study. Yuechuan Fu and Ruobing Wang contributed to the data analyses, data interpretation, and manuscript drafting. Mayinuer Yusufu

1 contributed to revise of the manuscript; Yueye Wang checked the data
2
3 analyses. All authors commented on and approved the manuscript.
4
5

6 7 **Financial support** 8 9

10 This work was supported by the National Natural Science Foundation of
11
12 China (81770932 and 82171061) and the Natural Science Foundation of
13
14 Shanghai (22ZR1438400).
15
16
17

18 19 **Availability of data and materials** 20 21

22 UK Biobank data are available through the UK Biobank Access
23
24 Management System <https://www.ukbiobank.ac.uk/>.
25
26
27

28 29 **Declaration of interests** 30 31

32 The authors declare that they have no known competing financial
33
34 interests or personal relationships that could have appeared to influence
35
36 the work reported in this paper.
37
38
39
40
41
42
43
44

45 46 **References** 47

- 48 1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M,
49
50 Nichols M (2016) Cardiovascular disease in Europe: epidemiological
51
52 update 2016. Eur Heart J 37: 3232-3245 DOI
53
54 10.1093/eurheartj/ehw334
55
56
57
58
- 59 2. Le Gloan L, Chakor H, Mercier LA, Harasymowycz P, Dore A,
60
61
62
63
64
65

- 1 Lachapelle P, Pressacco J, Thibault B, Marcotte F, Proietti A, Leduc H,
2
3 Mondesert B, Mongeon FP, Tardif JC, Khairy P (2014) Aortic
4
5 coarctation and the retinal microvasculature. *Int J Cardiol* 174: 25-
6
7 30 DOI 10.1016/j.ijcard.2014.03.129
8
9
- 10
11 3. Chen YJ, Khouri AS, Zarbin MA, Szirth BC (2021) Early Retinal
12
13 Microvascular Abnormalities in Young Adults with Type 1 Diabetes
14
15 Mellitus without Clinically Evident Diabetic Retinopathy. *Retina* 41:
16
17 1478-1486 DOI 10.1097/IAE.0000000000003047
18
19
20
21
22 4. Lim HB, Lee MW, Park JH, Kim K, Jo YJ, Kim JY (2019) Changes in
23
24 Ganglion Cell-Inner Plexiform Layer Thickness and Retinal
25
26 Microvasculature in Hypertension: An Optical Coherence
27
28 Tomography Angiography Study. *Am J Ophthalmol* 199: 167-176
29
30
31
32
33 DOI 10.1016/j.ajo.2018.11.016
34
35
- 36 5. Wu L, Gong X, Wang W, Zhang L, Zhou J, Ming X, Yuan M, Huang W,
37
38 Wang L (2022) Association of retinal fractal dimension and vessel
39
40 tortuosity with impaired renal function among healthy Chinese
41
42 adults. *Front Med (Lausanne)* 9: 925756 DOI
43
44
45 10.3389/fmed.2022.925756
46
47
48
49
- 50 6. Zekavat SM, Raghu VK, Trinder M, Ye Y, Koyama S, Honigberg MC, Yu
51
52 Z, Pampana A, Urbut S, Haidermota S, O'Regan DP, Zhao H, Ellinor
53
54 PT, Segre AV, Elze T, Wiggs JL, Martone J, Adelman RA, Zebardast N,
55
56 Del Priore L, Wang JC, Natarajan P (2022) Deep Learning of the
57
58
59
60
61
62
63
64
65

1 Retina Enables Phenome- and Genome-Wide Analyses of the
2
3 Microvasculature. Circulation 145: 134-150 DOI
4
5 10.1161/CIRCULATIONAHA.121.057709
6
7

- 8
9 7. Shi D, Lin Z, Wang W, Tan Z, Shang X, Zhang X, Meng W, Ge Z, He M
10
11 (2022) A Deep Learning System for Fully Automated Retinal Vessel
12
13 Measurement in High Throughput Image Analysis. Front Cardiovasc
14
15 Med 9: 823436 DOI 10.3389/fcvm.2022.823436
16
17
18
19
- 20 8. Rim TH, Teo AWJ, Yang HHS, Cheung CY, Wong TY (2020) Retinal
21
22 Vascular Signs and Cerebrovascular Diseases. J Neuroophthalmol 40:
23
24 44-59 DOI 10.1097/WNO.0000000000000888
25
26
27
- 28 9. Gok M, Ozer MA, Ozen S, Botan Yildirim B (2018) The evaluation of
29
30 retinal and choroidal structural changes by optical coherence
31
32 tomography in patients with chronic obstructive pulmonary disease.
33
34 Curr Eye Res 43: 116-121 DOI 10.1080/02713683.2017.1373824
35
36
37
38
- 39 10. Schuh DS, Piccoli AB, Paiani RL, Maciel CR, Pellanda LC, Vilela MA
40
41 (2017) Ocular Signs Related to Overweight and Arterial
42
43 Hypertension in Children: A Systematic Review. Open Ophthalmol J
44
45 11: 273-285 DOI 10.2174/1874364101711010273
46
47
48
49
- 50 11. Cheung CY, Xu D, Cheng CY, Sabanayagam C, Tham YC, Yu M, Rim TH,
51
52 Chai CY, Gopinath B, Mitchell P, Poulton R, Moffitt TE, Caspi A, Yam
53
54 JC, Tham CC, Jonas JB, Wang YX, Song SJ, Burrell LM, Farouque O, Li
55
56 LJ, Tan G, Ting DSW, Hsu W, Lee ML, Wong TY (2021) A deep-learning
57
58
59
60
61
62
63
64
65

- 1 system for the assessment of cardiovascular disease risk via the
2 measurement of retinal-vessel calibre. Nat Biomed Eng 5: 498-508
3 DOI 10.1038/s41551-020-00626-4
4
5
6
7
8
9 12. Sandoval-Garcia E, McLachlan S, Price AH, MacGillivray TJ, Strachan
10 MWJ, Wilson JF, Price JF (2021) Retinal arteriolar tortuosity and
11 fractal dimension are associated with long-term cardiovascular
12 outcomes in people with type 2 diabetes. Diabetologia 64: 2215-
13 2227 DOI 10.1007/s00125-021-05499-z
14
15
16
17
18
19
20
21
22 13. Cheung CY, Thomas GN, Tay W, Ikram MK, Hsu W, Lee ML, Lau QP,
23 Wong TY (2012) Retinal vascular fractal dimension and its
24 relationship with cardiovascular and ocular risk factors. Am J
25 Ophthalmol 154: 663-674 e661 DOI 10.1016/j.ajo.2012.04.016
26
27
28
29
30
31
32
33 14. Liew G, Wang JJ, Cheung N, Zhang YP, Hsu W, Lee ML, Mitchell P,
34 Tikellis G, Taylor B, Wong TY (2008) The retinal vasculature as a
35 fractal: methodology, reliability, and relationship to blood pressure.
36 Ophthalmology 115: 1951-1956 DOI 10.1016/j.opthta.2008.05.029
37
38
39
40
41
42
43
44 15. Qu Y, Lee JJ, Zhuo Y, Liu S, Thomas RL, Owens DR, Zee BC (2022) Risk
45 Assessment of CHD Using Retinal Images with Machine Learning
46 Approaches for People with Cardiometabolic Disorders. J Clin Med
47 11 DOI 10.3390/jcm11102687
48
49
50
51
52
53
54
55 16. Chesnutt JK, Han HC (2011) Tortuosity triggers platelet activation
56 and thrombus formation in microvessels. J Biomech Eng 133:
57
58
59
60
61
62
63
64
65

121004 DOI 10.1115/1.4005478

17. Cheng L, Barlis P, Gibson J, Colville D, Hutchinson A, Gleeson G, Lamoureux E, VanGaal W, Savige J (2018) Microvascular retinopathy and angiographically-demonstrated coronary artery disease: A cross-sectional, observational study. PLoS One 13: e0192350 DOI 10.1371/journal.pone.0192350
18. Theuerle JD, Al-Fiadh AH, Amirul Islam FM, Patel SK, Burrell LM, Wong TY, Farouque O (2021) Impaired retinal microvascular function predicts long-term adverse events in patients with cardiovascular disease. Cardiovasc Res 117: 1949-1957 DOI 10.1093/cvr/cvaa245
19. Tedeschi-Reiner E, Strozzi M, Skoric B, Reiner Z (2005) Relation of atherosclerotic changes in retinal arteries to the extent of coronary artery disease. Am J Cardiol 96: 1107-1109 DOI 10.1016/j.amjcard.2005.05.070
20. Flammer J, Konieczka K, Bruno RM, Virdis A, Flammer AJ, Taddei S (2013) The eye and the heart. Eur Heart J 34: 1270-1278 DOI 10.1093/eurheartj/eh023
21. Monteiro-Henriques I, Rocha-Sousa A, Barbosa-Breda J (2022) Optical coherence tomography angiography changes in cardiovascular systemic diseases and risk factors: A Review. Acta Ophthalmol 100: e1-e15 DOI 10.1111/aos.14851

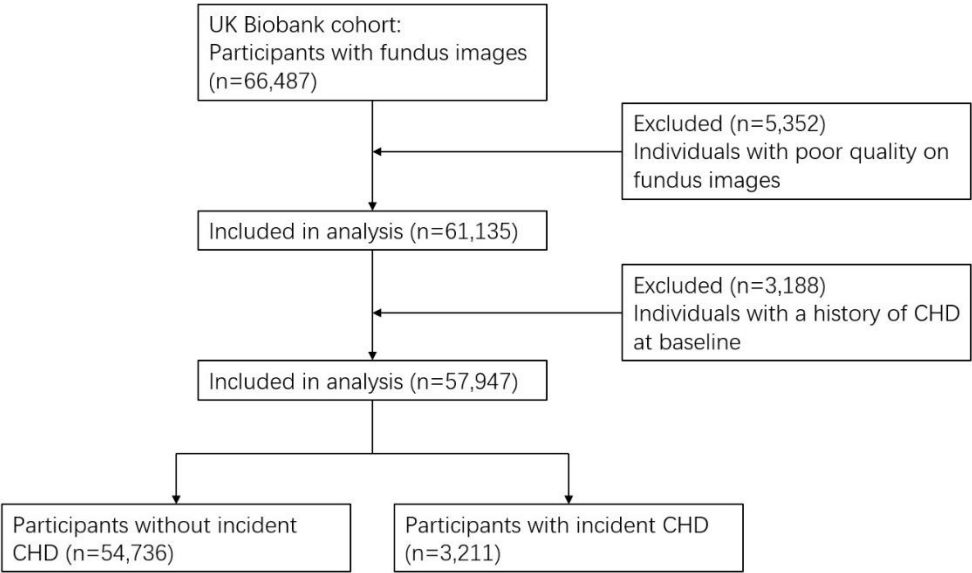
22. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, Garcia MJ, Gregson J, Pocock S, Falk E, Fuster V (2015) Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol* 65: 1065-1074 DOI 10.1016/j.jacc.2015.01.017
23. Ulutas HG, Guclu M, Aslanci ME, Karatas G (2022) The relationship between carotid intima-media thickness and microvascular changes in retinal zones and optic disc in patients with type 1 diabetes mellitus. *Eur J Ophthalmol* 32: 2328-2337 DOI 10.1177/11206721211064024
24. Liew G, Mitchell P, Rochtchina E, Wong TY, Hsu W, Lee ML, Wainwright A, Wang JJ (2011) Fractal analysis of retinal microvasculature and coronary heart disease mortality. *Eur Heart J* 32: 422-429 DOI 10.1093/eurheartj/ehq431
25. Popovic N, Radunovic M, Badnjar J, Popovic T (2018) Fractal dimension and lacunarity analysis of retinal microvascular morphology in hypertension and diabetes. *Microvasc Res* 118: 36-43 DOI 10.1016/j.mvr.2018.02.006
26. Wang SB, Mitchell P, Liew G, Wong TY, Phan K, Thiagalingam A, Joachim N, Burlutsky G, Gopinath B (2018) A spectrum of retinal vasculature measures and coronary artery disease. *Atherosclerosis* 268: 215-224 DOI 10.1016/j.atherosclerosis.2017.10.008

- 1 27. Tesouro M, Mauriello A, Rovella V, Annicchiarico-Petruzzelli M,
2
3 Cardillo C, Melino G, Di Daniele N (2017) Arterial ageing: from
4
5 endothelial dysfunction to vascular calcification. J Intern Med 281:
6
7 471-482 DOI 10.1111/joim.12605
8
9
- 10 28. Arbel Y, Sternfeld A, Barak A, Burgansky-Eliash Z, Halkin A, Berliner
11
12 S, Herz I, Keren G, Rubinstein A, Banai S, Finkelstein A (2014) Inverse
13
14 correlation between coronary and retinal blood flows in patients
15
16 with normal coronary arteries and slow coronary blood flow.
17
18 Atherosclerosis 232: 149-154 DOI
19
20 10.1016/j.atherosclerosis.2013.10.033
21
22
- 23 29. Barthelmes J, Nagele MP, Ludovici V, Ruschitzka F, Sudano I,
24
25 Flammer AJ (2017) Endothelial dysfunction in cardiovascular
26
27 disease and Flammer syndrome-similarities and differences. EPMA
28
29 J 8: 99-109 DOI 10.1007/s13167-017-0099-1
30
31
- 32 30. Kim AY, Chu Z, Shahidzadeh A, Wang RK, Puliafito CA, Kashani AH
33
34 (2016) Quantifying Microvascular Density and Morphology in
35
36 Diabetic Retinopathy Using Spectral-Domain Optical Coherence
37
38 Tomography Angiography. Invest Ophthalmol Vis Sci 57: OCT362-
39
40 370 DOI 10.1167/iovs.15-18904
41
42
- 43 31. Li J, Kokubo Y, Arafa A, Sheerah HA, Watanabe M, Nakao YM, Honda-
44
45 Kohmo K, Kashima R, Sakai Y, Watanabe E, Teramoto M, Dohi T, Koga
46
47 M (2022) Mild Hypertensive Retinopathy and Risk of Cardiovascular
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Disease: The Suita Study. J Atheroscler Thromb 29: 1663-1671 DOI
10.5551/jat.63317

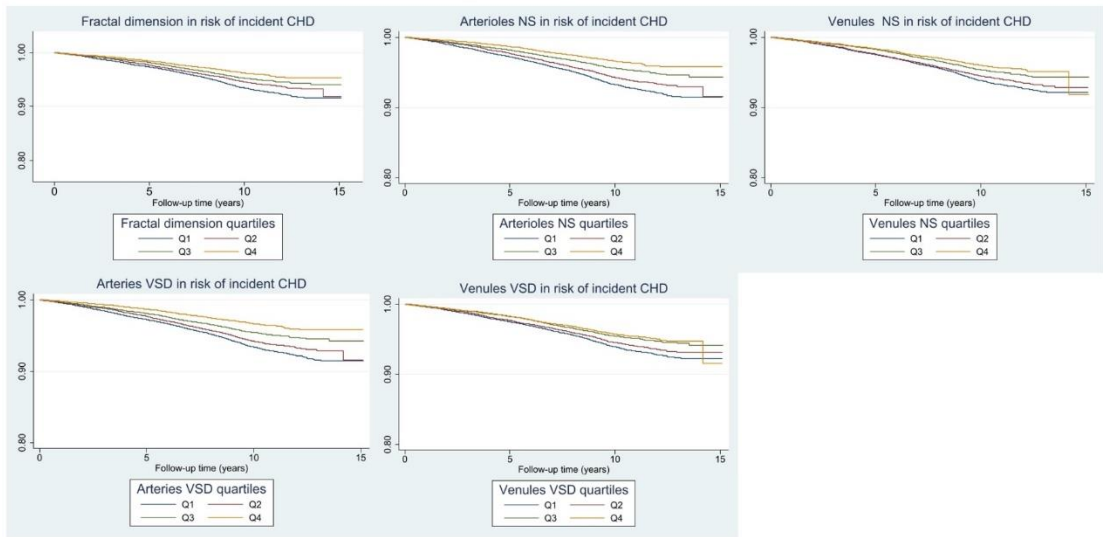
32. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Sharrett AR, Klein BE, Wang JJ, Chambless LE, Wong TY (2008) Risk prediction of coronary heart disease based on retinal vascular caliber (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 102: 58-63 DOI 10.1016/j.amjcard.2008.02.094
33. Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, Klein R, Di Carli M, Solomon SD (2016) Retinal Vessel Calibers in Predicting Long-Term Cardiovascular Outcomes: The Atherosclerosis Risk in Communities Study. Circulation 134: 1328-1338 DOI 10.1161/CIRCULATIONAHA.116.023425
34. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE (2017) Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol 186: 1026-1034 DOI 10.1093/aje/kwx246

Figure 1. Flowchart of participants' inclusion.



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure 2. Kaplan-Meier failure curves of incident CHD risk by quartiles of retinal microvascular parameters.



The first quartile represents the lowest level of the retinal microvascular parameter, while the fourth quartile represents the highest level of the retinal microvascular parameter

NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density

Fig. 3 Graphical abstract.

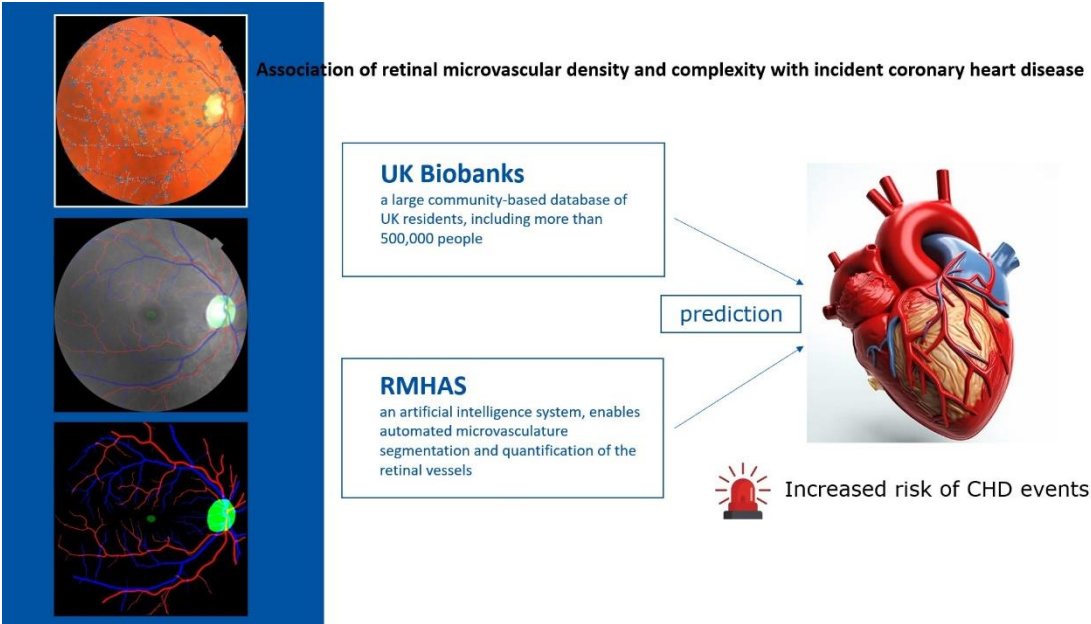


Table 1. Characteristics of study participants

	Participants without incident CHD	Participants with incident CHD	P-value
Participants, n	54736	3211	
Age (years)	55.3±8.1	59.6±6.9	<i>p</i> <0.001
Male gender (%)	23676(43.3%)	2013(62.7%)	<i>p</i> <0.001
White (%)	50125(91.6%)	2957(92.1%)	0.31
Townsend deprivation index	-1.21±2.96	-1.23±2.97	0.64
University or college degree (%)	21014(38.6%)	983(30.9%)	<i>p</i> <0.001
Smoking, current/ever (%)	22654(41.6%)	1605(50.3%)	<i>p</i> <0.001
BMI, kg/m ²	27.0±4.7	28.5±5.0	<i>p</i> <0.001
SBP: Mean, mmHg	135.9±18.2	143.1±18.4	<i>p</i> <0.001
HbA1c, mmol/mol	35.5±6.0	37.7±8.9	<i>p</i> <0.001
Total cholesterol (mmol/L)	5.7±1.1	5.7±1.2	0.34
Plasma HDL	1.5±0.4	1.4±0.4	<i>p</i> <0.001

cholesterol				
(mmol/L)				
TG (mmol/L)	1.6±0.9	1.9±1.1	<i>p</i> <0.001	
Diabetes	2358(4.3%)	334(10.4%)	<i>p</i> <0.001	
Hypertension	26146(47.8%)	2301(71.7%)	<i>p</i> <0.001	
Stroke	1244 (2.3%)	230(7.2%)	<i>p</i> <0.001	
DR	166(0.3%)	59(1.8%)	<i>p</i> <0.001	
Rein vascular	10(<1%)	1(<1%)	0.61	
occlusion				
Glaucoma	1187(2.2%)	127(4.0%)	<i>p</i> <0.001	
AMD	1083(2.0%)	100(3.1%)	<i>p</i> <0.001	
Df	0.68±0.20	0.63±0.20	<i>p</i> <0.001	
NS (arteriolar)	0.48±0.18	0.43±0.18	<i>p</i> <0.001	
NS (venular)	0.69±0.17	0.67±0.18	<i>p</i> <0.001	
VAD (arteriolar)	0.63±0.18	0.58±0.18	<i>p</i> <0.001	
VAD (venular)	0.63±0.18	0.62±0.18	<i>p</i> <0.001	
VSD (arteriolar)	0.62±0.17	0.58±0.17	<i>p</i> <0.001	
VSD (venular)	0.69±0.17	0.66±0.17	<i>p</i> <0.001	

BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; TG, triglyceride; DR, diabetic retinopathy; AMD, age-related macular degeneration; Df, fractal dimension; NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density.

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 2. Association of retinal microvascular parameters with incident CHD

Retinal microvascu lar parameters	Unadjusted			Model 1			Model 2			Model 3			Model 4		
	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value	HR	(95% CI)	P value
Fractal dimension	0.38(0.32, 0.45)		<0.001	0.75(0.62, 0.89)		0.002	0.78(0.64, 0.96)		0.018	0.79(0.64, 0.96)		0.021	0.80(0.65, 0.98)		0.033
Arterioles NS	0.23(0.19, 0.27)		<0.001	0.54(0.44, 0.67)		<0.001	0.64(0.51, 0.81)		<0.001	0.67(0.53, 0.86)		0.001	0.69(0.54, 0.88)		0.002
Venules NS	0.41(0.34, 0.50)		<0.001	0.79(0.64, 0.97)		0.024	0.75(0.60, 0.95)		0.016	0.75(0.60, 0.95)		0.015	0.77(0.61, 0.97)		0.024
Arterioles	0.26(0.22, 0.30)		<0.001	0.61(0.50, 0.74)		<0.001	0.80(0.64, 0.99)		0.052	0.83(0.66, 0.99)		0.117	0.85(0.67, 0.99)		0.154

VAD	0.32)		0.75)		1.00)		1.05)		1.06)
Venules	0.66(0.54, <0.001		1.08(0.89, 0.443		0.96(0.77, 0.705		0.92(0.73, 0.436		0.93(0.75, 0.542
VAD	0.80)		1.32)		1.19)		1.14)		1.17)
Arterioles	0.24(0.20, <0.001		0.56(0.46, <0.001		0.67(0.53, 0.001		0.70(0.55, 0.004		0.72(0.57, 0.007
VSD	0.29)		0.69)		0.85)		0.89)		0.91)
Venules	0.43(0.35, <0.001		0.80(0.65, 0.036		0.77(0.61, 0.028		0.76(0.61, 0.021		0.78(0.62, 0.034
VSD	0.52)		0.99)		0.97)		0.96)		0.98)

HR indicates hazard ratio; CI: confidence interval;

Model 1: adjusted for baseline age and sex;

Model 2: included model 1 variables plus BMI, total cholesterol, HbA1c, HDL, TG and SBP;

Model 3: included model 2 variables plus hypertension, diabetes, smoking and prior stroke;

Model 4: included model 3 variables plus DR, AMD, rein vascular occlusion and glaucoma.

NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

	Q4	Referenc	Refere	Reference	Referen	Referenc	Referen	Referenc	Referen	Reference	Referen
		e	nce		ce	e	ce	e	ce		ce
Arteriol	Q1	2.04(1.8	< 0.00	1.30(1.16,	< 0.001	1.21(1.0	0.002	1.17(1.0	0.012	1.16(1.02,	0.020
es NS		3,2.26)	1	1.45)		7,1.37)		3,1.33)		1.31)	
	Q2	1.72(1.5	< 0.00	1.19(1.06,	0.003	1.10(0.9	0.127	1.08(0.9	0.237	1.08(0.95,	0.249
		4,1.91)	1	1.33)		7,1.15)		5,1.22)		1.22)	
	Q3	1.30(1.1	< 0.00	1.02(0.91,	0.690	1.01(0.8	0.903	0.98(0.8	0.775	0.98(0.86,	0.765
		6,1.46)	1	1.15)		9,1.15)		6,1.12)		1.12)	
	Q4	Referenc	Refere	Reference	Referen	Referenc	Referen	Referenc	Referen	Reference	Referen
		e	nce		ce	e	ce	e	ce		ce
Venules	Q1	1.57(1.4	< 0.00	1.13(1.02,	0.025	1.15(1.0	0.018	1.16(1.0	0.016	1.14(1.02,	0.026
NS		2,1.74)	1	1.25)		2,1.30)		3,1.30)		1.29)	
	Q2	1.39(1.2	< 0.00	1.07(0.96,	0.223	1.12(0.9	0.062	1.13(1.0	0.046	1.12(1.00,	0.057

		5,1.54)	1	1.19)		9,1.26)		0,1.27)		1.26)	
	Q3	1.15(1.0	0.010	0.98(0.88,	0.782	1.02(0.9	0.790	1.03(0.9	0.685	1.02(0.90,	0.760
		3,1.28)		1.10)		0,1.15)		1,1.16)		1.15)	
	Q4	Referenc	Refere	Reference	Referen	Referenc	Referen	Referenc	Referen	Reference	Referen
		e	nce		ce	e	ce	e	ce		ce
Arteriol	Q1	2.03(1.8	<0.00	1.31(1.18,	<0.001	1.22(1.0	0.002	1.18(1.0	0.009	1.17(1.03,	0.014
es VSD		3,2.25)	1	1.46)		8,1.37)		4,1.33)		1.32)	
	Q2	1.75(1.5	<0.00	1.21(1.08,	0.001	1.11(0.9	0.094	1.09(0.9	0.162	1.09(0.96,	0.170
		7,1.95)	1	1.35)		8,1.26)		6,1.24)		1.24)	
	Q3	1.37(1.2	<0.00	1.09(0.98,	0.125	1.08(0.9	0.224	1.05(0.9	0.409	1.06(0.93,	0.403
		2,1.53)	1	1.23)		5,1.23)		3,1.20)		1.20)	
	Q4	Referenc	Refere	Reference	Referen	Referenc	Referen	Referenc	Referen	Reference	Referen
		e	nce		ce	e	ce	e	ce		ce

Venules	Q1	1.46(1.3	<0.00	1.05(0.95,	0.359	1.08(0.9	0.171	1.10(0.9	0.119	1.09(0.97,	0.165
VSD		3,1.62)	1	1.16)		7,1.22)		8,1.23)		1.22)	
	Q2	1.31(1.1	<0.00	0.99(0.90,	0.908	1.04(0.9	0.544	1.04(0.9	0.471	1.04(0.92,	0.519
		8,1.45)	1	1.10)		2,1.16)		3,1.17)		1.17)	
	Q3	1.07(0.9	0.234	0.90(0.81,	0.067	0.95(0.8	0.377	0.97(0.8	0.575	0.97(0.86,	0.569
		6,1.19)		1.01)		4,1.07)		6,1.09)		1.09)	
	Q4	Referenc	Refere	Reference	Referen	Referenc	Referen	Referenc	Referen	Reference	Referen
		e	nce		ce	e	ce	e	ce		ce

HR indicates hazard ratio; Q, quartile; CI: confidence interval;

Model 1: adjusted for baseline age and sex;

Model 2: included model 1 variables plus BMI, total cholesterol, HbA1c, HDL, TG and SBP;

Model 3: included model 2 variables plus hypertension, diabetes, smoking and prior stroke;

Model 4: included model 3 variables plus DR, AMD, rein vascular occlusion and glaucoma.

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density

Declaration of competing interest

The authors declare that they have no competing interests.



[Click here to access/download](#)

Supplementary Material for online publication only
supplementary table.docx



Table 1. Characteristics of study participants

	Participants without incident CHD	Participants with incident CHD	P-value
Participants, n	54736	3211	
Age (years)	55.3±8.1	59.6±6.9	P<0.001
Male gender (%)	23676(43.3%)	2013(62.7%)	P<0.001
White (%)	50125(91.6%)	2957(92.1%)	0.31
Townsend deprivation index	-1.21±2.96	-1.23±2.97	0.64
University or college degree (%)	21014(38.6%)	983(30.9%)	P<0.001
Smoking, current/ever (%)	22654(41.6%)	1605(50.3%)	P<0.001
BMI, kg/m ²	27.0±4.7	28.5±5.0	P<0.001
SBP: Mean, mmHg	135.9±18.2	143.1±18.4	P<0.001
HbA1c,	35.5±6.0	37.7±8.9	P<0.001

<hr/>				
mmol/mol				
Total		5.7±1.1	5.7±1.2	0.34
cholesterol				
(mmol/L)				
Plasma HDL		1.5±0.4	1.4±0.4	P<0.001
cholesterol				
(mmol/L)				
TG (mmol/L)		1.6±0.9	1.9±1.1	P<0.001
Diabetes		2358(4.3%)	334(10.4%)	P<0.001
Hypertension		26146(47.8%)	2301(71.7%)	P<0.001
Stroke		1244 (2.3%)	230(7.2%)	P<0.001
DR		166(0.3%)	59(1.8%)	P<0.001
Rein vascular		10(<1%)	1(<1%)	0.61
occlusion				
Glaucoma		1187(2.2%)	127(4.0%)	P<0.001
AMD		1083(2.0%)	100(3.1%)	P<0.001
Df		0.68±0.20	0.63±0.20	P<0.001
NS (arteriolar)		0.48±0.18	0.43±0.18	P<0.001
NS (venular)		0.69±0.17	0.67±0.18	P<0.001
VAD		0.63±0.18	0.58±0.18	P<0.001
(arteriolar)				
VAD (venular)		0.63±0.18	0.62±0.18	P<0.001
<hr/>				

VSD	0.62±0.17	0.58±0.17	P<0.001
(arteriolar)			
VSD (venular)	0.69±0.17	0.66±0.17	P<0.001

BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; TG, triglyceride; DR, diabetic retinopathy; AMD, age-related macular degeneration; Df, fractal dimension; NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density.

Table 2. Association of retinal microvascular parameters with incident CHD

Retinal microvas- cular paramet- ers	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	HR	P	HR	P	HR	P	HR	P	HR (95% CI)	P
	(95% CI)	value	(95% CI)	value	(95% CI)	value	(95% CI)	value		valu- e
Fractal dimensi- on	0.38(0.32,0.45)	<0.001	0.75(0.62,0.89)	0.002	0.78(0.64,0.96)	0.018	0.79(0.64,0.96)	0.021	0.80(0.65,0.98)	0.033
Arteriole s NS	0.23(0.19,0.27)	<0.001	0.54(0.44,0.67)	<0.001	0.64(0.51,0.81)	<0.001	0.67(0.53,0.86)	0.001	0.69(0.54,0.88)	0.002
Venules	0.41(0.32,0.51)	<0.001	0.79(0.62,0.99)	0.024	0.75(0.58,0.96)	0.016	0.75(0.58,0.96)	0.015	0.77(0.60,0.98)	0.02

NS	34,0.50	1	64,0.97		60,0.95		60,0.95		1,0.97)	4
))))			
Arteriole	0.26(0.	<0.00	0.61(0.	<0.00	0.80(0.	0.052	0.83(0.	0.117	0.85(0.6	0.15
s VAD	22,0.32	1	50,0.75	1	64,1.00		66,1.05		7,1.06)	4
))))			
Venules	0.66(0.	<0.00	1.08(0.	0.443	0.96(0.	0.705	0.92(0.	0.436	0.93(0.7	0.54
VAD	54,0.80	1	89,1.32		77,1.19		73,1.14		5,1.17)	2
))))			
Arteriole	0.24(0.	<0.00	0.56(0.	<0.00	0.67(0.	0.001	0.70(0.	0.004	0.72(0.5	0.00
s VSD	20,0.29	1	46,0.69	1	53,0.85		55,0.89		7,0.91)	7
))))			
Venules	0.43(0.	<0.00	0.80(0.	0.036	0.77(0.	0.028	0.76(0.	0.021	0.78(0.6	0.03
VSD	35,0.52	1	65,0.99		61,0.97		61,0.96		2,0.98)	4

)

)

)

)

HR indicates hazard ratio; CI: confidence interval;

Model 1: adjusted for baseline age and sex;

Model 2: included model 1 variables plus BMI, total cholesterol, HbA1c, HDL, TG and SBP;

Model 3: included model 2 variables plus hypertension, diabetes, smoking and prior stroke;

Model 4: included model 3 variables plus DR, AMD, rein vascular occlusion and glaucoma.

NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density

Table 3. Association of retinal microvascular parameters with incident CHD stratified by parameters quartiles

Retinal microvascular	Quartile	Unadjusted		Model 1		Model 2		Model 3		Model 4	
		HR	P value	HR	P value	HR	P value	HR	P value	HR	P value
Fractal dimension	Q1	1.79(1.62,1.98)	<0.001	1.18(1.06,1.31)	0.003	1.17(1.04,1.32)	0.009	1.16(1.03,1.18)	0.013	1.15(1.02,1.18)	0.020
	Q2	1.47(1.03,2.10)	<0.001	1.03(0.87,1.21)	0.595	1.01(0.86,1.18)	0.919	1.00(0.85,1.17)	0.993	1.00(0.85,1.17)	0.940

		32,1.63)	01	92,1.15)		89,1.14)		88,1.133)		88,1.13)	
	Q3	1.26(1.13,1.40)	<0.001	1.00(0.90,1.12)	0.980	1.05(0.93,1.19)	0.430	1.04(0.92,1.18)	0.506	1.04(0.92,1.18)	0.494
	Q4	Refere nce	Refe renc e	Referen ce	Refer ence	Refere nce	Refer ence	Refere nce	Refer ence	Referen ce	Refer ence
Arteri oles NS	Q1	2.04(1.83,2.26)	<0.001	1.30(1.16,1.45)	<0.001	1.21(1.07,1.37)	0.002	1.17(1.03,1.33)	0.012	1.16(1.02,1.31)	0.020
	Q2	1.72(1.54,1.9)	<0.001	1.19(1.06,1.33)	0.003	1.10(0.97,1.1)	0.127	1.08(0.95,1.2)	0.237	1.08(0.95,1.22)	0.249

		1))		5)		2))	
Q3		1.30(1.16,1.46)	<0.001	1.02(0.91,1.15)	0.690	1.01(0.89,1.1)	0.903	0.98(0.86,1.1)	0.775	0.98(0.86,1.12)	0.765
Q4		Refere nce	Refe renc e	Referen ce	Refer ence	Refere nce	Refer ence	Refere nce	Refer ence	Referen ce	Refer ence

Venul es NS	Q1	1.57(1.42,1.74)	<0.001	1.13(1.02,1.25)	0.025	1.15(1.02,1.30)	0.018	1.16(1.03,1.3)	0.016	1.14(1.02,1.29)	0.026
	Q2	1.39(1.25,1.54)	<0.001	1.07(0.96,1.19)	0.223	1.12(0.99,1.26)	0.062	1.13(1.00,1.27)	0.046	1.12(1.00,1.26)	0.057

Q3	1.15(1.03,1.28)	0.010	0.98(0.88,1.10)	0.782	1.02(0.90,1.15)	0.790	1.03(0.91,1.16)	0.685	1.02(0.90,1.15)	0.760
Q4	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

Arterioles VSD	Q1	2.03(1.83,2.25)	<0.001	1.31(1.18,1.46)	<0.001	1.22(1.08,1.37)	0.002	1.18(1.04,1.33)	0.009	1.17(1.03,1.32)	0.014
	Q2	1.75(1.57,1.95)	<0.001	1.21(1.08,1.35)	0.001	1.11(0.98,1.26)	0.094	1.09(0.96,1.24)	0.162	1.09(0.96,1.24)	0.170
	Q3	1.37(1.09,1.65)	<0.001	1.09(0.88,1.30)	0.125	1.08(0.85,1.31)	0.224	1.05(0.82,1.28)	0.409	1.06(0.83,1.29)	0.403

		22,1.53)	01	98,1.23)		95,1.23)		93,1.20)		93,1.20)	
	Q4	Refere nce	Refe renc e	Referen ce	Refer ence	Refere nce	Refer ence	Refere nce	Refer ence	Referen ce	Refer ence
Venul es VSD	Q1	1.46(1. 33,1.62)	<0.0 01	1.05(0. 95,1.16)	0.359	1.08(0. 97,1.22)	0.171	1.10(0. 98,1.23)	0.119	1.09(0. 97,1.22)	0.165
	Q2	1.31(1. 18,1.45)	<0.0 01	0.99(0. 90,1.10)	0.908	1.04(0. 92,1.16)	0.544	1.04(0. 93,1.17)	0.471	1.04(0. 92,1.17)	0.519
	Q3	1.07(0. 96,1.14)	0.23 4	0.90(0. 81,1.01)	0.067	0.95(0. 84,1.0)	0.377	0.97(0. 86,1.0)	0.575	0.97(0. 86,1.09)	0.569

	9))		7)		9))			
Q4	Refere	Refe	Referen	Refer	Refere	Refer	Refere	Refer	Referen	Refer
	nce	renc	ce	ence	nce	ence	nce	ence	ce	ence
		e								

HR indicates hazard ratio; Q, quartile; CI: confidence interval;

Model 1: adjusted for baseline age and sex;

Model 2: included model 1 variables plus BMI, total cholesterol, HbA1c, HDL, TG and SBP;

Model 3: included model 2 variables plus hypertension, diabetes, smoking and prior stroke;

Model 4: included model 3 variables plus DR, AMD, rein vascular occlusion and glaucoma.

NS, numbers of vascular segments; VAD, vascular area density; VSD, vascular skeleton density

Authors' contributions

Danli Shi and Mingguang He contributed to the conception and design of the study. Yuechuan Fu and Ruobing Wang contributed to the data analyses, data interpretation, and manuscript drafting. Mayinuer Yusufu contributed to revise of the manuscript; Yueye Wang checked the data analyses. All authors commented on and approved the manuscript.