Prospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Retinal oculomics and risk of incident aortic aneurysm and aortic adverse events: a population-based cohort study

Cong Li, PhD[a,b], Yu Huang, PhD[b,c], Jian Chen, PhD[c], Guangyao Hua, MSc [c], Fan Yang, PhD[a,c], Dongqin Cai, MSc[a,c], Yu Kuang, MSc[b], Xue He, MSc[a,b], Yan Wang, MSc[a,b], Jianrong Jiang, MSc[b], Zhenchao Du, MSc[b], Jingyan Peng, MSc[b], Heng Li, MSc[b], Zhishen Peng, MSc[b], Tengda Huang, MSc[a,b], Yun Ren, MSc[b], Wenli Zhang, MSc[b], Lei Liu, PhD[b,d], Danli Shi, PhD[e,f], Jianfang Luo, PhD[a,c,g], Honghua Yu, PhD[a,b,d], Xiaohong Yang, PhD[a,b]

Background: The asymptomatic onset and extremely high mortality rate of aortic aneurysm (AA) highlight the urgency of early detection and timely intervention. The alteration of retinal vascular features (RVFs) can reflect the systemic vascular properties, and be widely used as the biomarker for cardiovascular disease risk prediction. Therefore, we aimed to investigate associations of RVFs with AA and its progression.

Methods: In this prospective population-based cohort study, participants with eligible fundus images and without a history of AA at recruitment were included for analysis. A fully automated Retina-based Microvascular Health Assessment System was used to quantify multidimensional RVFs including the branching angle, caliber, complexity, density, length, and tortuosity. Univariable and multivariable Cox regressions were used to estimate the association of RVFs with the incidence of AA and aortic adverse events (AAE). Furthermore, propensity score matching was performed to mitigate the confounding effects of baseline characteristics.

Results: During a median follow-up of 11.0 years, 306 incident AA (164 with abdominal AA and 108 with thoracic AA) and 48 incident AAE were documented. In the fully adjusted model, the retinal arterial branching angle (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.77 to 0.99) and the central tendency and variability of minimum venular caliber were significantly associated with the risk of incident AA (HR 1.13-1.15), while the venular minimum angular asymmetry (0.48, 0.30 to 0.77) was significantly associated with the incidence of AAE. Moreover, specific alterations of RVFs were observed in different AA subtypes (caliber in abdominal AA [HR 1.21]; caliber [HR 1.21-1.28], complexity, length, and tortuosity [HR 0.77-0.82] in thoracic AA). Similar results were obtained after propensity score-matched analysis, confirming the stability of these associations.

Conclusions: We identified a significant association of certain RVFs with incident AA and AAE, implying that noninvasive, and convenient fundus photography could be a promising tool to facilitate the early detection of AA and subsequent preventative interventions.

Keywords: aortic adverse events, aortic aneurysm, cohort study, retinal vascular features

Introduction

Aortic aneurysm (AA) is a potentially life-threatening condition characterized by the pathological distension of the aorta, which represents the second most common disease affecting the aorta after atherosclerosis[1]. It typically develops in weakened areas of the aorta and is traditionally divided into abdominal aortic aneurysm (AAA) and thoracic aortic aneurysm (TAA). AA is often asymptomatic at the time of diagnosis, regardless of the severity. If left untreated, an AA can lead to catastrophic adverse events, with an overall fatality rate up to 90%[2]. According to the analysis of the Global Burden of Disease Study, the global number of AA-related deaths is expected to

[a]School of Medicine, South China University of Technology, Guangzhou, China, [b]Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China, [c]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital (Guangdong Academic of Medical Sciences), Southern Medical University, Guangzhou, China, [d]Guangdong Provincial Key Laboratory of Artificial Intelligence in Medical Image Analysis and Application, Guangzhou, China, [e]School of Optometry, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China, [f]Research Centre for SHARP Vision (RCSV), The Hong Kong Polytechnic University, Kowloon, Hong Kong, China and [g]Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Guangzhou, China

Cong Li, Yu Huang, Jian Chen, Guangyao Hua, and Fan Yang contributed equally to this work.

*Corresponding authors. Address: School of Optometry, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China. E-mail: danli.shi@polyu.edu.hk (D Shi); Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital (Guangdong Academic of Medical Sciences), Southern Medical University, Guangzhou, China. E-mail: jianfangluo@sina.com (J Luo); Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China. E-mail: yuhonghua@gdph.org.cn (H. Yu) and syyangxh@scut.edu.cn (X. Yang).

International Journal of Surgery (2025) 111:2478–2486

Received 12 September 2024; Accepted 2 December 2024

Published online 29 January 2025

http://dx.doi.org/10.1097/JS9.0000000000002236

continuously increase by 42% from 172 426 in 2019 to 244 685 in 2030[3], highlighting that the burden of aortic diseases remains high. Early detection and timely intervention are crucial for improving patient outcomes. However, the current international guidelines recommend AA screening mostly based on general biomarkers[1,4], such as age and sex, lacking specificity and precision. Further studies are warranted to investigate the AA-related risk factors, aiming to identify potential objective, precise, and personalized biomarkers for disease early screening.

The retina, being highly vascular and readily accessible through noninvasive imaging and assessments, can act as a surrogate indicator of systemic vascular health. Collective evidence has demonstrated that retinal vasculature could reflect age, sex, smoking status, hypertension, and hyperlipidemia[5,6], which are exactly the important risk factors of AA[1,4]. A few studies have revealed the association of retinal vascular signs with AAA and Marfan Syndrome, but only focusing on retinal vascular caliber and tortuosity[7,8]. Additionally, these retinal vascular signs lack specificity, and the observed associations became non-significant after adjusting for common disease risk factors[7,9-11]. With the advancements in deep learning algorithms, we can automatically segment and quantify retinal vascular networks at an omics scale from the fundus images with great efficacy and accuracy. Specifically, the Retina-based Microvascular Health Assessment System (RMHAS) can quantify hundreds of retinal vascular features (RVFs) within 2 seconds[12], containing more imaging biomarkers for AA and facilitating the early detection of high-risk population. Therefore, we hypothesized that non-invasive visualization of the retinal microvasculature has the potential to uncover significant vascular dysfunction and aid in predicting the incidence of AA and aortic adverse events (AAE) in the general population.

Herein, we aimed to identify specific and robust retinal vascular markers of AA and its subtypes that are independent of established risk factors. Furthermore, we also examined the association between RVFs and AAE. Retinal fundus photography, being non-invasive, and convenient, has confirmed its value for early population screening of cardiovascular diseases[6,13,14]. Given the asymptomatic nature and high mortality rate of AA, determining the association between RVFs and AA development is important for its early diagnosis and thereby improving patient prognosis.

Methods

Study population

We used data from the UK Biobank, a large-scale population-based prospective cohort with over 500 000 participants aged 40 to 69 years recruited between 2006 and 2010 at 22 assessment centres. The UK Biobank study protocols and population have been described in detail elsewhere[15]. During the baseline assessment, extensive phenotypic and genotypic details were collected for its participants, such as comprehensive questionnaires, physical measures, sample assays, multimodal imaging, and genome-wide genotyping. Detailed health-related events were recorded through linkage with Hospital Episode Statistics (HES) and death registers. Ophthalmic examinations, including retinal photography, were conducted at the baseline assessment in 2009 for six assessment centres.

The UK Biobank study was approved by the North West Multi-centre Ethics Committee (11/NW/0382). The current study adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants. This research has been conducted using the UK Biobank Resource under Application Number 82906 and only unidentifiable data was used. This study was reported in line with the STROCSS criteria[16].

RVFs quantification

The 45-degree non-mydriasis retinal fundus images were obtained using a spectral domain OCT for each eye (Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan). A total of 66,500 participants completed the retinal fundus photography with 131,238 images collected. For extraction of RVFs, we selected the images of the right eye first, and the left eye was used only when the right eye was unavailable. A deep learning system, named RMHAS, was utilized to automatically segment and quantify RVFs with great accuracy and required minimal time[12]. The algorithm demonstration is publicly available at https://www.retinavessel.com/. Briefly, the overall image quality was assessed by the image quality assessment module, and then the eligible images were segmented into arteries, veins, and optic disc. Based on segmentation, RVF measurements of branching angle, caliber, complexity, density, length, and tortuosity were obtained (Supplementary Table 1). Further, considering the hundreds of small vessel segments in the fundus images, the central tendency, variability, and distribution shape of the above measurements were summarized to capture their overall characteristics (Supplementary Table 2).

Outcomes ascertainment

The AA, its subtype, and AAE were ascertained by the International Classification of Diseases, Ninth and Tenth (ICD-9 and ICD-10) codes, death registry records (based on the ICD-10 code), Office of Population, Censuses, and Surveys: Classification of Interventions and Procedures (OPCS-4), and self-reporting (Supplementary Table 3). The definition of AAE was referred to in previous literature including aortic dissection, rupture, and death[17]. Specifically, the follow-up of the AAE was ascertained through the linkage of routinely available national health records, such as death registrations and hospital inpatient episodes. Aortic dissection or rupture incidents or deaths were coded using ICD-10 codes 'I71.0, I71.1, I71.3, I71.5, I71.8' and ICD-9 codes '4410, 4411, 4413, 4415' in hospital admissions or death records. Participants with any diagnosed or self-reported AA before baseline assessment were excluded. The follow-up period for each participant was calculated from the date of baseline examination to either the date of outcomes occurrence, the date of death, or the end of follow-up, whichever came first.

Covariates

The covariate data were collected by touchscreen questionnaires, physical examinations, and biochemical measurements in the UK Biobank. The potential covariates in the present analyses included age, sex, body mass index (BMI), smoking status (recorded as former/current and never), alcohol assumption (recorded as current/previous and never), systolic blood

pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and history of diabetes, hypertension and hyperlipidemia. Moreover, the genetic risk scores (GRSs) for AAA and TAA were also considered in the corresponding outcomes. The genetic information was taken from the updated genome-wide association studies (GWAS) for the AAA[18] and TAA[19]. The associated single nucleotide polymorphisms (SNPs) were used to generate GRSs for each participant by using the --score function in PLINK 2.0[20]. The magnitude of the association (GWAS beta coefficient) was used as the weighting factor.

Statistical analyses

The baseline characteristics of participants were described as mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables. Differences in continuous variables were analyzed using unpaired t-tests, while Chi-square tests were used to assess the categorical variables. For the RVFs, we excluded the sex-specific extreme outliers, and normalized the distribution of them enable rescale to SD unit. The hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the association between RVFs and outcomes by Cox proportional hazards regression models. Firstly, we preliminarily identified the potential RVFs for incident AA and AAE with no covariates adjusted, and *P* values were further adjusted by the false discovery rate method for AA. Thereafter, the significant associated RVFs were considered to be included in further analyses. Four Cox proportional hazards regression models were fitted respectively. Model 1 was unadjusted, Model 2 was adjusted for baseline age and sex, and Model 3 was further adjusted for BMI, smoking status, and history of diabetes, hypertension, and hyperlipidemia. For AAA and TAA, their GRSs were additionally adjusted in the Model 3.

To explore the effect-response association between RVFs and incident outcomes, values were transferred into a categorical variable by tertile. We further conducted the subgroup analyses to test whether the association between RVFs and outcomes differed from groups of sex (female, male), age (<65 years, ≧65 years), smoking history (never, former/current), and hypertension. The sensitivity analysis was performed to examine the association between RVFs and incident outcomes by excluding the participants who developed AA in the first two years of follow-up. We also performed the propensity score matching (PSM) using the nearest neighbour method which matched the baseline demographics and clinical characteristics, to maintain homogeneity between groups in the sensitivity analysis. The variables that used to generate a propensity score included baseline age, sex, BMI, smoking status, and histories of diabetes, hypertension, and hyperlipidemia. Standardized mean differences (SMD) before and after PSM were calculated to measure balance between groups. Additionally, as AA is a kind of degenerative disease, we further excluded participants less than 50 years to assess the robustness of the findings. Furthermore, the analyses were repeated among participants with hypertension or diabetes due to the lower probability of developing AA in healthy people.

All analyses were performed using R (version 4.2.2, R Foundation for Statistical Computing, www.R-project.org, Vienna, Austria) and Stata (version 17, StataCorp, TX, USA). A two-sided *P* value of <0.05 was regarded as statistical significance.

Results

Baseline characteristics

A total of 50,409 participants were included in the analysis after excluding participants without fundus images, with poor-quality images, or with AA at baseline (Fig. 1). At recruitment, the mean (SD) age of participants was 55.84 (8.21) years, and 55.2% were female. During a median follow-up duration of 11.27 years (interquartile range [IQR], 11.17-11.41), there were 306 participants who experienced incident AA, with 164 (53.60%) having incident AAA, 108 (35.29%) experiencing TAA, and 34 (11.11%) encountering other types of AA, including thoracoabdominal AA, and unspecified site AA. Additionally, 48 participants experienced incident aortic aneurysm events (AAE). Table 1 shows the baseline

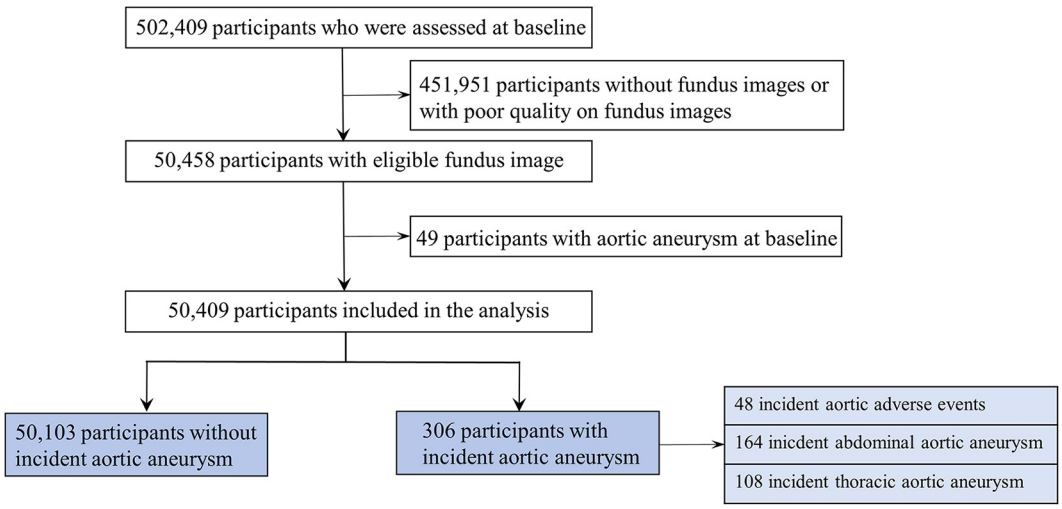

Figure 1. Flowchart for population selection in the UK Biobank.

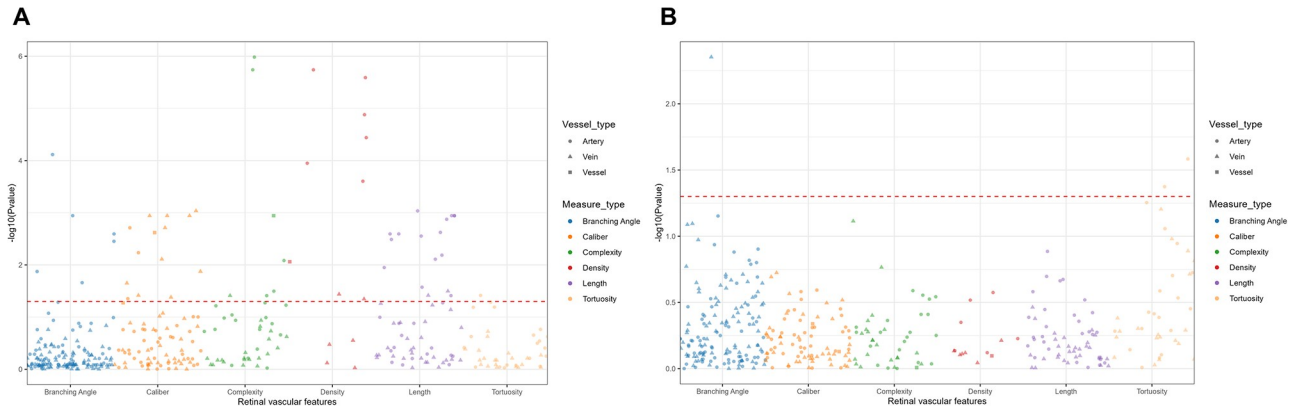

Figure 2. Retinal vascular features associated with aortic aneurysm and aortic adverse events were identified in the unadjusted Cox model. (A) The –log10 (*P* value) of retinal vascular features for aortic aneurysm. (B) The –log10 (*P* value) of retinal vascular features for aortic adverse events.

characteristics of study participants by incident AA. All features were significantly different among individuals with and without incident AA except for alcohol assumption (P = 0.460). The participants with incident AA were related to the older age, male gender, higher BMI, former/current smoking, higher SBP and DBP, lower total cholesterol, HDL and LDL, higher triglycerides, and higher proportions of diabetes mellitus, hypertension, and hyperlipidemia at baseline. Moreover, the participants with incident AA were more likely to have a high proportion of lipid-lowering medication use compared with those without AA.

RVFs and incident AA

A total of 54 RVFs from the six major categories were significantly associated with the incident AA (Fig. 2). After adjusting for age and sex in Model 2, 22 RVFs remained significant in this association. In the fully adjusted model (Model 3), 5 RVFs showed a significant association. Specifically, the arterial branching density in the category of branching angle was significantly related to the incidence of AA (HR = 0.87, 95%CI: 0.77-0.99, P = 0.036). Moreover, the central tendency and variability of minimum venular caliber also showed a significant association with incident AA: median absolute deviation (MAD, HR = 1.15, 95%CI: 1.03-1.29, P = 0.017), mean (HR = 1.13, 95%CI: 1.02-1.25, P = 0.025), median (HR = 1.14, 95%CI: 1.02-1.27, P = 0.027), and std (HR = 1.15, 95%CI: 1.03-1.28, P = 0.010) (Supplementary Table 2). Furthermore, we found that, compared with the participants with the lowest tertile of RVFs, the highest tertile of arterial branching density had a significantly lower risk of AA (P for trend = 0.033), and the highest tertile of central tendency and variability of minimum venular caliber had a significantly higher risk of AA than those in the lowest tertile (all P for trend < 0.05) after full adjust (Supplementary Table 4).

RVFs and incident AAE

For the incident AAE, 3 RVFs from the branching angle density and tortuosity categories showed significant association (Fig. 2). In Model 2, these 3 RVFs remained significant including the venular minimum angular asymmetry, and IQR and MAD of arterial tortuosity. After full adjustment in Model 3, only the venular minimum angular asymmetry (HR = 0.48, 95%CI: 0.30-0.77, P = 0.002) remained significant (Table 2). Meanwhile, the risk of AAE in participants with the venular minimum angular asymmetry in the highest was significantly lower than that of the lowest tertile (P for trend = 0.027). For the detailed AAE subtypes, the similar results

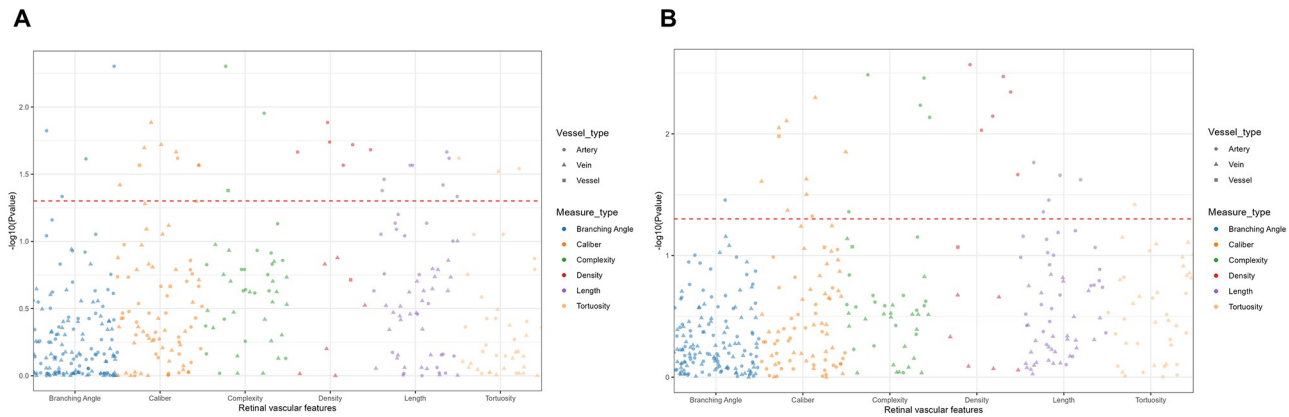

Figure 3. Retinal vascular features associated with abdominal aortic aneurysm and thoracic aortic aneurysm were identified in the unadjusted Cox model. (A) The –log10 (*P* value) of retinal vascular features for abdominal aortic aneurysm. (B) The –log10 (*P* value) of retinal vascular features for thoracic aortic aneurysm.

Table 1

Baseline characteristics of study participants

Baseline characteristics	Without incident aortic aneurysm (N=50,103)	Incident aortic aneurysm (N=306)	P value
Age, y	55.81 (8.20)	61.82 (6.03)	<0.001
Sex			<0.001
Female	27757 (55.4%)	65 (21.2%)	
Male	22346 (44.6%)	241 (78.8%)	
Body mass index, kg/m^2	27.27 (4.76)	28.56 (4.44)	<0.001
Smoking status			<0.001
Never	28227 (56.7%)	113 (37.0%)	
Former/current	21576 (43.3%)	192 (63.0%)	
Alcohol consumption			0.460
Never	4189 (8.4%)	22 (7.2%)	
Former/current	45720 (91.6%)	283 (92.8%)	
SBP (mmHg)	136.32 (18.28)	142.84 (16.84)	<0.001
DBP (mmHg)	81.73 (10.04)	84.24 (10.78)	<0.001
Total cholesterol (mmol/L)	5.69 (1.12)	5.37 (1.15)	<0.001
HDL (mmol/L)	1.48 (0.39)	1.29 (0.34)	<0.001
LDL (mmol/L)	3.54 (0.85)	3.39 (0.88)	0.004
Triglycerides (mmol/L)	1.66 (0.96)	1.97 (1.04)	<0.001
Diabetes (yes)	2744 (5.5%)	26 (8.5%)	0.021
Hypertension (yes)	25953 (51.8%)	244 (79.7%)	<0.001
Hyperlipidemia (yes)	8679 (17.3%)	111 (36.3%)	<0.001
Lipid-lowing medication (yes)	7937 (15.84%)	103 (33.66%)	<0.001

Data are mean (SD), or N (%). SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

were predominantly observed in the context of aortic dissection (Supplementary Table 5).

RVFs and incident AAA and TAA

In the analysis of AA subtypes, we found a total of 33 and 28 RVFs from the six major categories were identified to be associated with AAA and TAA, respectively (Fig. 3). Following adjustment for age and sex in Model 2, only 13 and 12 RVFs remained significant. Of which, 1 and 9 RVFs still presented a significant association with AAA and TAA after full adjustment, respectively (Table 3). For AAA, the MAD of maximum venular caliber (HR = 1.21, 95%CI: 1.02-1.43, P = 0.033) showed significant association. For TAA, the central tendency and variability of venular caliber (mad of mean, HR = 1.26, 95%CI: 1.04-1.47, P = 0.018; std of mean, HR = 1.28, 95%CI: 1.06-1.51, P = 0.010; MAD of min, HR = 1.26, 95%CI: 1.04-1.55, P = 0.020; mean of min, HR = 1.21, 95%CI: 1.04-1.44, P = 0.012; std of min, HR = 1.27, 95%CI: 1.07-1.53, P = 0.007), complexity of arterial distribution shape (kurt of level, HR = 0.81, 95%CI: 0.66-0.92, P = 0.048; skew of level, HR = 0.82, 95%CI: 0.67-0.91, P = 0.043), length of arterial distribution shape (kurt of arc, HR = 0.77, 95%CI: 0.60-0.95, P = 0.042), and variability of venular tortuosity (MAD, HR = 0.81, 95%CI: 0.67-0.99, P = 0.044) remained significant in the full adjusted model. When the participants were divided into tertiles by associated RVFs, compared with the lowest tertile, those with the highest MAD of maximum venular caliber had significantly higher AAA risk (P for trend = 0.032) (Supplementary Table 6). Moreover, those with the

Table 2

Association of retinal vascular features with incident aortic aneurysm and aortic adverse events

	Model 1		Model 2		Model 3	
RVF	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Aortic aneurysm						
Branching Angle						
branchingdensity_a	0.73 (0.65, 0.83)	<0.001	0.86 (0.75, 0.97)	0.014	0.87 (0.77, 0.99)	0.036
Caliber						
calibre_min_MAD_v	1.27 (1.14, 1.42)	<0.001	1.19 (1.06, 1.33)	0.003	1.15 (1.03, 1.29)	0.017
calibre_min_mean_v	1.20 (1.10, 1.32)	<0.001	1.16 (1.05, 1.27)	0.003	1.13 (1.02, 1.25)	0.025
calibre_min_median_v	1.25 (1.12, 1.40)	<0.001	1.17 (1.05, 1.31)	0.006	1.14 (1.02, 1.27)	0.027
calibre_min_std_v	1.20 (1.07, 1.33)	0.001	1.19 (1.07, 1.32)	0.001	1.15 (1.03, 1.28)	0.010
Aortic adverse events						
Branching Angle						
angularasymmetry_min_v	0.51 (0.32, 0.81)	0.004	0.51 (0.32, 0.80)	0.004	0.48 (0.30, 0.77)	0.002

RVF, retinal vascular feature; HR, hazard ratio; CI, confidence interval.

Model 1 is unadjusted; model 2 is adjusted for baseline age and sex; model 3 is adjusted for baseline age, sex, body mass index, smoking status, diabetes, hypertension, and hyperlipidemia.

Table 3

Association of retinal vascular features with incident abdominal aortic aneurysm and thoracic aortic aneurysm

	Model 1		Model 2		Model 3	
RVF	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Abdominal aortic aneurysm						
Caliber						
calibre_max_MAD_v	1.32 (1.11, 1.57)	0.002	1.29 (1.09, 1.52)	0.003	1.21 (1.02, 1.43)	0.033
Thoracic aortic aneurysm						
Caliber						
calibre_mean_mad_v	1.22 (1.01, 1.47)	0.043	1.24 (1.03, 1.50)	0.021	1.26 (1.04, 1.47)	0.018
calibre_mean_std_v	1.25 (1.03, 1.51)	0.024	1.27 (1.05, 1.53)	0.012	1.28 (1.06, 1.51)	0.010
calibre_min_MAD_v	1.29 (1.07, 1.55)	0.009	1.22 (1.01, 1.47)	0.042	1.26 (1.04, 1.55)	0.020
calibre_min_mean_v	1.24 (1.07, 1.44)	0.005	1.21 (1.03, 1.41)	0.018	1.21 (1.04, 1.44)	0.012
calibre_min_std_v	1.28 (1.07, 1.53)	0.008	1.27 (1.07, 1.52)	0.007	1.27 (1.07, 1.53)	0.007
Complexity						
level_kurt_a	0.75 (0.61, 0.92)	0.006	0.80 (0.65, 0.98)	0.028	0.81 (0.66, 0.92)	0.048
level_skew_a	0.75 (0.62, 0.91)	0.003	0.80 (0.66, 0.97)	0.026	0.82 (0.67, 0.91)	0.043
Length						
arc_kurt_a	0.73 (0.57, 0.95)	0.017	0.76 (0.59, 0.97)	0.027	0.77 (0.60, 0.95)	0.042
Tortuosity						
tortuosity_MAD_v	0.81 (0.66, 0.99)	0.038	0.81 (0.66, 0.98)	0.033	0.81 (0.67, 0.99)	0.044

RVF, retinal vascular feature; HR, hazard ratio; CI, confidence interval.

Model 1 is unadjusted; model 2 is adjusted for baseline age and sex; model 3 is adjusted for baseline age, sex, body mass index, smoking status, diabetes, hypertension, hyperlipidemia, and genetic risk score of abdominal aortic aneurysm/ thoracic aortic aneurysm.

highest central tendency and variability of venular caliber had significantly higher TAA risk (all *P* for trend < 0.05), and those with the highest kurt of arterial arc and MAD of venular tortuosity had significantly lower TAA risk (both *P* for trend < 0.05) (Supplementary Table 7).

Subgroup analysis

In addition, we implemented the subgroup analyses stratified by sex, age, smoking status, baseline hypertension, and hyperlipidemia to explore the relationship between RVF and outcomes of interest using multivariable Cox models (Supplementary Tables 8-11). After the full adjustment, the RVFs were found significantly associated with incident AA in the subgroup of males, age <65 years, former/current smoker, and hypertension. For AAE, the same trend was found, except for sex (significant both in male and female). With regards to subtypes of AA, the associations were found significant in the subgroup of males, age ≧65 years, former/current smokers, and hypertension. The retinal caliber features were significantly associated with TAA in the subgroup of males, age <65 years, never smoker, and with or without hypertension, while the other related RVFs were mainly significant in the subgroup of female, age <65 years, former/current smoker, non-hypertension.

Sensitivity analysis

After excluding participants who were diagnosed with AA within the first two years of follow-up, similar findings were observed (Supplementary Table 12). Another sensitivity analysis using the PSM method resulted in 306 participants of AA incidence matched with 1530 controls. The SMD of all variables included in PSM reduced to less than 0.1, demonstrating a good balance between two groups after PSM (Supplementary Table 13). The results of the multivariate Cox model after PSM were basically consistent with the main analysis (Supplementary Table 14). Besides, analyses that excluded participants less than 50 years showed similar trends to the main analyses (Supplementary Table 15). When focused on the participants with hypertension or diabetes, the significant RVFs was also found to be associated with incidence of AA, revealing the highly robust of these findings (Supplementary Table 16).

Discussion

In this large prospective population-based cohort study, we found the retinal arterial branching angle and venular caliber were associated with the risk of incident AA, while the venular angular asymmetry was associated with the incidence of AAE. Moreover, specific RVFs were observed to be associated with different subtypes of AA. The venular caliber was associated with an increased risk of AAA and TAA. Meanwhile, the arterial complexity and length, and venular tortuosity were found to be related to decreased TAA risk. Our findings indicated that the RVFs could potentially serve as a standalone biomarker or be used in conjunction with other clinical risk factors and biomarkers for early identification of AA and AAE, thereby aiding in clinical decision-making.

Our study demonstrated the association of RVFs with future incidence of AA and AAE. Growing evidence has shown that RVFs could be promising biomarkers for cardiovascular diseases, as the noninvasive, easily available, and inexpensive advantages of fundus imaging[21-23]. The previous study has documented the associated RVFs with the genetic risk of main types of aneurysms[24]. However, the potential association of RVFs with incident AA and its adverse outcomes remains unclear. It was found in the Atherosclerosis Risk in Communities (ARIC) Study that wider central retinal venular equivalent (CRVE) were associated with an increased risk of AAA in the crude model, but after adjusting the disease risk factors (particularly smoking) the association was no longer

significant. Meanwhile, no significant association was observed between the retinal arterial diameter and AAA risk[7]. Of note, our results revealed that the central tendency and variability of venular caliber, rather than the CRVE were associated with the AA (including both AAA and TAA), even after adjusting for related risk factors. With advances in deep learning-assisted retinal vasculature quantification, multidimensional and comprehensive RVFs can now be extracted and quantified within seconds. Our findings suggested that specific RVFs, particularly in central tendency and variability of venular caliber, could serve as unique biomarkers for AA development. Further research is required to validate these features and confirm their potential for noninvasive early screening of AA.

Additionally, the present study has demonstrated that the retinal branching angle, which reflected the reduced optimality of the branching geometry, was associated with both AA and AAE. Specifically, the lower arterial branching density and venular minimum angular asymmetry were associated with the increased incidence of AA and AAE, respectively. It might correspond to limited oxygen and nutrient supply in the context of low retinal branching density[25]. Previous studies have demonstrated that the retinal vascular branches were marked reduction in patients with hypertension[26], but these rarefactions of retinal vasculature could be improved after the effective antihypertensive treatment[27], implying the RVFs, as a potential biomarker, could dynamically reflect the systemic vascular health. Moreover, the decreased vascular branches might contribute to high wall shear stress, activating pro-inflammatory signaling in vascular smooth muscle cells (VSMCs) and cause AA formation[24,28].

Furthermore, different measure types of RVFs were found to be associated with the subtypes of AA. Apart from the venular caliber, the vascular complexity, length, and tortuosity were associated with TAA. Although many common risk factors are shared for both AAA and TAA, some studies have revealed their distinct pathophysiology. Lipid metabolism plays a more substantial role in AAA development compared to TAA[18,29]. Moreover, the lineage-mapping studies suggested that the embryologic origin of VSMCs in the thoracic aorta differed from the abdominal aorta[30]. In this study, we found the specific RVFs in different types of AA, further confirming the distinct pathologic processes between abdominal and thoracic aortic aneurysms are needed.

The underlying pathophysiological mechanisms for the association of RVFs alteration with future incidence of AA and AAE warrant further investigation. Several plausible mechanisms might explain our findings. Firstly, the vasculature of the eye and the heart share many common characteristics, and are often exposed to similar intrinsic and environmental influences[31]. As the nature of easily accessible vasculature and non-invasively visualized, the eye has been regarded as a window to cardiovascular health. Secondly, the dominant risk factors for AA, such as age, smoking, hypertension, and atherosclerosis, simultaneously caused the changes of vasculature in the retina[6,32,33]. Consistent with this finding, numerous studies have used retinal fundus images to predict cardiovascular risk factors, and further enhance its role as a biomarker for the prediction of cardiovascular disease profiles and events[6,13,14,33-36]. Additionally, similar pathological changes might affect both the aorta and retinal vasculature, including the dysfunction of VSMCs, degradation of extracellular matrix, and inflammation response[28,37-40].

Early diagnosis of AA is difficult due to its asymptomatic nature and high mortality if untreated[41,42], underscoring the need for effective screening in high-risk individuals. Retinal imaging, being noninvasive, fast, and cost-effective, could potentially enhance AA screening rates[43]. Unlike traditional biomarkers, retinal images offer a noninvasive, clear visualization of vascular health and are already widely utilized in routine screenings for older adults and diabetes patients[44]. Integrating retinal imaging into AA evaluation could facilitate earlier referrals and interventions. Further studies are required to validate its effectiveness and explore its combination with other biomarkers for improved AA risk assessment.

Despite the strength of the present study including a large sample size, relatively long duration of follow-up, standard acquisition and quantification of retinal fundus images, and comprehensive adjustment for confounding variables, several limitations warrant mention. First, the selection bias of participants in the UK Biobank should be noticed, which is relatively younger and healthier than the general population. However, we believe this did not affect the findings since in the sensitivity analysis focus on participants older than 50 years, similar associations were revealed. Second, although we have utilized comprehensive information sources to identify AA patients, early detection remains challenging due to the asymptomatic nature of the disease. Moreover, AA was categorized by location in this study, rather than by pathology, to reflect differences in aneurysm formation mechanisms. Further research is needed to explore the relationship between RVFs and specific pathological types of AA. Third, the number of incident AA and AAE, and individuals with eligible retinal images are limited within the UK Biobank. Therefore, further studies are needed to establish a more definitive association of RVF with AA and detailed AAE outcomes. Nevertheless, we have performed several sensitivity analyses to verify the robustness of our findings in the present study. In addition, the possibility of residual confounding effects could not be fully excluded. Lastly, we could not demonstrate the causal effect of RVFs on AA incidence and progression in the observational design.

Conclusions

This population-based cohort study demonstrated that RVFs automatically extracted from retinal images might provide an adjunct for detecting AA incidence and progression. Our findings suggested the retinal arterial branching angle and venular caliber were associated with the risk of incident AA, and the venular angular asymmetry was associated with the incidence of AAE. Additionally, specific alterations in RVFs were identified across different AA subtypes. The PSM analysis revealed similar results, demonstrating the robustness of these associations. Further research is needed to confirm the potential value of these RVFs in enhancing early detection and preventive healthcare for AA.

Ethical approval

The UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (11/NW/0382). All participants provided informed consent to participate. This research has been conducted using the UK Biobank Resource

under Application Number 86091 and only unidentifiable data was used.

Consent

All participants provided informed consent to participate.

Sources of funding

The present study was supported by grants from the National Natural Science Foundation of China (82271125, 81870663, 82171075, 82301246), Guangdong Basic and Applied Basic Research Foundation (2023B1515120028), the launch fund of Guangdong Provincial People's Hospital for NSFC (8217040449, 8227040339 and 8217040546), GDPH Supporting Fund for Talent Program (KY0120220263), the Science and Technology Program of Guangzhou (20220610092), the Outstanding Young Talent Trainee Program of Guangdong Provincial People's Hospital (KJ012019087), the GDPH Scientific Research Funds for Leading Medical Talents and Distinguished Young Scholars in Guangdong Province (KJ012019457), and Personalized Medical Incubator Project, The fund for Precision Medicine Research and Industry Development in SIMQ (2023-31), Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention (Y0120220151), National Foreign Experts Program (S20240245).

Author's contributions

X.Y., H.Y., and J.L.: conceived the idea for the study. C.L., Y. H., and G.H.: data acquisition and statistical analysis. C.L. and Y.H.: draft the manuscript; X.Y., H.Y., J.L., and D.S.: critically reviewed the manuscript and supervised the study. All authors read and approved the final manuscript.

Conflicts of interest disclosure

All authors declare no disclosure of interest for this contribution.

Research registration unique identifying number (UIN)

https://www.ukbiobank.ac.uk.

Guarantor

Xiaohong Yang.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

Data were obtained from UK Biobank and are available at https://www.ukbiobank.ac.uk with the permission of UK Biobank.

Acknowledgements

We thank all the staff and participants of the UK Biobank for their hard work and dedication in collecting the underlying data.

References

[1] Bossone E, Eagle KA. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes. Nat Rev Cardiol 2021;18:331–48.

[2] Rombouts KB, van Merrienboer TAR, Ket JCF, *et al*. The role of vascular smooth muscle cells in the development of aortic aneurysms and dissections. Eur J Clin Invest 2022;52:e13697.

[3] Huang X, Wang Z, Shen Z, *et al*. Projection of global burden and risk factors for aortic aneurysm - timely warning for greater emphasis on managing blood pressure. Ann Med 2022;54:553–64.

[4] Isselbacher EM, Preventza O, Hamilton Black J, *et al*. ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2022;146: e334–e482.

[5] Nusinovici S, Rim TH, Yu M, *et al*. Retinal photograph-based deep learning predicts biological age, and stratifies morbidity and mortality risk. Age Ageing 2022;51:afac065.

[6] Poplin R, Varadarajan AV, Blumer K, *et al*. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2018;2:158–64.

[7] Folsom AR, Lutsey PL, Klein R, *et al*. Retinal microvascular signs and incidence of abdominal aortic aneurysm: the atherosclerosis risk in communities study. Ophthalmic Epidemiol 2018;25:246–49.

[8] Ghoraba HH, Moshfeghi DM. Retinal arterial tortuosity in marfan and loeys-dietz syndromes. Ophthalmol Retina 2023;7:554–57.

[9] Wang SB, Mitchell P, Liew G, *et al*. A spectrum of retinal vasculature measures and coronary artery disease. Atherosclerosis 2018;268:215–24.

[10] Seidelmann SB, Claggett B, Bravo PE, *et al*. Retinal vessel calibers in predicting long-term cardiovascular outcomes: the atherosclerosis risk in communities study. Circulation 2016;134:1328–38.

[11] Xue CC, Li C, Hu JF, *et al*. Retinal vessel caliber and tortuosity and prediction of 5-year incidence of hypertension. Journal of Hypertension 2023;41:830–37.

[12] Shi D, Lin Z, Wang W, *et al*. A deep learning system for fully automated retinal vessel measurement in high throughput image analysis. Front Cardiovasc Med 2022;9:823436.

[13] Cheung CY, Xu D, Cheng C-Y, *et al*. A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre. Nat Biomed Eng 2021;5:498–508.

[14] Rim TH, Lee CJ, Tham Y-C, *et al*. Deep-learning-based cardiovascular risk stratification using coronary artery calcium scores predicted from retinal photographs. Lancet Digit Health 2021;3:e306–e16.

[15] Sudlow C, Gallacher J, Allen N, *et al*. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

[16] Mathew G, Agha R, Albrecht J, *et al*. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.

[17] Wu J, Zafar MA, Li Y, *et al*. Ascending aortic length and risk of aortic adverse events: the neglected dimension. J Am Coll Cardiol 2019;74:1883–94.

[18] Roychowdhury T, Klarin D, Levin MG, *et al*. Genome-wide association meta-analysis identifies risk loci for abdominal aortic aneurysm and highlights PCSK9 as a therapeutic target. Nat Genet 2023;55:1831–42.

[19] Klarin D, Devineni P, Sendamarai AK, *et al*. Genome-wide association study of thoracic aortic aneurysm and dissection in the Million Veteran Program. Nat Genet 2023;55:1106–15.

[20] Chang CC, Chow CC, Tellier LC, *et al*. Second-generation PLINK: Rising to the challenge of larger and richer datasets. Gigascience 2015;4:7.

[21] Dinesen S, Jensen PS, Bloksgaard M, *et al*. Retinal vascular fractal dimensions and their association with macrovascular cardiac disease. Ophthalmic Res 2021;64:561–66.

[22] Hanssen H, Streese L, Vilser W. Retinal vessel diameters and function in cardiovascular risk and disease. Prog Retin Eye Res 2022;91:101095.

[23] Fu Y, Yusufu M, Wang Y, *et al*. Association of retinal microvascular density and complexity with incident coronary heart disease. Atherosclerosis 2023;380:117196.
[24] Huang Y, Li C, Shi D, *et al*. Integrating oculomics with genomics reveals imaging biomarkers for preventive and personalized prediction of arterial aneurysms. EPMA J 2023;14:73–86.
[25] Murray CD. The physiological principle of minimum work applied to the angle of branching of arteries. J Gen Physiol 1926;9:835–41.
[26] Hughes AD, Martinez-Perez E, Jabbar AS, *et al*. Quantification of topological changes in retinal vascular architecture in essential and malignant hypertension. J Hypertens 2006;24:889–94.
[27] Hughes AD, Stanton AV, Jabbar AS, *et al*. Effect of antihypertensive treatment on retinal microvascular changes in hypertension. J Hypertens 2008;26:1703–07.
[28] Lu H, Du W, Ren L, *et al*. Vascular smooth muscle cells in aortic aneurysm: from genetics to mechanisms. J Am Heart Assoc 2021;10:e023601.
[29] Harrison SC, Holmes MV, Burgess S, *et al*. Genetic association of lipids and lipid drug targets with abdominal aortic aneurysm: a meta-analysis. JAMA Cardiol 2018;3:26–33.
[30] Majesky MW. Developmental basis of vascular smooth muscle diversity. Arterioscler Thromb Vasc Biol 2007;27:1248–58.
[31] Flammer J, Konieczka K, Bruno RM, *et al*. The eye and the heart. Eur Heart J 2013;34:1270–78.
[32] Chew SK, Xie J, Wang JJ. Retinal arteriolar diameter and the prevalence and incidence of hypertension: a systematic review and meta-analysis of their association. Curr Hypertens Rep 2012;14:144–51.
[33] Chang J, Ko A, Park SM, *et al*. Association of cardiovascular mortality and deep learning-funduscopic atherosclerosis score derived from retinal fundus images. Am J Ophthalmol 2020;217:121–30.
[34] Ting DSW, Wong TY. Eyeing cardiovascular risk factors. Nat Biomed Eng 2018;2:140–41.
[35] Lee YC, Cha J, Shim I, *et al*. Multimodal deep learning of fundus abnormalities and traditional risk factors for cardiovascular risk prediction. NPJ Digit Med 2023;6:14.
[36] Zhang W, Tian Z, Song F, *et al*. Enhancing stability in cardiovascular disease risk prediction: a deep learning approach leveraging retinal images. Inf Med Unlocked 2023;42:101366.
[37] Gurung R, Choong AM, Woo CC, *et al*. Genetic and epigenetic mechanisms underlying vascular smooth muscle cell phenotypic modulation in abdominal aortic aneurysm. Int J Mol Sci 2020;21:6334.
[38] Zekavat SM, Raghu VK, Trinder M, *et al*. Deep learning of the retina enables phenome- and genome-wide analyses of the microvasculature. Circulation 2022;145:134–50.
[39] Wong TY, Islam FM, Klein R, *et al*. Retinal vascular caliber, cardiovascular risk factors, and inflammation: The multi-ethnic study of atherosclerosis (MESA). Invest Ophthalmol Vis Sci 2006;47:2341–50.
[40] Chaqour B, Karrasch C. Eyeing the extracellular matrix in vascular development and microvascular diseases and bridging the divide between vascular mechanics and function. Int J Mol Sci 2020;21:3487.
[41] Khan H, Abu-Raisi M, Feasson M, *et al*. Current prognostic biomarkers for abdominal aortic aneurysm: a comprehensive scoping review of the literature. Biomolecules 2024;14:661.
[42] Hoornweg LL, Storm-Versloot MN, Ubbink DT, *et al*. Meta analysis on mortality of ruptured abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2008;35:558–70.
[43] Herb J, Strassle PD, Kalbaugh CA, *et al*. Limited adoption of abdominal aortic aneurysm screening guidelines associated with no improvement in aneurysm rupture rate. Surgery 2018;164:359–64.
[44] Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003-2016. Acta Diabetol 2017;54:515–25.