Sex-Specific Association Between Serum Uric Acid and Retinal Microvessels

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Background: As epidemiological findings are still controversial, animal experiments have probed into the potential link between uric acid (SUA) with the retinal vascular caliber and retinal vascular fractal dimension (Df) in males and females utilizing a cross-sectional study design.

Material/Methods: A total of 2169 subjects from 7 sampling units were enrolled. Retinal vascular parameters were analyzed with a semi-automated computer-based program. The central retinal arteriolar equivalent, central retinal venular equivalent, and Df were linearly and categorically measured in males and females at various SUA levels.

Results: The analysis revealed that per SD SUA increase was associated with an increase of 0.848 µm in the arteriolar caliber, and an increase of 1.618 µm in the venular caliber only in females. No significant correlation was found between Df and SUA in females or in males. Further adjusted for more cardiovascular risk factors did not change the results.

Conclusions: By exploring a Chinese coastal population, we elucidate the association between SUA with retinal arterioles and venules in females. Df, as a mathematical index of retinal blood vascular complexity, is not correlated with SUA or hyperuricemia.

MeSH Keywords: Microvessels • Retinal Artery • Retinal Vein • Uric Acid

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Authors’ Contribution:
- Study Design
- Data Collection
- Statistical Analysis
- Data Interpretation
- Manuscript Preparation
- Funds Collection

Supporting information

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Background

Hyperuricemia may induce endothelial dysfunction by reducing nitric oxide [1] and stimulate endothelial cell proliferation through activating the renin-angiotensin system [2], which eventually leads to microvascular damage [3].

The retina offers an optimal noninvasive opportunity to visualize and quantify microcirculation injury. In a case-control study of type 2 diabetes mellitus patients, Sacks et al. found retinopathy was associated with triglycerides and high-density lipoprotein cholesterol, but the difference was not significant after additional adjustment [4]. Retinal arteriolar variety has been proven to be associated with hypertension and may be a predictor of cardiovascular diseases [5,6]. Larger retinal venular caliber is associated with cigarette smoking, lower levels of high-density lipoprotein cholesterol (HDL-C), higher levels of HbA1c, and greater body mass index [7]. Interestingly, a recent study found that retinal microvascular response of cardiac patients improved during rehabilitation [8]. In addition, microvascular angiina is associated with retinal microvascular changes [9]. Retinal vascular fractal dimension (Df), a mathematical index of retinal blood vascular complexity, is associated with hypertension [10], diabetic retinopathy [11], chronic kidney disease [12], and coronary heart diseases [13]. A potential mechanism may be that the human circulatory system operates with optimal structural design to achieve adequate blood flow with sufficient energy consumption; therefore, suboptimal structure of microcirculation is considered as vascular integrity deficiency [14].

The relationship between uric acid and microcirculation is still epidemiologically unclear. A previous study has documented that high uric acid level is associated with poor myocardial perfusion [15], indicating that uric acid may induce coronary disease by advancing microangiopathy, but another study found that microvascular dysfunction was not significantly associated with serum uric acid (SUA) [16].

However, given the findings of animal experiments, we suspect that a potential link might exist between SUA and retinal microvessels. The only relevant study available analyzed the association between hyperuricemia and retinal vascular caliber by recruiting 869 subjects with a high risk for diabetes [17], which may not be considered as an adequate general model.

In view of the above and considering that SUA is linked to sex, we aimed to investigate the sex-specific association of SUA with retinal vascular calibers and Df in order to present a comprehensive picture of the microcirculation in a coastal Chinese population.

Material and Methods

Design and setting of the study

Cluster sampling was conducted for this cross-sectional study from July to November 2011. The individual administrative villages were taken as sampling clusters. Of the 14 villages of 2 specified townships, 7 sampling units were randomly chosen in Tailu, Beijiao, and Xiubang in Xiapu county in Fujian Province, China. The participants were local residents aged 30 years and above. Invitations to participate in the survey were distributed to 4616 subjects randomly sampled from a qualified pool of 8947. A total of 3343 subjects underwent investigation, after which we excluded 1174 for the following reasons: lacking data (421 subjects), infectious diseases (49 subjects with a C-reactive protein level >10 mg/L), arterial fibrillation (14 subjects), low ankle brachial index (15 subjects with an ABI <0.6), and poor or obscure fundus images (675 subjects). Finally, 2169 subjects were enrolled for the subsequent data analysis (Figure 1). The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fujian Provincial Hospital. Signed consent forms were obtained from all participants.

Characteristics of participants

The data were collected with a questionnaire inquiring about information related to the respondents’ age, smoking, passive smoking, alcohol consumption, educational level, family history, and medical history (including high blood pressure, diabetes mellitus, coronary heart disease, cerebral ischemia, hepatic and renal disorders, tumors, and perivascular diseases).

Figure 1. Flowchart of the study population.
Physical examination and noninvasive brachial-ankle pulse wave velocity (baPWV) measurement

The subjects’ waist circumference, hip circumference, heart rate, and blood pressure were measured in a standard process. The arterial pulse waveform was recorded for 5 min using an automatic arteriosclerosis detector (BP203RPE-II VP-1000, Japan), which displays the baPWV automatically.

Clinical measurements

Overnight fasting blood samples were collected to determine the levels of low-density lipoprotein cholesterol (LDL-C), triglyceride, total cholesterol, fasting glucose, serum creatinine, hypersensitive C-reactive protein (hs-CRP), HbA1c, and SUA. First morning urine was taken to test albumin and creatinine.

Retinal vascular parameters collection

Fundus photography were conducted with a digital non-mydriatic camera (Topcon NW-8 and Nikon D90, Japan) by 2 experienced ophthalmologists. We used a semi-automated computer-based program [Singapore I Vessel Assessment (SIVA) version 3.0, jointly developed by Singapore National University and Singapore Eye Research Institute] to analyze vascular parameters. The central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were calculated using the modified Knudtson-Parr-Hubbard formula [18]. Df, as a complexity index of retinal vessels, was computed from the skeletonized line tracing with box-counting method [10–12].

In a random sample of 100 fundus photographs, we found no differences between intra-grader measurements, while the intergrader correlation coefficient for CRAE, CRVE, and Df were 0.89 (95% CI: 0.89–0.90), 0.92 (95% CI: 0.92–0.93), and 0.90 (95% CI: 0.89–0.90).

Definitions

Hyperuricemia was defined as SUA level ≥420 µmol/L in men or ≥360 µmol/L in women [19]. Hypertension was designated as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg without any anti-hypertensive drug therapy. The definition was also applicable to those who had a history of hypertension and were using anti-hypertension drugs at the time of the study [20]. Diabetes indicated an HbA1c of 0.90 (95% CI: 0.89–0.90).

The arteriolar-to-venular ratio was defined as CRAE/CRVE. The SUA were grouped according to quartiles (Q1–Q4).

Statistics analysis

All data were analyzed with SPSS (Windows version 19.0, Chicago, USA). Continuous variables are presented as mean±standard deviation and categorical variables are expressed as count and percentages. Analysis of covariance (ANCOVA) and χ² test were used to compare demographic characteristics of participants with and without hyperuricemia for continuous variables and discrete variables, respectively. Meanwhile, ANCOVA was used to calculate age- and sex-adjusted differences across normal and hyperuricemia groups. Spearman correlation analysis was used to study the relationship between SUA and other cardiovascular risk factors. As the scale of Df was too small, we transformed it into 100 times the original value for analysis. The CRAE, CRVE, and 100*Df were estimated at different SUA levels both continuously and categorically between males and females. Two models were constructed: the first crude model was a linear regression, adjusted for age; the second model was a multivariable regression, additionally adjusted for smoking and passive smoking, mean arterial blood pressure (MABP), waist-to-hip ratio, triglyceride, total cholesterol, LDL-C, HDL-C, eGFR, and HbA1c. The coefficient provided an estimate of the change in the outcomes, with a 1-SD change in SUA.

All p values were two-sided, and statistical significance was set at p values <0.05.

Results

Table 1 summarizes the characteristics of the enrolled participants with and without hyperuricemia. The study recruited 2169 individuals with a baseline mean age of 52.90±11.95 years, of whom 37.4% were male. High prevalence rates of smoking and passive smoking (n=1144, 52.74%) and less than 1 year of primary education (n=835, 38.50%) were observed in the study population. Mean retinal arteriolar caliber was 134.10±11.13 µm, venular caliber was 184.03±16.52 µm, and mean Df was 1.37±0.05. Among the participants, 390 met the criteria of hyperuricemia and had a larger retinal arteriolar caliber (135.27±11.28 µm) and wider retinal venular caliber (185.78±17.32 µm). The Df was not associated with hyperuricemia in the age- and sex-adjusted analysis. This hyperuricemia group was more likely to have higher waist-to-hip ratio, body mass index, triglyceride, total cholesterol, LDL-C, and fasting glucose, and lower HDL-C and eGFR. In addition, a borderline significant difference in diastolic blood pressure, MABP, and incidence rates of smoking and passive smoking was found between hyperuricemia individuals and normal subjects (0.05<p<0.1).
Table 1. Characteristics of participants with and without hyperuricemia.

| Variables                        | All participants | Participants without hyperuricemia | Participants with hyperuricemia | p*          | Age- and sex-adjusted differences |
|----------------------------------|------------------|------------------------------------|--------------------------------|-------------|----------------------------------|
| N                                | 2169             | 1779                               | 390                            |             |                                  |
| CRAE (µm)                        | 134.10 (11.13)   | 133.84 (11.09)                     | 135.27 (11.28)                 | 0.022       | −1.47 (−2.68, −2.54)             |
| CRVE (µm)                        | 184.03 (16.62)   | 183.65 (16.45)                     | 185.78 (17.32)                 | 0.022       | −2.26 (−4.53, −4.07)             |
| Df                               | 1.37 (0.05)      | 1.37 (0.05)                        | 1.36 (0.05)                    | 0.845       | −0.01 (−0.06, 0.04)              |
| Age (years)                      | 52.90 (11.95)    | 51.74 (11.92)                      | 52.64 (12.10)                  | 0.170       | −0.90 (−2.21, 0.40)              |
| MABP (mmHg)                      | 94.67 (14.10)    | 94.42 (14.06)                      | 95.80 (14.21)                  | 0.081       | −0.98 (−2.39, 0.44)              |
| Systolic blood pressure (mmHg)   | 126.94 (21.94)   | 126.68 (22.04)                     | 128.11 (21.46)                 | 0.243       | −0.65 (−2.74, 1.44)              |
| Diastolic blood pressure (mmHg)  | 78.55 (11.85)    | 78.32 (11.74)                      | 79.62 (12.32)                  | 0.050       | −0.90 (−2.21, 0.40)              |
| Heart rate (bpm)                 | 71.22 (9.28)     | 71.26 (9.35)                       | 71.04 (8.92)                   | 0.178       | −0.90 (−2.21, 0.40)              |
| Waist-to-hip ratio               | 0.85 (0.07)      | 0.85 (0.07)                        | 0.87 (0.07)                    | 0.001       | −0.02 (−0.03, −0.01)             |
| Body mass index (kg/m²)          | 23.83 (3.42)     | 23.71 (3.37)                       | 24.36 (3.58)                   | 0.001       | −0.62 (−0.99, −0.25)             |
| Triglyceride (mmol/L)            | 0.86 (0.05)      | 0.82 (0.05)                        | 1.01 (0.05)                    | 0.001       | −0.22 (−0.74, 0.29)              |
| Total cholesterol (mmol/L)       | 5.03 (1.05)      | 4.96 (1.01)                        | 5.31 (1.17)                    | 0.001       | −0.34 (−0.45, −0.22)             |
| HDL-C (mmol/L)                   | 1.23 (0.33)      | 1.24 (0.33)                        | 1.14 (0.31)                    | 0.001       | 0.11 (0.01, 0.14)                |
| LDL-C (mmol/L)                   | 2.79 (0.88)      | 2.72 (0.87)                        | 3.07 (0.91)                    | 0.001       | −0.33 (−0.43, −0.24)             |
| Eating glucose (mmol/L)          | 5.11 (0.50)      | 5.25 (1.47)                        | 5.17 (2.22)                    | 0.001       | −0.22 (−0.40, −0.13)             |
| eGFR (ml/min*1.73 m²)            | 103.20 (33.66)   | 105.35 (34.31)                     | 93.36 (28.53)                  | 0.001       | 11.78 (8.28,15.28)               |
| hs-CRP (mg/L)                    | 1.36 (3.38)      | 1.34 (3.47)                        | 1.56 (2.89)                    | 0.240       | −0.18 (−0.55, 0.18)              |
| UACR (mg/mmol)                   | 2.48 (4.51)      | 2.41 (4.09)                        | 2.78 (6.06)                    | 0.149       | −0.32 (−0.81, 0.17)              |
| HbA1c (%)                        | 5.72 (0.69)      | 5.71 (0.70)                        | 5.75 (0.58)                    | 0.002       | −0.02 (−0.10, −0.05)             |
| baPWV (cm/s)                     | 1417.72 (338.07) | 1412.41 (339.90)                   | 1441.92 (328.92)               | 0.118       | −14.06 (−43.25, 15.14)           |
| Serum uric acid (µmol/L)         | 315.04 (84.82)   | 286.93 (59.30)                     | 443.28 (62.63)                 | 0.001       | −156.18 (−162.16, −150.20)       |
| Sex (% Male)                     | 812 (37.4%)      | 666 (37.4%)                        | 146 (37.4%)                    | 1.000       | −0.03 (−4.9, 5.6)                |
| Smoking (%)                      | 341 (15.72%)     | 278 (15.63%)                       | 63 (16.15%)                    | 0.260       | −0.5 (−3.9, 2.9)                 |
| HbA1c (%)                        | 5.72 (0.69)      | 5.71 (0.70)                        | 5.75 (0.58)                    | 0.289       | −0.03 (−0.10, −0.05)             |
| Less than 1 year primary education | 835 (38.5%)   | 675 (37.94%)                       | 160 (41.01%)                   | 0.257       | −1.7 (−6.5, 3.1)                 |
| Hypertension                     | 819 (37.76%)     | 655 (36.82%)                       | 164 (42.05%)                   | 0.117       | −3.7 (−8.4, 1.1)                 |

* p values refer to difference between hyperuricemia individuals and normal subjects. Hyperuricemia was defined as serum uric acid level ≥420 µmol/L in men or ≥360 µmol/L in women. CRAE – central retinal arteriolar equivalent; CRVE – central retinal venular equivalent; Df – fractal dimension; MABP – mean arterial blood pressure; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; eGFR – estimated glomerular filtration rate; hs-CRP – hypersensitive C-reactive protein; UACR – urinary albumin-creatinine ratio; baPWV – brachial-ankle pulse wave velocity.
No significant association was found between hyperuricemia and age, systolic blood pressure, pulse pressure, heart rate, hs-CRP, UACR, HbA1c, baPWV, sex, smoking, drinking, less than 1 year of primary education, hypertension, or diabetes mellitus.

Spearman correlation analysis showed that SUA was positively associated with age, systolic blood pressure, diastolic blood pressure, MABP, pulse pressure, waist-to-hip ratio, body mass index, triglyceride, total cholesterol, LDL-C, and HbA1c. However, it was negatively correlated with HDL-C and eGFR.

Tables 2 and 3 show the relationship between SUA changes and CRAE, CRVE, and DF. In females, SUA was linearly associated with the retinal vascular caliber. In the crude model (adjusted linear regression model Continuous uric acid* Quartiles of uric acid, median (interquartile range), µmol/L

| Linear regression model            | Continuous uric acid* | p* | Quartiles of uric acid | 248 (124–285) | 286 (286–334) | 316 (344–399) | 370 (400–688) | p |
|-----------------------------------|-----------------------|----|------------------------|---------------|---------------|---------------|---------------|----|
| Age-change in CRAE (SE)           | 0.350 (0.350)         | 0.359 | Referent               | 1.090 (1.109) | 0.326         | 0.763 (1.112) | 0.493         | 1.139 (1.111) | 0.305 |
| Multivariable change in CRAE (SE) | 0.005 (0.438)         | 0.991 | Referent               | 0.752 (1.165) | 0.519         | 0.001 (1.218) | 1.000         | 0.387 (1.315) | 0.769 |
| Age-change in CRVE (SE)           | 0.175 (0.613)         | 0.815 | Referent               | 0.480 (1.726) | 0.781         | 0.259 (1.733) | 0.661         | 0.728 (1.728) | 0.674 |
| Multivariable change in CRVE (SE) | 0.788 (0.701)         | 0.295 | Referent               | 0.914 (1.820) | 0.616         | 1.235 (1.903) | 0.517         | 2.978 (2.054) | 0.148 |
| Age-change in 100DF (SE)          | 0.175 (0.175)         | 0.254 | Referent               | 0.238 (0.465) | 0.610         | 0.467 (0.846) | 0.403         | 0.532 (0.466) | 0.254 |
| Multivariable change in 100DF (SE)| 0.114 (0.193)         | 0.569 | Referent               | 0.064 (0.494) | 0.895         | 0.322 (0.506) | 0.525         | 0.279 (0.547) | 0.610 |

Table 2. Association between uric acid and changes in CRAE, CRVE, and 100 Df for males.

* per each SD increase, SD=87.58 µmol/L. Multivariable models were adjusted for age, smoking and passive smoking, mean arterial blood pressure, waist-to-hip ratio, triglyceride, total cholesterol, LDL-C, HDL-C, eGFR, and HbA1c. CRAE – central retinal arteriolar equivalent; CRVE – central retinal venular equivalent; DF – fractal dimension; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein; eGFR – The Estimated Glomerular filtration rate.

Table 3. Association between uric acid and changes in CRAE, CRVE, and 100Df for females.

* per each SD increase, SD=77.06 µmol/L. Multivariable models were adjusted for age, smoking and passive smoking, mean arterial blood pressure, waist-to-hip ratio, triglyceride, total cholesterol, LDL-C, HDL-C, eGFR, and HbA1c. CRAE – central retinal arteriolar equivalent; CRVE – central retinal venular equivalent; DF – fractal dimension; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein; eGFR – estimated glomerular filtration rate.
for age), the retinal arteriolar caliber was the largest in the fourth SUA quartile, and per SD increase of SUA was associated with an increase of 0.848 µm in the arteriolar caliber. In Model 1, venular calibers were wider in the third and fourth SUA quartiles, with a p-trend of 0.001, and per SD increase of SUA was related with a rise of 1.618 µm in the venular caliber. In linear regression models, no significant correlation was found between Df and SUA when the latter was treated as a continuous variable and categorized data both in males and females. We found no significant relationship between arteriolar-to-venular ratio and SUA. In the multivariable model, which was further adjusted for smoking and passive smoking, MABP, waist-to-hip ratio, triglyceride, total cholesterol, LDL-C, HDL-C, eGFR, and HbA1c, the results were not changed.

Discussion

By recruiting a large subject population (2169 persons, aged 30 years and over) from the southeast of China, the current study demonstrated that while SUA levels were not correlated with Df, some correlation was observed within SUA increase augmented retinal and venular caliber.

Our findings are quite different from those of previous studies. In a comparable study reported in 2011 [17], the elevated SUA was associated with smaller retinal arteriolar caliber and larger retinal venular caliber, and the associations were more pronounced in men than in women. That study was the first to show a relationship between SUA and retinal microcirculation in vivo, and was based on volunteers who had an increased risk for developing type 2 diabetes, which may have contributed to some selection bias. Moreover, the study did not take into account critical confounders such as alcohol consumption, eGFR, and UACR, which can affect SUA levels. The present study considered and eliminated the confounding effects originating from the volunteers. In addition, as retinal vessel atherosclerosis was long ago confirmed to be associated with coronary artery disease and lipoproteins [6,22], we measured related covariates, such as serum lipids, eGFR, UACR, and even baPWV, representing the arterial elasticity, to lessen confounding errors. Thus far, studies have established that SUA showed a stronger correlation with coronary heart disease [23], insulin resistance, and plasma glucose levels [24] in females than in males. Our study was consistent with those results, in contrast to the rare finding of the 2011 study. It could also be reasoned that the elevation in uric acid by increased xanthine oxidase activity may be localized in tissue other than the endothelium, whereas in obesity there is considerable elevation in circulating xanthine oxidase. As in the 2011 study, some of the recruited persons were obese, and the higher xanthine oxidase has greater affinity for glycosaminoglycans on the endothelial surface, resulting in binding and sequestration of xanthine oxidase. This amplifies vascular oxidant generation and induces endothelial dysfunction, which could also serve to explain, in part, differences between the 2011 study and the present study.

An underlying mechanism for the association between uric acid and microcirculation is that uric acid can promote the proliferation of smooth muscle cells [25,26]. Wijnands et al. explored the relationship between SUA and cutaneous microcirculation determined by capillary density, and found no significant associations [16]. They suggested that the underlying pathophysiological mechanism could be the endothelium-independent response of skin microcirculation. On the contrary, it is the myogenic response that is responsible for the autoregulation of blood flow in cerebral, retinal, renal, and coronary vessels. We suggest that the sex-specific difference in the association was caused by not only by the SUA levels in males and females, but also by sex hormones affecting the retinal vessels [27].

It has been well-documented that elevated SUA can lead to hypertension. As a matter of fact, retinal or renal vasoconstriction, indicating an arteriolar narrowing, is probably associated with hyperuricemia or increased SUA level. However, the present study found no significant difference in hypertension prevalence between hyperuricemic participants and normal subjects, and found a negative correlation between SUA and retinal arteriolar diameters. These findings may result from methodological and demographic differences. The low incidence of hypertension in the present study population probably results from the fact that the participants are residents along the coast, who have a higher dietary intake of proteins, unsaturated fatty acid, magnesium, zinc, and calcium. This dietary difference, as well as poorer educational background and lower economic level, is different from that of the subjects in other parallel studies [28]. On the basis of the above results, a higher SUA is not accompanied by an arteriolar narrowing, which would independently predict hypertension. On the contrary, a positive correlation was found between SUA and arteriolar dilatation after controlling the confounding factors, including blood pressure.

To the best of our knowledge, such a finding is first reported in the literature, and the pathophysiological explanations are still ambiguous. One tentative explanation may be that uric acid plays an antioxidant role to benefit the patients, especially those with acute stroke, Parkinson’s disease, and COPD [29–31], as arteriolar narrowing is a predictor for cardiovascular disease and SUA would protect vessels from reactive oxygen species, or even result in a favorable arteriolar dilatation. As 52.74% of subjects in the present study were smokers or passive smokers, and thus were exposed to chronic oxidative stress on a long-term basis, SUA, accounting for 50% of the human blood antioxidant capacity, may self-regulate to a moderate level.
Another reason may be that uric acid acts as an inhibitor of xanthine oxidase by inhibiting a critical source of superoxide in the vasculature [32]. In agreement with a previous study [17], our cross-sectional analysis showed that CRVE was independently associated with SUA in females [33]. Uric acid is an important pro-inflammatory factor [34] and has a role similar to that of CRP. High SUA concentrations are associated with microvascular dysfunction [35,36]. Although our study did not report an association between CRVE and hs-CRP, we speculate that the correlation between SUA and CRVE may derive from the inflammation induced by cardiovascular diseases.

As a traditional parameter, arteriolar-to-venular ratio combining arterioles and venules is not relevant to SUA concentrations, indicating that a separate measurement of arteriolar and venular diameters can provide more information. Unfortunately, the present findings do not show an association between the retinal index Df and SUA. Therefore, further research into this potential association is needed.

The strengths of this study included the use of new semi-automated software to quantitatively analyze this population-based cross-section. Other studies have examined the correlation between the microvascular diameters and SUA [17,28]. However, the present study is novel in regards to its general coastal Chinese population instead of a high-risk population or other ethnic groups. In addition, a new cardiovascular indicator, Df, was examined in the study. Due to funding and manpower limitations, the present study has the following limitations: first, as a cross-sectional study, it cannot explain the causality between retinal vascular parameters and SUA; second, the participant exclusion and the regional selection may contribute to bias in the study; third, some indicators, such as genes, hormone levels, cell factors, and detailed medication such as usage of statin [37] which may have affected retinal vascular parameters, SUA, and residual confounding factors, were not included; finally, some bias may have existed since retinal vessel diameters are affected by the cardiac cycle. In order to establish a more standard research, world-wide studies including multiple ethnic groups and life styles may be required.

Conclusions

By exploring a Chinese coastal population, we found an association between SUA with retinal arterioles and venules in females. Df, as a mathematical index of retinal blood vascular complexity, is not correlated with SUA or hyperuricemia.

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