Intraocular pressure (IOP) is determined by the balance of aqueous humor secretion and outflow. The increase in IOP is caused by an increase in trabecular meshwork resistance leading to an decrease in aqueous humor outflow. Intraocular pressure (IOP) is one of the important diagnostic basis for glaucoma, and it is also the only controllable method and target for the prevention and treatment of glaucoma. Glaucoma is a chronic ocular neurodegenerative disease, characterized by visual field damage, optic nerve head cupping, and elevated IOP. It is the leading cause of global irreversible blindness. Studies had reported that elevated IOP was a risk factor for glaucoma. In addition, emerging evidence demonstrated that lowering IOP might reduce the risk of glaucoma in individuals with elevated IOP. Therefore, it is of important practical clinical significance to understand the potential risk factors of IOP for glaucoma prevention and prognosis.

Many previous studies had shown that elevated IOP was clearly associated with some cardiovascular risk factors, such as hypertension, diabetes, obesity, and metabolic syndrome. One study had shown that systemic inflammation reflected by serum C-reactive protein levels were associated with high IOP. Therefore, chronic inflammation may increase IOP. It had been reported that there was a statistically significant correlation among human trabecular meshwork DNA damage, visual field damage, and IOP. Moreover, oxidative stress could cause degeneration of human trabecular meshwork, favoring an IOP increase, thus causing the glaucoma pathogenetic cascade.

Serum uric acid (SUA) is the end product of purine metabolism. Epidemiological studies had shown that SUA was a predictor for cardiovascular events, kidney disease, and metabolic syndrome. Uric acid is an antioxidant in the extracellular environment, which may prevent aging and oxidative stress. Studies had shown that uric acid had...
Figure 1. Describe the sample flow chart for screening studies for statistical analysis.

A protective effect on primary angle-closure (PACG) glaucoma. However, it also is an oxidant in cells. One study had shown that uric acid levels were elevated in patients with glaucoma. Researches on the relationship between uric acid and glaucoma were still controversial. However, there was no research on uric acid and high IOP. We hypothesized that chronic inflammation, reflected by SUA levels, had an effect on elevating IOP.

Therefore, we analyzed the relationship between SUA and high IOP in the Chinese population by a retrospective cross-sectional study, and explored whether there was a dose response relationship between them.

Materials and Methods

Study Population

This study analyzed data from The First Affiliated Hospital of Soochow University. A total of 54,634 participants underwent health examination in 2018. Among them, 4616 participants with cataract or glaucoma, and 105 participants with gout were excluded. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² were also excluded. Also removed were those who lacked uric acid, body mass index (BMI), and had not tested for IOP. Finally, 19,147 participants (11,009 men and 8138 women) aged 18 to 93 years were included in this study. Data clean steps are presented in Figure 1. This study was approved by the Ethical Committee and the Institutional Review Board of The First Affiliated Hospital of Soochow University, Suzhou. The informed consent was waived and the need for waiving the informed consent was also supported by the Ethical Committee. All methods were performed in accordance with the Declaration of Helsinki and the relevant guidelines.

Assessment of SUA

Serum uric acid (SUA) levels were determined at the First Affiliated Hospital of Soochow University laboratory with Uricase Method by Siemens ADVIA 2400. The SUA levels were categorized into four groups (Q1–Q4) according to the quartiles of gender-specific distribution: Q1: < 237.30; Q2: 237.30 to 273.05; Q3: 273.06 to 316.30; and Q4: > 316.30 μmol/L for women; Q1: < 335.40; Q2: 335.40 to 382.00; Q3: 382.01 to 435.20; and Q4: > 435.20 μmol/L for men.

Questionnaire Data

A standard questionnaire was conducted by trained staff to obtain information about demographic characteristics (age and gender). The interview included questions related to the diagnosis and treatment of diabetes, hypertension, cataract, glaucoma, and gout.

Anthropometrics Measurement

When measuring height and weight, the participants stood upright, wearing a single layer of clothing, without wearing a hat or shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²), taking rest for 5 minutes before measuring blood pressure. Hypertension was defined as blood pressure ≥ 140/90 mmHg or a self-reported physician diagnosed with hypertension, or an individual currently using antihypertensive drugs. Diabetes was defined as fasting glucose level ≥ 7.0 mmol/L, or a self-reported physician diagnosis of diabetes, or taking oral hypoglycemic medication or insulin.

Laboratory Testing

After fasting for at least 8 hours, blood samples were collected from the anterior cubital vein in the morning. Fasting blood glucose levels were determined by a hexokinase method (Siemens ADVIA 2400). Enzymatic methods were used to measure creatinine, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL; Siemens ADVIA 2400). The eGFR was estimated by using the Modification of Diet in Renal Disease (MDRD)-4 equation: eGFR = 186 × serum creatinine−1.154 × age−0.203 × 0.742 (in women) × 1.212.

Definition of High Intraocular Pressure

An eye examination was performed by a trained ophthalmologist. Fundus photography was completed following a standardized protocol. The IOP values of the left and right eyes were measured by a professional ophthalmologist and recorded (TOMY FT-1000, Non-Contact Tonometer). The IOP was normally measured between 8:00 AM and 10:30 AM. The left IOP > 21 mm Hg or the right IOP > 21 mm Hg or the physicians recorded
### Table 1. Characteristics of the Study Participants According to Serum Uric Acid Quartiles by Gender

| Characteristics | Males | Females | p Trend | p Trend |
|-----------------|-------|---------|---------|---------|
|                 | Q1    | Q2      | Q3      | Q4      |
| N (participants, %) | 2752 (25.0) | 2750 (25.0) | 2749 (24.9) | 2758 (25.1) |
| Age, y          | 47 (38, 55) | 46 (36, 55) | 44 (36, 54) | 43 (34, 53) |
| BMI, kg/m²      | 23.8 (21.9, 25.8) | 24.6 (22.7, 26.5) | 25.1 (23.3, 27.0) | 26.1 (24.2, 28.0) |
| SBP, mmHg       | 123 (114, 135) | 124 (114, 135) | 125 (115, 135) | 126 (117, 137) |
| DBP, mmHg       | 76 (69, 84) | 77 (70, 85) | 78 (70, 85) | 79 (72, 87) |
| FBG, mmol/L     | 109.2 (92.9, 126.7) | 111.5 (95.8, 129.0) | 113.3 (96.3, 132.2) | 115.8 (97.8, 136.6) |
| eGFR, mL/min/1.73 m² | 1.3 (0.9, 1.8) | 1.5 (1.0, 2.1) | 1.6 (1.1, 2.3) | 1.9 (1.3, 2.8) |
| TG, mmol/L      | 4.8 (4.2, 5.3) | 4.8 (4.3, 5.4) | 4.9 (4.5, 5.5) | 5.0 (4.5, 5.6) |
| HDL, mmol/L     | 1.2 (1.0, 1.4) | 1.1 (1.0, 1.3) | 1.1 (1.0, 1.3) | 1.1 (0.9, 1.2) |
| LDL, mmol/L     | 2.7 (2.3, 5.2) | 2.8 (2.3, 5.3) | 2.9 (2.4, 5.4) | 2.9 (2.4, 5.4) |
| Hypertension, N (%) | 796 (28.9) | 803 (29.2) | 845 (30.7) | 1025 (37.1) |
| Diabetes, N (%) | 1956 (71.1) | 1947 (70.8) | 1904 (69.3) | 1735 (62.9) |
| High intraocular pressure, N (%) | 313 (11.4) | 205 (7.4) | 157 (5.3) | 165 (5.4) |
| Yes             | 1994 (81.6) | 2045 (92.6) | 2600 (94.7) | 2593 (94.0) |
| No              | 96 (3.5) | 93 (3.4) | 107 (3.9) | 140 (5.1) |

Cut-points: Serum uric acid quartiles (Q1–Q4) in men (Q1: < 335.40; Q2: 335.40–382.00; Q3: 382.01–435.20; and Q4: > 435.20 μ mol/L or Q1: < 3.99; Q2: 3.99–4.59; Q3: 4.60–5.31; and Q4: > 5.31 mg/dL). In women (Q1: < 237.30; Q2: 237.30–273.05; Q3: 273.06–316.30; and Q4: > 316.30 μ mol/L or Q1: < 3.99; Q2: 3.99–4.59; Q3: 4.60–5.31; and Q4: > 5.31 mg/dL). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein. Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as frequency (percent).
participants with right/left IOP > 21 mm Hg as high IOP.}

Statistical Analyses

All participants were classified according to the quartiles of SUA. The baseline characteristics were compared across the SUA quartiles of men and women. Baseline characteristics of the participants were reported as medians (quartile intervals) for continuous variables (the continuous variables were not normally distributed) and numbers (percentages) for categorical variables. Kruskal–Wallis tests were used to compare continuous variables, whereas categorical variables were compared by χ² trend tests. Univariate and multivariate logistic regression analysis were used to estimated odds ratios (ORs) and 95% confidence intervals (CIs) for changes in SUA in men and women.

To detect any possible linear or nonlinear dependency in regression models and to allow for flexible interpretation of the relationship between continuous covariates and study outcomes, continuous changes in SUA were assessed in regression models and to allow for flexible interpretation of SUA in men and women. Elevated levels of serum uric acid were independently associated with an increased risk of SUA quartiles were an independent risk of increasing high IOP incidence after adjustment for age, BMI, SBP, DBP, FBG, diabetes, and hypertension, eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein.

Model 1: Unadjusted.
Model 2: Adjusted for age, gender, BMI, SBP, DBP, FBG, diabetes, and hypertension.
Model 3: Adjusted for age, gender, BMI, SBP, DBP, FBG, diabetes, hypertension, eGFR, TG, TC, LDL, and HDL.
No adjustment for gender in men and women.

RESULTS

Characteristics of Study Population

Baseline characteristics of participants in men and women are shown in Table 1. Men had higher levels of SUA than women. Among men, participants with higher SUA levels tended to be younger, had higher BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL), body mass index (BMI), serum uric acid (SUA), and serum uric acid (SUA) levels were higher, whereas HDL were lower in participants with lower SUA levels, age, BMI, SBP, DBP, FBG, TG, TC, LDL, and HDL, had lower HDL, and the incidence of diabetes than those with lower SUA. Among women, compared with those with lower SUA levels, age, BMI, SBP, DBP, FBG, TG, TC, LDL, the incidence of hypertension, diabetes, and high IOP were higher, whereas HDL were lower in participants with higher SUA levels (see Table 1).

Relationship Between SUA and the Incidence of High Intraocular Pressure

As what was shown in Table 2, we found that, in women, SUA quartiles were an independent risk of increasing high IOP incidence after adjustment for age, BMI, SBP, DBP, FBG, diabetes, hypertension, eGFR, TG, TC, LDL, and HDL, compared with the first quartile of SUA level. The OR with 95% CI for Q2 to Q4 were 1.33 (0.89, 1.93) with P = 0.1757, 1.77 (1.22, 2.57) with P = 0.0025, and 1.51 (1.01, 2.26) with P = 0.0438, respectively. In men, the OR with 95% CI for Q2 to Q4 were 0.92 (0.68, 1.23) with P = 0.5573, 0.99 (0.74, 1.33) with P = 0.7058, respectively. The association between SUA and high IOP was different in men and women. Elevated levels of serum uric acid were independently associated with an increased risk

### Table 2. OR and 95% CI for Changes in SUA for High Intraocular Pressure Incidence According to Quartiles of SUA

| Variable | Model 1 | Model 2 | Model 3 |
|----------|---------|---------|---------|
|          | OR, 95% CI | P Value | OR, 95% CI | P Value | OR, 95% CI | P Value |
| Males    |         |         |         |         |         |         |
| Q1       | 1.00 (refer) | - | 1.00 (refer) | - | 1.00 (refer) | - |
| Q2       | 0.97 (0.72, 1.29) | 0.8282 | 0.91 (0.68, 1.22) | 0.5319 | 0.92 (0.68, 1.23) | 0.5573 |
| Q3       | 1.12 (0.85, 1.48) | 0.4271 | 1.00 (0.75, 1.33) | 0.9780 | 0.99 (0.74, 1.33) | 0.9576 |
| Q4       | 1.48 (1.14, 1.93) | 0.0038 | 1.10 (0.83, 1.45) | 0.5229 | 1.06 (0.79, 1.42) | 0.7058 |
| p for trend | 0.0015 | - | 0.3839 | - | 0.5650 | - |
| Females  |         |         |         |         |         |         |
| Q1       | 1.00 (refer) | - | 1.00 (refer) | - | 1.00 (refer) | - |
| Q2       | 1.30 (0.89, 1.91) | 0.1780 | 1.27 (0.87, 1.87) | 0.2163 | 1.31 (0.89, 1.93) | 0.1675 |
| Q3       | 1.79 (1.25, 2.56) | 0.0016 | 1.69 (1.18, 2.43) | 0.0046 | 1.77 (1.22, 2.57) | 0.0025 |
| Q4       | 1.58 (1.10, 2.28) | 0.0146 | 1.42 (0.97, 2.09) | 0.0716 | 1.51 (1.01, 2.26) | 0.0438 |
| p for trend | 0.0045 | - | 0.0315 | - | 0.0174 | - |
| Total    |         |         |         |         |         |         |
| Q1       | 1.00 (refer) | - | 1.00 (refer) | - | 1.00 (refer) | - |
| Q2       | 1.08 (0.86, 1.36) | 0.5177 | 1.03 (0.82, 1.30) | 0.8011 | 1.04 (0.82, 1.31) | 0.7459 |
| Q3       | 1.34 (1.08, 1.67) | 0.0089 | 1.22 (0.97, 1.52) | 0.0855 | 1.23 (0.98, 1.54) | 0.0799 |
| Q4       | 1.51 (1.22, 1.88) | 0.0002 | 1.20 (0.96, 1.50) | 0.1193 | 1.19 (0.94, 1.50) | 0.1511 |
| p for trend | < 0.0001 | - | 0.0554 | - | 0.0771 | - |

Notes: Serum uric acid quartiles (Q1–Q4) in MEN (Q1: < 335.40; Q2: 335.40–382.00; Q3: 382.01–435.20; and Q4: > 435.20 μ mol/L or Q1: < 5.63; Q2: 5.63–6.42; Q3: 6.43–7.31; and Q4: > 7.31 mg/dL). In women (Q1: < 237.30; Q2: 237.30–273.05; Q3: 273.06–316.30; and Q4: > 316.30 μ mol/L or Q1: < 3.99; Q2: 3.99–4.59; Q3: 4.60–5.31; and Q4: > 5.31 mg/dL). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein.

Model 1: Unadjusted.
Model 2: Adjusted for age, gender, BMI, SBP, DBP, FBG, diabetes, and hypertension.
Model 3: Adjusted for age, gender, BMI, SBP, DBP, FBG, diabetes, hypertension, eGFR, TG, TC, LDL, and HDL.
No adjustment for gender in men and women.
of high IOP in women, but not in men. There was no statistically significant relationship between uric acid and high IOP in the total population.

Figure 2 shows the dose–response relationships between SUA and the risk of high IOP. The association between SUA and the incidence of high IOP was modeled through multivariable-adjusted spline regression models with four knots, and revealed nonlinear dose–response relationships between SUA and high IOP in women ($P = 0.0171$). However, there was no significant linear or nonlinear dose–response relationship in men ($P = 0.1433$ or $P = 0.3906$). As can be seen from Figure 2, there was an inverted U-shaped nonlinear dose–response relationship between uric acid and high IOP in women.

**Subgroup Analysis for Association of SUA with Incident High Intraocular Pressure**

In subgroup analysis stratified by age, BMI, hypertension, and diabetes, there were statistically significant differences in the association between SUA and the incidence of high IOP among women. However, in men, there was no statistically significant difference in each subgroup analysis.

Table 3 shows the analysis of the relationship between SUA and high IOP by age, BMI, hypertension, and diabetes subgroup analysis in different groups. We could find that in women age $\leq 50$ years, after adjusting for BMI, SBP, DBP, FBG, hypertension, diabetes, eGFR, TG, TC, LDL, and HDL, the Q3 and Q4 of SUA were independent risk factors for the incidence of high IOP, Q1 as a reference. The OR with 95% CI for Q2 to Q4 were 1.45 (0.94, 2.22) with $P = 0.0914$, 1.79 (1.18, 2.73) with $P = 0.0066$ and 1.67 (1.05, 2.64) with $P = 0.0291$, respectively. There were no statistically significant differences in the association between SUA and the incidence of high IOP in women age $> 50$ years, and men age $\leq 50$ years. In the age subgroup analysis, there was a gender difference in the relationship between SUA and the incidence of high IOP, which was statistically significant in women and not statistically significant in men.

In women, BMI $\leq 25$ kg/m$^2$, after adjusting for age, SBP, DBP, FBG, hypertension, diabetes, eGFR, TG, TC, LDL, and HDL, the Q3 of SUA was an independent risk factor for the incidence of high IOP, Q1 as a reference. The OR with 95% CI for Q2 to Q4 were 1.28 (0.85, 1.93) with $P = 0.2443$, 1.59 (1.07, 2.39) with $P = 0.0235$ and 1.50 (0.97, 2.33) with $P = 0.3902$, respectively. There were no statistically significant differences in the association between SUA and the incidence of high IOP in men's BMI $\leq 25$ kg/m$^2$ and BMI $> 25$ kg/m$^2$. In the BMI subgroup analysis, there was a gender difference in the relationship between SUA and the incidence of high IOP, which was statistically significant in women and not statistically significant in men.

In women in the without hypertension subgroup, after adjusting for age, BMI, SBP, DBP, FBG, diabetes, eGFR, TG, TC, LDL, and HDL, the Q2 and Q3 of SUA were independent risk factors for the incidence of high IOP, Q1 as a reference. The OR with 95% CI for Q2 to Q4 were 1.61 (0.53, 4.87) with $P = 0.3968$, 2.82 (1.03, 7.72) with $P = 0.0440$, and 1.73 (0.63, 4.78) with $P = 0.2883$, respectively. There were no statistically significant differences in the association between SUA and the incidence of high IOP in women in the with or without hypertension subgroup, and in men in the with or without diabetes subgroup. In the hypertension subgroup analysis, there was a gender difference in the relationship between SUA and the incidence of high IOP, which was statistically significant in women and not statistically significant in men.

In women in the without diabetes subgroup, after adjusting for age, BMI, SBP, DBP, FBG, hypertension, diabetes, eGFR, TG, TC, LDL, and HDL, the Q3 of SUA was an independent risk factor for the incidence of high IOP, Q1 as a reference. The OR with 95% CI for Q2 to Q4 were 1.26 (0.85, 1.85) with $P = 0.0485$, 1.79 (1.18, 2.71) with $P = 0.0064$ and 1.70 (1.08, 2.68) with $P = 0.0214$, respectively. There were no statistically significant differences in the association between SUA and the incidence of high IOP in men in the with hyper-tension subgroup, and in men in the with or without hypertension subgroup. In the diabetes subgroup analysis, there was a gender difference in the relationship between SUA and the incidence of high IOP, which was statistically significant in women and not statistically significant in men.
the diabetes subgroup analysis, there was a gender difference in the relationship between SUA and the incidence of high IOP, which was statistically significant in women and not statistically significant in men.

There was no statistically significant difference between the interaction of various subgroup variables with uric acid and the incidence of high IOP ($P_{interaction} > 0.05$ all).

In the age subgroup analysis, which revealed linear dose–response relationships between uric acid and high IOP in women age < 50 years ($P = 0.0416$). In women age > 50 years, there were nonlinear dose–response relationships between uric acid and high IOP ($P = 0.0286$; Fig. 3). In women, the dose–response relationship between uric acid and high IOP was inverted U-shaped and this relationship might be affected by age.

In the BMI subgroup analysis, which revealed no linear dose–response relationships between SUA and high IOP in men BMI $\leq 25$ kg/m$^2$ and BMI $> 25$ kg/m$^2$ ($P = 0.1484$ and $P = 0.1255$), and in women BMI $\leq 25$ kg/m$^2$ and BMI $> 25$ kg/m$^2$ ($P = 0.1933$ and $P = 0.8763$; Fig. 4).

In the hypertension subgroup analysis, which revealed no linear dose–response relationships between SUA and high IOP in men with or without hypertension ($P = 0.1170$ and $P = 0.7106$), and in women with or without hypertension ($P = 0.5376$ and $P = 0.0513$; Fig. 5).

In the diabetes subgroup analysis, which revealed nonlinear dose–response relationships between uric acid and high IOP in women without diabetes ($P = 0.0156$; Fig. 6). In women without diabetes, there was a nonlinear dose–response relationship between uric acid and high IOP, and showing an inverted U-shape.

**DISCUSSION**

In this large retrospective cross-sectional study from hospital medical examination data, we found that the incidence of high IOP was positively association with SUA levels. Our study demonstrated that elevated SUA levels were an independent risk factor for high IOP after adjustment for other potential confounding risk factors in women. Moreover, there was an inverted U-shaped nonlinear dose–response relationship between higher SUA levels and the incidence of high IOP in women. These findings provided pivotal evidence that elevated SUA might increase high IOP risk and represented a potential therapeutic target in the primary prevention of high IOP.

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**Table 3. Subgroup Analysis of Adjusted ORs (95% CIs) of High Intraocular Pressure Incidence According to Uric Acid Quartiles**

| Subgroup | Uric Acid (μ mol/L) | Q1 | Q2 | Q3 | Q4 |
|----------|---------------------|----|----|----|----|
| **Males** |                     |    |    |    |    |
| Age, y   |                     |    |    |    |    |
| ≤ 50     | 1.00 (0.89, 1.27)    | 0.5107 | 0.98 (0.69, 1.39) | 0.9130 | 1.11 (0.79, 1.56) | 0.5632 | 0.4011 |
| > 50     | 1.00 (1.03, 1.75)    | 0.9046 | 1.18 (0.69, 2.01) | 0.5482 | 1.26 (0.73, 2.18) | 0.3999 | 0.3503 |
| BMI, kg/m$^2$ |                     |    |    |    |    |
| ≤ 25     | 1.00 (0.72, 1.65)    | 0.6869 | 1.10 (0.71, 1.70) | 0.6596 | 1.32 (0.83, 2.08) | 0.2398 | 0.2736 |
| > 25     | 1.00 (0.79, 1.52, 1.21) | 0.2758 | 0.97 (0.65, 1.44) | 0.8710 | 1.02 (0.70, 1.48) | 0.9168 | 0.5406 |
| Hypertension |                  |    |    |    |    |
| Yes      | 1.00 (0.84, 2.24)    | 0.2128 | 1.43 (0.87, 2.33) | 0.1580 | 1.39 (0.86, 2.24) | 0.1804 | 0.0684 |
| No       | 1.00 (0.50, 1.05)    | 0.0891 | 0.80 (0.56, 1.16) | 0.2398 | 0.89 (0.61, 1.29) | 0.5361 | 0.6978 |
| Diabetes |                     |    |    |    |    |
| Yes      | 1.00 (0.44, 2.12)    | 0.9391 | 0.82 (0.32, 2.10) | 0.6723 | 0.63 (0.25, 1.60) | 0.3516 | 0.3224 |
| No       | 1.00 (0.66, 1.26)    | 0.5815 | 1.02 (0.75, 1.40) | 0.8893 | 1.10 (0.81, 1.51) | 0.5446 | 0.3818 |
| **Females** |                  |    |    |    |    |
| Age, y   |                     |    |    |    |    |
| ≤ 50     | 1.00 (0.94, 2.22)    | 0.0914 | 1.79 (1.18, 2.73) | 0.0066 | 1.67 (1.05, 2.64) | 0.0291 | 0.0134 |
| > 50     | 1.00 (0.46, 2.73)    | 0.7943 | 2.18 (0.99, 4.79) | 0.0538 | 1.66 (0.74, 3.74) | 0.2230 | 0.1276 |
| BMI, kg/m$^2$ |                     |    |    |    |    |
| ≤ 25     | 1.00 (0.85, 1.93)    | 0.2443 | 1.59 (0.72, 3.09) | 0.0235 | 1.50 (0.97, 2.33) | 0.0700 | 0.0316 |
| > 25     | 1.00 (0.53, 4.87)    | 0.3968 | 2.82 (1.03, 7.72) | 0.0440 | 1.73 (0.65, 4.78) | 0.2883 | 0.3778 |
| Hypertension |                  |    |    |    |    |
| Yes      | 1.00 (0.19, 1.54)    | 0.2441 | 1.56 (0.68, 3.55) | 0.2926 | 0.99 (0.42, 2.33) | 0.9718 | 0.5805 |
| No       | 1.00 (1.00, 2.32)    | 0.0485 | 1.79 (1.18, 2.71) | 0.0064 | 1.70 (1.08, 2.68) | 0.0214 | 0.0147 |
| Diabetes |                     |    |    |    |    |
| Yes      | 1.00 (0.33, 1.52)    | 0.5815 | 1.72 (1.19, 2.50) | 0.0043 | 1.47 (0.98, 2.20) | 0.0635 | 0.0230 |
| No       | 1.00 (0.85, 1.85)    | 0.2502 | -    | -    | -    | -    | -    |

Notes: Serum uric acid quartiles (Q1–Q4) in men (Q1: < 335.40; Q2: 335.40–382.00; Q3: 382.01–435.20; and Q4: > 435.20 μ mol/L) or Q1: < 5.63; Q2: 5.63–6.42; Q3: 6.43–7.31; and Q4: > 7.31 mg/dL). In women (Q1: < 237.30; Q2: 237.30–273.05; Q3: 273.06–316.30; and Q4: > 316.30 μ mol/L or Q1: < 3.99; Q2: 3.99–4.59; Q3: 4.60–5.31; and Q4: > 5.31 mg/dL). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein.

Model: Adjusted for age, BMI, SBP, DBP, FBG, diabetes, hypertension, eGFR, TG, TC, LDL, and HDL. Corresponding factors were not adjusted for each subgroup.
Although the pathological mechanisms between systemic inflammation and IOP were unclear, studies have suggested that glaucoma was associated with oxidative stress, mitochondrial damage, inflammation, endothelial dysfunction, and hypoxia. In vitro and in vivo findings suggested that uric acid may contribute to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production. Endothelial dysfunction was characterized by the alteration of the vascular lining, was prone to prothrombotic, pro-inflammatory, and proconstrictive. In addition, the collagen bundles of the trabecular meshwork were covered by endothelial cells, and the extracellular matrix (ECM) filled the space between the beams. Mucopolysaccharides of endothelial cells were related to macrophage function and were involved in the components of the ECM. The change in the ECM might lead to an increase in the resistance of the trabecular meshwork, resulting in a decrease in outflow, which might induce high IOP. Our results supported the view that systemic inflammation might lead to increased IOP. Previous studies have shown that there were important associations between systemic endothelial dysfunction and open-angle glaucoma. Our study found that the possible mechanism of the relationship between uric acid and IOP was related to uric acid-induced endothelial dysfunction.

Uric acid induced hepatic fat accumulation and insulin resistance through NLRP3 inflammasome activation. Recent studies have shown that insulin resistance, obesity, and hepatic steatosis were independent risk factors for elevated IOP. In addition, insulin resistance might contribute to an explanation that would account for many previous findings concerning the association among IOP and obesity, hypertension, and diabetes. Therefore, we speculated that the possible mechanism of the association between elevated uric acid and high IOP might include fatty liver degeneration and insulin resistance, except inflammation and endothelial dysfunction.

Previous studies have shown that the prevalence of glaucoma in men was higher than that in women. This study was consistent with previous research results in which the incidence of high IOP was 3.96% in men and 3.31% in women. Although studies have shown that IOP was associated with cardiovascular risk factors, the results were inconsistent. Most studies have shown a positive correlation between age and IOP. In contrast, studies have found that IOP tended to decrease with age. Other studies suggested that there was an inverted U-shaped relationship between age and IOP. In our study, the incidence of high IOP also decreased with age, and there was a gender difference in the relationship between elevated SUA and high IOP only in women. Our results were consistent with previous studies. Although IOP was affected by age, in order to exclude the effect of age on high IOP, we adjusted the age in the statistical analysis and also performed a subgroup analysis of age. We found that there was no interaction between age and uric acid for high IOP.
FIGURE 4. In the BMI subgroups, association of SUA with the incidence of high intraocular pressure according to restricted cubic spline regressions using four knots in men and women (percentiles 5, 35, 65, and 95), with the reference point set at percentile 12.5. (a–d) Odds ratios were adjusted for age, SBP, DBP, FBG, hypertension, diabetes, eGFR, TG, TC, LDL, and HDL, respectively.

Therefore, we could suggest that there was an association between elevated SUA and high IOP in women age ≤ 50 years. The mechanism of the association between uric acid and high IOP in women age ≤ 50 years is not clear, it may be the effect of different dietary habits, lifestyle, and hormones, and more research is needed to confirm this result.

Previous studies have found that IOP was higher in women than in men, but the converse was reported in some studies of Asian populations. In our study, although the incidence of high IOP in men was higher than that in women, after adjusting for cardiovascular risk factors, gender was not an independent factor for IOP. Moreover, we found that elevated SUA was an independent factor for high IOP in women but not in men. We suggested that there was a gender difference in the association between uric acid and high IOP. Hormone differences may play a role in gender differences in the association between uric acid and IOP.

Several studies have shown a relationship between BMI and IOP; however, the results have been inconsistent. Some studies have shown that BMI was associated with high IOP, but other studies have shown that BMI was not related to high IOP. In our study, we performed BMI subgroup analysis, and, after adjusting other confounding factors, the Q3 of uric acid was an independent risk factor for high IOP in women, but not in men. Although, we found that there was no interaction between BMI and uric acid on the incidence of high IOP. Therefore, we could suggest that there was an association between elevated SUA and high IOP in women BMI ≤ 25 kg/m² or BMI > 25 kg/m², and the association between uric acid and high IOP was not affected by BMI. Because there are few studies on the relationship between uric acid and IOP, the specific mechanism is not yet clear, and more studies are needed to confirm this result.

Several studies showed that the high IOP was associated with diabetes mellitus and systemic hypertension. Therefore, during the statistical analysis, we adjusted for confounding factors, such as hypertension, diabetes, BMI, blood lipids, and further performed subgroup analysis. We found that there was a statistically significant association between elevated uric acid and high IOP in women without diabetes or without hypertension, this association was not found in other subgroups, because there was no previous study on uric acid and IOP, and only few researches on uric acid and glaucoma. Then we thought possible explanations were that uric acid was a risk factor for metabolic and cardiovascular diseases, and metabolic syndrome was an important intermediate factor. Therefore, we suggested that there were several possible mechanisms between uric acid and IOP, such as inflammation, oxidative stress, endothelial dysfunction, and insulin resistance. Moreover, our study found that the relationship between uric acid and high IOP was statistically significant, and there were gender differences. It could provide practical significance for the clinic. At the same time, more attention should be paid to the uric acid.
Uric Acid and High Intraocular Pressure

FIGURE 5. In the hypertension subgroups, association of SUA with the incidence of high intraocular pressure according to restricted cubic spline regressions using four knots in men and women (percentiles 5, 35, 65, and 95), with the reference point set at percentile 12.5. (a-d) Odds ratios were adjusted for age, BMI, SBP, DBP, FBG, diabetes, eGFR, TG, TC, LDL, and HDL, respectively.

Acid levels of nondiabetic or nonhypertensive women and further IOP examinations should be performed in the physical examination population. Furthermore, it can also provide reference value to the prevention and control of glaucoma.

This study finally included 19,147 people, which was including 5781 people who had IOP values. Others were recorded as high IOP. As there was good correlation between the measurements in both eyes, only the readings from the right eye were used for analysis ($r = 0.7798$, $P < 0.0001$). Among men, the mean value of the right IOP was $14.75 \pm 4.26$ mm Hg, and the range of right IOP was $7.00$ to $43.00$ mm Hg. The median (interquartile range) right IOP of the participants was $14.00$ mm Hg ($11.00, 18.00$ mm Hg). Among women, the mean value of the right IOP was $14.33 \pm 4.16$ mm Hg, and the range of right IOP was $7.00$ to $31.00$ mm Hg. The median (interquartile range) right intraocular pressure of the participants was $14.00$ mm Hg ($11.00, 17.00$ mmHg; Supplementary Table S1). We used right IOP as a continuous variable to analyze the relationship between uric acid and IOP, and the results are shown in Supplementary Table S2. The results of linear regression were basically consistent with the results in our paper. However, the IOP values were skewed distribution, and the residuals in the linear model were non-normally distributed in men, women, and total (all normality test $P < 0.01$). The distribution of age and right IOP in the total population are shown in Supplementary Figure S1 and Figure S2. Therefore, our study was not suitable for multiple linear regression analysis with continuous IOP values.

We classified 5781 people with IOP values into two categories, and the right IOP $> 21$ mm Hg was defined as high IOP. The univariate and multivariate logistic regression results between high IOP and uric acid are shown in Supplementary Table S3. This result was consistent with the result in our paper. In addition, among people with IOP, there was also an inverted U-shaped relationship between uric acid and high IOP in women (Supplementary Fig. S3).

There were still some limitations in this study. First, given the cross-sectional design, we could not establish a causal relationship between SUA elevation and high IOP. Second, the study results obtained from a retrospective observational analysis, uric acid measurements, and questionnaire-based information might have inaccuracies. Third, our research data did not include corneal thickness, which may have some influences on the relationship between uric acid and high IOP. Moreover, our participants were from healthy medical examiners with a large sample size, men and women were analyzed separately, which ensured sufficient parameters and accurate results, and drew a solid conclusion that there was a difference between men and women. Finally, a future prospective study is needed to determine whether the serum uric acid level is an independent predictor of long-term high IOP outcomes, and whether its reduction could reduce the occurrence of adverse high IOP events.
**Figure 6.** In the diabetes subgroups, association of SUA with the incidence of high intraocular pressure according to restricted cubic spline regressions using four knots in men and women (percentiles 5, 35, 65, and 95), with the reference point set at percentile 12.5. (a–c) Odds ratios were adjusted for age, BMI, SBP, DBP, FBG, hypertension, eGFR, TG, TC, LDL, and HDL, respectively.

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