Increased Impact of Serum Uric Acid on Arterial Stiffness and Atherosclerosis in Females

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Aims: Serum uric acid increases with metabolic disorders; however, whether the effects of uric acid on atherosclerosis are different in females and males has not been sufficiently evaluated. Therefore, this study compared the impact of uric acid on arterial stiffness and atherosclerosis between females and males.

Methods: We enrolled 10196 untreated middle-aged subjects (46 ± 8 years, 3021 females and 7175 males) who underwent periodic health check-ups. Serum uric acid levels were measured and arterial stiffness and atherosclerosis were assessed by the cardio-ankle vascular index (CAVI), carotid intima-media thickness (IMT), and plaque, using ultrasound imaging.

Results: Females with increased arterial stiffness (CAVI ≥ 8.0) or carotid plaques had higher uric acid than those without (P<0.0001), but males did not. In multivariable regression analyses including overall participants, uric acid was significantly associated with the CAVI, where sex interacted with uric acid. In sex-specific analyses, uric acid was significantly associated with the CAVI, but not with carotid IMT, in both sexes. However, logistic regression analyses revealed that serum uric acid was independently associated with the presence of carotid plaques in females. The exclusion of subjects with abdominal obesity or metabolic syndrome from the analysis did not alter the results in females.

Conclusions: Serum uric acid was significantly associated with the CAVI in both sexes, but the interaction of sex was confirmed and associated with a carotid plaque only in females. These findings support the increased impact of serum uric acid on arterial stiffness and atherosclerosis in females.

Key words: Uric acid, Female, Sex difference, Atherosclerosis, Carotid plaque

Introduction

Uric acid is a major metabolic product of purines, whether they are obtained from the diet or produced endogenously. An increased serum uric acid level (hyperuricemia) is a classical risk factor for gout, one of the most common forms of arthritis1-4. Hyperuricemia is associated with lifestyles and metabolic disorders5-7, and accumulating evidence from epidemiological studies has supported an association between hyperuricemia and metabolic syndrome8-15. As hyperuricemia often occurs concurrently with metabolic syndrome and each of its components, hyperuricemia has been suggested as a candidate risk factor for metabolic syndrome16-18. Consequently, the serum uric acid level may serve as a
Uric Acid and Atherosclerosis in Females

Uric acid is synthesized from xanthine, through an enzymatic modification of xanthine oxidase. In physiological conditions, uric acid is an antioxidant. However, in pathological conditions, high uric acid levels were positively associated with oxidative stress, through the production of excess reactive oxygen species (ROS)\(^{19-21}\). Several studies have demonstrated that serum uric acid was related to vascular function and arterial stiffness, and that increased uric acid contributed to impaired vascular function and atherosclerosis progression\(^{22-27}\). Although the relationship between uric acid and atherosclerotic examinations has been reported, these associations were inconclusive, especially by sex\(^{28-30}\). Some previous Japanese studies showed a positive association between uric acid and arterial stiffness in both sexes\(^{22, 24}\), whereas others reported a sex-specific association\(^{28-30}\). Similarly, sex differences in the association between uric acid and carotid atherosclerosis remain controversial\(^{31, 32}\). Herein, we hypothesized that the impact of uric acid on arterial stiffness and morphological atherosclerosis could be different between the sexes. Thus, this study aimed to investigate the impact of uric acid on arterial stiffness and morphological atherosclerotic parameters, from the viewpoint of sex. To that end, we compared these features between females and males, in a group of untreated, middle-aged subjects without apparent cardiovascular diseases.

**Methods**

This study enrolled subjects who attended periodic physical check-ups. The study was performed in accordance with the principles of the Declaration of Helsinki, and the ethics committees of the Toyota Memorial Hospital approved the protocol. All data used in the analysis were anonymized, and opt-out opportunities were provided for participants.

**Subjects**

This study screened 15764 individuals who visited the Health Support Center, WELPO, for a periodic health check-up. The center provided healthcare for Toyota Motor Corporation (Toyota, Japan) employees and spouses. All employees receive annual medical examinations, in accordance with the Industrial Safety and Health Law of Japan. This study retrieved the data available in medical examination records. Of the 15764 individuals screened, 2312 were excluded, because of renal insufficiency (serum creatinine \(>1.5\) mg/dL), low ankle-brachial index (\(< 0.9\)), or missing data (including atherosclerotic examination findings). To eliminate the effects of medications, we excluded 3256 individuals who were taking medications for hypertension, dyslipidemia, diabetes, or hyperuricemia and gout, or with a history of atherosclerotic cardiovascular disease, heart failure, or frequent arrhythmia, such as atrial fibrillation and atrial flutter. Thus, the final analyses included 10196 untreated subjects.

After an overnight fast, participants’ body height and weight were measured using an automated BF-220 instrument (Tanita, Tokyo, Japan). Systolic and diastolic blood pressure (BP) was measured in a seated position with a validated oscillometric technique. Blood samples were drawn from the antecubital vein in the morning for laboratory measurements. The cardio-ankle vascular index (CAVI) and carotid intima-media thickness (IMT) were measured to assess subclinical atherosclerosis. The CAVI was measured in a supine position to evaluate peripheral artery disease or arterial stiffness. Next, an ultrasound examination was performed to measure carotid IMT.

Subjects with a systolic BP \(\geq 140\) mmHg and/or diastolic BP \(\geq 90\) mmHg were diagnosed with hypertension\(^{33}\). Subjects with high-density lipoprotein cholesterol (HDL-C) levels \(<40\) mg/dL, low-density lipoprotein cholesterol (LDL-C) levels \(\geq 140\) mg/dL, or triglycerides \(\geq 150\) mg/dL were diagnosed with dyslipidemia\(^{34}\). Subjects with a fasting blood glucose (FBG) level \(\geq 126\) mg/dL were diagnosed with diabetes\(^{35}\). Abdominal obesity was defined as a waist circumference \(\geq 85\) cm for men and \(\geq 90\) cm for women\(^{18}\). Metabolic syndrome was diagnosed on the basis of either abdominal obesity and two or more of the following three criteria: (1) triglycerides \(\geq 150\) mg/dL and/or HDL-C \(<40\) mg/dL; (2) systolic BP \(\geq 130\) mmHg and/or diastolic BP \(\geq 85\) mmHg; and (3) FBG \(\geq 110\) mg/dL\(^{19}\). Individuals who had a habit of cigarette smoking or alcohol drinking at the time of the current examination were defined as current smokers or alcohol drinkers. As information regarding menopausal status could not be obtained, we defined age over 50 years as postmenopausal status using the Japanese standard menopausal age (50 years)\(^{36}\).

**Biochemical Analyses**

Biochemical tests included determinations of total cholesterol, LDL-C, HDL-C, triglycerides, creatinine, FBG, and uric acid. These tests were performed with standard laboratory assays, as described previously\(^{37}\). Concentrations of glycated hemoglobin A1c were measured using high-performance liquid chromatography. Results are expressed according to the National Glycohemoglobin
Assessment of Arterial Stiffness

Arterial stiffness was assessed with the CAVI, measured using a Vasera VS-1000 automatic system (Fukuda Denshi, Tokyo, Japan), as described previously. Briefly, after resting in the supine position, electrocardiogram electrodes and a microphone were placed on both wrists and the sternum to detect heart sounds. Cuffs were wrapped around both upper arms and both ankles. Then, the distance was measured from the aortic valve to the ankle artery (daa). Next, the difference was calculated between the time that the pulse waves were transmitted to the brachium (PWb) and the time they were transmitted to the ankle (PWa). Then, we calculated the time difference between the second heart sound on the phonocardiogram (hsP) and that on the notch of the brachial pulse wave (hsB). With these variables, the cardio-ankle pulse wave velocity (PWV) was calculated, as follows:

\[ PWV (\text{cm/s}) = \frac{daa}{(PWb - PWa) + (hsP - hsB)} \]

Finally, the CAVI was expressed as the stiffness parameter, \( \beta \), according to the following equation:

\[ \text{CAVI} = a \left( \frac{2\rho}{PP} \times \left[ \ln \frac{Ps}{Pd} \right] \right)^{\frac{1}{3}} + b, \]

where \( a \) and \( b \) are constants, \( \rho \) is the blood density, \( PP \) is the pulse pressure, \( Ps \) is the systolic pressure, and \( Pd \) is the diastolic pressure. The mean CAVI of the left and right parts of the body was used in the analyses. We considered a CAVI value \( \geq 8.0 \) as increased arterial stiffness predicting subclinical atherosclerosis.

Assessment of Carotid IMT and Plaque

The carotid artery IMT was assessed on ultrasound images acquired with the Aplio 500 device (Canon Medical Systems, Otawara, Japan), as described previously. All estimations of carotid IMT and plaques were performed by well-trained clinical laboratory technicians who were blinded to other clinical information. The common carotid artery (CCA) IMT and the presence of a plaque were evaluated manually with a 7.5-MHz frequency probe, with the subject in the supine position. The CCA IMT was measured in the far wall at \( \approx 20 \) mm from the carotid bifurcation, identified in recorded ultrasound images of the carotid artery. The mean IMT of both sides was used in the analysis. A carotid plaque, which is representative of subclinical atherosclerosis, was identified as an elevated lesion with a maximum thickness \( \geq 1.1 \) mm and a point of inflection on the surface of the intima-media complex in the CCA, carotid bulb, and internal carotid artery. The presence of a carotid plaque was taken as the representation of subclinical atherosclerosis.

Statistical Analyses

Data were analyzed using SPSS Statistics 19 (IBM Corp., Chicago, IL, USA). Data that were normally distributed are expressed as the mean ± standard deviation. Comparative analyses of continuous variables were performed using \( t \)-tests. Sex, smoking, and drinking status were considered dichotomous variables, with a value of 0 for males, non-smokers, and non-drinkers; or 1 for females, current smokers, and habitual drinkers. Correlations among continuous variables were analyzed using Pearson's correlation (\( r \)). Differences in continuous variables among more than three groups were tested using analysis of variance (ANOVA), followed by Scheffe's post hoc analysis. Multivariable regression analyses were performed to determine associations between the serum uric acid and CAVI or carotid IMT. Multivariable logistic regression analyses were performed to evaluate the contribution of serum uric acid to an increased arterial stiffness in a CAVI value \( \geq 8.0 \) or the presence of a carotid plaque. A two-tailed \( P \) value \(< 0.05 \) was considered significant.

Results

This study enrolled 10196 untreated subjects, including 3021 females and 7175 males, aged 35–65 years (Table 1). Males were younger and had a higher body mass index (BMI) and uric acid than females, and CAVI and IMT values were higher in males than females, similar to the proportion of individuals with increased arterial stiffness or the presence of carotid plaques. The number of subjects with increased arterial stiffness or a carotid plaque was 329 (10.9%) and 315 (10.4%) in females, and 1272 (17.7%) and 1070 (14.9%) in males, respectively. The characteristics of subjects with increased arterial stiffness or with a carotid plaque are presented in Table 1. In both sexes, subjects with abdominal obesity or metabolic syndrome had significantly higher uric acid levels than those without (Fig. 1a, 1b). In males, uric acid levels were higher in alcohol drinkers than in non-drinkers but were lower in current smokers than in non-smokers (Fig. 1c, 1d). On the other hand, in females, uric acid levels were higher in smokers than in non-smokers (Fig. 1c, 1d). Similarly, females with increased arterial stiffness (CAVI \( \geq 8.0 \)) or those with the presence of carotid plaques had higher uric acid levels than those without; however, such differences were not observed in males (Fig. 1e, 1f).

In relationships of each parameter and
Table 1. Characteristics of enrolled subjects

| Characteristic                  | All participants (n=10196) | Females (n=3021) | Males (n=7175) |
|--------------------------------|-----------------------------|------------------|----------------|
| Age (years)                    | 46.2 ± 7.8                  | 48.5 ± 6.2       | 45.2 ± 8.2*    |
| BMI (kg/m²)                    | 22.6 ± 3.1                  | 21.7 ± 3.3       | 22.9 ± 3.0*    |
| Waist circumference (cm)       | 80.7 ± 8.6                  | 77.9 ± 9.1       | 81.9 ± 8.1*    |
| Systolic BP (mmHg)             | 119 ± 15                    | 120 ± 18         | 118 ± 16**     |
| Diastolic BP (mmHg)            | 75 ± 10                     | 73 ± 11          | 75 ± 9*        |
| Creatinine (mg/dL)             | 0.75 ± 0.14                 | 0.61 ± 0.09      | 0.81 ± 0.12*   |
| BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; CAVI, cardio-ankle vascular index; IMT, intima-media thickness. Increased arterial stiffness indicates a CAVI value ≥ 8.0. Abdominal obesity was defined as waist circumference ≥ 90 cm for females and ≥ 85 cm for males. Metabolic syndrome was diagnosed on the basis of abdominal obesity and two or more of the following three criteria: (1) triglycerides ≥ 150 mg/dL and/or HDL-C < 40 mg/dL; (2) systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; and (3) FBG ≥ 110 mg/dL.

Fig. 1. Impacts of having (a) abdominal obesity, (b) metabolic syndrome, (c) alcohol drinking, (d) current smoking, (e) increased arterial stiffness (CAVI value ≥ 8.0), and (f) the presence of carotid plaques, on serum uric acid levels in each sex.
was analyzed as quartiles of its serum levels in each sex (first quartile \([Q1]\), \(≤ 3.6\) mg/dL in females and \(≤ 5.1\) mg/dL in males; second quartile \([Q2]\), 3.7–4.1 mg/dL in females and 5.2–5.8 mg/dL in males; third quartile

\[\text{Table 2. Correlation of each parameter and atherosclerotic examinations in all participants (}\text{\(n=10196\)}, \text{females (}\text{\(n=3021\)}, \text{and males (}\text{\(n=7175\)})}\]

| Variable                                      | CAVI         | Carotid IMT               |
|-----------------------------------------------|--------------|---------------------------|
|                                               | Coefficient (r) | P value | Coefficient (r) | P value |
| All participants (\(n=10196\))               |              |                |                |                |
| Uric acid (mg/dL)                             | 0.109        | <0.0001        | 0.064          | <0.0001        |
| Age (years)                                   | 0.452        | <0.0001        | 0.421          | <0.0001        |
| BMI (kg/m²)                                   | -0.147       | <0.0001        | 0.174          | <0.0001        |
| Waist circumference (cm)                      | -0.025       | <0.05          | 0.199          | <0.0001        |
| Systolic BP (mmHg)                            | 0.195        | <0.0001        | 0.204          | <0.0001        |
| Diastolic BP (mmHg)                           | 0.195        | <0.0001        | 0.180          | <0.0001        |
| Creatinine (mg/dL)                            | 0.106        | <0.0001        | 0.060          | <0.0001        |
| HDL-C (mg/dL)                                 | -0.025       | <0.05          | -0.084         | <0.05          |
| LDL-C (mg/dL)                                 | 0.050        | <0.0001        | 0.152          | <0.0001        |
| Triglyceride (mg/dL)                          | 0.071        | <0.0001        | 0.080          | <0.0001        |
| FBG (mg/dL)                                   | 0.197        | <0.0001        | 0.184          | <0.0001        |
| HaA1c (%)                                     | 0.182        | <0.0001        | 0.192          | <0.0001        |
| Current smoking (% of total)                  | 0.122        | <0.0001        | 0.061          | <0.0001        |
| Alcohol drinking (% of total)                 | 0.038        | <0.001         | -0.023         | <0.05          |
| Sex female (% of total)                       | -0.180       | <0.0001        | -0.050         | <0.0001        |
| Females (\(n=3021\))                         |              |                |                |                |
| Uric acid (mg/dL)                             | 0.170        | <0.0001        | 0.163          | <0.0001        |
| Age (years)                                   | 0.468        | <0.0001        | 0.416          | <0.0001        |
| BMI (kg/m²)                                   | -0.087       | <0.0001        | 0.195          | <0.0001        |
| Waist circumference (cm)                      | 0.261        | <0.0001        | 0.021          | 0.249          |
| Systolic BP (mmHg)                            | 0.280        | <0.0001        | 0.290          | <0.0001        |
| Diastolic BP (mmHg)                           | 0.236        | <0.0001        | 0.225          | <0.0001        |
| Creatinine (mg/dL)                            | -0.023       | 0.056          | -0.004         | 0.812          |
| HDL-C (mg/dL)                                 | 0.023        | 0.204          | -0.117         | <0.0001        |
| LDL-C (mg/dL)                                 | 0.190        | <0.0001        | 0.238          | <0.0001        |
| Triglyceride (mg/dL)                          | 0.165        | <0.0001        | 0.200          | <0.0001        |
| FBG (mg/dL)                                   | 0.187        | <0.0001        | 0.150          | <0.0001        |
| HaA1c (%)                                     | 0.211        | <0.0001        | 0.175          | <0.0001        |
| Current smoking (% of females)                | 0.052        | <0.0001        | 0.025          | 0.174          |
| Alcohol drinking (% of females)               | -0.002       | 0.853          | -0.027         | <0.05          |
| Males (\(n=7175\))                           |              |                |                |                |
| Uric acid (mg/dL)                             | -0.040       | <0.001         | 0.008          | 0.498          |
| Age (years)                                   | 0.523        | <0.0001        | 0.449          | <0.0001        |
| BMI (kg/m²)                                   | -0.229       | <0.0001        | 0.157          | <0.0001        |
| Waist circumference (cm)                      | 0.254        | <0.0001        | -0.108         | <0.0001        |
| Systolic BP (mmHg)                            | 0.166        | <0.0001        | 0.168          | <0.0001        |
| Diastolic BP (mmHg)                           | 0.166        | <0.0001        | 0.156          | <0.0001        |
| Creatinine (mg/dL)                            | 0.004        | 0.834          | 0.048          | <0.0001        |
| HDL-C (mg/dL)                                 | 0.051        | <0.0001        | -0.084         | <0.05          |
| LDL-C (mg/dL)                                 | 0.005        | 0.702          | 0.122          | <0.0001        |
| Triglyceride (mg/dL)                          | 0.005        | 0.664          | 0.041          | <0.001         |
| FBG (mg/dL)                                   | 0.189        | <0.0001        | 0.199          | <0.0001        |
| HaA1c (%)                                     | 0.211        | <0.0001        | 0.207          | <0.0001        |
| Current smoking (% of males)                  | 0.069        | <0.0001        | 0.052          | <0.0001        |
| Alcohol drinking (% of males)                 | -0.048       | <0.01          | -0.070         | <0.001         |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HaA1c, hemoglobin A1c.

atherosclerotic examinations, uric acid was positively correlated with both the CAVI and carotid IMT in all participants or females, but such positive correlations were not shown in males (Table 2). When uric acid
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levels were significantly associated with the CAVI in both sexes after adjustment for potential confounders, whereas no significant association between uric acid and carotid IMT was observed in both sexes (Table 4).

Then, to investigate whether menopausal age interacts with uric acid in the association between uric acid and atherosclerotic examinations, we divided subjects into ages under 50 years and over 50 years (Supplementary Table 2). Serum uric acid was higher in females over 50 years than in those under 50 years. Furthermore, in females, age over 50 years interacted with uric acid in the association between uric acid and the CAVI, but such an association was not observed in males (Supplementary Table 3). Multivariable regression analysis showed a significant association between uric acid and the CAVI only in females aged over 50 years, but not in those less than 50 years (Supplementary Table 4).

Next, to investigate the relationship between uric acid and increase of arterial stiffness or the presence of carotid plaques in females and males, we performed multivariable logistic regression analyses, with the endpoint of increased arterial stiffness (CAVI ≥ 8.0) or the presence of carotid plaques (Table 5). Uric acid levels were significantly associated with the CAVI in both sexes after adjustment for potential confounders, whereas no significant association between uric acid and carotid IMT was observed in both sexes (Table 4).

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In a sex-specific subanalysis, serum uric acid levels were significantly associated with the CAVI in both sexes after adjustment for potential confounders, whereas no significant association between uric acid and carotid IMT was observed in both sexes (Table 4). Then, to investigate whether menopausal age interacts with uric acid in the association between uric acid and atherosclerotic examinations, we divided subjects into ages under 50 years and over 50 years (Supplementary Table 2). Serum uric acid was higher in females over 50 years than in those under 50 years. Furthermore, in females, age over 50 years interacted with uric acid in the association between uric acid and the CAVI, but such an association was not observed in males (Supplementary Table 3). Multivariable regression analysis showed a significant association between uric acid and the CAVI only in females aged over 50 years, but not in those less than 50 years (Supplementary Table 4).

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In subgroup analyses excluding subjects with metabolic syndrome, associations similar to the analyses not excluding metabolic syndrome were observed between uric acid and increased arterial stiffness or the presence of carotid plaques (Supplementary Table 7). Subgroup analyses excluding subjects with abdominal obesity showed a consistent association between uric acid and increased arterial stiffness in females, but the association was attenuated in males (Supplementary Table 8).

Discussion

The main findings of this study were as follows: (i) females with increased arterial stiffness or carotid plaques had higher uric acid than those without, but...
Atherosclerosis are greater in females than in males. Interestingly, although uric acid and the CAVI or increased arterial stiffness was significantly associated in both sexes, we found an interaction of sex in the association between uric acid and the CAVI or increased arterial stiffness. Indeed, the correlation coefficient ($\beta$) and OR in the relationship between uric acid and the CAVI was higher in females than in males. Previous cross-sectional and longitudinal studies supported a positive association between uric acid and arterial stiffness\textsuperscript{22-27}. However, several studies have shown that the association between uric acid and arterial stiffness was

### Table 4. Multivariable regression analysis showing the possible association between uric acid and cardio-ankle vascular index or carotid intima-media thickness, evaluated separately in females ($n = 3021$) and males ($n = 7175$)

#### a) Females ($n = 3021$)

| Variable          | CAVI         |        | Carotid IMT   |        |
|-------------------|--------------|--------|---------------|--------|
|                   | Standardized coefficient ($\beta$) | $P$ value | Standardized coefficient ($\beta$) | $P$ value |
| Uric acid (mg/dL) | 0.080        | $<0.0001$ | 0.014         | 0.458  |
| Age (years)       | 0.383        | $<0.0001$ | 0.341         | $<0.0001$ |
| BMI (kg/m$^2$)    | -0.291       | $<0.0001$ | 0.057         | $<0.01$ |
| Systolic BP (mmHg)| 0.211        | $<0.0001$ | 0.152         | $<0.0001$ |
| Creatinine (mg/dL)| 0.013        | 0.419   | 0.015         | 0.382   |
| HDL-C (mg/dL)     | -0.013       | 0.449   | -0.066        | $<0.001$ |
| LDL-C (mg/dL)     | 0.010        | 0.585   | 0.044         | $<0.05$ |
| Triglyceride (mg/dL)| 0.058    | $<0.01$  | 0.019         | 0.343   |
| FBG (mg/dL)       | 0.109        | $<0.0001$ | -0.006        | 0.728   |
| Current smoking   | 0.063        | $<0.0001$ | 0.021         | 0.192   |
| Alcohol drinking  | 0.005        | 0.745   | 0.001         | 0.938   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose

Listed variables were simultaneously evaluated in the multivariable regression analysis.

#### a) Males ($n = 7175$)

| Variable          | CAVI         |        | Carotid IMT   |        |
|-------------------|--------------|--------|---------------|--------|
|                   | Standardized coefficient ($\beta$) | $P$ value | Standardized coefficient ($\beta$) | $P$ value |
| Uric acid (mg/dL) | 0.043        | $<0.0001$ | -0.013        | 0.235  |
| Age (years)       | 0.479        | $<0.0001$ | 0.431         | $<0.0001$ |
| BMI (kg/m$^2$)    | -0.290       | $<0.0001$ | 0.145         | $<0.0001$ |
| Systolic BP (mmHg)| 0.138        | $<0.0001$ | 0.075         | $<0.0001$ |
| Creatinine (mg/dL)| 0.004        | 0.676   | 0.039         | $<0.001$ |
| HDL-C (mg/dL)     | -0.052       | $<0.0001$ | -0.017        | 0.164   |
| LDL-C (mg/dL)     | -0.007       | 0.509   | 0.024         | $<0.05$ |
| Triglyceride (mg/dL)| 0.024    | $<0.05$  | -0.033        | $<0.01$ |
| FBG (mg/dL)       | 0.073        | $<0.0001$ | 0.032         | $<0.01$ |
| Current smoking   | 0.081        | $<0.0001$ | 0.087         | $<0.0001$ |
| Alcohol drinking  | -0.016       | 0.102   | -0.023        | $<0.05$ |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose

Listed variables were simultaneously evaluated in the multivariable regression analysis.
that study, implying that the impact of uric acid on arterial stiffness could be different in females and males.

Although the detailed mechanisms underlying these sex differences related to uric acid were not elucidated, plasma estrogen could be a candidate. Plasma estrogen suppresses renal proximal tubular urate reabsorption by organic anion transporters and promotes the renal clearance of uric acid. Indeed, serum uric acid levels are maintained at lower levels in females than in males, and thus, females could be sex-specific. For example, some studies reported a significant association between uric acid and arterial stiffness in females but not in males, and another longitudinal study reported the opposite finding. These studies had different sample sizes, were conducted in different nations, and employed different analytical methods. A cross-sectional study on a Japanese population comprising large samples of each sex showed that uric acid and the CAVI were significantly associated in both sexes, however, females were more sensitive to uric acid than males in

| Variable                  | Increased arterial stiffness (CAVI ≥ 8.0) | Presence of carotid plaques |
|---------------------------|-----------------------------------------|-----------------------------|
|                           | Odds ratio (95% CI)                      | P value                     |
| Uric acid (mg/dL)         | 1.302 (1.129 – 1.501)                   | 1.181 (1.032 – 1.352)       |
| Age (years)               | 1.155 (1.125 – 1.184)                   | 1.095 (1.070 – 1.120)       |
| BMI (kg/m²)               | 0.874 (0.833 – 0.918)                   | 0.977 (0.937 – 1.020)       |
| Systolic BP (mmHg)        | 1.033 (1.025 – 1.040)                   | 1.011 (1.004 – 1.018)       |
| Creatinine (mg/dL)        | 0.296 (0.072 – 1.214)                   | 1.402 (0.366 – 5.274)       |
| HDL-C (mg/dL)             | 1.001 (0.991 – 1.009)                   | 0.989 (0.980 – 0.998)       |
| LDL-C (mg/dL)             | 1.001 (0.997 – 1.005)                   | 1.009 (1.004 – 1.013)       |
| Triglyceride (mg/dL)      | 1.002 (1.000 – 1.005)                   | 0.999 (0.996 – 1.002)       |
| FBG (mg/dL)               | 1.011 (1.005 – 1.018)                   | 1.007 (1.001 – 1.013)       |
| Current smoking           | 1.520 (0.912 – 2.535)                   | 1.839 (1.181 – 2.865)       |
| Alcohol drinking          | 0.834 (0.633 – 1.098)                   | 0.918 (0.707 – 1.192)       |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose. The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Listed variables were simultaneously evaluated in the multivariable analysis.

| Variable                  | Increased arterial stiffness (CAVI ≥ 8.0) | Presence of carotid plaques |
|---------------------------|-----------------------------------------|-----------------------------|
|                           | Odds ratio (95% CI)                      | P value                     |
| Uric acid (mg/dL)         | 1.078 (1.012 – 1.147)                   | 1.002 (0.942 – 1.066)       |
| Age (years)               | 1.155 (1.144 – 1.167)                   | 1.121 (1.111 – 1.131)       |
| BMI (kg/m²)               | 0.836 (0.810 – 0.863)                   | 0.989 (0.962 – 1.018)       |
| Systolic BP (mmHg)        | 1.029 (1.024 – 1.035)                   | 1.012 (1.007 – 1.017)       |
| Creatinine (mg/dL)        | 1.076 (0.575 – 2.011)                   | 0.519 (0.278 – 0.970)       |
| HDL-C (mg/dL)             | 0.994 (0.989 – 0.999)                   | 0.993 (0.987 – 0.998)       |
| LDL-C (mg/dL)             | 1.000 (0.998 – 1.003)                   | 1.006 (1.003 – 1.009)       |
| Triglyceride (mg/dL)      | 1.001 (1.000 – 1.002)                   | 0.999 (0.998 – 1.001)       |
| FBG (mg/dL)               | 1.012 (1.007 – 1.017)                   | 1.004 (1.000 – 1.009)       |
| Current smoking           | 1.392 (1.198 – 1.616)                   | 1.057 (0.911 – 1.226)       |
| Alcohol drinking          | 0.976 (0.825 – 1.156)                   | 1.009 (0.855 – 1.190)       |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose. The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Listed variables were simultaneously evaluated in the multivariable analysis.
more sensitive to increased uric acid than males. Furthermore, increased uric acid was shown to be associated with oxidative stress because of elevated xanthine oxidase activity and reduced nitric oxide levels, leading to increases in superoxide and ROS production. Oxidative stress has been associated with the initiation and progression of atherosclerosis, a chronic inflammatory vascular disease characterized by functional and structural alterations in the vascular wall. Surely, more than 40% of females enrolled in this study were over 50 years and could be in a postmenopausal state lacking estrogen. Moreover, age over 50 years interacted with uric acid in the association between uric acid and the CAVI. This finding may explain that females are more susceptible to arterial stiffness with increasing serum uric acid levels.

In addition to arterial stiffness, carotid IMT and plaques are representative atherosclerotic factors that can be used to evaluate subclinical atherosclerosis. In this study, serum uric acid was not associated with carotid IMT in both sexes but was independently associated with the presence of carotid plaques only in females. Although the difference in the impact of uric acid on carotid IMT and plaques was not clear, discordance between the CAVI and carotid IMT could be explained by the difference in the properties of examinations. The CAVI and PWV are used to evaluate arterial stiffness, which represents a functional feature of arteriosclerosis. Pathologically, arterial stiffness is characterized by reduced arterial distensibility, caused by elastin degradation and collagen accumulation. The CAVI is calculated based on the stiffness parameter $\beta$ and the PWV, it reflects arterial stiffness, and it includes both muscular and elastic arteries. In contrast, the carotid IMT and plaque is a morphological index of pathological arterial wall thickening, and it reflects vascular structural changes from atherosclerosis. Furthermore, serum uric acid has been associated with vascular endothelial function in addition to oxidative stress, implying the close association with functional examinations. Compared with arterial stiffness, the influence of increased uric acid might not be linear on morphological atherosclerosis in the early stages. In the examination of morphological atherosclerosis, carotid IMT is an index showing the continuous progression of atherosclerosis, whereas the presence of a carotid plaque is a categorical index presenting focal atherosclerosis. Hence, the nonlinear effects of uric acid on atherosclerosis might at least partly explain the difference between uric acid and carotid IMT or the presence of a carotid plaque. The fact that the exclusion of subjects with abdominal obesity or metabolic syndrome, who might have an association with hyperuricemia, did not alter the results in females, supporting that the impact of uric acid on morphological atherosclerosis could be more conspicuous in females than in males.

The present results that uric acid levels were associated with arterial stiffness and atherosclerosis in females imply that a reduced uric acid level is favorable for the prevention of arterial stiffening and atherosclerosis, though the cross-sectional nature of this study neither clarifies this point nor presents the target level of uric acid. However, uric acid levels under 4.2 mg/dL may be favorable for healthy, particularly postmenopausal Japanese females. Indeed, in this study, females with the third and fourth quartiles of serum uric acid levels ($\geq 4.2$ mg/dL) showed a greater CAVI and carotid IMT than those with the first quartiles (uric acid levels $\leq 3.6$ mg/dL). Furthermore, the mean uric acid levels in females with increased arterial stiffness or the presence of carotid plaques (4.6 or 4.5 mg/dL) were greater than those without. These speculations are compatible with a previous Japanese study with healthy subjects, where a target level of serum uric acid for increasing the CAVI was reported to be 4.6 mg/dL, whereas other previous studies reported slightly different results on the relationship between uric acid and atherosclerotic examination possibly because subjects’ backgrounds (age, medications) were different from this study. Although a significant association between uric acid levels and increased CAVI was observed for males in this study, the correlation coefficient and OR were lower than those for females. Moreover, the uric acid levels were similar in males with and without increased arterial stiffness or carotid atherosclerosis. Hence, it is difficult to indicate the target uric acid level for healthy males from this study. Instead, the previous Japanese cross-sectional study that enrolled healthy subjects or a longitudinal study that enrolled subjects of older age than this study suggested that uric acid levels $>6.6$ or 6.2 mg/dL were associated with increased arterial stiffness. Therefore, these uric acid levels are possible target levels for healthy middle-aged males or older males.

This study had several limitations; thus, the findings should be interpreted with caution. First, the study design was cross-sectional, and the cohort was heterogeneous in terms of background. Second, the causes underlying the identified associations were not investigated in this study. Third, the parameters associated with oxidative stress were not evaluated. Future investigations with a longitudinal design should be conducted.
Conclusions

In conclusion, we demonstrated a close association between serum uric acid and the CAVI in an untreated middle-aged population and independent associations between increased arterial stiffness in both sexes and the presence of carotid plaques in females. Moreover, the interaction of sex was confirmed in the association between uric acid and the CAVI. These findings support the fact that the impacts of uric acid on arterial stiffness and morphological atherosclerosis are greater in females than in males.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Table 1. Characteristics of subjects with increased arterial stiffness or not and carotid plaques or not, in each sex

| Variables                        | Increased arterial stiffness | Carotid plaques |
|---------------------------------|-----------------------------|-----------------|
|                                 | (-) (n=2692)                | (+) (n=329)     | (-) (n=2706) | (+) (n=315) |
| Age (years)                     | 47.9 ± 6.0                  | 53.9 ± 5.0*     | 48.1 ± 6.1 | 51.9 ± 7.3* |
| BMI (kg/m²)                     | 21.7 ± 3.3                  | 21.9 ± 3.6      | 21.7 ± 3.3 | 22.4 ± 3.4* |
| Waist circumference (cm)        | 77.7 ± 9.0                  | 79.7 ± 9.9**    | 77.6 ± 9.0 | 80.6 ± 9.1* |
| Systolic BP (mmHg)              | 118 ± 17                    | 132 ± 22*       | 119 ± 18  | 127 ± 20*   |
| Diastolic BP (mmHg)             | 72 ± 11                     | 79 ± 13*        | 73 ± 11   | 77 ± 12*    |
| Creatinine (mg/dL)              | 0.6 ± 0.09                  | 0.6 ± 0.09      | 0.61 ± 0.09 | 0.61 ± 0.10 |
| HDL-C (mg/dL)                   | 72 ± 16                     | 71 ± 16         | 73 ± 16   | 69 ± 17*    |
| LDL-C (mg/dL)                   | 121 ± 30                    | 135 ± 33*       | 121 ± 30  | 138 ± 33*   |
| Triglyceride (mg/dL)            | 85 ± 46                     | 107 ± 60*       | 85 ± 48   | 102 ± 49*   |
| FBG (mg/dL)                     | 92 ± 13                     | 100 ± 31*       | 92 ± 14   | 98 ± 25*    |
| HbA1c (%)                       | 5.7 ± 0.4                   | 6.0 ± 1.0*      | 5.7 ± 0.5 | 5.9 ± 0.9*  |
| Uric acid (mg/dL)               | 4.2 ± 0.9                   | 4.6 ± 1.1*      | 4.2 ± 0.9 | 4.5 ± 1.1*  |
| Current smoking (n [%])         | 161 [6.0]                   | 25 [7.6]        | 156 [5.8] | 30 [9.5]*   |
| Alcohol drinking (n [%])        | 1191 [44.2]                 | 113 [34.3]**    | 1190 [44.0] | 114 [36.2]** |
| Atherosclerotic examination     |                             |                |           |            |
| CAVI                            | 6.84 ± 0.63                 | 8.43 ± 0.38*    | 6.97 ± 0.78 | 7.34 ± 0.77* |
| Carotid IMT (mm)                | 0.53 ± 0.10                 | 0.60 ± 0.11*    | 0.53 ± 0.09 | 0.61 ± 0.11* |
| Hypertension (n [%])            | 300 [11.1]                  | 124 [37.7]*     | 339 [12.5] | 85 [27.0]*  |
| Dyslipidemia (n [%])            | 772 [28.7]                  | 150 [45.6]*     | 769 [28.4] | 153 [48.6]* |
| Diabetes (n [%])                | 68 [2.5]                    | 30 [9.1]*       | 71 [2.6]  | 27 [8.6]*   |
| Abdominal obesity (n [%])       | 242 [9.0]                   | 44 [13.4]****   | 239 [32.1] | 47 [13.4]*  |
| Metabolic syndrome (n [%])      | 45 [1.7]                    | 22 [6.7]*       | 52 [1.9]  | 15 [2.2]*   |

Data are presented as the mean ± standard deviation or number (%), as indicated. *P<0.0001, **P<0.001, ***P<0.01, ****P<0.05 vs. females without increased arterial stiffness or carotid plaque. BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; CAVI, cardio-ankle vascular index; IMT, intima-media thickness. Increased arterial stiffness indicates a CAVI value ≥ 8.0.

| Variables                        | Increased arterial stiffness | Carotid plaques |
|---------------------------------|-----------------------------|-----------------|
|                                 | (-) (n=5913)                | (+) (n=1272)    | (-) (n=6105) | (+) (n=1070) |
| Age (years)                     | 54.5 ± 7.4                  | 53.0 ± 7.1*     | 44.0 ± 7.8 | 51.9 ± 7.3* |
| BMI (kg/m²)                     | 23.0 ± 3.0                  | 22.3 ± 2.8*     | 22.9 ± 3.0 | 23.0 ± 2.9* |
| Waist circumference (cm)        | 82.0 ± 8.1                  | 81.7 ± 7.7      | 81.8 ± 8.1 | 82.7 ± 7.8**|
| Systolic BP (mmHg)              | 117 ± 13                    | 124 ± 15*       | 118 ± 13  | 122 ± 14*   |
| Diastolic BP (mmHg)             | 75 ± 9                      | 79 ± 10*        | 75 ± 9    | 78 ± 9*     |
| Creatinine (mg/dL)              | 0.81 ± 0.11                 | 0.81 ± 0.12     | 0.81 ± 0.11 | 0.81 ± 0.13 |
| HDL-C (mg/dL)                   | 59 ± 15                     | 60 ± 16*        | 59 ± 15   | 59 ± 16     |
| LDL-C (mg/dL)                   | 119 ± 28                    | 121 ± 28***     | 118 ± 28  | 125 ± 28*   |
| Triglyceride (mg/dL)            | 116 ± 78                    | 120 ± 70        | 116 ± 78  | 119 ± 67    |
| FBG (mg/dL)                     | 94 ± 11                     | 100 ± 18*       | 94 ± 11   | 99 ± 18*    |
| HbA1c (%)                       | 5.6 ± 0.4                   | 5.8 ± 0.6*      | 5.6 ± 0.4 | 5.8 ± 0.6*  |
| Uric acid (mg/dL)               | 5.9 ± 1.2                   | 5.8 ± 1.3       | 5.9 ± 1.2 | 5.8 ± 1.2   |
| Current smoking (n [%])         | 2423 [41.0]                 | 584 [45.9]***   | 2557 [41.9] | 450 [42.1] |
| Alcohol drinking (n [%])        | 4413 [74.6]                 | 946 [74.4]      | 4573 [74.9] | 786 [73.5] |
| Atherosclerotic examination     |                             |                |           |            |
| CAVI                            | 7.06 ± 0.53                 | 8.54 ± 0.51*    | 7.24 ± 0.74 | 7.75 ± 0.82* |
| Carotid IMT (mm)                | 0.54 ± 0.10                 | 0.61 ± 0.12*    | 0.54 ± 0.10 | 0.62 ± 0.12* |
| Hypertension (n [%])            | 382 [6.5]                   | 218 [17.1]*     | 447 [7.3]  | 153 [14.3]* |
| Dyslipidemia (n [%])            | 2178 [36.8]                 | 532 [41.8]*     | 2234 [36.6] | 476 [44.5]* |
| Diabetes (n [%])                | 118 [2.0]                   | 106 [8.3]*      | 144 [2.4]  | 80 [7.5]*   |
| Abdominal obesity (n [%])       | 1901 [32.1]                 | 402 [31.6]      | 1913 [31.3] | 390 [36.4]**|
| Metabolic syndrome (n [%])      | 289 [4.9]                   | 118 [9.3]*      | 316 [5.2]  | 91 [8.5]*   |

Data are presented as the mean ± standard deviation or number [%], as indicated. *P<0.0001, **P<0.001. ***P<0.01 vs. males without increased arterial stiffness or carotid plaque. BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; CAVI, cardio-ankle vascular index; IMT, intima-media thickness. Increased arterial stiffness indicates a CAVI value ≥ 8.0.
Supplementary Table 2. Characteristics of females and males divided into subgroups with age < 50 years or age ≥ 50 years

| Characteristic                  | Females (n=3021) |                  | Males (n=7175) |                  |
|---------------------------------|------------------|-----------------|----------------|-----------------|
|                                 | Age < 50 years   | Age ≥ 50 years  | Age < 50 years | Age ≥ 50 years  |
|                                 | (n=1712)         | (n=1309)        | (n=4960)       | (n=2215)        |
| Age (years)                     | 43.9 ± 3.0       | 54.7 ± 3.0*     | 40.4 ± 4.4     | 55.9 ± 3.2*     |
| BMI (kg/m²)                     | 21.4 ± 3.4       | 22.1 ± 3.2*     | 23.0 ± 3.1     | 22.8 ± 2.7***   |
| Systolic BP (mmHg)              | 116 ± 16         | 125 ± 19*       | 117 ± 13       | 122 ± 15*       |
| Diastolic BP (mmHg)             | 71 ± 11          | 76 ± 11*        | 74 ± 9         | 78 ± 9*         |
| Creatinine (mg/dL)              | 0.61 ± 0.09      | 0.60 ± 0.09***  | 0.81 ± 0.11    | 0.81 ± 0.13     |
| HDL-C (mg/dL)                   | 72 ± 16          | 72 ± 17         | 59 ± 14        | 60 ± 16*        |
| LDL-C (mg/dL)                   | 113 ± 27         | 135 ± 30*       | 117 ± 28       | 122 ± 28*       |
| Triglyceride (mg/dL)            | 78 ± 42          | 99 ± 53*        | 117 ± 81       | 117 ± 65        |
| FBG (mg/dL)                     | 90 ± 10          | 96 ± 21*        | 92 ± 10        | 100 ± 16*       |
| HbA1c (%)                       | 5.6 ± 0.5        | 5.8 ± 0.7*      | 5.6 ± 0.4      | 5.8 ± 0.5*      |
| Uric acid (mg/dL)               | 4.0 ± 0.9        | 4.4 ± 1.0*      | 5.9 ± 1.2      | 5.8 ± 1.3*      |
| Current smoking (n [%])         | 103 [6.0]        | 83 [6.3]        | 2091 [42.2]    | 916 [41.4]      |
| Alcohol drinking (n [%])        | 833 [48.7]       | 471 [36.0]*     | 3721 [75.0]    | 1638 [74.0]     |

Examination of atherosclerosis

| CAVI                            | 6.73 ± 0.67      | 7.38 ± 0.76*    | 7.07 ± 0.62    | 7.87 ± 0.80*    |
| Increased arterial stiffness (n [%]) | 63 [3.7]       | 266 [20.3]*     | 353 [7.1]      | 919 [41.5]*     |
| Carotid IMT (mm)                 | 0.51 ± 0.09      | 0.58 ± 0.10*    | 0.52 ± 0.09    | 0.62 ± 0.12*    |
| Carotid plaques (n [%])          | 84 [4.9]         | 231 [17.6]*     | 357 [7.2]      | 713 [32.2]*     |
| Hypertension (n [%])             | 147 [8.6]        | 277 [21.2]*     | 276 [5.6]      | 324 [14.6]*     |
| Dyslipidemia (n [%])             | 311 [18.2]       | 611 [6.4]*      | 1791 [39.9]    | 919 [41.5]*     |
| Diabetes (n [%])                 | 24 [1.4]         | 74 [5.7]*       | 53 [1.1]       | 171 [7.7]*      |
| Abdominal obesity (n [%])        | 134 [7.8]        | 152 [11.6]**    | 1510 [30.4]    | 793 [35.8]*     |
| Metabolic syndrome (n [%])       | 23 [1.3]         | 44 [3.4]**      | 218 [4.4]      | 189 [8.5]*      |

Data are presented as the mean ± standard deviation or number [%], as indicated.

*P<0.0001, **P<0.001, ***P<0.05 vs. subjects with age < 50 years in each sex.

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.
Supplementary Table 3. Multivariable regression analysis showing the possible association between uric acid and cardio-ankle vascular index or carotid intima-media thickness based on age over or under 50 years, evaluated separately in females (n=3021) and males (n=7175)

### a) Females (n=3021)

| Variable | CAVI | P value | Carotid IMT | P value |
|----------|------|---------|-------------|---------|
|          | Standardized coefficient (β) |       | Standardized coefficient (β) |       |
| Non-interaction Model |       |         |             |         |
| Uric acid (mg/dL) | 0.085 | <0.0001 | 0.017 | 0.357 |
| Age over 50 years | 0.314 | <0.0001 | 0.289 | <0.0001 |
| BMI (kg/m²) | -0.296 | <0.0001 | 0.053 | 0.007 |
| Systolic BP (mmHg) | 0.236 | <0.0001 | 0.172 | <0.0001 |
| Creatinine (mg/dL) | 0.012 | 0.463 | 0.015 | 0.395 |
| HDL-C (mg/dL) | -0.010 | 0.596 | -0.064 | <0.001 |
| LDL-C (mg/dL) | 0.031 | 0.083 | 0.061 | <0.01 |
| Triglyceride (mg/dL) | 0.067 | <0.0001 | 0.026 | 0.193 |
| FBG (mg/dL) | 0.116 | <0.0001 | -0.001 | 0.958 |
| Current smoking | 0.064 | <0.0001 | 0.022 | 0.186 |
| Alcohol drinking | -0.003 | 0.846 | -0.005 | 0.758 |
| Interaction Model |       |         |             |         |
| Product term of uric acid and age over 50 years | 0.165 | <0.05 | 0.004 | 0.961 |
| Uric acid (mg/dL) | 0.050 | <0.05 | 0.016 | 0.520 |
| Age over 50 years | 0.163 | <0.05 | 0.285 | <0.001 |
| BMI (kg/m²) | -0.294 | <0.0001 | 0.053 | 0.074 |
| Systolic BP (mmHg) | 0.236 | <0.0001 | 0.172 | <0.0001 |
| Creatinine (mg/dL) | 0.013 | 0.438 | 0.015 | 0.395 |
| HDL-C (mg/dL) | -0.009 | 0.636 | -0.064 | <0.001 |
| LDL-C (mg/dL) | 0.032 | 0.074 | 0.061 | <0.01 |
| Triglyceride (mg/dL) | 0.066 | <0.0001 | 0.026 | 0.193 |
| FBG (mg/dL) | 0.116 | <0.0001 | -0.001 | 0.958 |
| Current smoking | 0.064 | <0.0001 | 0.022 | 0.186 |
| Alcohol drinking | -0.003 | 0.833 | -0.005 | 0.758 |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

Listed variables were simultaneously evaluated in the multivariable regression analysis.

### b) Males (n=7175)

| Variable | CAVI | P value | Carotid IMT | P value |
|----------|------|---------|-------------|---------|
|          | Standardized coefficient (β) |       | Standardized coefficient (β) |       |
| Non-interaction Model |       |         |             |         |
| Uric acid (mg/dL) | 0.033 | <0.01 | -0.022 | 0.060 |
| Age over 50 years | 0.421 | <0.0001 | 0.379 | <0.0001 |
| BMI (kg/m²) | -0.300 | <0.0001 | 0.137 | <0.0001 |
| Systolic BP (mmHg) | 0.133 | <0.0001 | 0.070 | <0.0001 |
| Creatinine (mg/dL) | 0.015 | 0.155 | 0.049 | <0.0001 |
| HDL-C (mg/dL) | -0.044 | <0.001 | -0.009 | 0.466 |
| LDL-C (mg/dL) | 0.011 | 0.310 | 0.039 | <0.001 |
| Triglyceride (mg/dL) | 0.031 | <0.01 | -0.027 | <0.05 |
| FBG (mg/dL) | 0.100 | <0.0001 | 0.056 | <0.0001 |
| Current smoking | 0.079 | <0.0001 | 0.082 | <0.0001 |
| Alcohol drinking | -0.009 | 0.350 | -0.017 | 0.111 |
| Interaction Model |       |         |             |         |
| Product term of uric acid and age over 50 years | 0.008 | 0.864 | -0.050 | 0.322 |
| Uric acid (mg/dL) | 0.032 | <0.05 | -0.014 | 0.298 |
| Age over 50 years | 0.413 | <0.0001 | 0.428 | <0.0001 |
| BMI (kg/m²) | -0.300 | <0.0001 | 0.137 | <0.0001 |
| Systolic BP (mmHg) | 0.133 | <0.0001 | 0.070 | <0.0001 |
| Creatinine (mg/dL) | 0.015 | 0.159 | 0.049 | <0.0001 |
| HDL-C (mg/dL) | -0.044 | <0.001 | -0.009 | 0.451 |
| LDL-C (mg/dL) | 0.011 | 0.307 | 0.039 | <0.001 |
| Triglyceride (mg/dL) | 0.031 | <0.01 | -0.027 | <0.05 |
| FBG (mg/dL) | 0.100 | <0.0001 | 0.056 | <0.0001 |
| Current smoking | 0.079 | <0.0001 | 0.082 | <0.0001 |
| Alcohol drinking | -0.009 | 0.350 | -0.017 | 0.112 |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

Listed variables were simultaneously evaluated in the multivariable regression analysis.
Supplementary Table 4. Multivariable regression analysis showing the relationship between uric acid and cardio-ankle vascular index or carotid intima-media thickness, separately evaluated with age under or over 50 years in females (n=3021)

a) Females with age < 50 years (n=1712)

| Variable            | CAVI                      | Carotid IMT                |
|---------------------|---------------------------|---------------------------|
|                     | Standardized coefficient (β) | P value | Standardized coefficient (β) | P value |
| Uric acid (mg/dL)   | 0.042                      | 0.090                     | 0.026                      | 0.311   |
| Age (years)         | 0.174                      | <0.0001                   | 0.190                      | <0.0001 |
| BMI (kg/m²)         | -0.341                     | <0.0001                   | 0.087                      | <0.05   |
| Systolic BP (mmHg)  | 0.236                      | <0.0001                   | 0.116                      | <0.0001 |
| Creatinine (mg/dL)  | 0.045                      | 0.057                     | 0.005                      | 0.846   |
| HDL-C (mg/dL)       | 0.001                      | 0.963                     | -0.043                     | 0.105   |
| LDL-C (mg/dL)       | 0.030                      | 0.222                     | 0.020                      | 0.426   |
| Triglyceride (mg/dL)| 0.088                      | <0.01                     | 0.035                      | 0.205   |
| FBG (mg/dL)         | 0.046                      | 0.064                     | 0.001                      | 0.977   |
| Current smoking     | 0.100                      | <0.0001                   | 0.060                      | <0.05   |
| Alcohol drinking    | 0.002                      | 0.933                     | 0.002                      | 0.948   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
Listed variables were simultaneously evaluated in the multivariable regression analysis.

b) Females with age ≥ 50 years (n=1309)

| Variable            | CAVI                      | Carotid IMT                |
|---------------------|---------------------------|---------------------------|
|                     | Standardized coefficient (β) | P value | Standardized coefficient (β) | P value |
| Uric acid (mg/dL)   | 0.122                      | <0.0001                   | 0.003                      | 0.910   |
| Age (years)         | 0.243                      | <0.0001                   | 0.149                      | <0.0001 |
| BMI (kg/m²)         | -0.279                     | <0.0001                   | 0.042                      | 0.173   |
| Systolic BP (mmHg)  | 0.240                      | <0.0001                   | 0.191                      | <0.0001 |
| Creatinine (mg/dL)  | -0.012                     | 0.641                     | 0.029                      | 0.300   |
| HDL-C (mg/dL)       | -0.028                     | 0.339                     | -0.096                     | <0.01   |
| LDL-C (mg/dL)       | -0.007                     | 0.781                     | 0.059                      | <0.05   |
| Triglyceride (mg/dL)| 0.041                      | 0.172                     | 0.006                      | 0.840   |
| FBG (mg/dL)         | 0.161                      | <0.0001                   | -0.014                     | 0.615   |
| Current smoking     | 0.041                      | 0.109                     | -0.014                     | 0.596   |
| Alcohol drinking    | 0.017                      | 0.511                     | 0.004                      | 0.890   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
Listed variables were simultaneously evaluated in the multivariable regression analysis.
**Supplementary Table 5.** Multivariable logistic regression analysis showing the possible association between uric acid and increased arterial stiffness or the presence of carotid plaques, separately evaluated with age under or over 50 years in females (n=3021)

### a) Females with age <50 years (n=1712)

| Variable          | Increased arterial stiffness (CAVI ≥ 8.0) | Presence of carotid plaques |
|-------------------|------------------------------------------|-----------------------------|
|                   | Odds ratio (95% CI)                      | P value | Odds ratio (95% CI) | P value |
| Uric acid (mg/dL) | 1.079 (0.774 – 1.504)                   | 0.655   | 1.032 (0.783 – 1.360) | 0.823   |
| Age (years)       | 1.159 (1.051 – 1.278)                   | <0.01   | 1.117 (1.031 – 1.211) | <0.01   |
| BMI (kg/m²)       | 0.849 (0.764 – 0.944)                   | <0.01   | 0.920 (0.847 – 0.999) | <0.05   |
| Systolic BP (mmHg)| 1.051 (1.035 – 1.067)                  | <0.0001 | 1.013 (0.999 – 1.027) | 0.079   |
| Creatinine (mg/dL)| 0.491 (0.025 – 9.774)                  | 0.091   | 6.820 (0.564 – 82.50) | 0.131   |
| HDL-C (mg/dL)     | 1.002 (0.983 – 1.021)                   | 0.872   | 0.974 (0.957 – 0.992) | <0.01   |
| Triglyceride (mg/dL)| 1.004 (0.994 – 1.015)         | 0.387   | 1.017 (1.009 – 1.026) | <0.0001 |
| FBG (mg/dL)       | 0.990 (0.961 – 1.019)                  | 0.488   | 0.999 (0.993 – 1.004) | 0.651   |
| Current smoking   | 2.327 (0.960 – 5.640)                  | 0.061   | 3.623 (1.855 – 7.077) | <0.001  |
| Alcohol drinking  | 0.610 (0.348 – 1.069)                  | 0.084   | 1.024 (0.645 – 1.627) | 0.919   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Listed variables were simultaneously evaluated in the multivariable analysis.

### b) Females with age ≥ 50 years (n=1309)

| Variable          | Increased arterial stiffness (CAVI ≥ 8.0) | Presence of carotid plaques |
|-------------------|------------------------------------------|-----------------------------|
|                   | Odds ratio (95% CI)                      | P value | Odds ratio (95% CI) | P value |
| Uric acid (mg/dL) | 1.355 (1.156 – 1.589)                   | <0.001 | 1.235 (1.057 – 1.444) | <0.01   |
| Age (years)       | 1.158 (1.104 – 1.215)                   | <0.0001 | 1.039 (0.991 – 1.090) | 0.116   |
| BMI (kg/m²)       | 0.880 (0.834 – 0.930)                   | <0.0001 | 0.986 (0.937 – 1.038) | 0.592   |
| Systolic BP (mmHg)| 1.027 (1.019 – 1.036)                  | <0.0001 | 1.010 (1.002 – 1.019) | <0.05   |
| Creatinine (mg/dL)| 0.273 (0.055 – 1.360)                  | 0.113   | 0.917 (0.183 – 4.590) | 0.916   |
| HDL-C (mg/dL)     | 0.999 (0.989 – 1.009)                   | 0.779   | 0.993 (0.982 – 1.003) | 0.169   |
| LDL-C (mg/dL)     | 1.000 (0.995 – 1.005)                   | 0.902   | 1.005 (1.000 – 1.010) | <0.05   |
| Triglyceride (mg/dL)| 1.002 (0.999 – 1.005)         | 0.277   | 0.999 (0.995 – 1.002) | 0.383   |
| FBG (mg/dL)       | 1.013 (1.006 – 1.020)                  | <0.001 | 1.005 (0.999 – 1.012) | 0.108   |
| Current smoking   | 1.205 (0.648 – 2.240)                  | 0.556   | 1.194 (0.660 – 2.160) | 0.557   |
| Alcohol drinking  | 0.937 (0.683 – 1.285)                  | 0.687   | 0.895 (0.653 – 1.228) | 0.499   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Listed variables were simultaneously evaluated in the multivariable analysis.
**Supplementary Table 6.** Multivariable logistic regression analysis showing the possible association between uric acid and the greater carotid intima-media thickness than the median value in each sex

**a) Females (n=3021)**

| Variable           | Odds ratio (95% CI) | P value |
|--------------------|---------------------|---------|
| Uric acid (mg/dL)  | 1.056 (0.964 – 1.158) | 0.243   |
| Age (years)        | 1.111 (1.095 – 1.128) | < 0.0001 |
| BMI (kg/m^2)       | 1.040 (1.010 – 1.069) | < 0.01   |
| Systolic BP (mmHg) | 1.014 (1.009 – 1.019) | < 0.0001 |
| Creatinine (mg/dL) | 1.649 (0.687 – 3.961) | 0.263   |
| HDL-C (mg/dL)      | 0.997 (0.991 – 1.002) | 0.226   |
| LDL-C (mg/dL)      | 1.001 (0.998 – 1.004) | 0.331   |
| Triglyceride (mg/dL)| 1.002 (1.000 – 1.004) | 0.131   |
| FBG (mg/dL)        | 1.203 (0.867 – 1.669) | 0.270   |
| Current smoking    | 1.056 (0.814 – 1.322) | 0.579   |

IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
The endpoint was a greater carotid IMT value than the median value (0.50mm), and the number of females with carotid IMT >0.50mm was 1505.
Listed variables were simultaneously evaluated in the multivariable analysis.

**b) Males (n=7175)**

| Variable           | Odds ratio (95% CI) | P value |
|--------------------|---------------------|---------|
| Uric acid (mg/dL)  | 0.984 (0.938 – 1.031) | 0.489   |
| Age (years)        | 1.102 (1.095 – 1.110) | < 0.0001 |
| BMI (kg/m^2)       | 1.113 (1.090 – 1.136) | < 0.0001 |
| Systolic BP (mmHg) | 1.010 (1.006 – 1.015) | < 0.0001 |
| Creatinine (mg/dL) | 1.539 (0.953 – 2.485) | 0.078   |
| HDL-C (mg/dL)      | 0.998 (0.994 – 1.002) | 0.257   |
| LDL-C (mg/dL)      | 1.002 (1.000 – 1.004) | < 0.05   |
| Triglyceride (mg/dL)| 0.999 (0.998 – 1.000) | 0.080   |
| FBG (mg/dL)        | 1.003 (0.999 – 1.008) | 0.138   |
| Current smoking    | 1.471 (1.315 – 1.645) | < 0.0001 |
| Alcohol drinking   | 0.891 (0.786 – 1.009) | 0.068   |

IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.
The endpoint was a greater carotid IMT value than the median value (0.55mm), and the number of males with carotid IMT >0.55mm was 2589.
Listed variables were simultaneously evaluated in the multivariable analysis.
Supplementary Table 7. Multivariable logistic regression analysis showing the possible association between uric acid and increased arterial stiffness or the presence of carotid plaques, evaluated separately in females and males without metabolic syndrome

| Variable               | Increased arterial stiffness (CAVI ≥ 8.0) | Carotid plaques |
|------------------------|------------------------------------------|-----------------|
|                        | Odds ratio (95% CI)  | P value | Odds ratio (95% CI)  | P value |
| Uric acid (mg/dL)      | 1.322 (1.140 – 1.533) | <0.001  | 1.195 (1.039 – 1.375) | <0.05   |
| Age (years)            | 1.159 (1.129 – 1.190) | <0.0001 | 1.094 (1.069 – 1.121) | <0.0001 |
| BMI (kg/m²)            | 0.853 (0.809 – 0.900) | <0.0001 | 0.980 (0.936 – 1.026) | 0.384   |
| Systolic BP (mmHg)     | 1.033 (1.025 – 1.041) | <0.0001 | 1.011 (1.004 – 1.018) | <0.01   |
| Creatinine (mg/dL)     | 0.268 (0.063 – 1.140) | 0.075   | 1.019 (0.256 – 4.045) | 0.979   |
| HDL-C (mg/dL)          | 0.997 (0.988 – 1.007) | 0.579   | 0.990 (0.981 – 0.999) | <0.05   |
| LDL-C (mg/dL)          | 1.001 (0.996 – 1.005) | 0.790   | 1.009 (1.005 – 1.014) | <0.0001 |
| Triglyceride (mg/dL)   | 1.002 (0.999 – 1.005) | 0.259   | 0.999 (0.996 – 1.002) | 0.338   |
| FBG (mg/dL)            | 1.005 (0.997 – 1.014) | 0.216   | 1.009 (1.001 – 1.017) | <0.05   |
| Current smoking        | 1.547 (0.922 – 2.595) | 0.098   | 1.855 (1.181 – 2.914) | <0.01   |
| Alcohol drinking       | 0.861 (0.651 – 1.140) | 0.297   | 0.931 (0.714 – 1.215) | 0.601   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Abdominal obesity was defined as waist circumference ≥ 90 cm for females. Metabolic syndrome was diagnosed on the basis of abdominal obesity and two or more of the following three criteria: (1) triglycerides ≥ 150 mg/dL and/or HDL-C < 40 mg/dL; (2) systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; and (3) FBG ≥ 110 mg/dL.

Listed variables were simultaneously evaluated in the multivariable analysis.

| Variable               | Increased arterial stiffness (CAVI ≥ 8.0) | Carotid plaques |
|------------------------|------------------------------------------|-----------------|
|                        | Odds ratio (95% CI)  | P value | Odds ratio (95% CI)  | P value |
| Uric acid (mg/dL)      | 1.070 (1.002 – 1.143) | <0.05   | 0.990 (0.927 – 1.057) | 0.753   |
| Age (years)            | 1.154 (1.143 – 1.166) | <0.0001 | 1.120 (1.109 – 1.131) | <0.0001 |
| BMI (kg/m²)            | 0.827 (0.799 – 0.855) | <0.0001 | 0.987 (0.958 – 1.018) | 0.421   |
| Systolic BP (mmHg)     | 1.029 (1.023 – 1.034) | <0.0001 | 1.013 (1.007 – 1.018) | <0.0001 |
| Creatinine (mg/dL)     | 1.215 (0.632 – 2.339) | 0.559   | 0.565 (0.294 – 1.087) | <0.05   |
| HDL-C (mg/dL)          | 0.995 (0.989 – 0.999) | <0.05   | 0.991 (0.986 – 0.997) | <0.01   |
| LDL-C (mg/dL)          | 1.000 (0.998 – 1.003) | 0.759   | 1.005 (1.002 – 1.008) | <0.001   |
| Triglyceride (mg/dL)   | 1.001 (1.000 – 1.002) | 0.066   | 0.999 (0.998 – 1.001) | 0.243   |
| FBG (mg/dL)            | 1.011 (1.005 – 1.017) | <0.001  | 1.004 (0.998 – 1.010) | 0.147   |
| Current smoking        | 1.372 (1.174 – 1.603) | <0.0001 | 1.045 (0.896 – 1.221) | 0.573   |
| Alcohol drinking       | 0.985 (0.826 – 1.174) | 0.865   | 1.028 (0.865 – 1.221) | 0.752   |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Abdominal obesity was defined as waist circumference ≥ 90 cm for females. Metabolic syndrome was diagnosed on the basis of abdominal obesity and two or more of the following three criteria: (1) triglycerides ≥ 150 mg/dL and/or HDL-C < 40 mg/dL; (2) systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; and (3) FBG ≥ 110 mg/dL.

Listed variables were simultaneously evaluated in the multivariable analysis.
Supplementary Table 8. Multivariable logistic regression analysis showing the possible association between uric acid and increased arterial stiffness or presence of carotid plaques, evaluated separately in females and males without abdominal obesity

### a) Females without abdominal obesity (n=2740)

| Variable               | Increased arterial stiffness (CAVI ≥ 8.0) | Carotid plaques |
|------------------------|-----------------------------------------|-----------------|
|                        | Odds ratio (95% CI)                     | P value         | Odds ratio (95% CI) | P value         |
| Uric acid (mg/dL)      | 1.325 (1.136 – 1.546)                  | < 0.001         | 1.193 (1.029 – 1.383) | < 0.05         |
| Age (years)            | 1.162 (1.130 – 1.189)                  | < 0.0001        | 1.095 (1.067 – 1.122) | < 0.0001       |
| BMI (kg/m²)            | 0.832 (0.781 – 0.886)                  | < 0.0001        | 0.972 (0.917 – 1.030) | 0.333          |
| Systolic BP (mmHg)     | 1.032 (1.024 – 1.040)                  | < 0.0001        | 1.010 (1.002 – 1.018) | < 0.05         |
| Creatinine (mg/dL)     | 0.228 (0.051 – 1.022)                  | 0.053           | 0.984 (0.232 – 4.171) | 0.984          |
| HDL-C (mg/dL)          | 0.996 (0.986 – 1.006)                  | 0.408           | 0.990 (0.980 – 0.999) | < 0.05         |
| LDL-C (mg/dL)          | 1.002 (0.997 – 1.007)                  | 0.374           | 1.009 (1.005 – 1.014) | < 0.0001       |
| Triglyceride (mg/dL)   | 1.002 (0.999 – 1.005)                  | 0.214           | 0.998 (0.995 – 1.002) | 0.318          |
| FBG (mg/dL)            | 1.005 (0.997 – 1.014)                  | 0.236           | 1.008 (0.999 – 1.016) | < 0.05         |
| Current smoking        | 1.516 (0.888 – 2.589)                  | 0.127           | 2.003 (1.259 – 3.187) | < 0.01         |
| Alcohol drinking       | 0.855 (0.640 – 1.144)                  | 0.292           | 0.911 (0.689 – 1.205) | 0.514          |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Abdominal obesity was defined as waist circumference ≥ 90 cm for females.

Listed variables were simultaneously evaluated in the multivariable analysis.

### b) Males without abdominal obesity (n=4933)

| Variable               | Increased arterial stiffness (CAVI ≥ 8.0) | Carotid plaques |
|------------------------|-----------------------------------------|-----------------|
|                        | Odds ratio (95% CI)                     | P value         | Odds ratio (95% CI) | P value         |
| Uric acid (mg/dL)      | 1.066 (0.987 – 1.152)                  | 0.103           | 0.966 (0.892 – 1.045) | 0.387          |
| Age (years)            | 1.150 (1.137 – 1.163)                  | < 0.0001        | 1.125 (1.112 – 1.139) | < 0.0001       |
| BMI (kg/m²)            | 0.782 (0.744 – 0.882)                  | < 0.0001        | 1.004 (0.956 – 1.055) | 0.871          |
| Systolic BP (mmHg)     | 1.028 (1.021 – 1.034)                  | < 0.0001        | 1.014 (1.007 – 1.020) | < 0.0001       |
| Creatinine (mg/dL)     | 1.686 (0.792 – 3.592)                  | 0.176           | 0.413 (0.189 – 0.902) | < 0.05         |
| HDL-C (mg/dL)          | 0.992 (0.986 – 0.998)                  | < 0.05          | 0.996 (0.989 – 1.002) | 0.160          |
| LDL-C (mg/dL)          | 1.001 (0.997 – 1.004)                  | 0.649           | 1.006 (1.003 – 1.010) | < 0.001        |
| Triglyceride (mg/dL)   | 1.001 (1.000 – 1.002)                  | 0.108           | 1.000 (0.998 – 1.001) | 0.562          |
| FBG (mg/dL)            | 1.012 (1.007 – 1.017)                  | < 0.0001        | 1.000 (0.993 – 1.007) | 0.925          |
| Current smoking        | 1.447 (1.208 – 1.732)                  | < 0.0001        | 1.040 (0.864 – 1.252) | 0.680          |
| Alcohol drinking       | 0.981 (0.802 – 1.202)                  | 0.856           | 1.021 (0.831 – 1.255) | 0.840          |

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

The endpoint was a CAVI value ≥ 8.0 or the presence of carotid plaques. Abdominal obesity was defined as waist circumference ≥ 85 cm for males.

Listed variables were simultaneously evaluated in the multivariable analysis.