Published in final edited form as:

Exp Gerontol. 2017 March ; 89: 57–63. doi:10.1016/j.exger.2016.12.012.

Uric acid and endothelial function in elderly community-dwelling subjects

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Abstract

The role of serum uric acid (SUA), an inflammatory agent and potential mediator of cardiovascular diseases, in endothelial function (EF) has been tested only in middle-aged subjects affected by specific diseases. Our aim was to assess the relationship between SUA and measures of EF in a cohort of elderly community-dwellers. This study involved 424 males and 426 females aged 70 years from the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS), having complete data on SUA and EF assessed by flow-mediated vasodilation (FMD) and by intra-arterial infusion of acetylcholine (endothelium-dependent vasodilation, EDV) and sodium nitroprusside (endothelium-independent vasodilation, EIDV). Univariate and multivariate regression models obtained by backward selection from initial fully-adjusted models were built to assess the relationship between SUA and measures of EF in both genders. Cardiovascular risk factors, serum hormonal and metabolic mediators, and body composition were considered as potential confounders. In the univariate model, SUA was inversely associated in both genders with log(EDV) ($\beta \pm SE$ males -0.39 ± 0.17 , $p = 0.03$; females -0.57 ± 0.19 , $p = 0.003$) and log(EIDV) (males -0.23 ± 0.12 , $p = 0.05$; females -0.49 ± 0.15 , $p = 0.002$), but not with log(FMD). After adjustment for BMI, only the association between SUA and log(EIDV) in females persisted, though attenuated (-0.32 ± 0.16 , $p = 0.049$), and was no longer significant in the fully-adjusted

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Disclosure statement

The authors have nothing to disclose.

Conflict of interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.exger.2016.12.012>.

multivariate model including waist/hip ratio. In conclusion, in older subjects, especially women, SUA is associated with EF not independently of a list of confounders including BMI and trunk fat mass, suggesting a role as surrogate metabolic marker rather than an active player in EF.

Keywords

Endothelium; Vasodilation; Metabolism; Nitric oxide; Aging

1. Introduction

In adult subjects, serum uric acid (SUA) levels have been positively associated with cardiovascular diseases including hypertension, coronary artery disease (CAD), heart failure and stroke (Kanbay et al., 2013). However, the physio-pathological correlates of this epidemiological association are still controversial.

Despite having some *anti*-oxidant properties, demonstrated in experimental intervention studies under controlled conditions (Waring et al., 2004; Waring et al., 2006), uric acid is widely recognized as a pro-oxidative and inflammatory agent (Ruggiero et al., 2006; Kang et al., 2005). In fact, it induces the activation of renin-angiotensin system and impairs nitric oxide (NO) release by endothelial cells (Kang et al., 2005; Yu et al., 2010). These mechanisms may result in endothelial dysfunction, a marker of high cardiovascular risk and adverse events in both adult and elderly subjects (Maruhashi et al., 2013b; Lind et al., 2011).

In selected adult cohorts with hyperuricemia or high cardiovascular risk profile, elevated SUA levels have been negatively associated with brachial artery flow-mediated vasodilation (FMD), an indirect measurement of endothelial function (Ho et al., 2010; Kato et al., 2005; Kanbay et al., 2011; Mercuro et al., 2004; Tomiyama et al., 2011). However, the gold standard technique for endothelial function assessment, the endothelium-dependent vasodilation (EDV) measurement after intra-arterial acetylcholine infusion, is not optimally correlated with FMD (Lind, 2013). Only few studies have assessed the effects of SUA on EDV, particularly on older individuals.

Moreover, the relationship between SUA and endothelium-independent vasodilation (EIDV), evaluated by invasive forearm technique with intra-arterial infusion of sodium nitroprussiate, has been poorly investigated as well. This is somewhat surprising because EIDV is related to Framingham risk score (Lind et al., 2005) and is considered an indicator of age-related vascular stiffness (Maggio et al., 2014). In a study carried out on healthy adult volunteers, SUA exhibited an inverse correlation with endothelium-independent vasodilation (EIDV) but not with EDV (Jalal et al., 2012). Data about older individuals are however lacking. As such, the evaluation of the possible association between SUA and EIDV in this age-group may be of paramount importance to assess the physio-pathological role of SUA in the processes of vascular aging and disease-related vascular dysfunction.

Thus, using data from a population-based cross-sectional study of 70-year-old community-dwellers, we assessed the relationship between SUA and measures of endothelium-dependent and independent vascular function. We hypothesized that SUA is inversely

associated with both EDV and EIDV, modulating endothelial function through oxidative stress and inflammation and representing a marker of altered metabolic status. However, given the known strong negative association between fat mass and measures of endothelium-dependent and -independent vasodilation (Corretti et al., 2002; Maggio et al., 2013), we also hypothesized the role of proxies of body fat mass, such as waist/hip ratio, as potential mediators of this association.

2. Materials and methods

2.1. Study population

We studied subjects enrolled in the large population-based Prospective Study of the Vasculature in Uppsala Seniors (PIVUS). All community-dwelling subjects aged 70 years in Uppsala, Sweden, were eligible for study enrolment. The study population was chosen from a registry of community-living individuals and invited in randomized order by letter within 2 months from their 70th birthday. The final number of participants was 1016 (507 M, 509 F), out of 2025 invited subjects (participation rate 50.1%). The baseline investigation began in April 2001 and was completed in June 2004. For the purposes of the present analysis, we excluded those individuals, with lacking information on SUA and complete measures of EF. Subjects with severe comorbidities (including malnutrition, NYHA class III–IV congestive heart failure, active cancer, cirrhosis), subjects under active urate-lowering treatment and with severe hypertriglyceridemia (> 400 mg/dl) were excluded as well. Thus, 166 subjects (83 M, 83 F) were excluded so that the analysis was performed on 850 subjects (424 M, 426 F).

The study protocol was approved by the Ethics Committee of Uppsala University. All participants signed an informed participation consent form after having received a detailed description of the purposes and design of the study. All investigations were carried out in line with the principles expressed in the Declaration of Helsinki.

2.2. Baseline clinical investigations

A complete questionnaire about personal medical history, regular medications, dietary and smoking habits was answered by each participant. Namely, history of any cardiovascular diagnosis or medication, hypertension (ongoing antihypertensive treatment or blood pressure $> 140/90$ mm Hg), diabetes (specific dietary or pharmacological treatment or fasting blood glucose > 6.1 mmol/L), hyperlipidemia (ongoing lipid-lowering treatment, low-density lipoprotein [LDL]-cholesterol > 3.5 mmol/L, or serum triglycerides > 1.7 mmol/L) were addressed. Blood pressure was measured with a calibrated mercury sphygmomanometer after at least 30 min of rest, considering the average of three different recordings. Standing height was measured to the nearest whole 0.5 cm with a Harpenden Stadiometer (Holtain Ltd.), and body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight / (height)² (kg/m²). Obesity was defined as BMI > 30 kg/m². Exercise habits were categorized as follows: very light exercise (no sweat) less than two times per week, light exercise two times per week, moderate exercise (sweat) one or two times per week, heavy exercise (sweat) more than two times per week.

Waist/hip ratio was measured for each participant and considered as a proxy of body composition.

2.3. Laboratory investigations

Blood samples were collected in the morning, after an overnight fast. Medications and smoking were not allowed in the 8-hour period before blood sample collection. SUA was analyzed with an uricase method on an Architect Ci8200 Analyzer (Abbott Laboratories, Abbott Park, Ill., USA) with reagents (7D76-20) from the same manufacturer. Reference values (90% CI) based on the study population were from 3.98 (3.73–4.25) to 9.26 (8.83–9.7) mg/dL in males and from 3.18 (2.99–3.36) to 7.92 (7.58–8.25) mg/dL in females. These reference values are consistent with those found for healthy individuals from Scandinavian countries in the Nordic Reference Interval Project (NORIP) (Carlsson et al., 2010).

Liver function was assessed through plasma alanine aminotransferase (ALT, normal range 0–40 U/L) and plasma albumin (spectrophotometry using bromine cresol purple, normal range 37–48 g/L). Renal function was assessed with creatinine clearance calculated through the Cockcroft-Gault formula (normal range 97–137 mL/min in men, 88–128 mL/min in women). Plasma creatinine was analyzed with spectrophotometry using a modified Jaffe's reaction (normal range, 60–106 μ mol/L). Total plasma cholesterol (normal range 2.6–7.1 mmol/L) and plasma high-density lipoprotein (HDL) cholesterol (normal range 0.8–1.9 mmol/L) were assessed through enzymatic assay. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. High-sensitivity C-reactive protein (hs-CRP) was measured in serum by latex-enhanced turbidimetry (Architect Ci8200 Analyzer, Abbott Laboratories).

Serum sex-hormone binding-globulin (SHBG) and total testosterone (T) were assessed by chemiluminescence immunoassay on the immunochemistry platform Access (Beckman Coulter). The minimal detectable concentrations were 2 nmol/L and 0.35 nmol/L, respectively. Plasma fasting insulin was determined through chemiluminescence assay (Roche). Vitamin D was assessed in serum by chemiluminescence immunoassay technology (LIAISON 25-hydroxyvitamin D Assay, DiaSorin).

2.4. Measures of endothelial and vascular function

Endothelium-dependent vasodilation (EDV) in the peripheral circulation was simultaneously assessed through different methods, whose details have been previously described elsewhere (Lind et al., 2005). Endothelium-independent vasodilation (EIDV) was also assessed contextually.

Briefly, the resting forearm blood flow (FBF) was determined by venous occlusion plethysmography (Elektromedicina). Local intra-arterial drug infusions were then given over 5 min for each dose. To evaluate EDV, 25 and then 50 μ g/min of acetylcholine (Clin-Alpha) were administered. EDV was calculated as FBF during infusion of 50 μ g/min of acetylcholine minus resting FBF divided by resting FBF. To evaluate EIDV, 5 and then 10 μ g/min of sodium nitroprussiate were administered. EIDV was calculated as FBF during infusion of 10 μ g/min sodium nitroprusside minus resting FBF divided by resting FBF.

Flow-mediated vasodilation (FMD) was also measured as index of EF. It was induced by inflation of a pneumatic cuff placed around the forearm to a pressure at least 50 mm Hg above the subject's systolic blood pressure for 5 min. Brachial arterial diameter before and during the procedure was measured through external B-mode ultrasound imaging 2–3 cm above the elbow (Acuson XP128 with a 10 MHz linear transducer, Acuson), according to international consensus (Lind et al., 2007). FMD was defined as the maximal brachial artery diameter recorded between 30 and 90 s after cuff release minus diameter at rest divided by the diameter at rest.

2.5. Statistical analysis

Since relevant gender-related interaction terms between some of the variables considered in the present analysis and measures of endothelium-dependent and -independent vasodilation have already been demonstrated in the same study cohort (Maggio et al., 2014; Maggio et al., 2013), the interaction term between gender and SUA regarding measures of endothelial function was calculated. A separate analysis for men and women was then performed. Categorical variables were expressed in percentages. Continuous variables were reported as means $\pm$ standard deviation (SD) or, for variables with non-normally skewed distributions, as medians and interquartile range (IQR). To approximate normal distributions, log-transformed values for FMD, EDV, EIDV, SUA, ALT, creatinine clearance, hsCRP, insulin, testosterone, SHBG and waist/hip ratio were used in the analysis and back-transformed for data presentation.

SUA was considered as independent variable, while log(FMD), log(EDV) and log(EIDV) were considered as dependent variables, and their correlations were first assessed in unadjusted analysis. To identify possible confounders, the Pearson correlations between measures of endothelial function (EDV, EIDV, FMD) and all available covariates (including serum ALT, albumin, total bilirubin, creatinine, total cholesterol, LDL-cholesterol, HDL-cholesterol, testosterone, 25-hydroxyvitamin D, SHBG, insulin, hsCRP, BMI, TFM, caloric intake, exercise, diabetes, hypertension, cardiovascular drugs) were also assessed.

The possible association between SUA and each dependent variable was first tested with univariate regression models (model 1). Since BMI is a well-known determinant of EF (Corretti et al., 2002; Maggio et al., 2013), BMI-adjusted regression models were also built for each gender (model 2). Then, parsimonious models obtained by backward selection from initial models were used to identify the independent correlates of EF in both sexes. Potential confounders included in these models were selected according to the results of Pearson correlations between measures of endothelial function (EDV, EIDV, FMD) and covariates. Namely, only covariates with a significant correlation ($p < 0.05$) and with a possibly significant correlation ($p < 0.10$) were considered for the backward logistic regression models. Thus, model 3 included all possible laboratory and clinical covariates identified by previous analysis (fasting insulin, SHBG, testosterone, vitamin D, hsCRP, ALT, HDL-cholesterol, exercise, hypertension, diabetes, any cardiovascular drug used), not considering BMI and waist/hip ratio. Model 4 included all the above mentioned covariates plus BMI. Finally, the fully-adjusted multivariable model (model 5) also considered waist/hip ratio as proxy of body composition, and therefore included BMI, waist/hip ratio, insulin, SHBG,

testosterone, 25-hydroxyvitamin D, hsCRP, ALT, HDL cholesterol, exercise, hypertension, diabetes, any cardiovascular drug used.

Statistical significance was set for $p < 0.05$. The analyses were performed using the SAS statistical package, version 9.1 (SAS Institute Inc.).

3. Results

3.1. Preliminary analyses

The characteristics of the study population (424 males and 426 females aged 70 years old) are shown in Table 1. Average SUA levels were 6.30 ± 1.29 mg/dL in males and 5.16 ± 1.18 mg/dL in females. A significant interaction term between gender and SUA regarding endothelial function (EIDV) was found in the whole cohort (EIDV*SUA $p = 0.02$). Thus, a separate analysis between men and women was carried out.

Unadjusted correlations between each of the dependent variables (EDV, EIDV, FMD) and all other covariates considered in the study were calculated for both men and women to select potential confounders in the association between SUA and measures of vasodilation. The results of these analyses are fully shown in Supplementary material.

The results of univariate and multivariate backward-selection regression models exploring the association of SUA with the three considered indexes of EF, performed separately in men and women, are shown in Tables 2 and 3.

3.2. SUA and EF in men

In unadjusted regression models (model 1), SUA was inversely associated with log(EDV) ($\beta \pm SE -0.39 \pm 0.17$, $p = 0.03$) and log(EIDV) (-0.23 ± 0.12 , $p = 0.05$) but not significantly associated with log(FMD) (Tables 2 and 3, model 1). The unadjusted correlations between SUA and indices of EF in males are also shown in Fig. 1, plot a), b) and c).

The association between SUA and both log(EDV) and log(EIDV) was no longer significant after adjustment for BMI (Table 2, model 2) and for further adjustment for all other covariates (Table 2, models 3, 4 and 5).

3.3. SUA and EF in women

In unadjusted regression models (model 1), SUA was inversely associated with log(EDV) ($\beta \pm SE -0.57 \pm 0.19$, $p = 0.003$) and log(EIDV) (-0.49 ± 0.15 , $p = 0.002$). The unadjusted correlations between SUA and indices of EF in females are also shown in Fig. 1, plot d), e) and f). The strength of the association between SUA and log(EIDV) was attenuated, though maintaining statistical significance, after adjustment for BMI ($\beta \pm SE -0.32 \pm 0.16$, $p = 0.049$). On the contrary, the association between SUA and log(EDV) was no longer statistically significant in model 2 (Table 3). Similarly, these associations, particularly between SUA and log(EIDV), were no longer statistically significant after including in the multivariate models (models 4 and 5) BMI and waist/hip ratio as covariates (Table 3). SUA was not significantly associated with log(FMD) in the crude model 1 (Tables 2 and 3).

4. Discussion

In a large community-based cohort of 70-year-old subjects, we found that SUA is not independently associated with any of the considered measures of vasodilation (EDV, EIDV, FMD) in both genders.

Our initial hypothesis, that uric acid influences EF and affects endothelium-independent function in arteries of community-dwelling healthy seniors, should therefore be partially rejected. A significant inverse association between SUA and EIDV, detected particularly in females, was not confirmed after inclusion of proxies of body composition, including BMI and waist/hip ratio, in multivariate models.

These results may provide new insights in the controversial role of SUA in cardiovascular disease in the elderly population. To our knowledge, this is the first study assessing the relationship between SUA and measures of EF in elderly subjects. Previous investigations focused on middle-aged subjects, with various degrees of cardiovascular risk, and mainly provided information on surrogate markers of vascular disease or noninvasive measures of EF, such as FMD.

For example, in adult subjects, SUA showed a direct association with carotid intima-media thickness (Montalcini et al., 2007), vascular stiffness (Cicero et al., 2013), risk of hypertension and diabetes (Forman et al., 2009; Perticone et al., 2013) and an inverse association with FMD (Ho et al., 2010; Kato et al., 2005; Kanbay et al., 2011; Mercuro et al., 2004; Tomiyama et al., 2011).

Up to date, possible aging-related changes of the relationship between SUA and measures of vascular function have never been extensively studied. In a large cohort of Japanese women categorized according to their menopausal status, hyperuricemia proved to be a significant marker of endothelial dysfunction only in the early post-menopausal group (Maruhashi et al., 2013a). As such, one may speculate that hormonal and metabolic rearrangements that occur with age may modulate the relationship between SUA and vascular function.

A significant positive association between SUA and inflammatory markers has been previously demonstrated in senior community-dwellers (Ruggiero et al., 2006). Inflammation is considered a central process linking aging with many geriatric syndromes, including cardiovascular disease (Michaud et al., 2013). Moreover, an inverse association between levels of hsCRP and measures of EF has been previously found in the PIVUS cohort (Lind et al., 2008). Therefore, according to this patho-physiological model, SUA should exert a significant influence on EF.

However, in the present analysis we failed to demonstrate such an influence in both genders. The significant associations between SUA and EDV/EIDV in unadjusted models, were in fact not confirmed after introducing in the multivariate model proxies of body composition such as BMI and waist/hip ratio. Thus, in elderly subjects and particularly in females, SUA may not play an active role in modulating EF. Uric acid can be instead considered as a surrogate marker of an altered metabolic status secondary to an increased body fat content. The association between adiposity and cardiovascular disease (or EF) has already been

demonstrated in adults (Britton et al., 2013). Aging-related changes in body composition, with loss of muscle mass and increase in fat mass, a condition defined as sarcopenic obesity, have been associated with increased risk of cardiovascular disease and adverse outcomes (Atkins et al., 2014). Moreover, BMI and body composition were shown to be possible determinants of EDV and EIDV (Lind et al., 2007; Gonzalez et al., 2013).

The role of uric acid as a possible surrogate marker, and not as an active player, in EF is also suggested by other existing evidence. First, the administration of a medical food enhancing endothelium-derived nitric oxide determines a reduction in SUA levels, suggesting the primary role of endothelial dysfunction in determining uric acid levels (Maxwell and Bruinsma, 2001). The alternative hypothesis of a central role of SUA has been tested in intervention studies performed in adult subjects and using allopurinol treatment. In these trials the improvement in EF occurred independently of the ability of this medication to lower SUA, possibly through a reduction in oxidative stress (George et al., 2006). Interestingly, changes in FMD and EIDV were not correlated with variations of SUA (Eskurza et al., 2006).

The hypothesis generated by our data, that uric acid is not an active player in vascular function, apparently discourages the prescription of urate-lowering medications in elderly subjects with asymptomatic hyperuricemia. As such, treatments leading to body weight reduction, such as exercise or diet, could be more effective in enhancing endothelial and vascular function, as demonstrated in adult subjects (Klonizakis et al., 2014). However, allopurinol may have beneficial vascular actions independently of SUA levels. Thus, further research should clarify the relationship between SUA, urate-lowering treatments and vascular function in older individuals.

Some limitations should be taken into account when considering the results of the present analysis. First, the cross-sectional study design does not allow to establish whether SUA and the measures of EF (FMD, EDV and EIDV) are causally related. The observational design does not permit to investigate the changes in EF related to variations in SUA as well. Future intervention studies with lifestyle measures (diet, exercise) or urate-lowering medications are needed to clarify the association between SUA and EF in older individuals. Moreover, the high percentage of participants taking cardiovascular medications might have influenced the accuracy of vascular function measurements. Given the lack of similar studies performed in an elderly population, no comparison was possible with other cohorts including not only Caucasian subjects. Determinants of EF may in fact be also dependent on race and genetic background that could not be tested in the present analysis. The similar ethnicity of all enrolled subjects could also represent a limitation, particularly considering the relatively high reference values for SUA in Scandinavians (Carlsson et al., 2010) and the inclusion in the study of some subjects with asymptomatic hyperuricemia. These aspects should be considered when interpreting results.

Moreover, direct measures of body composition were not performed, using waist/hip ratio as a proxy of total adiposity. This ratio, although significantly correlated with gold standard measures of body composition in population-based studies (Barreira et al., 2012), may not be the best tool to represent the complex influence that adiposity has on endothelial function.

Finally, the possibility of a chance finding cannot be excluded. Thus, the present analysis should be regarded as a generating hypothesis needing further confirmation in the future.

However, these limitations are counterbalanced by strengths. This is the first study investigating the role of SUA as possible determinant of direct measures of EF exclusively focusing on elderly population. The invasive assessment of EF performed in this population implies a high level of accuracy, that cannot be reached by the simple non-invasive measurement of FMD used in most studies. Moreover, the high number of participants, their homogeneity and the high number of possible covariates available, including proxies of body composition, improved the accuracy of the results.

5. Conclusions

In a group of community-dwelling 70-year old subjects, serum uric acid was weakly associated with endothelial function (EDV and EIDV), especially in women. This relationship was not independent of confounders, including BMI and waist/hip ratio, suggesting that in this age-group SUA may simply represent a surrogate marker of an altered body composition rather than an active player in EF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support

This work was supported by the Swedish Research Council.

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Fig. 1.

Graph plots showing the unadjusted correlations between measures of endothelial function and SUA in the studied population of 70-year-old Swedish community-dwellers ($n = 850$, 424 M, 426 F). a) Correlation between EDV and SUA in males. b) Correlation between EIDV and SUA in males. c) Correlation between FMD and SUA in males. d) Correlation between EDV and SUA in females. e) Correlation between EIDV and SUA in females. f) Correlation between FMD and SUA in females. (SUA = serum uric acid; EDV = endothelium-dependent vasodilation; EIDV = endothelium-independent vasodilation; FMD

= flow-mediated dilation). Beta coefficients and standard errors are indicated in Tables 2 and 3.

Table 1

Characteristics of the PIVUS (Prospective Study of the Vasculature in Uppsala Seniors) participants ($N = 850$) included in the present analysis.

	Men ($N = 424$)	Women ($N = 426$)	p^a
BMI (kg/m ²)	26.74 ± 3.46	26.74 ± 4.71	0.96
FMD % ^b	4.65 (2.38–6.98)	3.57 (2.70–6.45)	0.31
EDV % ^b	449.90 (296.87–646.01)	479.31 (322.91–479.31)	0.16
EIDV % ^b	327.56 (227.21–448.72)	334.36 (217.34–478.85)	0.38
Uric acid (mg/dL)	6.30 ± 1.29	5.16 ± 1.18	<0.001
Total cholesterol (mg/dL)	195.30 ± 112.51	179.24 ± 114.66	0.005
LDL-cholesterol (mmol/L)	3.27 ± 0.83	3.53 ± 0.84	<0.001
HDL-cholesterol (mmol/L)	1.37 ± 0.36	1.67 ± 0.43	<0.001
Creatinine clearance (mL/24 h)	86.17 ± 19.55	71.93 ± 15.86	<0.001
ALT (U/L)	36 ± 19	32 ± 27	0.007
Albumin (g/L)	40.51 ± 2.81	40.20 ± 2.74	0.11
Total bilirubin (mg/dL)	1.07 ± 0.46	0.83 ± 0.30	<0.001
25-Hydroxyvitamin D (ng/dL)	57.16 ± 19.41	58.28 ± 19.89	0.40
SHBG (nmol/L) ^b	42.06 (32.45–54.23)	55.50 (42.06–73.87)	<0.001
Total testosterone (ng/dl) ^b	12.79 (10.13–15.56)	0.41 (0.14–0.80)	<0.001
hsCRP (mg/L) ^b	1.20 (0.59–2.24)	1.26 (0.64–2.34)	0.47
Fasting insulin (mIU/L) ^b	7.30 (5.20–10.92)	7.32 (5.10–10.21)	0.11
Waist/hip ratio	0.92 ± 0.05	0.85 ± 0.05	<0.001
Smoke ^c	44 (5.2)	52 (6.2)	0.46
Hypertension ^c	146 (34.4)	152 (35.6)	<0.001
Diabetes ^c	41 (9.6)	33 (7.8)	0.35
Any cardiovascular drug use ^{c,d}	265 (61.9)	315 (74.3)	<0.001
Antihypertensive drug use ^c	123 (29.0)	125 (29.3)	0.84
Lipid-lowering drug use ^c	61 (14.3)	54 (12.7)	0.47
Antidiabetic drug use ^c	40 (9.4)	33 (7.7)	0.35
Caloric intake (Kcal/die)	992.92 ± 358.55	938.04 ± 278.41	0.02
Physical exercise (n)			0.48
Light intensity	50	39	
Moderate intensity	235	256	
High intensity	140	132	

Data are reported as mean ± standard deviation unless otherwise specified.

BMI = body mass index; FMD = flow-mediated vasodilation; EDV = endothelium-dependent vasodilation; EIDV = endothelium-independent vasodilation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ALT = alanine aminotransferase; SHBG = sex-hormone binding-globulin; hsCRP = high-sensitivity C-reactive protein; TBF = total body fat.

^a p calculated with ANOVA for continuous variables with normal distribution, Kruskal-Wallis test for continuous variables with non-normal distribution and chi-square test for categorical variables. Significant p values are indicated in bold.

^bMedian (interquartile range).

^cNumber (%).

^dIncluding antihypertensive treatment, glucose-lowering treatment, statins, anti-platelet drugs, anticoagulants, antiarrhythmic drugs.

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Table 2

Relationship between serum uric acid and measures of endothelium-dependent and -independent vasodilation in 70-year old male community dwellers ($n = 424$).

	$\beta \pm SE$	p
Model 1 — unadjusted.		
Log(EDV)	-0.40 ± 0.17	0.03
Log(EIDV)	-0.23 ± 0.13	0.05
Log(FMD)	0.002 ± 0.002	0.47
Model 2 — adjusted for BMI.		
Log(EDV)	-0.13 ± 0.18	0.45
Log(EIDV)	-0.06 ± 0.12	0.59
Log(FMD)	0.002 ± 0.002	0.41
Model 3 — adjusted for insulin, SHBG, testosterone, vitamin D, exercise, hsCRP, ALT, HDL cholesterol, diabetes, hypertension, any cardiovascular drug use.		
Log(EDV)	-0.12 ± 0.19	0.53
Log(EIDV)	-0.07 ± 0.14	0.63
Log(FMD)	0.003 ± 0.002	0.27
Model 4 — adjusted for BMI, insulin, SHBG, testosterone, vitamin D, exercise, hsCRP, ALT, HDL cholesterol, diabetes, hypertension, any cardiovascular drug use.		
Log(EDV)	0.03 ± 0.19	0.86
Log(EIDV)	-0.04 ± 0.14	0.80
Log(FMD)	0.003 ± 0.002	0.27
Model 5 — fully-adjusted (waist/hip ratio, BMI, insulin, SHBG, testosterone, 25-hydroxyvitamin D, exercise, hsCRP, ALT, HDL cholesterol, diabetes, hypertension, any cardiovascular drug use).		
Log(EDV)	0.05 ± 0.19	0.79
Log(EIDV)	-0.05 ± 0.14	0.73
Log(FMD)	0.003 ± 0.003	0.19

BMI = body mass index; FMD = flow-mediated vasodilation; EDV = endothelium-dependent vasodilation; EIDV = endothelium-independent vasodilation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ALT = alanine aminotransferase; SHBG = sex-hormone binding-globulin; hsCRP = high-sensitivity C-reactive protein.

Table 3

Relationship between serum uric acid and measures of endothelium-dependent and -independent vasodilation in 70-year old female community dwellers ($n = 426$).

	$\beta \pm SE$	p
Model 1 — unadjusted.		
Log(EDV)	-0.57 ± 0.19	0.003
Log(EIDV)	-0.49 ± 0.15	0.002
Log(FMD)	-0.002 ± 0.003	0.47
Model 2 — adjusted for BMI.		
Log(EDV)	-0.32 ± 0.20	0.12
Log(EIDV)	-0.32 ± 0.16	0.049
Log(FMD)	-0.0003 ± 0.003	0.91
Model 3 — adjusted for insulin, SHBG, testosterone, vitamin D, exercise, hsCRP, ALT, HDL cholesterol, diabetes, hypertension, any cardiovascular drug use		
Log(EDV)	-0.43 ± 0.22	0.048
Log(EIDV)	-0.40 ± 0.17	0.02
Log(FMD)	-0.003 ± 0.002	0.31
Model 4 — adjusted for BMI, insulin, SHBG, testosterone, vitamin D, exercise, hsCRP, ALT, HDL-cholesterol, diabetes, hypertension, any cardiovascular drug use		
Log(EDV)	-0.27 ± 0.22	0.23
Log(EIDV)	-0.32 ± 0.18	0.06
Log(FMD)	-0.003 ± 0.003	0.31
Model 5 — fully-adjusted (waist/hip ratio, BMI, insulin, SHBG, testosterone, vitamin D, exercise, hsCRP, ALT, HDL cholesterol, diabetes, hypertension, any cardiovascular drug use).		
Log(EDV)	-0.34 ± 0.22	0.12
Log(EIDV)	-0.33 ± 0.17	0.07
Log(FMD)	-0.003 ± 0.03	0.36

BMI = body mass index; FMD = flow-mediated vasodilation; EDV = endothelium-dependent vasodilation; EIDV = endothelium-independent vasodilation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ALT = alanine aminotransferase; SHBG = sex-hormone binding-globulin; hsCRP = high-sensitivity C-reactive protein.