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Uric acid correlates to oxidation and inflammation in opposite directions in women

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Abstract

Objective—To evaluate the association of uric acid (UA) levels with a panel of markers of oxidative stress and inflammation.

Methods—Plasma UA levels, along with a panel of oxidative stress and inflammatory markers, were measured in 755 Chinese women.

Results—Plasma UA levels were inversely associated with urinary levels of the oxidative stress marker F₂-isoprostanes and positively correlated to levels of inflammatory markers such as C-reactive protein and some proinflammatory cytokines (tumor necrosis factor- α and interleukin-6) in blood as well as prostaglandin E₂ metabolites in urine.

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Declaration of interest

The authors report no declarations of interest.

Conclusions—Plasma UA levels correlate to oxidation and inflammation biomarkers in opposite directions in women.

Keywords

uric acid; inflammation; oxidative stress; biomarker

Introduction

In humans, oxidative stress is thought to be involved in the development of many diseases such as cancer (Halliwell, 2007), neurodegenerative disease (Valko, 2007), and cardiovascular disease (Ramond, 2011; Singh, 1995). Uric acid (UA), the end product of enzymatic degradation of xanthine in humans, is a potent endogenous antioxidant that effectively scavenges superoxide ions, singlet oxygen, hydroxyl radicals, and peroxynitrites and chelates transitional metal ions (Ames, 1981; Squadrito, 2000). For this reason, it has been hypothesized that higher UA may be beneficial to human aging (Ames, 1981). Higher circulating UA levels have been associated with a lower risk of some neurodegenerative diseases such as Parkinson's disease (Chen, 2009; de Lau, 2005) and better clinical outcomes in patients with ischemic stroke (Chamorro, 2002), although results are not entirely consistent (Weir, 2003). On the other hand, it has been shown that UA is notoriously involved in chronic inflammation. UA can stimulate the release of interleukin-1 β (IL-1 β) and IL-6 and the synthesis of tumor necrosis factor (TNF)- α in animal models (Johnson, 2005), and upregulate C-reactive protein (CRP) expression in cultured human vascular cells (Kanellis, 2005; Kono, 2010). Higher UA levels have been associated with greater risk of many inflammatory diseases, including cardiovascular disease and diabetes (Culleton, 1999; Dehghan, 2008; Fang, 2000). Therefore, it appears that UA correlates to oxidation and inflammation in opposite directions. To our knowledge, there have been very few studies that have directly evaluated the association of UA with both inflammation and oxidative stress markers in humans (Dohi, 2007).

F₂-isoprostanes (F₂-IsoPs), products of free-radical-catalyzed peroxidation of arachidonic acid, have been accepted as an accurate and reliable biomarker of *in vivo* oxidative stress (Milne, 2007b; Roberts, 2000). F₂-IsoPs are stable compounds and their levels are not affected by the lipid content of the diet. The main advantage of measurement of F₂-IsoPs in urine is that the compounds are not formed *ex vivo* because urine does not contain high lipid contents (Roberts, 2000). Currently, mass spectrometric-based methods are considered to be the gold standard for F₂-IsoPs quantification because of their high sensitivity and specificity (Milne, 2007b; Roberts, 2000). Several small observational studies have evaluated the association between UA and F₂-IsoPs, yielding mixed results with an inverse association in one study (Polidori, 2004) and a null association in another (Hershfield, 2010). In this study, we evaluated the association of UA levels with a panel of markers of oxidative stress and inflammation in 755 middle-aged women.

Methods

Study participants

In this cross-sectional analysis, 755 women were originally selected for a nested case-control study of colorectal cancer from the Shanghai Women's Health Study (SWHS). The SWHS is an ongoing prospective cohort study in Shanghai, China. Both selected cases and controls were cancer-free at baseline. The design and methods of the SWHS have been described in details elsewhere (Shu, 2004; Zheng, 2005). Briefly, at the baseline survey conducted between 1997 and 2000, 74 941 women aged 40–70 years from 7 typical urban communities of Shanghai were recruited (participation rate: 92.7%). All women completed a detailed baseline survey that collected information on demographic characteristics, lifestyle and dietary habits, medical history, and other exposures. Habitual dietary intake over the preceding 12 months was collected during in-person interviews using a validated food-frequency questionnaire (Shu, 2004). Anthropometric measurements, including weight, height, and circumferences of the waist and hips, were also taken according to a standard protocol (Zhang, 2007). A detailed assessment of physical activity was obtained using a validated questionnaire (Matthews, 2003). The study was approved by the institutional review boards for human research at the Shanghai Cancer Institute in China and the National Cancer Institute and the Vanderbilt University in the United States (IRB: 081406). Written informed consent was obtained from all study participants.

At study enrollment, 76% of cohort members donated blood and urine samples; an additional 12% provided a urine sample at the first follow-up survey approximately 2 years later after the baseline survey (Zheng, 2005). After collection, samples were kept at 4 °C and aliquoted into cryovials for long-term storage within 6 hours. Immediately after processing, all samples were stored at –70 °C until laboratory analyses were conducted.

Biomarker measurement

Levels of UA in plasma were measured by using the ACE® Uric Acid Reagent on an ACE® Clinical Chemistry System (Alfa Wassermann, Inc, West Caldwell, NJ) following the manufacturer's protocol at the Vanderbilt Lipids Laboratory, Vanderbilt University, Nashville, USA. Hyperuricemia was defined as UA > 7.0 mg/dL (Villegas, 2012).

Urinary levels of F₂-IsoPs and their major metabolite 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP (F₂-IsoP-M) were measured by gas chromatography/negative ion chemical ionization mass spectrometry (GC/NICI MS) in the Eicosanoid Core Laboratory at Vanderbilt University. Details of this method have been described elsewhere (Milne, 2007a). Urinary levels of the major urinary metabolite of prostaglandin E₂ (PGE-M) were measured using the liquid chromatography/tandem MS method by the same lab, as reported (Cai, 2006). Concentrations of F₂-IsoPs, F₂-IsoP-M and PGE-M were expressed as ng/mg creatinine. The lower limits of sensitivity were 5 pg for F₂-IsoPs and F₂-IsoP-M and 40 pg for PGE-M. The precision was ±6% and the accuracy was 96% for F₂-IsoPs and F₂-IsoP-M (Milne, 2007a). The coefficient of variation for samples analyzed in multiple batches was 7.2% for PGE-M (Cai, 2006).

Plasma levels of cytokines and their receptors were measured by using Millipore's MILLIPLEX® MAP High Sensitivity Human Cytokine multiplex kit for IL-1 β , TNF- α , and IL-6 and the MILLIPLEX® MAP Human Soluble Cytokine Receptor Panel multiplex kits for soluble IL-6 receptor (sIL-6R), soluble GP130 (sGP130, a regulator of IL-6/sIL-6R complex signaling), soluble TNF receptor 1 (sTNF-R1), and sTNF-R2. Assays were conducted in duplicate at the Vanderbilt Hormone Assay & Analytical Services Core. High-sensitivity CRP measurements were performed at the Vanderbilt Lipid Laboratory using the ACE® High Sensitivity C-Reactive Protein Reagent (ACI-22) for the first batch and the CRP (HS) Wide Range kit (Pointe Scientific, Canton, MI) for the other batches. Thus, we adjusted for batch in all analyses. Intra-assay coefficients of variation were 11.8% for TNF- α , 7.5% for sTNF-R1, 5.5% for sTNF-R2, 17.4% for IL 1 β , 15.5% for IL-6, 3.6% for sGP130 and 3.8% for sIL-6R in this study; and inter-assay coefficients of variation were < 21%.

Statistical analysis

Log-transformation was conducted to normalize the distribution of biomarker data in parametric analyses. Correlations between UA and biomarkers were assessed by Pearson correlation, and correlations between UA and categorical lifestyle factors or health conditions were assessed by biserial correlation. Multivariable-adjusted geometric means of UA were obtained based on least square means estimated using a general linear model. We also used a restricted cubic spline linear regression analysis (Harrell, 2001) to evaluate the association between UA and selected biomarkers. Knots were placed at the 5th, 50th, and 95th percentiles of the distribution of UA levels. We also calculated odds ratio (OR) for hyperuricemia associated with certain chronic diseases using unconditional logistic regression models. Covariates adjusted for in multivariable models included age, education, occupation, physical activity, history of infectious or inflammation-related diseases (tuberculosis, gastritis, asthma, chronic hepatitis, cholelithiasis and chronic pancreatitis), cigarette smoking, alcohol consumption, regular use of aspirin or other non-steroidal anti-inflammatory drugs (NSAID), regular use of vitamin supplements, dietary intakes of total calories, fruits and vegetables, as well as assay batch. We further evaluated whether the association between UA levels and oxidative stress or inflammation markers differed by infectious or inflammatory diseases. All statistical tests were two-sided and were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC).

Results

Study participants' characteristics are presented in Table 1. The mean circulating level of UA was 5.2 ± 1.3 mg/dL. The prevalence of obesity (BMI ≥ 30 kg/m², 6.8%), ever smoking (3.6%), ever drinking alcohol (2.9%), and ever using NSAIDs (3.6%) was very low. Approximately half of participants had a history of chronic disease, including hypertension (30.5%), diabetes (7.2%), and coronary heart disease (CHD, 10.1%). Women with higher levels of circulating UA were more likely to be old and obese and have a chronic disease such as diabetes, hypertension and CHD. We also found that UA levels were higher among regular users of NSAIDs and participants with higher education in a crude analysis. However, these differences disappeared after adjustment for age ($r=0.04$ for NSAID use

[$P=0.29$] and $r=0.001$ for higher education [$P=0.97$]). Other low grade inflammation-related characteristics, such as physical activity, cigarette smoking, alcohol drinking, vitamin supplementation, or dietary antioxidant intake, were not associated with circulating levels of UA.

Compared to women with normal UA levels (UA ≤ 7.0 mg/dL), hyperuricemic women had significantly lower levels of the oxidative stress marker F₂-IsoPs but higher levels of inflammatory markers CRP, IL-6, TNF- α and sTNF-R2 (Table 2). Similarly, we found that, after adjustment for age and assay batch (Table 3), UA concentrations were inversely correlated to levels of F₂-IsoPs (Pearson $r = -0.18$, $P < 0.0001$) but positively correlated to levels of inflammatory markers CRP, IL-6, TNF- α , sTNF-R2, and PGE-M, with Pearson r 's ranging from 0.12 for PGE-M to 0.42 for CRP (all $P < 0.05$). UA levels were not correlated to F₂-IsoP-M levels ($r = 0.01$, $P = 0.75$). We also used a restricted cubic spline linear regression model to account for possible non-linear effects. As illustrated graphically, associations between UA and F₂-IsoPs, CRP and TNF- α appeared monotonic and approximately linear (Figure 1, **Panels A, B and C**). In addition, UA levels were positively correlated to age (Pearson $r = 0.34$) and BMI ($r = 0.31$) in multivariable models (both $P < 0.05$; data not shown in tables).

Table 4 presents the relationship between plasma UA levels and prevalent medical conditions. After adjustment for age and assay batch, UA levels were significantly higher among participants with a history of diabetes, hypertension, or CHD (all $P < 0.05$). This association was attenuated after further adjusting for lifestyle factors, dietary and supplement antioxidants, NSAIDs, and other inflammatory diseases. We also calculated odds ratio for having hyperuricemia (UA > 7.0 mg/dL). Compared with non-diabetic individuals, patients with diabetes were nearly 2.4-fold more likely to have hyperuricemia (95% CI 1.09–5.31).

We further evaluated whether the association between UA levels and oxidative stress or inflammation differed by prevalent health conditions. No significant effect modification by the status of these health conditions was suggested (all P for interaction > 0.05). In addition, exclusion of participants with a history of renal disease ($n = 4$) did not markedly change the results.

Discussion

In this population-based sample of 755 Chinese women, we found that circulating UA levels were inversely correlated to levels of the oxidative stress marker F₂-IsoPs and positively correlated to levels of inflammatory markers such as CRP, IL-6, TNF- α , sTNF-R2, and PGE-M. In addition, UA levels were positively associated with BMI, and a higher UA level was associated with a higher prevalence of hypertension and diabetes after adjustment for age and other potential confounding factors.

We were faced with the paradoxical fact that UA is a potent endogenous antioxidant and a risk factor for some chronic diseases such as CHD (Feig, 2008), in which oxidative stress plays an important pathophysiological role. UA can scavenge various free radicals (Ames,

1981; Squadrito, 2000). Some prospective cohort studies suggest that UA may be a protective factor against Parkinson's disease (Chen, 2009; de Lau, 2005), a neurodegenerative disease where oxidative stress has been implicated. An inverse association between F₂-IsoPs and UA levels was also suggested in a small study of patients with congestive heart failure (Polidori, 2004). Moreover, administration of UA to healthy individuals during acute high-intensity aerobic exercise has been found to reduce oxidative stress (Waring, 2003).

However, increased levels of UA may act as a pro-oxidant that activates a complex vicious cycle involving mechanisms related to inflammation and oxidative stress and negatively influences the health. Cumulative evidence from animal studies suggests that UA stimulates inflammatory responses, characterized by increased production of IL-1 β , IL-6, and TNF α (Johnson, 2003) and upregulation of cyclooxygenase-2 activity and vascular CRP (Johnson, 2003; Watanabe, 2002). Higher levels of UA have been repeatedly observed in patients with inflammation-related diseases, such as metabolic syndrome, diabetes and CHD (Choi, 2005; Culleton, 1999; Dehghan, 2008). As observed in our study and two other studies (Frohlich, 2000; Ruggiero, 2006), UA levels were positively correlated to levels of inflammatory markers as well as a history of chronic inflammation-related diseases (Dorjgochoo, 2011a; Fang, 2000; Hershfield, 2010; Kodama, 2009; Sundstrom, 2005; Wu, 2013).

A potential dual effect of UA on neuronal tissues has been recently reported in a prospective follow-up study of ischemic stroke (Seet, 2010). The study found a U-shaped relationship between UA levels and clinical outcomes of stroke. Patients with low and high levels of UA were associated with poor functional outcomes, compared with those in the median level group. Kanellis et al suggested that whether UA is an anti- or pro-oxidant may depend on the cellular environment (Kanellis, 2005). In patients with ischemic stroke, serum urate is significantly lower in the acute phase and replacement of urate lowers levels of malondialdehyde, a marker of lipid peroxidation (Amaro, 2007). On the other hand, an *in vivo* experimental study recently found no significant changes in plasma F₂-IsoP concentrations during treatment with pegloticase, a very potent urate-lowering therapy, among refractory gout patients (Hershfield, 2010). In the study, levels of UA before treatment in patients with refractory gout were positively associated with levels of plasma F₂-IsoPs, which is in contrast to the finding of an inverse correlation between UA and urinary F₂-IsoPs observed in our study conducted among apparently healthy individuals with a very low prevalence of hyperuricemia (8.6%). There is no clear explanation for the discrepancy. We speculate that UA-mediated oxidative stress and redox homeostasis in refractory gout patients with significantly elevated levels of UA may not reflect the impact of UA on oxidative stress in healthy individuals. A positive relationship between UA and oxidative stress in refractory gout patients suggests that the pro-oxidant effect of UA is predominant over the antioxidant effect. On the other hand, antioxidant effect of UA may be more evident among individuals with normal UA levels such as our study population. Further investigation is clearly needed to clarify the association between UA and oxidative stress in humans.

We did not observe an association between UA and urinary F₂-IsoP-M in this study. F₂-IsoP-M is a β -oxidation metabolite of F₂-IsoPs, with a moderate correlation to the level of the

parent compound in urine (Dorjgochoo, 2011b). It has been shown that the strength of the association with oxidative stress differs by different F₂-IsoP measurements (Dorjgochoo, 2011b; Seet, 2011). Chronic cigarette smoking is associated with higher levels of F₂-IsoPs but not the metabolite F₂-IsoP-M in urine (Dorjgochoo, 2011b; Seet, 2011). However, it appears that urinary F₂-IsoP-M is a more sensitive biomarker for obesity than its parent compound F₂-IsoPs (Dorjgochoo, 2011b; Wu, 2013). Therefore, it is reasonable to take advantage of multiple rather than single F₂-IsoP markers when studying diverse health conditions or disease mechanisms.

This study has several notable strengths. To our knowledge, this is the largest study to date to examine the association of UA with both oxidative stress and inflammation in a population-based sample. Concentrations of F₂-IsoPs were measured by a GC/NICI MS-based assay. Several methodological limitations of this study should be also considered. The study was cross-sectional in design; thus, causal relationships cannot be inferred. We could not completely rule out the possibility of residual confounding due to unmeasured or inadequately measured covariates. For example, we did not consider gout treatments in the analysis because of relevant information unavailable in the study. Another concern is that biomarkers were measured in a single sample. We evaluated the intra-person variation of F₂-IsoPs and PGE-M measurements in a validation study (Wu, 2010). Four spot urine samples were collected in each season over a 1-year period. The intraclass correlation coefficients for F₂-IsoPs, F₂-IsoP-M and PGE-M were 0.69, 0.76 and 0.67, respectively, similar to that for serum cholesterol levels that is generally accepted as being measured reasonably well by a single blood sample. Moreover, although lipid peroxidation products F₂-isoprostanes have been accepted as an accurate and reliable biomarker of *in vivo* oxidative stress (Milne, 2007b; Roberts, 2000), inclusion of other oxidative stress parameters such as markers of DNA and protein oxidative damage may provide additional information on the association of UA and *in vivo* oxidation in future studies.

Conclusions

This study found that circulating UA levels are inversely correlated to oxidative stress and positively correlated to inflammatory markers, BMI and prevalence of hypertension and diabetes in women. Because of the potential dual effect of UA as an anti and pro-oxidant, both low and high UA levels could be associated with various comorbidities (Alvarez-Lario, 2011). Further investigations are certainly warranted to fully characterize the dual effect of UA and understand its health effects.

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Abbreviations

BMI	body mass index
CHD	Coronary heart disease
CI	confidence interval
CRP	C-reactive protein
F₂-IsoPs	15-F _{2t} -isoprostanes
F₂-IsoP-M	2,3-dinor-5,6-dihydro-15-F _{2t} -isoprostanes
GC/NICI MS	gas chromatography/negative ion chemical ionization mass spectrometry
MET	metabolic equivalent values
NSAID	non-steroidal anti-inflammatory drug
NHANES III	National Health and Nutrition Examination Survey
PGE-M	prostaglandin E ₂ metabolite
SD	standard deviation
sGP130	soluble GP130
sIL-6R	soluble IL-6 receptor
sTNF-R1	soluble tumor necrosis factor receptor 1
sTNF-R2	soluble tumor necrosis factor receptor 2
SWHS	Shanghai Women's Health Study
TNF-α	tumor necrosis factor- α
UA	Uric acid

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Panel A

Panel B

Panel C

Figure 1.

Smoothed plot of logarithmically transformed concentrations of oxidative stress and inflammatory markers according to plasma UA levels. The value of the studied markers at the median level of the first quartile of UA was treated as the reference point. The difference in log-transformed concentrations of the markers by UA levels were estimated by restricted cubic-spline linear regression analyses with knots placed at the 5th (3.7 mg/dL), 50th (4.9 mg/dL), and 95th (7.8 mg/dL) percentiles of UA levels after adjustment for age and assay batch. Point estimates are indicated by a solid line and 95% CIs by dashed lines. CRP: C-reactive protein; F₂-IsoPs: 15-F_{2t}-isoprostanes; TNF- α : tumor necrosis factor α .

Table 1

Correlation between selected factors and uric acid in 755 women

Continuous variable	mean (SD)	Pearson <i>r</i>	<i>P</i>
Uric acid (mg/dL)	5.2 (1.3)	-	-
Age (y)	57.8 (9.1)	0.338	<0.0001
Body mass index (kg/m ²)	24.7 (3.5)	0.311	<0.0001
Physical activity (MET hours/week)	109.3 (44.3)	-0.028	0.439
Dietary intakes			
Purine-rich food and nutrients (g/d)			
Fish	37.1 (36.8)	0.023	0.52
Shellfish	17.8 (20.2)	0.052	0.16
Meat	66.6 (48.3)	-0.051	0.17
Protein	66.6 (21.9)	0.014	0.70
Purine-rich vegetables *	50.1 (34.7)	-0.006	0.88
Dietary antioxidants (μg/d)			
Vitamin A	676.2 (369.0)	-0.043	0.24
Vitamin C	91.1 (50.4)	-0.012	0.74
Vitamin E	13.5 (5.9)	0.026	0.47
Selenium	44.0 (22.6)	0.002	0.95
Categorical variable	%	Biserial <i>r</i>	<i>P</i>
Education, high school and above	32.4	-0.08	0.03
Regularly smoked cigarettes	3.6	0.06	0.11
Regularly consumed alcohol	2.9	0.03	0.41
Regularly used NSAIDs	3.6	0.08	0.03
Regularly used antioxidant vitamin supplements	17.2	0.05	0.14
History of chronic disease †	46.0	0.21	<0.0001
Diabetes	7.2	0.14	0.0002
Hypertension	30.5	0.27	<0.0001
Coronary heart disease	10.1	0.13	0.0002

Abbreviations: MET: metabolic equivalent; NSAID: non-steroidal anti-inflammatory drug.

* Purine-rich vegetables: beans, peas, spinach, cauliflower, and mushrooms.

† History of hypertension, diabetes and coronary heart disease.

Table 2

Geometric concentrations of biomarkers in non-hyperuricemic and hyperuricemic women

Biomarkers	All participants, mean (SD)	Without hyperuricemia (uric acid $\leq$ 7 mg/dL), mean (SD)	With hyperuricemia (uric acid > 7 mg/dL), mean (SD)
Uric acid (mg/dL)	5.03 (1.26)	4.81 (1.20)	8.11 (1.12) *
F ₂ -IsoPs (ng/mg)	1.48 (1.65)	1.51 (1.64)	1.21 (1.69) *
F ₂ -IsoP-M (ng/mg)	0.59 (1.64)	0.59 (1.63)	0.61 (1.77)
CRP (mg/L)	1.03 (3.67)	0.92 (3.59)	3.46 (2.20) *
PGE-M (ng/mg)	6.73 (2.37)	6.60 (2.36)	8.21 (2.42)
IL-6 (pg/mL)	4.04 (4.26)	3.89 (4.36)	5.92 (3.10) *
sGP130 (pg/mL)	169393.01 (1.88)	167929.58 (1.93)	184259.43 (1.37)
sIL-6R (pg/mL)	19699.93 (2.1)	19516.2 (2.15)	21575.2 (1.61)
IL-1 β (pg/mL)	1.04 (5.83)	1.05 (5.68)	0.95 (7.55)
TNF- α (pg/mL)	6.26 (2.16)	6.08 (2.17)	8.48 (1.96) *
sTNF-R1 (pg/mL)	1110.34 (1.79)	1102.68 (1.70)	1187.14 (2.56)
sTNF-R2 (pg/mL)	4292.87 (1.47)	4228.49 (1.47)	4969.13 (1.41) *

* $P < 0.05$, derived from t-test between individuals with and without hyperuricemia.

Abbreviations: CRP: C-reactive protein; F₂-IsoPs: 15-F_{2t}-isoprostanes; F₂-IsoP-M: 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes; IL-1 β : interleukin 1 β ; IL-6: interleukin 6; PGE-M: prostaglandin E₂ metabolite; sGP130: soluble GP130; sIL-6R: soluble IL-6 receptor; sTNF-R1: soluble tumor necrosis factor receptor 1; sTNF-R2: soluble tumor necrosis factor receptor 2; TNF- α : tumor necrosis factor α .

Table 3

Age, batch-adjusted Pearson correlations between log-transformed concentrations of uric acid and markers of oxidative stress and inflammation

Biomarkers	<i>n</i>	<i>r</i>	<i>P</i>
F ₂ -IsoPs (ng/mg)	657	−0.18	<0.0001
F ₂ -IsoP-M (ng/mg)	630	0.01	0.75
CRP (mg/L)	755	0.42	<0.0001
PGE-M (ng/mg)	394	0.12	0.02
IL-6 (pg/mL)	658	0.13	<0.0001
sGP130 (pg/mL)	618	0.04	0.38
sIL-6R (pg/mL)	618	0.06	0.16
IL-1β (pg/mL)	658	−0.002	0.96
TNF-α (pg/mL)	658	0.19	<0.0001
sTNF-R1 (pg/mL)	618	0.06	0.17
sTNF-R2 (pg/mL)	618	0.14	<0.0001

Abbreviations: CRP: C-reactive protein; F₂-IsoPs: 15-F_{2t}-isoprostanes; F₂-IsoP-M: 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes; IL-1β: interleukin 1β; IL-6: interleukin 6; PGE-M: prostaglandin E₂ metabolite; sGP130: soluble GP130; sIL-6R: soluble IL-6 receptor; sTNF-R1: soluble tumor necrosis factor receptor 1; sTNF-R2: soluble tumor necrosis factor receptor 2; TNF-α: tumor necrosis factor α.

Table 4

Associations between uric acid concentrations and health conditions

Health condition	Age, batch-adjusted model				Multivariable-adjusted model*			
	n	Geometric mean	Standard error	P	Geometric mean	Standard error	P	
Diabetes								
No	701	5.01	1.01	0.03	5.01	1.01	0.16	
Yes	54	5.35	1.03		5.24	1.03		
Hypertension								
No	525	4.89	1.01	<0.0001	4.93	1.01	<0.001	
Yes	230	5.36	1.01		5.27	1.01		
Coronary heart disease								
No	679	5.00	1.01	0.04	5.02	1.01	0.29	
Yes	76	5.28	1.03		5.16	1.02		

* Adjusted for age, cigarette smoking, alcohol consumption, body mass index, education, physical activity, regular NSAID use, regular antioxidant vitamin use, dietary intakes of fish and shellfish, meat and antioxidant vitamins (A, C and E) and selenium, history of other infectious/inflammation-related diseases, and assay batch using linear regression models.