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Urine angiotensinogen and salt-sensitivity and potassium-sensitivity of blood pressure

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Abstract

Objective—Urinary excretion of angiotensinogen [urine angiotensinogen (UAGT)] has been proposed as a biomarker of intrarenal renin–angiotensin system activity. We investigated the association between UAGT and salt-sensitivity and potassium-sensitivity of blood pressure (BP) among Genetic Epidemiology Network of Salt Sensitivity study participants.

Methods—The intervention consisted of a 7-day low-sodium diet (51.3 mmol sodium/day), 7-day high-sodium diet (307.8 mmol sodium/day), and 7-day high-sodium diet with potassium supplementation (307.8 mmol sodium/day and 60 mmol potassium/day). Twenty-four-hour UAGT was estimated at baseline and at the end of each intervention for 100 randomly selected participants.

Results—Median UAGT ($\mu\text{g}/24\text{ h}$) and UAGT-to-creatinine ratio (UAGT/Cr, $\mu\text{g}/\text{g}$) were significantly reduced during the low-sodium and potassium-supplementation interventions and increased during the high-sodium intervention (both $P = 0.01$). Baseline log-transformed UAGT and UAGT/Cr ratio were significantly positively associated with BP at baseline and at the end of each intervention. For example, one standard deviation higher log-UAGT/Cr ratio ($1.2\text{ }\mu\text{g}/\text{g}$) was associated with a 5.0-mmHg (95% confidence interval 2.3–7.8) higher SBP at the end of the high-sodium intervention, after adjusting for multiple covariates ($P = 0.003$). In addition, one standard

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Conflicts of interest

There are no conflicts of interest.

deviation higher log-UAGT/Cr ratio was associated with a 1.6-mmHg increase in age-adjusted and sex-adjusted SBP from the low-sodium intervention to the high-sodium intervention (95% confidence interval 0.1–3.1, $P = 0.04$). This association was no longer statistically significant after multivariable adjustment.

Conclusion—These data indicate that elevated UAGT are associated with BP sodium sensitivity. Augmentation of intrarenal renin–angiotensin system activity may play an important role in developing salt-sensitive hypertension.

Keywords

angiotensinogen; blood pressure; dietary sodium; hypertension; renin–angiotensin system; salt-sensitivity

INTRODUCTION

Previous studies have documented that blood pressure (BP) responses to dietary sodium intake vary among individuals, a phenomenon called ‘salt-sensitivity’ [1,2]. BP salt-sensitivity is an important public health issue due to its association with an increased risk of hypertension and cardiovascular disease [1–4]. Heterogeneity in salt-sensitivity has been shown to be influenced by a variety of demographic, behavioral, clinical, and genetic factors [2,5–8]. In particular, dietary potassium may ameliorate salt-sensitivity of BP by mediating excretion of sodium and calcium, or by altering the vasculature either directly or through vasoactive hormones [7,9,10]. However, the underlying biologic mechanism of salt-sensitivity and potassium-sensitivity is not fully understood.

The fundamental role of the circulating renin–angiotensin system in regulating BP and sodium homeostasis is well documented [11]. In recent years, the emphasis has been on the role of renin–angiotensin system activity localized in the kidneys as it contributes to sodium retention and hypertension pathogenesis [12–15]. Urinary excretion of angiotensinogen has been proposed as a biomarker of intrarenal renin–angiotensin system activity, as it is the precursor to angiotensin I and is highly related to intrarenal angiotensinogen and angiotensin II levels [16–18]. Several cross-sectional studies have reported increased urinary levels of angiotensinogen in hypertensive, chronic kidney disease, and diabetic patients, and a direct relationship between urinary angiotensinogen level and indicators of disease severity, including BP and glomerular filtration rate [19–24].

The evidence supporting a relationship between the intrarenal renin–angiotensin system activity and salt-sensitivity is limited. Animal experiments have shown that Dahl salt-sensitive rats and other animal models that are fed a high-salt diet have a significant increase in BP, intrarenal angiotensin II, intrarenal angiotensinogen, and urine excretion of angiotensinogen [25,26]. One small study among kidney disease patients reported a significant correlation between log-transformed angiotensinogen-to-creatinine ratio (UAGT/Cr) and salt-sensitivity index [27]. The association between urinary excretion of angiotensinogen and BP response to dietary sodium and potassium intake has not been previously examined in a population without kidney disease. We undertook a dietary feeding study to examine the association of genetic and other risk factors with BP salt-sensitivity

and potassium-sensitivity among a rural population residing in northern China. In this article, we assessed the hypothesis that higher levels of urinary excretion of angiotensinogen are associated with greater salt-sensitivity and potassium-sensitivity of BP.

METHODS

Study participants

Details of the study participants and methods for the Genetic Epidemiology Network of Salt-Sensitivity (GenSalt) study have been published elsewhere [28]. In brief, a community-based BP screening was conducted among people aged 18–60 years in the study villages to identify potential probands and their families. Probands with mean SBP of 130–160 mmHg and/or mean DBP of 85–100 mmHg and no use of antihypertensive medications were recruited for the dietary feeding study, along with their siblings, spouses, and offspring aged 16 years or older. Exclusion criteria included stage 2 hypertension (BP ≥ 160/100 mmHg), secondary hypertension, clinical cardiovascular disease, diabetes (fasting plasma glucose ≥ 7.0 mmol/l), chronic kidney disease (positive urine albumin test by dipstick measurement), pregnancy, heavy alcohol consumption, a low-sodium diet, or use of antihypertensive or antidiabetic medications or insulin. Among the 1906 GenSalt dietary intervention participants, a random sample of 100 participants was selected for UAGT measures and included in the current analysis.

Institutional review boards or ethics committees at all participating institutions approved the study protocol. Written informed consent was obtained from each participant before baseline data collection and before the intervention. Procedures were followed in accordance with institutional guidelines and principles of the Declaration of Helsinki.

Intervention

After 3 days on their usual diet, study participants received a low-sodium diet (3 g sodium chloride or 51.3 mmol sodium/day) for 7 days, followed by a high-sodium diet (18 g sodium chloride or 307.8 mmol sodium/day) for an additional 7 days. In the final week, study participants maintained the high-sodium diet and took a 60-mmol potassium supplement. In previous studies assessing salt-sensitivity, 10–70 mmol sodium/day has been used for low-sodium interventions and 180–345 mmol sodium/day has been used for high-sodium interventions [29]. Other nutrient intake was consistent over the entire dietary intervention. Dietary total energy intake varied according to the baseline energy intake of each participant. All foods were cooked without salt, and prepackaged salt was added to the individual study participant's meal when it was served by the study staff. Study participants were not blinded to their dietary sodium intake, as it was not possible to blind the taste. To ensure compliance with the intervention program, participants were required to eat breakfast, lunch, and dinner at the study kitchen under the supervision of study staff during the entire study. Study participants were instructed to avoid consumption of any food or beverages that were not provided by the study. Excellent compliance to the intervention was demonstrated with the mean 24-h urinary excretion of sodium and potassium of 227.7 and 37.3 mmol at baseline, 52.7 and 30.5 mmol during the low-sodium intervention, 238.3 and

36.6 mmol during the high-sodium intervention, and 242.9 and 76.8 mmol during the high-sodium and potassium-supplementation intervention, respectively (Table 1).

Data collection

A standard questionnaire was administered to participants by trained staff at the baseline examination to obtain information about demographic characteristics, personal, and family medical history, and lifestyle risk factors, including cigarette smoking, alcohol consumption, and physical activity.

Three BP measurements were obtained every morning during the 3-day baseline observation period and on days 5, 6, and 7 of each intervention period by trained and certified individuals using a random-zero sphygmomanometer according to a standard protocol adapted from procedures recommended by the American Heart Association [30]. BP was measured with the participant in the sitting position after resting for 5 min. Participants were advised to avoid consumption of alcohol, coffee, or tea; cigarette smoking; and exercise for at least 30 min before their BP measurements. The first and fifth Korotkoff sounds were recorded as SBP and DBP, respectively. BP was measured by the same technician using the same sphygmomanometer to avoid observation variation. BP observers were blinded to the participant's dietary intervention. Body weight, height, and waist circumference were measured twice with the participant in light indoor clothing without shoes during their baseline examination. Waist circumference was measured 1 cm above the participant's navel during light breathing.

Three timed urine specimens (one 24-h and two overnight collections) were obtained at baseline and during the last 3 days of each intervention period. The completeness of urine collection, including start and end time of collection, was recorded. Urine specimens were mixed well and stored at -80°C until laboratory analysis.

Urinary levels of angiotensinogen were measured with a commercially available human total angiotensinogen sandwich enzyme-linked immunosorbent assay kit (Immuno-Biological Laboratories Co, Ltd, Minneapolis, Minnesota, USA). All urine specimens were measured in duplicate, and the average value was used for analysis. Repeated samples with a coefficient of variation greater than 10% were reanalyzed. An eight-fold dilution was used for the preparation of the majority of samples, a 2.4-fold dilution was used for samples with an initial measurement below the lowest standard, and a 40-fold dilution was used for samples with elevated absorbance values. The coefficient of variation of this assay ranged from 2.1 to 5.0%. Urinary creatinine was measured by the modified kinetic Jaffé reaction using the Olympus AU400e chemistry analyzer (Beckman Coulter, Brea, California, USA) and commercial reagents (Kamiya Biochemical Company, Seattle, Washington, USA).

Statistical analysis

BP levels at baseline and during the dietary interventions were calculated as the mean of nine measurements from three clinical visits during the 3-day baseline observation and on days 5, 6, and 7 of each intervention phase. BP salt-sensitivity was defined as absolute and percentage change in mean BP during the low-sodium intervention to mean BP during the high-sodium intervention. Potassium-sensitivity of BP was defined as absolute and

percentage change in mean BP during the high-sodium intervention to mean BP during the potassium-supplement intervention. In addition, high salt-sensitivity was defined as an increase in absolute SBP of at least 5 mmHg or an increase in percentage SBP of at least 5% from the low-sodium intervention to the high-sodium intervention $[(BP \text{ on high-sodium diet} - BP \text{ on low-sodium diet})/BP \text{ on low-sodium diet}]$. High potassium-sensitivity was defined as an increase in absolute SBP of at least 5 mmHg or an increase in percentage SBP of at least 5% from the high-sodium intervention to the potassium-supplement intervention $[(BP \text{ on potassium supplement} - BP \text{ on high-sodium diet})/BP \text{ on high-sodium diet}]$. Absolute UAGT ($\mu\text{g}/24 \text{ h}$) and UAGT/Cr ratio ($\mu\text{g}/\text{g}$) were estimated at baseline and at the end of each intervention period and were log-transformed due to the nonnormal distribution.

Basic descriptive statistics were used to describe the study population and estimate UAGT and UAGT/Cr ratio at baseline and at the end of each intervention phase. Kruskal–Wallis nonparametric analysis of variance was used to test for differences in medians of UAGT and UAGT/Cr ratio by intervention phase. The associations between one standard deviation (SD) higher log-transformed UAGT ($1.3 \mu\text{g}/24 \text{ h}$) and log-transformed UAGT/Cr ($1.2 \mu\text{g}/\text{g}$) and BP were assessed using linear and logistic regression models. Multivariate models were adjusted for age, sex, BMI, physical activity, education level, current cigarette smoking status, current alcohol drinking status, urinary excretion of sodium, and potassium. All tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina, USA).

RESULTS

The baseline characteristics of the 100 GenSalt study participants are shown in Table 2. The mean age of the participants was 44 years, and half were men. The mean SBP was 123.8 mmHg and mean DBP was 81.1 mmHg.

Average levels of UAGT and UAGT/Cr ratio were significantly different across intervention phases (both $P = 0.01$). Median (25th, 75th percentile) levels of UAGT and UAGT/Cr, respectively, were lower during the low-sodium intervention [7.16 (4.16, 13.38); 8.36 (4.26, 17.04)] and potassium-supplementation intervention [6.96 (3.24, 10.85); 8.02 (3.50, 14.31)] and higher at baseline [8.28 (4.54, 17.28); 9.40 (4.71, 16.45)] and during the high-sodium intervention [8.84 (4.64, 14.76); 10.92 (5.00, 17.66)] (Table 1).

Log-transformed UAGT and UAGT/Cr ratio at baseline was significantly and positively associated with SBP levels at baseline and at the end of each intervention (Table 3). This association persisted after adjustment for multiple covariates. For example, one SD higher log-transformed UAGT/Cr ratio ($1.2 \mu\text{g}/\text{g}$) was associated with a 5.0-mmHg [95% confidence interval (CI) 2.3–7.8] higher SBP level at the end of the high-sodium intervention, after adjusting for sex, race/ethnicity, BMI, physical activity, education level, current smoker, current drinker, and urinary excretion of sodium and potassium excretion ($P = 0.003$).

The associations between log-transformed UAGT and UAGT/Cr ratio with salt-sensitivity of SBP are reported in Table 4. Log-transformed UAGT and UAGT/Cr ratio at baseline was positively and significantly correlated with SBP change from low-sodium to high-sodium interventions ($r = 0.19$, $P = 0.05$ for log-UAGT and $r = 0.23$, $P = 0.02$ for log-UAGT/Cr). In linear regression models, after adjusting for age and sex, one SD higher log-transformed UAGT/Cr (1.2 $\mu\text{g/g}$) was associated with 1.6 mmHg higher SBP level (95% CI 0.1–3.1, $P = 0.04$). However, after multivariable adjustment, this association was no longer statistically significant (1.3 mmHg, 95% CI –0.2 to 2.9, $P = 0.10$). In general, similar patterns were observed for UAGT and UAGT/Cr and for both estimates of salt-sensitivity, using absolute and percentage change in SBP. The effect sizes for the association between UAGT and potassium-sensitivity, expressed as absolute and percentage change in SBP, were small and not statistically significant.

Odds ratios of high salt-sensitivity and potassium-sensitivity associated with baseline levels of UAGT and UAGT/Cr ratio are shown in Table 5. In a logistic regression model, one SD higher log-transformed UAGT/Cr ratio (1.2 $\mu\text{g/g}$) was associated with 1.58-times increased odds of high salt-sensitivity (5% change) of SBP (95% CI 1.00–2.50, $P = 0.05$). However, after adjusting for demographic characteristics, risk factors for hypertension, and urinary excretion of sodium and potassium excretion, the association was attenuated and no longer statistically significant.

DISCUSSION

This population-based dietary feeding study identified a direct relationship between intrarenal angiotensinogen and BP. Elevated levels of UAGT and UAGT/Cr ratio at baseline were associated with higher BP levels during the high-sodium intervention. The association between UAGT and absolute and percentage changes in BP levels was attenuated after accounting for covariates. Increased UAGT and UAGT/Cr ratio at baseline were statistically significantly associated with salt-sensitivity of SBP, expressed as absolute BP change. Associations between UAGT and BP change during the potassium-supplementation phase were weaker and not statistically significant.

The present study is the first to report the relationship between BP salt-sensitivity and intrarenal renin–angiotensin system activity, as measured by UAGT, among individuals without kidney disease. Prior research on intrarenal activity has focused on chronic kidney disease patients. Only one other study has been conducted on salt-sensitivity and UAGT [27]. In a crossover study, 41 patients with immunoglobulin A nephropathy were admitted to the hospital and were provided an ordinary-salt diet (12 g sodium chloride/day) for 1 week and a low-salt diet (5 g sodium chloride/day) for 1 week. The investigators reported a significant positive correlation between salt-sensitivity index and log-transformed UAGT/Cr ratio ($r = 0.37$, $P = 0.017$), and the association remained significant after multivariable adjustment for kidney disease severity measures.

The association of increased urinary excretion levels of angiotensinogen with BP responses to high sodium intake might occur through several potential mechanisms. Higher levels of intrarenal angiotensinogen, as the precursor to intrarenal angiotensin II, increase

concentrations of this powerful biologically active product and paracrine-signaling factor. Among its many functions, angiotensin II regulates sodium transport by renal epithelial cells, leading to increased water and sodium retention [12–15]. This pathway is amplified through positive feedback in which increased levels of angiotensin II in the kidney stimulate additional angiotensinogen mRNA and protein production in the proximal tubule cells, resulting in a greater effect on sodium retention and subsequent hypertension [13,31–33]. Oxidative stress may be involved in intrarenal angiotensinogen activity and salt-sensitivity [34,35]. In two similar experiments with Dahl salt-sensitive rats fed a high-salt diet, reactive oxygen species modulated changes in levels of intrarenal angiotensinogen and BP responses to salt intake [36,37].

This study has several noteworthy strengths. This investigation is the first population-based feeding study to examine the association between salt-sensitivity and potassium-sensitivity and urinary angiotensinogen among individuals without kidney disease. Strict data quality control was enforced at every stage of the study to ensure validity of the data. To minimize the possibility of measurement error in the estimation of urinary angiotensinogen levels, all samples were measured in duplicate and the average value was used in analysis. Furthermore, duplicate measurements that varied considerably were repeated. With respect to the minimization of error due to BP measurement, nine BP readings were obtained from multiple clinical visits by the same trained observers using the same random-zero sphygmomanometer during each phase of the study.

One potential limitation of this study is the small sample size. A larger study with sufficient statistical power to investigate the association between UAGT and BP responses is warranted, particularly for assessment of potassium-sensitivity given the observed small effect size. In addition, the intervention periods were short in duration. However, the 1-week low-sodium and 1-week high-sodium intervention duration is the standard procedure for assessing salt-sensitivity [38,39]. This study was conducted in a rural population residing in northern China and may not be broadly generalizable.

In this population-based dietary feeding study, elevated baseline levels of urine angiotensinogen were associated with higher BP levels and salt-sensitivity of SBP during the high-sodium intervention. Associations between urine angiotensinogen and potassium-sensitivity of BP were weaker and not statistically significant. This study suggests that augmentation of the intrarenal renin–angiotensin system activity may play an important role in the development of salt-sensitive hypertension. Furthermore, elevated levels of UAGT may help predict BP sodium-sensitivity, BP levels, and related cardiovascular disease consequences. Further studies are needed to confirm this observation. In addition, clinical trials that test the effect of blocking renin–angiotensin system activity on BP sensitivity to sodium are warranted.

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Abbreviations

BP	blood pressure
GenSalt study	Genetic Epidemiology Network of Salt Sensitivity study
UAGT	urine angiotensinogen
UAGT/Cr	urine angiotensinogen-to-creatinine ratio

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TABLE 1

Mean (standard deviation) of blood pressure and urinary excretion of sodium, potassium, and angiotensinogen during low-sodium, high-sodium, and potassium-supplement interventions

	Low-sodium interventions	High-sodium interventions	Potassium-supplement interventions	<i>P</i> value for group difference
Absolute BP (mmHg)				
SBP	108.6 (10.2)	115.1 (12.4)	109.9 (10.5)	<0.001
DBP	70.0 (8.9)	73.1 (9.3)	69.8 (7.4)	0.006
BP changes (mmHg) ^a				
SBP	−7.0 (6.9)	6.5 (9.0)	−5.2 (7.3)	<0.001
DBP	−3.7 (6.7)	3.1 (9.2)	−3.3 (5.8)	<0.001
Urinary excretion (/24 h)				
Sodium (mmol)	52.7 (18.7)	238.3 (32.4)	242.9 (32.7)	<0.001
Potassium (mmol)	30.5 (10.8)	36.6 (7.2)	76.8 (14.5)	<0.001
UAGT (μg) ^b	7.16 (4.16, 13.38)	8.84 (4.64, 14.76)	6.96 (3.24, 10.85)	0.01
UAGT/Cr (μg/g) ^b	8.36 (4.26, 17.04)	10.92 (5.00, 17.66)	8.02 (3.50, 14.31)	0.01

BP, blood pressure; UAGT/Cr, urinary angiotensinogen-to-creatinine ratio; UAGT, urinary angiotensinogen.

^a BP change due to low-sodium intervention = BP at low-sodium – BP at baseline; BP change due to high-sodium intervention = BP at high-sodium – BP at low-sodium; and BP change due to potassium-supplement intervention = BP at high-sodium and potassium supplementation – BP at high-sodium.

^b Median (25th, 75th percentile).

TABLE 2Baseline characteristics of GenSalt study participants ($N = 100$)

	Mean (SD) or %
Age (years)	44.1 (7.4)
Male (%)	50.0
At least high school education (%)	12.0
Current smoker (%)	30.0
Current drinker (%)	28.0
BMI (kg/m ²)	24.5 (3.3)
Waist circumference (cm)	82.4 (10.4)
Urinary sodium (mmol/24 h)	227.7 (65.1)
Urinary potassium (mmol/24 h)	37.3 (10.9)
UAGT (μg/24 h) ^a	8.28 (4.54, 17.28)
UAGT/Cr (μg/g) ^a	9.40 (4.71, 16.45)
SBP (mmHg)	123.8 (16.0)
DBP (mmHg)	81.1 (9.7)
Hypertensive (≥ 140/90 mmHg) (%)	24.0

SD, standard deviation; UAGT/Cr, urinary angiotensinogen-to-creatinine ratio; UAGT, urinary angiotensinogen.

^aMedian (25th, 75th percentile).

TABLE 3

Regression coefficients (95% confidence intervals) of SBP (mmHg) at baseline and at the end of each intervention associated with one standard deviation higher in log-transformed urinary angiotensinogen and urinary angiotensinogen-to-creatinine ratio at baseline^a

Intervention phase	Model	log(UAGT)		log(UAGT/Cr)	
		β (95% CI)	P	β (95% CI)	P
Baseline	Unadjusted	4.4 (1.6–7.2)	0.004	3.5 (0.3–6.7)	0.03
	Age adjusted and sex adjusted	4.7 (1.9–7.5)	0.003	3.9 (1.1–6.7)	0.01
	Multivariable adjusted ^b	5.3 (2.4–8.2)	0.003	4.7 (1.7–7.8)	0.01
Low sodium	Unadjusted	4.0 (1.5–6.5)	0.004	2.7 (0.1–5.4)	0.047
	Age adjusted and sex adjusted	4.1 (1.4–6.7)	0.005	3.9 (1.3–6.6)	0.01
	Multivariable adjusted ^b	4.4 (1.9–6.8)	0.004	3.9 (1.3–6.6)	0.01
High sodium	Unadjusted	5.1 (2.7–7.5)	0.0003	4.3 (1.8–6.9)	0.003
	Age adjusted and sex adjusted	5.3 (2.8–7.8)	0.0005	4.5 (1.8–7.2)	0.003
	Multivariable adjusted ^b	5.3 (2.7–7.8)	0.002	5.0 (2.3–7.8)	0.003
Potassium supplement	Unadjusted	4.6 (2.4–6.7)	0.0004	4.4 (2.3–6.4)	0.0004
	Age adjusted and sex adjusted	4.6 (2.5–6.8)	0.0004	4.5 (2.3–6.6)	0.0005
	Multivariable adjusted ^b	4.7 (2.4–7.0)	0.002	5.3 (3.0–7.5)	0.0009

CI, confidence interval; SD, standard deviation; UAGT/Cr, urinary angiotensinogen-to-creatinine ratio; UAGT, urinary angiotensinogen.

^aOne SD in log-transformed UAGT: 1.3 µg/24 h; one SD in log-transformed UAGT/Cr: 1.2 µg/g.

^bAdjusted for age, sex, BMI, physical activity, education level, current cigarette smoking status, current alcohol drinking status, urinary excretion of sodium, and potassium.

Regression coefficients (95% confidence intervals) of salt-sensitivity and potassium-sensitivity associated with one standard deviation change in log-transformed urinary angiotensinogen and urinary angiotensinogen-to-creatinine ratio at baseline^a

TABLE 4

	Model	log(UAGT)		log(UAGT/Cr)	
		β (95% CI)	P	β (95% CI)	P
Salt-sensitivity					
Absolute change (mmHg)	Unadjusted	1.5 (0.0–3.1)	0.05	1.8 (0.3–3.4)	0.02
	Age adjusted and sex adjusted	1.5 (0.0–3.0)	0.05	1.6 (0.1–3.1)	0.04
	Multivariable adjusted ^b	1.3 (–0.3 to 2.9)	0.10	1.3 (–0.2 to 2.9)	0.10
Percentage change (%)	Unadjusted	1.1 (–0.3 to 2.5)	0.12	1.4 (0.0–2.8)	0.05
	Age adjusted and sex adjusted	1.1 (–0.3 to 2.4)	0.12	1.2 (–0.1 to 2.5)	0.08
	Multivariable adjusted ^b	0.9 (–0.5 to 2.3)	0.20	0.9 (–0.4 to 2.3)	0.18
Potassium-sensitivity					
Absolute change (mmHg)	Unadjusted	–0.4 (–1.8 to 1.0)	0.58	0.2 (–1.2 to 1.6)	0.80
	Age adjusted and sex adjusted	–0.4 (–1.8 to 1.0)	0.57	0.2 (–1.2 to 1.6)	0.76
	Multivariable adjusted ^b	–0.4 (–1.8 to 1.1)	0.63	0.4 (–1.1 to 1.8)	0.61
Percentage change (%)	Unadjusted	–0.2 (–1.3 to 0.8)	0.68	0.2 (–0.8 to 1.3)	0.65
	Age adjusted and sex adjusted	–0.2 (–1.3 to 0.8)	0.68	0.3 (–0.8 to 1.3)	0.62
	Multivariable adjusted ^b	–0.2 (–1.3 to 0.9)	0.69	0.4 (–0.8 to 1.5)	0.52

CI, confidence interval; SD, standard deviation; UAGT/Cr, urinary angiotensinogen-to-creatinine ratio; UAGT, urinary angiotensinogen.

^a One SD in log-transformed UAGT: 1.3 µg/24 h; one SD in log-transformed UAGT/Cr: 1.2 µg/g.

^b Adjusted for age, sex, BMI, physical activity, education level, current cigarette smoking status, current alcohol drinking status, urinary excretion of sodium, and potassium.

TABLE 5

Odds ratios (95% confidence intervals) for high salt-sensitivity and potassium-sensitivity of SBP (5%) associated with one standard deviation change in log-transformed urinary angiotensinogen and urinary angiotensinogen-to-creatinine ratio at baseline^a

	Model	log(UAGT)		log(UAGT/Cr)	
		OR (95% CI)	P	OR (95% CI)	P
Salt-sensitivity	Unadjusted	1.35 (0.89–2.05)	0.16	1.58 (1.00–2.50)	0.05
	Age adjusted and sex adjusted	1.36 (0.88–2.11)	0.16	1.52 (0.96–2.41)	0.07
	Multivariable adjusted ^b	1.27 (0.79–2.03)	0.33	1.39 (0.86–2.25)	0.18
Potassium-sensitivity	Unadjusted	1.07 (0.70–1.63)	0.77	0.93 (0.61–1.41)	0.73
	Age adjusted and sex adjusted	1.07 (0.70–1.64)	0.74	0.94 (0.61–1.43)	0.76
	Multivariable adjusted ^b	1.06 (0.65–1.72)	0.82	0.93 (0.58–1.49)	0.75

CI, confidence interval; OR, odds ratio; SD, standard deviation; UAGT/Cr, urinary angiotensinogen-to-creatinine ratio; UAGT, urinary angiotensinogen.

^aOne SD in log-transformed UAGT: 1.3 µg/24 h; one SD in log-transformed UAGT/Cr: 1.2 µg/g.

^bAdjusted for age, sex, BMI, physical activity, education level, current cigarette smoking status, current alcohol drinking status, urinary excretion of sodium, and potassium.