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Sodium Intake Is Associated With Renal Resistive Index in an Adult Population-Based Study

David A. Jaques, Menno Pruijm, Daniel Ackermann, Bruno Vogt, Idris Guessous, Michel Burnier, Antoinette Pechere-Bertschi, Murielle Bochud, Belen Ponte

Abstract—Renal resistive index (RRI) has been associated with adverse renal and cardiovascular outcomes. Although traditionally considered a marker of intrinsic renal damage, RRI could also reflect systemic vascular dysfunction. As sodium intake was linked to alterations in vascular properties, we wished to characterize the association of salt consumption with RRI in the general adult population. Participants were recruited in a population-based study in Switzerland. RRI was measured by ultrasound in 3 segmental arteries. Sodium intake (UNa; mmol/24 h) was estimated on 24-hour urine samples. Carotido-femoral pulse wave velocity was obtained by applanation tonometry. Mixed multivariate regression models were used with RRI or pulse wave velocity as independent variables and UNa as dependent variable, adjusting for possible confounders. We included 1002 patients in the analyses with 528 (52.7%) women and mean age of 47.2±17.4. Mean values of UNa and RRI were 141.8±61.1 mmol/24 h and 63.8±5.5%, respectively. In multivariate analysis, UNa was positively associated with RRI (P=0.002) but not with pulse wave velocity (P=0.344). Plasma renin activity and aldosterone did not modify the relationship between UNa and RRI (P=0.087 for interaction). UNa/urinary potassium ratio was positively associated with pulse wave velocity ≥12 m/s (P=0.033). Our results suggest that dietary salt consumption has a direct impact on renal hemodynamic in the adult general population. Alterations in vascular properties likely explain those findings, but inadequate renal vaso-motor response is also possible. Sodium intake could thus potentially be linked to underlying structural systemic damages affecting this population. **(*Hypertension*. 2020;76:1898-1905. DOI: 10.1161/HYPERTENSIONAHA.120.15932.)** ● **Data Supplement**

Key Words: aldosterone ■ blood pressure ■ hypertension ■ renin ■ sodium vascular stiffness

Renal resistive index (RRI) is defined as the difference between maximum systolic velocity and end-diastolic velocity divided by maximum systolic velocity, as measured by Doppler ultrasound in interlobar or segmental arteries.[1] Evidences exist that RRI represents intrinsic organ damage as it has been found to correlate with albuminuria, chronic interstitial nephropathy, progression of chronic kidney disease as well as renal pathology.[2–5] However, as RRI was also associated with adverse cardiovascular outcomes, it could be the reflection of broader systemic damages.[2,6] In this regard, RRI can be mathematically formulated as depending on pulse pressure (PP) and vascular compliance only.[7] This theoretical view is supported by clinical studies linking RRI to PP and vascular stiffness measured by carotido-femoral pulse wave velocity (PWV).[8,9] RRI was also associated with levels of inactive MGP (matrix gamma-carboxyglutamate) protein as a marker of systemic vascular calcification.[9]

Dietary habit in the Western world is characterized by an increased consumption of refined and processed food providing sodium-rich and potassium-poor intakes.[10] The causal relationship between excessive dietary sodium and hypertension is well established, and several studies demonstrated a decrease in blood pressure (BP) following sodium intake lowering both in hypertensive and normotensive individuals.[11,12] Beyond its functional hemodynamic effect, sodium intake could also alter structural vascular properties. Elevated dietary salt consumption was thus suggested to adversely affect endothelial function and arterial stiffness independently of BP control.[13–16] High sodium intake could also affect renal physiology independently of classical risk factors as it was associated with faster renal function decline in the general adult population.[17] The potential link between salt consumption and RRI has, however, not been previously evaluated.

In the present study, we wished to characterize the association of salt consumption estimated on 24-hour urinary collection with RRI in the general adult population. Our primary hypothesis was that an elevated sodium intake would be linked to an increased RRI consequently to alterations in structural vascular properties. A secondary objective was to

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characterize vascular stiffness as well as renin and aldosterone regulation in this setting.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participant Selection

SKIPOGH (Swiss Kidney Project on Genes in Hypertension) is a family-based cross-sectional study exploring the role of genes and kidney hemodynamics in BP regulation and kidney function in the general population.[18] From December 2009 to March 2013, adult participants were recruited in 2 regions (Bern and Geneva) and one city (Lausanne) of Switzerland. Population sampling has been described in detail previously.[18] Briefly, inclusion criteria were (1) being of European ancestry, (2) having other first-degree family members willing to participate, and (3) providing a written informed consent. Exclusion criteria were (1) age <18 and (2) pregnant or breastfeeding women. Family members willing to participate were included based on the same inclusion and exclusion criteria. Participants were seen in the morning after an overnight fast. Every clinical and para-clinical data were collected during the same visit.

Clinical and Laboratory Data

BP was measured 5× after a resting period of ≥10 minutes in the sitting position with a nonmercury manual auscultatory sphygmomanometer (A&D UM-101; A&D Company Ltd, Toshima Ku, Tokyo, Japan), according to the guidelines of the European Society of Hypertension.[19] For the analyses, we used the mean of the past 4 BP and heart rate (HR) measurements. Blood glucose, electrolytes, kidney, and liver function tests as well as serum cholesterol levels were analyzed by standard clinical laboratory methods. Plasma renin activity (PRA) was measured using a radioimmunoassay commercial kit for the quantitative determination of angiotensin I in human plasma (REN-CT2; CISBio International, Yvette, France). Aldosterone quantification was performed with Aldo-Riact RIA kit (CISBio International, Yvette, France). The precision of these assays, based on intra- and inter-assay coefficients of variations, were respectively 3.4% and 7.0% for PRA with a limit of quantification of 0.08 ng/(mL·h) and 2.8% and 8.7% for aldosterone with a limit of quantification of 18 pg/mL. Twenty-four hour urine samples were collected from morning to the next morning. First morning urine was discarded.

Renal Doppler Ultrasound

In each study centre, the same experienced operator performed renal gray scale and color duplex ultrasounds according to a standardized procedure as described previously.[20] Briefly, RRI was measured in 3 segmental arteries (superior, middle, and inferior) of each kidney. The values were then averaged to obtain a mean value for each participant. Values were multiplied by 100 to express the RRI results as percentage.

Arterial Waveform

Arterial waveforms were assessed during an 8 second period in the supine position after 15 minutes of rest at the carotid and femoral arteries by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc, Houston), interfaced with a laptop computer running the SphygmoCor software version 8.0 or 8.2 (AtCor Medical Pty. Ltd, West Ryde, Australia). In each study centre, the same experienced operator obtained the arterial waveforms and recorded PWV, as previously described.[21] PWV were directly measured, and a validated transfer function was used to obtain central augmentation index (AI) adjusted for heart frequency and central augmented pressure (AP) as central hemodynamic parameters.[22] AP is the difference between the second and the first systolic peaks. AI is the ratio of AP to aortic PP calculated as the difference between respective systolic and diastolic pressures.

Definitions

Diabetes mellitus was defined as present when reported or treated or when fasting blood glucose level was ≥7 mmol/L. Hypertension was considered present when treated or when mean office BP was ≥140/90 mm Hg according to European Guidelines.[19] PP was defined as systolic BP (SBP) minus diastolic BP (DBP). The chronic kidney disease epidemiology collaboration formula was used to estimate glomerular filtration rate (eGFR).

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD) or median and interquartile range according to distribution. Categorical variables are expressed as number and relative frequency (%). Normality of distribution was assessed graphically. Variables were compared between groups (tertiles) using 1-way ANOVA or Kruskal-Wallis (depending on Bartlett test) and χ^2 for continuous and categorical variables, respectively.

In main analysis, multivariate linear regressions were used in 3 sequential steps. First, variables associated with RRI were considered amongst the following a priori selected variables: age, gender, body mass index (BMI), body height, hypertension, diabetes mellitus, SBP, DBP, HR, eGFR, serum glucose, low-density lipoprotein, high-density lipoprotein, smoking, history of cardiovascular disease, and study centre. Second, variables associated with urinary sodium (UNa; mmol/24 h) were considered among the same variables with the addition of the following a priori selected variables: urinary potassium (UK), urinary creatinine, urinary albumin, and 24-hour urinary volume. Eventually, significant variables commonly found in both model were integrated as covariables in a third model where RRI was the dependent variable and UNa the main independent variable. Significant covariables were kept in the final model. As age was demonstrated to have a quadratic relationship with RRI, age and the square of age were considered in multivariate models.[20]

In secondary analyses, PRA and aldosterone as well aldosterone/PRA ratio (ARR) were added to other considered covariates in 2 distinct models, excluding patients treated for hypertension. Models construction and specification were identical to main analysis. The relationship between UNa and markers of vascular stiffness (PWV, AI, and AP) was also investigated in 3 distinct models. Models construction and specification were identical to main analysis.

Sensitivity analyses were conducted with UNa/UK instead of UNa as the main independent variable. Multi-level mixed effect was implemented in every regression model to account for inter-dependence of family clusters. Family identification was considered as the grouping variable, and random effect was applied to the intercept. In final models, interactions were tested for selected variables. Interaction was considered significant if *P* value for likelihood ratio test (LRT) comparing models with and without interaction term was <0.05. Sub-group analyses were conducted in case of significant interaction only. R^2 was estimated with Snijders and Bosker method.[23] Linearity of relationship, normality of residuals, and homoscedasticity of residuals were assessed graphically. Log-normal variables were log-transformed when used in regression models. Data were considered to be missing completely at random, and therefore, patients with any missing value were excluded from the multivariate analyses. For every model, results are presented as β coefficients and associated 95% CI as well as *P* values. UNa was standardized to a mean of 0 and a SD of 1, so that every unit increase in the models represents an increase in 1 SD. A 2-sided $P<0.05$ was considered significant in every analysis. Statistical analyses were conducted using STATA version 15 (StataCorp, 4905 Lakeway Drive, College Station, TX 77845).

Ethics

Institutional ethical committees of each participating university hospitals approved the SKIPOGH study. This study was conducted according to the declaration of Helsinki.

Results

The complete cohort included 1026 participants. As 24 patients had missing values on UNa and RRI and no

outliers were specified, 1002 patients were included in the present analyses.

Mean values of UNa and RRI were 141.8±61.1 mmol/24 h and 63.8±5.5%, respectively. Overall, 528 (52.7%) of participants were women, and mean age was 47.2±17.4. Participant's characteristics are described according to tertiles of UNa in Table 1. Low, medium, and high UNa cutoff tertile values were <110.4 mmol/24 h, 110.4 mmol/24 h to 160.5 mmol/24 h, and >160.5 mmol/24 h. Across increasing tertiles of UNa, participants had less frequently chronic kidney disease (defined as eGFR <60 ml/min/1.73m^2), were more frequently men and were younger and taller (P<0.05 for all). They had higher BMI, SBP, and DBP as well as lower HR (P<0.05 for all). Increasing UNa was also associated with higher eGFR, lower high-density lipoprotein, and lower aldosterone (P<0.001 for all). UK, UNa/UK, creatininuria, and urinary volume were higher with increasing UNa (P<0.001 for all). RRI and PWV were not different across UNA tertiles, while AI and AP were lower with increasing UNa (P<0.05 for both).

Association Between UNa and RRI

In univariate analysis, UNa was negatively associated with RRI: every 1 SD (61.1 mmol/24 h) increase in UNa was associated with a decrease of 0.38% in RRI (P=0.025).

Multivariate analysis included 977 participants without missing values on considered covariables. In the final model, factors positively associated with RRI were (Table 2): UNa, age, female gender, BMI, SBP, and serum glucose. Factors negatively associated with RRI were DBP, HR, urinary creatinine, and urinary volume. In the final model, every 1 SD (61.1 mmol/24 h) increase in UNa was associated with a 0.42% increase in RRI (Figure). Adjusted R^2 for the final model was 62.7%. Significant variables contributed to R^2 in the following descending order: age, DBP, SBP, gender, HR, BMI, serum glucose, UNa, urinary volume, and urinary creatinine. The following variables were not associated with RRI in the final model: body height, hypertension, diabetes mellitus, eGFR, low-density lipoprotein, high-density lipoprotein, smoking, history of cardiovascular disease, UK, and urinary albumin. In interaction testing, no modification effect was found between UNa and age, gender, SBP or DBP (P>0.05 for LRT for all). Specifically, while female gender was positively associated with RRI, gender did not modify the relationship between UNa and RRI in the final model (P=0.775 for LRT; Figure S1 in the Data Supplement).

Several sensitivity analyses were conducted. First, the main analysis was repeated excluding patients with creatininuria in umol/(kg·24 h) below or above fifth and 95th percentile, respectively. Ninety-six observations were thus excluded, and the model included 881 participants. Results were similar to the main model, and UNa was positively associated with RRI (β=0.38 [95% CI, 0.10–0.66], P=0.007; Table S1). Second, the main analysis was repeated with the omission of SBP and DBP as covariables. Results were similar, and UNa was positively associated with RRI (β=0.51 [95% CI, 0.23–0.80], P<0.001). Third, the main analysis was repeated with the addition of PWV as a covariable. Results were similar, and UNa was positively associated with RRI (β=0.45 [95% CI, 0.18–0.72], P=0.001). Fourth, UNa/UK was substituted in the final model instead of UNa, while urinary creatinine and urine volume were omitted. In this model, UNa/UK was also positively associated with RRI (β=0.51 [95% CI, 0.03–0.98], P=0.035). Fifth, UNa/urinary creatinine was substituted in the final model instead of UNa, while urinary creatinine was omitted. Results were similar, and UNa/urinary creatinine was positively associated with RRI (β=0.09 [95% CI, 0.04–0.15], P<0.001). Sixth, the main analysis was repeated excluding patients taking antihypertensive medications. Eight hundred twenty-two patients were considered, and results were similar as UNa remained positively associated with RRI (β=0.49 [95% CI, 0.22–0.77], P<0.001). Finally, the main analysis was repeated with PP as a covariate instead of SBP and DBP. Results were similar, and UNa remained positively associated with RRI (β=0.40 [95% CI, 0.13–0.68], P=0.003), while PP was positively associated with RRI (β=0.12 [95% CI, 0.10–0.14], P<0.001).

Effect of PRA and Aldosterone on the Association Between UNa and RRI

PRA and aldosterone were available in 624 patients not treated for hypertension. When accounting for PRA and aldosterone, neither variable was associated with RRI in the final model. No interaction was found between PRA or aldosterone and UNa (P=0.382 and P=0.437 for LRT, respectively). When accounting for ARR, this variable was negatively associated with RRI in the final model (β=−0.31 [95% CI, −0.61 to −0.02], P=0.034). UNa remained positively associated with RRI (β=0.46 [95% CI, 0.14–0.78], P=0.004). No interaction was found between ARR and UNa (P=0.087 for LRT).

Association Between UNa and Arterial Waveform

PWV, AI, and AP were available in 925, 955, and 964 patients, respectively. In the final model, factors associated with an increase in PWV were (Table 3) age, BMI, diabetes mellitus, SBP, and serum glucose. No factor was associated with a decrease in PWV. UNa was not associated with PWV. In sensitivity analysis, the binary variable PWV ≥12 m/s was substituted instead of the continuous variable PWV, and UNa/UK was substituted instead of UNa. In this model, UNa/UK was positively associated with PWV ≥12 m/s (β=1.05 [95% CI, 0.08–2.02], P=0.033; Table S2).

In the final model, factors positively associated with AI were age, female gender, DBP, and smoking. Factors negatively associated with AI were body height and HR. Factors positively associated with AP were age, female gender, SBP, and smoking. Factors negatively associated with AP were BMI, body height, and HR. UNa was neither associated with AI (β=−0.29 [95% CI, −0.91 to 0.32], P=0.356) nor AP (β=−0.16 [95% CI, −0.54 to 0.21], P=0.391). UNa/UK was substituted instead of UNa. UNa/UK was neither associated with AI (β=−0.65 [95% CI, −1.92 to 0.61], P=0.309) nor AP (β=0.14 [95% CI, −0.61 to 0.90], P=0.713).

Discussion

This study shows how sodium and potassium intakes estimated on 24-hour urinary sample, are associated with renal hemodynamic, as assessed by renal Doppler ultrasound. We could not find an association with arterial stiffness except when considering sodium to potassium ratio and a highly pathological value of PWV ≥12 m/s.

Table 1. Patients Characteristics According to Tertiles of UNa (mmol/24 h)

Characteristics	Overall, N=1002	Low UNa (<110.4 mmol/24 h), N=334	Medium UNa (110.4–160.5 mmol/24 h), N=334	High UNa (>160.5 mmol/24 h), N=334	*P* Value
Categorical variables and comorbidities, n (%)					
Gender, female	528 (52.7%)	237 (71.1%)	176 (52.6%)	115 (34.3%)	<0.001
Smoker	240 (24.1%)	87 (26.5%)	79 (23.7%)	74 (22.2%)	0.424
Diabetes mellitus	39 (3.8%)	11 (3.2%)	15 (4.4%)	13 (3.8%)	0.726
Treated for diabetes mellitus	14 (1.4%)	5 (1.5%)	5 (1.5%)	4 (1.2%)	0.925
Hypertension	228 (22.9%)	72 (21.8%)	74 (22.2%)	82 (24.5%)	0.678
Treated for hypertension	154 (15.4%)	52 (15.7%)	45 (13.5%)	57 (17%)	0.439
CV disease	108 (10.9%)	38 (11.8%)	30 (9%)	40 (12%)	0.383
Treated for dyslipidemia	43 (4.3%)	12 (3.6%)	13 (3.9%)	18 (5.3%)	0.487
Obesity*	138 (13.7%)	42 (12.5%)	45 (13.4%)	51 (15.2%)	0.589
Chronic kidney disease†	31 (3.0%)	18 (5.3%)	7 (2.1%)	6 (1.8%)	0.012
Clinical characteristics, mean±SD or median (IQR)					
Age, y	47.2±17.4	49.2±18	47±17.7	45.4±16.2	0.019
Body height, cm	170.6±9.1	167.2±8.8	170.5±8.8	174±8.6	<0.001
BMI, kg/m^2	25±4.5	24.2±4.6	25±4.4	26±4.4	<0.001
SBP, mm Hg	118.1±16.9	116.1±16.6	118.4±18	119.7±15.9	0.017
DBP, mm Hg	75.5±9.5	74.5±9.4	75.3±9.7	76.8±9.5	0.008
PP, mm Hg	42.5±12.5	41.5±12	43.1±13.6	42.9±12	0.217
HR, 1/min	67.1±10.9	69.2±11.6	66.5±10.9	65.6±9.8	<0.001
Laboratory characteristics, mean±SD or median (IQR)					
eGFR, mL/(min·1.73 m^2)	96.5±17.9	93.5±18.5	96.9±17.9	99.2±17	<0.001
LDL, mmol/L	3.1±0.92	3.13±0.87	3.11±0.92	3.07±0.96	0.726
HDL, mmol/L	1.5±0.39	1.56±0.44	1.54±0.42	1.41±0.39	<0.001
Glucose, mmol/L	5.19±0.74	5.16±0.7	5.18±0.77	5.22±0.73	0.519
PRA, ng/(mL·h)‡	0.48 (0.24–0.76)	0.50 (0.24–0.84)	0.47 (0.24–0.74)	0.45 (0.24–0.71)	0.475
Aldosterone, pg/mL‡	60.7 (41.5–94.3)	68.7 (47–130)	62.5 (42–94.3)	54.5 (37–83)	<0.001
Urinary characteristics, mean±SD or median (IQR)					
UNa, mmol/24 h	141.8±61.1	81.6±22	134.9±13.9	209±48.4	<0.001
UK, mmol/24 h	63.7±23.1	53.7±21.3	63.1±18.5	74.4±24.4	<0.001
UNa/UK	2.1 (1.6–2.8)	1.6 (1.1–2.1)	2.1 (1.7–2.7)	2.8 (2.2–3.6)	<0.001
Urinary creatinine, mmol/24 h	12.7±4.2	10.6±3.2	12.6±3.5	15±4.4	<0.001
Urinary albumin, mg/24 h	5.9 (3.7–10.2)	5.8 (3.6–8.8)	5.9 (3.9–10.8)	6 (3.8–11.2)	0.204
Urinary volume, l/24 h	1.7±0.75	1.44±0.68	1.71±0.76	1.96±0.7	<0.001
Other relevant characteristics, mean±SD or median (IQR)					
RRI, %	63.8±5.5	64.1±5.6	63.8±5.9	63.4±5.1	0.225
PWV, m/s	7.4 (6.4–8.9)	7.5 (6.4–9.1)	7.3 (6.3–8.8)	7.5 (6.4–8.9)	0.668
AI, %§	22.8±15.7	26±16.3	22.3±16.3	20.2±14	<0.001
AP, mm Hg‖	9.5±9.1	10.4±8.8	10 +/. 10.5	8.1±7.5	0.001

AI indicates augmentation index; AP, augmented pressure; BMI, body mass index; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; IQR, interquartile range; LDL, low-density lipoprotein; PP, pulse pressure; PRA, plasma renin activity; PWV, pulse wave velocity; RRI, renal resistive index; SBP, systolic blood pressure; UK, urinary potassium; and UNa, urinary sodium.

*Defined as BMI ≥30 kg/m^2.

†Defined as eGFR <60 mL/min per 1.73m^2.

‡Available in a sub-group of 624 patients not treated for hypertension.

§Available in a sub-group of 955 patients.

‖Available in a sub-group of 964 patients.

Table 2. Factors Associated With RRI (%) in Final Multivariate Model

Independent Variables	Final Model		
	B	95% CI	*P* Value
UNa, mmol/24 h*	0.42	0.15 to 0.68	0.002
Age, y	0.11	0.09 to 0.12	<0.001
Gender, women	1.5	0.91 to 2.08	<0.001
BMI, kg/m^2	0.11	0.05 to 0.16	<0.001
SBP, mm Hg	0.12	0.11 to 0.15	<0.001
DBP, mm Hg	−0.24	−0.27 to −0.2	<0.001
HR, L/min	−0.04	−0.06 to −0.027	<0.001
Glucose, mmol/L	0.73	0.38 to 1.08	<0.001
Urinary creatinine, mmol/24 h	−0.1	−0.18 to −0.02	0.010
Urinary volume, L/24 h	−0.52	−0.83 to −0.21	0.001

Model is also adjusted for age^2 and centre (not shown in the table). BMI indicates body mass index; DBP, diastolic blood pressure; HR, heart rate; RRI, renal resistive index; SBP, systolic blood pressure; and UNa, urinary sodium.

*Standardized to a mean of 0 and a SD of 1.

As implied by its name, RRI has long been considered a marker of renal pathology based on the assumption that structural changes in the kidney would alter renal vascular resistance (RVR).[24] This concept has, however, shifted over time as systemic rather than organic factors could in fact be the main determinants of RRI.[7] In favor of this view, RRI can mathematically be formulated as[7]: $RRI = 1 - \frac{DBP - P0}{SBP - P0} \times \frac{LAsys}{LAdia}$, where P0 corresponds to the combination of venous and interstitial pressures while LAsys and LAdia correspond to systolic and diastolic vessel lumen area, respectively. As P0 is negligible in most clinical situations, RRI is thus directly proportional to PP and inversely proportional to vascular compliance. Animal studies support this theory as RRI showed a strong linear correlation with PP in rabbit perfused kidney.[25] Clinical studies also support this view as RRI was correlated with both PP and PWV in hypertensive patients as well as in the adult general population.[8,9] This preponderance of vascular compliance in RRI physiology has also been shown in a simple experimental setting where RRI became less dependent on vascular resistance as compliance decreased to the point of resistance independence with zero compliance.[26]

The main finding of our study is the positive association between salt intake estimated on a 24-hour urinary collection and RRI in a large adult general population. This relationship was found to be independent of previously known predictors of RRI (age, gender, BMI, HR, SBP, and DBP), cardiovascular risk factors (diabetes mellitus, hypertension, and smoking), renal function (eGFR), and urinary characteristics (creatinine, potassium, and volume). Conceptually, salt intake could thus affect RRI locally via modification of RVR or systemically via influence on vascular properties. Evidences exist supporting both hypotheses.

First, although previous studies showed that salt intake had no influence on RVR in salt-resistant subjects, high sodium diet was associated with increased RVR in salt-sensitive patients.[27,28] As RVR can be seen as the mean arterial pressure divided by the renal blood flow, this local hemodynamic alteration might reflect the inability to increase renal blood flow in response to high sodium load in those patients.[28] In our cohort, 228 (22.9%) patients had hypertension, but salt-sensitivity was not assessed. However, as salt-sensitivity has overall been estimated to be present in 51% of patients with hypertension and 26% of normotensive subjects, it can be assumed that this physiological behaviour was present in a significant proportion of participants in our study.[29] Thus, although no direct evidence can be provided, our findings are in agreement with a NaCl-induced vasoconstriction as described in salt-sensitive patients.[30]

Second, our results could highlight an effect of sodium intake on systemic vascular properties. Epidemiological studies have established a link between salt consumption and arterial stiffness independent of BP control. In a first study,

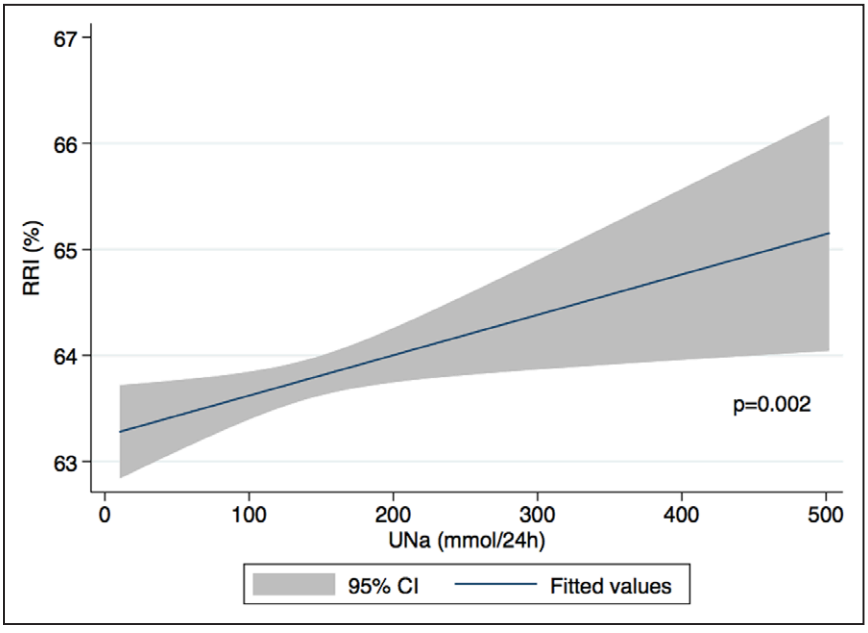

Figure. Multivariate association between urinary sodium (UNa; mmol/24 h) and renal resistive index (RRI; %). This association is based on the final multivariate model and is thus adjusted for age, age^2, gender, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, serum glucose, urinary creatinine, urinary volume, and center.

Table 3. Factors Associated With PWV* (m/s) in Final Multivariate Model

	Final Model		
Independent Variables	B	95% CI	*P* Value
UNa, mmol/24 h†	−0.004	−0.014 to 0.005	0.344
Age, y	0.007	0.006 to 0.008	<0.001
BMI, kg/m^2	0.006	0.003 to 0.008	<0.001
Diabetes mellitus	0.096	0.035 to 0.157	0.002
SBP, mm Hg	0.004	0.004 to 0.005	<0.001
Glucose, mmol/L	0.031	0.014 to 0.048	<0.001

Model is also adjusted for age^2 and centre (not shown in the table). BMI indicates body mass index; PWV, pulse wave velocity; SBP, systolic blood pressure; and UNa, urinary sodium.

*Log-transformed.

†Standardized to a mean of 0 and a SD of 1.

high-salt consumption was associated with higher PWV compared with low-salt consumption after adjustment for BP in 2 distinct Chinese communities.[14] The same group showed that PWV was lower in Australian normotensive subjects adhering to a low-salt diet compared with age and BP matched participants.[15] Subsequently, numerous clinical trials investigated the effect on sodium restriction on arterial stiffness, but their results were inconsistent and several failed to reveal a significant effect on PWV.[31–33] Given this uncertainty, a meta-analysis was recently published pooling 11 randomized controlled trials and 14 independent cohorts focusing on the effect of sodium intake.[16] Results indicated a positive and independent association between dietary salt intake and arterial stiffness measured by PWV beyond BP alterations. It should be noted, however, that sub-group analysis revealed that the presence and magnitude of this effect mainly applied to treated hypertension patients whereas untreated normotensive or prehypertensive subjects seemed to behave differently. Our findings did not show a direct relationship between dietary sodium intake and vascular stiffness in the overall cohort. A false negative result seems highly unlikely as the observed power was 96.8% to detect a 0.5% increase in R^2 by adding UNa to other significant predictors of PWV. Nonetheless, inherent inaccuracy in UNa and PWV measurements could potentially have biased the results. However, in our view, the most likely explanation for this negative finding lies in the studied population. As our cohort included only a minority of treated patients with hypertension, our findings strengthen the dichotomous effect of sodium intake on vascular stiffness according to the underlying cardiovascular status of individuals as previously described. In agreement with this hypothesis, we described a positive association between the UNa/K ratio and PWV above 12 m/s, a cutoff value suggestive of vascular alterations.[19] Of note, as previously described, this association was also independent of BP control and presence of hypertension itself.[34]

Aldosterone has been suggested to induce target organ damage independently of BP control and previous studies have reported that an elevated ARR was linked to arterial stiffness, cardiovascular events, and kidney function decline.[35–37] In our study, however, ARR was negatively associated with RRI. Given that renal function was preserved in the vast majority of patients and that RRI itself was not associated with eGFR, it would be probably incorrect to interpret RRI as a marker of structural organ damage in this setting. On the opposite, a low ARR might in fact represent a high renin and angiotensin II relative activity that could induce an increase in RVR and thus in RRI.[38,39] More importantly, as accounting for PRA, aldosterone and ARR did not significantly modified the relationship between UNa and RRI, this would suggest that salt intake has a direct impact on systemic vascular properties at least partly independent of this endocrine regulation.

All things considered, it has to be stressed that dietary sodium intake did not alter the relationship between RRI and its previously described determinants. Moreover, the absence of interaction between sodium intake and main predictors of RRI such as age, gender, and BP control suggest that sodium balance acts on distinct physiological pathways. This would thus support previous evidences where excessive salt intake was associated with albuminuria and kidney function decline independently of BP control.[17,40,41] Our findings would then also be in agreement with the BP-independent increase in RVR induced by salt loading in spontaneously hypertensive rats.[42] It has to be noted that, although highly significant, the contribution of sodium intake to RRI variation is several order of magnitude lower than that from the previously known predictors of RRI.[20] This would suggest that reduction of dietary salt consumption would not counterbalance the negative effect of established markers of vascular alterations. Finally, while UNa/K ratio and UNa showed similar effect on RRI, UK did not have a significant impact when considered independently along with UNa. Potassium intake has generally been associated with favorable cardiovascular and renal outcomes in previous epidemiological studies.[43–45] This could be mediated by opposite cellular effects of potassium compared with sodium in particular on nitric oxide release, vascular stiffness, and BP sensitivity so salt intake.[46,47] Such discordance with previous reports is, however, not exceptional as other studies described a nonsignificant, or even adverse, relationship between UK and progression of kidney disease.[17,48] That being said, as no previous study reported on the association between dietary intake of electrolytes and RRI, our results cannot be directly compared with other evidences.

Limitations

Our study has limitations that should be considered when interpreting the results. First, the observational and cross-sectional nature of the design hampers definitive conclusions on causal relationship between considered variables. Namely, as the interplay between sodium intake, vascular properties and renal function is intricate, residual confounding should be considered. We believe, however, that the number of considered covariables as well as the mentioned pathophysiologic considerations help comfort our conclusions. Second, as in most similar studies, a single 24-h urinary sample was collected. As such, results might not accurately reflect long-term salt intake of participants. However, RRI shows short dynamic variability and was measured simultaneously to urinary collection thus preserving the potential causal relationship between those 2 variables. Finally, participants of European descent exclusively were included in our cohort. Whether our conclusions are valid in other ethnicities remain questioned. The exclusion

of Black participants would, however, be thought to introduce a conservative bias in our results owing to their higher propensity to salt-sensitivity.

Perspectives

In this observational study, we describe a robust positive association between sodium intake assessed by 24-hour urinary collection and RRI in a large adult general population. This suggests that dietary salt consumption has a direct impact on renal hemodynamic in adults beyond other classical demographic and cardiovascular factors. Those alterations are likely the reflection of a diffuse systemic vascular damage induced by high-salt intake resulting in decreased arterial compliance. An induced renal vasoconstrictive response is, however, also a potential mechanism. As an elevated RRI is associated with adverse renal and cardiovascular outcomes, the functional alterations induced by high-salt intake could be linked to structural systemic damage in the general adult population. Whether reduction in salt consumption would result in meaningful improvement in vascular and renal outcomes remains to be demonstrated in adequately powered randomized controlled trials.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We characterized the association of salt consumption estimated on 24-hour urinary collection with renal resistive index in a general adult population.
- We also described vascular stiffness measured by pulse wave velocity as well as renin and aldosterone regulation in this setting.

What is Relevant?

- Sodium intake is positively associated with renal resistive index, independently of previously known predictors, cardiovascular risk factors, and renal function.
- Renin and aldosterone regulation did not modify this relationship, while a link between salt consumption and vascular stiffness could only be found when considering highly pathological values of pulse wave velocity.
- Those findings suggest that dietary salt consumption has a direct impact on renal hemodynamic in adults that could reflect diffuse systemic vascular damage.

Summary

In a general adult population, salt consumption is positively associated with renal resistive index as a potential reflection of altered systemic vascular properties.