Kidney and Blood Pressure Research

Research Article

Kidney Blood Press Res 2024;49:184–195
DOI: 10.1159/000535977

Received: June 7, 2023
Accepted: December 7, 2023
Published online: February 21, 2024

The Association between Urinary Sodium-Potassium Ratio, Kidney Function, and Blood Pressure in a Cohort from the General Population

Karl Marius Brobak[a, b] Toralf Melsom[a, b] Bjørn Odvar Eriksen[a, b]
Aud Høieggen[c, d] Jon Viljar Norvik[a, b] Marit Dahl Solbu[a, b]

[a]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway; [b]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; [c]Department of Nephrology, Oslo University Hospital Ullevål, Oslo, Norway; [d]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Keywords
Blood pressure · Sodium · Potassium · Sodium-potassium ratio · Kidney dysfunction

Abstract
Introduction: Subclinical kidney dysfunction may contribute to salt-sensitive hypertension. We assessed the association between the urinary sodium-potassium ratio (Na/K ratio) and blood pressure (BP) in a general population cohort without diabetes, chronic kidney disease, cardiovascular disease, or treated hypertension. We investigated whether any such association was mediated by the kidney function markers measured glomerular filtration rate (mGFR), urinary albumin-creatinine ratio (ACR), and urinary epidermal growth factor-creatinine ratio (EGF-Cr). ***Methods:*** The Tromsø Study is a population-based study of inhabitants of the municipality of Tromsø, Northern Norway. Participants aged 50–62 years, without diabetes, chronic kidney disease, or cardiovascular disease, were invited to the substudy Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6; 2007–09). For the present study, we excluded participants reporting the use of 1 or more antihypertensive agents, leaving 1,311 RENIS-T6 participants for a cross-sectional analysis. We measured office BP, 24-h ambulatory blood pressure (ABP), and mGFR using iohexol clearance. Na/K ratio, ACR, and EGF-Cr were measured in morning urine samples. ***Results:*** Urinary Na/K ratio was significantly associated with systolic office BP and ABP independently of cardiovascular risk factors and kidney function markers. A one-standard deviation unit increase in the Na/K ratio was associated with increased systolic ABP by 1.0 (0.3–1.6) mm Hg. Urinary Na/K ratio showed a stronger association with office BP than ABP. EGF-Cr, ACR, and mGFR did not mediate the relationship between urinary Na/K ratio and systolic BP. ***Conclusions:*** In a representative sample of the middle-aged North-European population without diabetes, chronic kidney disease, cardiovascular disease, or treated hypertension, there was a consistent association between urinary Na/K ratio and BP. The association with BP was not mediated through kidney function measures, suggesting a relationship between a diet with high sodium and low potassium and higher BP regardless of kidney function.

karger@karger.com
www.karger.com/kbr

Correspondence to:
Karl Marius Brobak, karl.m.brobak@uit.no

Introduction

Hypertension is globally the most significant contributor to morbidity and mortality [1]. All patients should be empowered to make lifestyle changes that may prevent and improve hypertension and reduce the need for antihypertensive drug therapy [2]. An advisable lifestyle modification is sodium restriction [2]. The global mean daily sodium intake is estimated to be approximately 4 g/day, equivalent to 10 g/day of salt [3], and about twice the WHO recommended limit [4]. A high sodium intake in the general population is associated with hypertension, chronic kidney disease, and cardiovascular disease [5, 6], and sodium restriction has a blood pressure (BP)-lowering effect [7]. However, BP response to a change in sodium consumption is heterogeneous, and the term salt sensitivity has been applied to persons with the greatest change in BP due to altered sodium intake [8]. Subclinical kidney dysfunction with a decrease in whole kidney ultrafiltration and an increase in tubular sodium reabsorption has been implicated as a cause of salt sensitivity [9]. The renal abnormalities leading to this increased reabsorption have not yet been fully elucidated. A diet high in sodium and low in potassium can stimulate salt reabsorption along the distal nephron [10]. A low potassium intake may also catalyst renal vasoconstriction, leading to persistent preglomerular arteriolopathy, tubular ischemia, and interstitial inflammation, generating deviant renal sodium handling, and increasing BP [11]. On the other hand, a high potassium intake is associated with lower BP and reduced risk of cardiovascular disease [12, 13]. Replacing salt with a potassium chloride salt substitute has reduced the risk of stroke and cardiovascular disease mortality [14, 15]. The urinary sodium-potassium ratio (Na/K ratio) is a proxy for sodium and potassium intake. It is independent of urine volume and body weight and has a higher correlation with 24-h urinary excretion of each electrolyte than the urinary Na or K concentration alone [16]. Na/K ratio has shown a stronger association with BP, hypertension, and cardiovascular disease than urinary sodium or potassium alone [17, 18], and the association between Na/K ratio and BP is independent of the individual urinary levels of Na and K [19].

No population-based studies have addressed the association between Na/K ratio and BP in the specific context of kidney function. The present cross-sectional study aimed to assess the associations between Na/K ratio, BP, and hypertension in a cohort of individuals representative for the North-European general population without diabetes, chronic kidney disease, or cardiovascular disease [20, 21]. Further, we aimed to examine if an association is mediated through the kidney function variables measured glomerular filtration rate (mGFR), urine albumin-creatinine ratio (ACR), and urine epidermal growth factor (EGF). We hypothesized that the U-Na/K ratio is associated with BP and different hypertension phenotypes independently of traditional cardiovascular risk factors and that mGFR, urine ACR, and urine EGF modify this association.

Materials and Methods

Materials

The Renal Iohexol Clearance Survey in Tromsø6 (RENIS-T6) is a substudy of the population-based Tromsø Study, a prospective study of inhabitants of the municipality of Tromsø, Northern Norway. The sixth survey (Tromsø6) was conducted in 2007–2008. An age-stratified random sample of 19,762 inhabitants between 40 and 87 years of age was invited to participate. A total of 12,984 persons attended (66%). Among the 3,564 participants aged 50–62, 2,825 reported no previous myocardial infarction, angina pectoris, stroke, diabetes mellitus, or renal disease. These individuals were invited to RENIS-T6. A total of 2,107 agreed. One hundred and twenty-five were excluded because of allergy to contrast media, iodine, latex, or for other reasons, including 48 who withdrew. Five subjects were excluded due to technical failure of the iohexol clearance measurement, and 1,627 subjects were included according to a predetermined target of 1,600. For the present study, 17 were excluded due to missing ambulatory blood pressure (ABP) measurements after repeated attempts. Further, 299 participants reporting the use of one or more antihypertensive agents (beta-blocking agents, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, or diuretics) were excluded to limit the possibilities of reverse causality and because antihypertensive treatments could potentially affect urinary Na or K excretion, leaving 1,311 participants for our study, shown in Figure 1.

Measurements

The details of sample procurement in the RENIS-T6 have previously been described [22]. All data were collected during the RENIS-T6 visit, besides urine ACR which was measured in the forerunner Tromsø6 survey. In the RENIS-T6 study, participants met between 08:00 and 10:00 a.m. at the Clinical Research Unit at the University Hospital of Northern Norway after an overnight fast. Office BP, urine Na and K were measured simultaneously, and ABP over the following day and night.

Office BP was recorded in triplet by trained personnel using an automatic device (model UA 799; A&D, Tokyo, Japan). The cuff was chosen according to the measured circumference of the upper right arm. After a 2-min rest, three attended readings were taken in a sitting position, separated by 1-min intervals [23]. We used the mean of the second and third readings in the analyses.

ABP was measured from the completion of the iohexol clearance measurement, just before the participant left the clinical research unit, to the next day. A Spacelabs 90207 device was applied (Spacelab Inc., Redmond, WA, USA), using the appropriate cuff size. The persons were instructed to keep their arm still during measurement and avoid strenuous exercise during the measurement period, but otherwise participate in their normal daily activities. BP was measured at 20-minute intervals from 08:00 to 22:00 h and at 45 min intervals from 22:00 to 08:00 h. The registration was valid if it

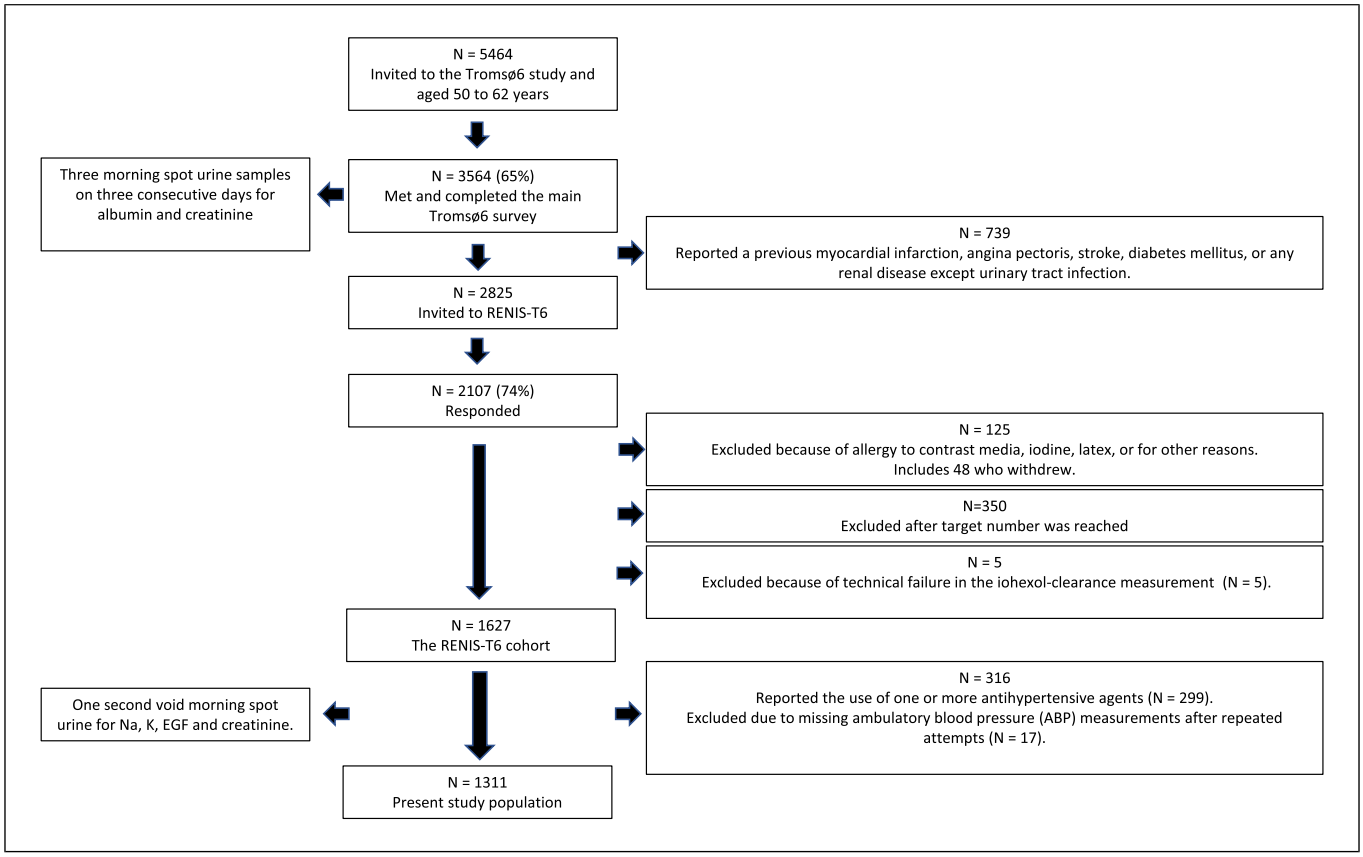

Fig. 1. Inclusion of participants in the Renal Iohexol Clearance Survey (RENIS-T6) from the main part of the sixth Tromsø survey (Tromsø6).

was of at least 22 h duration, at least ten readings between 10:00 and 22:00 h, and if there were five readings between midnight and 06:00 h. These criteria were adopted from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome study [24]. Persons with invalid registration had their ABP monitoring repeated as soon as possible. The fall in BP during sleep, the nighttime BP dip, was defined as the difference between daytime mean pressure and nighttime mean pressure, expressed as a percentage of the daytime value.

The ambulatory white coat effect was defined as the difference between the office BP and daytime mean ABP (office BP minus daytime mean ABP) [2]. Hypertension phenotypes were defined as white coat hypertension, the untreated condition in which office BP was ≥140/90 mm Hg, but 24-h ABP <130/80 mm Hg, masked hypertension, the untreated condition in which office BP was <140/90 mm Hg, but 24-h ABP ≥130/80 mm Hg, and sustained hypertension as the untreated condition in which office BP was ≥140/90 mm Hg, and 24-h ABP ≥130/80 mm Hg [2].

GFR was measured with single-sample plasma clearance of iohexol (mGFR). The serum iohexol concentration was measured by HPLC. The interassay coefficient of variation for the iohexol analysis with HPLC during the study period was 3.0%. External quality control was provided by Equalis (Equalis AB, Uppsala, Sweden). This method has been validated against gold standard methods and is accurately described in a previous publication [22].

From the RENIS-T6 survey, we used a second void morning spot urine, stored at −80°C, to measure urine Na, K, EGF, and creatinine. Urine Na and K were measured via the ion-selective electrode method using a COBAS 8000 autoanalyzer (Roche Diagnostic, Indianapolis, IN, USA). Urine EGF was measured using a human EGF immunoassay Quantikine enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA). EGF was assessed in duplicate. Urine creatinine was measured using a colorimetric method with a COBAS 8000 autoanalyzer (Roche Diagnostic, Indianapolis, IN, USA). We calculated the ratios of urine EGF to the urine creatinine concentration (EGF-Cr) to adjust for differences in urine concentration [25].

In Tromsø6, morning spot urine samples were collected on three consecutive days. Albumin and creatinine concentrations were measured at the time of collection in unfrozen samples. Urine albumin concentration was measured by an immunoturbidimetric method with the ABX Pentra Micro Albumin CP (Horiba ABX, Montpelier, France), whereas creatinine was analyzed by a colorimetric method (Jaffe's reaction) using an autoanalyzer (ABX Pentra, Horiba ABX, Montpellier, France). For each urine sample, we calculated the ACR, and the median of the values assessed on days 1, 2, and 3 were used.

The subjects completed a questionnaire regarding medication use. Body mass index (BMI; kg/m^2) was calculated from measured height and weight. Fasting blood samples were drawn to measure

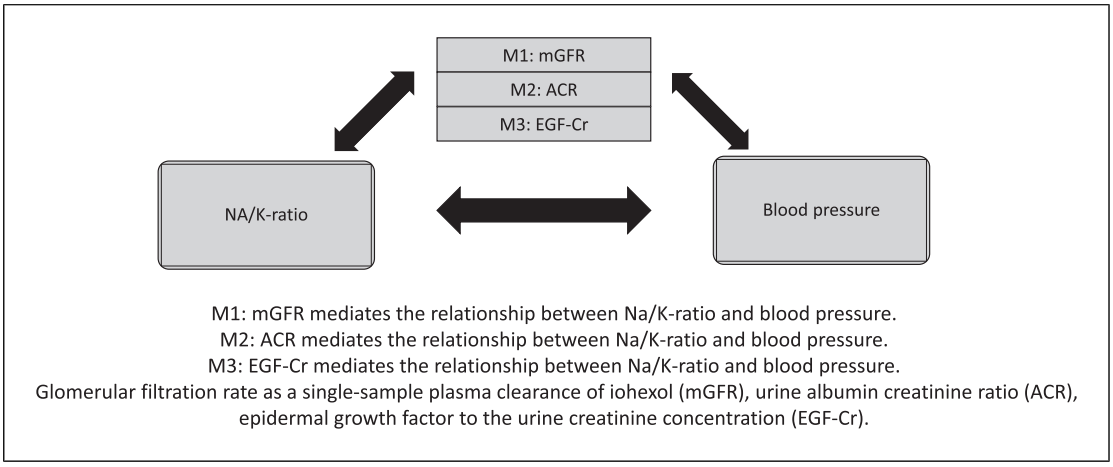

Fig. 2. Two component mediation analysis.

lipids, HbA1c, creatinine, and cystatin C, as previously described [22]. We calculated creatinine-cystatin C-based estimated GFR by applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26].

Statistical Analyses

Baseline characteristics are summarized for the cohort with a mean (SD) for normally distributed variables, median for skewed variables, and n (percentage) for categorical variables. We used statistical mediation analysis with bootstrapping as implemented in model 4 of the PROCESS macro for SPSS [27] to assess the associations between the BP variables and hypertension phenotypes as dependent variables in separate models, and Na/K ratio as the independent variable of interest. We did a two component mediation analysis to examine the direct and indirect effects, shown in Figure 2.

The direct effect was the effect of urinary Na/K ratio on BP and hypertension phenotypes, and the indirect effect of Na/K ratio was through the mediators mGFR, ACR, and EGF-Cr on BP and hypertension phenotypes. We report the results of all the pathways shown in Figure 2. We adjusted the mediation analysis for the covariates age, sex, and traditional cardiometabolic risk factors (waist-hip ratio, HbA1c, triglycerides, and HDL cholesterol). We report the mediation analyses direct and indirect effects as beta coefficients or odds ratios for the Na/K ratio per SD.

The urine albumin assay's limit of detection in Tromsø 6 is given at 4 mg/L, but the PENTRA instrument reports albumin concentrations as low as 1 mg/L. Seventy percent of the participants had albumin concentration under the limit of detection. Due to a large number of observations below the limit and only a fewparticipants with moderately or severely increased ACR, we 1) used all values of albumin, including those below limit of detection, 2) substituted all observations of albumin concentration lower than 4 mg/L with 4 mg/L in each urine sample, calculated the ratio of albumin concentrations with the urine creatinine concentration, and used the median value of the three samples in the repeated mediation analysis. As so, we preserved the relative standing of persons with values below the limit relative to those above the limit and a relative standing accounting for different urine volumes. The limit of detection for the EGF assay was 0.7 pg/mL. No participants had EGF lower than the limit of detection. In multivariate linear regression analyses, we tested for collinearity with the variance inflation factor, tolerance statistics, the eigenvalue of the scaled, uncentered cross-products matrix, and variance proportions. Statistical significance was defined as two-sided $p < 0.05$ and the correspondent t-statistics value 1.96 in all analyses. We used SPSS Statistics for Windows, Version 29.0 (IBM SPSS Statistics for Windows, Version 29 0.0; Armonk, NY: IBM Corp.) and Hayes' PROCESS macro for SPSS (Hayes, 2022).

Results

Baseline Characteristics

A total of 1,311 participants with a mean (SD) age of 58 (3.8) years, BMI of 26.8 (3.8) kg/m^2, Na/K ratio 1.43 (0.76), and mGFR 94.3 (14.2) mL/min/1.73 m^2 were included in the study (Table 1). Office BP was 128/82 (17.5/9.6) mm Hg, 24-h ABP 122/76 (12.3/7.9) mm Hg (Table 2). Figure 3 shows the distribution of mGFR stratified by sex. Among the 360 participants with urine albumin above the assay's limit of detection, 73 participants had high normal ACR (ACR 1.13–<3.40 mg/mmol), 12 participants had moderately increased ACR (ACR 3.40–≤34 mg/mmol), and one participant had severely increased ACR (ACR >34 mg/mmol).

The Associations between Na/K Ratio and ABP

We found no sign of multicollinearity in the multivariate linear regression analyses. Results of the regression analysis are presented in the supplementary Tables 1–3 (for all online suppl. material, see https://doi.org/10.1159/000535977).

Table 1. Characteristics of the study population (n = 1,311)

Female sex, *n* (%)	679	51.8
Age, years	57.9	3.8
Waist-hip ratio women	0.86	0.06
Waist-hip ratio men	0.95	0.06
BMI, kg/m^2	26.8	3.8
Cholesterol, mmol/L	5.6	0.9
HDL cholesterol, mmol/L	1.6	0.4
LDL cholesterol, mmol/L	3.7	0.9
Triglycerides, mmol/L	1.2	0.6
HbA1c, %	5.5	0.4
U-Na, mmol/L	54.0	33–89
U-K, mmol/L	45.0	26–74
U-Na/K ratio	1.43	0.76
Serum creatinine, µmol/L	66.5	12.0
Cystatin C, mg/L	0.73	0.11
Estimated GFR, mL/min/1.73 m^2	103.7	11.2
GFR as single-sample plasma iohexol clearance, mL/min/1.73 m^2	94.3	14.2
ACR (left censored at limit of detection), mg/mmol	0.75	0.49–1.16
EGF, µg/L	12.3	6.2–23.3
EGF-Cr, µg/mmol	1.91	0.73

Data are mean (SD), median (interquartile range), or number (%) as appropriate. Estimated GFR, glomerular filtration rate, calculated using the creatinine-cystatin C-based CKD-EPI equation. ACR, urine albumin-to-creatinine ratio. EGF, urine epidermal growth factor. EGF-Cr, urine epidermal growth factor to creatinine ratio.

Table 2. BP characteristics of the study population (n = 1,311)

Office systolic BP, mm Hg	127.7	17.5
Office diastolic BP, mm Hg	82.3	9.6
Ambulatory systolic BP, 24-h mean, mm Hg	122.2	12.3
Ambulatory diastolic BP, 24-h mean, mm Hg	75.8	7.9
Ambulatory systolic BP, daytime mean, mm Hg	129.2	13.2
Ambulatory diastolic BP, daytime mean, mm Hg	81.4	8.5
Ambulatory systolic BP, nighttime mean, mm Hg	110.0	12.2
Ambulatory diastolic BP, nighttime mean, mm Hg	65.8	8.2
Nighttime systolic BP dip, %	14.7	6.2
Nighttime diastolic BP dip, %	19.1	7.2
Normotensive, *n* (%)	756	57.7
White coat hypertension, *n* (%)	103	7.9
Masked hypertension, *n* (%)	167	12.7
Sustained hypertension, *n* (%)	285	21.7

Data are mean (SD) or number (%) as appropriate. Normotensive: office BP <140/90 and 24-h mean ABP <130/80. White coat hypertension: office BP ≥140/90 and 24-h mean ABP <130/80. Masked hypertension: office BP ≤140/90 and 24-h mean ABP ≥130/80. Sustained hypertension: office BP ≥140/90 and 24-h mean ABP ≥130/80.

There was a significant direct effect of Na/K ratio on systolic ABP and a borderline significant direct effect on 24-h mean and daytime diastolic ABP. A 1 SD increase in Na/K ratio corresponded to approximately 1 mm Hg increase in systolic 24-h mean ABP (Table 3 and online suppl. Table 1). We found no significant indirect effects of Na/K ratio through mGFR, ACR, or EGF-Cr (Table 3). Mediation analysis with ACR substituted for values under the limit of detection did not change the results (online suppl. Table 4). Hence, none of the three kidney function variables mediated the relationship between Na/K ratio and ABP.

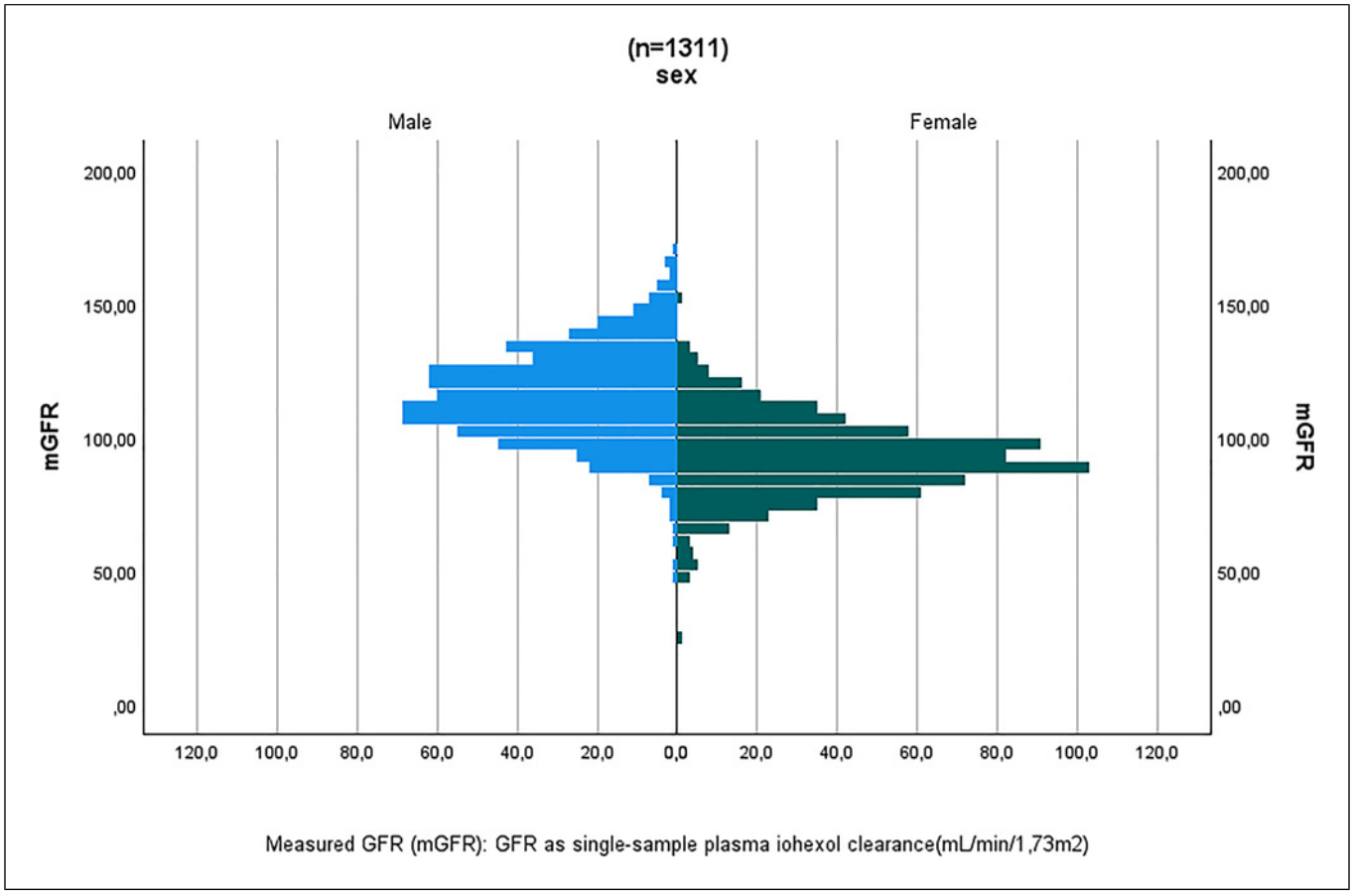

Fig. 3. Population pyramid showing the frequency of mGFR by sex.

The Na/K ratio was not significantly associated with nighttime BP dipping, and we found no significant indirect effects of Na/K ratio through mGFR, ACR, or EGF-Cr on the dipping pattern (online suppl. Tables 2, 5). Mediation analysis with ACR substituted for values under the limit of detection did not change the results (online suppl. Table 6).

The Associations between Na/K Ratio, Office BP, and the Ambulatory White Coat Effect

Na/K ratio showed a stronger direct effect with office BP than ABP (Table 4). The standardized regression coefficients indicated a 3.6 mm Hg increase in systolic office BP per SD unit increase in Na/K ratio (Table 4; online suppl. Table 3). For the diastolic office BP, the rise was 1.4 mm Hg per SD unit Na/K ratio increase (Table 4; online suppl. Table 3).

We found no significant indirect effects of Na/K ratio through mGFR, ACR, or EGF-Cr (Table 4). Mediation analysis with ACR substituted for values under the limit of detection did not change the results (online suppl. Table 7).

There were significant associations between the Na/K ratio and the ambulatory white coat effect (office BP minus daytime mean ABP) (Table 4; online suppl. Table 3). The estimated increase in the systolic white coat effect was 2.7 mm Hg per SD unit increase in Na/K ratio. The corresponding value for the diastolic white coat effect was 1.0 mm Hg per SD unit (Table 4; online suppl. Table 3). We found no significant indirect effects of Na/K ratio through our kidney function variables (Table 4). Mediation analysis with ACR substituted for values under the limit of detection did not change the results (online suppl. Table 7).

The Associations between Na/K Ratio and Hypertension Phenotypes

There was a significant direct effect of Na/K for white coat hypertension and sustained hypertension, but not for masked hypertension (Table 5). We found no significant indirect effects of Na/K ratio through mGFR, ACR, or

Table 3. Mediation analysis for the urinary Na/K ratio for the associations with ABP (n = 1,311)

	Total effect	p value	Direct effect	p value	Relationship	Indirect effect	T-statistic	Conclusion
24-h mean ABP as dependent variable								
Systolic BP	0.93	0.035	0.94 (0.31–1.56)	0.033	M1	−0.00 (−0.04 to 0.23)	−0.08	No mediation
					M2	0.02 (−0.00 to 0.09)	0.83	No mediation
					M3	−0.02 (−0.11 to 0.06)	−0.57	No mediation
Diastolic BP	0.37	0.072	0.37 (−0.03–0.77)	0.070	M1	−0.00 (−0.02 to 0.01)	−0.19	No mediation
					M2	0.00 (−0.02 to 0.06)	0.15	No mediation
					M3	−0.01 (−0.06 to 0.05)	−0.20	No mediation
Mean daytime ABP as dependent variable								
Systolic BP	0.93	0.007	0.94 (0.27–1.62)	0.006	M1	−0.00 (−0.04 to 0.03)	−0.23	No mediation
					M2	0.02 (−0.00 to 0.09)	0.62	No mediation
					M3	−0.02 (−0.11 to 0.06)	−0.55	No mediation
Diastolic BP	0.41	0.063	0.41 (−0.03–0.85)	0.065	M1	0.00 (−0.02 to 0.02)	0.04	No mediation
					M2	0.00 (−0.02 to 0.07)	0.07	No mediation
					M3	−0.00 (−0.05 to 0.05)	0.06	No mediation
Mean nighttime ABP as dependent variable								
Systolic BP	0.89	0.006	0.90 (0.26–1.54)	0.006	M1	−0.00 (−0.03 to 0.02)	−0.09	No mediation
					M2	0.03 (−0.00 to 0.09)	0.97	No mediation
					M3	−0.04 (−0.12 to 0.04)	−0.81	No mediation
Diastolic BP	0.29	0.18	0.30 (−0.13–0.73)	0.17	M1	−0.00 (−0.02 to 0.02)	−0.18	No mediation
					M2	0.01 (−0.00 to 0.06)	0.45	No mediation
					M3	−0.02 (−0.07 to 0.03)	0.67	No mediation

The total effect is the direct and indirect effect of urinary Na/K ratio on ABP. The direct effect is the effect of urinary Na/K ratio on ABP, and the indirect effect of Na/K ratio is through the mediators mGFR, ACR, and EGF-Cr on ABP. Direct and indirect effects are reported beta coefficients (95% confidence intervals based on 5,000 bootstrap samples) for the Na/K ratio per SD. Relationships: M1: Na/K ratio (SD)> mGFR> ABP (mm Hg). M2: Na/K ratio (SD)>ACR> ABP (mm Hg). M3: Na/K ratio (SD)>EGF-Cr> ABP (mm Hg). Covariates: age, sex (male or female), waist-hip ratio, HbA1c, triglycerides, and HDL cholesterol, ambulatory blood pressure (ABP), glomerular filtration rate as a single-sample plasma clearance of iohexol (mGFR), urine albumin creatinine ratio (ACR), urine epidermal growth factor to the urine creatinine concentration (EGF-Cr).

EGF-Cr for masked- or sustained hypertension, but a partial complementary mediation effect through EGF-Cr for white coat hypertension (Table 5). Mediation analysis with ACR substituted for values under the limit of detection did not change the results (online suppl. Table 8). Hence, the kidney function variables in our study did not mediate the relationship between Na/K ratio and sustained hypertension.

Discussion

The present study is, according to our knowledge, the first study to assess the association between urinary Na/K ratio, BP, and hypertension phenotypes in the context of kidney function markers including GFR assessed with gold standard measurement, ACR, and a validated biomarker of functional renal tubular mass (EGF-Cr). In multivariate models, the Na/K ratio was significantly associated with systolic ABP, office BP, and sustained hypertension. Compared to ABP measurements, the Na/K ratio showed a stronger association with office BP, and the increase in the standardized coefficient for the Na/K ratio corresponded to the white coat effect. The markers of kidney function did not mediate the relationship between urinary Na/K ratio, systolic BP, or sustained hypertension.

No population-based studies have addressed the association between Na/K ratio and BP in the specific context of kidney function, but some studies included the estimated glomerular filtration rate as a covariate in the data analyses [18, 28]. In a cross-sectional study by Tabara et al. of a middle-aged population in Japan, the association between Na/K ratio and office BP was independent of cardiovascular risk factors and estimated GFR (standardized coefficient of urinary Na/K ratio to systolic office BP 0.12 [$p < 0.001$]).

Table 4. Mediation analysis for the urinary Na/K ratio for the associations with office BP and the white coat effect as dependent variables (n = 1,311)

	Total effect	p value	Direct effect	p value	Relationship	Indirect effect	T-statistic	Conclusion
Office BP								
Systolic BP	3.68	<0.001	3.68 (2.81–4.54)	<0.001	M1	0.01 (−0.03 to 0.06)	0.33	No mediation
					M2	0.01 (−0.01 to 0.09)	0.51	No mediation
					M3	−0.02 (−0.14 to 0.10)	−0.30	No mediation
Diastolic BP	1.39	<0.001	1.39 (0.91–1.86)	<0.001	M1	0.01 (−0.03 to 0.05)	0.42	No mediation
					M2	0.00 (−0.08 to 0.05)	0.16	No mediation
					M3	−0.01 (−0.06 to 0.05)	−0.22	No mediation
Ambulatory white coat effect								
Systolic BP	2.74	<0.001	2.72 (2.10–3.34)	<0.001	M1	0.01 (−0.03 to 0.06)	0.33	No mediation
					M2	0.01 (−0.01 to 0.09)	0.51	No mediation
					M3	−0.02 (−0.14 to 0.10)	−0.30	No mediation
Diastolic BP	0.98	<0.001	0.98 (0.63–1.33)	<0.001	M1	0.01 (−0.03 to 0.05)	0.42	No mediation
					M2	0.00 (−0.08 to 0.05)	0.16	No mediation
					M3	−0.01 (−0.06 to 0.05)	−0.22	No mediation

The total effect is the direct and indirect effect of urinary Na/K ratio on office BP and the white coat effect. The direct effect is the total effect is the direct and indirect effect of urinary Na/K ratio on office BP and the white coat effect. The direct effect is the effect of urinary Na/K ratio on office BP and the white coat effect, and the indirect effect of Na/K ratio is through the mediators mGFR, ACR, and EGF-Cr on office BP and the white coat effect. Direct and indirect effects are reported beta coefficients (95% confidence intervals based on 5,000 bootstrap samples) for the Na/K ratio per SD. Relationships: M1: Na/K ratio (SD) > mGFR > office BP (mm Hg) and white coat effect (mm Hg). M2: Na/K ratio (SD) >ACR-> office BP (mm Hg) and white coat effect (mm Hg). M3: Na/K ratio (SD) >EGF-Cr > office BP (mm Hg) and white coat effect (mm Hg). Covariates: age, sex (male or female), waist-hip ratio, HbA1c, triglycerides, and HDL cholesterol, ambulatory blood pressure (ABP), glomerular filtration rate as a single-sample plasma clearance of iohexol (mGFR), urine albumin-creatinine ratio (ACR), urine epidermal growth factor to the urine creatinine concentration (EGF-Cr).

Only one previous study has included estimated GFR and ACR as covariates in its analyses [28]. This cross-sectional study by Hedayati et al. [28], which also included a large African American population, showed a significant association between Na/K ratio and office BP after adjustment for cardiovascular risk factors, including estimated GFR and ACR. However, these studies included subjects with diabetes and treated hypertension, and the Na/K ratios were substantially larger than observed in the present study [18, 28]. Although in line with our results, the individual or combined effect of adjustments for estimated GFR and ACR was not reported.

However, estimated GFR is an insensitive marker early of renal impairment [29]. Estimated GFR is influenced by non-GFR components such as age, sex, muscle mass, dietary protein intake, and exercise, resulting in systematic overestimation and underestimation of kidney function, which may influence the effect of kidney function on BP [30]. Previous studies [18, 28] may have biased results from non-GFR-related confounders. Accordingly, to investigate the influence of GFR on the Na/K-BP association, we measured the GFR using plasma iohexol clearance. Further, ACR is a marker of kidney damage and endothelial dysfunction, and thus may be an important mediator for the effect of Na/K ratio on BP [29, 31]. High sodium and low potassium consumption may disrupt the endothelial glycocalyx barrier, induce endothelial stiffening, and trigger endothelial dysfunction with increasing ACR and BP [32–34]. A diet high in sodium and low in potassium may also cause kidney glomerular and tubulointerstitial injury, leading to an increased ACR, deviant salt handling, and salt-sensitive hypertension [11, 35]. In our study, mGFR and ACR did not mediate the association between the Na/k ratio, BP, and hypertension.

Furthermore, EGF, a marker of functional tubular mass, may contribute to BP regulation [36–38]. In animal studies, EGF has been shown to regulate ENaC-mediated sodium transport in the distal part of the kidney tubule [38]. An increased renal cortical expression of the EGF receptor has been found in salt-sensitive prehypertensive and hypertensive rats [37]. However, it is unknown whether this expression is a cause or a consequence of salt-sensitive hypertension [36]. Intrarenal EGF may represent a potential molecular mechanism underlying kidney dysfunction and

Table 5. Mediation analysis for the urinary Na/K ratio for the associations with hypertension phenotypes (n = 1,311)

Direct effect	p value	Relationship	Indirect effect	Conclusion
Normotension versus white coat hypertension (n = 824)				
1.31 (1.06–160)	0.011	M1	1.0 (0.99–1.01)	No mediation
		M2	1.0 (0.99–1.02)	No mediation
		M3	1.04 (1.01–1.10)	Partial mediation
Normotension versus masked hypertension (n = 889)				
0.88 (0.71–1.07)	0.21	M1	1.0 (0.98–1.01)	No mediation
		M2	1.02 (0.99–1.09)	No mediation
		M3	1.01 (0.99–1.04)	No mediation
Normotension versus sustained hypertension (n = 1,041)				
1.27 (1.09–1.48)	0.012	M1	1.0 (0.99–1.01)	No mediation
		M2	1.0 (0.99–1.02)	No mediation
		M3	1.0 (0.99–1.02)	No mediation

The direct effect is the effect of urinary Na/K ratio on hypertension phenotype, and the indirect effect of Na/K ratio is through the mediators mGFR, ACR, and EGF-Cr on hypertension phenotype. Effects are expressed as odds ratios (95% confidence intervals based on 5,000 bootstrap samples) for the Na/K ratio per SD. Relationships: M1: Na/K ratio (SD) > mGFR > hypertension phenotype. M2: Na/K ratio (SD)->ACR-> hypertension phenotype. M3: Na/K ratio (SD) >EGF-Cr > hypertension phenotype. Covariates: age, sex (male or female), waist-hip ratio, HbA1c, triglycerides, and HDL cholesterol, ambulatory blood pressure (ABP), glomerular filtration rate as a single-sample plasma clearance of iohexol (mGFR), urine albumin-creatinine ratio (ACR), urine epidermal growth factor to the urine creatinine concentration (EGF-Cr).

salt sensitivity [36]. We have not found previous studies that have assessed the association between Na/K ratio and BP in the context of EGF. In our study, urine EGF-Cr did not mediate the association between Na/K ratio, BP, masked- or sustained hypertension. Inconsistent effect modification by urine EGF-Cr was demonstrated with a small partial mediation effect on white coat hypertension, but no significant mediation effect was shown with the ambulatory white coat effect as a continuous dependent variable. Thus, the mediation effects via EGF on white coat hypertension cannot be ascribed significance until confirmatory findings in other cohorts [39].

The Na/K ratio showed a stronger association with office BP than ABP, and the increase in the standardized coefficients corresponded to the ambulatory white coat effect. The ambulatory white coat effect has been shown to increase with increasing age and BMI [40]. The direct effect of urinary Na/K ratio was highly significant after adjustment for cardiometabolic risk factors, and we found no significant indirect effects through mGFR, ACR, or EGF-Cr.

Guyton and coworkers proposed that hypertension could not occur with a preserved natriuresis, which would restore plasma volume and normotension [41]. Recent studies have shown that subclinical kidney dysfunction may be implicated as a cause of salt sensitivity [9, 42]. In our study of a middle-aged population without diabetes, chronic kidney disease, cardiovascular disease, or treated hypertension, kidney function variables did not mediate the association between urinary Na/K ratio, systolic BP, or sustained hypertension. Thus, although we cannot make inferences about causality in this cross-sectional study, the findings support that a high-sodium and/or low-potassium diet alone may stimulate salt reabsorption along the distal nephron, leading to an increased BP [43, 44]. However, recent insights have launched new hypotheses as potential explanations for salt sensitivity, suggesting primary vascular dysfunction, primary sympathetic nervous system dysfunction, immune activation, and skin hypertonicity to be involved [10].

A strength of this general population cohort study is the exclusion of participants with cardiovascular disease, kidney disease, diabetes, and antihypertensive medication at baseline, limiting the possibility for reverse causality. Previous studies on the association between Na/K ratio and BP have included subjects with either cardiovascular disease, diabetes, or treated hypertension [18, 28, 45–48]. Further, the accurate measurement of GFR using iohexol clearance reduces the risk of bias and residual confounding or effect modification compared to using estimated GFR. Also, ABP measurements are more strongly associated with target organ damage than

office BP and provide the opportunity to study dipping patterns and the ambulatory white coat effect [2, 49].

However, there are several limitations. Excretion measured in multiple controlled 24-hour urine collections is the gold standard method to assess electrolyte intake [50]. Controlled 24-hour urine collection is also the gold standard method for urine biomarker quantification. However, the method is subjected to error by incompleteness of the collection and is demanding to perform adequately in population studies [50]. Thorough control of 24-hour urine collections is crucial for accurate and reliable results. Neglecting this process can introduce a systematic bias in the estimation of electrolyte intake [50, 51]. However, when strict control measures are applied in larger population studies, there is a chance of unintentionally introducing a similar bias. In this regard, we would like to emphasize that the utilization of the Na/K ratio offers advantages in mitigating systemic errors arising from incomplete 24-hour urine collections that can confound results in association studies [51, 52]. There is a moderate correlation between 24-h urine collections and single-second void morning spot urine Na/K ratio (r = 0.6) and between 24-h urine collections and single-spot urine EGF-Cr (r = 0.6) [16, 25, 51]. Spot urine samples, on the other hand, will give rise to greater random errors in estimates of sodium and potassium intake and will bias the relationship between Na and K intake and BP toward the null. Furthermore, potassium intake is negatively correlated with sodium intake and BP and modifies the relationship between sodium intake and BP. When potassium and sodium are measured in spot urine samples, the correlation of their errors may complicate the interpretation of coefficients in linear models. It is important to acknowledge that this study should be considered as hypothesis-generating, and additional investigations employing multiple random spot urine samples for a more accurate estimation of the urinary Na/K ratio are warranted [52]. Moreover, the population in the RENIS-T6 consists almost exclusively of North-European middle-aged persons with generally normal or near normal kidney function, limiting broad generalizations to other healthy and sick populations. Further limitations include residual confounding, and we did not exclude potential hypertension patients with ongoing BP follow-up and guided lifestyle interventions.

Conclusion

In this study of a healthy middle-aged population, the Na/K ratio showed a consistent association with systolic BP and sustained hypertension. This effect was not mediated through the kidney function variables mGFR, ACR, or EGF-Cr. Our findings do not support the suggestion that kidney function mediates the relationship between sodium and potassium intake and BP. A high-sodium and low-potassium diet may be sufficient to stimulate salt reabsorption, leading to increased BP. Longitudinal and interventional studies should address this and other explanations for salt sensitivity.

Statement of Ethics

The present study obtained ethical approval from the Regional Ethical Committee (REK Nord 2017/1970), adhered to the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all participating individuals. The registration and handling of patient data were conducted in compliance with national personal laws and received approval from local data safety officers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The RENIS is funded by the Northern Norway Regional Health Authority (SFP 1100-13), UiT, the Arctic University of Norway, and an unrestricted grant from Boehringer Ingelheim (1235.104 IIS). The present study was supported financially by the Northern Norway Regional Health Authority (HNF 1446-19) and the Research Council of Norway (273536).

Author Contributions

Research idea and study design: K.M.B., T.M., and M.D.S; data acquisition: B.O.E., T.M., and M.D.S.; data analysis/interpretation: K.M.B., M.D.S., T.M., and B.O.E.; statistical analysis: K.M.B.; supervision or mentorship: M.D.S., T.M., B.O.E., A.H., and J.V.N.; drafting of the manuscript: K.M.B. and MDS; revision of the article: M.D.S., T.M., B.O.E., A.H., and J.V.N.; approval of final version: all authors.

Data Availability Statement

The data underlying this article cannot be shared publicly due to ethical considerations and the privacy of individuals that participated in the study. The data are available from the corresponding author on reasonable request (Karl.Brobak@unn.no).

References

1 GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223–49.
2 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 practice guidelines for the management of arterial hypertension of the European society of hypertension and the European society of cardiology: ESH/ESC task force for the management of arterial hypertension. J Hypertens. 2018;36(12):2284–309.
3 Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, et al. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. BMJ Open. 2013;3(12):e003733.
4 Organization WH. Guideline: sodium intake for adults and children. Geneva2012: WHO Guidelines Approved by the Guidelines Review Committee.
5 Sugiura T, Takase H, Ohte N, Dohi Y. Dietary salt intake is a significant determinant of impaired kidney function in the general population. Kidney Blood Press Res. 2018;43(4):1245–54.
6 Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ. 2013;346:f1326.
7 He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev. 2013(4):CD004937.
8 Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med. 1978;64(2):193–8.
9 Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Engl J Med. 2002;346(12):913–23.
10 Ellison DH, Welling P. Insights into salt handling and blood pressure. N Engl J Med. 2021;385(21):1981–93.
11 Suga SI, Phillips MI, Ray PE, Raleigh JA, Vio CP, Kim YG, et al. Hypokalemia induces renal injury and alterations in vasoactive mediators that favor salt sensitivity. Am J Physiol Renal Physiol. 2001;281(4):F620–9.
12 Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013;346:f1378.
13 Ma Y, He FJ, Sun Q, Yuan C, Kieneker LM, Curhan GC, et al. 24-Hour urinary sodium and potassium excretion and cardiovascular risk. N Engl J Med. 2022;386(3):252–63.
14 Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et al. Effect of salt substitution on cardiovascular events and death. N Engl J Med. 2021;385(12):1067–77.
15 Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr. 2006;83(6):1289–96.
16 Iwahori T, Miura K, Ueshima H, Chan Q, Dyer AR, Elliott P, et al. Estimating 24-h urinary sodium/potassium ratio from casual ("spot") urinary sodium/potassium ratio: the INTERSALT Study. Int J Epidemiol. 2017;46(5):1564–72.
17 Perez V, Chang ET. Sodium-to-potassium ratio and blood pressure, hypertension, and related factors. Adv Nutr. 2014;5(6):712–41.
18 Tabara Y, Takahashi Y, Kumagai K, Setoh K, Kawaguchi T, Takahashi M, et al. Descriptive epidemiology of spot urine sodium-to-potassium ratio clarified close relationship with blood pressure level: the Nagahama study. J Hypertens. 2015;33(12):2407–13.
19 Higo Y, Nagashima S, Tabara Y, Setoh K, Kawaguchi T, Takahashi Y, et al. Association of the spot urine sodium-to-potassium ratio with blood pressure is independent of urinary Na and K levels: the Nagahama study. Hypertens Res. 2019;42(10):1624–30.
20 Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, et al. Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. Kidney Int. 2010;78(12):1305–11.
21 Melsom T, Norvik JV, Enoksen IT, Stefansson V, Mathisen UD, Fuskevag OM, et al. Sex differences in age-related loss of kidney function. J Am Soc Nephrol. 2022;33(10):1891–902.
22 Melsom T, Mathisen UD, Eilertsen BA, Ingebretsen OC, Jenssen T, Njølstad I, et al. Physical exercise, fasting glucose, and renal hyperfiltration in the general population: the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). Clin J Am Soc Nephrol. 2012;7(11):1801–10.
23 European Society of Hypertension-European Society of Cardiology Guidelines C. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21(6):1011–53.
24 Kikuya M, Hansen TW, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, Ohkubo T, et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. Circulation. 2007;115(16):2145–52.
25 Segarra A, Carnicer C, Jatem E, Martin M, Molina M, Perich C, et al. Accuracy of urinary epidermal growth factor to creatinine ratio to predict 24-hour urine epidermal growth factor and interstitial kidney fibrosis in patients with IgA nephropathy. Clin Lab. 2019;65(6).
26 Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51(3):395–406.
27 Hayes AF. Introduction to mediation, moderation, and conditional process analysis. 3rd edn A Regression-Based Approach2022.
28 Hedayati SS, Minhajuddin AT, Ijaz A, Moe OW, Elsayed EF, Reilly RF, et al. Association of urinary sodium/potassium ratio with blood pressure: sex and racial differences. Clin J Am Soc Nephrol. 2012;7(2):315–22.
29 Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825–30.
30 Mathisen UD, Melsom T, Ingebretsen OC, Jenssen T, Njølstad I, Solbu MD, et al. Estimated GFR associates with cardiovascular risk factors independently of measured GFR. J Am Soc Nephrol. 2011;22(5):927–37.
31 Kusche-Vihrog K, Schmitz B, Brand E. Salt controls endothelial and vascular phenotype. Pflugers Arch. 2015;467(3):499–512.
32 He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. Hypertension. 2009;54(3):482–8.
33 Oberleithner H, Riethmuller C, Schillers H, Macgregor GA, de Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proc Natl Acad Sci U S A. 2007;104(41):16281–6.
34 Korte S, Strater AS, Druppel V, Oberleithner H, Jeggle P, Grossmann C, et al. Feedforward activation of endothelial ENaC by high sodium. FASEB J. 2014;28(9):4015–25.
35 Teixeira DE, Peruchetti DB, Souza MC, das Graças Henriques MG, Pinheiro AAS, Caruso-Neves C. A high salt diet induces tubular damage associated with a pro-inflammatory and pro-fibrotic response in a hypertension-independent manner. Biochim Biophys Acta, Mol Basis Dis. 2020;1866(11):165907.
36 Staruschenko A, Palygin O, Ilatovskaya DV, Pavlov TS. Epidermal growth factors in the kidney and relationship to hypertension. Am J Physiol Renal Physiol. 2013;305(1):F12–20.
37 Ying WZ, Sanders PW. Enhanced expression of EGF receptor in a model of salt-sensitive hypertension. Am J Physiol Renal Physiol. 2005;289(2):F314–21.

38 Pavlov TS, Levchenko V, O'Connor PM, Ilatovskaya DV, Palygin O, Mori T, et al. Deficiency of renal cortical EGF increases ENaC activity and contributes to salt-sensitive hypertension. J Am Soc Nephrol. 2013;24(7):1053–62.
39 Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. AJNR Am J Neuroradiol. 2011;32(3):437–40.
40 Celis H, Fagard RH. White-coat hypertension: a clinical review. Eur J Intern Med. 2004;15(6):348–57.
41 Guyton AC. Blood pressure control: special role of the kidneys and body fluids. Science. 1991;252(5014):1813–6.
42 Chiolero A, Wurzner G, Burnier M. Renal determinants of the salt sensitivity of blood pressure. Nephrol Dial Transplant. 2001;16(3):452–8.
43 Ellison DH, Terker AS. Why your mother was right: how potassium intake reduces blood pressure. Trans Am Clin Climatol Assoc. 2015;126:46–55.
44 Krishna GG, Miller E, Kapoor S. Increased blood pressure during potassium depletion in normotensive men. N Engl J Med. 1989;320(18):1177–82.
45 Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 h urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ. 1988;297(6644):319–28.
46 Dyer AR, Elliott P, Shipley M, Stamler R, Stamler J. Body mass index and associations of sodium and potassium with blood pressure in INTERSALT. Hypertension. 1994;23(6 Pt 1):729–36.
47 Hsiao ZK, Wang SY, Hong ZG, Liu K, Cheng TY, Stamler J, et al. Timed overnight sodium and potassium excretion and blood pressure in steel workers in North China. J Hypertens. 1986;4(3):345–50.
48 Kwok TC, Chan TY, Woo J. Relationship of urinary sodium/potassium excretion and calcium intake to blood pressure and prevalence of hypertension among older Chinese vegetarians. Eur J Clin Nutr. 2003;57(2):299–304.
49 Gaborieau V, Delarche N, Gosse P. Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage. J Hypertens. 2008;26(10):1919–27.
50 Cobb LK, Anderson CAM, Elliott P, Hu FB, Liu K, Neaton JD, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. Circulation. 2014;129(10):1173–86.
51 Iwahori T, Miura K, Ueshima H. Time to consider use of the sodium-to-potassium ratio for practical sodium reduction and potassium increase. Nutrients. 2017;9(7):700.
52 Campbell NRC, Whelton PK, Orias M, Cobb LL, Jones ESW, Garg R, et al. It is strongly recommended to not conduct, fund, or publish research studies that use spot urine samples with estimating equations to assess individuals' sodium (salt) intake in association with health outcomes: a policy statement of the World Hypertension League, International Society of Hypertension and Resolve to Save Lives. J Hypertens. 2023;41(5):683–6.