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ORIGINAL RESEARCH

Urinary Sodium Excretion and Salt Intake Are Not Associated With Blood Pressure Variability in a White General Population

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BACKGROUND: Salt restriction may lower blood pressure variability (BPV), but previous studies have shown inconsistent results. Therefore, we investigated in an observational study and intervention trial whether urinary sodium excretion and salt intake are associated with 24-hour BPV.

METHODS AND RESULTS: We used data from the cross-sectional population-based Maastricht Study (n=2652; 60±8 years; 52% men) and from a randomized crossover trial (n=40; 49±11 years; 33% men). In the observational study, we measured 24-hour urinary sodium excretion and 24-hour BPV and performed linear regression adjusted for age, sex, mean blood pressure, lifestyle, and cardiovascular risk factors. In the intervention study, participants adhered to a 7-day low- and high-salt diet (50 and 250 mmol NaCl/24 h) with a washout period of 14 days, 24-hour BPV was measured during each diet. We used linear mixed models adjusted for order of diet, mean blood pressure, and body mass index. In the observational study, 24-hour urinary sodium excretion was not associated with 24-hour systolic or diastolic BPV (β, per 1 g/24 h urinary sodium excretion: 0.05 mm Hg [95% CI, −0.02 to 0.11] and 0.04 mm Hg [95% CI, −0.01 to 0.09], respectively). In the intervention trial, mean difference in 24-hour systolic and diastolic BPV between the low- and high-salt diet was not statistically significantly different (0.62 mm Hg [95% CI, −0.10 to 1.35] and 0.04 mm Hg [95% CI, −0.54 to 0.63], respectively).

CONCLUSIONS: Urinary sodium excretion and salt intake are not independently associated with 24-hour BPV. These findings suggest that salt restriction is not an effective strategy to lower BPV in the White general population.

REGISTRATION: URL: https://clinicaltrials.gov/ct2/show/NCT02068781

Key Words: blood pressure variability ■ crossover design ■ population-based ■ potassium ■ salt ■ sodium

Greater blood pressure (BP) variability (BPV) has been associated with cardiovascular disease and mortality,[1] but effective therapies to lower BPV are currently lacking. We hypothesized that reduced salt intake may be an intervention to lower BPV.

A potential mechanism explaining how higher salt intake may cause greater BPV is via arterial stiffness. Previous studies have shown that high salt intake has been associated with increased arterial stiffness,[2,3] which is a determinant of greater BPV,[4] potentially via damage to the vascular endothelium and collagen accumulation in the vessel wall.[5]

Previous investigations have shown inconsistent results with regard to the association between urinary sodium excretion or salt intake on BPV.[6–9] On the one hand, 2 previous observational studies have shown an association between higher 24-hour urinary sodium excretion and greater short-term BPV but did not adjust for potentially important confounders, such as mean BP.[6,7] On the other hand, 2 previous intervention

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CLINICAL PERSPECTIVE

What Is New?

- Greater blood pressure variability (BPV) is associated with an increased risk of cardiovascular disease, but effective intervention to lower BPV is lacking; we investigated whether salt restriction could be an effective intervention.
- In a population-based study, we found that urinary sodium excretion was not independently associated with 24-hour BPV.
- In an intervention study, that is, a crossover trial with a low- and high-salt diet, we did not find a statistically significant difference in 24-hour BPV during a low- or high-salt diet.

What Are the Clinical Implications?

- These findings suggest that salt restriction is not an effective intervention to lower 24-hour BPV in the White general population.

Nonstandard Abbreviation and Acronym

BPV	blood pressure variability

studies did not observe an association between restricted salt intake and lower BPV. However, one study did not correct for baseline BPV values,[8] and the other study did not use a control group.[9]

In view of this, we investigated, in the observational population-based Maastricht Study and a randomized crossover trial with low- and high-salt diets, whether higher 24-hour urinary sodium excretion and increased salt intake are associated with greater 24-hour BPV.

METHODS

Study Design

Observational Study

The Maastricht Study is an observational prospective population-based cohort study. The rationale and methodology have been described previously.[10] In brief, the study focuses on the pathogenesis, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals with type 2 diabetes, for reasons of efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131 088-105 234-PG). All participants gave written informed consent. Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

Intervention Study

We did a post hoc analysis of a crossover trial where the aim was to investigate the effect of a low- and high-salt diet on BP, whole-body glucose disposal, and insulin-mediated muscle microvascular recruitment in lean and abdominally obese but otherwise healthy individuals. The results of the primary end points, microvascular function and mean arterial pressure, have been reported previously.[11] Briefly, participants were recruited at the Maastricht University Medical Center, Maastricht, the Netherlands, between September 2014 and August 2016 via advertisements in local newspapers and among participants in previous investigations. Participants were aged 18 to 65 years, nonsmoking, free of diabetes and cardiovascular disease, and had a waist circumference <80 cm (lean women)/<94 cm (lean men) or >88 cm (abdominally obese women)/>102 cm (abdominally obese men). Exclusion criteria were fasting plasma glucose >6.1 mmol/L, office BP >180/110 mm Hg, unstable or severe pulmonary or thyroid disease, a recent history of malignancy, inflammatory diseases, impairment of renal or hepatic function, pregnancy or lactation, and use of glucose-lowering medication, nonsteroidal anti-inflammatory drugs, or corticosteroids.

Before the first and second set of measurements, participants adhered to a diet aimed at either a low-(50 mmol NaCl/24 h, equivalent to 2.922g NaCl/24 h) or a high-(250 mmol NaCl/24 h, equivalent to 14.61g NaCl/24u) salt intake for 7 days in randomized order in a 1:1 ratio, with a washout period of 14 days. Randomization was performed by an independent investigator using block randomization with variable block sizes. A dietician provided an isocaloric diet containing 50 mmol NaCl and 70 to 80 mmol K^+ for each individual, which was supplemented with sodium capsules (9 per day, containing 1.3 g [22.2 mmol] NaCl per capsule [BasicPharma, Geleen, The Netherlands]) during the high-salt week, and with matched placebo

capsules (BasicPharma, Geleen, The Netherlands) in the same amount during the low-salt week. To prevent side effects, capsules with delayed release properties were used (DRcaps, Capsugel; Morristown, NJ, USA). The containers with capsules were labeled in accordance with the randomization numbers and handed to the participants by a member of the research team; both were unaware of the treatment allocation. All participants gave written informed consent. The study was approved by the local ethics committee, performed in accordance with the Declaration of Helsinki, and registered at clinicaltrials.gov (NCT02068781).

Measurements in Observational Study

Twenty-Four-Hour Urinary Sodium and Potassium Excretion

To assess 24-hour urinary sodium and potassium excretion, sodium and potassium concentrations were determined in a sample from a single 24-hour urine collection. Urine samples were stored at −80° for 5 to 8 years. Sodium and potassium concentrations were measured in mmol/L by indirect potentiometry on a Roche Cobas 6000 analyzer and multiplied by collection volume to obtain the 24-hour urinary sodium and potassium excretion in mmol/24 h and converted to g/24 h by multiplying by 22.99 and 39.10, respectively. Only urine collections with a collection time between 20 hours and 28 hours were considered valid. If collection time did not equal 24 hours, urinary sodium and potassium excretions were extrapolated to a 24-hour excretion.

Blood Pressure Measurements and Blood Pressure Variability

A detailed description of the 24-hour ambulatory BP measurements and variability has been reported previously.[12] Briefly, 24-hour BPV was calculated as the average real variability of BP readings taken every 15 minutes between 8:00 AM and 23:00 PM, and every 30 minutes between 23:00 PM and 8.00 AM (WatchBP® O3; Microlife, Widnau, Switzerland) when >70% of data were available. In addition, we calculated within-visit (705-IT; Omron Healthcare, Kyoto, Japan) and 7-day BPV (WatchBP Home; Microlife) as the SD of 3 consecutive office BP measurements (with a 1-minute interval, after 10 minutes of rest) and as the SD of 7-day home BP measurements (taken twice, with a 1-minute interval, each morning and evening, for 7 consecutive days).

Covariates

Sociodemographic variables included age, sex, partner status, and socioeconomic status (education level [low, intermediate, or high], occupational status, and income). Lifestyle variables included alcohol consumption (none, low, or high), smoking status (never, former, or current), amount of moderate-to-vigorous physical activity, and the Dietary Approach to Stop Hypertension score[13] ("diet score"). Cardiovascular variables included glucose metabolism status (normal glucose metabolism, prediabetes, or type 2 diabetes), body mass index, prior cardiovascular disease, estimated glomerular filtration rate, urinary albumin excretion, lipid profile, use of lipid-modifying medication, and the individual classes of antihypertensive medication (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, and others [aldosterone antagonists, α blockers, and centrally acting antihypertensives]). Further details and definitions of potential confounders are provided in Data S1.

Measurements in the Intervention Study

Twenty-Four-Hour Urinary Sodium and Potassium Excretion

On the seventh day of both the low- and high-salt weeks, 24-hour urine was collected for assessment of sodium and potassium. Urinary sodium and potassium were determined with the ion-selective electrode method (Roche Diagnostics, Mannheim, Germany).

Twenty-Four-Hour Blood Pressure Measurements

On the same day as the 24-hour urine collections, 24-hour ambulatory BP measurements were performed (Mobilograph (New Generation), I.E.M., Stolberg, Germany) at the nondominant arm with appropriately sized cuffs at 15-minute intervals from 8:00 AM to 11:00 PM and at 30-minute intervals from 11:00 PM to 8:00 AM. Sufficient data (ie, >70%) were available to calculate average real variability in 35 participants.

Statistical Analysis

We performed 2 main analyses. For the observational study, we used multiple linear regression to examine the association between urinary sodium excretion and 24-hour BPV. We adjusted for age, sex, glucose metabolism status, and education level (model 1), and additionally for mean 24-hour systolic or diastolic BP (model 2), and additionally for the individual classes of antihypertensive medication (model 3), and additionally for alcohol consumption, smoking status, body mass index, total-to-high-density-lipoprotein cholesterol ratio and use of lipid-modifying medication (model 4). Akaike information criterion was lowest in model 4 for both 24-hour systolic and diastolic BPV (Table S1). For

the intervention study, we used linear mixed models with an unstructured covariance matrix to examine the effect of a low- and high-salt diet on 24-hour BPV. The models included diet (low or high salt) and order of diet (model 1), and additionally mean 24-hour systolic or diastolic BP, and obesity (ie, body mass index, due to study design) (model 2) as fixed factors. To investigate whether there was any carryover effect, we included the interaction term diet*order of diet to model 2.

We performed several additional analyses in the observational study. First, we tested for interactions with age, sex, body mass index, type 2 diabetes, and hypertension, as salt sensitivity may differ according to these factors.[14] Second, we repeated the analyses with urinary potassium excretion as the determinant, as it has been suggested that high potassium intake is associated with lower BP.[15]Third, we repeated the analyses with within-visit and 7-day BPV as the outcome. Fourth, we excluded individuals who used antihypertensive medication. Fifth, we additionally adjusted for estimated glomerular filtration rate, urinary albumin excretion, prior cardiovascular disease, pulse pressure (as a proxy for arterial stiffness), moderate-to-vigorous physical activity, diet score, income, and occupational status. We did not adjust for these variables in the main analysis, owing to either potential overadjustment bias[16] (ie, estimated glomerular filtration rate, urinary albumin excretion, prior cardiovascular disease, and arterial stiffening may lie in the causal pathway of urinary sodium excretion to BPV) or a large number of missing variables (physical activity, n=299; income, n=616; occupational status, n=1000). Sixth, in order to investigate BPV patterns in more detail, we analyzed 24-hour BPV divided into day and night separately. Seventh, age squared was added as a confounder in analyses with diastolic BPV, owing to the curvilinear relationship between age and diastolic BP. Finally, we used pulse pressure as the outcome a proxy for arterial compliance to conduct exploratory analyses.

Baseline characteristics are presented as n (%), mean±SD or median (interquartile range). High and low urinary sodium excretion was based on the median urinary sodium excretion. All analyses were performed with IBM SPSS software version 25.0 for Windows (IBM Corp., Somers, NY). All associations were visually checked for linearity, and a quadratic term was fitted if deemed necessary (indicated when used). A 2-sided *P* value of <0.05 was considered statistically significant for all analyses.

RESULTS

Characteristics of the Study Populations

Of the initial 3451 participants, we excluded 718 participants for the following reasons (not mutually exclusive): other types of diabetes than type 2 (n=41), missing urinary sodium excretion (n=176), or 24-hour BPV (n=559). After exclusion of 81 participants with missing data on confounders, the final study population consisted of 2652 participants (Figure 1). The clinical characteristics of the participants excluded compared with those included in the analysis were largely similar (Table S2).

Table 1 and Table S3 show the characteristics of The Maastricht Study population as a whole and according to median urinary sodium excretion. In general, individuals with a high compared with a low urinary sodium excretion had a higher body mass index and mean BP, more often suffered from type 2 diabetes, and more often used lipid-modifying and antihypertensive medication. Table 2 shows the characteristics of the interventional study population. In general, individuals had, during the high- compared with the low-salt diet, a higher mean systolic and diastolic BP.

Observational Study: Associations Between Urinary Sodium Excretion and 24-Hour Systolic and Diastolic BPV

We observed in The Maastricht Study that, after adjustment for age, sex, glucose metabolism status, education level, mean 24-hour systolic or diastolic BP (where appropriate), use of the individual classes of antihypertensive medication, alcohol use, smoking status, body mass index, total-to-high-density-lipoprotein cholesterol ratio, and use of lipid-modifying medication (Table 3; model 4), urinary sodium excretion was not associated with 24-hour systolic and diastolic BPV (regression coefficient β [per 1 g/24 h increment of urinary sodium excretion] with 95% CI: 0.05 mm Hg [95% CI, −0.02 to 0.11] and 0.04 mm Hg [95% CI, −0.01 to 0.09], respectively). Of these covariates, adjustments for mean 24-hour systolic or diastolic BP and body mass index strongly attenuated these associations.

Intervention Study: Associations Between Low- and High-Salt Diet and 24-Hour Systolic and Diastolic BPV

We found in the intervention study that, after adjustment for order of diet (model 1), a low- or high-salt diet was not associated with a change 24-hour systolic or diastolic BPV. The mean difference in 24-hour systolic and diastolic BPV between the low- and high-salt diet was −0.11 mm Hg (95% CI, −0.82 to 0.60) and −0.09 (95% CI, −0.67 to 0.48), respectively (Figure 2). After further adjustments for mean 24-hour systolic or diastolic BP (where appropriate), and obesity (model 2), a low- or high-salt diet remained not associated with a change 24-hour systolic or diastolic BPV (mean difference between low- and high-salt diet 0.62 mm Hg [95% CI, −0.10 to 1.35] and 0.04 mm Hg [95% CI,

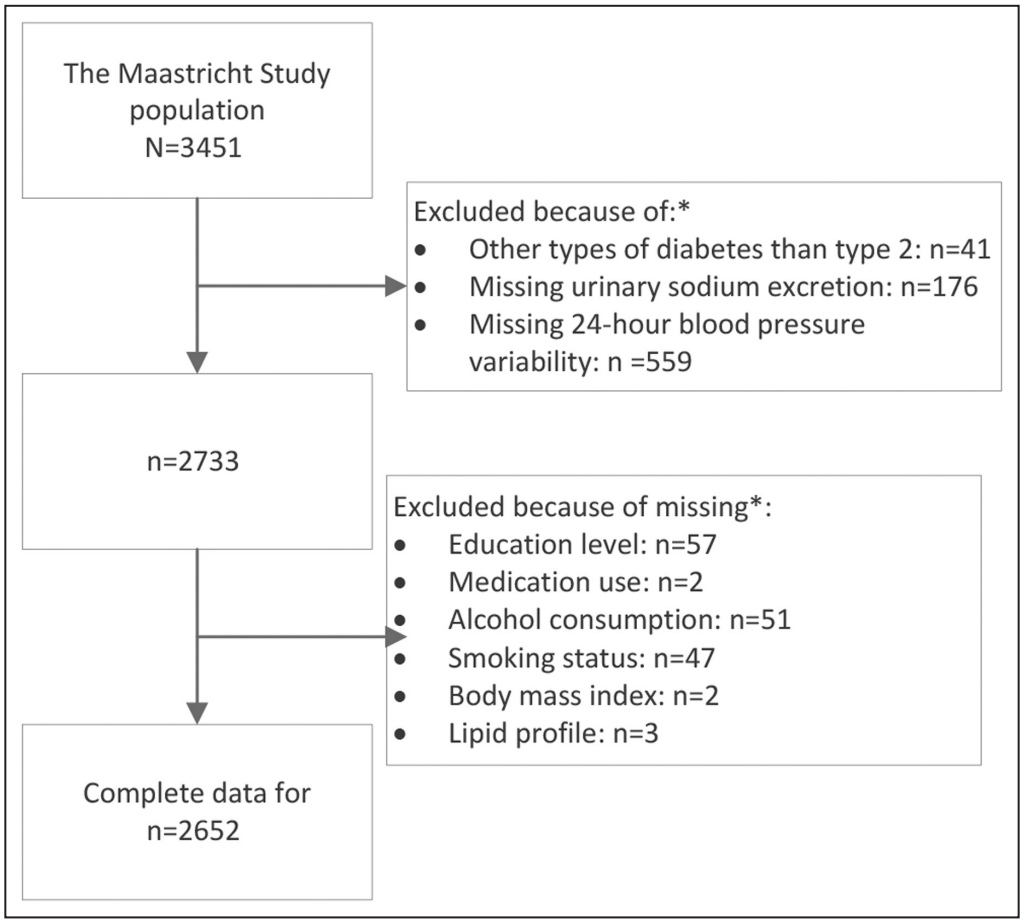

Figure 1. Flow chart delineating the final study population.
*Denotes not mutually exclusive.

–0.54 to 0.63], respectively). There was no carryover effect for either systolic or diastolic BPV (*P* value for interaction 0.96 and 0.94, respectively).

Additional Analyses

In the observational study, we did not find any interaction with age, sex, body mass index, type 2 diabetes, or hypertension (*P* values for interaction all >0.05). In addition, we did not find any association between urinary potassium excretion and 24-hour BPV (Table S4). When we repeated the analysis with within-visit BPV as the outcome, we also did not find any association. However, we observed a positive quadratic association between urinary sodium excretion and 7-day BPV (Table S5). The associations remained similar when we excluded individuals who used antihypertensive medication (n=1601, Table S6). Results also did not materially change when we additionally adjusted for estimated glomerular filtration rate, urinary albumin excretion, prior cardiovascular disease, moderate-to-vigorous physical activity, diet score, income, or occupational status (Table S7). When we analyzed day and night BPV separately, results were similar to 24-hour BPV in the observational study. In the intervention study, results were quantitively similar (Table S8, Figure S1), but day systolic BPV was statistically significantly lower in the high-salt compared with the low-salt diet (mean difference between low- and high-salt diet 0.78 mm Hg [95% CI, –0.03 to 1.54]). When age squared was added as a confounder in the analyses with diastolic BPV, results did not differ in the observational study (Table S7) or in the intervention study (mean difference in diastolic BPV between low- and high-salt diets –0.01 mm Hg [95% CI, –0.58 to 0.56]). When we analyzed pulse pressure as the outcome, after full adjustment, higher urinary sodium excretion was statistically significantly associated with greater pulse pressure (β, per 1 g/24 h increment of urinary sodium excretion: 0.20 mm Hg [95% CI, 0.01 to 0.39]; Table S9). Similarly, we observed that pulse pressure was higher in the high-salt diet compared with the low-salt diet (mean difference 2.18 mm Hg [95% CI, 0.69 to 3.67]; Figure S2).

DISCUSSION

Our study showed that urinary sodium excretion and salt intake are not associated with 24-hour BPV in both

Table 1. General Characteristics of the Observational Study (Maastricht Study) Population

Characteristic	Study population (n=2652)	Low urinary sodium excretion* (n=1326)	High urinary sodium excretion* (n=1326)
Demographics			
Age, y	60.0±8.2	60.0±8.2	60.0±8.1
Men	1373 (51.8%)	448 (33.8%)	925 (69.8%)
Education level			
Low	877 (33.1%)	438 (33.0%)	139 (33.1%)
Intermediate	758 (28.6%)	370 (27.9%)	388 (29.3%)
High	1017 (38.3%)	518 (39.1%)	499 (37.6%)
Lifestyle variables			
Smoking behavior			
Never	940 (35.4%)	487 (36.7%)	453 (34.2%)
Former	1384 (52.2%)	668 (50.4%)	716 (54.0%)
Current	328 (12.4%)	171 (12.9%)	157 (11.8%)
Alcohol consumption			
None	481 (18.1%)	258 (19.5%)	223 (16.8%)
Low	1483 (55.9%)	701 (52.9%)	782 (59.0%)
High	688 (25.9%)	367 (27.7%)	321 (24.0%)
Clinical characteristics			
Glucose metabolism status			
Normal glucose metabolism	1519 (57.3%)	837 (63.1%)	682 (51.4%)
Prediabetes	400 (15.1%)	198 (14.9%)	202 (15.2%)
Type 2 diabetes	733 (27.6%)	291 (21.9%)	442 (33.3%)
Body mass index, kg/m^2	27.0±4.4	26.0±4.1	27.9±4.4
Total-to-high-density-lipoprotein cholesterol ratio	3.7±1.2	3.5±1.1	3.9±1.2
Use of lipid-modifying medication	955 (36.0%)	428 (32.3%)	527 (39.7%)
Use of antihypertensive medication			
Angiotensin-converting enzyme inhibitor	324 (12.2%)	134 (10.1%)	190 (14.3%)
Angiotensin II receptor blocker	471 (17.8%)	209 (15.8%)	262 (19.8%)
β blocker	463 (17.5%)	216 (16.3%)	247 (18.6%)
Calcium channel blocker	238 (9.0%)	95 (7.2%)	143 (10.8%)
Diuretics	431 (16.3%)	187 (14.1%)	262 (19.8%)
Other†	31 (1.2%)	13 (1.0%)	18 (1.4%)
24-h systolic BP, mm Hg	120.1±11.9	118.0±11.3	122.2±12.0
24-h diastolic BP, mm Hg	74.4±7.2	73.5±7.0	75.3±7.2
Blood pressure variability			
24-h systolic BPV, mm Hg	10.03±2.50	10.00±2.51	10.05±2.49
24-h diastolic BPV, mm Hg	7.01±1.86	6.94±1.84	7.07±1.86
Urinary sodium and potassium excretion			
Urinary sodium excretion, g/24 h‡	3.85±1.47	2.72±0.64	4.97±1.19
Urinary potassium excretion, g/24 h‡	3.05±0.92	2.73±0.82	3.38±0.91

Data are presented as mean±SD or n (%). BP indicates blood pressure; and BPV, blood pressure variability.
*Based on median value, low ≤3.65 g/24 h and high >3.66 g/24 h urinary sodium excretion.
†Other antihypertensive medication classes include aldosterone antagonists, α -blockers, and centrally acting antihypertensives.
‡To convert to urinary sodium excretion to mmol/24 h, multiply by 43.2; to convert urinary potassium excretion to mmol/24 h, multiply by 25.6.

Table 2. General Characteristics of the Interventional Crossover Trial Study Population

Characteristic	Study population (n=40)	
At inclusion		
Age, y	49.1±10.6	
Men	13 (32.5%)	
Total-to-high-density-lipoprotein cholesterol ratio	3.1±1.0	
Use of lipid-modifying medication	1 (2.5%)	
Use of antihypertensive medication*	4 (10.0%)	
	Low-salt diet	High-salt diet
Fasting plasma glucose, mmol/L	5.0±0.4	4.8±0.4
Body mass index, kg/m^2	26.0±5.5	26.4±5.5
24-h systolic BP, mm Hg	117.9±12.4	124.3±12.9
24-h diastolic BP, mm Hg	75.6±9.4	78.8±9.3
Blood pressure variability		
24-h systolic BPV, mm Hg†	9.38±1.99	9.57±2.62
24-h diastolic BPV, mm Hg†	7.85±1.65	8.05±1.90
Urinary sodium and potassium excretion		
Urinary sodium excretion, g/24 h‡	1.63±0.72	5.38±1.54
Urinary potassium excretion, g/24 h‡	2.09±0.96	2.20±0.96

Data are presented as mean± SD or n (%), n=40 participants. BP indicates blood pressure; and BPV, blood pressure variability.
*Discontinued 3 weeks before the intervention.
†Data available for n=35 participants.
‡To convert to urinary sodium excretion to mmol/24 h, multiply by 43.2; to convert urinary potassium excretion to mmol/24 h, multiply by 25.6.

a large White population-based cohort study and in an intervention study. Therefore, our results do not indicate that salt restriction would be an effective strategy to lower BPV, at least not in a White population-based setting with relatively healthy individuals.

Our findings are in line with 2 previous intervention studies[8,9] but not with 2 previous observational studies.[6,7] Our study differs from these studies, as we were able to adjust for a large series of potential confounders, including mean BP, and could exclude those who used antihypertensive medication.

Several reasons may explain why we did not find an association between urinary sodium excretion, salt intake, and 24-hour BPV. First, associations may be different in salt-sensitive individuals only. Indeed, salt-sensitive individuals exhibit a stronger BP-increasing reaction to salt intake than salt-resistant individuals,[14] which may lead to greater BPV. However, we did perform interaction analyses with higher age, female sex, type 2 diabetes, or hypertension, all factors associated with higher salt sensitivity,[14] and these were not statistically significant. Further study of the effect of increased salt intake on BPV in salt-sensitive individuals is therefore required. Second, the association between urinary sodium excretion and BPV was strongly attenuated when adjusted for body mass index. This attenuation was not fully explained by potentially different dietary habits in individuals with a higher body mass index, because when we additionally adjusted for diet score, the regression coefficient for body mass index remained similar (data not shown). Other factors may thus explain the strong influence of higher body mass index. One such factor may be that individuals with a higher body mass index are more salt sensitive.[17] However, we did not observe any interaction with higher body mass index. Another factor could be that the associations may have been overadjusted, as higher body mass index may lie in the causal pathway between salt intake and BPV. Indeed, it has been suggested that higher salt intake may be associated with obesity via pathways other than excessive energy intake,[18,19] such as increased endogenous fructose production[20] and adipocyte insulin sensitivity,[21] and obesity has been associated with greater short-term BPV as well.[22] Third, in The Maastricht Study, the range of urinary sodium excretion was moderate (ie, the interquartile range was 2.8 to 4.6 g/24 h), which may have limited our ability to detect an association. However, we also did not find any association in the crossover trial, where the low- and high-salt diets were very effective with regard to decreasing and increasing salt intake, substantiated by the corresponding mean urinary sodium excretion (ie, 2.1 and 5.4 g/24 h, respectively). Fourth, we may have underestimated associations in The Maastricht Study because of regression dilution bias.[23] We measured sodium excretion in only 1 24-hour urine sample, but there is substantial day-to-day variability in urinary sodium excretion.[24] Fifth, other biological factors may explain why we did not find an association, such as chronic kidney disease,[25,26] prior cardiovascular

Table 3. Associations Between Urinary Sodium and 24-Hour Systolic and Diastolic Blood Pressure Variability in the Observational Study

		24-h systolic BPV		24-h diastolic BPV	
	Model	β	(95% CI)	β	(95% CI)
Urinary sodium excretion, g/24 h	1	0.13	(0.06 to 0.20)	0.09	(0.04 to 0.13)
	2	0.10	(0.03 to 0.16)	0.08	(0.03 to 0.12)
	3	0.10	(0.04 to 0.16)	0.08	(0.03 to 0.12)
	4	0.05	(−0.02 to 0.11)	0.04	(−0.01 to 0.09)

Regression coefficient (β) represent mm Hg difference in blood pressure variability for every 1 gram/24 h increment in urinary sodium excretion. Model 1: age, sex, glucose metabolism status, and education level; model 2: model 1+mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2+individual classes of antihypertensive medication (ie, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3+alcohol use, smoking status, body mass index, total-to-high-density-lipoprotein cholesterol ratio, use of lipid-modifying medication. BPV indicates blood pressure variability.

disease,[27] physical activity,[28,29] or socioeconomic status.[30,31] However, results remained similar when we adjusted for these factors.

Interestingly, we observed a U-shaped (ie, positive quadratic) association between 24-hour urinary sodium excretion and 7-day BPV but not for any of the other BPV indices. Although it has been shown that the relation between urinary sodium excretion and mean BP is linear,[15,32–35] the association between urinary sodium excretion and cardiovascular events has been suggested to be U shaped as well.[32,34,36] Potential explanations for our finding may be activation of the renin-angiotensin-aldosterone system and sympathetic nervous system,[37] but this does not explain why we did not observe similar findings with within-visit or 24-hour BPV. Further investigation on potential U-shaped associations between urinary sodium excretion and mid- to long-term BPV is needed.

In addition, when we divided 24-hour BPV into day and night, systolic day BPV was significantly lower in the high-salt diet compared with the low-salt diet, for which we do not have a biologically plausible explanation. However, results were quantitively similar to the main analyses, and such multiple testing may have produced a chance finding.

We did not find an association between urinary potassium excretion and BPV. Although increased potassium intake has been associated with a lower risk of cardiovascular disease,[38] our findings suggest that the beneficial effects of increased potassium intake are not mediated by a reduction in BPV. These effects may be mainly mediated via reductions in mean BP[38] and improvements in endothelial function.[39]

In addition, in exploratory analyses, we observed that higher urinary sodium excretion was associated with higher pulse pressure and that pulse pressure was higher in the high-salt diet compared with the low-salt diet. These findings suggest that higher salt intake is associated with arterial stiffening which may explain,

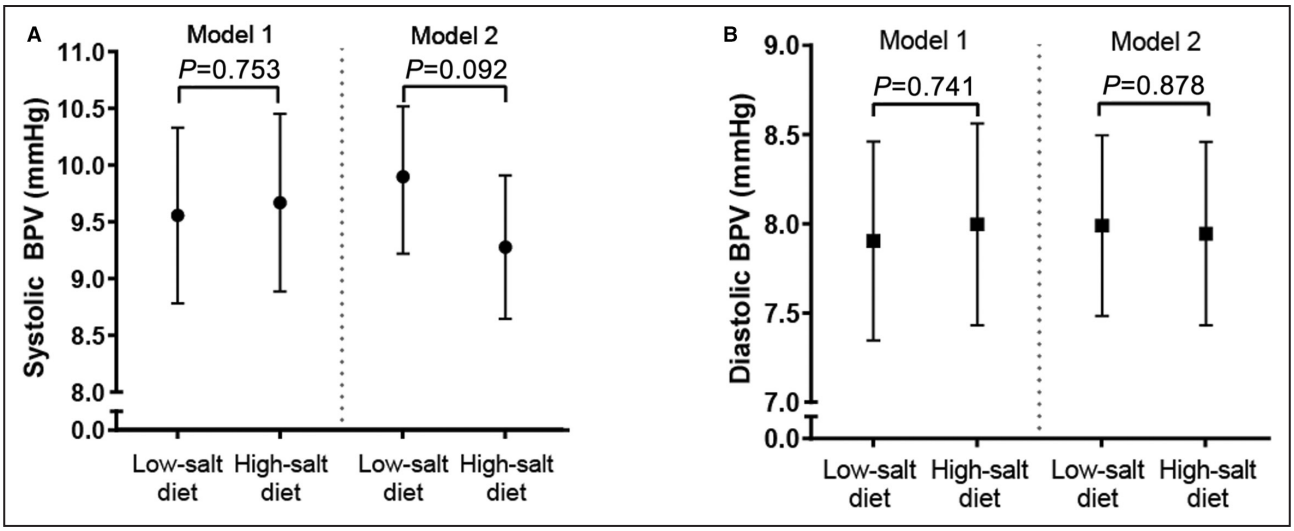

Figure 2. Effect of low- and high-salt diet on 24-hour systolic (A) and diastolic (B) BPV in the intervention study, after adjustments for order of diet (model 1), and additionally for mean 24-hour systolic or diastolic blood pressure and body mass index (model 2).
Error bars represent 95% CIs. BPV indicates blood pressure variability.

at least partly, the association with increased cardiovascular disease, consistent with previous studies.[5,40]

Our study had several limitations. First, urinary sodium excretion was measured once, and the day-to-day variability of urinary sodium excretion may have led to an underestimation of associations. Second, we could not determine salt sensitivity of individuals in The Maastricht Study, which may play a role in greater BPV. Third, although the crossover trial was not designed to detect differences in 24-hour BPV, there was sufficient power to detect a clinically relevant[41] difference of 2 mm Hg in 24-hour BPV. Finally, the generalizability of our study populations may be limited to individuals of White race only, and salt sensitivity and BPV may vary among different ethnicities.[14]

An important strength of the current study is that both the observational population-based study and intervention trial show similar results, which is substantial evidence for a null association. Further strengths of this study include the ability to adjust for a large series of potential confounders, where we could show that additional adjustments, for prior cardiovascular disease for example, did not change results, and the large study population allowed us to show that after exclusion of individuals using antihypertensive medication, results were similar.

CONCLUSIONS

In conclusion, higher urinary sodium excretion and increased salt intake are not independently associated with greater 24-hour BPV in the White general population. These findings suggest that salt restriction is not an effective strategy to lower BPV in the White general population.

ARTICLE INFORMATION

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

In The Maastricht Study, we assessed education level, socio-economic status (occupational status and income level), alcohol consumption, smoking status, history of cardiovascular disease, and moderate-to-vigorous level of physical activity by questionnaire.[10] Education level was classified into three groups: low (none or primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education) or high (higher vocational education or university level of education). Occupational status was categorized into tertiles according to the International Socio-Economic Index 2008 (ISEI-08),[42] with a higher tertile indicating a higher occupational status. Income level was calculated as the household income divided by the square root of household size. Alcohol consumption was defined as non-consumer, low consumer (≤7 alcoholic drinks/week for women; ≤14 alcoholic drinks/week for men) or high consumer (>7 alcoholic drinks/week for women; >14 alcohol drinks/week for men). Smoking status was categorized into never, former or current smoker. Glucose metabolism status was categorized into normal glucose metabolism, prediabetes (impaired fasting glucose and/or impaired glucose tolerance) or type 2 diabetes, according to the World Health Organization 2006 criteria.[43] Estimated glomerular filtration rate was computed with the CKD-EPI (Chronic Kidney Disease Epidemiology collaboration) formula, using serum creatinine and cystatin C.[44] To assess albuminuria, participants were requested to collect two 24-hour urine samples. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyzer (due to a change of supplier, by the Beckman Synchron LX20 and the Roche Cobas 6000) and multiplied by collection volume to obtain 24-hour urinary albumin excretion, as described previously.[10]

Table S1. R squared and AIC values for models in the association between urinary sodium excretion and 24-hour BPV in the observational study

		24-hour systolic BPV		24-hour diastolic BPV	
	Model	R^2	AIC	R^2	AIC
Urinary sodium excretion, g/24h	1	0.070	4684.2	0.020	3233.3
	2	0.181	4347.7	0.045	3165.6
	3	0.192	4324.6	0.054	3146.8
	4	0.211	4274.4	0.072	3103.5

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

Table S2. Characteristics of participants in- and excluded from the analysis in the observational study

Characteristic	Included (n=2,652)	Missing in included	Excluded (n=799)	Missing in excluded	P-value
Demographics					
Age, years	60.0 ± 8.2	0	58.9 ± 8.6	0	.003
Men	1,373 (51.8%)	0	402 (50.3%)	0	.471
Education level		0		77	.464
Low	877 (33.1%)		256 (35.5%)		
Intermediate	758 (28.6%)		195 (27.0%)		
High	1017 (38.3%)		271 (37.5%)		
Income, euro/month	2022 ± 811	616	1998 ± 854	263	.556
Occupational status		349		278	.002
Low	667 (30.3%)		226 (36.5%)		
Intermediate	773 (35.1%)		222 (35.8%)		
High	764 (34.7%)		172 (27.7%)		
Lifestyle variables					
Smoking behavior		0		63	<.001
Never	940 (35.4%)		230 (31.3%)		
Former	1,384 (52.2%)		365 (49.6%)		
Current	328 (12.4%)		141 (19.2%)		
Alcohol consumption		0		69	.381
None	481 (18.1%)		148 (20.3%)		
Low	1,483 (55.9%)		392 (53.7%)		
High	688 (25.9%)		190 (26.0%)		
Moderate-to-vigorous physical activity, h/wk	4.5 [2.3 – 8.0]	299	4.5 [1.8 – 7.5]	158	.009
Diet score	23.9 ± 4.6	117	23.3 ± 4.6	111	.009

Clinical characteristics					
Glucose metabolism status		0		41	.074
Normal glucose metabolism	1,519 (57.3%)		405 (53.4%)		
Prediabetes	400 (15.1%)		111 (14.6%)		
Type 2 diabetes	733 (27.6%)		242 (31.9%)		
Body mass index, kg/m^2	27.0 ± 4.4	0	27.5 ± 5.1	3	.007
Total-to-HDL cholesterol ratio	3.7 ± 1.2	0	3.6 ± 1.2	4	.209
Use of lipid-modifying medication	955 (36.0%)		303 (38.1%)	4	.284
Use of antihypertensive medication		0		4	
ACE-inhibitor	324 (12.2%)		102 (12.8%)		.648
Angiotensin II receptor blocker	471 (17.8%)		150 (18.9%)		.478
β-blocker	463 (17.5%)		157 (19.7%)		.138
Calcium channel blocker	238 (9.0%)		88 (11.1%)		.083
Diuretics	429 (16.4%)		129 (17.8%)		.361
Other*	31 (1.2%)		17 (2.1%)		.042
Prior cardiovascular disease	429 (16.2%)	33	129 (17.8%)	75	.358
Estimated GFR, ml/min/1.73m^2	88.0 ± 14.7	2	88.5 ± 15.9	31	.437
Urinary albumin excretion, mg/24h	6.7 [4.0 – 11.7]	0	6.8 [4.1 – 13.5]	42	.282
Office SBP, mmHg	135.0 ± 18.1	2	135.1 ± 18.6	0	.901
Office DBP, mmHg	76.2 ± 9.9	2	75.9 ± 9.8	0	.471
24-hour SBP, mmHg	12.01 ± 11.9	0	120.9 ± 12.1	559	.323
24-hour DBP, mmHg	74.4 ± 7.2	0	73.9 ± 7.0	559	.287
7-day SBP, mmHg	127.4 ± 13.4	760	128.3 ± 14.1	244	.137
7-day DBP, mmHg	77.2 ± 8.1	760	77.5 ± 8.6	244	.555
Blood pressure variability					
Within-visit systolic BPV, mmHg	4.68 ± 2.91	7	4.50 ± 2.87	1	.113
Within-visit diastolic BPV, mmHg	2.51 ± 1.67	7	2.53 ± 1.88	1	.811

24-hour systolic BPV, mmHg	10.03 ± 2.50	0	10.22 ± 2.48	559	.242
24-hour diastolic BPV, mmHg	7.01 ± 1.86	0	7.03 ± 1.90	559	.882
7-day systolic BPV, mmHg	9.20 ± 3.71	780	9.81 ± 4.34	245	.003
7-day diastolic BPV, mmHg	5.73 ± 2.84	780	6.32 ± 3.73	245	.001
Urinary sodium and potassium excretion					
Urinary sodium excretion, g/24h	3.85 ± 1.47	0	3.98 ± 1.56	176	.064
Urinary potassium excretion, g/24h	3.05 ± 0.92	0	3.03 ± 0.97	176	.578

Data are presented as mean ± standard deviation (SD),median [interquartile range] or n (%).

Abbreviations: GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPV, blood pressure variability

* Other antihypertensive medication classes include aldosterone antagonists, α-blockers and centrally acting antihypertensives

Table S3. Additional study population characteristics in the observational study

Characteristic	Study population (n=2,652)	Low urinary sodium excretion* (n=1,326)	High urinary sodium excretion* (n=1,326)
Demographics			
Income, euro/month	2022 ± 811	2026 ± 811	2017 ± 810
Occupational status			
Low	667 (30.3%)	313 (28.5%)	354 (32.0%)
Intermediate	773 (35.1%)	414 (37.7%)	359 (32.5%)
High	764 (34.7%)	371 (33.8%)	393 (35.5%)
Lifestyle variables			
Moderate-to-vigorous physical activity, h/wk	4.5 [2.3 – 8.0]	4.5 [2.5 – 7.8]	4.5 [2.3 – 8.0]
Diet score	23.9 ± 4.6	24.1 ± 4.7	23.7 ± 4.5
Clinical characteristics			
Prior cardiovascular disease	429 (16.2%)	205 (15.6%)	224 (17.1%)
Estimated GFR, ml/min/1.73m^2	88.0 ± 14.7	87.6 ± 14.7	88.5 ± 14.6
Urinary albumin excretion, mg/24h	6.7 [4.0 – 11.7]	6.2 [3.8 – 10.4]	7.3 [4.3 – 13.6]
Office SBP, mmHg	135.0 ± 18.1	132.7 ± 18.5	137.4 ± 17.3
Office DBP, mmHg	76.2 ± 9.9	75.0 ± 9.8	77.5 ± 9.7
7-day SBP, mmHg	127.4 ± 13.4	125.1 ± 13.3	129.7 ± 13.1
7-day DBP, mmHg	77.2 ± 8.1	75.8 ± 7.9	78.7 ± 8.0
Blood pressure variability			
Within-visit systolic BPV, mmHg	4.68 ± 2.91	4.72 ± 2.92	4.65 ± 2.91
Within-visit diastolic BPV, mmHg	2.51 ± 1.67	2.50 ± 1.62	2.53 ± 1.72
7-day systolic BPV, mmHg	9.20 ± 3.71	9.16 ± 3.79	9.24 ± 3.64
7-day diastolic BPV, mmHg	5.73 ± 2.84	5.69 ± 2.83	5.77 ± 2.85

Data are presented as mean ± standard deviation (SD),median [interquartile range] or n (%).

* Based on median value, low ≤ 3.65 g/24h and high >3.66 g/24h urinary sodium excretion.

Data available for: income, n=2,036, occupational status, n=1,652; moderate-to-vigorous physical activity, n=2,353; diet score, n=2,513; prior cardiovascular disease, n=2,652; estimated GFR, n=2,630; urinary albumin excretion, n=2,652; office blood pressure, n=2,650; 7-day blood pressure, n=1,892; within-visit BPV, n=2,645; 7-day BPV, n=1,872

Abbreviations: GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPV, blood pressure variability

Table S4. Associations between urinary potassium excretion and 24-hour systolic and diastolic blood pressure variability in the observational study

		24-hour systolic BPV		24-hour diastolic BPV	
	Model	β	(95% CI)	β	(95% CI)
Urinary potassium excretion, g/24h	1	0.07	(-0.03; 0.18)	0.03	(-0.05; 0.11)
	2	0.03	(-0.07; 0.13)	0.01	(-0.07; 0.09)
	3	0.04	(-0.06; 0.14)	0.02	(-0.06; 0.10)
	4	0.01	(-0.08; 0.11)	0.00	(-0.08; 0.08)

Regression coefficients(β) represent mmHg difference in blood pressure variability for every 1 gram/24h increment in urinary potassium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

Table S5. Associations between urinary sodium excretion and within-visit and 7-day systolic and diastolic blood pressure variability in the observational study

		Within-visit systolic BPV, mmHg		Within-visit diastolic BPV, mmHg	
	Model	β	(95% CI)	β	(95% CI)
Urinary sodium excretion, g/24h	1	0.00	(-0.07; 0.08)	0.00	(-0.04; 0.05)
	2	-0.01	(-0.09; 0.06)	-0.01	(-0.05; 0.04)
	3	-0.01	(-0.08; 0.07)	-0.01	(-0.05; 0.04)
	4	0.03	(-0.05; 0.10)	0.01	(-0.04; 0.05)
Urinary sodium excretion, g/24h		7-day systolic BPV, mmHg		7-day diastolic BPV, mmHg	
Linear	1	-0.06	(-0.18; 0.07)	-0.01	(-0.10; 0.09)
	2	-0.08	(-0.21; 0.06)	-0.04	(-0.14; 0.07)
	3	-0.10	(-0.23; 0.03)	-0.04	(-0.15; 0.06)
	4	-0.10	(-0.23; 0.03)	-0.05	(-0.15; 0.06)
Quadratic	1	0.04	(0.00; 0.08)	0.04	(0.01; 0.08)
	2	0.04	(0.00; 0.08)	0.04	(0.01; 0.08)
	3	0.04	(0.01; 0.08)	0.04	(0.01; 0.08)
	4	0.04	(0.01; 0.09)	0.04	(0.01; 0.08)

Regression coefficients(β) represent mmHg difference in blood pressure variability for every 1 gram/24h increment in urinary sodium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

Table S6. Associations between urinary sodium excretion and 24-hour systolic and diastolic blood pressure variability in individuals without antihypertensive medication use in the observational study

		24-hour systolic BPV		24-hour diastolic BPV	
	Model	β	(95% CI)	β	(95% CI)
Urinary sodium excretion, g/24h	1	0.17	(0.08; 0.26)	0.10	(0.03; 0.17)
n=1,601	2	0.12	(0.04; 0.21)	0.09	(0.02; 0.16)
	3	0.08	(-0.01; 0.16)	0.05	(-0.02; 0.11)

Regression coefficients(β) represent mmHg difference in blood pressure variability for every 1 gram/24h increment in urinary sodium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

Table S7. Associations between urinary sodium excretion and 24-hour systolic and diastolic blood pressure variability with additional adjustments in the observational study

		24-hour systolic BPV		24-hour diastolic BPV	
	Model	β	(95% CI)	β	(95% CI)
Urinary sodium excretion, g/24h	1	0.13	(0.06; 0.20)	0.10	(0.04; 0.15)
	2	0.10	(0.03; 0.16)	0.09	(0.04; 0.14)
	3	0.10	(0.04; 0.17)	0.08	(0.04; 0.14)
	4	0.05	(-0.02; 0.11)	0.04	(-0.01; 0.09)
+ eGFR and UAE (n=2,630)	5	0.05	(-0.02; 0.12)	0.034	(-0.01; 0.09)
Urinary sodium excretion, g/24h	1	0.14	(0.07; 0.21)	0.10	(0.04; 0.15)
	2	0.10	(0.04; 0.17)	0.09	(0.04; 0.14)
	3	0.11	(0.04; 0.17)	0.09	(0.04; 0.14)
	4	0.05	(-0.02; 0.12)	0.04	(-0.01; 0.09)
+ prior cardiovascular disease (n=2,619)	5	0.05	(-0.02; 0.12)	0.04	(-0.01; 0.09)
Urinary sodium excretion, g/24h	1	0.13	(0.06; 0.20)	0.10	(0.05; 0.15)
	2	0.09	(0.02; 0.16)	0.09	(0.03; 0.14)
	3	0.10	(0.03; 0.16)	0.09	(0.03; 0.14)
	4	0.03	(-0.04; 0.10)	0.04	(-0.02; 0.10)
+ MVPA (n=2,353)	5	0.03	(-0.04; 0.10)	0.04	(-0.02; 0.09)
Urinary sodium excretion, g/24h	1	0.13	(0.06; 0.20)	0.09	(0.04; 0.15)
	2	0.09	(0.03; 0.16)	0.08	(0.03; 0.13)
	3	0.10	(0.03; 0.16)	0.08	(0.03; 0.13)
	4	0.04	(-0.03; 0.11)	0.04	(-0.02; 0.09)
+ diet score (n=2,513)	5	0.04	(-0.03; 0.11)	0.03	(-0.02; 0.09)
Urinary sodium excretion, g/24h	1	0.14	(0.06; 0.21)	0.11	(0.05; 0.17)
	2	0.11	(0.04; 0.18)	0.10	(0.04; 0.16)
	3	0.11	(0.04; 0.18)	0.10	(0.04; 0.16)
	4	0.05	(-0.02; 0.13)	0.04	(-0.02; 0.10)

+ income (n=2,036)	5	0.05	(-0.02; 0.13)	0.04	(-0.02; 0.10)
Urinary sodium excretion, g/24h	1	0.16	(0.08; 0.23)	0.10	(0.04; 0.16)
	2	0.11	(0.04; 0.18)	0.09	(0.03; 0.14)
	3	0.12	(0.05; 0.19)	0.09	(0.03; 0.15)
	4	0.05	(-0.02; 0.13)	0.04	(-0.02; 0.10)
+ occupational status (n=2,204)	5	0.05	(-0.02; 0.12)	0.04	(-0.02; 0.10)
Urinary sodium excretion, g/24h	1	0.13	(0.06; 0.20)	0.09	(0.04; 0.16)
	2	0.10	(0.03; 0.16)	0.08	(0.03; 0.14)
	3	0.10	(0.04; 0.16)	0.08	(0.03; 0.14)
	4	0.05	(-0.02; 0.11)	0.04	(-0.01; 0.09)
+ pulse pressure (n=2,652)	5	0.05	(-0.01; 0.12)	0.04	(-0.01; 0.09)
Urinary sodium excretion, g/24h *	4	-	-	0.04	(-0.01; 0.09)

Regression coefficients (β) represent mmHg difference in blood pressure variability for every 1 gram/24h increment in urinary sodium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication; model 5: model 4 + adjustment for additional confounder.

* additionally adjusted for age and age squared.

Abbreviations: BPV, blood pressure variability; CI, confidence interval; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; MVPA, moderate-to-vigorous physical activity

Table S8. Associations between urinary sodium excretion and systolic and diastolic blood pressure variability divided into day and night

		24-hour systolic BPV				24-hour diastolic BPV			
		Day		Night		Day		Night	
	Model	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Urinary sodium excretion, g/24h	1	0.15	(0.06; 0.24)	0.14	(0.04; 0.24)	0.13	(0.05; 0.20)	0.09	(0.01; 0.17)
	2	0.12	(0.03; 0.21)	0.11	(0.01; 0.21)	0.12	(0.05; 0.20)	0.08	(0.00; 0.16)
	3	0.12	(0.04; 0.21)	0.12	(0.02; 0.22)	0.12	(0.05; 0.20)	0.08	(0.00; 0.16)
	4	0.07	(-0.02; 0.16)	0.05	(-0.05; 0.15)	0.07	(-0.01; 0.15)	0.03	(-0.05; 0.11)

Regression coefficient (β) represent mmHg difference in blood pressure variability for every 1 gram/24h increment in urinary sodium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour systolic or diastolic blood pressure (where appropriate); model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

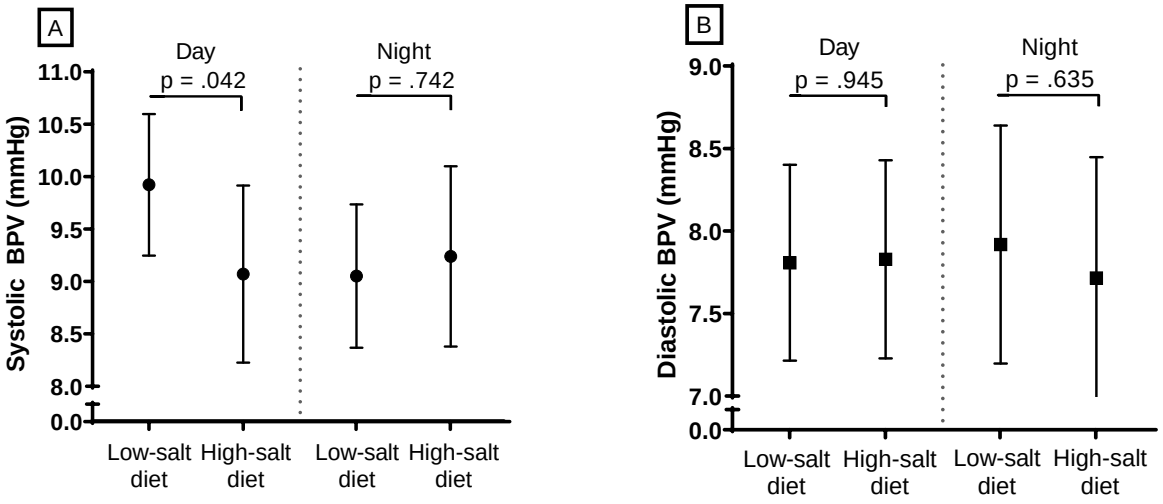
Table S9. Associations between urinary sodium excretion and pulse pressure

		Pulse pressure	
	Model	β	(95% CI)
Urinary sodium excretion, g/24h	1	0.25	(0.04; 0.46)
	2	0.12	(-0.07; 0.31)
	3	0.08	(-0.11; 0.27)
	4	0.20	(0.01; 0.39)

Regression coefficient (β) represent mmHg difference in pulse pressure for every 1 gram/24h increment in urinary sodium excretion.

Model 1: age, sex, glucose metabolism status and education level; model 2: model 1 + mean 24-hour blood pressure; model 3: model 2 + individual classes of antihypertensive medication (i.e. beta blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and others); model 4: model 3 + alcohol use, smoking status, body mass index, total-to-HDL cholesterol ratio, use of lipid-modifying medication

Figure S1. Effect of low- and high-salt diet on day and night systolic (panel A) and diastolic (panel B) blood pressure variability in the intervention study, after adjustments for order of diet, mean 24-hour systolic or diastolic blood pressure, and body mass index. Error bars represent 95% confidence intervals.

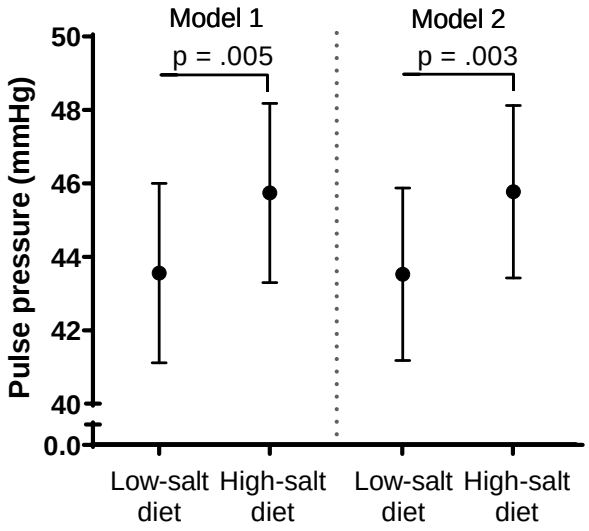


Mean differences for systolic BPV, day: 0.78 mmHg (95%CI 0.03; 1.54); night: 0.17 mmHg (95%CI -0.85; 1.19).

Mean differences for diastolic BPV, day: 0.21 mmHg (95%CI -0.60; 0.64); night: 0.20 mmhg (95%CI -0.65; 1.06).

Abbreviations: BPV, blood pressure variability

Figure S2. Effect of low- and high-salt diet on pulse pressure in the intervention study, after adjustments for order of diet (model 1), and additionally for mean 24-hour blood pressure, and body mass index (model 2).



Error bars represent 95% confidence intervals.