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Effects of the Dietary Approaches To Stop Hypertension (DASH) Diet and Sodium Intake on Serum Uric Acid

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Abstract

Objective—Randomized trial data guiding dietary recommendations to lower serum uric acid (SUA), the etiologic precursor of gout, are scarce. We examined the effects of the DASH diet (a well-established diet that lowers blood pressure) and levels of sodium intake, on SUA.

Methods—We conducted an ancillary study of a randomized, crossover feeding trial in 103 adults with pre- or stage 1 hypertension. Participants were randomly assigned to receive either the DASH diet or a control diet (typical of the average American diet) and were further fed low, medium, and high sodium levels for 30 days each in random order. Body weight was kept constant. SUA was measured at baseline and following each feeding period.

Results—Trial participants were 55% women and 75% black with a mean age of 52 (SD, 10) years and mean SUA of 5.0 (SD, 1.3) mg/dL. The DASH diet reduced SUA by -0.35 mg/dL (95%CI: -0.65 , -0.05 ; $P=0.02$) with a higher effect (-1.3 mg/dL; 95% CI -2.50 , -0.08) among participants ($N=8$) with a baseline SUA ≥ 7 mg/dL. Increasing sodium intake from the low level, decreased SUA by -0.3 mg/dL (95%CI: -0.5 , -0.2 ; $P<0.001$) during the medium sodium level and by -0.4 mg/dL (95%CI: -0.6 , -0.3 ; $P<0.001$) during the high sodium level.

Conclusions—The DASH diet lowered SUA, and this effect was greater among participants with hyperuricemia. Moreover, we found that higher sodium intake decreased SUA, which enhances our knowledge of urate pathophysiology and risk factors of hyperuricemia.

Serum uric acid (SUA) is an important factor in the causal pathway for gout (1). Furthermore, SUA has been implicated as a potential risk factor and/or mediator of cardiovascular disease outcomes and mortality in a large number of observational studies (2–6). Although many of the clinical trials targeting SUA reduction have focused on pharmacologic interventions (7–9), diet has long been identified as an important determinant

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Conflicts of interest

The authors have no conflicts of interest to report.

of SUA (10). However, much of the dietary evidence on SUA reduction is derived from observational studies (11–13). There is little evidence from randomized clinical trials in support of dietary interventions to lower SUA. Moreover, prior intervention studies have focused on isolated micronutrients such as vitamin C (14,15) or food types such as dairy (16). It remains unknown whether adopting a healthful dietary pattern might effectively lower SUA.

The DASH-sodium trial was a clinical feeding study designed to examine the impact of the DASH diet and varying amounts of sodium consumption on blood pressure (17). In the original trial, participants consumed either the DASH diet or a control diet (typical of the average American diet) with each of three sodium levels: 60, 120, and 180 mmol of sodium per day (based on a 2600 kcal diet). The trial found that the DASH diet lowered blood pressure substantially, and that low sodium consumption further lowered blood pressure (17). Ultimately the DASH diet redefined national dietary guidelines for the prevention of cardiovascular disease and has been adopted and nationally disseminated by NHLBI as the diet that should be implemented as the optimal non-pharmacologic approach to prevent and treat hypertension and lower cholesterol.

In this ancillary study of the DASH-sodium trial, we examine the effect of the DASH diet as well as varying sodium intake on SUA. We hypothesized that the DASH diet would lower uric acid levels as it contains many dietary components observed to be associated with lower uric acid levels, e.g. lower red meat (purine) consumption, greater low-fat dairy consumption, and higher intake of vitamin C-containing fruits and vegetables. We also hypothesized that reducing sodium intake would lower uric acid levels, given its association with high blood pressure.

MATERIALS and METHODS

DASH-Sodium was an investigator-initiated, multicenter, randomized trial sponsored by the National Heart, Lung, and Blood Institute between September 1997 through November 1999 (17). In brief, DASH-Sodium compared the effects of three levels of sodium intake on blood pressure in two distinct diets among adults with prehypertension or stage I hypertension (systolic blood pressure of 120–159 mm Hg or diastolic blood pressure of 80–95 mm Hg). The intervention diet was the DASH diet, emphasizing fruits, vegetables, and low-fat dairy foods and reduced consumption of saturated fat, total fat, and cholesterol; the control diet was typical of the average diet in the United States (18). The DASH diet also included whole grains, poultry, fish, and nuts and contained smaller amounts of red meat, sweets, and sugar-containing beverages than the typical diet in the United States. Participants were fed each of three sodium levels: low (a target of 60 mmol per day), medium (a target of 120 mmol per day), and high (a target of 180 mmol per day). The high sodium level (180 mmol/d) reflected typical sodium intake of a United States adult consuming 2600 kcal of food per day. The daily sodium intake was adjusted to reflect the total energy requirements of each participant, such that larger or more active participants received more food and sodium compared to smaller and less active participants. Detailed descriptions of the diets are in Table 1.

Participants

In the original study, adult men and women, aged 22 years and older, were recruited at four clinical centers. All participants had an average systolic blood pressure (based on three screening visits) of 120 to 159 mm Hg and an average diastolic blood pressure of 80 to 95 mm Hg. Persons with a prior diagnosis of heart disease, renal insufficiency, poorly controlled dyslipidemia, or diabetes mellitus were excluded (17). Persons using antihypertensive agents, insulin, or drinking more than 14 alcoholic drinks a week were also excluded.

This secondary analysis was limited to participants recruited at the Johns Hopkins University clinical center in Baltimore, Maryland, which analyzed serum specimens for uric acid collected as part of a comprehensive metabolic panel. The Institutional Review Board at Johns Hopkins University approved the original study protocol including subsequent analysis of stored specimens. Written, informed consent was provided by all participants.

Controlled feeding

Participants were provided all of their food, which included snacks and meals. Following a two-week run-in period during which participants ate the high sodium, control diet, they were randomized to either the DASH or control diet according to a parallel-arm design. These diets were consumed at each of the three sodium levels for 30 days in random order following a crossover design. Each sodium level was separated by a 5-day washout period. Participants resumed their home diets during the 5-day washout periods. Caloric intake was adjusted to maintain a constant weight throughout the trial. In the original study, over 98% of participants completed each of the intervention periods (17).

Serum uric acid measurement

At baseline and at the end of each sodium intake period, participants presented to the clinical center for phlebotomy (1997–1999). After fasting, Serum specimens were collected then centrifuged, aliquoted, and immediately delivered to Quest Diagnostics (Madison, New Jersey) for analysis without freezing or storage. Uric acid was measured via spectrophotometry.

Other covariate measurements and definitions

Additional covariates were ascertained via questionnaire, laboratory specimens, and physical examination. Blood pressure was the primary outcome of the original DASH-sodium trial. Using random-zero, mercury sphygmomanometers while participants were seated at three screening visits, twice during the run-in period, weekly during the first 3 weeks of each of the three 30-day intervention periods, and at five clinic visits during the last 9 days (at least two during the final 4 days) of each intervention period, blood pressure was recorded. A high blood pressure at baseline was defined by having a mean, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at baseline.

In addition to blood pressure, body mass index (BMI) was derived from standardized measurements of height and weight. Further, standard laboratory assays and techniques were used to measure serum creatinine, blood urea nitrogen, fasting glucose, and fasting

triglycerides. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation (19).

Statistical analysis

Study population characteristics were described using means (SD) and proportions. When evaluating the effect of the DASH diet on uric acid, the primary comparison was change in uric acid from baseline (i.e., end-of-period minus baseline measured at the end of the three sodium intake levels) between the DASH diet versus the control diet. When evaluating the impact of sodium intake on uric acid, the primary comparisons were within-person uric acid levels measured at the end of the high versus low sodium intake. Comparisons of high versus medium and medium versus low sodium were secondary. As there was no evidence of effect modification by diet on the relationship between sodium level and uric acid, we present the overall sodium effects (rather than stratified by diet). Carryover effects for the crossover design involving sodium levels were assessed with interaction terms involving visit and assignment order. These terms were not significant, suggesting that there were no order or carryover effects.

We also performed pre-specified subgroup analyses to assess for effect modification of baseline covariates known to influence uric acid concentrations, including sex (male, female), race (white, black), baseline SUA concentration (<4, 4 to <5, 5 to <6, 6 to <7, and ≥ 7 mg/dL), BMI category (<30 kg/m², ≥ 30 kg/m²), and baseline hypertension status. These comparisons were exploratory for the purpose of interpreting and elucidating the primary results.

All analyses were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA). Comparisons of SUA across diets at single sodium levels (i.e. baseline, low, medium, or high) were performed using t-tests following the trial's parallel design. All other SUA comparisons were performed using generalized estimating equation (GEE) regression models with a Huber and White robust variance estimator (20), which assumed an exchangeable working correlation matrix. Note that the robust variance estimator allows the model to produce valid standard errors even if the correlation structure is misspecified. In stratified analyses, *P*-values comparing strata were generated using interaction terms. The baseline uric acid interaction term was performed by replacing each category of uric acid (<4, 4 to <5, 5 to <6, 6 to <7, and ≥ 7 mg/dL) with the median baseline uric acid value for that category and treating it as a continuous variable. Statistical significance was defined as *P* ≤ 0.05.

Only 1 SUA value was missing from the control diet with medium sodium intake level, which was excluded from the analysis.

Results

Baseline characteristics

Baseline characteristics of the 103 study participants recruited by the Baltimore site are shown in Table 2. The mean age of participants was 51.5 ± 9.7 years, 55% were women, 75% were black, 42% were obese, and 34% had hypertension. The mean SUA level was 5.0

± 1.3 mg/dL. Eight participants (8%) had SUA ≥ 7 mg/dL at baseline. Alcohol consumption among study participants was low at 1.3 g/d.

Changes in uric acid from baseline are shown in Table 3. During the control diet, low sodium intake was associated with an increase in uric acid from baseline (0.4 mg/dL; $P < 0.001$). Meanwhile, during the DASH diet, high sodium was associated with a reduction in uric acid from baseline (-0.3 mg/dL; $P = 0.01$).

Effects of the DASH diet

The mean uric acid levels by diet, after consuming each sodium level, are shown in Figure 1. The DASH diet was associated with significantly lower SUA during both low (-0.53 mg/dL; $P = 0.03$) and medium (-0.56 mg/dL; $P = 0.03$) sodium intake, and a non-significant reduction in SUA levels during high sodium intake (-0.33 mg/dL; $P = 0.18$). There was no evidence of effect modification by diet on the relationship between sodium level and uric acid. Overall, the DASH diet reduced SUA by -0.35 mg/dL (95% CI: -0.65 , -0.05) compared with the control diet ($P = 0.02$).

Effects of sodium intake level

Regardless of diet, medium sodium intake significantly reduced SUA compared to low sodium intake (DASH: -0.35 mg/dL; $P = 0.04$; control: -0.33 mg/dL; $P < 0.001$). Similarly, compared to low sodium intake, high sodium intake significantly reduced SUA (DASH: -0.33 mg/dL; $P = 0.003$; control: -0.53 mg/dL; $P < 0.001$). Overall, when aggregated across both diets, compared to low sodium intake, medium sodium intake lowered SUA by -0.34 mg/dL ($P < 0.001$), while high sodium intake lowered SUA by -0.43 mg/dL ($P < 0.001$). There was no significant difference between high versus medium-sodium intake across both diets (-0.09 mg/dL; $P = 0.31$).

Effect modification

The effect of the DASH diet on SUA was nearly null when baseline SUA was either < 4 mg/dL or 4 to < 5 mg/dL. However, when baseline SUA was 5 to < 6 mg/dL, the DASH diet reduced SUA by -0.45 mg/dL. This effect was incrementally greater at -0.76 mg/dL in participants with a baseline SUA of 6 to < 7 mg/dL, and -1.29 mg/dL in participants with a baseline SUA ≥ 7 mg/dL (P -interaction=0.04) (Figure 2). The effect of the DASH diet on SUA appeared higher in men (-0.67 mg/dL) than women (-0.09 mg/dL); however, this difference was of borderline statistical significance ($P = 0.06$). Race, obesity, and high blood pressure did not modify the relationship between the DASH diet and SUA.

With regards to the effects of sodium intake levels on SUA, sex, race, baseline SUA level, and obesity did not modify the relationship between sodium intake and SUA (Figure 2). However, participants with high blood pressure at baseline demonstrated larger effects from the high versus low sodium intake (-0.66 mg/dL) than participants with low blood pressure at baseline (-0.31 mg/dL) (P -interaction=0.02).

Discussion

In this ancillary study of a single center of the DASH-sodium trial, we found that consuming the DASH diet, a widely recommended diet for the prevention and treatment of hypertension, significantly reduced SUA. Furthermore, in exploratory subgroup analyses, this reduction was larger among those with higher SUA at baseline with changes in SUA of -0.76 and -1.3 mg/dL among those with a baseline SUA level of 6 to <7 or ≥ 7 mg/dL, respectively. Notably, the latter effect size, approached that of pharmacologic urate-lowering therapy (7–9). We also found that increased levels of sodium intake reduced serum uric acid, and this effect was greater among participants with high blood pressure at baseline.

The DASH diet emphasizes whole grains, fruits, vegetables, and low-fat dairy products with a low intake of red meats, sweets, and saturated fats (18). Thus, the DASH diet encompasses many of the elements known to be inversely associated with hyperuricemia and gout, such as lower purine content (11–13), higher dairy content (13,16), and higher vitamin C (14,15,21) intake with fruits. Furthermore, recent evidence has shown that consuming a fruit and vegetable-based diet alkalizes urine, increasing uric acid excretion (22). In this study we further observed a trend of greater uric acid reduction in participants with higher uric acid levels at baseline. As participants consumed the same foods during the run-in period, differential effects according to baseline uric acid values may reflect underlying differences in the renal clearance of uric acid. Future study would be needed to clarify this speculation. Despite the large magnitude reduction observed in exploratory analyses of study participants with hyperuricemia (i.e. serum uric acid >7 mg/dL), additional research is needed to confirm these effects in a population with gout. As such, urate-lowering therapy should continue to be the cornerstone of gout treatment, whenever indicated (23).

The comorbidity benefit of any urate lowering approach is important, as hyperuricemia and gout are associated with cardiovascular-metabolic comorbidities (24,25) and sequelae (e.g., increased future risk of myocardial infarction and premature death) (25–27). However, the conventional low-purine, urate-lowering approach offers limited efficacy, palatability, and sustainability, and promotes increased consumption of refined carbohydrates and saturated fat that can worsen gout's cardiovascular-metabolic comorbidities by leading to insulin-resistance and increased levels of plasma glucose, triglycerides, and low density lipoprotein-cholesterol (28,29). In contrast, the DASH diet substantially reduces both systolic and diastolic blood pressure among hypertensive individuals (18). As a result, the American Heart Association guidelines for cardiovascular health and the dietary management of hypertension guidelines endorse dietary approaches that are similar to those included in the DASH diet (17,18,30). The DASH diet is also quite palatable. A post-hoc survey found that DASH-Sodium participants reported liking DASH more than control with a higher willingness to continue the DASH diet compared to control (31).

Our randomized trial analysis also found that high sodium intake lowers SUA. The relationship between sodium intake and uric acid is controversial, yet previous physiologic studies have suggested similar findings. For example, a study of 27 men showed that increasing sodium intake from 20 mmol/d to 200 mmol/d decreased uric acid levels by 1 mg/dL ($P < 0.001$) (32). In another crossover trial of 147 non-obese, normotensive adults, it

was found that 7 days of low versus high sodium intake (20 versus 300 mmol/d), significantly increased SUA approximately 1 mg/dL (33). We similarly show that higher sodium intake reduced SUA.

The mechanism by which increased sodium intake decreases uric acid is unclear. Prior studies have shown that both sodium and urate reabsorption often occur in response to similar physiologic stimuli (34–38). This would suggest that decreased sodium reabsorption in response to higher sodium intake would also decrease urate reabsorption. It is also possible that the inverse relationship between sodium intake and uric acid reflects action of the renin-angiotensin system, as uric acid is inversely related to renal blood flow (39) and vascular resistance (40). Similarly, angiotensin-II has been shown to decrease urate excretion after an acute infusion (41,42). Our study's findings are certainly consistent with the reported effects of thiazide diuretics on uric acid in both animals (43) and human studies (44,45). Thiazides act predominantly on the distal tubule to reduce sodium reabsorption, but are known to increase uric acid levels simultaneously (44). It should be noted that despite increasing uric acid, thiazides are associated with a lower risk of myocardial infarction and stroke (46).

In exploratory subgroup analyses, we observed that uric acid reduction from sodium intake was greatest in participants who had high blood pressure at baseline, similar to another study of patients with essential hypertension (47). This subgroup also represents a population that could likely benefit from a low sodium diet for blood pressure management. It should be noted that the higher sodium level in this trial (i.e. 180 mmol/d) is about equal to the average sodium consumed in a typical American diet, i.e. 1,659 mg per 1000 kcal per day or ~187 mmol/d at 2600 kcal/d (48). Interestingly, among participants consuming the DASH diet, increasing sodium intake from medium to high had practically no effect on uric acid. As a result, our findings do not support the idea that one should consume excessive or even the typical levels of sodium in the American diet to lower uric acid. Rather, just as with thiazide initiation, clinicians counselling their patients with gout on adopting a low sodium diet, should be wary of the potential for acute changes in uric acid, as uric acid fluctuations are known to precipitate gout flares (49).

This study has limitations. First, the study excluded persons with prior cardiovascular disease, advanced kidney disease, and medication-treated diabetes, which may limit its generalizability. Similarly, our study population differed from the usual gout population, having a low alcohol intake and being 55% women. Moreover, our study was conducted over 17 years ago. Further, the duration of interventions was relatively short, precluding conclusions related to the long-term effects of the DASH diet and sodium intake on SUA. Also, it is conceivable that the effects of the DASH diet and sodium intake might differ in a population of patients with gout, although the subgroup effects observed among hyperuricemic individuals are likely to be applicable to those with gout. Finally, our subgroup analyses are by nature exploratory. Differences between strata of baseline uric acid level (DASH vs. control, $P = 0.04$) or baseline high blood pressure (high vs. low sodium intake, $P = 0.02$) are at best marginal and warrant confirmation in a dedicated trial.

Notwithstanding these limitations, the present study possesses a number of important strengths. We employed a randomized, clinical trial to examine the impact of a dietary intervention on serum levels of uric acid. Further, the trial protocol maintained constant weight, minimizing effects from weight change (50). Moreover, the study population was diverse, diets were highly regulated, and participants were very compliant with the study diets throughout the trial period. Finally, the crossover design increased our power to observe the effects of diet and sodium levels on uric acid within study participants despite a modest sample size.

In conclusion, the DASH diet lowered SUA, and this effect was substantial among participants with hyperuricemia. Moreover, low sodium intake increased SUA, which enhances our knowledge of urate pathophysiology and hyperuricemic risk factors.

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Abbreviations used

BMI	body mass index
DASH	Dietary Approaches to Stop Hypertension
GEE	generalized estimating equation
CI	confidence interval

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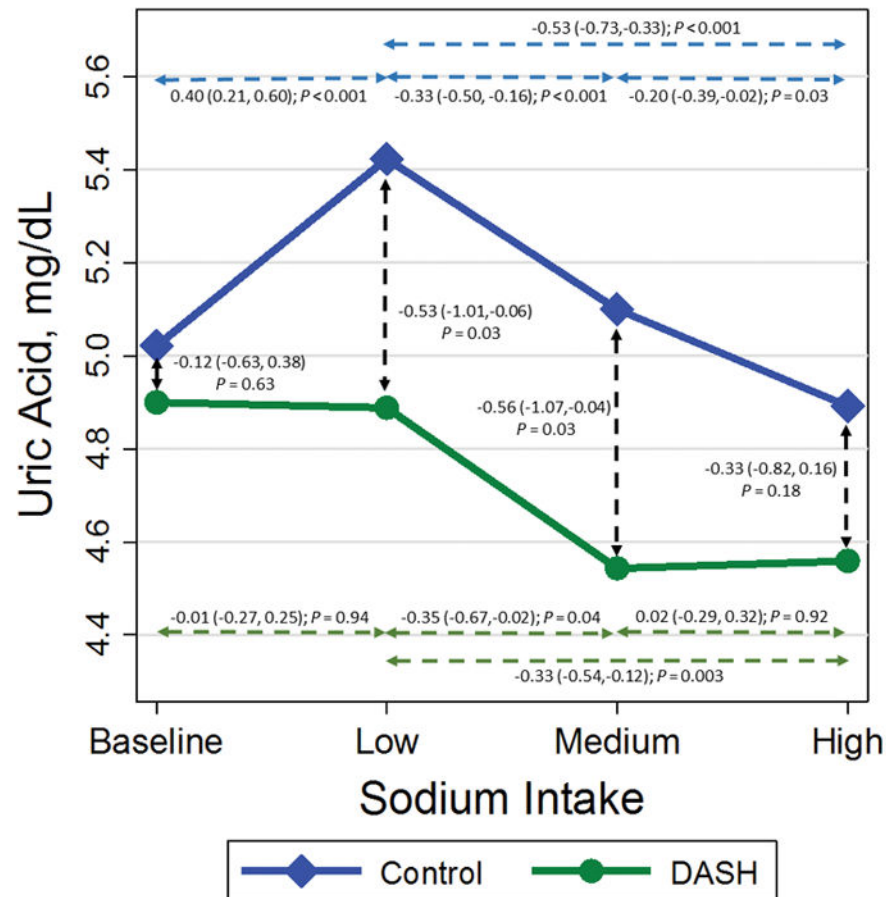
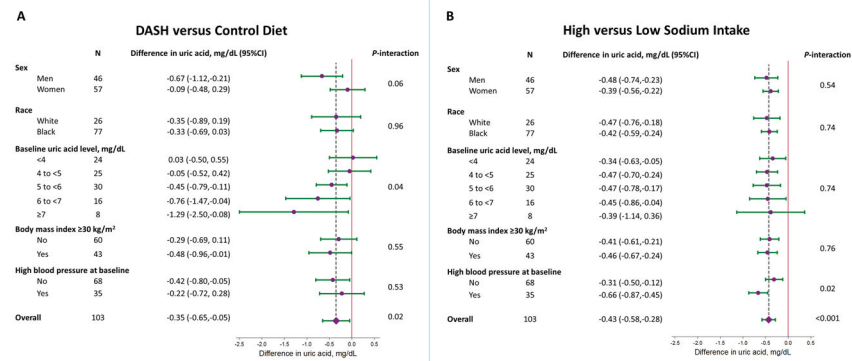


Figure 1.

Comparison of uric acid levels at baseline, the end of the low sodium feeding period, the end of the medium sodium feeding period, and the end of the high sodium feeding period for either the control (diamonds, blue) versus DASH (circles, green) diets. Vertical dashed lines represent differences at each of the sodium intake levels with P -values determined via t -tests). Horizontal lines represent differences between sodium intake levels (low versus baseline, medium versus low, high versus medium, and high versus low) determined using generalized estimating equations.

**Figure 2.**

Forest plots of the effects of **(A)** DASH versus Control diets and **(B)** high (180 mmol/d) versus low (60 mmol/d) sodium intake on uric acid (mg/dL, 95% CI) in subgroups of sex, race, baseline uric acid, baseline body mass index, and baseline high blood pressure (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg). Given that there was no salt-diet interaction, the comparison of DASH versus control diets utilized all three serum uric acid measures determined after each of the sodium feeding periods. Meanwhile the high versus low sodium comparison is presented in participants consuming either the control or DASH diet.

Table 1

Nutrient composition of the two diets used in DASH-Sodium

	DASH	Control
Energy, MJ	10.8 (2.1)	10.8 (2.1)
Energy, kcal	2576 (511)	2576 (493)
Total fat, % of energy	27.4 (0.2)	38.6 (4.2)
Saturated fat, % of energy	6.2 (0.1)	15.0 (0.2)
Polyunsaturated fat, % of energy	8.0 (0.2)	7.4 (0.3)
Monounsaturated fat, % of energy	11.2 (0.1)	12.5 (0.3)
Cholesterol, mg/d	194 (48)	324 (62.7)
Carbohydrate, % of energy	58.5 (0.3)	49.2 (0.3)
Fiber, g/d	35.0 (6.1)	17.3 (18.0)
Potassium, mg/d	5170 (685)	2029 (301)
Calcium, mg/d	1454 (224)	529 (72.9)
Magnesium, mg/d	558 (86)	212 (48.2)
Sodium, mg/d (higher sodium)	4486 (831)	4442 (850)
Sodium, mg/d (intermediate sodium)	3037 (570)	3048 (528)
Sodium, mg/d (lower sodium)	1480 (270)	1386 (234)

Mean (SD). Values calculated using Moore's Extended Nutrition (MENu) database (version 3.1, 1997; Pennington Biomedical Research Foundation, Baton Rouge, La) (51). These energy and nutrient values were based on an energy target of level of 2600 kcal (52).

Table 2

Baseline characteristics overall and according to diet

	Overall (N = 103)	Control Diet (N = 52)	DASH Diet (N = 51)
Age, years	51.5 (9.7)	53.0 (9.7)	49.9 (9.7)
Women, %	55.3	48.1	62.7
Black, %	74.8	69.2	80.4
High Blood Pressure [*] , %	34.0	38.5	29.4
Blood pressure, mm Hg			
Systolic	135.6 (8.7)	136.6 (8.8)	134.6 (8.7)
Diastolic	85.6 (3.8)	85.6 (3.7)	85.6 (4.0)
Body mass index, kg/m ²	29.5 (4.4)	30.0 (4.8)	29.1 (3.9)
Body mass index ≥30, %	41.7	46.2	37.3
eGFR, mL/min/1.73 m ²	93.7 (21.0)	93.9 (19.2)	93.4 (22.8)
Blood urea nitrogen, mg/dL	13.4 (3.1)	13.3 (3.0)	13.4 (3.2)
Fasting glucose, mg/dL	99.8 (18.5)	99.1 (20.3)	100.6 (16.6)
Fasting triglycerides, mg/dL	122.1 (151.7)	116.5 (65.4)	127.8 (206.2)
Uric acid, mg/dL	5.0 (1.3)	5.0 (1.3)	4.9 (1.3)
Alcohol intake, g/d	1.3 (2.5)	1.5 (2.6)	1.2 (2.3)

^{*} Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

Table 3

Within person change from baseline in uric acid (mg/dL) by diet and overall according to sodium intake

	Baseline Mean (SD) or Difference (95% CI)	Low Sodium		Medium Sodium		High Sodium		Average Difference from Baseline	
		Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Overall *	5.0 (1.3)	0.2 (0.0, 0.4)	0.02	-0.1 (-0.3, 0.1)	0.17	-0.2 (-0.4, -0.1)	0.01	-0.1 (-0.2, 0.1)	0.45
Control diet *	5.0 (1.3)	0.4 (0.2, 0.6)	<0.001	0.1 (-0.1, 0.3)	0.46	-0.1 (-0.4, 0.1)	0.29	0.1 (-0.1, 0.3)	0.22
DASH diet *	4.9 (1.3)	0.0 (-0.3, 0.2)	0.94	-0.4 (-0.7, 0.0)	0.04	-0.3 (-0.6, -0.1)	0.01	-0.2 (-0.5, 0.0)	0.06
Difference **	-0.1 (-0.6, 0.4)	-0.4 (-0.7, -0.1)	0.01	-0.4 (-0.8, 0.0)	0.04	-0.2 (-0.6, 0.2)	0.25	-0.4 (-0.7, -0.1) ***	0.02 ***

* Within-person comparisons of change from baseline performed using generalized estimating equations.

** Between diet comparisons performed using t-tests.

*** Based on change from baseline at the end of each salt diet. Performed using generalized estimating equations to account for within-person correlation of repeat measurements.