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ORIGINAL RESEARCH

Effects of the Dietary Approaches to Stop Hypertension Diet on Change in Cardiac Biomarkers Over Time: Results From the DASH-Sodium Trial

Matthew J. Belanger, MD; Lara C. Kovell, MD; Ruth-Alma Turkson-Ocran, PhD; Kenneth J. Mukamal, MD, MPH; Xiaoran Liu, PhD; Lawrence J. Appel, MD, MPH; Edgar R. Miller III, MD, PhD; Frank M. Sacks, MD; Robert H. Christenson, PhD; Heather Rebuck, MS; Alex R. Chang, MD, MHS; Stephen P. Juraschek, MD, PhD

BACKGROUND: The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to reduce biomarkers of cardiovascular disease. We aimed to characterize the time course of change in biomarkers of cardiac injury (high-sensitivity cardiac troponin I), cardiac strain (NT-proBNP [N-terminal pro-B-type natriuretic peptide]), and inflammation (hs-CRP [high-sensitivity C-reactive protein]) while consuming the DASH diet.

METHODS AND RESULTS: The DASH-Sodium trial was a randomized controlled trial of 412 adults with elevated blood pressure or hypertension. Participants were randomly assigned to 12 weeks of the DASH diet or a typical American diet. Energy intake was adjusted to maintain body weight. Measurements of high-sensitivity cardiac troponin I, NT-proBNP, and hs-CRP were performed in stored serum specimens, collected at baseline and ≈4, 8, and 12 weeks after randomization. In both the control diet and DASH diet, levels of NT-proBNP decreased; however, there was no difference between diets (*P*-trend compared with control=0.22). On the DASH diet versus control, levels of high-sensitivity cardiac troponin I decreased progressively during follow-up (*P*-trend compared with control=0.025), but a statistically significant between-diet difference in change from baseline levels was not observed until week 12 (% difference, 17.78% [95% CI, −29.51% to −4.09%]). A similar pattern was evident for hs-CRP (*P*-trend compared with control=0.01; % difference at week 12, 19.97% [95% CI, −31.94% to −5.89%]).

CONCLUSIONS: In comparison with a typical American diet, the DASH diet reduced high-sensitivity cardiac troponin I and hs-CRP progressively over 12 weeks. These results suggest that the DASH diet has cumulative benefits over time on biomarkers of subclinical cardiac injury and inflammation.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00000608.

Key Words: biomarkers ■ Dietary Approaches to Stop Hypertension diet ■ hs-CRP (high-sensitivity C-reactive protein) ■ high-sensitivity troponin ■ NT-proBNP (N-terminal pro-B-type natriuretic peptide)

Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] Most deaths from CVD can be attributed to specific modifiable risk factors,[2] with suboptimal diet being a leading risk factor for disability and death in the United States.[3] The Dietary Approaches to Stop Hypertension (DASH) diet, rich in

Correspondence to: Stephen P. Juraschek, MD, PhD, Section for Research, Division of General Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Ave, CO-1309, room 216, Boston, MA 02215. Email: sjurasch@bidmc.harvard.edu

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CLINICAL PERSPECTIVE

What Is New?

- In this secondary analysis of the DASH (Dietary Approaches to Stop Hypertension)–Sodium trial, the magnitude of the DASH diet's effects on high-sensitivity cardiac troponin I and hs-CRP (high-sensitivity C-reactive protein) increased over time.

What Are the Clinical Implications?

- The DASH diet has cumulative benefits over time on biomarkers of subclinical cardiac injury and systemic inflammation.
- Knowledge of the time course of change in biomarkers of cardiovascular disease is informative when counseling patients on the expected benefits of the DASH diet.
- Innovative strategies that support sustained adherence to the DASH diet are needed to improve population cardiovascular health.

Nonstandard Abbreviations and Acronyms

DASH	Dietary Approaches to Stop Hypertension
hs-cTnI	high-sensitivity cardiac troponin I

fruits, vegetables, and low-fat dairy and reduced in saturated fat and cholesterol,[4] is associated with a lower risk of CVD events over time[5–7] and has been promoted by the American Heart Association to improve population cardiovascular health.[8]

Although the beneficial effects of the DASH diet on traditional cardiovascular risk factors (ie, blood pressure and lipids) have been established,[4,9] we recently demonstrated that the DASH diet improves biomarkers of subclinical cardiac injury (high-sensitivity cardiac troponin I [hs-cTnI]) and inflammation (hs-CRP [high-sensitivity C-reactive protein]) but not a biomarker of cardiac strain (NT-proBNP [N-terminal pro-B-type natriuretic peptide]) during a 12-week feeding period.[10] However, our prior work did not address how soon these changes might be observed after the adoption of the DASH diet or whether they are sustained over time. Understanding the pattern of change is important as the duration of lifestyle change needed to see an effect is not known, and some have questioned whether the impact of diet on subclinical injury is temporary.

In this secondary analysis of the DASH-Sodium trial, we examined the time course of change in biomarkers of cardiac injury, strain, and inflammation (hs-cTnI, NT-proBNP, and hs-CRP) from consuming the DASH diet in comparison with a typical American diet using measurements obtained at baseline and at approximately weeks 4, 8, and 12 after randomization. We hypothesized the following: (1) changes in hs-cTnI and hs-CRP from the DASH diet would be observed as early as 4 weeks and sustained over the 12-week study period; and (2) there would be no difference in changes in NT-proBNP between diets at any of the measured time points.

METHODS

Deidentified data from the DASH-Sodium trial are available through the National Heart, Lung, and Blood Institute Biological Specimen and Data Repository Information Coordinating Center.

The DASH-Sodium trial was an investigator-initiated trial funded by the National Heart, Lung, and Blood Institute, conducted at 4 clinical centers (Baltimore, MD; Boston, MA; Durham, NC; and Baton Rouge, LA) from September 1997 through November 1999.[9] Details of the study rationale, design, and protocol have been reported previously.[9,11] In brief, the DASH-Sodium trial examined 2 dietary strategies to lower blood pressure: the DASH diet and a control diet typical of nutrient intakes in the United States. These diets were tested at 3 different levels of sodium consumption. The study protocol was approved by the institutional review boards at each respective study center. Participants provided written, informed consent for participation in the trial and the use of their stored biospecimens in subsequent analyses. The measurement of biomarkers in stored specimens curated by the Biological Specimen and Data Repository Information Coordinating Center in the present study was supported by the National Heart, Lung, and Blood Institute and was determined to be exempt research by the Beth Israel Deaconess Medical Center Institutional Review Board. The DASH-Sodium trial is registered at ClinicalTrials.gov, identifier: NCT00000608.

Participants

The DASH-Sodium trial recruited adult men and women, aged ≥22 years, with a mean systolic blood pressure of 120 to 159 mm Hg and a mean diastolic blood pressure of 80 to 95 mm Hg. Adults with a history of heart disease, including symptomatic ischemic heart disease, myocardial infarction, coronary artery bypass grafting, angioplasty, congestive heart failure, or stroke, were excluded.[9] Other criteria for exclusion were renal insufficiency, poorly controlled hyperlipidemia, diabetes, the use of antihypertensive medications or insulin, or intake of >14 alcoholic drinks per week. See Figure S1 for additional details of the trial's eligibility criteria.

Dietary Interventions

Participants in the DASH-Sodium trial were randomly assigned in a parallel-arm design to the DASH diet or a typical American diet (control) in a 1:1 ratio; hence, for each individual, there are measurements on the same diet over 12 weeks. On their assigned diet, there were 3 periods, each lasting 4 weeks, in which participants ate 3 levels of sodium intake in random order using a crossover design. The 3 sodium levels were characterized as high (1.6 mg/kcal), intermediate (1.1 mg/kcal), and low (0.5 mg/kcal). At the end of each period, ≈4, 8, and 12 weeks after randomization, fasting blood specimens. Given the random order of sodium assignments, about a third of the participants were consuming each of the 3 sodium levels during each period (Table S1). This article focuses on trends in cardiac biomarkers by dietary pattern given that there were 3 points over the 12 weeks. Because the laboratory specimens were only collected at the end of each 4-week sodium intake period, we could not assess trends in the biomarkers related to the different sodium levels.

The DASH dietary pattern emphasizes potassium-rich fruits and vegetables and low-fat dairy products; it includes whole grains, poultry, fish, and nuts; and it is reduced in red meat, sweets, and sugar-containing beverages. Accordingly, it was rich in potassium, magnesium, calcium, and fiber, and reduced in total fat, saturated fat, and cholesterol; it was also slightly increased in protein.[4] The control diet was designed to reflect a dietary pattern and nutrient composition that is typical of what many people eat in the United States (Table S2).

During a 2-week run-in and the 3 feeding periods, participants were provided with all meals (including cooked food and snacks) and were weighed daily to adjust energy intake as needed to maintain body weight throughout the study. All participants ate the high-sodium control diet during the 2-week run-in period before randomization. Feeding periods were separated by an average 5-day break, during which they ate their usual diets. Over 98% of participants completed each of the intervention periods.[9]

Outcomes of Interest

The primary outcomes of interest were hs-cTnI, NT-proBNP, and hs-CRP. Baseline serum specimens were collected during the trial after a 12-hour fast before feeding (while participants ate their usual diets) and at the end of each feeding period (ie, approximately weeks 4, 8, and 12 of the assigned dietary pattern). These outcomes were a specific aim of a National Institutes of Health R21 grant (R21HL144876) with an intent to publish made before examination of the data. Biospecimens were stored at −70 °C and underwent at least 1 freeze-thaw cycle before the present measurements. Laboratory equipment for the biomarker assays was donated by Siemens Healthineers (Malvern, PA). The biomarker measurement was completed in 2019 using the following: (1) ADVIA Centaur High-Sensitivity Troponin I (reported within-run coefficient of variation of 4.8% for a mean of 13.11 ng/L [or pg/mL]); (2) Dimension Vista N-Terminal Pro-Brain Natriuretic Peptide (reported within-run coefficient of variation of 1.4% for a mean 120 pg/mL); and (3) Dimension Vista High Sensitivity C-Reactive Protein (reported within-run coefficient of variation of 5.2% for a mean 2.39 mg/L). The manufacturer estimates of assay accuracy and precision performance have been previously reported.[12] The limits of detection, as specified in the manufacturer laboratory insert, were as follows: <1.60 ng/L (hs-cTnI), <5 pg/mL (NT-proBNP), and <0.160 mg/L (hs-CRP). A large number of hs-cTnI values were below the limit of detection of the ADVIA assay. We accounted for this by examining an alternate measurement cut point based on the assay's limit of blank (<0.5 ng/L) rather than the limit of detection (<1.60 ng/L), the rationale and details of which have been previously described.[10]

A total of 1547 specimens were available for our study, which comprises 93.9% of the 1648 specimens available for collection (412 participants with 4 visits). Of the available specimens, 1543 yielded results for all 3 biomarkers (93.6%). Missing data were evenly distributed across dietary assignments and time points (Figure 1).

Covariates

Blood pressure was measured using random-zero sphygmomanometers while participants were seated. Baseline blood pressure was defined as the average of 5 pairs of measurements obtained across 3 visits in the screening phase and 2 visits in the 2-week run-in period. Hypertension was defined in this trial as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Enzymatic calorimetry was used to measure high-density lipoprotein cholesterol, triglycerides, and total cholesterol, whereas low-density lipoprotein was estimated by the Friedewald equation.[13] Body mass index was calculated from measured height and weight. Obesity was defined as a body mass index ≥30 kg/m^2.

Statistical Analysis

Baseline population characteristics were described according to diet assignment using means (SDs) and proportions. Given data skew, the serum biomarkers were log transformed. Exponentiating the mean of a log-transformed variable yields the geometric mean.

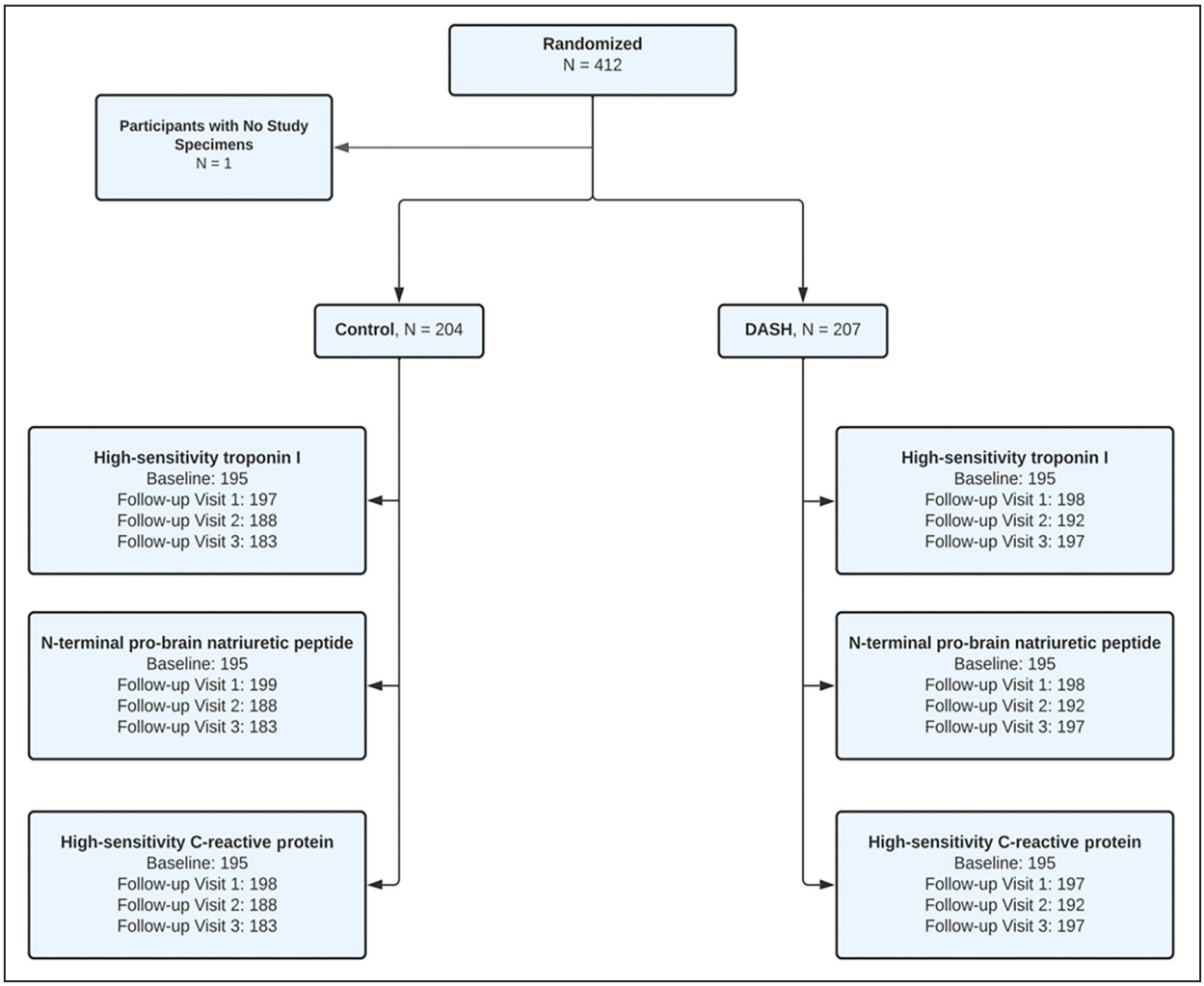

Figure 1. Specimen availability at baseline and according to follow-up visits in the DASH–Sodium trial.
DASH indicates Dietary Approaches to Stop Hypertension.

We used mixed effects tobit models (metobit command) to determine the geometric mean of serum concentrations (SD) of the log-transformed biomarkers. A tobit model was used to address informative left censoring that occurs below the limit of detection (or blank) for each assay, which allowed us to fit a linear regression model in the detectable range while designating undetectable biomarkers as below the detectable range.[14] All models were left truncated for the limits of detection or blank (hs-cTnI). The fixed portion of the tobit model included diet assignment (with value 0 for control or 1 for DASH), a visit variable (with values 0, 1, 2, and 3, corresponding to baseline and the end of the 3 feeding periods, spaced ≈4, 8, and 12 weeks after randomization), and the interaction of these terms. The random-effects portion of the tobit model included participant identifier (introducing a random intercept).

Trend analyses were performed using similar models by treating the visit variable as a continuous variable (versus a categorical variable for each visit). We further assessed for potential nonlinearity over time at the first visit, by using a linear spline with a single knot specified at 4 weeks to distinguish immediate changes from baseline from changes between 4 and 12 weeks. We compared coefficients of diet-by-time segment interactions (via the test command) to determine whether diet modified changes in biomarkers during the first 4 weeks differently from the latter 8 weeks.

All analyses were conducted using Stata version 15.1 (Stata Corporation, College Station, TX).

RESULTS

Baseline Characteristics

Baseline characteristics of the DASH-Sodium trial participants by dietary assignment are shown in Table 1. There were minimal differences by randomized

Table 1. Baseline Characteristics, According to Diet Assignment

Characteristic	Control diet (N=204)	DASH diet (N=208)
Age, y	49.1 (10.4)	47.4 (9.6)
Women, %	54.4	59.1
Black race, %	56.4	57.2
Blood pressure, mm Hg		
Systolic	135.4 (9.4)	134.2 (9.6)
Diastolic	85.8 (4.1)	85.6 (4.8)
Baseline SBP ≥140 mm Hg or DBP ≥90 mm Hg, %	40.7	40.9
High-density lipoprotein cholesterol, mg/dL	48.1 (13.1)	48.5 (12.5)
Low-density lipoprotein cholesterol, mg/dL*	131.8 (31.6)	130.7 (29.8)
Triglycerides, mg/dL	94.0 (67.0–140.5)	92.0 (67.0–130.5)
Total cholesterol, mg/dL	202.7 (36.0)	202.0 (36.4)
Body mass index, kg/m^2	29.5 (5.0)	28.8 (4.7)
Body mass index ≥30 kg/m^2, %	40.2	37.5

Values are mean (SD), percentage, or median (25th–75th percentile). DASH indicates Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*N=202 for the control diet and 204 for the DASH diet.

dietary assignment. One of the original participants was excluded because of lack of stored specimens (Figure 1).

Effects of the DASH Diet on Change in hs-cTnI

The mean baseline concentrations of hs-cTnI, NT-proBNP, and hs-CRP were similar between those assigned to control and those assigned to DASH (Table 2). The control diet had no effect on hs-cTnI at any of the measured time points. Among participants assigned the DASH diet, hs-cTnI was reduced from baseline by 0.18 ng/L (95% CI, −0.32 to −0.04 ng/L) at 4 weeks, 0.14 ng/L (95% CI, −0.29 to 0.00 ng/L) at 8 weeks, and 0.33 ng/L (95% CI, −0.48 to −0.18 ng/L) at 12 weeks (Table 2). This pattern of change over time differed significantly from the control group

Table 2. Absolute Change From Baseline in Concentration of Cardiac Biomarkers by Visit, According to Diet Assignment (N=411 Unique Individuals)

Variable	Control diet*	DASH diet*	Absolute difference†
High-sensitivity cardiac troponin I, ng/L			
Baseline‡	1.68 (0.19)	1.36 (0.15)	−0.32 (−0.73 to 0.09)
Change at 4 wk	−0.00 (−0.18 to 0.17)	−0.18 (−0.32 to −0.04)	−0.18 (−0.38 to 0.02)
Change at 8 wk	0.00 (−0.18 to 0.18)	−0.14 (−0.29 to 0.00)	−0.14 (−0.34 to 0.06)
Change at 12 wk	−0.13 (−0.30 to 0.04)	−0.33 (−0.48 to −0.18)	−0.22 (−0.41 to −0.03)
NT-proBNP, pg/mL			
Baseline‡	28.65 (1.89)	28.95 (1.90)	0.30 (−4.95 to 5.54)
Change at 4 wk	−6.01 (−8.50 to −3.53)	−6.46 (−8.97 to −3.95)	−0.38 (−3.37 to 2.60)
Change at 8 wk	−4.21 (−6.76 to −1.67)	−5.55 (−8.09 to −3.01)	−1.29 (−4.53 to 1.95)
Change at 12 wk	−4.88 (−7.43 to −2.33)	−6.76 (−9.27 to −4.24)	−1.83 (−4.98 to 1.32)
hs-CRP, mg/L			
Baseline‡	2.06 (0.18)	1.94 (0.17)	−0.13 (−0.61 to 0.35)
Change at 4 wk	−0.10 (−0.33 to 0.13)	−0.27 (−0.48 to −0.06)	−0.18 (−0.47 to 0.11)
Change at 8 wk	0.01 (−0.23 to 0.25)	−0.18 (−0.39 to 0.03)	−0.19 (−0.50 to 0.12)
Change at 12 wk	0.02 (−0.22 to 0.26)	−0.37 (−0.58 to −0.16)	−0.39 (−0.70 to −0.08)

Values are number (95% CI), unless otherwise indicated. There were 1545 high-sensitivity troponin I and hs-CRP measurements and 1547 NT-proBNP measurements. DASH indicates Dietary Approaches to Stop Hypertension; hs-CRP, high-sensitivity C-reactive protein; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Difference in exponentiated log-transformed markers (ie, difference in geometric means).

†The absolute difference may not directly compute from values listed in the table because of transformation and rounding of exponentiated log-transformed markers.

‡Baseline cardiac biomarkers presented as geometric mean (SE).

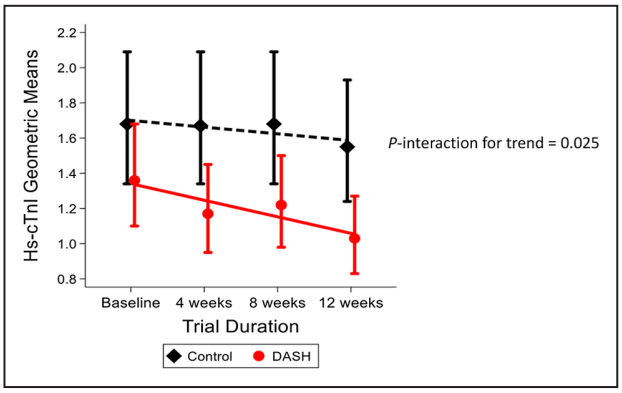

Figure 2. Effects of the DASH diet on hs-cTnI over time.
Geometric means (95% CIs) of hs-cTnI (ng/L), a marker of cardiac injury, according to diet assignment at baseline and the end of 3 feeding periods, ≈4, 8, and 12 weeks after randomization. Means are estimated using mixed-effect tobit models. The *P* interaction for trend is derived from an interaction term in the model between diet and visit. The dashed (control) and solid (DASH) lines represent a linear fit of the geometric means. DASH indicates Dietary Approaches to Stop Hypertension; and hs-cTnI, high-sensitivity cardiac troponin I.

(*P*-interaction for DASH versus control trends=0.025) (Figure 2). There was no evidence that early trial effects (baseline to 4 weeks) differed by diet from later trial effects (4 to 12 weeks) (*P* trend for nonlinear effects=0.32). Percentage changes over time had a similar pattern (Table 3). Similar findings were observed in sensitivity analyses using the limit of blank rather than the limit of detection and after adjusting for sodium assignment (Tables S3 through S5). When comparing the DASH diet versus control, a statistically significant between-diet difference in change from baseline levels of hs-cTnI was not observed until week 12 (% difference, 17.78% [95% CI, −29.51% to −4.09%]) (Table 3).

Effects of the DASH Diet on Change in NT-proBNP

In both the control and DASH diets, levels of NT-proBNP were reduced at weeks 4, 8, and 12 in comparison to baseline values; however, there were no significant differences between diets (*P*-interaction for trend=0.22) or evidence that dietary effects differed the first 4 weeks from the latter 8 weeks (*P* trend for nonlinear effects=0.87) (Figure 3 and Tables 2 and 3). Findings were similar in a sensitivity analysis adjusting for sodium assignment (Tables S4 and S5).

Effects of the DASH Diet on Change in hs-CRP

Among those assigned the control diet, levels of hs-CRP during follow-up did not differ from baseline levels (Table 2). In contrast, among those assigned the DASH diet, reduction in hs-CRP occurred by week

Table 3. Geometric Means, Percentage Change From Baseline, and Percentage Difference in Cardiac Biomarkers by Visit, Comparing the DASH Diet With the Control Diet (N=411 Unique Individuals)

Variable	Geometric mean (SE)*		% Change from baseline (95% CI)†		Between-diet comparison, % difference (95% CI)‡
	Control diet	DASH diet	Control diet	DASH diet	
High-sensitivity cardiac troponin I, ng/L					
Baseline	1.68 (0.19)	1.36 (0.15)	Reference	Reference	Reference
Change at 4 wk	1.67 (0.19)	1.17 (0.13)	−0.16 (−9.94 to 10.68)	−13.44 (−22.33 to −3.53)	−13.30 (−25.34 to 0.69)
Change at 8 wk	1.68 (0.19)	1.22 (0.13)	0.05 (−9.93 to 11.13)	−10.42 (−19.73 to −0.04)	−10.47 (−23.08 to 4.21)
Change at 12 wk	1.55 (0.18)	1.03 (0.11)	−7.74 (−17.09 to 2.66)	−24.14 (−32.11 to −15.24)	−17.78 (−29.51 to −4.09)
NT-proBNP, pg/mL					
Baseline	28.65 (1.89)	28.95 (1.90)	Reference	Reference	Reference
Change at 4 wk	22.64 (1.49)	22.49 (1.48)	−20.99 (−27.97 to −13.33)	−22.31 (−29.20 to −14.75)	−1.67 (−13.75 to 12.10)
Change at 8 wk	24.44 (1.62)	23.41 (1.54)	−14.70 (−22.37 to −6.28)	−19.16 (−26.39 to −11.21)	−5.22 (−17.01 to 8.25)
Change at 12 wk	23.78 (1.59)	22.19 (1.46)	−17.02 (−24.56 to −8.74)	−23.34 (−30.16 to −15.85)	−7.61 (−19.14 to 5.55)
hs-CRP, mg/L					
Baseline	2.06 (0.18)	1.94 (0.17)	Reference	Reference	Reference
Change at 4 wk	1.97 (0.17)	1.67 (0.14)	−4.72 (−14.89 to 6.66)	−13.87 (−23.07 to −3.57)	−9.60 (−22.94 to 6.05)
Change at 8 wk	2.07 (0.18)	1.75 (0.15)	0.53 (−10.37 to 12.76)	−9.41 (−19.18 to 1.54)	−9.89 (−23.35 to 5.94)
Change at 12 wk	2.09 (0.18)	1.57 (0.13)	1.06 (−10.01 to 13.48)	−19.12 (−27.77 to −9.43)	−19.97 (−31.94 to −5.89)

There were 1545 high-sensitivity troponin I and hs-CRP measurements and 1547 NT-proBNP measurements. DASH indicates Dietary Approaches to Stop Hypertension; hs-CRP, high-sensitivity C-reactive protein; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Exponentiated log-transformed markers or the geometric mean.

†Exponentiated differences of the change on the log scale.

‡The percentage difference may not directly compute from those listed in the table because of transformation and rounding of exponentiated log-transformed markers.

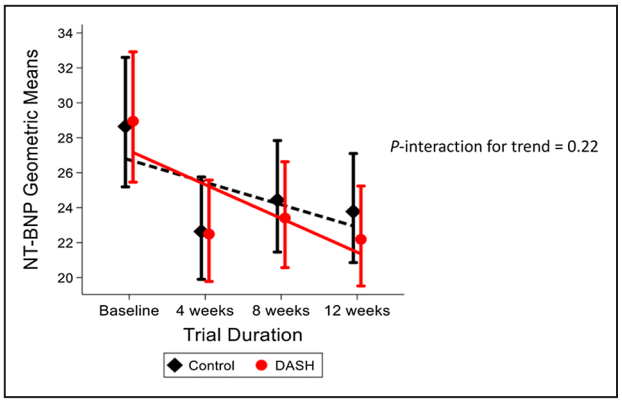

Figure 3. Effects of the DASH diet on NT-proBNP over time. Geometric means (95% CIs) of NT-proBNP (pg/mL), a marker of cardiac strain, according to diet assignment at baseline and the end of 3 feeding periods, spaced ≈4, 8, and 12 weeks after randomization. Means are estimated using mixed-effect tobit models. The *P* interaction for trend is derived from an interaction term in the model between diet and visit. The dashed (control) and solid (DASH) lines represent a linear fit of the geometric means. DASH indicates Dietary Approaches to Stop Hypertension; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

4 (–0.27 mg/L [95% CI, –0.48 to –0.06 mg/L]) and was further reduced at week 12 (–0.37 mg/L [95% CI, –0.58 to –0.16 mg/L]) (Table 2). This pattern of change differed significantly from the control group (*P*-interaction for trend=0.01), with no evidence that dietary effects differed the first 4 weeks from the latter 8 weeks (*P* trend for nonlinear effects=0.85) (Figure 4). A similar pattern was evident when the analyses were conducted on a relative scale (Table 3). Findings were also similar in a sensitivity analysis adjusting for sodium

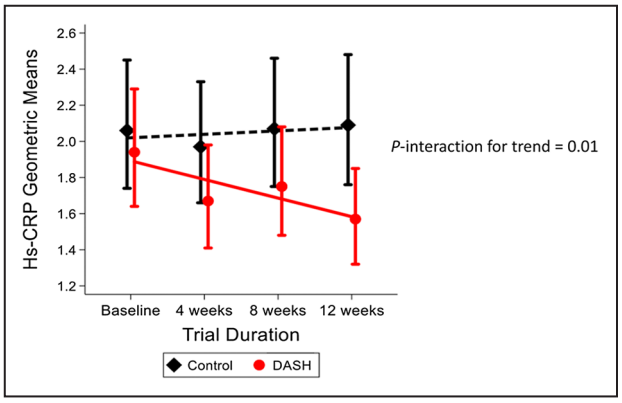

Figure 4. Effects of the DASH diet on hs-CRP over time. Geometric means (95% CIs) of hs-CRP (mg/L), a marker of inflammation, according to diet assignment at baseline and the end of 3 feeding periods, spaced ≈4, 8, and 12 weeks after randomization. Means are estimated using mixed-effect tobit models. The *P* interaction for trend is derived from an interaction term in the model between diet and visit. The dashed (control) and solid (DASH) lines represent a linear fit of the geometric means. DASH indicates Dietary Approaches to Stop Hypertension; and hs-CRP, high-sensitivity C-reactive protein.

assignment (Tables S4 and S5). When comparing the DASH diet with control diet, a statistically significant between-diet difference in change from baseline levels of hs-CRP was not observed until week 12 (% difference, –19.97% [95% CI, –31.94% to –5.89%]) (Table 3).

DISCUSSION

In this randomized trial of adults with elevated blood pressure or hypertension, in comparison with a typical American diet, the DASH diet reduced hs-cTnI and hs-CRP progressively over a 12-week period. These observations suggest that the benefits of the DASH diet are not only maintained over time but potentially underestimated by short-term feeding studies. Although longer-term evidence is needed, these findings offer a compelling rationale for sustained adherence to the DASH diet to promote cardiovascular health.

Several recent analyses of controlled feeding studies have demonstrated that DASH-pattern diets reduce biomarkers of subclinical cardiac injury[10,12,15] and inflammation.[10,15] The OmniHeart trial showed that 3 DASH-pattern diets emphasizing different macronutrient proportions reduced hs-cTnI and hs-CRP after 6 weeks of feeding.[15,16] In the DASH trial, the DASH diet was found to reduce hs-cTnI after 8 weeks of feeding, but there were no effects on hs-CRP.[12] Most recently, in the DASH-Sodium trial, which examined DASH dietary effects independent of sodium, the DASH diet lowered hs-cTnI and hs-CRP over 12 weeks of feeding.[10] However, these prior studies did not address how soon effects on hs-cTnI and hs-CRP might be realized by adopting the DASH diet or whether they were sustained over time, 2 of the main focuses of the present analysis.

Several population-based studies have shown that adherence to the DASH diet is associated with a lower risk of CVD events,[5–7] which is likely mediated in large part by the effects of the DASH diet on blood pressure and cholesterol.[4] However, our recent work suggests that the DASH diet may directly reduce subclinical cardiac damage.[10,12,15] Notably, biomarkers of subclinical myocardial damage, including hs-cTnI, may provide prognostic information on long-term CVD risk, independent of traditional risk factors.[17–19] We found that the DASH diet reduced hs-cTnI gradually over time in a trend that differed significantly from the control group. In the between-diet comparison, the DASH diet significantly reduced hs-cTnI from baseline at 12 weeks, whereas the changes at weeks 4 and 8 were modest and nonsignificant. Taken together, our findings suggest that benefits occur quickly and increase progressively over time. Although the time course of change in traditional risk factors (ie, blood pressure) from healthy

dietary interventions has been evaluated,[20] to our knowledge, there have been no studies on the time course of change in hs-cTnI from a healthy dietary pattern before the present analysis.

Inflammation is an established risk factor in the pathogenesis of atherosclerotic CVD, and several large observational studies have demonstrated the ability of hs-CRP to predict CVD events independently of conventional risk factors.[21] Moreover, greater cumulative exposure to elevated hs-CRP levels is associated with a higher risk of CVD events.[22] Similar to hs-cTnI, we observed a modest, nonsignificant reduction in hs-CRP at weeks 4 and 8 and a significant reduction at week 12 in participants assigned to the DASH diet. Although prior analyses of DASH feeding interventions found greater reductions in biomarkers of systemic inflammation in trials ≥8 weeks,[23,24] our study suggests that at least 12 weeks may be necessary to achieve the full effects of the DASH diet on hs-CRP.

In our prior analysis of DASH-Sodium trial, sodium reduction alone reduced NT-proBNP, whereas the DASH diet did not have a significant effect on NT-proBNP compared with the control diet.[10] We found that NT-proBNP was reduced at all time points for both the DASH and control diets. This likely reflects the fact that two-thirds of participants were on lower than typical sodium intakes at all times in the trial and is consistent with our previous findings that DASH did not lower NT-proBNP.[10] Notably, the time course of change in NT-proBNP appeared to differ from the trends in hs-cTnI and hs-CRP from the DASH diet; the maximal effect on NT-proBNP was observed quickly, whereas the effects of the DASH diet on hs-cTnI and hs-CRP appeared to increase progressively.

Our study has limitations. First, the duration of the DASH-Sodium trial was relatively short, which limited our ability to determine whether the effects of the DASH diet on hs-cTnI and hs-CRP would continue to grow beyond 12 weeks. Second, because the duration of each level of sodium consumption was only 4 weeks, we were unable to evaluate the effects of sodium reduction on the time course of change in these biomarkers, which is particularly relevant for NT-proBNP. Third, measurements of biomarkers were performed using stored serum samples from the DASH-Sodium trial; however, studies suggest stability of these biomarkers in the setting of long-term storage and freeze-thaw cycles.[25–27] Moreover, any drift would more likely bias our findings toward the null. Fourth, because NT-proBNP is a biologically inactive cleavage counterpart of the active peptide B-type natriuretic peptide, it is possible that B-type natriuretic peptide may be a more relevant biomarker of cardiac pathophysiological features than NT-proBNP. However, levels of NT-proBNP and B-type natriuretic peptide correlate sufficiently, and either may be used clinically for the diagnosis, risk stratification, and prognosis of heart failure.[28] Moreover, the measurement of B-type natriuretic peptide is limited by its relative instability in vivo and in vitro as well as by interference of inactive forms of the peptide in commercial immunoassays.[29] Fifth, there is analytical variability among commercially available hs-cTnI assays, particularly in the range of biomarker values below the 99th percentile value.[30,31] Although we were unable to perform head-to-head comparisons of the ADVIA Centaur assay with other hs-cTnI assays, we accounted for potential intra-assay precision variability at lower mean values of hs-cTnI by performing a sensitivity analysis using the less precise limit of blank, which yielded similar results to our analysis using the limit of detection. Nevertheless, future studies evaluating the effects of the DASH diet on hs-cTnI would benefit from confirmation using other hs-cTnI methods. Sixth, in this secondary analysis of the main trial data, we did not adjust for multiplicity of comparisons, and our findings may be subject to type I error. Finally, individuals with established CVD were excluded from the trial, thus limiting the generalizability of our findings.

Strengths of our study include the DASH-Sodium trial's rigorous design, with tightly controlled dietary interventions, high rates of follow-up, and data completeness. Second, energy intake was adjusted during the trial to maintain body weight, thus allowing us to evaluate the effects of the DASH diet on CVD biomarkers independent of weight loss. Third, serum specimens were collected at the end of each 4-week sodium sequence in the context of the assigned dietary intervention, which allowed us to evaluate the time course of change in biomarkers from the DASH diet at 3 points over a 12-week period.

This study has clinical implications. First, patients often inquire about the time frame of expected benefits after beginning the DASH diet. Our study provides information on the time course of the DASH diet's effects on subclinical myocardial injury and systemic inflammation, which may enhance the ability of clinicians to effectively communicate the cardiovascular health benefits of the DASH diet. Second, the progressive benefits on hs-cTnI and hs-CRP observed in our study highlight the importance of sustained adherence to the DASH diet and the need for innovative strategies and system-wide policies to support its adoption. Finally, our study may inform the design of future longitudinal studies evaluating the long-term effects of the DASH diet on cardiac biomarkers.

In conclusion, in comparison with a typical American diet, the DASH diet reduced hs-cTnI and hs-CRP progressively over a 12-week period, suggesting that the DASH diet has cumulative benefits over time on biomarkers of subclinical cardiac injury and inflammation. These findings provide further insight into the positive effects of the DASH diet on subclinical cardiac

injury and inflammation and highlight the need for public health policies and interventions that support sustained adherence to a healthy eating pattern for cardiovascular health.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD (M.J.B.); Division of Cardiology, University of Massachusetts Chan Medical School, Worcester, MA (L.C.K.); Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (R.-A.T., K.J.M., S.P.J.); Harvard T.H. Chan School of Public Health, Harvard Medical School, Brigham and Women's Hospital, Boston, MA (X.L., F.M.S.); The Johns Hopkins University School of Medicine, The Johns Hopkins Bloomberg School of Public Health, and The Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD (L.J.A., E.R.M.); Department of Pathology, University of Maryland School of Medicine, Baltimore, MD (R.H.C., H.R.); and Geisinger Health, Danville, PAGeisinger Health, Danville, PA (A.R.C.).

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Randomization of Participants According to Dietary Assignment and Sodium Sequence

Sodium Sequence*	Control	DASH
Low, Medium, High	35	36
Low, High, Medium	35	36
Medium, Low, High	36	35
Medium, High, Low	33	35
High, Low, Medium	33	34
High, Medium, Low	32	32
Total	**204**	**208**

*The 3 sodium levels were classified as high (1.6 mg/kcal), medium (1.1 mg/kcal), and low (0.5 mg/kcal).
Abbreviations: DASH, Dietary Approaches to Stop Hypertension.

Table S2. Nutrient Composition of the Two Diets 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 from nutrient database.
Abbreviations: DASH, Dietary Approaches to Stop Hypertension; SD, standard deviation.

Reproduced from the original publication: Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. N Engl J Med. 2001 Jan;344(1):3-10.

Table S3. Geometric Means and Percent Change from Baseline in High-sensitivity Cardiac Troponin I (ng/l) by Visit According to Diet Assignment Using the Limit of Blank (Sensitivity), N = 411 Unique Persons

	Geometric Means (SE)*		Percent Change from Baseline (95% CI)†		
	Control	DASH	Control	DASH	%-Difference‡
Baseline	1.95 (0.19)	1.78 (0.17)	*ref*	*ref*	*ref*
Change at 4 weeks	2.00 (0.20)	1.50 (0.15)	2.66 (-7.33, 13.72)	-15.91 (-24.17, -6.75)	-18.08 (-29.18, -5.26)
Change at 8 weeks	1.92 (0.19)	1.49 (0.15)	-1.41 (-11.20, 9.46)	-16.19 (-24.55, -6.89)	-14.99 (-26.70, -1.40)
Change at 12 weeks	1.76 (0.18)	1.30 (0.13)	-9.46 (-18.57, 0.66)	-27.02 (-34.29, -18.95)	-19.40 (-30.57, -6.43)

There were 1,545 high-sensitivity troponin I measurements. The limit of blank for the assay was defined as < 0.5 ng/l.

*Exponentiated log-transformed markers or the geometric mean.

†Exponentiated differences of the change on the log-scale.

‡The %-difference may not directly compute from those listed in the table due to transformation and rounding of exponentiated log-transformed markers.

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; N, number; Ref, reference; SE, standard error.

Table S4. Absolute Change from Baseline in Concentration of Cardiac Biomarkers by Visit According to Diet with Adjustment for Sodium Assignment (N = 411 Unique Persons)

	Control*	DASH*	Absolute Difference†
High-sensitivity cardiac troponin I, ng/l			
Baseline‡	1.67 (0.19)	1.36 (0.15)	-0.32 (-0.73, 0.09)
Change at 4 weeks	-0.05 (-0.24, 0.13)	-0.22 (-0.37, -0.07)	-0.18 (-0.37, 0.02)
Change at 8 weeks	-0.05 (-0.24, 0.14)	-0.18 (-0.33, -0.02)	-0.14 (-0.33, 0.06)
Change at 12 weeks	-0.18 (-0.36, 0.01)	-0.35 (-0.51, -0.20)	-0.21 (-0.40, -0.03)
N-terminal pro-brain natriuretic peptide, pg/mL			
Baseline‡	28.64 (1.88)	28.97 (1.89)	0.33 (-4.90, 5.55)
Change at 4 weeks	-8.17 (-10.72, -5.61)	-8.58 (-11.16, -5.99)	-0.32 (-2.97, 2.34)
Change at 8 weeks	-6.64 (-9.25, -4.04)	-7.82 (-10.43, -5.22)	-1.10 (-3.97, 1.77)
Change at 12 weeks	-7.31 (-9.92, -4.69)	-8.99 (-11.59, -6.40)	-1.60 (-4.38, 1.18)
High-sensitivity C-reactive protein, mg/l			
Baseline‡	2.06 (0.18)	1.94 (0.17)	-0.13 (-0.61, 0.35)
Change at 4 weeks	-0.05 (-0.30, 0.19)	-0.23 (-0.46, -0.01)	-0.18 (-0.48, 0.11)
Change at 8 weeks	0.06 (-0.20, 0.32)	-0.14 (-0.37, 0.09)	-0.20 (-0.51, 0.12)
Change at 12 weeks	0.08 (-0.19, 0.34)	-0.33 (-0.55, -0.11)	-0.40 (-0.72, -0.09)

Values are n (95% CI) unless otherwise indicated. There were 1,545 high sensitivity troponin I and C-reactive protein measurements and 1,547 N-terminal pro-brain natriuretic peptide measurements.

*Difference in exponentiated log-transformed markers (i.e., difference in geometric means).

†The absolute difference may not directly compute from values listed in the table due to transformation and rounding of exponentiated log-transformed markers.

‡Baseline cardiac biomarkers presented as geometric mean (SE).

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; N, number.

Table S5. Geometric Means and Percent Change from Baseline in Cardiac Biomarkers by Visit According to Diet with Adjustment for Sodium Assignment (N = 411 Unique Persons)

	Geometric means (SE)*		Percent Change from Baseline (95% CI)†		
	Control	DASH	Control	DASH	%-Difference‡
High-sensitivity cardiac troponin I, ng/l					
Baseline	1.67 (0.19)	1.36 (0.15)	*Ref*	*Ref*	*Ref*
Change at 4 weeks	1.62 (0.19)	1.14 (0.13)	-3.12 (-13.39, 8.37)	-16.10 (-25.42, -5.62)	-13.40 (-25.42, 0.55)
Change at 8 weeks	1.62 (0.19)	1.18 (0.13)	-2.95 (-13.42, 8.78)	-13.10 (-22.80, -2.18)	-10.46 (-23.06, 4.20)
Change at 12 weeks	1.50 (0.17)	1.00 (0.11)	-10.48 (-20.25, 0.48)	-26.17 (-34.37, -16.94)	-17.52 (-29.28, -3.81)
N-terminal pro-brain natriuretic peptide, pg/mL					
Baseline	28.64 (1.88)	28.97 (1.89)	*Ref*	*Ref*	*Ref*
Change at 4 weeks	20.48 (1.40)	20.39 (1.39)	-28.51 (-35.18, -21.14)	-29.60 (-36.20, -22.32)	-1.54 (-13.43, 11.98)
Change at 8 weeks	22.00 (1.52)	21.15 (1.44)	-23.19 (-30.51, -15.11)	-27.01 (-33.90, -19.39)	-4.96 (-16.59, 8.28)
Change at 12 weeks	21.34 (1.48)	19.98 (1.36)	-25.51 (-32.68, -17.58)	-31.04 (-37.54, -23.86)	-7.42 (-18.77, 5.52)
High-sensitivity C-reactive protein, mg/l					
Baseline	2.06 (0.18)	1.94 (0.17)	*Ref*	*Ref*	*Ref*
Change at 4 weeks	2.01 (0.18)	1.70 (0.15)	-2.55 (-13.70, 10.05)	-12.07 (-22.13, -0.71)	-9.77 (-23.05, 5.80)
Change at 8 weeks	2.12 (0.19)	1.80 (0.16)	2.93 (-9.06, 16.51)	-7.20 (-17.91, 4.91)	-9.84 (-23.28, 5.94)
Change at 12 weeks	2.14 (0.19)	1.61 (0.14)	3.76 (-8.45, 17.59)	-17.04 (-26.57, -6.27)	-20.04 (-31.97, -6.03)

There were 1,545 high sensitivity troponin I and C-reactive protein measurements and 1,547 N-terminal pro-brain natriuretic peptide measurements.

*Exponentiated log-transformed markers or the geometric mean.

†Exponentiated differences of the change on the log-scale.

‡The %-difference may not directly compute from values listed in the table due to transformation and rounding of exponentiated log-transformed markers.

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; N, number; Ref, reference; SE, standard error.

Figure S1. DASH-Sodium Study Eligibility Criteria

Inclusion criteria

- Blood pressure 120 to 159 mm Hg systolic and 80 to 95 mm Hg diastolic based on mean values over 3 screening visits
- Age ≥22 years
- Willing to eat at least 1 on-site meal per day, 5 days per week, and willing to eat study diets and nothing else for the 15 weeks of controlled feeding
- Willing and able to provide informed consent

Exclusion criteria

- Taking blood pressure medications
- Taking nutritional supplements and unwilling to discontinue
- History of cardiovascular disease
- Renal disease (urine dipstick protein level ≥2+; or serum creatinine level >1.2 mg/dL for women or >1.5 mg/dL for men, unless Cockgroft-Gault estimate of glomerular filtration rate ≥60 mL/min)
- Type 1 or poorly controlled diabetes mellitus (defined as taking insulin regularly; or randomly checked glucose value ≥180 mg/dL or urine dipstick result positive for glucose, unless fasting glucose <140 mg/dL, or HbA1c < 8.0)
- Poorly controlled hyperlipidemia (defined as total cholesterol >260 mg/dL, unless fasting low-density lipoprotein cholesterol below National Cholesterol Education Program sex-specific and risk factor-specific guidelines for initiating pharmacotherapy)
- Body mass index >40 kg/m^2
- Consumption of >14 alcoholic beverages per week
- Pregnant or breast-feeding
- Other conditions, special dietary requirements, or medications that would affect blood pressure or nutrient metabolism

Reproduced from the original publication: Svetkey LP, Sacks FM, Obarzanek E, et al. The DASH Diet, Sodium Intake and Blood Pressure Trial (DASH-sodium): rationale and design. DASH-Sodium Collaborative Research Group. J Am Diet Assoc. 1999 Aug;99(8 Suppl):S96-104.