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Feasibility and Efficacy of Sodium Reduction in the Trials of Hypertension Prevention, Phase I

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Phase I of the Trials of Hypertension Prevention was a multicenter, randomized trial of the feasibility and efficacy of seven nonpharmacologic interventions, including sodium reduction, in lowering blood pressure in 30- to 54-year-old individuals with a diastolic blood pressure of 80 to 89 mm Hg. Six centers tested an intervention designed to reduce dietary sodium to 80 mmol (1800 mg)/24 h with a total of 327 active intervention and 417 control subjects. The intervention consisted of eight group and two one-to-one meetings during the first 3 months, followed by less-intensive counseling and support for the duration of the study. The mean net decrease in sodium excretion was 43.9 mmol/24 h at 18 months. Women had lower sodium intake at baseline and were therefore more likely to decrease to less than 80 mmol/24 h. Black subjects were less likely to decrease to less than 80 mmol/d, independent of sex or baseline sodium excretion. The mean (95% confidence interval) net decrease associated with treatment was −2.1 (−3.3, −0.8) mm Hg for systolic blood pressure and −1.2 (−2.0, −0.3) mm Hg for diastolic blood pressure at 18 months (both $P<.01$). Multivariate analyses indicated a larger systolic blood pressure effect in women (−4.44 versus −1.23 mm Hg in men), adjusted for age, race, baseline blood pressure, and baseline 24-hour urinary sodium excretion ($P=.02$). Dose-response analyses indicated an adjusted decrease of −1.4 mm Hg for systolic blood pressure and −0.9 mm Hg for diastolic blood pressure for a decrease of 100 mmol/24 h in 18-month sodium excretion. These results support the utility of sodium reduction as a population strategy for hypertension prevention and raise questions about possible differences in dose response associated with gender and initial level of sodium intake. (*Hypertension*. 1993;22:502-512.)

KEY WORDS • **hypertension, sodium-dependent • blood pressure • sodium, dietary • primary prevention • blacks • women**

Primary prevention of hypertension, ie, preventing people at risk of hypertension from developing it, could potentially lower death rates from cardiovascular disease, reduce the need for antihypertensive medications, and reduce hypertension-related medical costs and job absenteeism.[1-4] However, the feasibility and efficacy of sodium reduction in lowering blood pressure among people with normal blood pressure in the general population have not been clearly established. Several lines of evidence suggest that sodium reduction is a logical candidate for incorporation into a primary prevention strategy. The well-established blood pressure–lowering effect of sodium reduction as a component of hypertension treatment is not confined to blood pressures above the physiologically arbitrary cutoffs used to define high blood pressure. Small, controlled trials have demonstrated the efficacy of moderate sodium reduction in reducing blood pressure in normotensive and hypertensive people.[5,6] In addition, data from the INTERSALT study have confirmed that, over a wide range of sodium intake, populations with low sodium consumption have lower blood pressures than those with high sodium consumption.[7,8]

Phase I of the Trials of Hypertension Prevention (TOHP-I) was a multicenter, randomized trial designed to test the short-term efficacy and safety of several nonpharmacologic interventions, including sodium reduction, in reducing blood pressure in a large cohort of men and women without hypertension in the context of their usual patterns of living.[9] TOHP-I attempted to provide an unambiguous answer regarding the potential for lowering the average blood pressure levels in the

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normotensive population-at-large by reducing only dietary sodium. At the time TOHP-I was initiated, other randomized intervention trials addressing primary prevention of hypertension either had not established the feasibility of sodium reduction[10] or had studied sodium reduction as part of a program that combined several lifestyle changes.[11]

The overall TOHP-I results have been published.[12] This article provides an in-depth presentation of the sodium intervention and results, including (1) assessment of the magnitude of the reduction in sodium intake achieved in the context of this intervention program, (2) examination of the relation between both the size of the reduction in sodium intake and its absolute level with change in blood pressure, and (3) exploration of treatment effects within race and sex subgroups.

Methods

Design

The design and participant recruitment for TOHP-I have been described elsewhere.[9,13] Briefly, healthy 30- to 54-year-old men and women were eligible for TOHP-I if their diastolic blood pressure (DBP) was between 80 and 89 mm Hg averaged over three screening visits with three measurements per visit and if they did not fit certain medical history, potential adherence, or weight exclusions.

The sodium intervention was tested at six of the 10 TOHP-I clinical centers: The University of California, Davis; Johns Hopkins University, Baltimore; University of Mississippi, Jackson; St Louis University, St Louis; New Jersey Medical School, Newark; and the University of Tennessee, Memphis. Participants were randomly allocated to either active (n=327) or control (n=417) treatment arms. Control subjects received no intervention program but had baseline and follow-up measurements on the same schedule and under the same conditions as the active intervention participants. Enrollment began in September 1987, and data collection ended in January 1990. The follow-up period for the lifestyle interventions was approximately 18 months from the time of randomization, which provided a reasonable test of maintenance of behavioral changes.

Data Collection

Blood pressure screening was completed over a series of three clinic visits, 7 to 30 days apart. Blood pressure assessments were made by trained, certified observers who were blinded to participants' treatment assignments during follow-up. Measurements were made with a random-zero sphygmomanometer after the participant sat for 5 minutes at rest. Three readings were recorded at each visit and averaged. Subjects were eligible if the mean of all nine DBP readings was in the range of 80 to 89 mm Hg. Follow-up blood pressure measurements were obtained at 6, 12, and 18 months. At 12 and 18 months these measurements were taken over a series of three clinic visits. Thus, as for the baseline values, blood pressure at these major follow-up visits was based on an average of nine readings.

Sodium intake at baseline was assessed from the sodium content in two 24-hour urine specimens and from the sodium content in one 24-hour urine sample at 6, 12, and 18 months of follow-up. Weight was measured at baseline and at each follow-up visit. Dietary intake of sodium and other nutrients was assessed by 24-hour diet recalls and food frequency questionnaires at baseline and selected follow-up visits. The 24-hour diet recall data were collected by TOHP staff trained and certified by registered dietitians at the TOHP Nutrient Data Center (Tufts University), where recalls also were coded and analyzed for nutrient content. The food frequency questionnaire was a self-administered version of the National Cancer Institute Health Habits and History Questionnaire.[14] A psychological General Well-Being Index[15] was used to measure overall quality of life. This index is a 22-item instrument that measures subjective well-being by assessing an individual's level of anxiety, depression, positive well-being, self-control, general health, and vitality.

Intervention Program

Features of the approach to sodium reduction in TOHP-I are listed in Table 1. The objective was to reduce urinary sodium excretion in the active treatment group to an average of 80 mmol (1800 mg)/24 h. In the context of an expectation of less-than-full compliance and the tendency of food diaries to overestimate adherence to low-sodium diets, the individual counseling goal was 60 mmol/d (1400 mg).

The core intervention program was a nutrition and behavior change counseling program incorporating and adapting elements used in other multicenter hypertension or cardiovascular risk reduction trials.[10,11,16-18] Factors that may render long-term sodium reduction even more difficult than other aspects of dietary behavior change[19] were identified and taken into account in the intervention design. For example, with the expectation that participants would view changing to a lower sodium diet as medicinal, requiring resignation to eating tasteless foods, the name "Sodium Light Lifestyle" was used to give a confident, positive tone to the program. To further counteract the view of lower sodium diets as bland, liberal use of strong alternative flavors such as curries or herbs to offset removal of salty or sodium-enhanced flavors was emphasized. To provide persuasive sensory experiences, carefully selected commercial or home-prepared reduced-sodium foods were routinely available for taste testing at group meetings, with take-home samples for continued use or for family members to try.

Overnight (8-hour) urine samples (less burdensome to collect than 24-hour urine samples) were used to approximate the level of sodium reduction achieved (ie, change from baseline, with the overnight component of the baseline urine samples as the reference point). Overnight samples were collected midway during and directly after the intensive intervention and at approximately quarterly intervals during the extended intervention. The Data Coordinating Center provided guidelines for estimating adherence to the counseling goal of 60 mmol (1400 mg) sodium/24 h from the average sodium excretion in two 8-hour urine samples collected at least 2 days apart.

The intervention was delivered initially in a series of eight group and two individual counseling sessions over a 3-month period (see Table 1). After the intensive intervention, follow-up was implemented to provide

TABLE 1. Sodium Light Lifestyle Intervention Approach in Phase I of the Trials of Hypertension Prevention

Intervention objectives
To reduce the group average 24-hour urinary sodium excretion to a mean of 80 mmol (1800 mg)
Nutrition counseling objective
To reduce the individual's 24-hour sodium intake to 60 mmol (1400 mg) without changing other nutrient intakes
Contact pattern
Eight group and two individual counseling sessions over a 3-month period
Periodic group meetings and individual telephone or in-person contacts throughout follow-up
Program content
Sodium content of foods
Food shopping, label reading, recipe modification, restaurant selections
Sodium-specific dietary behavior problem solving
Food tasting
Take-home packages of low-sodium foods and product samples
Local shopping guide for sodium-reduced products
Peer support and family involvement
Field trips (eg, to restaurants, supermarkets)
Motivational activities
Adherence monitoring/enhancement
Food diaries
Attendance
Overnight (8-hour) urinary sodium excretion

continued information, support, and counseling through telephone mail, and, at minimum, bimonthly in-person group or individual meetings. Participants were guided through a behavioral change process that focused on action goals and implementation steps specific to social, emotional, or practical problems encountered in sodium reduction. Food diaries, from which participants calculated their own sodium intake, were used to facilitate self-monitoring of sodium intake and learning of the sodium content of foods. Intervention staff reviewed and provided written comments on participants' food records. Group meetings included discussions to generate peer support and share effective strategies for achieving sodium-related behavior changes. Special invitations were sent to encourage participation of spouses or significant others in certain group meetings. The format and content of meetings were designed to motivate attendance, and the importance of attendance was stressed. Some of the low-sodium products that were distributed periodically were donated by local or national food companies.

Although the sodium reduction objective in this study was not as extreme as in some programs, it was recognized that, with the present level of sodium in prepared foods and the high percentage of meals eaten away from home, participants could meet the study goals only by adopting special food-preparation and food-selection practices. Because these participants did not currently have hypertension and therefore did not face the alternative of having to take medication, special efforts were made to identify and support relevant motivations for adherence. In addition to the ongoing supportive contacts by the intervention staff, motivational strategies included special presentations about the importance of and rationale for the study and incentives in the form of useful food products and cooking aids. Some TOHP centers also offered special cooking demonstrations, contests (eg, low-sodium "cookoffs"), or door prizes at group meetings.

Statistical Analysis

Baseline characteristics in the intervention and control groups, overall and by race-sex subgroups, were first examined to assess the similarity of the active intervention and control groups (treatment groups). Statistical procedures included Student's two-sample t tests (means) and χ^2 tests of association (proportions).

The two formal adherence measures were attendance and change in 24-hour urinary sodium excretion. Neither the food records nor overnight urine samples that were used as counseling tools were used for study-wide data analyses. These measures were not intended to be systematic measures of adherence and were not standardized across centers. Dietary data were used primarily to monitor changes in nutrients not targeted in the intervention and to permit analyses of food pattern changes. Mean treatment group differences in 24-hour urinary sodium excretion and net change from baseline at each follow-up visit were calculated and tested for statistical significance (Student's t tests), overall and within race-sex subgroups. The effect of missing urinary sodium excretion data at follow-up on estimates of the absolute change from baseline was assessed by assuming no change (the baseline sodium excretion value was

imputed). To reduce the likelihood that estimates of treatment group differences were influenced by the inclusion of incomplete samples, mean differences in urinary sodium excretion at 6, 12, and 18 months were recalculated excluding urine values associated with a volume less than 500 g or, in separate analyses, associated with creatinine or creatinine per kilogram of body weight less than 85% of the within-person average. Mean treatment group differences with these exclusions were very similar to each other and to those calculated when all samples were included.

An analysis of variance approach was used to assess the representativeness of a single 24-hour urinary sodium excretion value at 18 months in estimating overall adherence of an individual during follow-up. Although there was a strong component of within-person variability, the means also changed over time, among control subjects in particular. This suggests that the 18-month sodium excretion value was more appropriate than an average of the 6-, 12-, and 18-month measurements for analyses on 18-month blood pressure, because the effect of sodium on blood pressure is expected to be relatively short-term. However, individual adherence in the active intervention group was also examined as an average of the sodium content in at least two 24-hour urine specimens collected at 6, 12, and 18 months. Logistic regression analyses were used to analyze the association of goal attainment (defined as urinary sodium excretion less than versus greater than or equal to 80 mmol/24 h) with age, race, sex, and the number of intervention contacts completed.

Mean differences in systolic blood pressure (SBP) and DBP between active intervention and control subjects were used to evaluate efficacy (treatment effect). For those participants placed on antihypertensive medications during follow-up, attempts were made to obtain termination blood pressures over three visits before medication was started. For each follow-up visit, the most recent blood pressure before the start of medications was used. If a participant missed a 6-, 12-, or 18-month visit for reasons unrelated to blood pressure, he or she was excluded from that analysis. However, for the final termination blood pressure comparison, the last valid blood pressure obtained was used when subjects missed the visit for reasons unrelated to blood pressure. Participants with no follow-up visits (n=13; seven active and six control) were assigned a zero value for blood pressure change ("intention-to-treat" analysis). Linear regression analyses were used to adjust treatment effects for age, race, sex (where appropriate), baseline blood pressure, baseline sodium excretion, and, in some models, sodium excretion at 18 months. Differences in the treatment effects by sex and race were tested in regression models with respective sex-by-treatment and race-by-treatment interaction terms. Mean treatment group differences in variables potentially related to the treatment effect (eg, weight, other dietary variables, psychological well-being) were also assessed at each follow-up visit.

To assess dose response, blood pressure at 18 months was examined in relation to categories of urinary sodium excretion at 18 months or of change in sodium excretion. The categories for change corresponded to quartiles or quintiles within the active intervention group. Absolute sodium excretion levels were also used because analyses based on change or percent change in sodium excretion at 18 months might obscure possible differences in dose response at low versus high levels of intake. Categories were again defined using quartiles or quintiles of the distribution of urinary sodium excretion at 18 months in the active intervention group.

Results

Participant Characteristics

Table 2 shows selected initial demographic, medical history, and behavioral characteristics of TOHP-I participants who were randomized to the active sodium intervention or to the lifestyle control group, for all participants and separately for black and white men and women. Most participants were white, male, college educated, employed full-time, and married. The age range of participants was restricted to 30 to 54 years by design. Those randomized to sodium reduction or lifestyle control were approximately 43 years old. Fewer than half had ever smoked cigarettes and only about 10% were current smokers. Less than 10% of participants reported that one of their parents had died of cardiovascular disease before the age of 60 (not shown).[12]

Mean SBP and DBP were 125 and 84 mm Hg, respectively, in the active treatment and control groups. Mean body mass index was 27 kg/m^2. Macronutrient composition of the diet was approximately 36% kilocalories from fat, 16% from protein, 46% from carbohydrate, and 2% from alcohol. Estimates of sodium and potassium intake from 24-hour recall data and urinary sodium excretion were similar, somewhat lower in the urine data in both cases. The urine data showed that these participants excreted approximately 156 mmol (3600 mg) sodium and 62 mmol (2400 mg) potassium/24 h at baseline.

DBP, for which the range was controlled by design, was similar across race-sex groups, but several other baseline characteristics varied by race or sex (Table 2). For example, the percentage of college graduates was higher in white men than in white women or blacks. A lower percentage of white women were employed full-time compared with the other three race-sex groups. White men were most likely and black women least likely to be married. Sodium and potassium excretions were lower in women than men. Within sex, potassium intake and excretion and calcium intake were lower in blacks than in whites.

Although randomization was effective, in that treatment groups were similar overall, participants were not randomized within race-sex groups, and some differences between active and control subjects within race-sex groups can be noted. Among white women there were significant differences in the percent married (control subjects less likely to be married) and heart rate (control subjects higher). Among black women psychological well-being scores were significantly higher in control subjects. The data in Table 2 for black men also suggest treatment group differences in percent college graduates; percent married; weight; percent current smokers; percent of kilocalories from alcohol; reported intake of sodium, potassium, and calcium; and urinary excretion of sodium and potassium. The difference in weight was statistically significant.

TABLE 2. Baseline Characteristics of Sodium Light Lifestyle and Control Participants in Phase I of the Trials of Hypertension Prevention

	All Participants		White Men		Black Men	
Variable	**Active (n=327)**	**Control (n=417)**	**Active (n=199)**	**Control (n=246)**	**Active (n=26)**	**Control (n=45)**
Male, %	70.9	71.7				
Age, y	43.4±6.6	42.6±6.5	43.7±6.8	42.4±6.7*	42.0±7.0	42.5±7.0
College graduate, %	54.1	56.3	65.3	65.3	34.6	53.3
Employed full time, %	92.0	91.6	96.5	97.1	92.3	97.8
Married, %	77.7	76.2	84.9	84.9	57.7	80.0
Systolic BP, mm Hg	124.8±8.5	125.1±8.1	124.5±8.0	125.6±7.6	124.8±8.9	124.2±6.5
Diastolic BP, mm Hg	83.7±2.7	83.9±2.8	83.8±2.6	83.8±2.8	83.8±3.0	83.5±2.8
Heart rate, bpm	73.2±9.0	73.8±9.5	73.0±9.0	72.2±8.9	71.0±7.3	73.4±9.4
Weight, kg	82.7±14.3	82.8±14.0	87.9±12.8	86.6±12.1	81.5±14.4	89.0±14.3*
Body mass index, kg/m²	27.1±3.8	27.1±3.6	27.4±3.6	27.1±3.3	25.9±3.6	27.5±3.5
Psychological well-being score	81.2±11.1	80.9±12.2	82.1±10.9	81.7±12.1	87.1±7.9	85.7±9.1
Cigarette smoking, %						
Never	55.0	58.9	50.3	55.9	65.4	62.2
Former	33.3	30.8	39.7	35.5	15.4	26.7
Current	11.6	10.3	10.1	8.6	19.2	11.1
Dietary intake, 24-hour recall						
Fat, % kcal	35.2±8.7	35.9±9.7	34.7±8.6	35.9±9.6	35.3±8.2	37.4±10.0
Saturated fat, % kcal	12.2±4.0	12.6±4.4	12.3±4.3	12.7±4.7	11.7±3.5	12.7±3.9
Protein, % kcal	16.4±5.7	16.2±5.8	16.7±5.6	15.8±5.5	16.1±5.3	17.2±5.8
Carbohydrate, % kcal	45.8±11.0	45.7±11.7	45.7±11.2	45.6±11.7	45.8±9.3	44.3±10.7
Alcohol, % kcal	2.4±5.3	2.2±5.0	2.8±5.8	2.6±5.1	2.7±6.0	1.1±3.4
Sodium, mmol/24 h	165.2±93.9	162.6±88.7	184.8±96.0	179.7±92.8	140.2±102.8	171.3±69.5
Potassium, mmol/24 h	77.9±32.7	79.9±36.2	85.8±32.8	89.1±36.4	68.8±34.8	76.7±32.9
Calcium, mmol/24 h	19.7±12.2	21.7±16.3	22.7±13.1	24.3±17.6	12.6±8.7	16.8±8.2
Urinary electrolyte excretion, mmol/24 h						
Sodium	154.6±59.9	156.4±60.5	168.8±61.4	168.8±60.7	146.1±63.5	160.2±65.1
Potassium	61.8±23.4	62.8±23.8	69.7±24.2	71.1±23.3	47.9±17.9	53.1±19.2

BP indicates blood pressure; and bpm, beats per minute. Data are expressed as mean±SD unless otherwise noted.
*$P<.05$; †$P<.01$ for difference between active and control subjects within race-sex group.

Intervention Adherence

Attendance during intensive intervention sessions was 93% at the first group meeting but declined to 81% at the eighth group meeting, with 60% to 70% of this total as regular (versus makeup) contacts. The overall number of intervention visits ranged from 1 to 26; the mean (SD) was 18.4 (6.1). Mean (SD) percent of scheduled visits completed was 80.7 (25.7). No racial or gender differences in attendance patterns were observed.

Changes in sodium excretion are shown in Table 3. No significant treatment group differences were observed at baseline. Small decreases were observed in control subjects, but decreases in the active intervention group were significantly larger. The net treatment group differences in mean sodium excretion (millimoles per 24 hours) were 56.4 at 6 months, 51.9 at 12 months, and 47.2 at 18 months. The overall 18-month net decrease from baseline was 43.9 mmol/24 h. In the "worst-case" analyses of change from baseline, imputing the baseline value for participants with missing data to assume no change, the 18-month net decrease from baseline was 30.2 mmol/24 h, 14 mmol less (not shown).

Women had lower sodium excretion than men at baseline and 18 months. Absolute decreases in sodium were somewhat larger in men, but the 18-month mean of 84 mmol/24 h for women in the active intervention group was close to the intervention goal of 80 mmol, whereas for men the mean of 105 mmol/24 h was above the goal. Percent change in sodium excretion was approximately 40% for both men and women in the active intervention group.

Table 4 indicates the proportions of active intervention group subjects whose average sodium excretion during follow-up fell between 60 and 100 mmol/24 h. White women had the highest proportion (33%), with an average follow-up sodium excretion at or less than the 60 mmol/24 h targeted in individual counseling. Only 19% of white men attained this level of sodium

TABLE 2. Continued

White Women		Black Women	
Active (n=56)	Control (n=73)	Active (n=38)	Control (n=42)
44.3±6.0	43.2±6.2	42.8±5.8	41.9±5.4
39.3	38.4	26.3	38.1
73.2	69.9	94.7	95.2
80.4	53.4†	47.4	59.5
126.2±9.8	125.1±9.4	125.0±9.5	123.8±9.6
83.7±2.7	84.1±2.9	83.9±2.9	84.6±3.0
74.0±9.2	77.8±11.0*	74.8±9.2	77.5±7.3
71.5±11.9	71.9±13.3	74.3±11.2	74.5±11.6
26.3±4.2	26.2±4.6	27.8±4.1	28.3±4.0
78.8±10.8	75.1±12.5	77.0±11.1	82.3±12.4*
64.3	65.8	55.3	61.9
26.8	20.6	23.7	21.4
8.9	13.7	21.1	16.7
34.9±8.9	34.6±9.7	38.0±9.3	37.0±9.3
11.8±3.5	12.4±4.2	12.4±3.8	13.0±3.8
15.9±5.4	16.7±6.6	16.6±7.2	16.8±6.5
47.0±9.8	46.9±11.4	44.8±13.3	44.3±13.7
2.2±4.7	1.7±4.3	0.7±2.2	1.9±6.6
129.9±62.4	130.0±80.5	127.2±91.0	111.4±59.3
67.8±23.7	63.9±24.3	59.2±32.2	53.3±32.6
17.3±9.7	18.6±10.5	13.2±7.4	17.8±21.9
128.5±45.7	123.4±45.9	126.6±47.7	136.3±57.5
54.7±15.2	51.6±17.1	43.9±14.5	43.2±18.9

reduction, and only 11% and 5% of black women and men, respectively. Sodium excretion was less than 100 mmol/24 h for at least 55% of whites and for black women but for only 26% of black men.

The significance of attendance, gender, and race as predictors of adherence to a sodium intake of less than 80 mmol/d (active intervention group only) was assessed with multiple logistic regression analysis, adjusting for age and baseline sodium excretion. Completing more than the median percent of all contacts was associated with an odds ratio (95% confidence interval) of 2.8 (1.6, 4.9) for having an average sodium excretion of less than 80 mmol/24 h. The odds of failing to achieve this level of sodium excretion in black versus other participants were 4.1 (1.8, 9.6). An independent effect of gender was not observed (P=.24).

Effect of Sodium Intervention on Blood Pressure (Randomized Groups Comparison)

Mean changes in SBP and DBP at follow-up assessments are shown in Table 5. There was an overall effect of the sodium intervention at 18 months of approximately 1 mm Hg decrease in DBP and 2 mm Hg decrease in SBP (P<.01 for both). The incidence of hypertension (mean of nine DBP readings ≥90 mm Hg at either 12 or 18 months of follow-up) was 8.6% (28 events) in the active treatment group and 11.3% (47 events) in the control group (not shown).[13] Fig 1 shows mean net decreases in blood pressure both overall and stratified by race and sex. To evaluate further the apparent advantages for women and blacks, we conducted multivariate analyses controlling for age, sex, or race, as appropriate, baseline DBP or SBP, and baseline 24-hour urinary sodium excretion including an interaction term for treatment by race or sex. There were no significant differences in the treatment effect in blacks versus whites for either SBP (P=.40) or DBP (P=.57) and no significant difference in the treatment effect in men versus women for DBP (P=.49). However, there was a significant difference in the treatment effects between men and women for SBP, with an adjusted treatment effect of −1.23 mm Hg for men and −4.44 mm Hg for women (P=.02).

Other Treatment Effects

The possibility that being in the active intervention group resulted in changes other than those targeted in the intervention was assessed by examining net changes from baseline in other dietary and behavioral variables. There were small but statistically significant differences in weight between active intervention and control groups at 6 and 12 months (−1.23 kg, P<.0001; and −0.82 kg, P=.002), but the net difference of −0.39 kg at 18 months was not statistically significant (P=.19). There were also no consistent net differences when weight changes were analyzed using body mass index and within race, sex, and race-sex groups. No significant treatment group differences (net change from baseline) were observed at 6 or 18 months in the reported intakes of alcohol, potassium, magnesium, calcium, vitamins A or C, thiamine, riboflavin, niacin, or saturated fat. Total calories decreased (net change from baseline at 18 months, 207 kcal; P=.012), as did total fat (net change from baseline at 18 months, −11.4 g; P=.016) and iron (net change from baseline at 18 months, −3.6 mg; P=.007). In sex-specific analyses the decrease in total calories was significant in men (−234 kcal, P=.02) but not women (−134 kcal, P=.30). For total fat, the changes of −11 and −12 g in men and women, respectively, were not significant (P>.05). A significant decrease in iron intake was observed for men (−5.0 mg, P<.001) but not women (net change, 0.13 mg; P=.96). The mean iron intake of 15 mg at 18 months for both men and women in the active intervention group was at or above the recommended dietary allowances of 10 mg/d for men and 15 mg/d for women aged 25 to 50 years.[20]

Psychological General Well-Being scores improved significantly in the active treatment group compared with control subjects. Scores at 18 months were higher than at baseline, and the net improvement in overall well-being at 18 months was significant (P<.01). The net improvement from baseline was observed for almost all subscales for men, especially white men, and in many instances for women, especially black women.

TABLE 3. Changes in Urinary Sodium Excretion at 6, 12, and 18 Months of Follow-up, Total and Within-Sex Subgroup

	Active			Control				
Follow-up Variable	n	Mean	SD	n	Mean	SD	Difference	P
All subjects								
Baseline	314	154.6	59.9	401	156.4	60.5	−1.8	.70
6 Months	238	103.0	61.3	336	159.3	81.0	−56.4	<.0001
12 Months	244	100.2	60.9	342	152.1	73.6	−51.9	<.0001
18 Months	242	99.4	60.0	341	146.5	79.2	−47.2	<.0001
18-Month change from baseline	232	−55.2	76.9	330	−11.3	77.7	−43.9	<.0001
18-Month % change from baseline*	232	−42.4	40.4	330	−12.4	45.4	−30.1	.0001
Men								
Baseline	219	166.4	61.5	288	167.3	60.9	−0.9	.88
6 Months	173	107.7	67.1	245	169.1	80.6	−61.4	<.0001
12 Months	173	105.0	62.2	252	160.5	74.1	−55.5	<.0001
18 Months	176	105.0	64.4	246	156.1	82.9	−51.1	<.0001
18-Month change from baseline	166	−60.5	82.9	238	−14.2	80.6	−46.3	<.0001
18-Month % change from baseline*	166	−43.7	41.1	238	−14.0	42.7	−29.7	.0001
Women								
Baseline	95	127.5	46.1	113	128.8	50.2	−1.3	.85
6 Months	65	90.3	40.3	91	133.0	76.4	−42.7	<.0001
12 Months	71	88.5	56.3	90	128.7	67.3	−40.2	.0001
18 Months	66	84.4	42.9	95	121.8	62.9	−37.4	<.0001
18-Month change from baseline	66	−42.0	57.9	92	−4.0	69.5	−38.0	.0004
18-Month % change from baseline*	66	−39.1	37.8	92	−7.9	52.4	−31.1	<.0001

Urinary sodium excretion values are in millimoles per 24 hours.
*Log transformation was used to compute means and test for differences; first-order Taylor series approximation was used to estimate variances.

Overall Effect of Sodium Reduction (Dose Response)

The association of change in blood pressure with quintile of sodium excretion at 18 months is shown in Fig 2 using pooled data for active and control participants (adjusted for age, sex, race, baseline blood pressure, and baseline sodium excretion). Larger blood pressure declines were associated with lower levels of urinary sodium excretion (P trend=.014 for DBP and .0009 for SBP). The dose-response relation was further explored in the pooled data with linear regression analyses per unit change in blood pressure on change in 18-month sodium excretion adjusting for age, sex, race, baseline urinary sodium excretion, and baseline DBP or SBP: For each millimole decrease in urinary sodium

TABLE 4. Distribution of Average Individual Urinary Sodium Excretion During Follow-up in Sodium Intervention Active Treatment Group, Total and by Race-Sex Subgroup

Urinary Sodium Excretion, mmol/24 h	Total* (n=246)	White Men (n=158)	Black Men (n=19)	White Women (n=42)	Black Women (n=27)
<60	19.5	19.0	5.3	33.3	11.1
60-79	19.5	22.2	5.3	16.7	18.5
80-99	17.1	15.8	15.8	16.7	25.9
≥100	43.9	43.0	73.7	33.3	44.4
Total	100.0	100.0	100.1	100.0	99.9

Average individual urinary sodium excretion based on an average of the sodium content of two or three 24-hour urine samples collected from each subject at 6, 12, and 18 months of follow-up; does not reflect net differences when compared with control subjects. Values are percentages.
*Includes blacks and whites; eight participants of other races were eliminated.

TABLE 5. Blood Pressure Changes and Net Treatment Effects at 6, 12, and 18 Months of Follow-up and at Termination in Active Sodium Intervention and Control Participants

Change Variable	Baseline n	Baseline Mean±SD	6 Months n	6 Months Mean±SD	12 Months n	12 Months Mean±SD	18 Months n	18 Months Mean±SD	Termination n	Termination Mean±SD
Systolic blood pressure, mm Hg										
Sodium intervention	327	124.8±8.5	305	−5.86±7.95	301	−5.83±7.46	304	−5.08±7.94	327	−4.86±7.81
Control	417	125.1±8.1	397	−3.83±8.46	392	−3.93±7.43	395	−3.02±8.31	417	−3.16±8.11
Δ				−2.03 (−3.26, −0.80)*		−1.90 (−3.02, −0.78)*		−2.06 (−3.28, −0.84)*		−1.69 (−2.85, −0.54)*
Diastolic blood pressure, mm Hg										
Sodium intervention	327	83.7±2.7	305	−3.88±6.42	301	−4.44±5.38	304	−4.35±5.65	327	−4.12±5.71
Control	417	83.9±2.8	397	−2.88±6.32	392	−3.37±5.74	395	−3.18±5.80	417	−3.27±5.73
Δ				−1.00 (−1.95, −0.04)†		−1.06 (−1.90, −0.22)†		−1.17 (2.03, −0.31)*		−0.85 (−1.68, −0.02)†

Values in parentheses show 95% confidence intervals.
*$P<.01$, †$P<.05$.

excretion, from baseline to 18 months, there was an average decrease (mean [SEM]) of 0.009 (0.003) mm Hg in DBP ($P=.006$) and 0.014 (0.005) mm Hg in SBP ($P=.004$), or 0.9 and 1.4 mm Hg DBP and SBP, respectively, per 100 mmol decrease in sodium excretion. Nonlinear terms, such as percent change in sodium or the log of 18-month sodium excretion, did not improve the fit of the model. Weight change was also a significant predictor of blood pressure change. When weight change at 18 months was added to the model with linear sodium change and baseline weight, the sodium dose response was smaller (ie, the coefficients for 18-month blood pressure change per millimole of 18-month change in sodium excretion decreased to 0.006 for DBP and 0.009 for SBP) and was of borderline significance ($P=.07$ for DBP and .06 for SBP).

Relation of Dose Response to Treatment Group Effects

A term for treatment group (ie, active versus control status) was then included in the pooled analyses to determine if any active versus control difference in blood pressure change would be observed when changes in sodium intake had been accounted for, ie, because the treatment effect was presumably an effect mediated primarily by sodium reduction. The treatment effect was significant in this model for SBP ($P=.04$) but not DBP ($P=.15$). This suggested that changes in SBP occurred in the active intervention group over and above those associated with the linear effect of change in sodium excretion. Attempts to explain this additional treatment effect with the variables available were not successful. As previously noted, other net differences between the active and control groups that might have affected SBP were not observed (eg, net differences in weight, potassium excretion, or alcohol intake). However, as a precaution and because weight change influenced the dose response, exploratory analyses adding weight at 18 months to the models were done. The residual treatment effect for the sodium intervention was still significant for SBP ($P=.09$ for DBP and .03 for SBP) in linear regres-

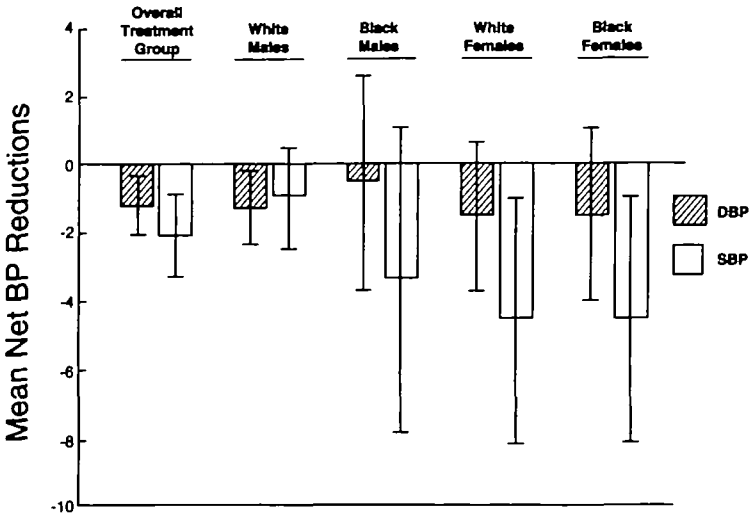

FIG 1. *Bar graph shows mean (and 95% confidence interval) net systolic blood pressure (SBP) and diastolic blood pressure (DBP) reductions at 18 months (in millimeters of mercury) overall and by race-sex group. Net blood pressure (BP) is calculated by subtracting change in the control group from change in the active treatment group.*

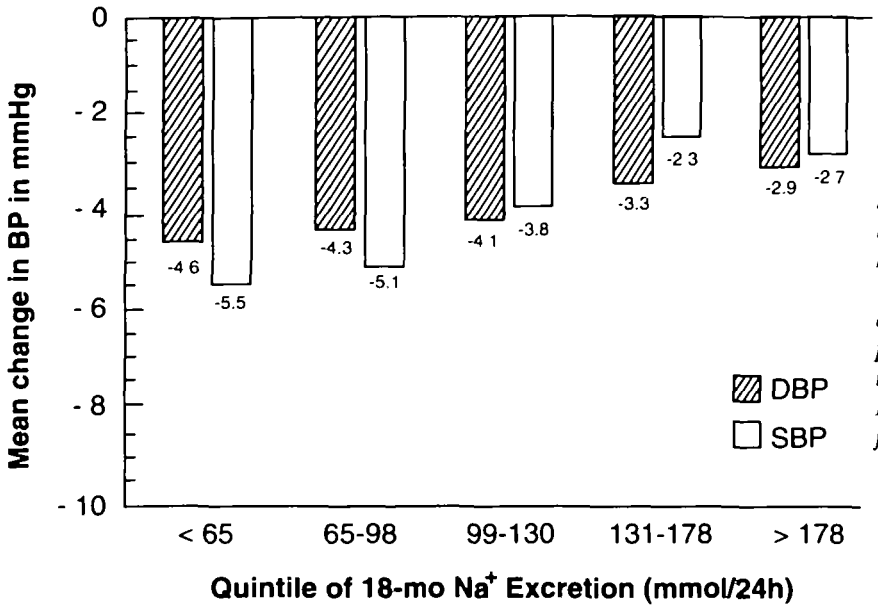

FIG 2. *Bar graph shows mean change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) (in millimeters of mercury) by quintile of sodium excretion (millimoles per 24 hours) at 18 months adjusted for age, sex, race, baseline blood pressure (BP), and baseline sodium excretion (P trend=.0009 for SBP and .014 for DBP). Active treatment and control subjects were pooled for these analyses.*

sion analyses with both change in weight and change in sodium excretion in the model, suggesting that there were other mediating variables or that changes in sodium for individuals were insufficiently characterized.[21]

In addition, the apparent gender×treatment group interaction for SBP, ie, the possibility that there was a difference in dose response for men and women, was examined through multiple regression analyses, adjusting for age, race, baseline sodium excretion, baseline blood pressure, and weight at 18 months. The coefficients for the association of blood pressure change with sodium change were not significantly different for men and women for either DBP or SBP using quintiles or a linear term for sodium level. The overall treatment×gender interaction was, however, somewhat reduced by the addition of sodium excretion to the model, but it remained marginally significant (P=.06). Although taken together the gender difference in treatment effect and the lower sodium excretion in women suggested a larger dose response at lower levels of sodium intake, exploratory analyses with nonlinear terms or interactions between the treatment effect and baseline sodium excretion failed to identify a significant difference in dose response across quintiles of 18-month sodium excretion.

Discussion

These results attest to the feasibility of lowering sodium intake of free-living adults by about one third and of maintaining this effect with this type of intensive intervention program. Sodium reduction was achieved without significant changes in weight at the end of the study and generally without changes in other dietary constituents, including calcium and potassium. Thus, any associated changes in blood pressure can be attributed to sodium reduction with considerable confidence. The level of sodium reduction achieved in TOHP-I (30%) approximates the best results observed in similar nonpharmacologic trials of hypertension prevention or treatment, some of which included larger proportions of participants who were black or from lower socioeconomic groups.[10,22-24]

The feasibility of the intervention appeared to be similar for men and women in that the percent by which sodium excretion decreased was comparable across sex. However, although the sodium density (millimoles per 1000 kilocalories) of the diets of men and women is similar,[25] the lower total sodium intake in women resulted in greater adherence from the perspective of achieving a specified urinary excretion goal. This relation of the achievement of sodium reduction goals to female sex or smaller body size has been noted previously.[17,26-28]

The reason for the lesser feasibility in blacks than whites is less readily apparent. The Dietary Intervention Study in Hypertension (DISH) data also suggest larger sodium change in white subjects, but the authors' overall conclusion was that "equal success was obtained in reducing sodium for blacks and whites."[16] Race-specific sodium reduction results for other similar trials were not identified. This issue needs further study with larger numbers of black participants than were included in TOHP-I.

Safety, or the absence of adverse effects, is the other critical dimension of feasibility that must be considered with respect to dietary change interventions of this type. For example, it is appropriate to raise the possibility that sodium reduction might inadvertently compromise dietary adequacy for essential vitamins or minerals (such as iron intake of women). However, this was not observed here or in DISH.[16] This is encouraging as to the feasibility of long-term sodium reduction. Quality of life concerns such as the potential burden of having to avoid processed foods, refrain from eating in restaurants, or tolerate unsalted foods can also be raised as arguments against population-wide sodium reduction. However, we found no indication that sodium reduction was associated either with a deterioration in the quality of life or, as reported in the Trial of Antihypertensive Interventions and Management (TAIM),[29] with increased fatigue. The lack of change in scores on the "vitality" subscale of the General Well-Being Index was the basis for inferring that fatigue was not a side effect of sodium reduction.

The data indicate a net decrease of approximately 2 mm Hg in SBP and 1 mm Hg in DBP associated with a net decrease in sodium excretion of approximately 40 mmol/d. The dose response calculated from pooled data from active and control subjects shows a response of about one half this size, suggesting that some of the effect observed in the intention-to-treat analysis may have been attributable to factors other than sodium reduction as such or, more likely, that the individuals' sodium intake levels were not well characterized.[21] The meta-analysis by Law et al,[6] which excluded studies in which sodium reduction was combined with other interventions or in which subjects were also taking antihypertensive drugs, yielded an estimate that a decrease of 50 mmol in sodium would result in a minimum decrease of 5 mm Hg in SBP and an effect on DBP of about half this magnitude in normotensive people 50 years of age and older. This effect is about twice as large as that observed in TOHP-I. The overview analysis by Cutler et al[5] suggested an SBP/DBP decrease of 2/1 mm Hg associated with a decrease of 50 to 100 mmol in sodium excretion, more similar to that observed here. Most of the studies reviewed by either Law or Cutler were of shorter duration than TOHP-I, but both analyses indicated an increasing effect with duration of treatment. Both Law and Cutler also reported that a smaller effect would be expected in normotensive than in hypertensive subjects.

The blood pressure decreases observed in TOHP-I are far from inconsquential in terms of the potential effect on morbidity and mortality. Prof Rose Stamler has pointed out that a 2 mm Hg lower SBP predicts a reduction of stroke mortality by 6%, coronary heart disease mortality by 4%, and all-cause mortality by 3%.[30] These effect estimates must be increased by one half to one third to account for regression dilution bias. Considering that larger reductions in sodium intake than those in TOHP-I may result from appropriate changes in processed foods, the possible effect of sodium reduction on hypertension prevention may be even greater. The deaths averted in the US population each year due to such society-wide changes would number in the tens of thousands.

Possible racial differences in sodium sensitivity that would suggest a larger blood pressure response to a given level of sodium reduction in blacks are widely discussed in the literature[31] and may be assumed by some authors to have been clearly established.[32,33] Our subgroup analyses of black-white differences in the response to sodium reduction were inconclusive. Any related inferences must rely on the indirect observation that a lesser blood pressure response to sodium reduction was not observed in black participants in spite of less sodium reduction. Also, the black-white differences in adherence suggest that cultural factors may somehow influence the results of attempted dietary changes. As this continues to be an area of possible interest, careful attention to separating black-white differences in adherence from differences in dose response is warranted not only for sodium reduction but, from another analysis of TOHP-I data, for weight reduction.[34]

A larger blood pressure response to sodium reduction in women than in men, identified in both the INTERSALT data[7] and in Elliott's epidemiologic meta-analysis,[35] was also observed here for SBP in preliminary and more detailed analyses involving statistical controls for a variety of possible explanatory variables. Our data suggest that this observation may be explained by the lower absolute levels of sodium intake in women. We were unable to demonstrate a nonlinear component in the sodium–blood pressure dose response, but the data were somewhat consistent with a larger blood pressure SBP decrease at lower levels of sodium intake. Data from the double-blind crossover study of MacGregor et al[36] support this line of reasoning. The reported mean supine blood pressures associated with sodium intakes of approximately 200, 100, and 50 mmol/d suggested a larger decrease in blood pressure from 100 to 50 mmol sodium/d (13.6/6.8 mm Hg SBP and DBP, respectively) than from 200 to 100 mmol sodium/d (9.8/6.1 mm Hg).

Race- or gender-specific comparisons were not an aspect of the TOHP-I study design, and the statistical power associated with such comparisons was inadequate to support definitive inferences; therefore, it should be emphasized that all such analyses were exploratory. These analyses were included primarily to raise considerations for the design of future studies of sodium and blood pressure. For example, properly designed studies may be able to clarify whether the range of sodium intake influences the blood pressure response to sodium reduction, either additively or interactively with the relative degree of sodium reduction, or whether other factors are responsible for the apparent gender effect. Such clarifications would have direct implications for recommendations to the public regarding the optimum sodium intake range.

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