Effect of Dietary Sodium on Blood Pressure: A Crossover Trial

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Effect of Dietary Sodium on Blood Pressure: A Crossover Trial

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Abstract | Full Text

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This crossover trial assesses whether high-sodium and low-sodium dietary interventions affect 24-hour ambulatory blood pressure measures among middle-aged to elderly adults with normotension, controlled hypertension, uncontrolled hypertension, or untreated hypertension.

Introduction

- Sodium is a dietary component that substantially contributes to blood pressure

- Daily average sodium intake in middle-aged to elderly US adults:
- 3.5gr ⟶ World Health Organization

- Variability in the BP response to variation in sodium intake:
- ✓ Personalized treatment responses from clinical trials challenging
- ✓ Within-individual BP response to variation in sodium intake: salt sensitivity of BP (**SSBP**)
- 50% and 25% of individuals with and without hypertension show SSBP

- Exclusion of individuals taking antihypertensive medications from research:
- ✖ Dietary sodium reduction lowers BP
- ✖ Antihypertensive pharmacotherapies are associated with lessening of SSBP

Goals

- Coronary Artery Risk Development in Young Adults (CARDIA)–SSBP study:
  - ✓ Population of middle-aged to elderly persons including:
  - ✓ Normotension
  - ✓ Treated and untreated hypertension

- Diet crossover design of high-sodium and low-sodium diets:
  - ✓ (1) Distribution of within-individual BP response to dietary sodium
  - ✓ (2) Difference in BP between individuals to high- or low-sodium diet
  - ✓ (3) Varied by baseline BP and antihypertensive medication use

Methods
Participants

- CARDIA is a prospective, multicenter, observational cohort study the aims:
- Identify the factors in young adulthood influencing development of cardiovascular disease

- Participant enrollment occurred in 1985-1986 and was balanced:
- Sex, race (Black or White)
- Age (18-24 or 25-30 years)
- Education (high school or more than high school)

- Between April 2021 and February 2023, enrollment into CARDIA-SSBP:
- non-CARDIA
- Inclusion criteri:
- Age 50 to 75 years
- Exclusion criteria:
- Systolic or diastolic BP outside of 90 to 160mm Hg or 50 to 100mm Hg
- Resistant hypertension
- Contraindications to high- or low-sodium diets

Methods
Study Protocol

- Assessment of dietary adherence were based on the American Heart Association's SSBP recommendations:
- ✓ Sodium content and 1-week duration of diets
- ✓ 24-hour ambulatory BP monitoring (ABPM)
- ✓ 24-hour urine collections

- ۴ study visits:
- Enrollment
- Baseline
- End of the first diet week
- End of the second diet week (latter 3 occurring over consecutive 1-week intervals)

- The high-sodium diet:
- 2 bullion packets, each containing 1100 mg of sodium
- The low-sodium diet:
- 500 mg of sodium, 4500 mg of potassium, and 1000 mg of calcium

Methods
Outcomes

- 24-hour ABPM and 24-hour urine collections:
- Day before each of the baseline, end of first diet week, and end of second diet week visits

- Fasting for 6 hours or longer
- Participants reported adverse events while consuming study diets

- End of each diet week the averages from 24-hour ABPM:
- Systolic BP
- Diastolic BP
- Mean arterial pressure
- Pulse pressure

- Urine sodium and creatinine were measured using flame photometry and ELISA

Statistical Analysis

- SSBP:
  - ✓ 24-hour BP during a high sodium diet - 24-hour BP during a low-sodium diet
  - ✓ provides a continuous measure of within-individual BP response to variation in sodium loading

- Prospective allocation to either diet order with a crossover design:
  - ✓ Within-individual analysis examining SSBP between high- and low-sodium diets
  - ✓ Examining contrast in BP between groups at the end of the first diet week

- Baseline characteristics were calculated:
  - ✓ Medians
  - ✓ IQRs
  - ✓ Counts and percentages

Statistical Analysis

- Distribution of SSBP for mean arterial pressure (MAP) was summarized as medians and IQRs in the overall cohort and within prespecified subgroups:
  - ✓ Age, sex, race
  - ✓ Hypertension status
  - ✓ Antihypertensive medication
  - ✓ Baseline BP
  - ✓ BMI
  - ✓ Diabetes

- Distributions of SSBP for systolic BP, diastolic BP, and pulse pressure in the overall cohort were analyzed

Statistical Analysis

- Exploratory analysis:
  - ✓ SSBP differed between individuals with baseline normotension, controlled hypertension, untreated hypertension, and uncontrolled hypertension was analyzed: Kruskal-Wallis test
  - ✓ Associations between classes of antihypertensive medications and SSBP were examined in ordinary least-squares models adjusted for demographic and clinical covariates

- The proportion of individuals with any decline, no change, or any increase in BP between high- and low-sodium diets was quantified and then repeated using commonly used thresholds (MAP):
  - ✓ 5–mm Hg or greater decrease: salt sensitivity
  - ✓ 7–mm Hg or greater increase: inverse salt sensitivity

Statistical Analysis

- Analysis for within-individual BP changes was also recalculated between the usual and low-sodium diets and between the usual and high sodium diets
- Examine contrast in BP at the end of just the first diet week between the groups
- Calculate mean between-group differences and 95% CIs
- Adjustment covariates included:
- Age, sex, race, baseline BP, history of hypertension, number of antihypertensive medications, diabetes, body mass index, end of first diet week urine potassium, study site, and CARDIA vs non-CARDIA participants
- Overall between group parallel analysis was then repeated using just the BP from the end of the second diet week
- The proportion of participants reporting adverse events while consuming high- and low-sodium diets was tabulated

Results

- Enrollment characteristics for the 213 individuals who completed both high- and low-sodium diet visits according

- Assessed by 24-hour urine excretion:
- ✓ High-sodium diet significantly increased sodium intake above the low-sodium and usual diets

- Individuals not taking antihypertensive medications at baseline provides population estimates:
- ✓ Usual sodium consumption
- ✓ Contrast between high- and low-sodium diets

- Participants' usual diets were already high in sodium: median, 4.45 g/d
- High-sodium diets: medians, 5.00 g/d
- Low-sodium diets: medians, 1.27 g/d

Table. Enrollment Characteristics According to Allocation to High-Sodium Diet First or Low-Sodium Diet First

Characteristics	High-sodium diet first (n = 118)	Low-sodium diet first (n = 95)
Age, median (IQR), y	61 (56-64)	61 (58-65)
Sex, No. (%)		
Female	76 (64)	63 (66)
Male	42 (36)	32 (34)
Race, No. (%)		
Black	75 (64)	61 (65)
White	39 (33)	31 (33)
Other or unknown	4 (3)	3 (3)
Enrollment source, No. (%)		
CARDIA	85 (72)	70 (74)
Non-CARDIA	33 (28)	25 (26)
Location, No. (%)		
Birmingham	84 (71)	47 (49)
Chicago	34 (29)	48 (51)
Hypertension, No. (%)	59 (50)	44 (47)
No. of antihypertensive medications, No. (%)		
0	59 (50)	50 (53)
1	34 (29)	29 (31)
2	21 (18)	12 (13)
≥3	4 (3)	3 (3)
Use of antihypertensive medication, by drug class, No. (%)		
ACE inhibitor or ARB	31 (26)	27 (28)
β-Blocker	13 (11)	5 (5)
Calcium channel blocker	20 (17)	19 (20)
Diuretic	17 (14)	12 (13)
Systolic blood pressure, median (IQR), mm Hg[a]	128 (117-139)	127 (119-137)
Diastolic blood pressure, median (IQR), mm Hg[a]	80 (73-87)	77 (73-86)
Mean arterial pressure, median (IQR), mm Hg[a]	96 (88-104)	94 (88-103)
Pulse pressure, median (IQR), mm Hg[a]	47 (40-56)	49 (45-56)
Heart rate, median (IQR), /min[a]	69 (60-78)	68 (59-75)
Diabetes, No. (%)	22 (19)	23 (24)
Body mass index, median (IQR)[b]	31.2 (27.0-36.8)	30.7 (26.6-34.6)
24-h Urine volume, median (IQR), L[c]	1.47 (0.96-2.04)	1.54 (1.08-2.36)
24-h Urine sodium, median (IQR), g[c]	4.57 (2.57-5.73)	4.88 (3.16-6.62)
24-h Urine creatinine,	1.12 (0.76-1.46)	1.15 (0.84-1.53)

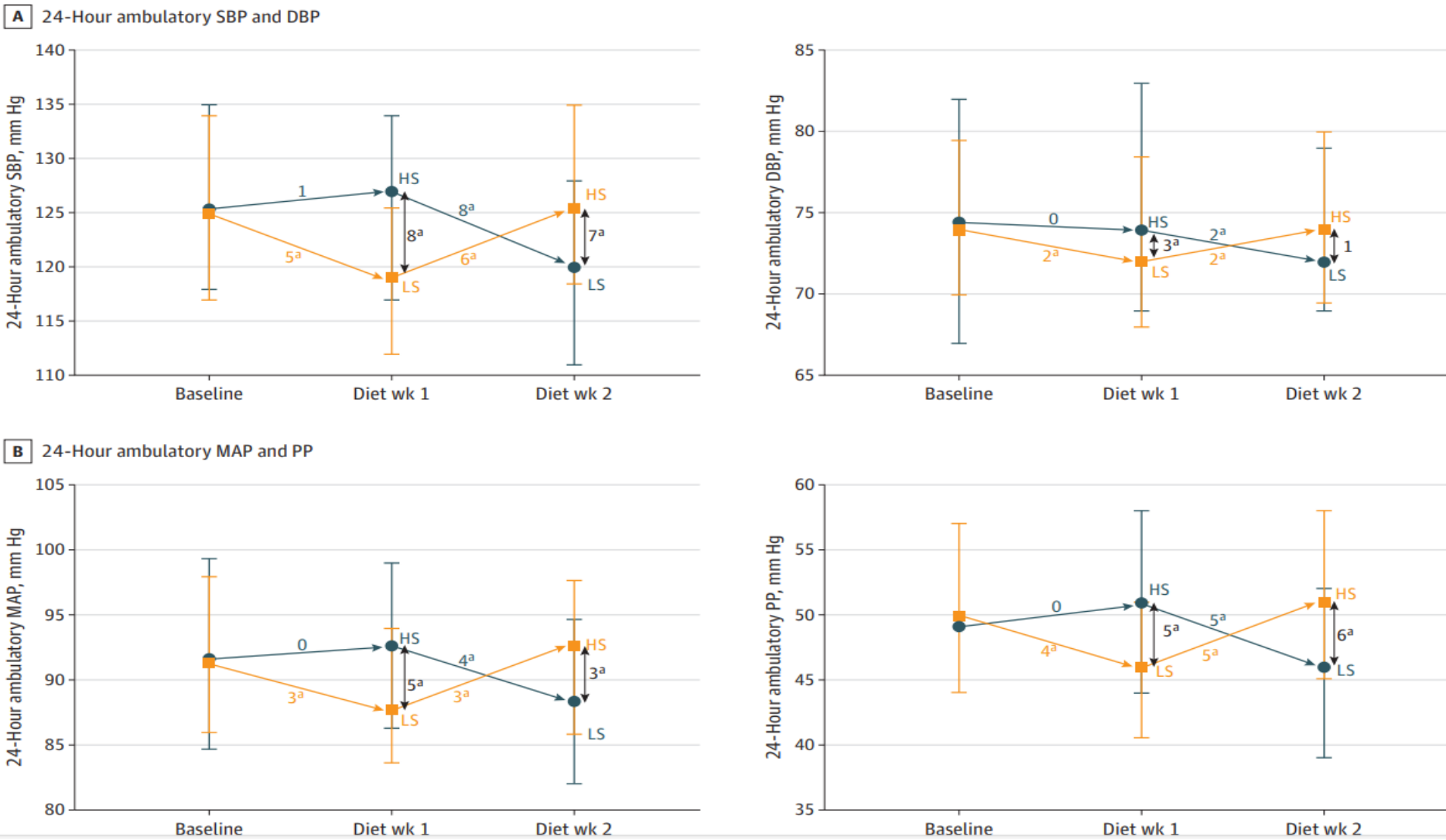
Results

- In the parallel-group analysis performed to examine the differences in BP at the end of the first diet week between:
- ✓ Systolic BP was 8 mm Hg lower ($P < .001$) in those allocated to a low-sodium diet first vs with a high-sodium diet first

- This between-group effect was also consistent comparing low- and high-sodium diet groups using just the end of the second diet week BP ($P < .001$)

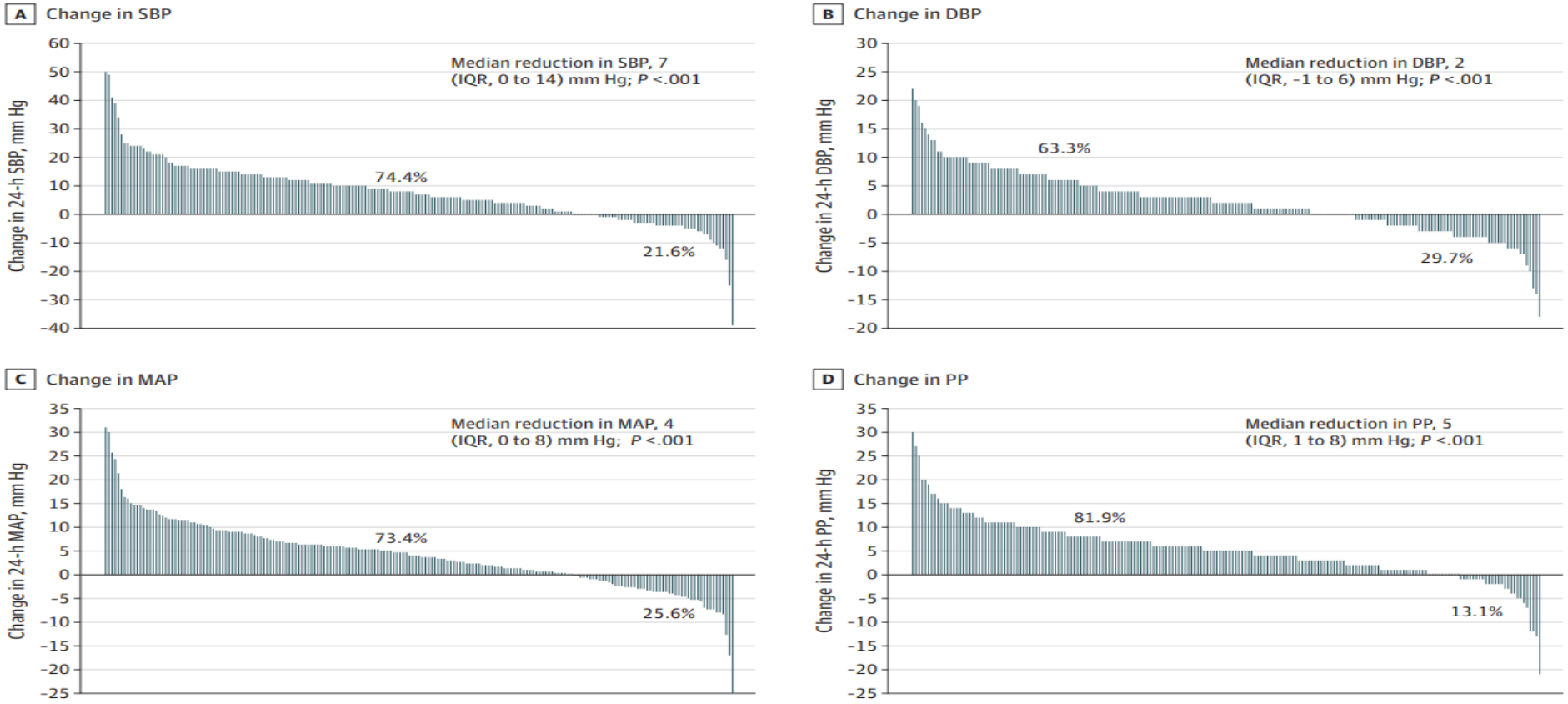
- Mean differences in diastolic BP, mean arterial pressure, and pulse pressure between individuals randomized to a high- vs low-sodium diet first were also significant

Figure 1. 24-Hour Ambulatory BP According to Allocated Diet Order and Study Visit



- ✓ Mean differences in BP, mean arterial pressure, and pulse pressure between individuals randomized to a high- vs low-sodium diet first were also significant

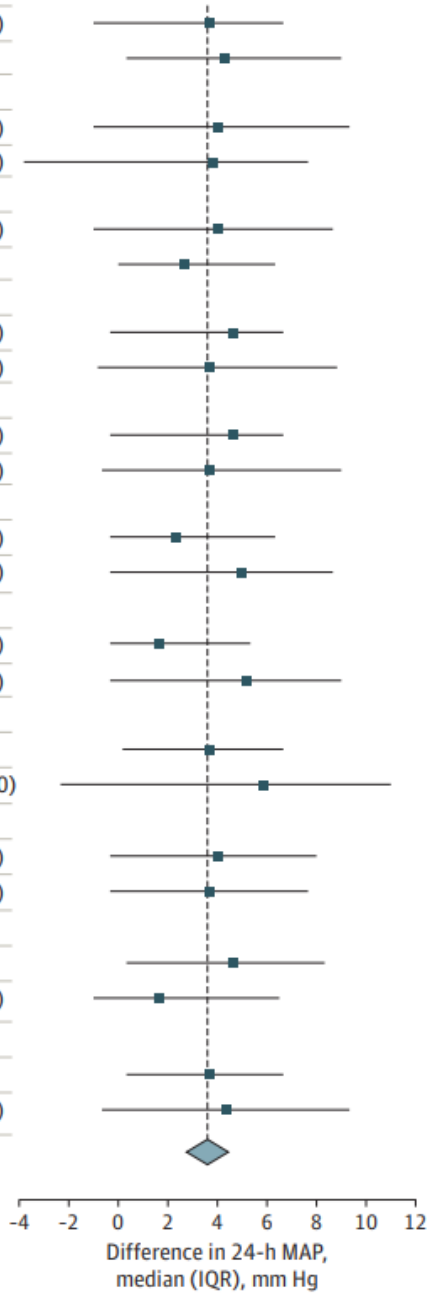
Figure 2. Distributions of Within-Individual 24-Hour Ambulatory BP Response to Dietary Sodium Intake, Calculated From High-Sodium Diet Minus Low-Sodium Diet



- Percentages above 0 reflect:
- ✓ Reduction in BP during low-sodium diet vs high-sodium diet
- Percentages below 0 reflect:
- ✓ Increase in BP during low-sodium diet vs high-sodium diet

Figure 3. Variation in Salt Sensitivity of Blood Pressure for MAP Across Subgroups

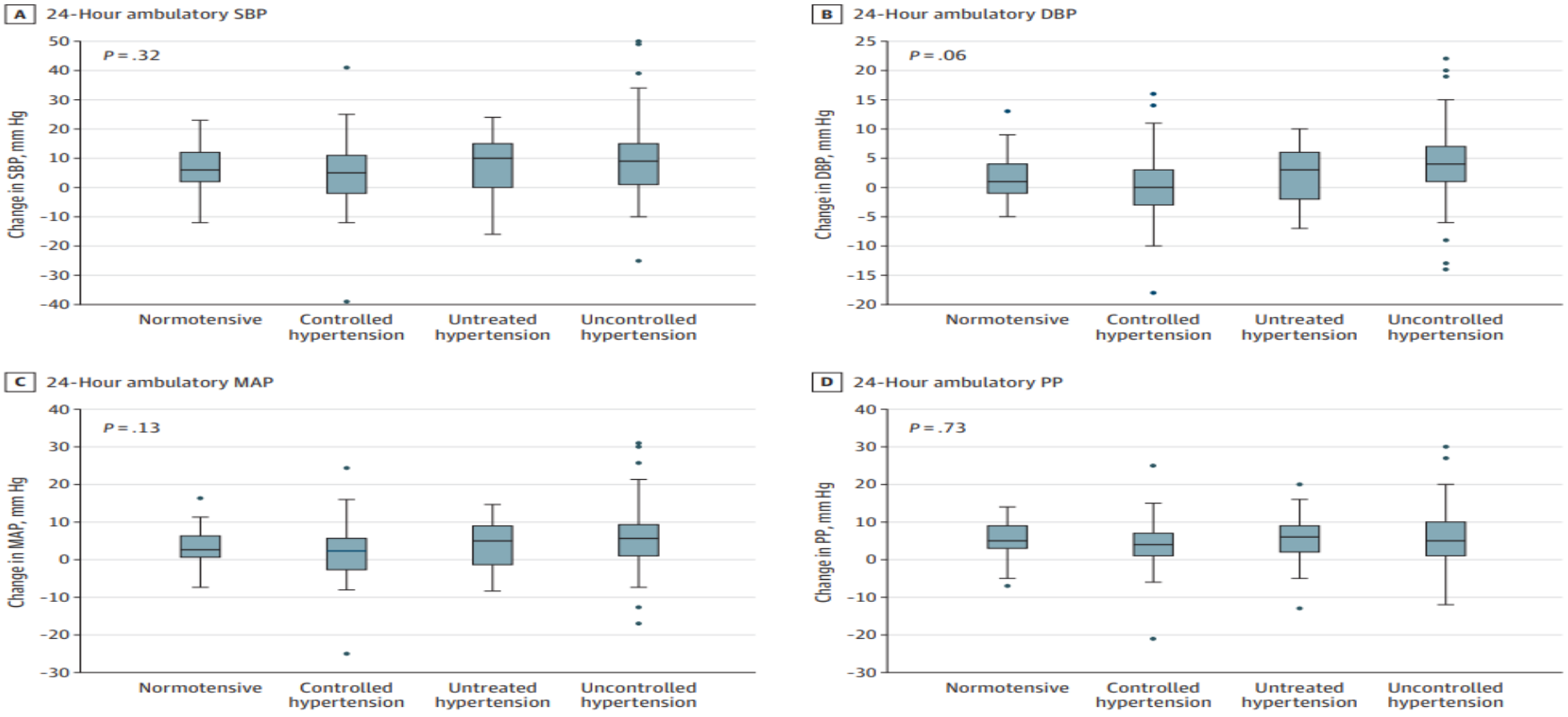
Subgroup	Median (IQR)
Age, y	
≤61	3.66 (-1.00 to 6.66)
>61	4.33 (0.33 to 9.00)
Sex	
Male	4.00 (-1.00 to 9.33)
Female	3.83 (-3.81 to 7.66)
Race	
Black	4.00 (-1.00 to 8.66)
White	2.66 (0.00 to 6.33)
Hypertension	
Yes	4.66 (-0.33 to 6.66)
No	3.66 (-0.83 to 8.83)
Antihypertensive medication	
Yes	4.66 (-0.33 to 6.66)
No	3.66 (-0.66 to 9.00)
Baseline SBP, mm Hg	
≤125	2.33 (-0.33 to 6.33)
>125	5.00 (-0.33 to 8.66)
Baseline DBP, mm Hg	
≤74	1.66 (-0.33 to 5.33)
>74	5.16 (-0.33 to 9.00)
Diabetes	
Yes	3.66 (0.17 to 6.66)
No	5.83 (-2.33 to 11.00)
Body mass index[a]	
≤31	4.00 (-0.33 to 8.00)
>31	3.66 (-0.33 to 7.66)
Source population	
CARDIA	4.66 (0.33 to 8.33)
Non-CARDIA	1.66 (-1.00 to 6.50)
Location	
Birmingham	3.66 (0.33 to 6.66)
Chicago	4.33 (-0.66 to 9.33)
Overall	3.60 (2.75 to 4.44)



- ❖ SSBP for MAP:
- ✓ For each of the subgroups shown, the within-individual difference in MAP was significant at P < .001 for all except for non-CARDIA participants (P = .003)

- ✓ For each of the subgroup comparisons, eg, male vs female, the Wilcoxon rank sum tests were nonsignificant (P .10) for all except by **DBP** (P = .04)

Figure 4. Within-Individual 24-Hour Ambulatory BP Response to Low-Sodium vs High-Sodium Diets Stratified According to Baseline Hypertension Status



- Change in BP was calculated as BP during high-sodium diet minus BP during low-sodium diet
- The within-individual SSBP response to high- minus low-sodium diets was similar between individuals with normotension (n = 49), controlled hypertension (n = 39), untreated hypertension (n = 50), and uncontrolled hypertension (n = 61)

Results

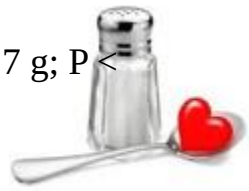
- Antihypertensive drug classes (β-blockers, calcium channel blockers, and diuretics) were not consistently associated with SSBP

- Threshold of a 5–mm Hg or greater decline in MAP from high- to low-sodium diets: 46% of individuals "salt sensitive"
  - ✓ This group had a median difference in 24-hour urine sodium in high-sodium minus low-sodium diet of 3.4 g (IQR, 1.4-4.9 g;P < .001)

- Threshold of a 7–mm Hg or greater increase in MAP from a high- to a low-sodium diet: 5% of individuals "inverse salt sensitive"
  - ✓ These individuals had a median difference in 24-hour urine sodium in high-sodium minus low sodium diet of 0.3 g (IQR, −4.6 to 1.4 g; P = .92)

- Compared with usual diet:
  - ✓ low-sodium diet reduced daily sodium intake by a median of 2.3 g (IQR, 0.4- g; P < .001)
  - ✓ 71.7% of individuals demonstrated a decline in systolic BP with the low-sodium diet

- In contrast, the high-sodium diet raised dietary sodium intake by a median of 1.1 g (IQR, −0.4 to 2.7 g; P < .001), but without significant changes in BP



Results

- The reduction in systolic BP resulting from a low-sodium diet compared with a high-sodium diet was largely consistent across subgroups, including:
- ✓ Age, sex, and race…

- A total of 35 and 24 adverse events were reported in 21 (9.9%) and 17 (8.0%) individuals while consuming high- and low-sodium diets, respectively

- These were generally mild and self-remitted
- The most frequent symptoms while consuming the high-sodium diet:
- ✓ Headache
- ✓ Gastrointestinal discomfort
- ✓ Edema

- low-sodium diet:
- ✓ weakness

Discussion

- Sample of middle-aged to elderly individuals, sodium reduction significantly lowered BP compared with a high-sodium diet after a 1-week diet study period

- within-individual and between group declines in BP independent:
- Hypertension status
- Antihypertensive medication use

- ✓ Did not result in excess adverse events

Discussion

- Compared with usual diet, the low-sodium diet resulted in a median reduction of about 1 tsp of table salt (2.3 g of sodium) per day with a corresponding median 6–mm Hg reduction in systolic BP

- The magnitude of this 24-hour ABP effect is similar:
- ✓ The mean 6.7–mm Hg reduction in clinic systolic BP via a low-sodium diet of 1.5 g/d observed in the DASH-Sodium trial, in which individuals consumed fully controlled sodium diets for 30 days each
- ✓ The average effect observed with 12.5 mg of hydrochlorothiazide

- Recommendations to patients:
- Clinically meaningful lowering of BP through dietary sodium reduction can be achieved safely and rapidly within 1 week; an effect comparable with that of a common first-line antihypertensive medication

Discussion

- Increasing daily sodium intake by approximately 0.5 tsp of table salt (about 1.1 g of sodium) did not lead to parallel increases in blood pressure
- ✓ Reflect real-life variability in sodium intake
- ✓ Usual diets may already have been sodium saturated

- Inverse salt sensitivity:
- ✓ BP increase with sodium reduction
- ✓ Smaller difference in 24-hour urine sodium between high- and low sodium diets, raising consideration for dietary nonadherence

Discussion

- In contrast to most prior studies evaluating dietary sodium's effect on BP, we included individuals across the spectrum of normotensive to hypertensive, treated and untreated, controlled and uncontrolled

- ✓ The reduction in BP between high- and low-sodium diets was similar across these groups

- Moreover, in exploratory analyses, we did not find different classes of anti hypertensive medications consistently associated with the BP response to variation in dietary sodium:
- ✓ Importance of continued lifestyle modification even among individuals with treated hypertension

Limitations

- The 24-hour urine sodium levels on the low-sodium diet were higher than expected for the provided standardized low-sodium meals, suggesting that there was dietary nonadherence
- ✓ Sodium content of food and day-today dietary patterns vary

- The usual, high-sodium, and low-sodium diets were not fully controlled:
- ✓ we cannot exclude contributions of non sodium dietary components

- Our study design does not allow assessment of BP effects of longer time consuming high- or low-sodium diets

- Our study does not address sustainability of a low-sodium diet:
- ✓ DASH-Sodium

- Our results may not be generalizable outside of the community-based population studied

- Intraindividual variability in BP can make interpreting individual treatment responses from parallel-design trials challenging:
- ✓ Our study design enabled us to assess both the between-group and within-individual BP difference between high- and low sodium diets

Conclusions

- Sodium reduction significantly lowered BP in the majority of middle-aged to elderly adults in this study

- The decline in BP from a high-sodium diet to a low-sodium diet was independent:
- Hypertension status
- Antihypertensive medication use
- Generally consistent across subgroups
- Did not result in excess adverse events

Thank You For Your Attention