2023

Intent-to-Treat Versus Per Protocol Analysis of a Crossover Feeding Trial: Effect of Dietary Sodium on Obstructive Sleep Apnea

Gabrielle Gloston
University Of Alabama At Birmingham

INTENT-TO-TREAT VERSUS PER PROTOCOL ANALYSIS OF A CROSSOVER FEEDING TRIAL: EFFECT OF DIETARY SODIUM ON OBSTRUCTIVE SLEEP APNEA

by

GABRIELLE GLOSTON

S. JUSTIN THOMAS, COMMITTEE CHAIR
LLOYD EDWARDS
BUREL GOODIN
ORLANDO GUTIERREZ

A THESIS

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Master of Arts

BIRMINGHAM, ALABAMA

2023

INTENT-TO-TREAT VERSUS PER PROTOCOL ANALYSIS OF A CROSSOVER FEEDING TRIAL: EFFECT OF DIETARY SODIUM ON OBSTRUCTIVE SLEEP APNEA

GABRIELLE GLOSTON

MEDICAL/CLINICAL PSYCHOLOGY

ABSTRACT

Obstructive sleep apnea (OSA) is a common form of sleep disordered breathing that leads to poor daytime functioning. It is strongly associated with hypertension (HTN) and apneic events in individuals with OSA can drive blood pressure (BP) surges at night. Treating OSA with continuous positive airway pressure (CPAP) has led to reductions in day- and nighttime BP and treatment of HTN has also been reported to have beneficial effects on OSA severity. Dietary sodium has long been implicated in HTN and dietary sodium restriction improves BP levels. Recently, dietary sodium restriction was found to reduce OSA severity in men with severe OSA. While CPAP is effective in treating OSA, adherence is low; therefore, additional therapies may be needed. The goal of the current study was to determine the effect of dietary sodium restriction on OSA severity in adults with nocturnal HTN.

Secondary data analysis was performed on 59 participants with nocturnal HTN who were recruited from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Participants were enrolled into a randomized crossover feeding trial, which consisted of a high (6.0 g) and low sodium (1.5 g) diet period separated by a four-week washout period. They completed pre- and post-diet assessments, including clinic BP, 24-hour ambulatory BP, home sleep test (HST) and 24-hour urine collection. Change

in OSA severity (apnea/hypopnea index, AHI) was examined according to both the intent-to-treat (ITT) and per protocol (PP) principles.

No significant diet effect was observed in the ITT analysis. A sensitivity analysis was performed to examine the influence of HST evaluation duration; however, results were consistent with the initial findings. There was also no significant diet effect observed in participants when stratified by sex or race. Effect of dietary sodium restriction on OSA severity could not be assessed in the reduced sample of only adherent participants according to the PP principle due to a significant carryover effect. The current study suggests that dietary sodium restriction may not be an effective OSA treatment in adults with nocturnal HTN. Limitations, implications, and future directions are discussed.

Keywords: obstructive sleep apnea, dietary sodium

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by episodes of partial or complete obstruction of the upper airway, leading to reduced (hypopnea) or no (apnea) airflow for at least 10 seconds per event. The resulting excessive daytime sleepiness and fatigue can lead to impairments in daily functioning and overall diminished quality of life (Chervin, 2000; Gottlieb & Punjabi, 2020). For example, OSA has been associated with increased vehicular and occupational accidents, as well as increased risk for cardiovascular morbidity and mortality (Vanderveken et al., 2011). The prevalence of OSA in American adults is approximately 25%, occurring nearly twice as much in men (34%) as in women (17%) (Peppard et al., 2013; Punjabi, 2008; Young et al., 2002). Studies also demonstrate that OSA is more prevalent and severe in Black individuals compared to White individualsacross the lifespan (Ancoli-Israel et al., 1995; Johnson et al., 2018; Pranathiageswaran et al., 2013; Redline et al., 1999; Rudnick et al., 2007). OSA is closely associated with hypertension (HTN) and as severity increases, so does the occurrence of HTN (Hla et al., 1994; Young et al., 1997). About 40% of hypertensive patients also have OSA and this number nearly doubles (70-90%) in people with treatment resistant HTN (FLETCHER et al., 1985; Gonçalves et al., 2007; Lavie et al., 1984; Logan et al., 2001; Muxfeldt et al., 2014; WORSNOP et al., 1998). Evidence suggests that OSA not only increases daytime blood pressure (BP), but can also increase

nighttime BP due to surges as high as 220/130 mmHg at the end of an apneic event (Okabe et al., 1995; Somers et al., 1995) .

OSA and BP

Clinic BP is routinely monitored but is susceptible to the "white coat effect" (elevated clinic BP despite otherwise normotensive 24-hour BP) and may not be the best predictor of cardiovascular events compared to out-of-office BP. Ambulatory blood pressure monitoring (ABPM) obtains BP readings, typically every 30 minutes, over a 24-hour period. Elevated nighttime BP has been found to be more predictive of cardiovascular morbidity and mortality than clinic or daytime BP (Boggia et al., 2007; Sega et al., 2005). Compared to White adults, Black adults have a higher prevalence of nocturnal HTN (defined as systolic BP and/or diastolic BP ≥120/70 mmHg), non-dipping BP (defined as a decrease in mean systolic BP from daytime to nighttime less than 10%), OSA (Booth et al., 2019; Coca, 1994; Conen & Bamberg, 2008; Fan et al., 2010; Hansen et al., 2011; Mancia et al., 1993; Thomas & Calhoun, 2017; Thomas et al., 2020), and salt-sensitivity (Madhavan & Alderman, 1994). Just as OSA is associated with daytime HTN, it is also associated with nocturnal HTN(Konecny et al., 2014). The gold standard for OSA treatment, continuous positive airway pressure (CPAP), has been shown to lower daytime and nighttime BP levels (Bazzano et al., 2007; Fava et al., 2014; Haentjens et al., 2007). Considering the impact of OSA on nighttime BP, individuals with a healthy daytime BP could have nocturnal HTN, , putting them at risk for poor cardiovascular health (Okabe et al., 1995; Thomas et al., 2020).

Previous research identified aldosterone, a steroid hormone, as a mediator of the association between OSA severity and treatment-resistant HTN (Gonzaga et al., 2010; Pratt-Ubunama et al., 2007). Aldosterone is believed to increase fluid accumulation in the upper airway via increased sodium retention, which may in turn increase OSA severity (Florczak et al., 2013; Sim et al., 2011). Spironolactone, an aldosterone antagonist and diuretic used to treat HTN, has been shown to reduce OSA severity (Gaddam et al., 2010). Furthermore, high levels of urinary sodium have been associated with OSA severity in patients with RHTN (Pimenta et al., 2013). This is especially important for Black individuals with OSA and nocturnal HTN because they may be more salt-sensitive compared to White individuals (Pilic et al., 2016). A growing body of evidence suggests that dietary sodium restriction is effective in reducing both daytime and nighttime BP; however, it is unclear whether these modest antihypertensive effects can be produced in patients with RHTN or nocturnal HTN (Cutler et al., 1997; Law et al., 1991; Midgley et al., 1996). Dietary sodium may play a key role in the association between OSA and nocturnal HTN.

OSA and Dietary Sodium

High dietary sodium has been proposed as a contributor to increased OSA severity. Previous work established an association between dietary sodium intake and OSA severity in normo- and hypertensive individuals. Dietary sodium intake has been positively associated with OSA severity among patients with congestive heart failure (CHF). Based on food record entries, CHF patients who also had OSA consumed significantly more sodium (3.0 ± 1.3 g/day) than patients without OSA (1.9 ± 0.8 g/day; (Kasai et al., 2011). OSA severity and dietary sodium intake has also been associated in

individuals with RHTN. Participants provided 24-hour urine samples while completing overnight polysomnography and maintaining their typical diet. In this sample, approximately 77% of participants had OSA and 28% had hyperaldosteronism. Dietary sodium was a significant predictor of OSA severity in individuals with hyperaldosteronism, suggesting an important role for dietary sodium in OSA severity and a potential interaction with aldosterone (Pimenta et al., 2013). In a larger sample (n=1,946), participants with HTN had higher levels of sodium excretion compared to participants without HTN, regardless of OSA history. Sodium excretion was also significantly associated with OSA in participants with HTN, with OSA severity increasing as the grams of sodium intake increased. Further, these results suggest that dietary sodium intake may primarily contribute to OSA severity in cases of high sodium intake (Giatti et al., 2021). Taken together, these findings support dietary sodium restriction as a supplemental treatment recommendation to reduce OSA severity patients with hypertension. While CPAP is considered the gold standard and first-line treatment for OSA, there has been minimal improvement in improving adherence rates and the literature suggests that these rates are lowest among people of color (May & Billings, 2022; Rotenberg et al., 2016). This is even more reason to explore additional treatment options for OSA.

Dietary Sodium Restriction

Dietary sodium restriction has been consistently found to reduce BP, albeit modestly as described in meta-analytic studies (Cutler et al., 1997; Law et al., 1991; Midgley et al., 1996). In a study by Pimenta et al (2009), participants were recruited from the UAB Hypertension Clinic into a randomized crossover feeding trial to assess the

effects of dietary sodium restriction on BP. Participants were randomly assigned to eat a high (6.0 g/day) and low (1.5 g/day) sodium diet for 7 days and were evaluated at the beginning and end of each dietary period. Low sodium meals were provided to participants to eat at home and participants received sodium chloride (NaCl) tablets to supplement home meals to reach the desired salt intake (6g/day) for the high sodium diet condition. Participants exhibited decreases in daytime clinic systolic BP (23 mmHg) and diastolic BP (10 mmHg) as well as 24-hour BP (20/10 mmHg) after adhering to the low sodium diet (Pimenta et al., 2009). Only one study has been published examining the effect of dietary sodium restriction on OSA severity. Men with severe OSA were randomized to complete one week of either diuretic treatment, sodium restriction plus placebo pill or the placebo pill only. Both intervention groups experienced significant reductions in OSA severity, but the largest reduction was seen in the dietary sodium group (Fiori et al., 2018). Previous studies have mainly focused on the impact of dietary sodium restriction on BP and suggest that dietary sodium restriction decreases BP. There is some evidence to suggest that dietary sodium restriction also reduces OSA severity, perhaps most effectively in patients with high sodium intake, those who are salt-sensitive, or those with severe OSA. The current study provides novel information about the potential therapeutic effects of dietary sodium restriction in adults with nocturnal HTN.

SPECIFIC AIMS

AIM 1: To determine the effect of dietary sodium restriction on OSA severity using an intent-to-treat statistical approach.

Hypothesis 1.1: Dietary sodium restriction will significantly reduce obstructive sleep apnea severity. There will be a greater mean difference between pre- and post-diet AHI after completing the low sodium diet (1.5 g/day) compared to the high sodium diet (6.0 g/day).

Hypothesis 1.2: Male participants will have significantly higher reductions in obstructive sleep apnea severity as a result of dietary sodium restriction compared to female participants. There will be a greater mean difference between pre- and post-diet AHI after completing the low sodium diet (1.5 g/day) among male participants compared to female participants.

Hypothesis 1.3: Black participants will have significantly higher reductions obstructive sleep apnea severity because of dietary sodium restriction than White participants. Due to higher salt sensitivity, Black participants will display significantly larger reductions in AHI after completing the low sodium diet compared to White participants.

AIM 2: To determine the effect of dietary sodium restriction on OSA severity using a per protocol (PP) statistical approach.

Hypothesis 2.1: Dietary sodium restriction will significantly reduce obstructive sleep apnea severity. There will be a greater mean difference between pre- and

post-diet AHI after completing the low sodium diet (1.5 g/day) compared to the high sodium diet (6.0 g/day).

Hypothesis 2.2: Male participants will have significantly higher reductions in obstructive sleep apnea severity as a result of dietary sodium restriction compared to female participants. There will be a greater mean difference between pre- and post-diet AHI after completing the low sodium diet (1.5 g/day) among male participants compared to female participants.

Hypothesis 2.3: Black participants will have significantly higher reductions obstructive sleep apnea severity because of dietary sodium restriction than White participants. Due to higher salt sensitivity, Black participants will display significantly larger reductions in AHI after completing the low sodium diet compared to White participants.

METHODS

Participants

Participants were recruited from the Coronary Artery Risk Development in Young Adults (CARDIA) ABPM ancillary study, which consisted of 700 Black and White adults who completed ABPM and actigraphy monitoring. The CARDIA study examines the determinants of cardiovascular disease and lifestyle factors associated with increased CVD risk in 4 sites across the country (Friedman et al., 1988). Eligible participants included men and women from the Birmingham field center who were between the ages of 48-60 years old, presented with nocturnal hypertension identified during the ABPM ancillary study, had clinic BP less than 160/100 mmHg, and BMI between 18.5-39.0 kg/m^2. Participants with illnesses that affect nocturnal BP levels were excluded, including people with coronary artery disease, chronic kidney disease, congestive heart failure, diabetes, chronic obstructive pulmonary disease, and chronic insomnia. Participants who took medications that affect BP levels (e.g., nonsteroidal anti-inflammatory drugs, steroids and/or stimulants), consumed specialized diets (e.g., vegetarian, vegan, etc.) or were treating OSA with CPAP or other oral devices were also excluded. Eligible CARDIA participants were contacted via phone and provided an overview of the study. Participants who were interested were then seen at the UAB Hypertension Clinic to provide a detailed explanation of the study protocol before providing written informed consent.

Study Procedures

The study protocol consisted of a randomized, crossover feeding trial previously performed by Pimenta et al. (2009). Upon study enrollment, participants were randomly assigned to either a high (6.0 g/day) or low (1.5 g/day) sodium diet for 7 days, followed by a 4-week washout period, then crossed over to the second diet. Random assignment was generated using the permuted block technique and was stratified by race to balance groups. Once assigned to a dietary group, participants received their respective meals and snacks created in the Metabolic Kitchen housed in the UAB Clinical Research Unit (CRU). The diets differed only on sodium content (1.5 g/day or 6.0 g/day) and consisted of macronutrients that reflect the typical American diet. In either dietary group, each participant received a 2,000- or 2,500-calorie diet depending on their caloric intake. Caloric intake was estimated based on body weight, height, and age. Participants picked up food every 3 to 4 days and met with a CRU research nutritionist to address dietary issues and emphasize adherence. Dietary adherence was assessed by both food diary and 24-hour urinary sodium excretion. Food diaries were reviewed at time of meal pickup, so that CRU nutritionists could assist in overcoming barriers to adherence if indicated. Participants completed a total of 4 assessments, one at the beginning and end of each dietary period. Pre- and post-diet assessments included home sleep test (HST) monitoring to assess OSA severity, ABPM to capture 24-hour BP, clinic BP, and 24-hour urine collection to measure sodium excretion.

Measures

Participants underwent pre- (day zero) and post-diet (day seven) assessments for each dietary period for a total of four assessment timepoints including all measures described below. Clinic BP was measured at the UAB Hypertension Clinic, and the following measures were completed at home: 24-hour urine collection, HST, and ABPM. Research staff demonstrated how to operate devices and collect samples and provided written instructions to each participant to take home. Research staff were available after hours to address participant questions or concerns. Participants returned samples to the UAB Hypertension Clinic.

Dietary Sodium. 24-hr urine samples were collected to measure sodium excretion and determine diet adherence, as over 95% of sodium consumed is excreted through the kidneys (Bates, 1997; Lucko et al., 2018). Participants were provided a container by research staff and instructed to begin the timed urine collection after the first morning void and record the start and end times. Adequate adherence was defined as urinary sodium excretion within ±20% of the daily dietary sodium content (either 1.5 g/day or 6.0 g/day). Samples were submitted to Mayo Clinic Laboratories to complete biochemical assays (Rochester, MN). Remaining samples were stored at -80ºC for future use. Urinary creatinine excretion was also measured as a control for incomplete collections and to calculate the standardized sodium-to-creatinine ratio (Corder et al., 2018),

Obstructive Sleep Apnea Severity. OSA severity was measured at the beginning and end of each diet using a HST device (Resmed ApneaLink). Research staff

demonstrated how to operate the HST, watched the participant apply the device for verification and provided written instructions to take home and a link to an online video demonstrating the device's use. The Resmed ApneaLink is a 5-channel (snoring, nasal airflow, oxygen saturation, respiratory effort, and heart rate) portable device that has been validated against laboratory-based polysomnography (Erman et al., 2007). An apneic event was defined as ≥10 seconds of no airflow. A hypopneic event was defined as an airflow reduction of ≥ 30% and a reduction in oxygen saturation of ≥ 4%. OSA severity was measured by the apnea hypopnea index (AHI), which was determined by calculating the average respiratory events (apneic and hypopneic) per hour. Results of the HST were manually checked and validated by a certified sleep technician and a board-certified sleep specialist. Inadequate HST recordings required participants to repeat the HST.

Ambulatory Blood Pressure. Ambulatory BP was measured using the SpaceLabs 90207 monitor over a 24-hour period (Cates, 1990; O'Brien et al., 1991). Research staff first measured the circumference of each participant's nondominant arm between the acromion and olecranon to determine the appropriate cuff size, placed the cuff on the participant's arm, and then initialized the SpaceLabs monitor to measure BP every 30 minutes. A verification reading was then performed to ensure proper functioning of the device. The monitor alerts the participants of an upcoming BP reading with a sharp tone to allow the participant time to maintain a still position with his/her arm rested in a neutral position. Alerting tones were programmed to be silenced based on each participant's typical sleep-wake schedule. Participants were informed about failed BP

readings and were provided with contact information in the event of a question of problem with the ABPM device.

Clinic Blood Pressure. Clinic BP was measured at the UAB Hypertension Clinic. Participants were seated quietly for at least five minutes before the first BP reading. A BP cuff was placed on the participants' nondominant arm between the acromion and olecranon to get an accurate reading. BP was measured three times and clinic BP was obtained from the average of the last 2 readings.

Statistical Analyses

Analyses were performed in Microsoft Excel, SPSS 29.0 and GraphPad Prism 9.0. The dataset was initially inspected for missing values and outliers in the variables of interest. Change in AHI was the primary outcome in Aim 1 and 2 analyses. Aim 1 analyses were performed according to the intent-to-treat (ITT) principle, which allows for analysis of data from all participants randomized into the study, regardless of adherence to treatment, treatment deviations, or participant withdrawal (Fisher et al., 2017). ITT is advantageous in preserving sample size and providing an unbiased estimate of treatment effect; however the estimate of treatment effect is likely unrealistic due to inclusion of participants who either did not complete the study or were not adherent to the prescribed treatment (Heritier et al., 2003; Montori & Guyatt, 2001; Wertz, 1995) (D'Agostino Sr et al., 2003; Matilde Sanchez & Chen, 2006; Sainani, 2010). Aim 2 analyses were subsequently performed as PP analyses, which only includes a subset of the originally

randomized sample and excludes participants who were non-compliant to the prescribed treatment (Matilde Sanchez & Chen, 2006).

ITT analyses were performed as outlined by Wellek and Blettner (2012). A preliminary *t*-test for independent samples were performed to test the assumption of a negligible carryover effect from diet period 1 to diet period 2. Participants' OSA severity (AHI) was measured pre- and post-diet. Carryover effect was determined using a t-test of independent samples to compare the mean within-subject sums of AHI values for participants in both diet sequence groups (High/Low and Low/High). The T statistic for carryover effect is calculated according to the standard formula used for independent samples t-test; however, within-subject sums of AHI include both the pre- and post-diet AHI values. The formula to calculate carryover effect can also be found in Wellek and Blettner (2012). If the test to assess carryover effect were found to be significant, then the classic test to determine treatment effect would not be performed. A second *t*-test for independent samples was then performed using the full dataset to determine treatment effect of low and high sodium diets on OSA severity. Treatment (diet) effect was determined by comparing the mean within-subject difference of the differences in AHI values after each diet period. The formula to calculate the T statistic for diet effect is the same as described above with the exception of calculating mean within-subject differences instead of sums (Wellek & Blettner). A sensitivity analysis was then conducted to examine the impact of HST evaluation duration. Another t-test of independent samples was performed using only participants with sufficient (≥4 hour) HST recordings.

In Aim 2 (PP analysis), only participants who were adherent to low- and high-sodium diets were included in analyses. Participants were considered adherent if their 24-hour urinary sodium values were within 20% of the expected sodium excretion for either the low (1.5 g/day) or high (6.0 g/day) sodium diets. *T*-tests for independent samples were again performed as described above to determine carryover and treatment effects.

RESULTS

Baseline Characteristics

A total of 59 adults with nocturnal HTN were recruited from the UAB Hypertension Center, including 19 Black men (32%), 22 Black women (38%), 12 White men (20%) and 6 White women (10%). Mean age was 58.0 ± 1.0 years old. White women were underrepresented in this sample, which is consistent with low risk and prevalence of nocturnal HTN in this population (Booth et al., 2019). After randomization, 28 participants (14 men, 14 women) were assigned to the High/Low diet sequence and 31 participants (16 men, 15 women) were assigned to the Low/High diet sequence. A total of six participants (three in each randomized diet sequence) either withdrew from the study or did not complete at least one pre- or post-diet HST recording. Baseline characteristics are presented in Table 1. Overall mean clinic BP at baseline was 133/80 mm Hg. Participants had an overall mean 24-hour BP of 133/81 mm Hg, daytime BP of 137/84 mm Hg and nighttime BP of 125/75 mm Hg. The mean overall AHI score was 12.2 ± 2.62. Both groups were similar in all baseline characteristics except for 24-hour and nighttime diastolic blood pressure (see **Table 1**).

Table 1. Baseline Characteristics

Characteristics	High-Low (N=28)	Low-High (N=31)	p-value
Male, %	14, 50%	16, 52%	.76
Age	58.7 ± 6.0	57.3 ± 7.1	.28
Black, %	18, 64%	22, 71%	.96
BMI, kg/m^2	30.5 ± 4.9	29.4 ± 5.0	.37
AHI	14.0 ± 14.6	10.3 ± 12.9	.63
HST evaluation duration	353.8 ± 137.2	311.9 ± 138.4	.65
Urinary sodium:creatinine	0.1 ± 0.0	0.1 ± 0.0	.15
Clinic Blood Pressure			
Systolic	131.0 ± 11.9	134.5 ± 17.6	.95
Diastolic	78.3 ± 6.7	82.6 ± 10.3	.10
Ambulatory Blood Pressure			
24-Hour Systolic	132.3 ± 13.6	132.8 ± 17.4	.96
24-Hour Diastolic	78.7 ± 7.3	82.4 ± 9.5	.03*
Daytime Systolic	136.1 ± 14.0	136.9 ± 18.7	.05
Daytime Diastolic	81.5 ± 7.6	85.8 ± 10.7	.91
Nighttime Systolic	125.1 ± 15.1	124.6 ± 15.8	.93
Nighttime Diastolic	73.4 ± 9.1	75.6 ± 9.1	.04*

Values represented as mean ± standard deviation for continuous variables. Categorical variables represented as total, percentage. Asterisk indicates significance at $p < .05$.

Effect of Dietary Sodium on Obstructive Sleep Apnea using Intent-to-Treat Approach

Overall, the 4-week washout period was sufficient wherein there was no carryover effect among the total sample, $t(58)$ =0.302, p=.764. There was also no diet effect in that dietary sodium restriction did not significantly change OSA severity (see **Figure 1**), $t(58)$ =0.058, p =.954. The full dataset was then stratified by race and sex. Again, there was no carryover effect among Black and White participants, $t(40)$ = -0.637, p =.528; $t(18)$ =0.761, p =.458. There was also no diet effect in either Black or White participants, $t(40)$

= 0.362, p =.719; $t(18)$ = -0.015, p =.988. Lastly, there was no diet effect in male or female participants, $t(30)$ = -0.005, p =.996; $t(26)$ = 0.984, p =.716.

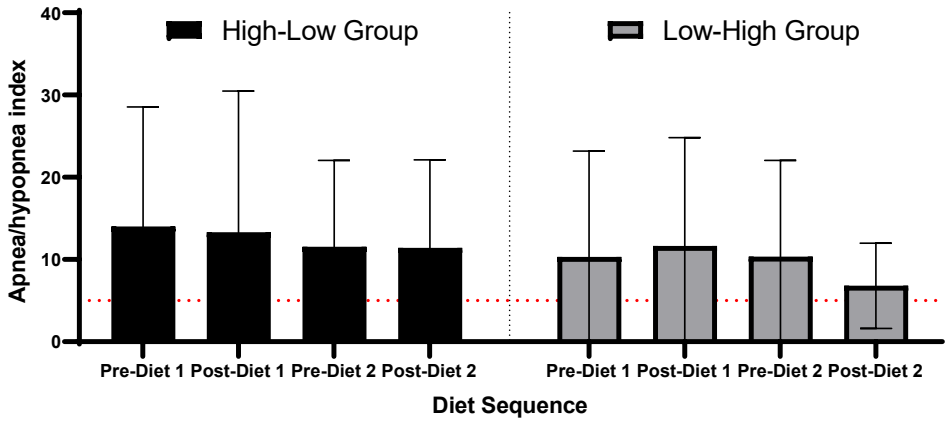

Figure 1. Dietary sodium restriction did not significantly affect OSA severity. OSA severity (AHI) was assessed by home sleep test before and after each diet condition (high or low sodium). Independent samples t-test revealed no significant difference in change between pre- and post-AHIs. Bars represent mean AHI with standard deviation. Red dashed line indicates OSA diagnostic threshold (AHI ≥ 5).

Table 2. Values during Low- and High-Salt Diets

High-Low Group (N=28)				
Values	**Pre-High Salt Diet**	**Post-High Salt Diet**	**Pre-Low Salt Diet**	**Post-Low Salt Diet**
Weight, lbs	201.4 ± 36.6	195.2 ± 42.3	199.6 ± 37.0	197.6 ± 35.4
BMI, kg/m^2	30.5 ± 4.9	30.2 ± 4.7	30.2 ± 4.9	29.9 ± 4.7
AHI	14.0 ± 14.6	13.3 ± 17.2	11.6 ± 10.5	11.4 ± 10.7
Serum sodium, mmol/L	138.8 ± 2.4	138.7 ± 2.5	139.4 ± 3.3	137.2 ± 3.9
Urinary sodium, mEq/L/day	160.0 ±71.0	186.7 ± 74.2	173.36 ± 116.83	95.14 ± 61.03
Urinary creatinine, mg/day	1599.6 ± 527.5	1776.6 ± 68.6	1792.6 ± 723.0	1752.0 ± 547.5
Ratio of sodium:creatinine	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1
Clinic SBP, mmHg	131.0 ± 11.9	127.8 ± 14.3	128.2 ± 13.4	125.3 ± 14.0
Clinic DBP, mmHg	78.3 ± 6.7	76.3 ± 8.5	77.2 ± 7.3	76.4 ± 8.0
Daytime SBP	136.1 ± 14.0	130.4 ± 14.7	131.2 ± 14.0	126.0 ± 14.1
Daytime DBP	81.5 ± 7.6	78.4 ± 7.2	79.3 ± 9.0	78.1 ± 7.7
Nighttime SBP	125.1 ± 15.2	119.0 ± 17.0	120.5 ± 16.8	115.5 ± 13.8
Nighttime DBP	73.4 ± 9.2	69.2 ± 9.2	70.2 ± 9.8	68.6 ± 9.6
Mean 24-hr SBP	13.3 ± 13.6	126.5 ± 14.5	127.7 ± 14.4	122.4 ± 13.3
Mean 24-hr DBP	78.7 ±7.3	75.4 ± 6.7	76.4 ± 8.7	74.7 ± 8.1
Low-High Group (N=31)				
Values	**Pre-Low Salt Diet**	**Post-Low Salt Diet**	**Pre-High Salt Diet**	**Post-Low Salt Diet**
Weight, lbs	188.4 ± 36.9	186.0 ± 35.4	186.1 ± 36.6	186.1 ± 37.2
BMI, kg/m^2	29.4 ± 5.0	29.0 ± 4.9	29.2 ± 5.1	29.0 ± 5.0
AHI	10.3 ± 12.9	11.6 ± 13.2	10.4 ± 11.7	6.8 ± 5.2
Serum sodium, mmol/L	139.4 ± 3.7	137.7 ± 2.6	138.9 ± 2.2	139.1 ± 1.7
Urinary sodium, mEq/L/day	134.3 ± 73.9	83.6 ± 32.6	145.6 ± 87.0	182.2 ± 99.9
Urinary creatinine, mg/day	1674.5 ± 677.5	1903.5 ± 878.0	1703.4 ± 672.24	1627.6 ± 632.8
Ratio of sodium:creatinine	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.1
Clinic SBP, mmHg	134.5 ± 17.7	127.9 ± 13.4	135.0 ± 15.7	134.7 ± 14.6
Clinic DBP, mmHg	82.6 ± 10.3	80.1 ± 7.8	84.0 ± 8.4	83.6 ± 7.4
Daytime SBP	136.9 ± 18.7	131.3 ± 15.8	134.5 ± 16.1	139.5 ± 14.0
Daytime DBP	85.8 ± 10.7	83.4 ± 9.1	84.1 ± 9.3	87.0 ± 8.4
Nighttime SBP	124.6 ± 15.8	119.2 ± 12.8	123.9 ± 17.0	130.0 ± 17.0
Nighttime DBP	75.6 ± 9.1	74.3 ± 7.7	75.5 ± 8.1	79.1 ± 9.1
Mean 24-hr SBP	132.8 ± 17.4	127.2 ± 14.3	130.8 ± 16.2	136.4 ± 14.3
Mean 24-hr DBP	82.4 ± 10.0	80.2 ± 8.2	81.1 ± 8.7	84.4 ± 8.4

BMI: body mass index; AHI: apnea/hypopnea index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Values represented as mean ± standard deviation.

Sensitivity Analyses

Sensitivity analyses were conducted to determine the impact of invalid HST recordings by reducing the sample size to include only participants with HST recordings with at least 4 hours of valid oximetry and air flow recording. HST recording time varied widely ranging from 0.00 to 11.12 hours and an overall average of 5.7 ± 0.2 hours. There were 27 participants (47% of total sample) with invalid HST recordings; 13 participants belonged to the high/low diet sequence and 14 participants belonged to the low/high diet sequence. Sensitivity analyses included the remaining 31 participants (see **Appendix Table 1** for baseline characteristics). There was no carryover effect among the 31 participants, $t(46) = 1.944$, $p = .058$. Again, there was no significant diet effect on OSA severity among participants with valid HST recordings, $t(46) = 0.096$, $p = .923$ (see **Figure 2**). The reduced dataset was stratified by race and sex. There were no diet effects among Black and White participants, $t(30) = 0.380$, $p = .790$; $t(16) = -0.110$, $p = .914$. Similarly, there were no significant diet effects among male and female participants, $t(23) = -0.142$, $p = .888$, $t(23) = 0.421$, $p = .678$. See **Appendix Table 2** for table of values before and after high and low salt diets.

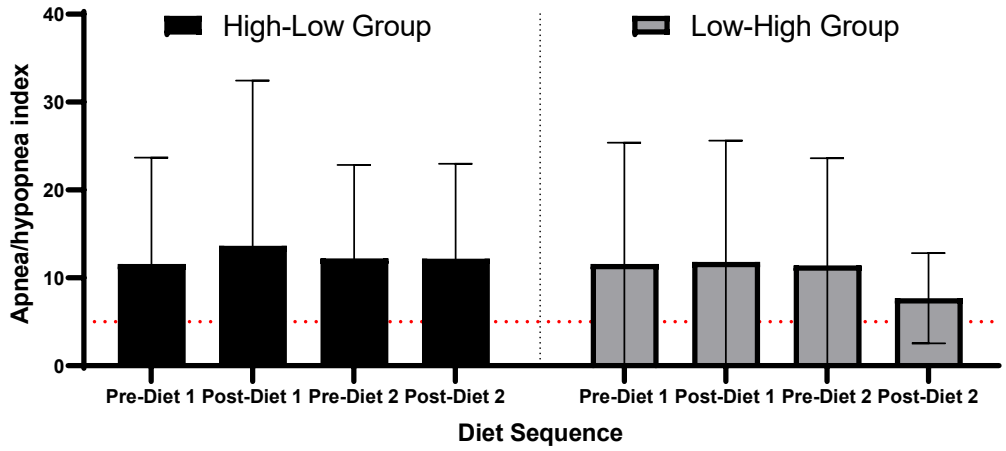

Figure 2. Home sleep testing duration did not influence diet effect on OSA severity. Sensitivity analysis was performed in reduced sample set including only participants with HST duration of 4 hours of longer. Again, no significant diet effect was detected using independent samples t-test. Bars represent mean AHI with standard deviation. Red dashed line indicates OSA diagnostic threshold (AHI ≥ 5).

Effect of Dietary Sodium on Obstructive Sleep Apnea using Per Protocol Approach

Dietary adherence was determined by calculating the expected sodium excretion value per diet condition and setting a range within 10, 15, or 20% of those values. The expected urinary excretion of the high sodium diet was 5.7 grams (5,700 milligrams) and 1.4 grams (1,425 milligrams) for the low sodium diet. Results are based on being within 20% of the expected sodium excretion values. In total, 21 participants were adherent to the high sodium diet and 16 were adherent to the low sodium diet between the two randomized groups. Only 5 participants were considered adherent to both high and low sodium diet conditions. Post hoc power analysis indicated that the reduced sample had only 29% statistical power to detect a moderate effect of diet on sleep apnea severity. Despite this, independent samples t-tests were performed to determine carryover and diet effect. There was no significant carryover effect among diet-adherent participants $t(19) = 1.10$, $p = .284$. There was no significant diet effect in OSA severity among diet-adherent

participants, *t(19)* = 0.045, p = .965 (see **Figure 3**). Due to the small number of participants who were adherent in both diet conditions, the sample was not further stratified by race or sex.

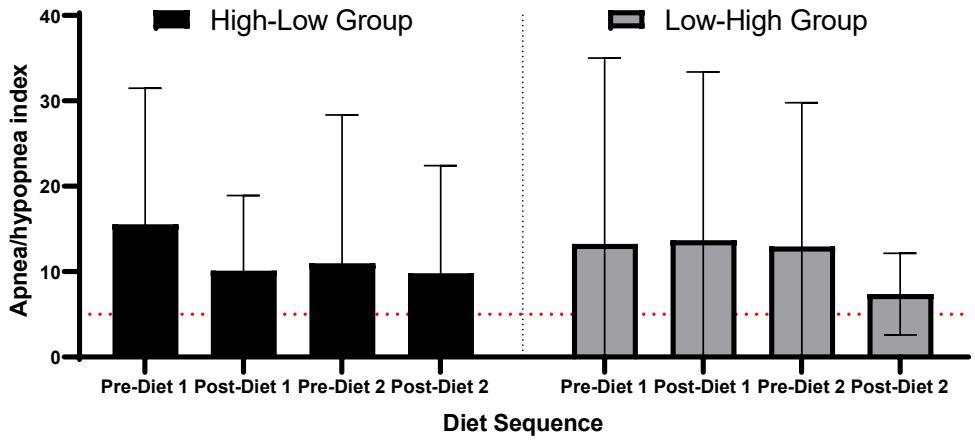

Figure 3. Dietary sodium restriction did not significantly improve OSA severity among adherent participants. Independent samples t-test revealed no significant change in pre- and post-diet AHIs among a small subset of participants considered to be adherent to the high- and low-sodium diet. Bars represent mean AHI with standard deviation. Red dashed line indicates OSA diagnostic threshold (AHI ≥ 5).

DISCUSSION

This is the first study to examine the effect of dietary sodium restriction on OSA severity using a randomized crossover design. Analyses were performed using both the ITT and PP statistical approach to examine the impact of a dietary intervention on OSA severity under both realistic and ideal conditions. In the current study, dietary sodium restriction did not significantly reduce sleep apnea severity in participants with nocturnal HTN regardless of race, biological sex, or dietary adherence. Although the overall mean HST evaluation duration was 344.4 ± 13.3 minutes (5.7 hours), almost half (47%) of participants' recording was less than 4 hours. Sensitivity analysis revealed that HST evaluation duration did not substantially change the effect of dietary sodium restriction on participants' OSA severity. Participants also demonstrated difficulty adhering to the diet conditions, particularly the low sodium condition (1.5 grams sodium). Even among the remaining subset of adherent participants, there was not a significant effect of dietary sodium restriction on OSA severity.

The findings overall suggest that dietary sodium restriction does not significantly reduce OSA severity. Statistical analyses presented here were performed in parallel with Dr. Lloyd Edwards and produced consistent results. This study is one of few to examine the effect of dietary sodium restriction on OSA severity in adults with nocturnal HTN and had several strengths. Participants served as their own control by undergoing both diet conditions, which eliminates confounding variables related to individual differences and reduces sample size needed to achieve adequate statistical power (Wellek & Blettner).

This study was also derived from a large longitudinal study that included both Black and White adults. Importantly, this study filled a gap in the literature examining the effect of sodium on OSA severity in a sample of adults with nocturnal HTN. Previous studies focused primarily on BP, which is closely linked to OSA.

The ITT approach used in Aim 1 provided insight into the effect of dietary sodium restriction on OSA severity in adults with nocturnal HTN. There was no significant diet effect observed; however, there was still a possibility that the diet effect was masked due to non-adherence by participants included in the original analyses. The PP approach taken in Aim 2 reflected the effect of dietary sodium under ideal conditions; however, many participants committed protocol violations and removing non-adherent participants severely reduced statistical power. It is also worth noting that after removing non-adherent participants, the balance among groups due to randomization may have been lost and could influence overall results (Tripepi et al., 2020). Despite removing non-adherent participants from the analysis, there was still no significant effect of dietary sodium restriction on OSA severity detected.

The finding that dietary sodium restriction did not significantly affect OSA severity is consistent with a recent study that suggests dietary sodium may contribute to OSA severity in a limited context, specifically when salt intake is excessive or in the presence of hypertension. There was no association between sleep apnea and urinary sodium excretion in the overall sample of over 1,000 adults (Giatti et al., 2021). The only study to demonstrate the ability to reduce OSA severity using dietary sodium restriction was performed in men with severe (AHI $\geq$ 30) sleep apnea. In this case, both 7-day interventions (diuretic and dietary sodium restriction) significantly decreased sleep apnea,

suggesting that fluid retention reduction is a potential therapeutic strategy to treat severe OSA in men (Fiori et al., 2018). Our sample included both men and women, which may have contributed to differences in results. It's also important to note that the discrepancy between improved OSA severity reported by Fiori et al (2018) and null findings in the current study may be due to the initial OSA severity of participants in each study. All participants in the former study had severe OSA (AHI ≥ 30); whereas the AHI of most participants in the current study fell within the mild range (AHI 5-15).

Sodium restriction may still be beneficial for sleep apnea management despite our lack of significant results. Although sodium intake is traditionally linked to blood pressure, it has also been associated with weight or obesity (Allison, 2018; Lanaspa et al., 2018; Ma et al., 2015; Zhou et al., 2019). Two theorized explanations for this association is that increased salt intake may lead to increased consumption of sweetened beverages or energy intake (Grimes et al., 2013; He et al., 2008). A cross-sectional study measuring salt intake from urinary sodium excretion found an association between salt intake and independent of energy intake and consumption of sweet beverages (Ma et al., 2015). Excess weight greatly contributes to OSA pathology, has been identified as a predictor of sleep-disordered breathing in large population studies and is proportionately associated with OSA severity (Pillar & Shehadeh, 2008). Weight loss has been demonstrated to improve OSA severity and a loss of 7-11% has been recommended to yield clinically significant benefits (Garvey et al., 2014). Weight loss for OSA management may be beneficial for comorbidities as well and growing literature suggests that dietary sodium restriction may indirectly facilitate this (Tham et al., 2019).

The current study's most significant methodological limitations involve the device used to assess OSA severity. The ResMed ApneaLink Air device used in the current study did not measure sleeping body position. Literature dating back at least 20 years have consistently reported an association between the supine position (lying flat on one's back) and more severe OSA in adults (Menon & Kumar, 2013). Without recording body position during sleep, it is unclear whether participants maintained the same position during all four HST recordings. Although there was no significant diet effect in our sample, it is still possible that differences in body position between pre- and post-diet assessment may have contributed to changes in OSA severity. While participants could have been asked to report either habitual sleeping body position or record their body position during each HST, self-report of sleeping body position during sleep has been shown to be unreliable (Russo & Bianchi, 2016). Sleep stages also contribute to variability in OSA severity (Carberry et al., 2015). OSA is more severe during rapid eye movement (REM) sleep and apneic or hypopneic events can be more prevalent during REM sleep (Cartwright et al., 1991; Haba-Rubio et al., 2005). Future studies that involve examining changes in OSA severity are strongly encouraged to use devices that measure sleeping body position if polysomnography will not be used; however, polysomnography is preferential to rule out significant changes in sleep architecture.

HST recording duration in our sample varied widely among participants, spanning from 0 to 11 hours. Participants were given a live demonstration of how to apply and operate the Resmed device and asked to repeat the demonstration in office, consistent with recent recommendations on optimizing HST use in research (Miller et al., 2018). Short evaluation duration despite hands on instruction suggests compromised fidelity to

the research protocol by research staff and/or user error. It is possible that research staff considered increased risk of participant burnout or attrition and prioritized participant retention instead of requiring repeat HST recordings. It would also be difficult logistically to repeat pre-diet HST once the participant has already begun the diet condition. Previous randomized controlled trials (RCTs) evaluating the diagnostic accuracy of HST have used a minimum duration of 4 hours; however other studies have found that using HST with 2 or 3 recording duration did not significantly compromise accuracy (Berry et al., 2008; Kuna et al., 2011; Rosen et al., 2012; Skomro et al., 2010). Less than half of the total sample recorded at least 4 hours of valid data. It is possible that these methodological flaws influenced results because we were unable to fully capture OSA severity throughout an entire night of sleep. These are especially important to consider if only one night of HST evaluations will be used to determine changes in OSA severity.

Low diet adherence was also a major limitation in the present study. Less than half of the enrolled participants were adherent to either the high or low sodium diets despite being provided meals and supplements and having to complete food diaries. Adhering to the low sodium diet (1.5 grams sodium) appeared to be more difficult than adhering to the high sodium diet. This is consistent with the literature on salt consumption in the U.S. Sodium intake estimations based on 24-hour urine collection in a nationally representative study including over 800 adults revealed an estimated mean sodium intake of 4,000 mg/day (Cogswell et al., 2018). Another large study assessing sodium intake trends in the United States provided similar amounts (3232 mg/day), with differences among sex, race, and chronic disease groups (Brouillard et al., 2019). It is

estimated that approximately 10% of American adults consume dietary sodium consistent with recommendations from the World Health Organization, so it highly likely that a substantial number of participants consume an excessive amount of sodium in their daily diet (Bailey et al., 2016). The low sodium diet may have been too intense for participants to maintain for seven days, and diet adherence may have been higher if the low sodium condition was set to 3 g/day like the study conducted by Fiori et al (2018). Poor diet adherence made it difficult to observe any diet effect that may have been present and further, may suggest that a real-world intervention with this prescribed sodium intake would be unsuccessful in a similar demographic. Although the average salt intake of the participants in the current study was consistent with nationwide salt intake estimates based on 24-urine collection, it should be noted that there may be substantial variability in sodium excretion values taken from a single 24-hour collection. Repeated, consecutive 24-hour urine collections (ex. three or seven days) increase the accuracy of identifying changes in salt intake; therefore, relying on a single collection in the current study may have limited our ability to monitor changes in urinary sodium excretion (Lerchl et al., 2015). Our findings suggest that dietary sodium restriction is most effective in the setting of high sodium intake and/or severe OSA.

CONCLUSION

In summary, our findings suggest that dietary sodium restriction is not an effective intervention on its own to reduce OSA severity in adults with nocturnal HTN. This was the first randomized crossover design study used to investigate the effect of sodium restriction on OSA severity in adults with nocturnal HTN. The present study aimed to examine these effects using both ITT and PP approaches to understand whether non-adherence influenced observed changes in OSA severity in preliminary analyses. Despite null results, the relationship between dietary sodium and OSA warrant further investigation to better understand under what circumstances this intervention might be beneficial. It's also important to note that these results should be considered with the limitations of the study (HST device, HST duration, and poor adherence). Together these factors may have negatively impacted the sample and prevented observation of a diet effect with even a large effect size. Future studies will be helpful to determine whether these factors did contribute to the present results and provide further clarity on this relationship, as literature in this area is very limited

REFERENCES

Allison, S. J. (2018). High salt intake as a driver of obesity. *Nature Reviews Nephrology*, *14*(5), 285-285.

Ancoli-Israel, S., Klauber, M. R., Stepnowsky, C., Estline, E., Chinn, A., & Fell, R. (1995). Sleep-disordered breathing in African-American elderly. *American journal of respiratory and critical care medicine*, *152*(6), 1946-1949.

Bates, C. J. (1997). Biochemical markers of nutrient intake. *Designconcepts in nutritional epidemiology*, 170-240.

Bazzano, L. A., Khan, Z., Reynolds, K., & He, J. (2007). Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*, *50*(2), 417-423.

Berry, R. B., Hill, G., Thompson, L., & McLaurin, V. (2008). Portable monitoring and autotitration versus polysomnography for the diagnosis and treatment of sleep apnea. *Sleep*, *31*(10), 1423-1431.

Boggia, J., Li, Y., Thijs, L., Hansen, T. W., Kikuya, M., Björklund-Bodegård, K., Richart, T., Ohkubo, T., Kuznetsova, T., & Torp-Pedersen, C. (2007). Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *The Lancet*, *370*(9594), 1219-1229.

Booth, J. N., Anstey, D. E., Bello, N. A., Jaeger, B. C., Pugliese, D. N., Thomas, S. J., Deng, L., Shikany, J. M., Lloyd-Jones, D., & Schwartz, J. E. (2019). Race and sex differences in asleep blood pressure: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *The Journal of Clinical Hypertension*, *21*(2), 184-192.

Brouillard, A. M., Kraja, A. T., & Rich, M. W. (2019). Trends in dietary sodium intake in the United States and the impact of USDA guidelines: NHANES 1999-2016. *The American journal of medicine*, *132*(10), 1199-1206. e1195.

Carberry, J. C., Hensen, H., Fisher, L. P., Saboisky, J. P., Butler, J. E., Gandevia, S. C., & Eckert, D. J. (2015). Mechanisms contributing to the response of upper-airway muscles to changes in airway pressure. *Journal of Applied Physiology*, *118*(10), 1221-1228.

Cartwright, R. D., Diaz, F., & Lloyd, S. (1991). The effects of sleep posture and sleep stage on apnea frequency. *Sleep*, *14*(4), 351-353.

Cates, E. (1990). A validation study of the Spacelabs 90207 ambulatory blood pressure monitor. *J ambulatory monitoring*, *3*, 149-154.

Chervin, R. D. (2000). Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest*, *118*(2), 372-379.

Coca, A. (1994). Circadian rhythm and blood pressure control: physiological and pathophysiological factors. *Journal of hypertension. Supplement: official journal of the International Society of Hypertension*, *12*(5), S13-21.

Cogswell, M. E., Loria, C. M., Terry, A. L., Zhao, L., Wang, C.-Y., Chen, T.-C., Wright, J. D., Pfeiffer, C. M., Merritt, R., Moy, C. S., & Appel, L. J. (2018). Estimated

24-Hour Urinary Sodium and Potassium Excretion in US Adults. *Jama*, *319*(12), 1209-1220. https://doi.org/10.1001/jama.2018.1156 Conen, D., & Bamberg, F. (2008). Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis. *Journal of hypertension*, *26*(7), 1290-1299.

Corder, C. J., Rathi, B. M., Sharif, S., & Leslie, S. W. (2018). 24-hour urine collection.

Cutler, J. A., Follmann, D., & Allender, P. S. (1997). Randomized trials of sodium reduction: an overview. *The American journal of clinical nutrition*, *65*(2), 643S-651S.

D'Agostino Sr, R. B., Massaro, J. M., & Sullivan, L. M. (2003). Non-inferiority trials: design concepts and issues–the encounters of academic consultants in statistics. *Statistics in medicine*, *22*(2), 169-186.

Erman, M. K., Stewart, D., Einhorn, D., Gordon, N., & Casal, E. (2007). Validation of the ApneaLink™ for the screening of sleep apnea: a novel and simple single-channel recording device. *Journal of Clinical Sleep Medicine*, *3*(4), 387-392.

Fan, H.-Q., Li, Y., Thijs, L., Hansen, T. W., Boggia, J., Kikuya, M., Björklund-Bodegård, K., Richart, T., Ohkubo, T., & Jeppesen, J. (2010). Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *Journal of hypertension*, *28*(10), 2036-2045.

Fava, C., Dorigoni, S., Dalle Vedove, F., Danese, E., Montagnana, M., Guidi, G. C., Narkiewicz, K., & Minuz, P. (2014). Effect of CPAP on blood pressure in patients with OSA/hypopnea: a systematic review and meta-analysis. *Chest*, *145*(4), 762-771.

Fiori, C. Z., Martinez, D., Montanari, C. C., Lopez, P., Camargo, R., Sezerá, L., Gonçalves, S. C., & Fuchs, F. D. (2018). Diuretic or sodium-restricted diet for obstructive sleep apnea—a randomized trial. *Sleep*, *41*(4), zsy016.

Fisher, L. D., Dixon, D. O., Herson, J., Frankowski, R. F., Hearron, M. S., & Peace, K. E. (2017). Intention to treat in clinical trials. *Statistical issues in drug research and development*, 331-350.

FLETCHER, E. C., DeBEHNKE, R. D., LOVOI, M. S., & GORIN, A. B. (1985). Undiagnosed sleep apnea in patients with essential hypertension. *Annals of internal medicine*, *103*(2), 190-195.

Florczak, E., Prejbisz, A., Szwench-Pietrasz, E., Śliwiński, P., Bieleń, P., Klisiewicz, A., Michałowska, I., Warchoł, E., Januszewicz, M., & Kała, M. (2013). Clinical characteristics of patients with resistant hypertension: the RESIST-POL study. *Journal of human hypertension*, *27*(11), 678-685.

Friedman, G. D., Cutter, G. R., Donahue, R. P., Hughes, G. H., Hulley, S. B., Jacobs Jr, D. R., Liu, K., & Savage, P. J. (1988). CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology*, *41*(11), 1105-1116.

Gaddam, K., Pimenta, E., Thomas, S. J., Cofield, S. S., Oparil, S., Harding, S. M., & Calhoun, D. A. (2010). Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *Journal of human hypertension*, *24*(8), 532-537.

Garvey, W. T., Garber, A. J., Mechanick, J. I., Bray, G. A., Dagogo-Jack, S., Einhorn, D., Grunberger, G., Handelsman, Y., Hennekens, C. H., & Hurley, D. L. (2014). American Association of Clinical Endocrinologists and American College of

Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocrine Practice*, *20*(9), 977-989.
Giatti, S., Santos, R. B., Aielo, A. N., Silva, W. A., Parise, B. K., Souza, S. P., Pio-Abreu, A., Bortolotto, L. A., Lotufo, P. A., & Bensenor, I. M. (2021). Association of Sodium with Obstructive Sleep Apnea. The ELSA-Brasil Study. *Annals of the American Thoracic Society*, *18*(3), 502-510.
Gonçalves, S. C., Martinez, D., Gus, M., de Abreu-Silva, E. O., Bertoluci, C., Dutra, I., Branchi, T., Moreira, L. B., Fuchs, S. C., & de Oliveira, A. C. T. (2007). Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest*, *132*(6), 1858-1862.
Gonzaga, C. C., Gaddam, K. K., Ahmed, M. I., Pimenta, E., Thomas, S. J., Harding, S. M., Oparil, S., Cofield, S. S., & Calhoun, D. A. (2010). Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *Journal of Clinical Sleep Medicine*, *6*(4), 363-368.
Gottlieb, D. J., & Punjabi, N. M. (2020). Diagnosis and management of obstructive sleep apnea: a review. *Jama*, *323*(14), 1389-1400.
Grimes, C. A., Riddell, L. J., Campbell, K. J., & Nowson, C. A. (2013). Dietary salt intake, sugar-sweetened beverage consumption, and obesity risk. *Pediatrics*, *131*(1), 14-21.
Haba-Rubio, J., Janssens, J.-P., Rochat, T., & Sforza, E. (2005). Rapid eye movement-related disordered breathing: clinical and polysomnographic features. *Chest*, *128*(5), 3350-3357.
Haentjens, P., Van Meerhaeghe, A., Moscariello, A., De Weerdt, S., Poppe, K., Dupont, A., & Velkeniers, B. (2007). The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. *Archives of internal medicine*, *167*(8), 757-764.
Hansen, T. W., Li, Y., Boggia, J., Thijs, L., Richart, T., & Staessen, J. A. (2011). Predictive role of the nighttime blood pressure. *Hypertension*, *57*(1), 3-10.
He, F. J., Marrero, N. M., & MacGregor, G. A. (2008). Salt intake is related to soft drink consumption in children and adolescents: a link to obesity? *Hypertension*, *51*(3), 629-634.
Heritier, S. R., Gebski, V. J., & Keech, A. C. (2003). Inclusion of patients in clinical trial analysis: the intention-to-treat principle. *Medical Journal of Australia*, *179*(8), 438-440.
Hla, K. M., Young, T. B., Bidwell, T., Palta, M., Skatrud, J. B., & Dempsey, J. (1994). Sleep apnea and hypertension: a population-based study. *Annals of internal medicine*, *120*(5), 382-388.
Johnson, D. A., Guo, N., Rueschman, M., Wang, R., Wilson, J. G., & Redline, S. (2018). Prevalence and correlates of obstructive sleep apnea among African Americans: the Jackson Heart Sleep Study. *Sleep*, *41*(10), zsy154.
Kasai, T., Arcand, J., Allard, J. P., Mak, S., Azevedo, E. R., Newton, G. E., & Bradley, T. D. (2011). Relationship between sodium intake and sleep apnea in patients with heart failure. *Journal of the American College of Cardiology*, *58*(19), 1970-1974.
Konecny, T., Kara, T., & Somers, V. K. (2014). Obstructive sleep apnea and hypertension: an update. *Hypertension*, *63*(2), 203-209.

Kuna, S. T., Gurubhagavatula, I., Maislin, G., Hin, S., Hartwig, K. C., McCloskey, S., Hachadoorian, R., Hurley, S., Gupta, R., & Staley, B. (2011). Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea. *American journal of respiratory and critical care medicine*, *183*(9), 1238-1244.

Lanaspa, M. A., Kuwabara, M., Andres-Hernando, A., Li, N., Cicerchi, C., Jensen, T., Orlicky, D. J., Roncal-Jimenez, C. A., Ishimoto, T., & Nakagawa, T. (2018). High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proceedings of the National Academy of Sciences*, *115*(12), 3138-3143.

Lavie, P., Ben-Yosef, R., & Ami-hai, E. R. (1984). Prevalence of sleep apnea syndrome among patients with essential hypertension. *American heart journal*, *108*(2), 373-376.

Law, M. R., Frost, C., & Wald, N. (1991). By how much does dietary salt reduction lower blood pressure? I--Analysis of observational data among populations. *British Medical Journal*, *302*(6780), 811-815.

Lerchl, K., Rakova, N., Dahlmann, A., Rauh, M., Goller, U., Basner, M., Dinges, D. F., Beck, L., Agureev, A., & Larina, I. (2015). Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. *Hypertension*, *66*(4), 850-857.

Logan, A. G., Perlikowski, S. M., Mente, A., Tisler, A., Tkacova, R., Niroumand, M., Leung, R. S., & Bradley, T. D. (2001). High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *Journal of hypertension*, *19*(12), 2271-2277.

Lucko, A. M., Doktorchik, C., Woodward, M., Cogswell, M., Neal, B., Rabi, D., Anderson, C., He, F. J., MacGregor, G. A., & L'Abbe, M. (2018). Percentage of ingested sodium excreted in 24-hour urine collections: a systematic review and meta-analysis. *The Journal of Clinical Hypertension*, *20*(9), 1220.

Ma, Y., He, F. J., & MacGregor, G. A. (2015). High salt intake: independent risk factor for obesity? *Hypertension*, *66*(4), 843-849.

Madhavan, S., & Alderman, M. H. (1994). Ethnicity and the relationship of sodium intake to blood pressure. *Journal of hypertension*, *12*(1), 97-103.

Mancia, G., Di Rienzo, M., & Parati, G. (1993). Ambulatory blood pressure monitoring use in hypertension research and clinical practice. *Hypertension*, *21*(4), 510-524.

Matilde Sanchez, M., & Chen, X. (2006). Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Statistics in medicine*, *25*(7), 1169-1181.

May, A. M., & Billings, M. E. (2022). Racial Differences in Positive Airway Pressure Adherence in the Treatment of Sleep Apnea. *Sleep Medicine Clinics*, *17*(4), 543-550.

Menon, A., & Kumar, M. (2013). Influence of body position on severity of obstructive sleep apnea: a systematic review. *International Scholarly Research Notices*, *2013*.

Midgley, J. P., Matthew, A. G., Greenwood, C. M. T., & Logan, A. G. (1996). Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *Jama*, *275*(20), 1590-1597.

Miller, J. N., Schulz, P., Pozehl, B., Fiedler, D., Fial, A., & Berger, A. M. (2018). Methodological strategies in using home sleep apnea testing in research and practice. *Sleep and Breathing*, *22*, 569-577.

Montori, V. M., & Guyatt, G. H. (2001). Intention-to-treat principle. *Cmaj*, *165*(10), 1339-1341.

Muxfeldt, E. S., Margallo, V. S., Guimarães, G. M., & Salles, G. F. (2014). Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. *American journal of hypertension*, *27*(8), 1069-1078.

O'Brien, E., Mee, F., Atkins, N., & O'Malley, K. (1991). Accuracy of the SpaceLabs 90207, Novacor DIASYS 200, Del Mar Avionics Pressurometer IV and Takeda TM-2420 ambulatory systems according to British and American criteria. *Journal of hypertension*, *9*, S334.

Okabe, S., Hida, W., Kikuchi, Y., Taguchi, O., Ogawa, H., Mizusawa, A., Miki, H., & Shirato, K. (1995). Role of hypoxia on increased blood pressure in patients with obstructive sleep apnoea. *Thorax*, *50*(1), 28-34.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American journal of epidemiology*, *177*(9), 1006-1014.

Pilic, L., Pedlar, C. R., & Mavrommatis, Y. (2016). Salt-sensitive hypertension: mechanisms and effects of dietary and other lifestyle factors. *Nutrition reviews*, *74*(10), 645-658.

Pillar, G., & Shehadeh, N. (2008). Abdominal Fat and Sleep Apnea: The chicken or the egg? *Diabetes care*, *31*(Supplement_2), S303-S309. https://doi.org/10.2337/dc08-s272

Pimenta, E., Gaddam, K. K., Oparil, S., Aban, I., Husain, S., Dell'Italia, L. J., & Calhoun, D. A. (2009). Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension*, *54*(3), 475-481.

Pimenta, E., Stowasser, M., Gordon, R. D., Harding, S. M., Batlouni, M., Zhang, B., Oparil, S., & Calhoun, D. A. (2013). Increased dietary sodium is related to severity of obstructive sleep apnea in patients with resistant hypertension and hyperaldosteronism. *Chest*, *143*(4), 978-983.

Pranathiageswaran, S., Badr, M. S., Severson, R., & Rowley, J. A. (2013). The influence of race on the severity of sleep disordered breathing. *Journal of Clinical Sleep Medicine*, *9*(4), 303-309.

Pratt-Ubunama, M. N., Nishizaka, M. K., Boedefeld, R. L., Cofield, S. S., Harding, S. M., & Calhoun, D. A. (2007). Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*, *131*(2), 453-459.

Punjabi, N. M. (2008). The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society*, *5*(2), 136-143.

Redline, S., Tishler, P. V., Schluchter, M., Aylor, J., Clark, K., & Graham, G. (1999). Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. *American journal of respiratory and critical care medicine*, *159*(5), 1527-1532.

Rosen, C. L., Auckley, D., Benca, R., Foldvary-Schaefer, N., Iber, C., Kapur, V., Rueschman, M., Zee, P., & Redline, S. (2012). A multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. *Sleep*, *35*(6), 757-767.

Rotenberg, B. W., Murariu, D., & Pang, K. P. (2016). Trends in CPAP adherence over twenty years of data collection: a flattened curve. *Journal of Otolaryngology-Head & Neck Surgery*, *45*, 1-9.

Rudnick, E. F., Walsh, J. S., Hampton, M. C., & Mitchell, R. B. (2007). Prevalence and ethnicity of sleep-disordered breathing and obesity in children. *Otolaryngology–Head and Neck Surgery*, *137*(6), 878-882.

Russo, K., & Bianchi, M. T. (2016). How reliable is self-reported body position during sleep? *Journal of Clinical Sleep Medicine*, *12*(1), 127-128.

Sainani, K. L. (2010). Making sense of intention-to-treat. *PM&R*, *2*(3), 209-213.

Sega, R., Facchetti, R., Bombelli, M., Cesana, G., Corrao, G., Grassi, G., & Mancia, G. (2005). Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*, *111*(14), 1777-1783.

Sim, J. J., Yan, E. H., Liu, I. L. A., Rasgon, S. A., Kalantar-Zadeh, K., Calhoun, D. A., & Derose, S. F. (2011). Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population. *Journal of hypertension*, *29*(8), 1553-1559.

Skomro, R. P., Gjevre, J., Reid, J., McNab, B., Ghosh, S., Stiles, M., Jokic, R., Ward, H., & Cotton, D. (2010). Outcomes of home-based diagnosis and treatment of obstructive sleep apnea. *Chest*, *138*(2), 257-263.

Somers, V. K., Dyken, M. E., Clary, M. P., & Abboud, F. M. (1995). Sympathetic neural mechanisms in obstructive sleep apnea. *The Journal of clinical investigation*, *96*(4), 1897-1904.

Tham, K. W., Lee, P. C., & Lim, C. H. (2019). Weight management in obstructive sleep apnea: medical and surgical options. *Sleep Medicine Clinics*, *14*(1), 143-153.

Thomas, S. J., & Calhoun, D. (2017). Sleep, insomnia, and hypertension: current findings and future directions. *Journal of the American Society of Hypertension*, *11*(2), 122-129.

Thomas, S. J., Johnson, D. A., Guo, N., Abdalla, M., Booth III, J. N., Spruill, T. M., Jackson, C. L., Yano, Y., Sims, M., & Calhoun, D. (2020). Association of obstructive sleep apnea with nighttime blood pressure in African Americans: the Jackson Heart Study. *American journal of hypertension*, *33*(10), 949-957.

Tripepi, G., Chesnaye, N. C., Dekker, F. W., Zoccali, C., & Jager, K. J. (2020). Intention to treat and per protocol analysis in clinical trials. *Nephrology*, *25*(7), 513-517.

Vanderveken, O. M., Boudewyns, A., Ni, Q., Kashyap, B., Verbraecken, J., De Backer, W., & Van de Heyning, P. (2011). Cardiovascular implications in the treatment of obstructive sleep apnea. *Journal of cardiovascular translational research*, *4*(1), 53-60.

Wellek, S., & Blettner, M. On the Proper Use of the Crossover Design in Clinical Trials.

Wertz, R. T. (1995). Intention to treat: Once randomized, always analyzed. *Clinical Aphasiology*, *23*, 57-64.

WORSNOP, C. J., NAUGHTON, M. T., BARTER, C. E., MORGAN, T. O., ANDERSON, A. I., & PIERCE, R. J. (1998). The prevalence of obstructive sleep apnea in hypertensives. *American journal of respiratory and critical care medicine*, *157*(1), 111-115.

Young, T., Peppard, P., Palta, M., Hla, K. M., Finn, L., Morgan, B., & Skatrud, J. (1997). Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Archives of internal medicine*, *157*(15), 1746-1752.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *American journal of respiratory and critical care medicine*, *165*(9), 1217-1239.

Zhou, L., Stamler, J., Chan, Q., Van Horn, L., Daviglus, M. L., Dyer, A. R., Miura, K., Okuda, N., Wu, Y., & Ueshima, H. (2019). Salt intake and prevalence of overweight/obesity in Japan, China, the United Kingdom, and the United States: the INTERMAP Study. *The American journal of clinical nutrition*, *110*(1), 34-40.

APPENDIX A

BASELINE CHARACTERISTICS IN SENSITIVITY ANALYSIS

Table 2. Baseline Characteristics in Sensitivity Analysis

Characteristics	High/Low (N=14)	Low/High (N=17)	p-value
Male, %	6, 43%	9, 53%	.98
Age	60.2 ± 6.3	57.9 ± 7.1	.47
Black, %	7, 50%	12, 71%	.32
BMI, kg/m^2	31.4 ± 5.0	31.09 ± 4.41	.47
AHI	13.29 ± 13.92	11.56 ± 13.80	.39
HST evaluation duration	422.00 ± 119.33	335.75 ± 129.75	.07
Urinary sodium:creatinine	0.10 ± 0.03	0.10 ± 0.03	.58
Clinic Blood Pressure			
Systolic	128.7 ± 11.1	129.8 ± 11.0	.31
Diastolic	77.7 ± 7.7	77.8 ± 6.9	.34
Ambulatory Blood Pressure			
24-Hour Systolic	129.8 ± 14.9	129.4 ± 11.0	.80
24-Hour Diastolic	75.9 ± 7.2	78.6 ± 8.0	.21
Daytime Systolic	132.7 ± 15.5	133.3 ± 10.8	.81
Daytime Diastolic	78.4 ± 8.2	81.6 ± 7.7	.23
Nighttime Systolic	123.6 ± 14.6	122.5 ± 13.9	.81
Nighttime Diastolic	71.5 ± 7.9	72.9 ± 10.2	.34

Values represented as mean ± standard deviation for continuous variables. Categorical variables represented as total, percentage.

APPENDIX B

VALUES DURING LOW- AND HIGH-SALT DIETS IN SENSITIVITY ANALYSIS

Table 2. Values during Low- and High-Salt Diets in Sensitivity Analysis

High/Low Group (N=14)				
Values	**Pre-High Salt Diet**	**Post-High Salt Diet**	**Pre-Low Salt Diet**	**Post-Low Salt Diet**
Weight, lbs	202.8 ± 26.1	193.3 ± 42.3	180.1 ± 27.0	177.6 ± 26.1
BMI, kg/m^2	31.4 ± 5.0	30.9 ± 4.2	27.9 ± 4.9	27.5 ± 4.9
AHI	11.6 ± 12.1	13.7 ± 18.8	12.2 ± 10.6	12.2 ± 10.8
Serum sodium, mmol/L	139.2 ± 1.0	139.0 ± 2.1	140.3 ± 3.9	138.1 ± 4.0
Urinary sodium, mEq/L/day	162.6 ± 61.0	245.3 ± 24.2	104.6 ± 68.4	61.6 ± 6.7
Urinary creatinine, mg/day	1623.2 ± 473.8	1945.0 ± 425.2	1280.0 ± 441.5	1594.0 ± 538.2
Ratio of sodium:creatinine	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0
Clinic SBP, mmHg	128.7 ± 11.1	131.8 ± 18.4	123.0 ± 14.5	125.4 ± 16.3
Clinic DBP, mmHg	77.7 ± 7.7	78.2 ± 11.0	73.1 ± 4.1	76.3 ± 6.1
Daytime SBP	132.9 ± 15.5	130.8 ± 17.5	126.4 ± 21.8	125.6 ± 14.6
Daytime DBP	78.4 ± 8.2	79.1 ± 8.7	75.1 ± 12.1	77.9 ± 9.2
Nighttime SBP	123.6 ± 14.6	123.5 ± 18.9	115.1 ± 24.0	114.9 ± 16.6
Nighttime DBP	71.5 ± 7.9	72.6 ± 11.1	65.6 ± 13.0	66.4 ± 12.6
Mean 24-hr SBP	129.8 ± 14.9	128.3 ± 16.8	122.9 ± 22.0	122.1 ± 14.6
Mean 24-hr DBP	75.9 ± 7.2	77.0 ± 8.0	72.3 ± 12.1	73.7 ± 10.2
Low/High Group (N=17)				
Values	**Pre-Low Salt Diet**	**Post-Low Salt Diet**	**Pre-High Salt Diet**	**Post-Low Salt Diet**
Weight, lbs	186.7 ± 40.3	178.0 ± 39.8	207.63 ± 24.8	209.69 ± 23.1
BMI, kg/m^2	31.1 ± 4.4	27.2 ± 5.3	30.6 ± 2.5	30.8 ± 2.3
AHI	11.6 ± 13.8	11.8 ± 13.8	11.4 ± 12.2	7.7 ± 5.1
Serum sodium, mmol/L	141.4 ± 5.2	137.2 ± 3.0	138.6 ± 1.5	139.0 ± 1.3
Urinary sodium, mEq/L/day	130.7 ± 77.2	61.1 ± 6.1	164.3 ± 101.7	232.9 ± 30.4
Urinary creatinine, mg/day	1631.3 ± 66.9	1528.7 ± 530.8	2127.6 ± 672.9	2036.6 ± 426.3
Ratio of sodium:creatinine	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Clinic SBP, mmHg	129.8 ± 11.0	127.6 ± 10.6	141.9 ± 14.8	140.8 ± 12.5
Clinic DBP, mmHg	77.8 ± 6.9	79.9 ± 5.9	87.1 ± 8.3	83.9 ± 8.2
Daytime SBP	133.3 ± 10.8	127.8 ± 13.8	141.9 ± 17.4	145.1 ± 11.9
Daytime DBP	81.6 ± 7.7	81.1 ± 6.4	85.8 ± 9.3	87.1 ± 7.1
Nighttime SBP	122.5 ± 13.9	118.1 ± 14.5	135.9 ± 14.4	139.9 ± 20.6
Nighttime DBP	72.9 ± 10.2	72.9 ± 8.2	79.3 ± 8.5	82.4 ± 11.1
Mean 24-hr SBP	129.4 ± 11.0	124.7 ± 13.4	139.8 ± 16.4	143.3 ± 13.9
Mean 24-hr DBP	78.6 ± 8.0	78.4 ± 6.8	83.8 ± 9.1	85.4 ± 8.6