



Randomized Control Trials

DASH vs. Mediterranean diet on a salt restriction background in adults with high normal blood pressure or grade 1 hypertension: A randomized controlled trial



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SUMMARY

Background & aims: Non-pharmacological measures are recommended as the first-line treatment for individuals with high-normal blood pressure (BP) or mild hypertension. Studies directly comparing the BP effects of the Dietary Approaches to Stop Hypertension (DASH) vs. the Mediterranean diet (MedDiet) on a salt restriction background are currently lacking. Thus, our purpose was to assess the BP effects of a 3-month intensive dietary intervention implementing salt restriction either alone or in the context of the DASH, and the MedDiet compared to no/minimal intervention in adults with high normal BP or grade 1 hypertension.

Methods: We randomly assigned never drug-treated individuals to a control group (CG, n = 60), a salt restriction group (SRG, n = 60), a DASH diet with salt restriction group (DDG, n = 60), or a MedDiet with salt restriction group (MDG, n = 60). The primary outcome was the attained office systolic BP difference among the randomized arms during follow-up.

Results: A total of 240 patients were enrolled, while 204 (85%) completed the study. According to the intention-to-treat analysis, compared to the CG, office and 24 h ambulatory systolic and diastolic BP were reduced in all intervention groups. A greater reduction in the mean office systolic BP was observed in the MDG compared to all other study groups (MDG vs. CG: mean difference = −15.1 mmHg; MDG vs. SRG: mean difference = −7.5 mmHg, and MDG vs. DDG: mean difference = −3.2 mmHg, all P-values <0.001). The DDG and the MDG did not differ concerning the office diastolic BP and the 24 h ambulatory systolic and diastolic BP; however, both diets were more efficient in BP-lowering compared to the SRG.

Conclusions: On a background of salt restriction, the MedDiet was superior in office systolic BP-lowering, but the DASH and MedDiet reduced BP to an extent higher than salt restriction alone.

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Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CG, control group; DASH, dietary approaches to stop hypertension; DDG, dietary approaches to stop hypertension diet with salt restriction group; HMOD, hypertension-mediated organ damage; MDG, Mediterranean diet with salt restriction group; MedDiet, Mediterranean diet; RCT, randomized controlled trial; SRG, salt restriction group.

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1. Introduction

Inadequate blood pressure (BP) control remains one of the leading risk factors for premature morbidity and mortality worldwide, mainly due to cardiovascular causes and chronic kidney disease [1,2]. Non-pharmacological measures to reduce BP are recommended in (i) all individuals without hypertension or with high normal BP levels to prevent hypertension development, (ii) individuals with grade 1 hypertension and low-moderate cardiovascular disease risk, as the first-line treatment for 3–6 months to

postpone drug-treatment initiation, and (iii) patients already receiving antihypertensive drugs, as a complementary treatment [3].

Salt intake reduction and the extent of BP-lowering display a largely linear dose–response relationship, as suggested in recent meta-analyses of randomized controlled trials (RCTs) [4,5]. In addition, our previous meta-analyses of RCTs revealed that the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet (MedDiet) are both effective for BP reduction in adults with or without hypertension [6,7]. The DASH and the MedDiet include increased amounts of plant-based foods and a low intake of red/processed meat. Moreover, both diets are low in saturated fat and dietary cholesterol, but the MedDiet is high in total fat, obtained mainly from olive oil, whereas the DASH diet is low in total fat [8,9].

A higher BP reduction is produced when the DASH diet is combined with salt restriction, even though their combined effect is not strictly additive. Similar results for combining the MedDiet with salt restriction are unavailable [10]. The MedDiet has been considered less effective than the DASH diet for BP reduction [11]; however, most MedDiet studies were designed with different primary outcomes than BP-lowering. Moreover, head-to-head trials between the DASH and the MedDiet are currently lacking. For the management of hypertension, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the DASH diet as a heart-healthy diet [12]. In contrast, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines propose MedDiet as a healthy and balanced diet to adhere to [3], mainly because of cultural reasons.

To our knowledge, no clinical trials were designed to compare the BP-lowering effects of the DASH vs. the MedDiet with a concurrent salt restriction strategy over the BP effect of salt restriction as a stand-alone intervention. Thus, the purpose of the present trial was to assess the BP effects of a 3-month intensive dietary intervention implementing salt restriction either alone or in the context of the DASH and the MedDiet compared to no/minimal intervention in a population of never drug-treated adults with high normal BP or grade 1 hypertension.

2. Material & methods

2.1. Trial design

The DASH-MedDiet study was a 3-month, single-center, single-blinded, randomized, controlled, superiority trial, with 4 parallel groups and a 1:1:1:1 allocation. The study was designed according to the 2010 Consolidated Standards of Reporting Trials (CONSORT) [13,14]. The Scientific Board and the Research Committee of Hippokration General Hospital of Athens approved the study protocol. The trial was conducted following the Declaration of Helsinki [15] and was registered at the National Library of Medicine (NLM)/National Institutes of Health (NIH) database ([ClinicalTrials.gov](https://clinicaltrials.gov)) with identification number NCT05669404. Detailed information regarding the trial design is provided in the Supplementary Appendix.

2.2. Participants

Potential participants were adults aged 18 to 65 who visited the Hypertension Unit of the Hippokration General Hospital of Athens for the first time. According to standard procedures, a thorough medical history was obtained, and patients were subjected to physical examination, clinical investigations, and assessment of hypertension-mediated organ damage (HMOD). Patients: (i) with office high normal BP or grade 1 hypertension and low-moderate

cardiovascular disease risk [3], (ii) without previous antihypertensive drug treatment, (iii) with no major medical conditions (i.e., clinical or subclinical cardiovascular disease, renal disease, HMOD or diabetes mellitus), and (iv) willing to participate in a dietary intervention to control BP were referred to the clinical dietitian of the Hypertension Unit for further screening.

Initially-selected individuals were evaluated during two screen visits on two non-consecutive days over a period of 7–10 days to address the additional study's inclusion and exclusion criteria. Anthropometric measurements were recorded, and through a detailed interview conducted by the clinical dietitian self-reported data were collected regarding demographic characteristics, dietary intake, dietary supplements use, physical activity level, smoking history, alcohol consumption, and any recent attempts for weight loss. In addition, office BP measurements, ambulatory blood pressure monitoring (ABPM), and fasting blood samples were obtained by medical team members. Patients were eligible for inclusion if they had office high normal BP (i.e., systolic BP 130–139 mmHg and/or diastolic BP 85–89 mmHg) or grade 1 hypertension (systolic BP 140–159 mmHg and/or diastolic BP 90–99 mmHg) [3]. Averaged BP was based on the means of the last two out of three measurements made during the two screen visits. Patients were excluded if they (i) received any drugs or supplements affecting BP levels, (ii) were on a weight loss diet, or (iii) had any conditions demanding special dietary management. Detailed information regarding the study's inclusion and exclusion criteria is provided in the Supplementary Appendix. After the patients were fully informed about the aims and procedures of the study, they were asked to willingly provide a signed informed consent form for participation in the study, and they were included in the study sample.

2.3. Interventions

After eligibility assessment, enrolled patients were blindly randomized to one of the four study groups, i.e., control group (CG), salt restriction group (SRG), DASH diet combined with salt restriction group (DDG), or MedDiet combined with salt restriction group (MDG). Using a computerized system (random.org/sequences) [16], a randomized, ordered sequence of given numbers –the initial number corresponding to the first, and the final number corresponding to the last participant–was generated in four columns; the first column corresponding to the CG, the second to the SRG, the third to the DDG, and the fourth to the MDG. Each patient was sequentially assigned to the group indicated by the column in which his participation number was identified. All medical team members were blinded to patients' allocations, except for the clinical dietitian, who was solely responsible for the assignment of patients to the study groups. Patients were completely unaware of the other groups of the study.

After randomization, all patients were followed at the Hypertension Unit of Hippokration General Hospital, monthly for 3 months, i.e., at baseline, two times after baseline and a third time at the end of the study, in individual sessions coordinated by the clinical dietitian. The baseline individual session was conducted 7–10 days after the second screen visit. For the patients of all four study groups, the goal was to maintain the initial body weight unchanged to avoid the confounding effect of weight loss on BP reduction. They were also instructed not to change their physical activity level over the next 3 months.

Patients in the CG received general advice on dietary principles for BP control, i.e., salt restriction, consumption of a healthy balanced diet, and moderation of alcohol use. They were followed as frequently as the patients in the other study groups. However, they were subjected only to the study's intended measurements after the baseline, without any other intervention.

For the patients in the three intervention groups, the goal was to limit sodium intake to 2000 mg/day $\approx$ 87 mmol/day (equivalent to 5.0 g salt/day). Patients in the SRG were given a detailed booklet containing information about (i) table salt, (ii) foods rich in sodium, (iii) practical ways to decrease salt consumption, and (iv) nutrition facts labels. At the same time, in each 45-min individual session, they received intensive counseling and training to increase adherence to salt restriction.

Patients in the DDG and the MDG received a more extensive booklet, which in addition to the information regarding salt restriction, contained (i) information about foods included in each food group, (ii) nutritional value and BP effects of each food group, (iii) goals regarding the portions and the consumption frequencies of the various food items in accordance to the principles of the DASH and the MedDiet, respectively, and (iv) practical advice about how to start and stay on the given dietary plan. In addition to the booklet, each patient in these two intervention groups received an individualized dietary plan with six daily sample menus to facilitate the adoption of the assigned dietary pattern. The daily energy provided was calculated with the intention of keeping the body weight of the participant constant. The DASH dietary plans incorporated the goal of 27% of daily calories from fat. In contrast, the MedDiet dietary plans provided 37% of daily calories from fat, but both were low in saturated fat (6% of daily calories) and dietary cholesterol (150 mg/day). In addition, for a 2100-calorie level, the DASH dietary plans contained 1250 mg of calcium/day, whereas, in the MedDiet dietary plans, the corresponding level of daily calcium was 950 mg. However, both were low in sodium (2000 mg/day) and high in potassium (the DASH dietary plans provided 4700 mg/day, and the MedDiet dietary plans provided 4200 mg/day). During the 45-min individual sessions, patients were intensively counseled and trained to increase adherence to salt restriction and the assigned dietary pattern, motivated to achieve specific goals, and guided to consume unprocessed foods and home-prepared meals. Detailed information regarding the content of the intervention is provided in the Supplementary Appendix.

2.4. Assessments

Patients were assessed regarding anthropometric indices, dietary intake, physical activity level, and office BP at baseline and during the follow-up visits. In addition, ABPM and collection of fasting blood samples and 24-h urine samples were conducted at baseline and at the end of the 3-month intervention. A detailed description of all assessments is provided in the Supplementary Appendix.

Regarding anthropometric indices, body weight, height, and waist circumference (WC) were measured following standard procedures. Body mass index (BMI) was calculated, and patients were categorized as normal weight (if $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$), overweight (if $25 \leq \text{BMI} < 30 \text{ kg/m}^2$), or obese (if $\text{BMI} \geq 30 \text{ kg/m}^2$) [17]. Dietary intake was assessed at baseline and at the end of the study in all participants through two 24-h dietary recalls and a 76-item semi-quantitative food frequency questionnaire (FFQ) previously validated in the Greek population [18]. Patients in the three intervention groups were additionally given a 7-day food record, in which they were asked to record the type and the quantity of foods and beverages consumed during the week before each scheduled follow-up visit. Patients in the DDG were assessed for their adherence to the DASH diet using the DASH Adherence Score from Folsom and colleagues [19], modified by the researchers of the ENCORE study [20]. The score included 10 dietary components, whose sub-scores of 0–1 are summed to yield the total DASH Adherence Score, ranging from 0 to 10, with higher values indicating greater adherence to the DASH diet [20]. Patients in the MDG

were assessed for their adherence to the MedDiet using the Mediterranean Diet Score (MedDietScore) from Panagiotakos and colleagues [21], including 11 dietary components, whose sub-scores range from 0 to 5, and the total MedDietScore ranges from 0 to 55, with higher values indicating greater adherence to the MedDiet. Participants' physical activity level was assessed using the Short International Physical Activity Questionnaire (IPAQ), which refers to the past 7 days and is valid in the Greek population [22]. The mean time spent in physical activities per day (min/day) and the total minutes of metabolic equivalents of tasks per week (MET. min/week) were calculated for each participant [23].

Patients' office BP and heart rate were measured with an automatic oscillometric sphygmomanometer (Omron M6 Comfort, HEM-7321-E), using an appropriate cuff size for the arm circumference and following a standardized procedure [3]. If, at the first visit, there was a significant systolic BP difference between arms (i.e., $>15 \text{ mmHg}$), the arm with the higher BP was used for all subsequent measurements; otherwise, all measurements were performed in the left arm. After at least a 30-min period without eating, smoking, or being physically active, the patient remained seated for 5 min before beginning BP measurements. The cuff was positioned at the level of the heart, and three measurements were taken, separated by a 2-min interval; a fourth measurement was taken if the first two readings differed by $> 10 \text{ mmHg}$. The average of the last two BP and heart rate readings was recorded at each visit.

ABPM was performed with an ambulatory BP monitor (Space-labs Medical, 90,207-11Q), programmed to take BP and heart rate measurements over 24 h: at 15-min intervals during daytime (08:00 to 23:00) and at 30-min intervals during nighttime (23:00–08:00). Measurements recorded in the monitor were transmitted to a Spacelabs Medical ambulatory BP analysis system for report generation, in which the mean BP values were provided for 24 h, daytime, and night-time. The ambulatory BP monitor, carried in a pouch strapped and/or belted at the patient's side and connected with a pressure cuff attached around the patient's arm, was placed at 08:00 and removed at 08:00 the next morning. Patients were asked for their day to be usual, i.e., not to abstain from work and to keep a diary of their activities and sleep time. A minimum of 70% useable BP recordings were required for a valid ABPM measurement session; otherwise, ABPM was rescheduled for the next day.

Regarding laboratory assessments, a 12-h fasting blood sample and a 24-h urine sample were collected from each patient and analyzed in the Biochemical, Immunological, and Molecular Biology Unit of Hippokratia General Hospital. Blood tests included complete blood count, lipid and glycemic profile, liver and renal function indices, mineral profile, and inflammation markers. In addition, 24-h urine tests included diet-related indices, i.e., sodium, potassium, phosphorus, calcium, and magnesium, which were used to measure patients' adherence to salt restriction and the assigned dietary patterns.

2.5. Outcomes

The primary outcome of the DASH-MedDiet study was the attained mean office systolic BP difference among the randomized arms at the end of the study. Secondary outcomes included the attained between-group differences at 3 months post-intervention regarding the mean office diastolic BP and the mean ABPM measurements (during 24 h, daytime, and night-time). The attained office BP was calculated as the average from all visits following the baseline. In addition, the odds of hypertension according to the office BP measurements at the 3-month evaluation, the mean changes from baseline regarding office and ambulatory BP measurements in each study group (in the total population and

stratified by office BP category, i.e., high normal BP and grade 1 hypertension), and the changes in mean office BP over the three follow-up visits in each study group were also analyzed as secondary outcomes. Additional secondary outcomes were the mean changes from baseline regarding the anthropometric indices and the DASH/MedDiet adherence scores (absolute values and standardized z-scores), along with the attained mean differences among the four study groups concerning the diet-related indices in the 24-h urine sample at 3 months post-intervention. Correlations between diet-related indices in the 24-h urine sample and office BP changes were also conducted.

2.6. Statistical analysis

Taking into account the SD of the mean office systolic BP at baseline by the time 30 patients per group were recruited, it was estimated using the G*Power software (version 3.1.) that 50 patients per arm were required to achieve statistical power ($1-\beta$ err prob) of 80% to detect a significant between-group difference of 4 mmHg in the mean office systolic BP values 3 months after the intervention at a significance level (α err prob) of <0.05 . A 15% loss at follow-up led to a total sample of 240 subjects and a sample size of 60 participants per arm of the study [24].

Primary analyses were conducted using the intention-to-treat (ITT) approach, including all randomized participants. The variable normality in the total sample and each group separately was assessed through histograms and the Shapiro–Wilk test. Normally distributed numerical variables are presented as mean $\pm$ SD; non-normally distributed as median (interquartile range); and categorical variables as absolute numbers (relative frequency). At baseline, between-group comparisons were tested through one-way analysis of variance (ANOVA) for the numerical variables with normal distribution, the Kruskal–Wallis test for the numerical variables with non-normal distribution, and the chi-square test for the categorical variables. For the comparative evaluation of adherence to the DASH and MedDiet, standardized z-scores of the DASH Adherence Score and MedDietScore were calculated. Repeated measures ANOVA was conducted to compare group means over the three follow-up visits. Pearson's correlation coefficient (r) tested correlations between normally distributed numerical variables. Within-group changes were performed using paired samples t-test for the numerical variables with normal distribution and Wilcoxon signed-rank test for the numerical variables with non-normal distribution. Between-group differences were conducted through analysis of covariance (ANCOVA) for numerical variables and logistic regression analysis for categorical variables. Results are presented as mean difference (MD; 95% CI) and odds ratio (OR; 95% CI), respectively. The Bonferroni correction was used for the adjustment for multiple comparisons. The covariates used in all models were age, sex, and baseline levels of the dependent variables. P-values <0.05 were considered statistically significant for binary comparisons, while a Bonferroni correction reset statistical significance to <0.008 for the six comparisons among the four study groups. We also ran sensitivity analysis with the multiple imputation approach for the missing data (by creating copies of the dataset and replacing missing values with imputed values). All dietary records were analyzed using Nutritionist Pro™ software (Axxya Systems, USA, version 7.4.0.). All analyses were conducted using IBM SPSS Statistics 25.0.

3. Results

The flow diagram of the trial is presented in Fig. 1. A total of 301 patients were assessed for eligibility; 39 did not meet inclusion or exclusion criteria, and 22 declined to participate. A total of 240

patients were randomly assigned to one of the four study groups. At baseline, the four trial groups did not differ regarding demographic and clinical characteristics, except for the DDG and the MDG, which differed in standardized z-scores of the DASH/MedDiet adherence scores (Table 1). Among patients, 48.3% had high normal BP, and 51.7% had grade 1 hypertension. The mean baseline office systolic BP/diastolic BP was $137.7 \pm 5.7/88.4 \pm 5.9$ mmHg, and the mean baseline 24 h ambulatory systolic BP/diastolic BP was $132.9 \pm 9.4/83.1 \pm 7.4$ mmHg. No differences in baseline characteristics were observed between patients who completed the study ($n = 204$) and those who withdrew ($n = 36$) (Supplementary Table S1).

3.1. Primary outcome

Between-group differences in the mean office systolic BP at 3 months post-intervention, adjusted for age, sex, and baseline levels of office systolic BP, are presented in Table 2. Compared to the CG, the mean office systolic BP was reduced in all intervention groups (SRG vs. CG: MD = -7.6 mmHg; 95% CI: $-9.7, -5.4$, DDG vs. CG: MD = -11.9 mmHg; 95% CI: $-14.1, -9.6$, and MDG vs. CG: MD = -15.1 mmHg; 95% CI: $-17.3, -12.9$). Comparisons among the three intervention groups revealed greater reductions in the mean office systolic BP for both the DDG and the MDG, compared to the SRG (DDG vs. SRG: MD = -4.3 mmHg; 95% CI: $-6.5, -2.1$, and MDG vs. SRG: MD = -7.5 mmHg; 95% CI: $-9.8, -5.3$). Also, compared to the DDG, the MDG exhibited lower mean office systolic BP values (MDG vs. DDG: MD = -3.2 mmHg; 95% CI: $-5.4, -1.0$).

3.2. Secondary outcomes

Between-group differences in the mean office diastolic BP and ABPM measurements (during 24 h, daytime, and night-time) at the 3-month evaluation, adjusted for age, sex, and baseline levels of the dependent variables, are presented in Table 2. The attained differences in mean office diastolic BP were significant among all study groups, except for the difference between the DDG and the MDG. The study groups differed in the mean 24 h ambulatory systolic and diastolic BP, besides the SRG and the DDG, which during the 24 h reduced ambulatory diastolic BP equally. Moreover, the DDG and the MDG did not differ in the mean 24 h ambulatory systolic and diastolic BP. BP differences among groups during the day- and night-time are presented in Table 2.

At 3 months, the odds of hypertension according to the office BP measurements are presented in Table 2. Compared to the CG, there were trivial odds of hypertension in all three intervention groups. Compared to the SRG, the DDG and MDG exhibited 65% and 84% lower odds of hypertension, respectively. However, the odds of hypertension did not differ between the MDG and the DDG.

Within-group changes in office and 24 h ambulatory BP measurements, along with the between-group differences in the mean changes from baseline, are presented in Fig. 2 and Supplementary Tables S2 and S3. The MDG exhibited the greatest reduction from baseline in the mean office systolic BP and a reduction equal to the DDG in the mean office diastolic BP. On the contrary, regarding 24 h ambulatory BP, compared to all other groups, the MDG exhibited the greatest reduction in the mean ambulatory diastolic BP and a reduction equal to the DDG in the mean ambulatory systolic BP. Compared to the SRG, the DDG induced greater reductions in the mean office systolic and diastolic BP and in the mean 24 h ambulatory systolic BP, but not in the mean 24 h ambulatory diastolic BP. The corresponding BP changes and between-group differences during the day and night are presented in Supplementary Fig. S1 and Supplementary Tables S2 and S3. The mean changes from baseline regarding office and ambulatory BP measurements in each study group stratified by office BP category, i.e., high normal BP and

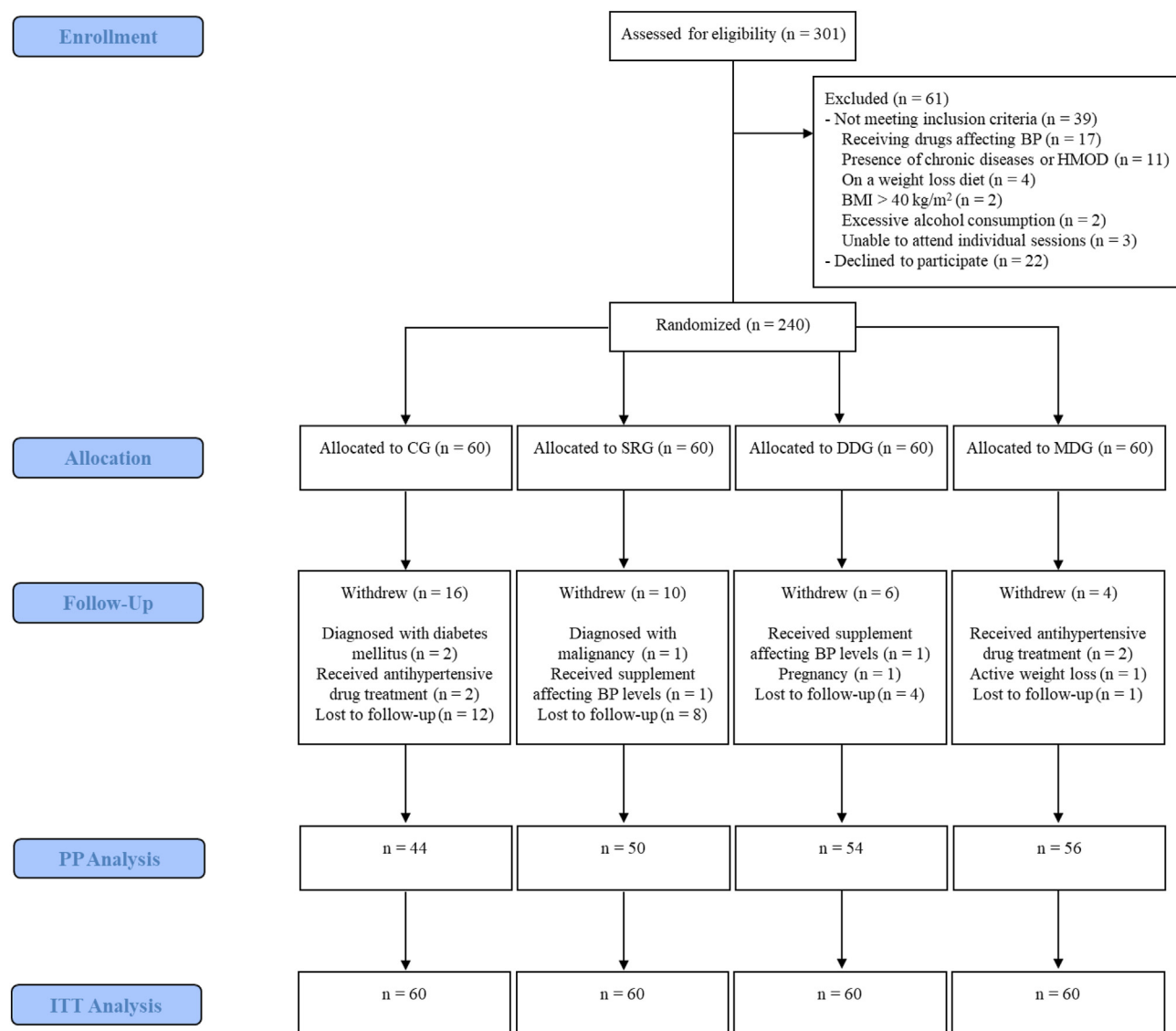


Fig. 1. CONSORT flow diagram of the trial. A total of 301 patients were screened for eligibility, of whom 39 did not meet the study's inclusion and exclusion criteria, and 22 declined to participate. A total of 240 patients were randomly assigned to one of the four study groups. After randomization, 11 patients were excluded from the study for certain reasons, and 25 were lost to follow-up. A total of 204 patients (85%) completed the 3-month intervention period. The first patient was assessed for eligibility on January 7, 2019, and the last on May 27, 2022, whereas the last patient's follow-up visit occurred on September 9, 2022. Primary analyses were conducted using the ITT approach, including all randomized participants (n = 240). BMI, body mass index; BP, blood pressure; CG, control group; DDG, dietary approaches to stop hypertension diet group; HMOD, hypertension-mediated organ damage; ITT, intention-to-treat; MDG, Mediterranean diet group; PP, per protocol; SRG, salt restriction group.

grade 1 hypertension, are presented in [Supplementary Table S4](#). Office BP at baseline and during the three follow-up visits in each study group are presented in [Supplementary Table S5](#).

3.3. Additional secondary outcomes

During the 3-month evaluation, anthropometric indices, energy intake, and physical activity levels did not change in any of the study groups ([Supplementary Table S6](#)). Patients in the DDG increased their adherence to the DASH diet; the absolute mean (95% CI) DASH Adherence Score change was +2.3 (2.0, 2.5). Patients in the MDG increased their adherence to the MedDiet; the absolute mean (95% CI) MedDietScore change was +13.5 (12.4, 14.6). However, the corresponding changes in standardized z-scores were not significant in either of the two groups ([Supplementary Table S6](#)).

Data from food records as a measure of patients' dietary adherence are not shown.

Between-group differences in the mean levels of the diet-related indices in the 24-h urine sample at 3 months post-intervention are presented in [Supplementary Fig. S2](#) and [Supplementary Table S7](#). Briefly, a greater reduction in the mean sodium levels was observed in the MDG, compared to the SRG, whereas the DDG produced a mean reduction equal to both the SRG and the MDG. Regarding the mean potassium and magnesium levels, the DDG and the MDG exhibited higher levels than the CG and the SRG. In contrast, compared to all other study groups, calcium, and phosphorus were increased only to the DDG. Correlations between diet-related indices in the 24-h urine sample and office systolic/diastolic BP changes in the total sample are presented in [Supplementary Table S8](#). Office systolic/diastolic BP changes correlated positively with sodium levels and negatively with

Table 1
Baseline characteristics of the total sample and the four randomized study groups^{a,b}.

	Total sample (n = 240)	CG (n = 60)	SRG (n = 60)	DDG (n = 60)	MDG (n = 60)	P ^c
Age, y	52.1 ± 11.9	53.2 ± 11.0	53.7 ± 11.5	50.9 ± 12.7	50.6 ± 12.6	0.39
Sex						
Male, n (%)	124 (51.7)	30 (50.0)	32 (53.3)	30 (50.0)	32 (53.3)	0.97
Ethnicity						
Greek, n (%)	229 (95.4)	58 (96.7)	57 (95.0)	56 (93.3)	58 (96.7)	0.79
Marital status						
Single, n (%)	60 (25.0)	15 (25.0)	14 (23.3)	15 (25.0)	16 (26.7)	0.91
Married, n (%)	141 (58.8)	35 (58.3)	35 (58.3)	37 (61.7)	34 (56.7)	
Divorced, n (%)	21 (8.8)	4 (6.7)	7 (11.7)	6 (10.0)	4 (6.7)	
Widowed, n (%)	18 (7.5)	6 (10.0)	4 (6.7)	2 (3.3)	6 (10.0)	
Educational status						
≤9 y, n (%)	6 (2.5)	1 (1.7)	2 (3.3)	1 (1.7)	2 (3.3)	0.99
>9 and ≤ 12 y, n (%)	125 (52.1)	32 (53.3)	32 (53.3)	31 (51.7)	30 (50.0)	
>12 and ≤ 16 y, n (%)	69 (28.7)	17 (28.3)	18 (30.0)	18 (30.0)	16 (26.7)	
>16 y, n (%)	40 (16.7)	10 (16.7)	8 (13.3)	10 (16.7)	12 (20.0)	
Occupational status						
Student, n (%)	6 (2.5)	1 (1.7)	1 (1.7)	2 (3.3)	2 (3.3)	0.95
Unemployed, n (%)	20 (8.3)	4 (6.7)	6 (10.0)	6 (10.0)	4 (6.7)	
Employed, n (%)	165 (68.8)	40 (66.7)	43 (71.7)	42 (70.0)	40 (66.7)	
Retired, n (%)	49 (20.4)	15 (25.0)	10 (16.7)	10 (16.7)	14 (23.3)	
Economic status						
<10,000 euros/y, n (%)	63 (26.3)	16 (26.7)	18 (30.0)	15 (25.0)	14 (23.3)	0.85
10,000–20,000 euros/y, n (%)	134 (55.8)	35 (58.3)	34 (56.7)	32 (53.3)	33 (55.0)	
>20,000 euros/y, n (%)	43 (17.9)	9 (15.0)	8 (13.3)	13 (21.7)	13 (21.7)	
Current smokers, n (%)	51 (21.3)	12 (20.0)	13 (21.7)	14 (23.3)	12 (20.0)	0.97
WC, cm	106.1 ± 11.2	107.3 ± 12.0	104.3 ± 10.6	105.9 ± 11.1	106.7 ± 11.3	0.49
BMI, kg/m ²	29.2 ± 4.1	29.8 ± 4.5	28.7 ± 4.2	28.6 ± 4.0	29.7 ± 3.8	0.22
Energy intake, kcal/d ^d	2219.9 ± 377.5	2184.2 ± 481.0	2290.7 ± 376.9	2209.0 ± 327.7	2195.8 ± 298.7	0.40
Physical activity, min/d	25.7 (15.5, 34.3)	21.4 (8.6, 32.1)	27.9 (15.0, 42.9)	25.8 (17.1, 34.3)	25.7 (17.8, 34.3)	0.11
Physical activity, MET. min/week	594.0 (358.9, 982.5)	516.0 (198.0, 876.0)	675.0 (346.5, 990.0)	669.0 (396.0, 960.0)	585.8 (495.0, 792.0)	0.15
DASH Adherence Score						
Absolute value (0–10)	—	—	—	4.2 ± 0.9	—	—
MedDietScore						
Absolute value (0–55)	—	—	—	—	30.2 ± 3.3	—
DASH/MedDiet Adherence Score						
Standardized z-scores	—	—	—	−0.97 ± 0.07	0.97 ± 0.24	<0.001
24-h urine sample						
Sodium, mmol/24 h	149.9 ± 56.8	149.2 ± 56.3	148.3 ± 51.1	151.2 ± 62.3	150.9 ± 58.5	0.99
Potassium, mmol/24 h	60.7 ± 19.8	59.7 ± 24.4	61.3 ± 21.7	60.5 ± 17.6	61.1 ± 14.6	0.97
Calcium, mg/24 h	175.6 ± 83.5	179.6 ± 95.8	175.9 ± 88.9	175.1 ± 28.5	171.7 ± 101.6	0.96
Phosphorus, mg/24 h	800.1 ± 281.3	794.6 ± 259.5	784.1 ± 280.4	832.7 ± 261.4	788.8 ± 323.8	0.78
Magnesium, mg/24 h	93.4 ± 30.3	94.1 ± 28.6	97.2 ± 28.9	92.0 ± 34.9	90.4 ± 28.5	0.64
Office BP						
SBP, mmHg	137.7 ± 5.7	137.2 ± 6.6	137.3 ± 5.3	138.1 ± 5.8	138.1 ± 5.1	0.72
DBP, mmHg	88.4 ± 5.9	88.6 ± 4.6	88.1 ± 4.8	87.9 ± 8.6	88.9 ± 4.6	0.76
Heart rate, beats/min	75.6 ± 7.9	76.3 ± 7.0	75.5 ± 7.1	75.4 ± 8.8	75.1 ± 8.6	0.86
ABPM						
24 h						
SBP, mmHg	132.9 ± 9.4	131.6 ± 8.4	133.6 ± 10.2	132.5 ± 10.8	133.9 ± 7.7	0.51
DBP, mmHg	83.1 ± 7.4	83.7 ± 6.1	82.4 ± 7.4	82.2 ± 9.1	84.0 ± 6.6	0.44
Heart rate, beats/min	73.3 ± 7.2	74.5 ± 6.1	72.4 ± 8.3	72.8 ± 7.5	73.5 ± 6.8	0.41
Daytime						
SBP, mmHg	137.3 ± 9.4	135.8 ± 8.8	137.5 ± 10.1	137.6 ± 10.0	138.1 ± 8.5	0.57
DBP, mmHg	86.7 ± 7.7	87.5 ± 6.5	85.6 ± 7.2	86.6 ± 9.2	87.5 ± 7.6	0.46
Heart rate, beats/min	77.4 ± 8.3	79.3 ± 7.7	75.7 ± 9.1	76.3 ± 7.5	78.2 ± 8.7	0.06
Night-time						
SBP, mmHg	124.1 ± 12.2	123.0 ± 10.1	125.6 ± 15.1	122.6 ± 13.5	125.4 ± 9.2	0.40
DBP, mmHg	75.6 ± 8.9	76.1 ± 7.3	75.7 ± 11.0	73.5 ± 9.8	77.3 ± 6.9	0.13
Heart rate, beats/min	67.3 ± 8.3	69.0 ± 9.1	66.2 ± 8.0	65.8 ± 8.4	67.9 ± 7.5	0.12
Office BP category ^e						
High normal BP, n (%)	116 (48.3)	30 (50.0)	30 (50.0)	28 (46.7)	28 (46.7)	0.97
Grade 1 hypertension, n (%)	124 (51.7)	30 (50.0)	30 (50.0)	32 (53.3)	32 (53.3)	
Dyslipidemia, n (%) ^f	159 (66.3)	38 (63.3)	39 (65.0)	42 (70.0)	40 (66.7)	0.88

^a Results are presented as mean ± SD or median (1st, 3rd quartile) for the normally and non-normally distributed numerical variables, respectively, and as absolute numbers (relative frequency) for the categorical variables. To convert mmol of sodium to mg multiply by 23, and to convert mmol of potassium to mg multiply by 39.

^b ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CG, control group; DASH, dietary approaches to stop hypertension; DBP, diastolic blood pressure; DDG, dietary approaches to stop hypertension diet group; MDG, Mediterranean diet group; MedDietScore, Mediterranean diet score; MET, metabolic equivalents of task; SBP, systolic blood pressure; SRG, salt restriction group; WC, waist circumference.

^c P-value for between-group comparisons, as derived from one-way analysis of variance (ANOVA) and Kruskal–Wallis test for the normally and non-normally distributed numerical variables, respectively, and chi-square test for the categorical variables. The statistical significance level was set at 0.008, according to the Bonferroni correction method.

^d Mean daily energy intake, as derived from the two 24-h dietary recalls performed during the two screen visits.

^e High normal BP: Office systolic BP: 130–139 mmHg and/or office diastolic BP: 85–89 mmHg; Grade 1 hypertension: Office systolic BP: 140–159 mmHg and/or office diastolic BP: 90–99 mmHg [3].

^f Dyslipidemia: Low-density lipoprotein cholesterol (LDL-c) ≥ 116 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-c) ≥ 130 mg/dL or triglycerides (TG) ≥ 150 mg/dL [33].

Table 2

Between-group differences in the mean office BP and ABPM measurements (during 24 h, daytime, and night-time) at 3 months post-intervention, according to the ITT analysis (n = 240)^{a,b}.

	SRG vs. CG	P ^c	DDG vs. CG	P ^c	MDG vs. CG	P ^c	DDG vs. SRG	P ^c	MDG vs. SRG	P ^c	MDG vs. DDG	P ^c
	MD/OR (95% CI)		MD/OR (95% CI)		MD/OR (95% CI)		MD/OR (95% CI)		MD/OR (95% CI)		MD/OR (95% CI)	
Office BP												
SBP, mmHg	−7.6 (−9.7, −5.4)	<0.001	−11.9 (−14.1, −9.6)	<0.001	−15.1 (−17.3, −12.9)	<0.001	−4.3 (−6.5, −2.1)	<0.001	−7.5 (−9.8, −5.3)	<0.001	−3.2 (−5.4, −1.0)	<0.001
DBP, mmHg	−4.4 (−6.1, −2.6)	<0.001	−6.6 (−8.4, −4.8)	<0.001	−8.1 (−9.8, −6.3)	<0.001	−2.2 (−4.0, −0.5)	0.006	−3.7 (−5.5, −1.9)	<0.001	−1.5 (−3.2, 0.3)	0.18
HR, beats/min	−1.1 (−3.6, 1.2)	0.99	−1.5 (−3.9, 0.9)	0.57	−0.5 (−2.9, 1.9)	0.99	−0.4 (−2.8, 2.0)	0.99	0.6 (−1.8, 3.1)	0.99	1.0 (−1.3, 3.4)	0.99
ABPM												
24 h												
SBP, mmHg	−5.6 (−8.8, −2.4)	<0.001	−10.1 (−13.3, −6.9)	<0.001	−12.0 (−15.2, −8.8)	<0.001	−4.5 (−7.7, −1.3)	<0.001	−6.4 (−9.6, −3.2)	<0.001	−1.9 (−5.1, 1.2)	0.64
DBP, mmHg	−3.9 (−6.2, −1.6)	<0.001	−5.5 (−7.8, −3.2)	<0.001	−7.6 (−9.8, −5.3)	<0.001	−1.5 (−3.9, 0.7)	0.42	−3.7 (−5.9, −1.3)	<0.001	−2.1 (−4.3, 0.2)	0.09
HR, beats/min	−0.4 (−2.5, 1.6)	0.99	−0.3 (−2.4, 1.8)	0.99	2.4 (0.3, 4.4)	0.02	0.1 (−1.9, 2.2)	0.99	2.8 (0.7, 4.8)	0.003	2.6 (0.6, 4.7)	0.005
Daytime												
SBP, mmHg	−6.8 (−10.2, −3.4)	<0.001	−9.9 (−13.2, −6.5)	<0.001	−11.9 (−15.4, −8.6)	<0.001	−3.0 (−6.5, 0.4)	0.11	−5.1 (−8.5, −1.7)	<0.001	−2.1 (−5.5, 1.3)	0.61
DBP, mmHg	−4.9 (−7.4, −2.5)	<0.001	−5.7 (−8.1, −3.2)	<0.001	−7.1 (−9.6, −4.7)	<0.001	−0.7 (−3.1, 1.7)	0.99	−2.1 (−4.6, 0.3)	0.12	−1.4 (−3.8, 1.0)	0.71
HR, beats/min	−0.5 (−2.9, 1.9)	0.99	−0.3 (−2.8, 2.1)	0.99	1.8 (−0.6, 4.2)	0.31	0.2 (−2.2, 2.6)	0.99	2.3 (−0.1, 4.7)	0.08	2.1 (−0.3, 4.5)	0.13
Night-time												
SBP, mmHg	−2.1 (−5.9, 1.5)	0.75	−10.2 (−13.8, −6.4)	<0.001	−11.7 (−15.5, −8.0)	<0.001	−8.0 (−11.7, −4.2)	<0.001	−9.6 (−13.3, −5.9)	<0.001	−1.6 (−5.3, 2.1)	0.99
DBP, mmHg	−1.1 (−3.8, 1.6)	0.99	−4.6 (−7.4, −1.9)	<0.001	−7.8 (−10.5, −5.1)	<0.001	−3.6 (−6.3, −0.8)	0.003	−6.7 (−9.4, −4.0)	<0.001	−3.1 (−5.8, −0.4)	0.02
HR, beats/min	−2.2 (−4.4, 0.0)	0.05	−2.2 (−4.4, 0.1)	0.06	−1.2 (−3.5, 0.9)	0.82	0.0 (−2.2, 2.2)	0.99	0.9 (−1.2, 3.1)	0.99	0.9 (−1.2, 3.1)	0.99
Hypertension ^d	0.08 (0.03, 0.19)	<0.001	0.03 (0.01, 0.08)	<0.001	0.02 (0.01, 0.04)	<0.001	0.35 (0.13, 0.93)	0.035	0.16 (0.05, 0.52)	0.002	0.45 (0.13, 1.60)	0.22

^a Results are presented as MD and OR (95% CI) for numerical and categorical variables, respectively.

^b ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CG, control group; CI, confidence interval; DBP, diastolic blood pressure; DDG, dietary approaches to stop hypertension diet group; HR, heart rate; ITT, intention-to-treat; MD, mean difference; MDG, Mediterranean diet group; OR, odds ratio; SBP, systolic blood pressure; SRG, salt restriction group.

^c P-value for between-group differences at 3 months post-intervention, as derived from analysis of covariance (ANCOVA) for numerical variables and logistic regression analysis for categorical variables. The Bonferroni correction was used for the adjustment for multiple comparisons. Age, sex, and baseline levels of the dependent variables were used as covariates in all models. The statistical significance level was set at 0.05.

^d Hypertension: Office systolic BP ≥ 140 mmHg and/or office diastolic BP ≥ 90 mmHg [3].

potassium and magnesium levels. Calcium levels correlated negatively with office systolic BP changes, whereas phosphorus levels did not correlate with systolic or diastolic BP changes. Correlations between diet-related indices in the 24-h urine sample and DASH/MedDiet Adherence Scores (absolute values) are also presented in [Supplementary Table S8](#). Sensitivity analysis with multiple imputations for the missing data revealed no difference in the primary outcome estimates (data not shown).

4. Discussion

4.1. Main findings

For the first time, our study provided evidence about the comparative BP effects of the DASH and the MedDiet on a salt restriction background in adults with high normal BP or grade 1 hypertension. Accordingly, the MedDiet was superior regarding office systolic BP reduction compared to the DASH diet, whereas equal effectiveness was proved for office diastolic BP reduction. At the 3-month follow-up, the DASH and the MedDiet did not differ concerning the 24 h ambulatory systolic and diastolic BP values.

Compared to salt restriction as the only intervention, both dietary patterns combined with salt restriction were more efficient concerning the office and 24 h ambulatory systolic/diastolic BP reduction. However, the DASH diet was not superior to salt restriction alone regarding the 24 h ambulatory diastolic BP reduction.

4.2. Filling the gap in the literature

In recent decades, consistent evidence from clinical trials has documented the BP-lowering effect of the DASH diet [6,25]. Although it was usually examined alone, there are available data regarding its effectiveness in combination with salt restriction. The most robust evidence was provided by the DASH and the DASH-Sodium trials, revealing that the greatest benefit on BP was observed when the DASH diet was accompanied by salt restriction [26,27]. In a secondary analysis of the DASH-Sodium trial, compared to the control diet with high sodium (3450 mg or 150 mmol), the DASH diet with low sodium (1150 mg or 50 mmol) lowered systolic BP by nearly 10 mmHg among those with a baseline systolic BP of 140–149 mmHg and by 20 mmHg among

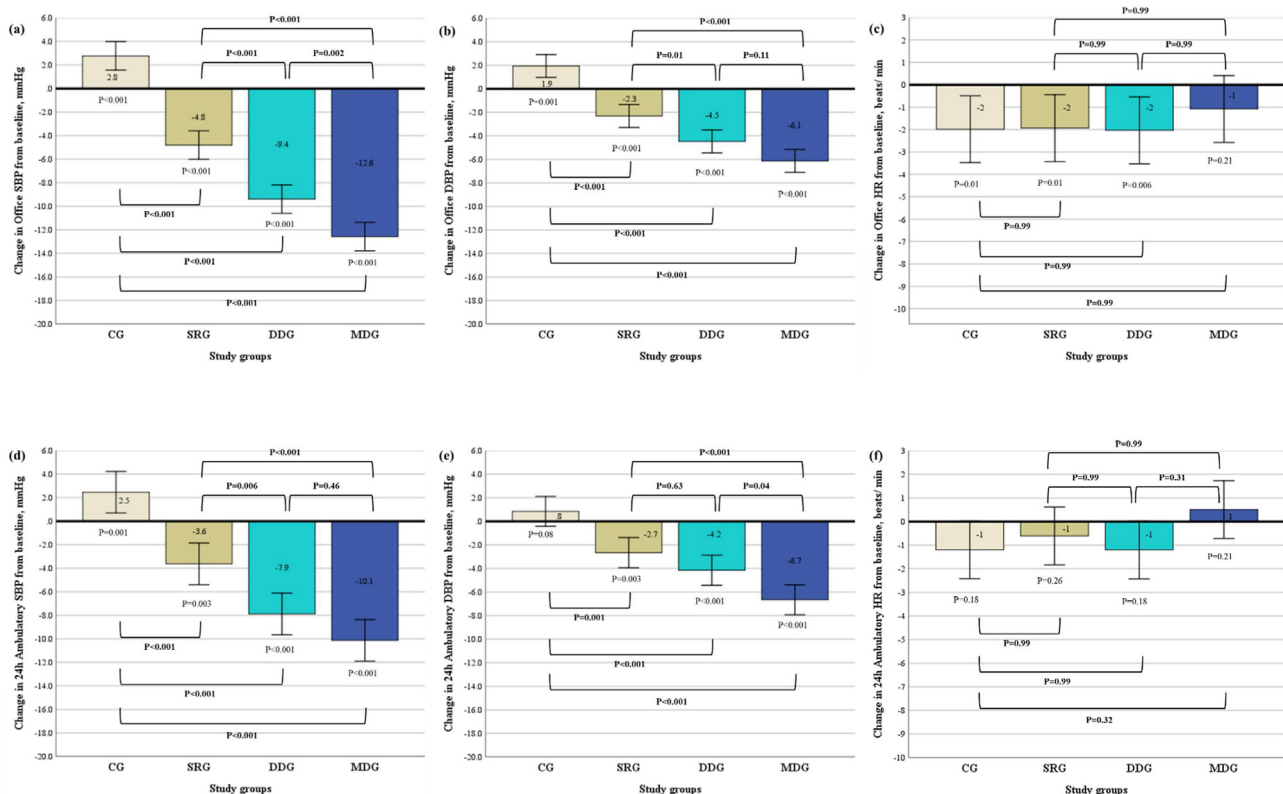


Fig. 2. Within-group changes and between-group differences in the mean changes from baseline at 3 months post-intervention, regarding office BP [(a)–(c)] and ABPM measurements during 24 h [(d)–(f)], according to the ITT analysis ($n = 240$). Estimated means on the Y axis refer to the mean changes from baseline in each of the four randomized groups presented on the X axis. The error bars (I) correspond to 95% CIs, and the P-values underneath correspond to within-group changes, as derived from paired samples t-test. Bold P-values with brackets correspond to between-group differences in the mean office BP and ABPM changes from baseline at 3 months post-intervention, as derived from analysis of covariance (ANCOVA). The Bonferroni correction was used for the adjustment for multiple comparisons. Age, sex, and baseline levels of the dependent variables were used as covariates in all models. The statistical significance level was set at 0.05. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CG, control group; CI, confidence interval; DBP, diastolic blood pressure; DDG, dietary approaches to stop hypertension diet group; HR, heart rate; ITT, intention-to-treat; MDG, Mediterranean diet group; SBP, systolic blood pressure; SRG, salt restriction group.

those with a baseline systolic BP of 150–159 mmHg [28]. However, these results cannot be straightly compared to ours, since (i) we used a different sodium level, i.e., 2000 mg or 87 mmol, (ii) we did not analyze data according to strata of baseline BP values, and (iii) our study involved comparisons among more than two groups. On the contrary, the MedDiet was mainly examined concerning cardiovascular disease risk factors and not particularly BP levels; thereby, no parallel salt restriction strategy was imposed [10]. Therefore, our study contributes towards the goal of determining the BP effect of salt restriction on top of the MedDiet and directly comparing it to the corresponding effect when it is implemented either alone or on top of the DASH diet since head-to-head trials between the DASH and the MedDiet are also lacking. A network meta-analysis that estimated the post-intervention difference in systolic/diastolic BP between different dietary interventions provides evidence for the superiority of the DASH vs. the MedDiet regarding systolic BP reduction (-3.31 mmHg; 95% CI: $-6.20, -0.42/-1.56$). However, due to its network nature, the DASH and the MedDiet arms were unequal, suggesting a loss of randomization. Thus, these results are not comparable to ours [29].

4.3. Strengths of the study

The strengths of this study include the randomized design and the conduction of the primary analyses according to the ITT approach, avoiding various types of bias. Office and 24 h ambulatory BP measurements were performed using certified and

validated BP monitors, following standardized procedures, increasing precision and minimizing bias. Patients in the CG were followed at the same frequency as those in the other study groups to conduct the study's intended measurements without any intervention, avoiding the confounding effect of the lack of personal contact with health professionals. Patients' adherence to salt restriction and the assigned dietary patterns was assessed with objective measures, i.e., measurement of diet-related indices in 24-h urine tests. Weight change as a potential confounder was absent. Last but not least, the implemented dietary intervention was feasible in the “real world”, reflecting a realistic plan for BP reduction.

4.4. Limitations

In this study, we acknowledge several limitations. This study design was a single-center clinical trial, so comparable interventions remain to be tested in additional, ideally multi-center settings. Regarding the generalizability of the trial findings, caution is needed, considering that our population consisted predominantly of Greek, middle-aged, overweight patients, free of major medical conditions, such as cardiovascular disease. The impact of potential conscious or unconscious bias on the results cannot be excluded, even though blinding the clinical dietician and trial participants was unfeasible. However, all medical team members who conducted the office/ambulatory BP measurements were blinded to patients' allocations. Although patients were

treated according to strict criteria, preventing deviations from the intended intervention, they were completely unaware of the other study groups, meaning they might have been free of any positive or negative predisposition towards the intended intervention. The withdrawal rate was higher in the CG (26.6%), suggesting that these patients, although followed at the same frequency as those in the other study groups, might have anticipated a more intensive intervention. However, in the total sample, the withdrawal rate was as frequent as we *a priori* predicted (=15%), and the ITT analysis provided the required statistical power. Results regarding within-group changes in office BP and ABPM measurements stratified by office BP category need to be seen cautiously, because of the limited and unequal number of patients in each subgroup. Except for the booklets and the prescribed dietary plans, no foods or beverages were provided, and patients were responsible for preparing their meals, which might have compromised patients' adherence. However, the objective and subjective adherence measures (24-h urine samples and food records) suggested good compliance. Moreover, interventions in free-living participants may be more pragmatic than the controlled-feeding studies, reflecting the intended effects in real-life situations. Dietary intake and physical activity levels were assessed through food records and questionnaires validated in the Greek population, but data were participant-reported. They might have been potentially influenced by knowledge of the intervention received, meaning that the Hawthorne effect cannot be excluded [30], even though explicit explanations were given and every possible effort was made to obtain accurate data. Moreover, the confounding effect of urinary minerals cannot be excluded because of (i) the correlation between levels of excreted sodium or potassium and BP in the total population and (ii) the differences in urinary minerals between different groups. Finally, the intervention period was relatively short (3 months), so the reported results need to be tested in trials with a longer follow-up period.

4.5. Perspectives

Future research is needed to determine the BP effect of salt restriction in the context of the MedDiet and the BP effect of the MedDiet directly compared to the BP effect of the DASH diet. Except for the risk of hypertension occurrence, cardiovascular disease risk, and other hard outcomes after such interventions of longer duration should also be determined. Through meta-regression analyses of BP-lowering trials, it has been previously shown that a 1 mmHg reduction of systolic or diastolic BP by any drug category is related to a 2% reduction in fatal and non-fatal major cardiovascular disease events [31]. Since, however, the cardiovascular disease risk reduction is solely correlated with BP reduction *per se*, i.e., not to specific properties of any BP-lowering drug, and given the substantial reductions in BP observed in this study, the significance of dietary interventions might be an effective alternative to antihypertensive drugs for hypertension management or among adults with borderline BP. At variance with dietary interventions, drug treatment might also be accompanied by side effects leading to permanent drug discontinuation and treatment benefit withdrawal. Finally, diet modification may reduce cardiovascular disease risk to an extent higher than expected because of its benefits in other cardiovascular disease risk factors, independently of BP reduction [32].

5. Conclusion

This 3-month intensive dietary intervention promoting salt restriction as a stand-alone intervention or combined with the DASH or the MedDiet had a meaningful effect on BP reduction compared

to no/minimal intervention. In this population of Greek adults with high normal BP or grade 1 hypertension MedDiet was superior regarding office systolic BP reduction. However, the DASH and the MedDiet combined with salt restriction reduced BP to an extent higher than salt restriction as the only intervention. Our findings further support the current hypertension guidelines, recommending the adoption of a healthy diet, such as the DASH and the MedDiet, on a salt restriction background to delay hypertension onset or drug treatment initiation.

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Author contribution

Konstantinos Tsioufis, Costas Thomopoulos, and Christina Filippou designed the study; Christina Filippou, Dimitrios Konstantinidis, Eirini Siafi, Fotis Tatakis, Eleni Manta, Sotiris Droghkaris, Dimitrios Polyzos, Konstantinos Kyriazopoulos, and Kalliopi Grigoriou were involved in patient recruitment and study's assessments; Christina Filippou delivered the dietary intervention; Costas Thomopoulos and Christina Filippou performed the statistical analyses; Christina Filippou wrote the paper; Dimitrios Tousoulis and Konstantinos Tsioufis assisted in the interpretation of the results and the revision of the manuscript; all authors have read and approved the final manuscript.

Conflicts of Interest

None related to the present work for all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2023.08.011>.

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