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ARTICLE

Chronobiologic assessment of the effect of the DASH diet on blood pressure

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Abstract
This study compares the effect of three diets on the circadian rhythm of blood pressure (BP). Hypertension and abnormal BP variability (BPV) are major risk factors leading to morbidity and mortality from cardiovascular disease. When detected early, a dietary approach may be preferred to medication. Data stemming from ambulatory BP monitoring (ABPM) from the Dietary Approaches to Stop Hypertension (DASH) study were re-analyzed from a chronobiologic perspective. Compared to the control diet ($N = 112$) that had no effect on BP (from 131.2/83.5 to 131.0/83.6 mmHg), both the Fruit and Vegetable (FV; $N = 113$) diet and the DASH ($N = 113$) diet were associated with a decrease in BP (FV: from 132.6/84.4 to 129.0/82.1 mmHg; DASH: from 131.9/83.6 to 127.2/80.9 mmHg). The decrease in BP was found to be circadian stage-dependent, and to differ between men and women. Nighttime BP was decreased to a larger extent with the DASH than with the FV diet, a difference observed in women but not in men. Study participants who had a higher BP during the reference stage were more likely to decrease their BP to a larger extent after the 8-week dietary intervention. The FV and DASH diets had different effects on BPV. In view of the relatively large day-to-day variability in BP in both normotensive and hypertensive people, it is recommended to monitor BP around the clock for longer than 24 h, and to individualize the optimization of dietary or other intervention.

Introduction

Cardiovascular disease affects a large portion of the population. According to the 2015 report on the Global Burden of Disease [1], there were an estimated 422.7 million cases of cardiovascular disease (CVD) and 17.92 million CVD deaths in 2015. As compared to 1990, the age-standardized CVD death rate declined in all high-income and some middle-income countries. Ischemic heart disease was the leading cause of CVD health lost globally, as well as in each world region, followed by stroke. As socio-demographics increased, the highest CVD mortality shifted from women to men. CVD mortality decreased sharply for both men and women in countries with a higher socio-demographic status [1].

Anti-hypertensive drugs are useful but have side effects. For patients with pre-hypertension or mildly hypertensive patients, lifestyle modification may be a viable alternative to medication. A review of the contributions of the Nurses' Health Studies to the understanding of cardiovascular disease etiology in women provided compelling evidence that most vascular events may be prevented, by avoiding smoking, participating in regular physical activity, maintaining normal body mass index, and eating a healthy diet [2]. Among lifestyle modifications, diet was addressed in the DASH (Dietary Approaches to Stop Hypertension) Study [3–5]. The blood pressure (BP) data originally collected as part of the DASH Study are re-analyzed herein from a chronobiological viewpoint. The circadian rhythm characteristics of BP are estimated to determine how they are affected by diet, overall and separately in men and women.

Materials and methods

This investigation is a re-analysis of data originally collected by others [3–5] and made publicly available by the National

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Institutes of Health (NIH). The original study [3–5] enrolled 459 volunteers of both genders, 45 ± 10 (mean ± SD, range: 22–70) years of age (47% female; 62% minorities), with a body mass index averaging 28 ± 4 kg/m^2. The participants, recruited in five separate cohorts [5], did not receive anti-hypertensive medication. All study participants were on a control diet for three weeks, prior to being randomly assigned to one of the three dietary regimens for 8 weeks. The control diet was low in fruits, vegetables, and dairy products, with an average fat content. Of the 459 study participants,154 remained on the control diet (C), 154 were assigned to a diet rich in fruits and vegetables (FV), and 151 were assigned to a diet rich in fruits, vegetables, and low-fat dairy products, with reduced saturated and total fat (DASH). Sodium intake and body weight did not change during the study.

At the end of the 3-week initial stage and at the end of the 8-week intervention diet span, 24-h ambulatory BP monitoring (ABPM) was performed in 345 participants, which represents 95% of the individuals in the last four enrollment groups [4], Fig. 1. Records available both at the end of the reference stage and at the end of the intervention stage were obtained from 341 participants, which represents 99% of all ABPM records, Fig. 1. Records that were too short (less than 18 h) or had too many missing values (more than 25%) were not used. Overall, 24-h ABPM records from 338 participants (112, 113, and 113 in the C, FV, and DASH groups, respectively) were analyzed, Fig. 1. While originally, data were collected at 30-min intervals, the data we obtained for analysis consist of hourly averages.

A model consisting of cosine curves with periods of 24 and 12 h, which approximates the non-sinusoidal waveform of BP well, was fitted to each record to estimate the rhythm-adjusted mean (MESOR, M), and the amplitude (A) and acrophase (ϕ) of each component [6]. Circadian rhythm characteristics were further summarized by population-mean cosinor [6]. Individual parameters were compared to reference values (derived as 90% prediction limits from clinically healthy peers matched by gender and age) to identify abnormal circadian characteristics, known as vascular variability disorders (VVDs) [7].

The effect of diet in each group was assessed by comparing results at the end of the diet span to the reference profile, using the chi-square test for categorical variables or paired *t*-test for continuous variables, since normal distributions were validated. Two-sided tests were used. Bingham's parameter tests [8] were used to compare the circadian population rhythm characteristics at the end of intervention among the three diets. They also served to compare the average circadian profiles at the end versus the start of intervention for each diet.

In order to reduce inter-individual differences in BP, hourly data of study participants were expressed as a percentage of their respective 24-h average during the reference stage. In order to assess the effect of diet, data of each study participant during the intervention stage were expressed as a percentage of the 24-h mean value of the corresponding profile recorded during the reference stage. In order to visualize the results, original and relative hourly data were averaged across all individuals in each group and differences between the intervention and reference stages were plotted as a function of time.

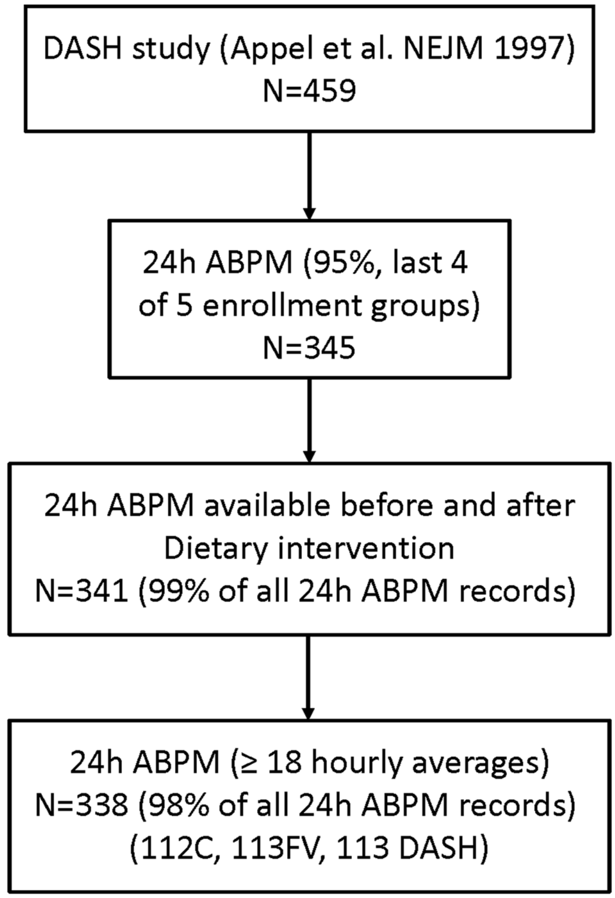

Fig. 1 Flowchart illustrating criteria used to select 24-h ABPM records for chronobiologic analysis. Of the 345 individuals who participated in around-the-clock blood pressure monitoring, four were eliminated because they were not monitored during both the reference and the intervention stages. Another three were eliminated because at least one of their two records had insufficient data to reliably estimate the circadian parameters. Overall, 98% of the 24-h ABPM records were used in this investigation.

The extent of change in systolic (S) and diastolic (D) BP associated with the dietary interventions observed in each study participant was assessed in relation to the 24-h average BP value during the reference stage by linear regression.

A *P* value below 0.05 was considered to indicate statistical significance. Correction for multiple testing was not deemed necessary as tests were independent and effects considerable.

Table 1 Circadian rhythm characteristics of systolic (S) and diastolic (D) blood pressure (BP).

Diet	*N*	*P* < 0.05 (%)	PR (%)	*P*	*M* (mmHg)	*SE* (mmHg)	*A* (mmHg)	95% CI (mmHg)	ϕ (degrees)	95% CI (degrees)	2*A*/*M* (%)
Reference stage											
SBP											
Cont	112	84.8	47	<0.001	131.2	1.0	9.61	(8.62, 10.60)	−227	(−221, −232)	14.69
FVeg	113	81.4	48	<0.001	132.6	1.0	9.63	(8.64, 10.62)	−231	(−225, −237)	14.15
DASH	113	84.1	48	<0.001	131.9	1.0	10.12	(9.10, 11.14)	−228	(−223, −232)	15.26
DBP											
Cont	112	81.3	45	<0.001	83.5	0.7	7.87	(7.00, 8.74)	−219	(−213, −225)	18.91
FVeg	113	82.3	46	<0.001	84.4	0.7	8.01	(7.23, 8.79)	−221	(−215, −227)	18.93
DASH	113	84.1	46	<0.001	83.6	0.6	8.74	(7.95, 9.53)	−222	(−218, −226)	20.83
Intervention stage											
SBP											
Cont	112	84.8	47	<0.001	131.0	1.1	9.43	(8.39, 10.47)	−224	(−217, −230)	14.37
FVeg	113	81.4	45	<0.001	129.0	1.0	8.69	(7.64, 9.73)	−228	(−221, −235)	13.26
DASH	113	85.8	47	<0.001	127.2	0.9	10.06	(9.06, 11.05)	−223	(−217, −230)	16.04
DBP											
Cont	112	79.5	45	<0.001	83.6	0.8	7.92	(7.07, 8.76)	−218	(−212, −224)	18.42
FVeg	113	83.2	45	<0.001	82.1	0.7	7.62	(6.76, 8.49)	−218	(−212, −225)	18.71
DASH	113	83.2	48	<0.001	80.9	0.6	8.75	(7.88, 9.62)	−220	(−214, −226)	22.42

Cont Control diet, *FVeg* Fruit and Vegetable diet, *DASH* Dietary Approaches to Stop Hypertension, *N* Number of study participants, $P < 0.05$, *%* Percentage of individual records showing a statistically significant 24-h rhythm ($P < 0.05$), *PR* Percentage Rhythm (proportion of variance accounted for by fitted 24-h cosine curve), *P* *P* value from zero-amplitude (no-rhythm) assumption, *M* MESOR (Midline Estimating Statistic Of Rhythm, a rhythm-adjusted mean), *A* 24-h Amplitude (half the extent of predictable change within a day), ϕ 24-h Acrophase (measure of the timing of overall high values recurring each day, expressed in negative degrees, with 360° = 24 h, 0° = local midnight), *SE* Standard Error, *95% CI* 95% Confidence Interval, *2 A/M* Relative daily change.

Results

A circadian rhythm was detected with statistical significance in most (>75%) cases. It was highly statistically significant ($P < 0.001$) by population-mean cosinor, Table 1. The control diet had little to no effect on the circadian rhythm of SBP or DBP, as determined by population-mean parameter tests ($P > 0.50$).

The incidence of individual MESORs of SBP and DBP above healthy-peer-derived upper 95% prediction limits (MESOR-hypertension) was slightly reduced on the DASH vs. C diet (SBP: 19.2% vs. 30.4%, $P = 0.054$; DBP: 21.9% vs. 36.6%, $P = 0.015$), not seen with the FV diet, Fig. 2 (left). By contrast, the FV diet (but not the DASH diet) was found to reduce the incidence of an excessive SBP-A (CHAT, brief for Circadian Hyper-Amplitude-Tension, one of the VVDs) (4.4% vs. 11.6%, $P = 0.045$), Fig. 2 (center). An odd timing (ecphasia) of the circadian rhythm of SBP was more frequently observed on the FV than on the DASH diet ($P = 0.043$), Fig. 2 (right).

The MESOR of SBP decreased on both the FV and DASH diets (FV: from 132.6 to 129.0 mmHg, $F = 6.560$, $P = 0.011$; DASH: from 131.9 to 127.2 mmHg, $F = 11.983$, $P < 0.001$). Similarly, the MESOR of DBP decreased on both diets (FV: from 84.4 to 82.1 mmHg, $F = 4.743$, $P = 0.031$; DASH: from 83.6 to 80.9 mmHg, $F = 9.557$, $P = 0.002$). The circadian amplitude and acrophase of SBP and DBP did not differ between the two study stages. The pulse pressure (PP) was decreased on both diets (FV: paired $t = 4.501$, $P < 0.001$; DASH: paired $t = 5.037$, $P < 0.001$), but not on the C diet ($P > 0.50$).

Population-mean cosinor estimates of the parameters served to reconstruct the circadian variation for comparison between the intervention and reference stages for each of the three diets. As seen in Fig. 3, the decrease in both SBP and DBP associated with the FV and DASH diets is absent on the C diet.

Not all study participants responded to the dietary intervention by a decrease in BP. On the FV diet, SBP and DBP decreased in 84 and 81 study participants, respectively, but increased in 29 and 32 others. SBP decreased up to 21.1 mmHg and DBP up to 17.3 mmHg. A decrease of at least 5 mmHg was found in 44 and 34 cases for SBP and DBP, respectively. An increase by 5 mmHg or more (by as much as 23.3 mmHg for SBP and 17.8 mmHg for DBP) was found in 11 and 10 cases, respectively. PP decreased in 77 cases, by up to 9.7 mmHg, but increased in 36 study participants, by up to 7.2 mmHg. On the DASH diet, SBP and

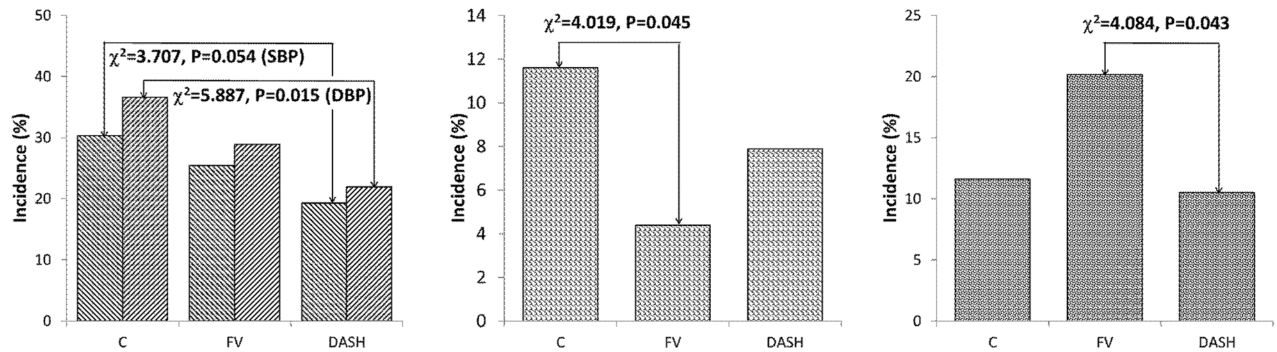

Fig. 2 As compared to reference values derived from clinically healthy peers matched by gender and age, the incidence of an elevated 24-h average (MESOR) SBP and DBP MESORs is slightly reduced on the DASH vs. Control (C) diet, not seen with the fruit and vegetable (FV) diet (left). By contrast, the incidence of an excessive 24-h amplitude of SBP is reduced on the FV diet (but not the DASH diet) (center). An odd timing (ecphasia) of the circadian rhythm of SBP was more frequently observed on the FV than on the DASH diet (right).

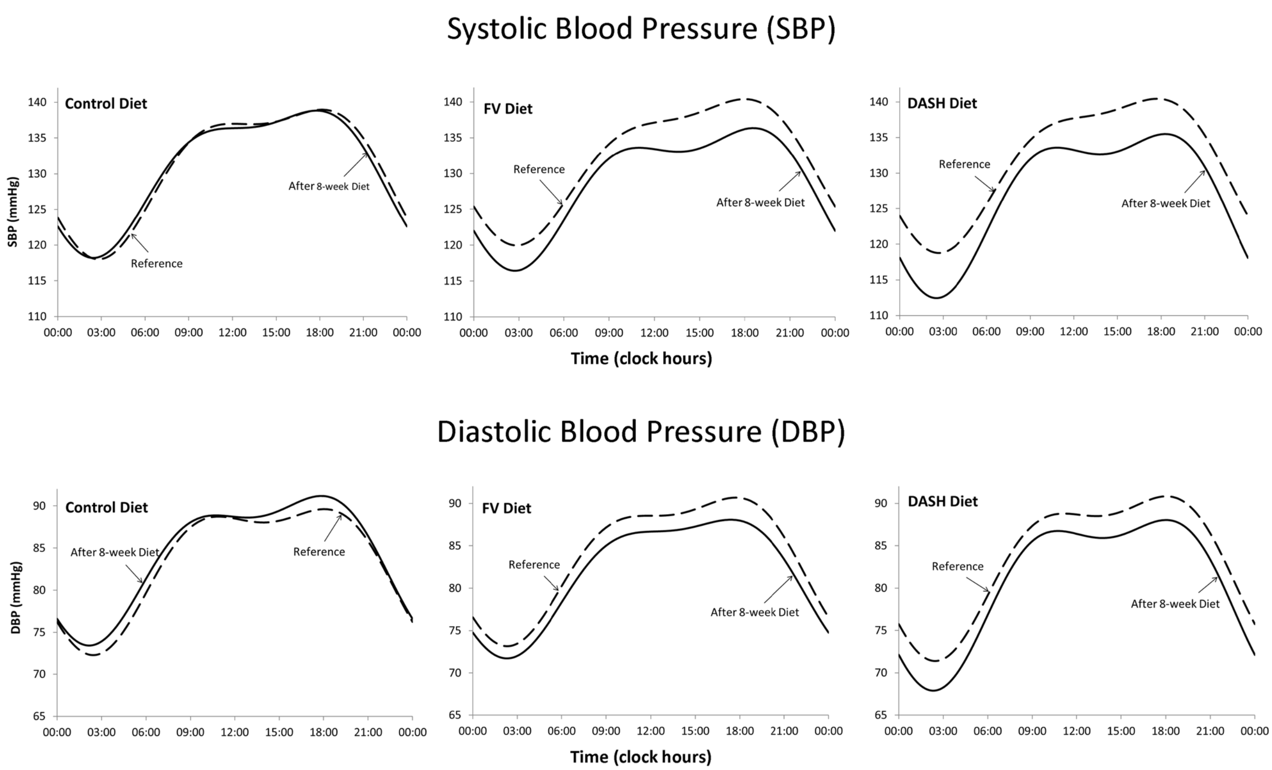

Fig. 3 Reconstructed circadian waveforms of systolic (top) and diastolic (bottom) blood pressure during the reference (dashed curves) and diet (solid curves) stage. The decrease in blood pressure associated with the fruit and vegetable (FV; center) and DASH (right) diets is absent on the control (C) diet (left).

DBP decreased in 84 and 75 study participants, respectively, but increased in 29 and 38 others. SBP decreased up to 32.4 mmHg and DBP up to 16.6 mmHg. A decrease by 5 mmHg or more was found in 43 and 36 cases for SBP and DBP, respectively. An increase by 5 mmHg or more (by as much as 13.6 mmHg for SBP and 10.2 mmHg for DBP) was found in 6 cases. PP decreased in 78 cases, by up to 15.9 mmHg, but increased in 35 study participants, by up to 9.2 mmHg.

The decrease in MESOR of SBP and DBP, and the decrease in PP did not differ significantly between the DASH and FV diets (SBP: Student $t = 1.034$, $P = 0.302$; DBP: Student $t = 0.579$, $P = 0.563$; PP: Student $t = 1.205$, $P = 0.230$). Since the FV and DASH diets had similar effects on the circadian rhythm of SBP and DBP, data from both diets were pooled to examine any gender and/or circadian-stage differences in response to the dietary intervention. Since PP was decreased by a larger

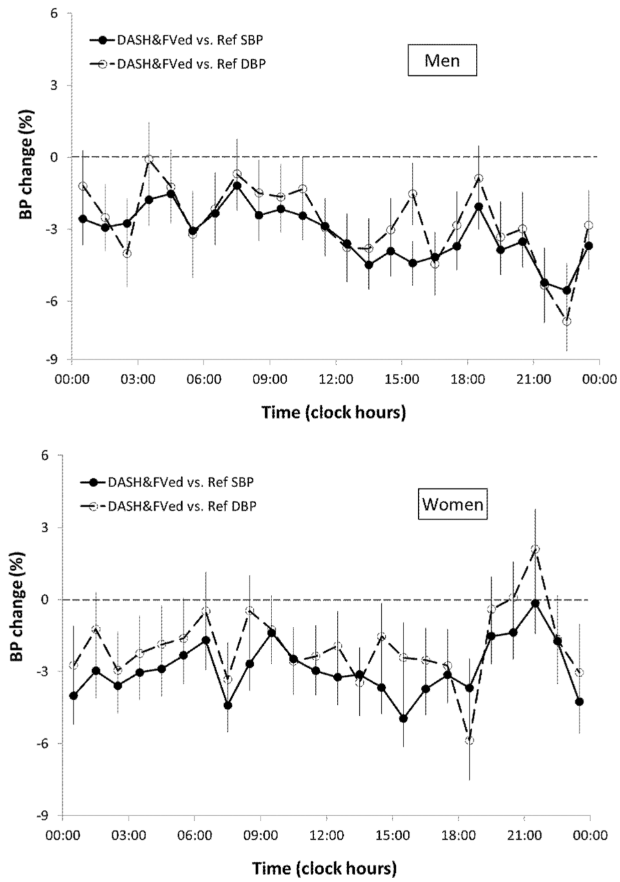

Fig. 4 The decrease in blood pressure resulting from the DASH or FV diet was not the same during the 24-h day. In men (top), blood pressure decreases most in the evening, whereas in women (bottom), blood pressure is lower throughout the day, except in the evening. Vertical scale is time-specified percentage change relative to 24-h average during the reference stage. Results shown as mean ± SE.

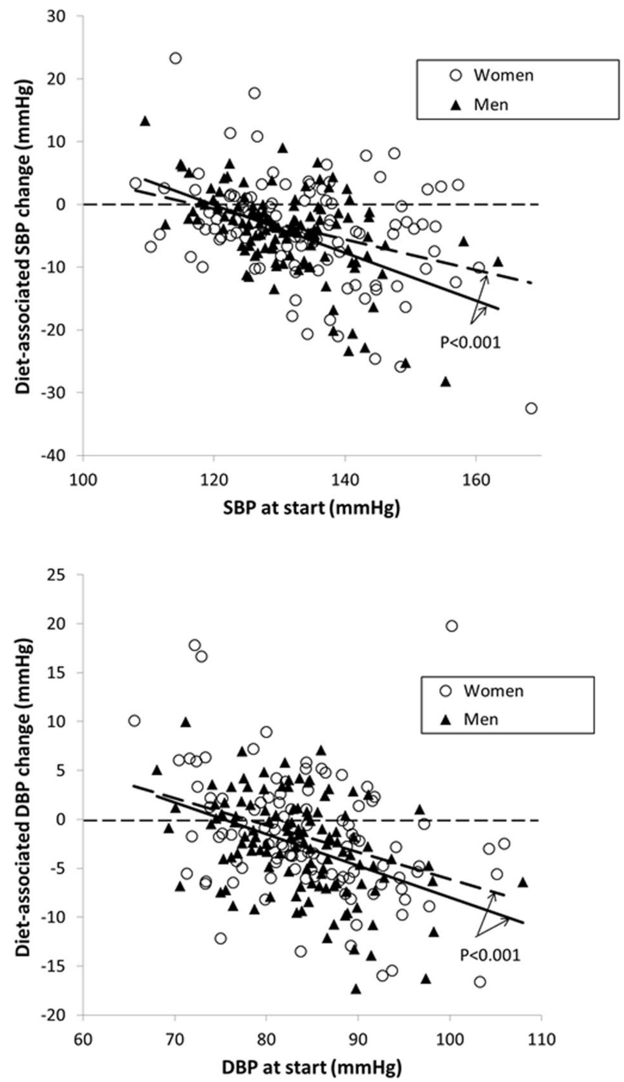

Fig. 5 Overall, most study participants on the fruit and vegetable (FV) or DASH diet responded with a decrease in systolic (top) and diastolic (bottom) blood pressure. Men (filled triangles, solid lines) and women (open circles, dashed lines) who had a higher blood pressure during the reference stage were more likely to respond with a decrease in blood pressure during the diet stage ($P < 0.001$).

extent in women than in men (Student $t = 2.561$, $P = 0.011$), the circadian response was assessed separately for men and women. As seen from Fig. 4, the decrease in BP resulting from the DASH or FV diet differs as a function of circadian stage and gender. While the BP drop is most pronounced in late evening in men, BP is slightly increased at that time in women. Depending on circadian stage, the decrease in BP can vary, on average, between 0 and about 6% of the 24-h average BP during the reference stage, which represents 8 (SBP) or 5 (DBP) mmHg, Fig. 4.

As seen from Fig. 5, both men and women who had a higher BP during the reference stage were more likely to decrease their SBP (F: $r = -0.355$, $P < 0.001$; M: $r = -0.519$, $P < 0.001$) and DBP (F: $r = -0.364$, $P < 0.001$; M: $r = -0.426$, $P < 0.001$) during the diet stage. Most study participants on the FV or DASH diet responded with a decrease in BP.

Discussion

Both the FV and DASH diets resulted, on average, in a decrease in BP, but individual responses varied greatly. Both men and women who had a higher BP during the reference stage were more likely to decrease their SBP and DBP during the diet stage (Fig. 5). On average, SBP (DBP) decreased by 3.4 (2.1) and 4.9 (2.7) mmHg in association with the FV and DASH diets, respectively. While these differences are relatively small, a dietary intervention may still be useful to reduce cardiovascular disease risk, notably since the study participants only had a mildly elevated BP at the outset. Results from the Framingham Heart Study indeed show that high-normal BP is associated with an increased risk of cardiovascular disease and that lowering high-normal BP can reduce the risk of cardiovascular disease [9]. The PREHIPER I Study yielded a similar result [10].

Like other diets such as the Mediterranean diet, the DASH diet promotes an increased intake of fruits and vegetables and reduced intake of saturated and total fat. Adherence to such healthy diets has been evaluated from the perspective of the impact of food consumption on cardiovascular disease in the light of a changing global food system [11]. It was concluded that the health effects of foods, macronutrients, and dietary patterns on cardiovascular disease was consistent across different countries, age/race/ethnicity/socioeconomic groups. Based on broad evidence gathered in their study, the optimal dietary pattern to reduce cardiovascular disease is one that emphasizes whole grains, fruits and vegetables, legumes, nuts, fish, poultry, and moderate dairy and heart-healthy vegetable oil intake. Such a dietary pattern was estimated to reduce cardiovascular disease risk by about a third [11].

Analysis of ABPM data from individuals not taking any anti-hypertensive medication shows that women have a lower BP and a higher HR than men [12]. Such differences between men and women are not observed in the DASH Study in view of the criteria used to select study participants. Differences between men and women were found, however, in the effect of dietary intervention on BP. PP was decreased by a larger extent in women than in men. Furthermore, the BP drop was most pronounced in the late evening in men, whereas BP was slightly increased at that time in women. How such differences may relate to known gender differences in coronary heart disease [13] remains to be elucidated.

As seen from Fig. 3, the most important difference between the DASH and FV diets is their effect on nighttime BP, which is decreased more on the DASH than on the FV diet. Considering data collected between 00:00 and 04:00, the DASH diet decreased SBP by 4.8 ± 0.7 mmHg, while the FV diet only decreased SBP by 2.4 ± 0.8 mmHg (Student $t = 2.284$, $P = 0.023$). This feature may have important implications in terms of cardiovascular disease risk in view of the risk associated with the lack of a sufficient BP drop by night [14, 15].

The choice between the DASH and FV diets should also consider the circadian pattern of BP at the outset, since cardiovascular disease risk is elevated not only in relation to an elevated BP mean but also in relation to an increased BP variability. This is particularly the case when the circadian amplitude of BP is excessive, a condition known as CHAT. Even in the absence of MESOR-hypertension, cardiovascular disease risk is increased in the presence of CHAT [7, 16, 17]. As shown herein, the FV and DASH diets indeed differed in their effect on the incidence of CHAT and ecphasia (Fig. 2). Whether the intervention is non-pharmacologic (such as adherence to a healthy diet) or pharmacologic [18], focus should be placed on restoring a healthy circadian variation, in addition to the desired lowering of an elevated BP.

Summary

What is known about topic

- For patients with pre-hypertension or mildly hypertensive patients, lifestyle modification may be a viable alternative to medication.
- Among lifestyle modifications, the AHA considers the DASH diet to be “specific and well-documented across age, sex and ethnically diverse groups”.
- Blood pressure undergoes a large-amplitude circadian rhythm with higher values during the active span and lower values during rest/sleep.

What this study adds

- The decrease in blood pressure associated with the DASH diet (or the fruit and vegetable diet) was not the same at all times of the day and night.
- In association with the DASH diet (or the fruit and vegetable diet), the pattern of blood pressure decrease over 24 h differs between men and women.
- Both men and women who had a higher blood pressure during the reference stage were more likely to decrease their blood pressure during the DASH (or fruit and vegetable) diet stage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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