Effect of a Walnut Diet on Office and 24-Hour Ambulatory Blood Pressure in Elderly Individuals

Findings From the WAHA Randomized Trial

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Abstract—Nut consumption lowers blood cholesterol and is associated with reduced cardiovascular disease, but effects on blood pressure (BP) are inconsistent. We assessed the 2-year effects of a walnut diet versus a control diet on office BP and 24-hours ambulatory BP in free-living elders participating in the Walnuts and Healthy Aging study, a randomized trial testing the effects of walnuts at ≥15% energy on age-related disorders. In a prespecified analysis, we enrolled 305 participants, of whom 236 (75%) completed the study (65% women; age, 69 years; 60% with mild hypertension). Walnuts were well tolerated, and compliance was >98%. Mean baseline office BP was 128/79 mm Hg. Adjusted changes from baseline in mean office systolic BP were −4.61 mm Hg (95% CI, −7.43 to −1.79 mm Hg) in the walnut group and −0.59 mm Hg (−3.38 to 2.21 mm Hg) in controls (P=0.051). Respective changes in mean systolic 24-hour ambulatory BP were −3.86 mm Hg (CI, 5.45 to −2.26 mm Hg) and −2.00 mm Hg (CI, −3.58 to −0.42 mm Hg; P=0.111). No changes in diastolic BP were observed. In participants in the upper tertile of baseline 24-hour ambulatory systolic BP (>125 mm Hg), mean 2-year systolic 24-hour BP was −8.5 mm Hg (CI, −12 to −5.0 mm Hg) in the walnut group and −2.5 mm Hg (CI, −6.3 to 1.3 mm Hg) in controls (P=0.034). During the trial, participants in the walnut group required less uptitration of antihypertensive medication and had better overall BP regulation than controls. Walnout consumption reduces systolic BP in elderly subjects, particularly in those with mild hypertension.

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High blood pressure (BP) and hypertension are major global risk factors for cardiovascular disease (CVD). The rapid pace of population aging in conjunction with the obesity epidemic is associated with a raising prevalence of metabolic disorders, which is expected to increase CVD rates in older populations. Given the social and economic burden of treating CVD and related comorbidities, identifying simple strategies to prevent CVD or delay its onset is a major public health concern.

The PREvención con Dieten MEDiterránea (PREDIMED) trial has provided high-level scientific evidence that Mediterranean diets enriched with extra-virgin olive oil or mixed nuts reduce rates of incident CVD, including stroke, in individuals at high cardiovascular risk. A sub-study of that trial showed that, compared with a control diet, both supplemented Mediterranean diets reduced BP as measured with 24-hour ambulatory BP monitoring. Besides the Mediterranean diet, other dietary patterns with high consumption of vegetables, fruit, legumes, nuts, whole grains, dairy products, and seafood and low consumption of total meat, processed meat, and sweets are associated with BP reductions in clinical trials. Among these foods, the consumption of nuts in prospective studies has been strongly and consistently associated with reduced rates of CVD and all-cause mortality. Nuts contain a variety of nutrients, including unsaturated fatty acids, fiber, tocopherols, folate, nonsodium minerals (potassium, magnesium, calcium, and selenium) and other bioactives, such as phytosterols and polyphenols. The healthy nutritional components of nuts may help explain the inverse association of their consumption with CVD. Regarding cardiovascular risk factors, there is robust clinical trial evidence that nuts reduce blood cholesterol in a dose-related manner. However, nut consumption appears...
to have little effect on office BP in clinical trials, although 24-hour ambulatory BP monitoring, the gold standard to define normal or abnormal BP values in clinical studies, have not been performed in nut studies using unrestricted-calorie diets.

The WAHA study (Walnuts and Healthy Aging) is a randomized, 2-year clinical trial conducted in free-living elders to evaluate the effects of walnut consumption on cognitive function and retinal health as primary outcomes and on systolic and diastolic office BP and 24-hour ambulatory BP (24-hour systolic and diastolic, and daytime and nighttime BP) as prespecified secondary outcomes in a sub-sample at the Barcelona site. We hypothesized that regular walnut consumption for 2 years would reduce BP in this elderly population. The findings of this WAHA sub-study are reported here.

Material and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. The WAHA study (ISRNCT01634841) is a dual center (Hospital Clinic, Barcelona; Spain; and Loma Linda University, CA), randomized, parallel-group, observer-blinded, controlled clinical trial aimed to assess whether the consumption of ≈15% of daily energy as walnuts for 2 years would prevent or slow down age-related cognitive decline and macular degeneration compared with a control diet (abstention from walnuts) in older, cognitively healthy individuals aged 65 to 75 years. To expedite recruitment, on April 9, 2014, the age range for inclusion was expanded from 63 to 79 years. The protocol has been reported in detail elsewhere. The present study was conducted only in participants recruited in the Barcelona site, where expertise and 24-hour ambulatory BP measurement devices were available. The study protocol complied with the Declaration of Helsinki, institutional review boards at each center approved the study, and all participants provided written informed consent.

Study Population

Participants were men and women aged 63 to 79 years and free of recent CVD, cancer, or neurodegenerative disorders. Exclusion criteria were: morbid obesity (body mass index ≥40 kg/m²), uncontrolled diabetes mellitus (HbA1c >8%), uncontrolled hypertension (on-treatment BP ≥150/100 mm Hg), prior stroke or major head trauma, and malignant neoplastic illness, advanced cognitive deterioration (mild cognitive impairment or frank dementia), other neurodegenerative diseases (ie, Parkinson disease), any chronic illness expected to shorten survival, bereavement, allergy to walnuts, and customary use of fish oil, flaxseed oil, or soy lecithin supplements. Thus, by randomization and masking, participants were normotensive or had mild hypertension (office BP <150/100 mm Hg) and all were at low cardiovascular risk because of absent comorbidities.

Randomization and Masking

We randomly assigned participants to either the walnut group (WG, consuming ≈15% of daily energy intake as walnuts on top of their habitual diet) or the control group (CG, following their usual diet with abstention from walnuts) using a computerized, web-based, random number table with stratification by sex and age range in a 1:1 ratio. Pairs of individuals (couples, members of the same household, and partners) entering the trial were allocated to the same group using the same stratification criteria. Walnut doses in the WG ranged from 30 to 60 g/d depending on energy requirements. All study clinicians and investigators were blind to participants’ intervention group, except for the dietitians in charge of dietary evaluations and walnut supply. All study data were recorded in a dedicated online database developed by Costaisa (Barcelona, Spain).

Procedures During Follow-up

After treatment allocation, participants were scheduled for visits with the study dietitians every 2 months for the duration of the trial. At baseline and 2 years we collected data on medical history, medication use and lifestyle, including dietary habits and physical activity, and performed anthropometric measurements, office BP and 24-hour ambulatory blood pressure monitoring, and urinary albumin excretion determinations. Throughout the duration of the study, participants were under the care of their primary care physicians, who maintained or changed medications, including antihypertensive drug treatment, according to their evaluation of risk factor levels.

Assessment of Risk Factors

Presence of hypertension, hyperlipidemia, or diabetes mellitus was diagnosed by clinical history, BP measurements or blood tests, and if participants were receiving drug treatment for these conditions. Smoking status was categorized as never, current or past smoking according to self-reports. Physical activity was assessed by a validated questionnaire and expressed in minutes at a given metabolic equivalent (MET-min) per week. Height, weight, and waist circumference were measured with standard methods. Urinary albumin excretion was measured in morning spot urine samples by turbidimetry. Albuminuria was expressed as albumin (mg)/creatinine (g) ratio; an elevated ratio was defined by values ranging between 30 and 300 mg/g.

Diet

Participants followed their self-selected diets, and no specific dietary recommendations were given except to consume the daily allotments of walnuts in the WG and to refrain from eating nuts in the CG. No advice on salt intake was provided. Every 2 months until study completion, dietitians collected and revised a 7-day weighed food record, of which 3 days (2 working days and 1 week-end day) were randomly selected. Food Processor Plus 10.0 (ESHA Research, Salem, OR) was used to translate food items into nutrients, using the built-in database of the software adapted to local foods, with data based on Spanish food composition tables. Compliance with walnuts in the WG was evaluated by recount of empty packages. As an additional measure of adherence, we assessed changes in the α-linolenic acid (ALA) proportion of red blood cell (RBC) membranes, as ALA is a fatty acid characteristic of walnuts, and its blood membrane content is an objective biomarker of consumption. Participants in the WG who had difficulty chewing because of dental problems were provided with a coffee grinder at no cost and instructed on how to eat the ground walnuts incorporated into semiliquid foods such as yogurt. All participants were advised to maintain their usual level of physical activity.

RBC Membrane Fatty Acid Analyses

Fasting blood samples were collected by venipuncture at baseline and 2 years, and aliquots of whole blood were stored at −80°C until fatty acids analysis. The RBC fatty acid profile was determined as described. In brief, cells contained in a 100 μL aliquot of EDTA-collected blood were hemolyzed and spun. The pellet (>99% RBC membranes) was dissolved in 1 mL BF3 methanol solution and heated to hydrolyze and methylate glycerophospholipid fatty acids. The fatty acid methyl esters were isolated by adding n-hexane and separated by gas-chromatography using an Agilent HP 7890 Gas Chromatograph equipped with a 30 m×0.25 mm SupraWAX-280 capillary column (Teknokroma, Barcelona, Spain), an autosampler, and a flame ionization detector. The amount of ALA was expressed as the proportion of the total fatty acids identified in the sample.

BP Measurements

Participants attended the clinic visit on a weekday between 8:00 to 10:00 AM. Office BP was measured according to current guidelines with a validated semiautomatic oscillometer (Omron HEM-705CP; Hoofddorp, the Netherlands).

Ambulatory BP monitoring was performed using SpaceLabs 90207/90217 devices (SpaceLabsW Inc, Richmond, WA), with readings scheduled every 20 minutes during the 24-hour time frame. Periods of activity and rest were determined on an individual basis.
according to a diary recording hours of sleep and waking time. The duration of the procedure in hours, the percentage of valid readings, and mean systolic BP (SBP) and diastolic BP during periods of activity and rest, and for the whole 24-hour period, were determined. We included all ambulatory BP recordings lasting 24 hours 30 minutes and having >70% measurements, including ≥1 valid measurement/h. Average 24-hour BP was defined as normal when values were <130/80 mm Hg according to the standard definition of the 7th Report of the Joint National Committee (JNC7) guidelines or <125/75 mm Hg according to the new 2017 guidelines proposed by the American College of Cardiology (ACC)/American Heart Association (AHA) and other societies.

### Statistical Analyses

The prespecified primary outcomes were the 2-year differences in office BP and 24-hour ambulatory blood pressure monitoring between the WG and CG. A target sample size of 77 individuals per group provided >80% power to detect a mean between-diet difference of 4 mm Hg (SD, 8.3) in 24-hour systolic ambulatory BP. Normal distribution of data was assessed using graphical methods and the Shapiro–Wilk test. Data are expressed as mean and SD for quantitative variables and absolute numbers (percentages) for qualitative variables. Between-group differences in cardiovascular risk factors at baseline were assessed using the χ² test or ANOVA, as appropriate. The effect of the intervention on changes in food and nutrient consumption, anthropometric variables, urinary albumin excretion, and office BP and 24-hour ambulatory BP was assessed using ANOVA. Mean BP values by group were calculated by ANOVA and, for differences, they were obtained by ANCOVA with multivariable adjustment by age, sex, body mass index, smoking, energy intake, changes in energy expenditure, baseline BP values, and use of antihypertensive medication and their on-treatment changes. Subgroup analyses were performed considering the effects of the intervention by tertiles of baseline office BP and 24-hour ambulatory BP. The same adjustments applied in the primary analysis were used for these secondary analyses. The differences in the proportions of individuals with well-controlled office BP and 24-hour ambulatory BP at baseline and at the end of the study by group assignment were calculated by the McNemar test using both the standard JNC7 cutoffs and the new 2017 ACC/AHA normality thresholds. Statistical significance was established at P<0.05 (2-tailed). Analyses were performed using SPSS software, release 19.0 (IBM Corp, Armonk, NY).

### Results

From April 2012 to December 2013, a total of 642 potential candidates were prescreened for eligibility. Eligible participants were recruited through nonprofit local organizations, advertisements in the study center, investigators contacts, and word of mouth (Figure 1). After they completed a short questionnaire, 198 candidates were excluded for various reasons, mainly for not meeting inclusion criteria. The remaining 444 candidates were formally assessed for eligibility in a face-to-face interview with the study clinician, who explained the protocol in detail, assessed potential compliance and reviewed the medical history, inclusion and exclusion criteria, and recent blood work and use of medication or supplements. This led to further exclusion of 139 candidates, leaving a final number of 305 participants who were recruited and randomly allocated to one of the 2 interventions. Because of logistic constraints, including availability of monitoring devices, ambulatory BP was not measured in 28 participants. From the 305 individuals considered for 24-hour BP measurement, 69 (23%) dropped out for various reasons, as shown in Figure 1, leaving 116 and 120 evaluable participants in the WG and CG, respectively. The characteristics of dropouts were similar to those of the whole cohort (data not shown). Follow-up was terminated after intervention for 2 years between April 2014 and December 2015.

The baseline characteristics of participants completing intervention for 2 years were well balanced between the 2 groups, except for body mass index, which was higher in the CG (Table 1). The mean age was 68.9 years, 41% were men, 53.4% had dyslipidemia, 11.1% were diabetic, and 60% had a JNC7 diagnosis of hypertension (72% by 2017 AHA cutoffs), with mean office BP values at baseline of 128.8/78.3 mm Hg. Among the 142 participants with a diagnosis of hypertension, 74 (52%) had well-controlled BP values by JNC7 standards (office BP <140/90 mm Hg).

### Tolerance and Side Effects

Supplemental walnuts were generally well tolerated. There were 4 dropouts in the WG because of severe dyspepsia attributed to walnuts, whereas 20 participants had milder dyspepsia, which was solved by temporarily reducing walnut doses. Additionally, 16 participants required grinding the walnuts because of difficulty chewing because of bad dentures. Concerning bowel habit, of 116 participants in the WG, 64 (55%), 44 (38%), and 8 (7%) reported no change, improvement (softening of previously hard stools), or worsening (harder or inconveniently soft stools), respectively. Respective values in 120 CG participants were 113 (94%), 4 (3.5%), and 3 (2.5%).

### Energy and Nutrient Intake

All participants followed a typical Mediterranean dietary pattern characterized by high-fat and high-monounsaturated fatty acid intake at baseline because of customary use of olive
increased significantly the intake of energy and total fat and potassium, which were higher in the WG (Table 2).

After 2 years of walnut supplementation, WG participants had a roughly equivalent level (units of energy expenditure in physical activity 1 MET-min is equivalent to 1 kcal).

Energy expenditure in physical activity, MET-min/wk

Hypertension, n (%)‡

Office systolic BP, mm Hg

Office diastolic BP, mm Hg

Dyslipidemia, n (%)†

Type 2 diabetes mellitus, n (%)‡

Educational level, n (%) 0.635

Primary education 44 (37.9) 52 (43.3)

Secondary education 28 (24.1) 24 (20.0)

Academic/graduate 44 (37.9) 44 (36.7)

Medication use, n (%) 0.791

Antihypertensive agents

ACE inhibitors/ARB

Diuretics

Calcium channel blockers

Other antihypertensive drugs

Antidiabetic medication

Oral hypoglycemic agents

Insulin

Hypolipidemic drugs

Statins

Other lipid-lowering drugs

Antiplaque therapy

Values are means (SD) except for qualitative variables, expressed as n (%).

ACE indicates angiotensin-converting enzyme; ARB, aldosterone receptor blockers; BP, blood pressure; and MET-min, minutes at a given metabolic equivalent level (units of energy expenditure in physical activity 1 MET-min is roughly equivalent to 1 kcal).

†P value for comparisons between groups by χ² test for categorical variables and 1-way ANOVA for continuous variables.

‡According to the JNC7 definition (BP ≥140/90 mm Hg or antihypertensive medication).

§According to the 2017 ACC definition (BP ≥130/80 mm Hg or antihypertensive medication).

Changes in Medication

There were few antihypertensive medication changes during the study, but they differed between the 2 groups, with 7 and 16 participants having add-on medication prescribed by their primary care physicians in the WG and CG, respectively (P=0.046).

Urinary Albumin Excretion

Similar urinary albumin excretion values were observed in the 2 groups at baseline and at the end of the study (Table S1). At baseline, 8 and 9 participants in WG and CG, respectively, disclosed an elevated urinary albumin-creatinine ratio, although at the end of the study there were 3 less participants per group, without between-group differences.

Changes in BP

In analyses were done by originally assigned group, baseline office BP and 24-hour BP values were similar between the 2 groups. Table 3 shows that office SBP and diastolic BP decreased significantly from baseline in the WG, but not in the CG, and between-group differences approached statistical significance for SBP (P=0.051). Twenty-four-hour and daytime ambulatory BP decreased significantly from baseline in the 2 groups, although nighttime ambulatory BP decreased significantly from baseline only in the WG. Whereas the changes in 24-hour, daytime and nighttime ambulatory BP were more pronounced in the WG compared with controls, confirming good adherence to the intervention.

Energy Expenditure and Adiposity

Small changes of energy expenditure in self-reported physical activity were observed in the 2 groups: −394 MET-min/wk (95% CI, −647 to −140) in the WG and −207 MET-min/wk (−459 to 44) in the CG (P=0.305 for between-group comparison). Respective changes in body weight were 0.27 kg (−0.22 to 0.75) and −0.29 kg (−0.77 to 0.19; P=0.112), although waist circumference increased slightly and to a similar extent in the 2 groups: 0.31 cm (0.14–0.76) in the WG and 0.47 cm (0.02–0.93) in the CG (P=0.613).

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To ascertain whether diet effects on BP related to baseline values, we categorized both office and ambulatory BP in
The results of this exploratory analyses (Table S2) show that, in the 2 groups, all measures of both systolic and diastolic BP tended to increase in the bottom tertile and to decrease in the middle tertile, although there was generally a marked reduction in the top tertile. Adjusted changes usually favored the WG and, for 24-hour ambulatory BP, were significantly different.
control rates of BP at baseline, defined by either JNC7 or 2017 AHA cutoffs, were similar between the 2 intervention groups according to both office BP and 24-hour BP (Tables S3a and S3b). By JNC7 standards, 24-hour and daytime ambulatory BP regulation improved significantly (\( P < 0.005 \)) at 2 years in the WG but not in the CG, whereas office BP and nighttime ambulatory BP control were similar between groups (Table S3a). When considering 2017 AHA thresholds, the control of office BP improved significantly (\( P = 0.004 \)) in the WG but not in the CG, whereas control by ambulatory BP improved similarly in the 2 intervention groups (Table S3b). White-coat hypertension, defined by elevated office BP with normal 24-hour ambulatory BP values, was present in <5% of participants at baseline and up to 10.4% at 2 years by JNC7 cutoffs, with similar rates in the 2 groups (Table S3a). The proportion of participants with white-coat hypertension was more than doubled at both baseline and study’s end when considering the new ACC/AHA thresholds (Table S3b).

### Discussion

In this prespecified sub-study of the WAHA trial, a diet supplemented with walnuts at \( \approx 15\% \) energy during 2 years resulted in a nearly significant (\( P = 0.051 \)) mean 4.6 mm Hg reduction in systolic office BP and nonsignificant reductions in office diastolic BP or 24-hour ambulatory BP values compared with a control diet in fit elders (mean age 69 years), of whom 60% had mild hypertension, treated pharmacologically in most of them and well controlled in 52%. Given the relatively low baseline office BP values in the cohort (mean 129/78 mm Hg) and the difficulty to detect net differences when the baseline level is low,\(^22\) we categorized BP in tertiles and found significant reductions of \( \approx 8 \) mm Hg in mean systolic 24-hour and nighttime ambulatory BP in the top tertile (mean 24-hour systolic ambulatory BP >125 mm Hg) of the WG compared with the CG. Importantly, during the trial, less participants in the WG required uptitration of antihypertensive medication for BP control than those in the CG and BP control by 24-hour and daytime ambulatory BP monitoring improved significantly in the WG but not in the CG. No other lifestyle recommendations were given, and at the end of the study the 2 groups had similar body weight and levels of physical activity and sodium intake, albeit WG participants increased intakes of energy, total and polyunsaturated fat, and nonsodium minerals, reflecting the energy and nutrient composition of walnuts. Thus, the beneficial effect of the intervention on BP can be reasonably ascribed to walnut consumption in itself.

Of note, walnut supplementation for 2 years did not lead to unwanted weight gain in spite of the extra energy they contributed to the diet. The lack of a weight-promoting effect of nuts has been attributed in part to their satiating effect, which leads to a reduction in energy intake and to a deficit of metabolizable energy because of inefficient energy absorption leading to

### Table 3. Office and Ambulatory Blood Pressure at Baseline and Changes at 2 y by Study Group

| Blood pressure, mm Hg | Walnuts (n=116) | Control Diet (n=120) | \( P \) Value* |
|-----------------------|----------------|---------------------|---------------|
| **Systolic**          |                |                     |               |
| Office Baseline       | 128.9 (125.9 to 132.0) | 127.0 (124.0 to 130.1) | 0.385         |
| Change                | -4.61 (−7.43 to −1.79) | -0.59 (−3.38 to 2.21) | 0.051         |
| 24-Hour Baseline      | 121.4 (119.4 to 123.3) | 120.8 (118.9 to 122.8) | 0.714         |
| Change                | -3.86 (−5.45 to −2.26) | -2.00 (−3.58 to −0.42) | 0.111         |
| Daytime Baseline      | 124.9 (122.9 to 126.9) | 124.2 (122.2 to 126.2) | 0.632         |
| Change                | -3.87 (−5.55 to −2.20) | -2.60 (−4.26 to −0.94) | 0.296         |
| Nighttime Baseline    | 113.0 (110.8 to 115.3) | 113.2 (110.9 to 115.4) | 0.939         |
| Change                | -2.29 (−4.33 to −0.25) | 0.08 (−1.97 to 2.13) | 0.114         |
| **Diastolic**         |                |                     |               |
| Office Baseline       | 79.3 (77.7 to 80.9) | 78.3 (76.7 to 79.8) | 0.350         |
| Change                | -1.76 (−3.34 to −0.18) | 0.02 (−1.54 to 1.59) | 0.121         |
| 24-Hour Baseline      | 70.3 (69.1 to 71.6) | 70.3 (69.0 to 71.5) | 0.945         |
| Change                | -2.86 (−3.88 to −1.85) | -2.59 (−3.59 to −1.58) | 0.707         |
| Daytime Baseline      | 73.4 (72.1 to 74.8) | 73.1 (71.8 to 74.5) | 0.764         |
| Change                | -2.99 (−4.08 to −1.91) | -2.96 (−4.03 to −1.88) | 0.962         |
| Nighttime Baseline    | 63.7 (62.3 to 65.2) | 63.8 (62.4 to 65.2) | 0.928         |
| Change                | -1.84 (−3.16 to −0.52) | -0.97 (−2.29 to 0.36) | 0.366         |

Data are expressed as mean (95% CI). Changes for which the 95% CI does not include zero are significantly different from baseline values.

* \( P \) value for comparisons between groups by 1-way ANOVA and for comparisons of changes by ANCOVA with multivariable adjustment by age, sex, BMI, smoking, energy intake, changes in energy expenditure, and use of antihypertensive medication and their on-treatment changes.

\( P = 0.034 \) from the CG for mean top tertile systolic ambulatory BP (−8.5 versus −4.2 mm Hg) but not mean diastolic ambulatory BP (−5.8 versus −5.3 mm Hg), as shown in Figure 2. Table S2 shows that nighttime ambulatory BP in the top tertile also decreased to a significantly greater extent (\( P = 0.023 \)) in the WG than in the CG (−8.3 versus −2.5 mm Hg).

Control rates of BP at baseline, defined by either JNC7 or 2017 AHA cutoffs, were similar between the 2 intervention groups according to both office BP and 24-hour BP (Tables S3a and S3b). By JNC7 standards, 24-hour and daytime ambulatory BP regulation improved significantly (\( P < 0.005 \)) at 2 years in the WG but not in the CG, whereas office BP and nighttime ambulatory BP control were similar between groups (Table S3a). When considering 2017 AHA thresholds, the control of office BP improved significantly (\( P = 0.004 \)) in the WG but not in the CG, whereas control by ambulatory BP improved similarly in the 2 intervention groups (Table S3b). White-coat hypertension, defined by elevated office BP with normal 24-hour ambulatory BP values, was present in <5% of participants at baseline and up to 10.4% at 2 years by JNC7 cutoffs, with similar rates in the 2 groups (Table S3a). The proportion of participants with white-coat hypertension was more than doubled at both baseline and study’s end when considering the new ACC/AHA thresholds (Table S3b).
The lack of fattening effect of the walnut doses used in the trial.23 A recent report from the Loma Linda site of the WAHA study confirms increased fecal fat excretion.5 Also, in our study, the decrease in total carbohydrate reciprocal to the increased fat intake from walnuts was associated with a significant reduction in intake of simple sugars, which may help curb weight gain. A recent report from the Loma Linda site of the WAHA study confirms the lack of fattening effect of the walnut doses used in the trial.23

The present results provide high-level scientific evidence on the effects of walnuts on BP in the elderly. Till now, the evidence from meta-analyses of randomized feeding studies has been that nuts in general11,12 or walnuts in particular24 have no effect on office BP. However, BP results in prior studies were usually derived from post hoc analyses, and most trials had low statistical power. To our knowledge, only 2 prior controlled trials assessed 24-hour ambulatory BP in response to nut feeding. A study by Doménech et al8 conducted within the frame of the PREvención con Dleta MEDiterránea (PREDIMED) trial in 235 individuals at high cardiovascular risk, most with treated hypertension, showed that Mediterranean diets supplemented with extra-virgin olive oil or mixed nuts (30 g per day: 15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts) reduced 24-hour ambulatory BP compared with the control diet after intervention for 1 year. However, as there were other dietary changes in the PREvención con Dleta MEDiterránea (PREDIMED) study, this beneficial effect cannot be solely ascribed to nut consumption. Dhillon et al25 conducted a 12-week study in overweight but otherwise healthy middle-aged adults undergoing an energy-restricted diet with or without almond supplementation and detected no changes in 24-hour ambulatory BP, but participants in the almond group who were good compliers with the intervention had a significant reduction in office diastolic BP compared with the CG.

Among nuts, walnuts are particularly well suited to have BP effects because they contain little sodium and possess a complex nutrient matrix, including sizable amounts of bioactive molecules: ALA, the vegetable n-3 fatty acid, the metabolism of which gives rise to vasodilatory and anti-inflammatory oxylipins; γ-tocopherol, a form of vitamin E active in reducing oxidation and inflammation; nonsodium minerals with BP-lowering effects such as potassium, magnesium and calcium; arginine, the amino acid precursor of the endogenous vasodilator nitrous oxide; and characteristic polyphenols disclosing potent antioxidative and anti-inflammatory actions.26 Indeed, walnuts are the only nut type shown to consistently improve endothelial function in controlled trials testing nut diets for effects on vascular reactivity.27

Presently compelling evidence has accumulated that the lowest incidence of cardiovascular complications is observed among individuals with normal SBP and even slightly elevated SBP significantly increase CVD risk and mortality, although the protective effect of antihypertensive therapy directly relates to the achieved SBP lowering.24 Such level of evidence underlies the lower thresholds to define hypertension for office BP and ambulatory BP monitoring proposed by the new ACC/AHA guidelines.20 Hence, the SBP-lowering effect of a walnut diet demonstrated by 24-hour ambulatory BP monitoring in participants with elevated BP or mild hypertension is particularly important. Recent data from a large registry indicating that 24-hour systolic ambulatory BP is a stronger predictor of all-cause and cardiovascular mortality than office SBP29 further support the clinical relevance of our findings. Together with their cholesterol-lowering effect, the antihypertensive effect of walnuts also helps explain the consistent reduction in CVD rates and mortality observed in prospective studies.30 That a safe, low-cost, nonpharmacological intervention such as regular walnut consumption helps lower SBP among individuals at low cardiovascular risk with elevated BP and mild hypertension is important, given that antihypertensive drug treatment in this situation appears to have little impact on CVD outcomes or mortality and could be associated with an increased risk of adverse events.30

Of note, the reduction in incident stroke observed with a Mediterranean diet supplemented with nuts in the PREvención con Dleta MEDiterránea (PREDIMED) trial3 supported a recommendation of the 2014 AHA/American Stroke Association guideline for the primary prevention of stroke.31 The benefit on stroke of such a diet, together with their demonstrated BP-lowering effect4 also informed the recent lifestyle recommendations of the ACC/AHA hypertension guidelines20 and the 2018 European Guidelines42 as the first attempt to reduce BP at high-normal range (SBP, 120–139 mm Hg) in individuals at low cardiovascular risk.

Our study has limitations. First, participants could not be blinded to the intervention, since it was made up of a whole food. Second, except for their age, participants were at low cardiovascular risk and their BP values were not elevated.

![Figure 2. Changes in systolic (A) and diastolic (B) 24-hour ambulatory blood pressure by tertiles of baseline ambulatory blood pressure. Values are means; error bars are 95% CIs. *P value for comparisons between groups by 1-way ANOVA and for comparisons of changes by ANCOVA are means; error bars are 95% CIs. *P value for comparisons between groups by 1-way ANOVA and for comparisons of changes by ANCOVA.
thus compromising the detection of BP changes because of the intervention. Finally, the study sample was an elderly cohort, thus the results cannot be easily extrapolated to younger individuals. The study has also strengths, such as the randomized design with a sizable population and long follow-up; the relatively good retention rate for such an elderly sample; the use of objective biomarkers to confirm adherence to the intervention; and the evaluation of BP outcomes with 24-hour ambulatory BP monitoring, a technique that minimizes imprecision and is of choice for clinical trials.

In conclusion, the results of our randomized feeding study provide good level scientific evidence that walnut consumption has BP-lowering effect and can be used safely in the dietary management of hypertension. The data support the recommendation to incorporate walnuts to a healthy dietary pattern to help control BP and reduce cardiovascular risk in individuals with elevated BP.

Perspectives

In a randomized controlled clinical trial conducted in 236 elderly individuals at low cardiovascular risk, we showed that supplementation of the usual diet with walnuts at ≥15% of energy during 2 years reduced office SBP in the whole cohort and mean systolic 24-hour ambulatory BP in those with elevated BP and mild hypertension compared with a control diet without nuts. That regular consumption of a single whole food appears to be a useful adjunct to dietary and pharmacological approaches for improving the control of high BP has public health implications because it might help reduce the burden and attendant side-effects of pharmacological treatment of mild hypertension. These results should be confirmed in younger individuals and in non-Mediterranean cohorts.

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**Novelty and Significance**

**What Is New?**

- The results of our randomized feeding trial provide high-level scientific evidence that regular walnut consumption has a blood pressure (BP)-lowering effect in elderly individuals at low cardiovascular risk.

**What Is Relevant?**

- Long-term consumption of a single whole food with a rich nutrient composition such as walnuts can help control BP and reduce the need of antihypertensive medication among individuals with elevated BP and mild hypertension, and might thus be used safely in the dietary management of hypertension.

**Summary**

Our data support the recommendation to incorporate walnuts to a healthy dietary pattern to reduce BP and increase BP control rates, particularly among individuals with elevated BP and low overall cardiovascular risk.