Systematic Review

The Effect of the Mediterranean Diet on Hypertension: A Systematic Review and Meta-Analysis
Mariela Nissensohn, PhD1,2; Blanca Román-Viñas, MD, PhD2,3,4; Almudena Sánchez-Villegas, PhD1,2; Suzanne Piscopo, PhD5; Lluis Serra-Majem, MD, PhD1,2

ABSTRACT
Objective: The adoption of a Mediterranean diet (MD) pattern of eating is often described as a strategy to help prevent or manage hypertension. However, this dietary regimen has not been reviewed systematically for its efficacy against hypertension. Therefore, the purpose of this study was to analyze the effect of interventions of at least 1 year duration on blood pressure (BP) values through a systematic review and meta-analysis. The focus was on interventions comparing an MD with a low-fat diet.

Design: The authors accessed and searched PubMed and Scopus databases up to March, 2015. Randomized control trials comparing MD vs low-fat diet were included. The researchers assessed the methodological quality, extracted the valid data, and conducted the meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: Six trials (more than 7,000 individuals) were identified. Meta-analysis showed that interventions aiming at adopting an MD pattern for at least 1 year reduced both the systolic BP and diastolic BP levels in individuals with normal BP or mild hypertension. The effect was higher for the systolic BP (–1.44 mm Hg) but also consistent for the diastolic BP (–0.70 mm Hg). However, the results have to be interpreted with caution owing to the reduced number of studies eligible for inclusion in this meta-analysis. This situation limited the statistical power of the analyses. Furthermore, in all analyses, the pooled effect estimation showed a high evidence of heterogeneity, which compromises the validity of the pooled estimates.

Conclusions and Implications: A positive and significant association was found between the MD and BP in adults. However, in all cases the magnitude of the effect was small. Based on this limited group of studies and their heterogeneity, the authors found insufficient convincing evidence to suggest that the MD decreased BP. Further standardized research is urgently needed to reach evidence-based conclusions to clarify the role of MD in BP management, particularly in Europe and other societies where prevalence of cardiovascular diseases is increasing.

Key Words: Mediterranean diet, low-fat diet, hypertension, meta-analysis (J Nutr Educ Behav. 2016;48:42-53.)

Accepted August 31, 2015. Published online October 21, 2015.

INTRODUCTION
The Mediterranean diet (MD) was identified as a healthy diet in the middle of the 20th century, after the end of World War II, when the Greek government invited the Rockefeller Foundation to conduct an epidemiological study of the island of Crete in 1953.1 Three decades later, Ancel Keys and colleagues2 evaluated the relationship between the current diet and other coronary risk factors in 7 countries, some of which were in the Mediterranean Basin. The results obtained demonstrated the protective effect of a Mediterranean dietary pattern on cardiovascular disease (CVD) and mortality.
From the second half of the 20th century (1960), when the 7 countries study was conducted, to the second decade of the current century, the prevalence of CVD has increased in the Mediterranean countries, in Europe, and globally.5 Although the number of deaths attributed to CVD have decreased in most of the developed countries or followed a flat pattern in some Mediterranean countries over the decades,4 in 2014 the leading cause of death worldwide was some type of CVD, even in most of the Mediterranean countries.6 The main risk factor for developing CVD is high blood pressure (BP). The prevalence of raised BP in adults (defined as systolic and/or diastolic BP ≥ 140/90 mm Hg) ranges from 19% (Israel) to 36% (Croatia) in the Mediterranean countries.5 The worldwide prevalence of high BP is 24% for males and 21% for females.5

Adoption of a healthy lifestyle, including consuming an adequate diet and engaging in moderate to vigorous activity, would reduce the prevalence of CVD by lowering its main risk factors, mainly hypertension, obesity, and dislipidemia.6 The American College of Cardiology and the American Heart Association recently published updated recommendations for lowering BP based on a review of randomized controlled trials (RCTs), observational studies, meta-analyses, and systematic reviews of studies carried out in adults. The analysis concluded with the recommendation to follow a dietary pattern that emphasizes intake of vegetables, fruit, and whole grains; it includes low-fat dairy products, poultry, fish, legumes, and nontraditional vegetable oils and nuts, and limits intake of sweets, sugar-sweetened beverages, and red meats.7 Such a pattern can be recognized in the Dietary Approaches to Stop Hypertension (DASH) diet and in the MD. According to the American College of Cardiology/American Heart Association report, there was strong evidence for recommending the DASH diet to reduce BP levels, but evidence for recommending the MD was low. Studies that evaluated the MD and its effect on BP levels that were included in the report were published up to 2009. The analysis included one observational study and 1 RCT.7

To evaluate the MD–BP relationship further, the purpose of this study was to conduct a systematic review and meta-analysis to analyze the effect of MD compared with low-fat diet (LFD) interventions, with at least 1 year duration, on BP values.

METHODS

Search Strategy

The researchers performed a systematic review and meta-analysis of RCTs that assessed the effects of MD on systolic BP (SBP) and diastolic BP (DBP). This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines,8 an assessment tool that helps ensure the quality of systematic reviews and meta-analyses.9 The searches were performed for literature published up to March, 2015. The authors accessed PubMed and Scopus using the search terms Mediterranean diet or Mediterranean diet score or Mediterranean diet pattern or Mediterranean food pattern or Mediterranean diet index AND hypertension or essential hypertension AND low fat diet AND adults AND randomized controlled trial or controlled clinical trial. The search strategy was adapted to each database methodology. No language or time restriction was applied. In addition, the reference list of the retrieved articles was searched to find other relevant articles.

Selection of Articles

Articles were considered eligible for inclusion if they were RCTs performed in adults and humans and if they examined the effect of MD on BP. Main outcomes of interest were mean and SD changes in systolic and diastolic BP in the MD study populations and in the LFD study populations, where the latter was employed as a control. To be included, the studies had to have lasted at least 12 months.

Exclusion criteria were studies conducted in animals; nonprimary studies (eg, letters and narrative literature reviews); duplicate publications; studies in which the MD to BP relationship was not reported or they were reported using estimators different from those used in the current analysis (mean difference and 95% confidence interval [CI]); studies with a period of intervention lower than 12 months; studies that investigated the effects of the MD on BP in terms of macronutrients; studies that used as a control group different kinds of diet other than one low in fat (rich in protein or in carbohydrate); studies published before 2000; and studies whose intervention was only an education program.

Two reviewers (BRV and MN) independently screened titles and abstracts obtained from the search strategy for eligibility. Discrepancies were discussed and resolved before screening the remaining references. The articles were included only when both reviewers agreed that titles and abstracts met the inclusion criteria. When a title and abstract could not be included with certainty, the full text of the article was obtained and then further evaluated. After the initial screening process, full-text articles were obtained. The procedure for the identification, selection of articles, and data extraction is illustrated in Figure 1.

Data Extraction

Data were extracted from each study and organized using a standard form. When necessary, data were requested from the authors. The data extracted were the name of first author, year of publication and country where the study was conducted, number of participants, duration of the intervention, type of intervention diet and control diet, mean and SD values of the SBP and DBP in the intervention group and in the control group, changes within the intervention group from baseline to the end of the intervention, and changes between the intervention vs the control groups at 24 months or earlier. Finally, the 95% CI and SE of change for each study were reported.

Assessment of Risk of Bias in Included Studies

To evaluate the quality of the studies, the risk of bias was assessed following internal validity indicators regarding RCT methodology. Items collected during data extraction were: (1) method of
sequence generation and (2) adequate allocation; (3) blinding to study protocol; (4) number of study participants at start, attrition numbers, and attrition reasons; (5) completeness of outcome data; (6) adequacy of funder acknowledgment; and (7) other potential funding bias. Based on these indicators, 2 reviewers (BRV and MN) assessed the overall risk of bias. Disagreements were resolved by discussion. Criteria for judging these indicators were adapted from the Cochrane Handbook for Systematic Reviews.10 Low risk of bias was indicated if the study was randomized, the randomization method was at least partially described, attrition numbers and attrition reasons were stated (or there were no attrition), the completeness of outcome data were reported, the funder was acknowledged, and there was other potential funding bias. All others studies were considered to have moderate bias if they met any of these criteria or to have a high risk of bias if they met none of the criteria.

Statistical Analyses

The method used to review differences systematically was a formal meta-analysis.11 A random-effects model was considered to be more appropriate than a fixed-effects model. A separate meta-analyses using changes in SBP and DBP after the nutritional intervention as the outcome variable was conducted. Two different interventions, MD intake and LFD intake, were considered. Thus, mean and SE of changes in SBP and DBP in each intervention group were calculated and used for the meta-analysis. With this information, the pooled effect as the average difference in BP changes between MD intake and LFD intake was calculated.

The model of DerSimonian and Laird12 was used to pool the estimates of mean differences across studies. With this model, a pooled mean difference estimate was calculated as a weighted average of the mean differences reported in each study. The formula used to estimate the weighted effect size13 was:

\[ ds = \frac{\Sigma d_i W_i}{\Sigma W_i} \]

where \( ds \) is the summary estimate of the difference in BP changes between participants assigned to the MD and those assigned to an LFD. The weight \( (W_i) \) of each study was computed as:

\[ W_i = \frac{1}{V_i + \chi^2} \]

where \( V \) is the variance of each study and \( \chi^2 \) is the interstudy variance.

Finally, \( d_i \) was calculated as the difference in BP changes between participants assigned to the MD and those assigned to an LFD in each individual study. Besides this, a 95% CI for the pooled estimated of effect size was calculated:

\[ 95\% \ CI = ds \text{ pooled} \pm (1.96 \times SE \text{ pooled}) \]

where SE is the SE of the pooled estimate.11

A test of heterogeneity was calculated, estimating Q statistics, which follows a chi-square distribution with degrees of freedom \( n-1 \), in which \( n \) is the number of studies included in the analysis. The \( I^2 \) index measures the extent of the heterogeneity. A low \( P \) for this statistic (lower than .05) indicates the presence of heterogeneity, which compromises the validity of the pooled estimates.14

Because significant heterogeneity was clearly evident in the pooled difference estimates for all studies combined in each outcome, potential sources of heterogeneity were evaluated by subset analysis. Sensitivity analyses were fitted, excluding the studies considered candidates to act as effect modifiers. Then, the pooled estimate of the differences of BP changes was recalculated.

The authors used SPSS for Windows (version 20.0, SPSS Inc, Chicago, IL, 2011), and Review Manager (version 5.3, The Cochrane Collaboration, Copenhagen, Denmark, 2014) to conduct the statistical analyses.

RESULTS

A total of 180 articles were identified in the initial search strategy. After applying the inclusion and exclusion criteria, 28 articles were potentially relevant. An additional 5 papers identified during the manual search process. After reading the full article and the details of each study, a total of 6 RCTs were selected for meta-analysis (Figure 1).

Table 1 lists descriptive characteristics of the studies included in the meta-analysis. The 6 studies included 7,987 participants with individual study sizes ranging from 50 to 2,441. Three studies were conducted in Italy,15-17 1 in Israel,18...
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Characteristics of Sample</th>
<th>Duration of Intervention</th>
<th>Characteristics of Intervention Group</th>
<th>Characteristics of Control Group</th>
<th>Combined With Antihypertensive Drugs</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al, 2003</td>
<td>Italy</td>
<td>Premenopausal obese women aged 20–46 y</td>
<td>24 mo</td>
<td>Low-energy MD: First year: 1,300 kcal/d Second year: 1,500 kcal/d 50% to 60% carbohydrates, 15% to 20% proteins, &lt; 30% total fat, &lt; 10% saturated fat, 10% to 15% monounsaturated fat, 5% to 8% polyunsaturated fat, 18 g fiber/1,000 kcal Individual guidance on physical activity Personalized education on reducing dietary calories Behavioral and psychological counseling</td>
<td>General information about healthy food choices and exercise at subsequent monthly visits. No individualized programs.</td>
<td>No drugs</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Esposito et al, 2004</td>
<td>Italy</td>
<td>Patients with metabolic syndrome</td>
<td>24 mo</td>
<td>No energy restriction was specifically advised Patients received personalized education in reducing dietary calories, personal goal setting, and self-monitoring using food diaries. Behavioral and psychological counseling was also offered. Composition of diet was: carbohydrates, 50% to 60%; proteins, 15% to 20%; total fat, &lt; 30%; saturated fat, &lt; 10%; and cholesterol consumption, &lt; 300 mg/d. Moreover, patients were advised to consume at least 250–300 g fruit, 125–150 g vegetables, and 25–50 g walnuts/d; and 400 g whole grains (legumes, rice, maize, and wheat) daily, and to increase consumption of olive oil. Guidance on increasing level of physical activity was also given</td>
<td>General oral and written information about healthy food choices at baseline and at subsequent visits was offered: macronutrient composition of diet was similar to that for intervention group (carbohydrates, 50% to 60%; proteins, 15% to 20%; and total fat, &lt; 30%) No individualized program Guidance on increasing level of physical activity was also given</td>
<td>No drugs</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Characteristics of Sample</th>
<th>Duration of Intervention</th>
<th>Characteristics of Intervention Group</th>
<th>Characteristics of Control Group</th>
<th>Combined With Antihypertensive Drugs</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al, 2009</td>
<td>Italy</td>
<td>Overweight people with newly diagnosed type 2 diabetes who were never treated with antihyperglycemic drugs and had glycated hemoglobin levels &lt; 11%</td>
<td>48 mo (only data of mo 24 were used in current meta-analysis)</td>
<td>Low-carbohydrate MD diet rich in vegetables and whole grains and low in red meat, which was replaced with poultry and fish. Restricted energy intake to 1,500 kcal/d for women and 1,800 kcal/d for men, no more than 50% of calories from complex carbohydrates, no less than 30% calories from fat. Main source of added fat was 30–50 g olive oil. Nutritionists and dietitians gave dietary advice to participants monthly. Also, they received guidance on increasing level of physical activity.</td>
<td>Based on American Heart Association guidelines, low-fat diet was rich in whole grains and restricted additional fats, sweets, and high-fat snacks. Energy intake was limited to 1,500 kcal/d for women and 1,800 kcal/d for men, with the goal of no more than 30% of calories from fat and no more than 10% of calories from saturated fat. Nutritionists and dietitians gave dietary advice to participants monthly. Participants also received guidance on increasing level of physical activity.</td>
<td>No drugs</td>
<td>Low risk</td>
</tr>
<tr>
<td>Toledo et al, 2013</td>
<td>Spain</td>
<td>Men (aged 55–80 y) and women (aged 60–80 y) who had high risk for cardiovascular disease</td>
<td>48 mo (only data of mo 24 were used in current meta-analysis)</td>
<td>1. MD plus extra virgin olive oil (free provision) (MD plus extra virgin olive oil) 2. MD plus mixed nuts (free provision) (MD plus nuts) No energy restriction was specifically advised No physical activity was promoted Virgin olive oil for cooking and dressings: ≥ 2 servings/d of vegetables; ≥ 3 servings/wk of fish or seafood; ≥ 3 servings/wk of nuts or seeds; white meat (poultry or rabbit) instead of red or processed meat; ≥ 7 glasses of wine/wk; ≥ 2 dishes with tomato-based sauce/wk</td>
<td>Usual care and dietary counseling (including group sessions) aimed to increase participants’ adherence to low-fat diet</td>
<td>Drugs were prescribed during regular medical care and were not influenced by intervention</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
Shai et al., 2008
Israel
Moderately obese subjects (mean age, 52 y; mean body-mass index, 31 kg/m²; male, 86%)

24 mo
Moderate-fat, restricted-calorie
MD was rich in vegetables and low in red meat, with poultry and fish replacing beef and lamb
Energy intake was restricted to 1,500 kcal/d for women and 1,800 kcal/d for men, with a goal of no more than 35% of calories from fat; main sources of added fat were 30–45 g olive oil and a handful of nuts (<20 g/d) No physical activity was promoted

Tuttle et al., 2008
US
Patients were recruited 6–48 mo only of mo 24
Reduce saturated fat calories to <7% and cholesterol intake to <200 mg/d
Increased intake of omega-3 fatty acids (>0.75% of calories) and monounsaturated (20% to 25% of calories) and whole grains
Increased consumption of cold-water fish (3–5 times/wk) and oils from olives, canola, and soybeans
Exercise and smoking cessation were encouraged but were not specific intervention targets
Individual dietary counseling sessions from study dietitians based on American Heart Association Step II diet: reduced saturated fat calories to <7% and cholesterol intake to <200 mg/d; increased intake of fresh fruits and vegetables (≥5 servings/d) and whole grains

Drug treatment for diabetes mellitus and hypertension condition

Low risk of bias was indicated if the study was randomized, the randomization method was described, and the study was not influenced by potential funding bias. All other studies were considered as having moderate bias if they met none of these criteria, or as being at high risk of bias if they met any of these criteria. (Higgins and Green 2009, Cochrane Handbook.)

MD indicates Mediterranean diet.

Note: Low risk of bias was indicated if the study was randomized, the randomization method was described, and the study was not influenced by potential funding bias. All other studies were considered as having moderate bias if they met none of these criteria, or as being at high risk of bias if they met any of these criteria. (Higgins and Green 2009, Cochrane Handbook.)
The duration of the interventions ranged from 12 to 24 months. The intervention in all the studies was dietary advice or education to follow an MD plus physical activity. In addition to the MD education and exercise, the PREDIMED study included a free gift for consumption of either extra virgin olive oil or nuts. For this reason, this study was considered to be 2 different estimations (MD plus extra virgin olive oil and MD plus nuts).

The 2003 study of Esposito et al included an energy restricted MD, but in the 2009 study by Esposito et al, the MD was low in carbohydrates and energy intake. In the intervention group, in the 2008 study by Shai et al, the intervention diet was restricted in fat and cholesterol. In the 2013 study of Toledo et al, there was no restriction in terms of fat or energy intake.

The control groups of the included studies followed an LFD and were given general information about healthy food choices.

The baseline health status of participants varied among studies and included premenopausal obese women, patients with metabolic syndrome, overweight people with newly diagnosed type 2 diabetes, individuals at high risk for CVD, moderately obese subjects with a mean of body mass index of 31, and patient survivors of first myocardial infarction.

Table 2 summarizes the internal validity of the studies. The risk of bias was low in 5 studies; 1 had a moderate risk. No studies had a high risk of bias.

Most of the studies found a significant and direct association between MD consumption and decrease of the systolic and diastolic BP values after 24 months of the intervention or earlier. To summarize the results, the authors performed a formal meta-analysis. Changes in BP between baseline and the end of the intervention (≤ 24 months) were measured in the intervention and control groups in each study. Then, differences in the change of BP values between the intervention group (MD) and the control group (LFD) were calculated. Using the 95% CI of those differences, the SE of the differences was calculated. These data are outlined in Table 3.

### Table 2. Assessment of Internal Validity of Randomized Controlled Trials Included

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Method of Sequence Generation</th>
<th>Adequate Allocation</th>
<th>Adequate Blinding</th>
<th>Number at Start, Attrition, and Attrition Reasons</th>
<th>Outcome Data Complete</th>
<th>Funder Appropriate</th>
<th>Other Potential Funding Bias</th>
<th>Overall Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito, 2003</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>Esposito, 2004</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Low risk</td>
</tr>
<tr>
<td>Esposito, 2009</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Low risk</td>
</tr>
<tr>
<td>Shai, 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Low risk</td>
</tr>
<tr>
<td>Toledo, 2013</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Low risk</td>
</tr>
<tr>
<td>Tuttle, 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Table 3. Systolic and Diastolic Blood Pressure Mean Difference, 95% Confidence Interval, and SE Between Mediterranean Diet Group and Low-Fat Group After 2 Years’ Follow-up

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n</th>
<th>Mean Difference</th>
<th>95% Confidence Interval of Difference</th>
<th>SE of Difference: (lsc – lic)/3.92</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esposito, 2003</td>
<td>60</td>
<td>–2</td>
<td>–3.5 to –0.5</td>
<td>0.7653</td>
</tr>
<tr>
<td>Esposito, 2004</td>
<td>90</td>
<td>–3</td>
<td>–3 to –1</td>
<td>0.5102</td>
</tr>
<tr>
<td>Esposito, 2009</td>
<td>108</td>
<td>–3.1</td>
<td>–4.9 to –1.2</td>
<td>0.9438</td>
</tr>
<tr>
<td>Shai, 2008</td>
<td>109</td>
<td>–1.2</td>
<td>–4.71 to 2.31</td>
<td>1.7908</td>
</tr>
<tr>
<td>Toledo, 2013</td>
<td>2,441</td>
<td>–0.16</td>
<td>–0.58 to 0.27</td>
<td>0.3979</td>
</tr>
<tr>
<td>2,367</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuttle, 2008</td>
<td>51</td>
<td>–3</td>
<td>–9.02 to 3.02</td>
<td>3.0714</td>
</tr>
</tbody>
</table>

| **Diastolic blood pressure** |       |                 |                                     |                                   |
| Esposito, 2003     | 60    | –1.7            | –3 to –0.4                           | 0.6632                            |
| Esposito, 2004     | 90    | –2              | –3.5 to –0.5                         | 0.7653                            |
| Esposito, 2009     | 108   | –1              | –4.0 to –1.0                         | 0.7653                            |
| Shai, 2008         | 109   | –1.3            | –3.67 to 1.07                        | 1.2091                            |
| Toledo, 2013       | 2,441| –0.16           | –0.58 to 0.27                       | 0.2168                            |
| 2,367              |       |                 |                                     |                                   |
| Tuttle, 2008       | 51    | –2.14           | –6.14 to 1.86                        | 2.0408                            |

EVOO indicates extra virgin olive oil; lic, lower limit of the confidence interval; lsc, upper limit of the confidence interval; MD, Mediterranean diet.
in Table 3. Using those data, the pooled analysis shown in Figures 2 and 3 was performed. The pooled estimation effect for the SBP was –1.44 mm Hg (95% CI, –2.88 to 0.01), and for DBP was –0.70 mm Hg (95% CI, –1.34 to –0.07). However, a substantial heterogeneity was present in the analyses (I² SBP = 87% and I² DBP = 63%).

To find the source of heterogeneity, the duration of the intervention and the studies including multi-interventions (stress reduction, physical activity, diet, etc) were considered as candidate variables that could act as effect modifiers. Sensitivity analyses were conducted, first excluding the study of Esposito et al,17 which was conducted over 12 months (not over 24 months as in the rest of the studies). This subgroup analysis did not reduce the I² indices in systolic or diastolic BP (Figures 4 and 5). Then, the study by Tuttle et al20 was removed because it was a multi-intervention study. However, in this case, substantial heterogeneity remained in the analyses (Figures 6 and 7). These results indicated that the problem of heterogeneity could not completely be solved by these analyses.

**DISCUSSION**

The findings of this study indicate that interventions involving study populations adopting a MD pattern for at least 1 year reduced both the systolic and diastolic BP levels in individuals with normal BP or mild hypertension. The effect was higher for the SBP (–1.44 mm Hg) but it was also consistent for the DBP (–0.70 mm Hg). However, the results should be interpreted with caution for a number of reasons. First, the number of studies that were eligible for inclusion in this meta-analysis was small, which limited the statistical power of the analyses to examine the relation between MD and BP. Thus, the small effect size found may be explained by the limited amount of available information. Furthermore, in all cases the pooled effect estimation had a high evidence of heterogeneity, which compromises the validity of the pooled estimates.

It is subject to debate whether the quality and adequacy of the different studies included in a meta-analysis may influence the outcome. It is logical that when each study is conducted within a rigorous methodological frame, the publishing of clear results and reliability of reached conclusions
will increase. In this sense, as mentioned before, the researchers conducted assessment of risk of bias in the studies included in this meta-analysis following an adaptation of the Cochrane Handbook for Systematic Reviews. The studies included in this analysis evaluated the effects of the MD after 2 years of intervention in more than 7,000 individuals. Other publications evaluating the effect of diet patterns on BP levels analyzed results from interventions lasting < 1 year: from 2 to 26 weeks, from 30 days to 8 weeks, a mean duration of 15.7 weeks, and a study combining the results of studies of 3 months to 2 years' duration. The current analysis is an update of values shown in the analysis by Nordmann et al, adding the BP results from interventions lasting from 2 to 6 weeks, from 30 days to 8 weeks, and an LFD, it is possible that these participants had a healthier profile, as suggested by their baseline information, and their adherence to the MD pattern remained high. Even though the overall diet was fat-reduced, individuals used olive oil as the main added fat. This is in keeping with the high consumption of olive oil in Spain, which explains the high levels of fat intake (up to 40%) found in nutritional surveys. For instance, data from the recent household budget survey conducted by the Spanish Ministry of Agriculture, Food, and Environment indicated a consumption of 9.3 L olive oil per capita (around 4 L virgin olive oil) in 2013.

Figure 4. Sensitivity analyses of systolic blood pressure: without Esposito et al (intervention time, 12 months). CI indicates confidence interval; EVOO, extra virgin olive oil; LF, low fat; MD, Mediterranean diet.

A meta-analysis combining observational and interventional studies evaluating the effect of the MD on metabolic syndrome showed a benefit for SBP and DBP when analyzing clinical trials, and no effect on BP when the data analyzed were obtained from observational studies. Since the seven countries study, the MD has been consistently evaluated and associated with a lower incidence of CVD. Main risk factors for developing CVD are hypertension, obesity, insulin resistance, tobacco consumption, and lack of physical activity. Hypertension is a heterogeneous disorder and several factors may contribute to its pathogenesis, including endothelial dysfunction, insulin resistance, excess sodium intake, stress, and genetic alterations. Although the MD health benefits cannot be attributed to a single food, several components of this diet pattern,
such as olive oil, fish, vegetables, and fruit, have been associated with a reduction in BP levels.\textsuperscript{32} The nutrients and substances most relevant to the relationship are fats, such as oleic acid and omega 3, as well as phytochemicals and antioxidants.\textsuperscript{33} Low sodium and high potassium, and magnesium and calcium content are also pertinent MD features.\textsuperscript{35} In synthesis, the MD pattern coincides with the levels of nutrients most relevant for hypertension prevention. However, compared with pharmacological studies, the relationship between diet and health is obscured by all of the intermediary agents (eg, soil, climate) and processes (eg, growth aids, pest management) that affect the composition of the food, and finally, its relation with health. Several studies have shown how the concentration of phytochemicals, antioxidants and volatile substances depend on the soil, maturation process, or manipulation process.\textsuperscript{36} Also, studies evaluating the benefits of organic foods indicate that they have a higher content of minerals and phenols compared with conventional foods.\textsuperscript{37}

**IMPLICATIONS FOR RESEARCH AND PRACTICE**

The MD was ascribed to the list of Intangible Cultural Heritage of UNESCO in November, 2010, as a cultural monument of Greece, Italy, Spain, and Morocco (decision 5.COM 6.41).\textsuperscript{38} Because of the effectiveness of this dietary pattern in preventing and managing several prevalent chronic diseases, it is necessary to promote its consumption not only in non-Mediterranean countries but also in the Mediterranean countries themselves, where adherence has been decreasing in past decades.\textsuperscript{39}

In conclusion, a positive and significant association was found between the MD and BP in adults. However, in all cases the magnitude of the effect was small. Based on this limited group of studies and their heterogeneity, insufficient information was found to determine that there is convincing evidence that the MD decreases BP. Further standardized research is urgently needed to reach evidence-based conclusions to clarify the role of MD in BP prevention and management, particularly in Europe and other societies where the prevalence and health burden of CVDs are high.

**ACKNOWLEDGMENTS**

Mariela Nissensohn and Blanca Román-Viñas contributed to the design of the strategy for the literature search. Lluis Serra-Majem prepared the main outline of the manuscript. Mariela Nissensohn and Blanca Román-Viñas selected the data and wrote the manuscript. Almudena Sánchez-Villegas contributed to the

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Study or Subgroup & Mean Difference & SE & Weight & IV, Random, 95% CI & \\
Esposito 2003 & -2 & 0.7653 & 20.1\% & -2.00 [-3.50, -0.50] & \\
Esposito 2004 & -3 & 0.5102 & 22.4\% & -3.00 [-4.00, -2.00] & \\
Shai 2008 & -1.2 & 1.7908 & 11.2\% & -1.20 [-4.71, 2.31] & \\
Toledo 2013 MD+EVOO & 0.74 & 0.3979 & 23.2\% & 0.74 [-0.04, 1.52] & \\
Toledo 2013 MD+nuts & -0.02 & 0.403 & 23.2\% & -0.02 [-0.81, 0.77] & \\
\hline
Total (95\% CI) & 100.0\% & -1.04 [-2.63, 0.55] & \\
Heterogeneity: $\tau^2 = 2.67$; $\chi^2 = 39.00$, df = 4 (P < 0.00001); $I^2 = 90\%$ & & \\
Test for overall effect: $Z = 1.29$ (P = 0.20) & & \\
\end{tabular}
\end{table}

\textbf{Figure 6.} Sensitivity analyses of systolic blood pressure: without Esposito et al\textsuperscript{17} (intervention time, 12 months) and Tuttle et al\textsuperscript{20} (multi-intervention). CI indicates confidence interval; EVOO, extra virgin olive oil; LF, low fat; MD, Mediterranean diet.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Study or Subgroup & Mean Difference & SE & Weight & IV, Random, 95% CI & \\
Esposito 2003 & -1.7 & 0.6632 & 16.2\% & -1.70 [-3.00, -0.40] & \\
Esposito 2004 & -2 & 0.7653 & 13.7\% & -2.00 [-3.50, -0.50] & \\
Shai 2008 & -1.3 & 1.2091 & 7.1\% & -1.30 [-3.67, 1.07] & \\
Toledo 2013 MD+EVOO & -0.16 & 0.2168 & 31.5\% & -0.16 [-0.58, 0.26] & \\
Toledo 2013 MD+nuts & 0.16 & 0.2168 & 31.5\% & 0.16 [-0.26, 0.58] & \\
\hline
Total (95\% CI) & 100.0\% & -0.64 [-1.35, 0.07] & \\
Heterogeneity: $\tau^2 = 0.37$; $\chi^2 = 14.23$, df = 4 (P = 0.007); $I^2 = 72\%$ & & \\
Test for overall effect: $Z = 1.78$ (P = 0.08) & & \\
\end{tabular}
\end{table}

\textbf{Figure 7.} Sensitivity analyses of diastolic blood pressure: without Esposito et al\textsuperscript{17} (intervention time, 12 months) and Tuttle et al\textsuperscript{20} (multi-intervention). CI indicates confidence interval; EVOO, extra virgin olive oil; LF, low fat; MD, Mediterranean diet.
statistical analyses. Suzanne Pisicop contributed to the selection of studies. All authors contributed to the preparation of the final manuscript. The authors acknowledge Professor Dr Pedro Saavedra Santana from the Department of Mathematics of the University of Palmas de Gran Canaria, Spain for assistance in the analyses.

REFERENCES


JNEB’s call for Reviewers in Nutrition Economics

With the recently expanded scope of Journal of Nutrition Education and Behavior (JNEB), we are planning a special issue devoted to nutrition economics. Dr. Joanne Guthrie will author the opening Perspective, and we are hoping for many excellent articles to progress through our peer review. To manage this effectively, we are encouraging new reviewers to sign up and current reviewers to expand their classifications.

To sign up to be a new reviewer, go to http://ees.elsevier.com/jneb/ and Register (menu at top of screen) in our peer-review system. If you already have an account, update your personal classifications under the Change Details link or contact Susan Pollock and Shauna Miller (managingeditor@jneb.org) for assistance.

Questions should be directed to the Editor-in-Chief, Dr. Karen Chapman-Novakofski at editor@jneb.org.
CONFLICT OF INTEREST

The authors have not stated conflicts of interest.