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The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials[1–3]

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ABSTRACT

Background: Although several studies have assessed the effects of nut consumption (tree nuts, peanuts, and soy nuts) on blood pressure (BP), the results are conflicting.

Objective: The aim was to conduct a systematic review and meta-analysis of published randomized controlled trials (RCTs) to estimate the effect of nut consumption on BP.

Design: The databases MEDLINE, SCOPUS, ISI Web of Science, and Google Scholar were searched for RCTs carried out between 1958 and October 2013 that reported the effect of consuming single or mixed nuts (including walnuts, almonds, pistachios, cashews, hazelnuts, macadamia nuts, pecans, peanuts, and soy nuts) on systolic BP (SBP) or diastolic BP (DBP) as primary or secondary outcomes in adult populations aged ≥18 y. Relevant articles were identified by screening the abstracts and titles and the full text. Studies that evaluated the effects for <2 wk or in which the control group ingested different healthy oils were excluded. Mean ± SD changes in SBP and DBP in each treatment group were recorded for meta-analysis.

Results: Twenty-one RCTs met the inclusion criteria. Our findings suggest that nut consumption leads to a significant reduction in SBP in participants without type 2 diabetes [mean difference (MD): −1.29; 95% CI: −2.35, −0.22; $P = 0.02$] but not in the total population. Subgroup analyses of different nut types suggest that pistachios, but not other nuts, significantly reduce SBP (MD: −1.82; 95% CI: −2.97, −0.67; $P = 0.002$). Our study suggests that pistachios (MD: −0.80; 95% CI: −1.43, −0.17; $P = 0.01$) and mixed nuts (MD: −1.19; 95% CI: −2.35, −0.03; $P = 0.04$) have a significant reducing effect on DBP. We found no significant changes in DBP after the consumption of other nuts.

Conclusions: Total nut consumption lowered SBP in participants without type 2 diabetes. Pistachios seemed to have the strongest effect on reducing SBP and DBP. Mixed nuts also reduced DBP. *Am J Clin Nutr* doi: 10.3945/ajcn.114.091595.

Keywords: nut, almond, walnut, pistachio, cashew, blood pressure, randomized controlled trials

INTRODUCTION

Hypertension is one of the leading causes of cardiovascular events (1, 2) and the main contributor to >7 million deaths/y worldwide (3). Lifestyle modifications have been shown to be effective in regulating blood pressure (BP)[4] (2). In particular, nutrition plays an important role in the prevention and control of hypertension (4).

Adherence to some dietary patterns, such as the DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets, seems to have a reducing effect on BP (5), which makes these patterns good choices for substantially reducing the risk of cardiovascular disease (CVD) (6). Nutrient-dense foods such as unprocessed nuts are one of the major components of these healthy diets. Nuts provide a wide variety of nutrients and phytochemicals but low amounts of sodium (4), which may affect BP (7). In this regard, the intake of nuts has been associated with lower BP measurements (8). For instance, some prospective longitudinal studies reported that individuals who consume nuts on a daily basis have a lower risk of hypertension and other cardiovascular disease risk factors than do individuals who do not consume nuts regularly (9, 10). Several studies have evaluated the effects of consumption of different types of nuts on BP measurements. However, randomized controlled trials (RCTs) provide conflicting results. These might be explained by the heterogeneity of the studies, which are of different designs, use different dosages, have different study durations, give the participants different types and amounts of nuts, target different populations, and have different eligibility criteria. For instance, after 3 mo of follow-up in the PREDIMED (Prevención con Dieta Mediterránea) trial, a Mediterranean diet supplemented with nuts was shown to reduce BP more than a low-fat diet (11).

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[4] Abbreviations used: BP, blood pressure; CVD, cardiovascular disease; CAD, coronary artery disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; MD, mean difference; RCT, randomized controlled trial; SBP, systolic blood pressure.

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However, most of the other RCTs reported that diets enriched with nuts have little effect on BP (12–14).

Furthermore, because the close association between BP and insulin resistance is a major problem for people with type 2 diabetes, and hypoglycemic approaches (including dietary modification and medications) can have an impact on blood pressure, the consumption of nuts could affect BP in patients with or without type 2 diabetes in different ways (15).

To the best of our knowledge, no systematic review has ever been published on the effect of nut consumption on blood pressure. Therefore, in the current study, we conducted a systematic review of RCTs in an attempt to summarize the evidence on primary and secondary effects of consuming nuts (pistachios, cashews, hazelnuts, almonds, walnuts, pecans, macadamia nuts, peanuts, and soy nuts) on systolic BP (SBP) and diastolic BP (DBP) in adults aged ≥18 y. When possible, we quantified the effect using meta-analysis while trying to find possible sources of heterogeneity among the RCT results. We also evaluated the effect of nut consumption in participants with and without type 2 diabetes.

METHODS

Data sources and search strategy

The present systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and was registered in an international prospective register of systematic reviews [PROSPERO (Prospective Register of Systematic Reviews); registration code CRD 42013005829] (16). The search results recorded studies conducted from 1958 to October 2013. To find relevant articles, searches were made in MEDLINE via PubMed (www.pubmed.com; National Library of Medicine), Scopus (www.scopus.com), ISI Web of Science (www.thomsonreuters.com), and Google Scholar (www.scholar.google.com). Searches were not restricted by language or anything else. Three groups of medical subject headings (MeSH) and non-MeSH keywords were selected to search the databases, as follows—keyword group 1: "nut*", "almond", "pistachio", "hazelnut", "walnut", "cashew", "macadamia", "pecan", "peanut", or "soy nut"; keyword group 2: "blood pressure", "serum lipids", "blood glucose", "CVD", "cholesterol", "lipoproteins, HDL", "lipoproteins, LDL", "triglyceride", "glucose tolerance test", "insulin", "blood glucose", "insulin resistance", "low density lipoprotein", "high density lipoprotein", "TG", "TC", "GTT", "FBS", "FBG", "FPG", "fasting insulin", "fasting blood sugar", "fasting blood glucose", "fasting plasma glucose", "insulin sensitivity", "blood sugar", "lipid profile", "serum lipid", "blood pressure", "hypertension", "cardiovascular disease", "coronary disease", "coronary artery disease", "CVD", coronary artery disease ("CAD"), "obesity", and "weight"; and keyword group 3: "randomized", "intervention", "controlled trial", "random", and "placebo". We searched keyword group 1 in combination with both keyword groups 2 and 3. We used keywords related to blood lipids, glucose, and CVDs because BP might be measured as a secondary outcome in some studies.

Inclusion criteria

The following inclusion criteria were used for the present systematic review and meta-analysis: *1*) RCTs; *2*) studies focusing on the effect on SBP or DBP as primary or secondary outcomes of consuming single or mixed nuts, including walnuts, almonds, pistachios, cashews, hazelnuts, macadamia nuts, pecans, peanuts, and soy nuts; and *3*) studies conducted in populations aged ≥18 y. Two investigators (NM and AS-A) screened the abstracts and titles and full texts of the articles that seemed to meet the inclusion criteria to identify relevant articles, which were then retrieved for further screening. A reference list of related articles was also checked for any missing related articles. In the case of multiple publications from the same trial we selected only the most recent or informative.

Exclusion criteria

Exclusion criteria were as follows: *1*) studies evaluating only postprandial and acute effects for <2 wk (17); *2*) trials not assessing BP as a primary or secondary outcome; *3*) studies in which the control group ingested different healthy oils such as olive, flaxseed, or soy protein oil (11, 12, 14, 17–20); *4*) RCTs that did not report mean (SD) changes in SBP and DBP in each treatment group and did not calculate changes from the data available; and *5*) articles that reported the results of the same studies (21, 22).

Data extraction

We recorded the following information about each of the studies: the last name of the first author, the year of publication, the country in which the study was implemented, the design of the study (crossover or parallel), the mean/range age of participants, the use of run-in or washout periods (which was mentioned only for descriptive purposes), the total number of participants by gender, the details of the intervention including the exact amount of nuts consumed (grams per day, percentage of energy from nuts), the kind of diet or any other intervention carried out in the control group, the treatment period, and the number of participants who completed the follow-up period. We also noted the specific inclusion and exclusion criteria of each study. Mean (SD) changes in SBP and DBP in each treatment group were used for meta-analysis. This was accomplished by calculating the correlation coefficient ($r = 0.70$) and using it to calculate changes in DBP and SBP for studies in which SDs for change were not reported (11, 12, 19, 26–40). Studies with multiple control groups (23) or multiple dosages of nuts (31, 32, 39) were included separately in the meta-analysis. For a study by Foster et al. (28), which reported the effect for 6 and 18 mo of follow-up, we considered the effect size over the longer follow-up period when its results were included in the meta-analysis. To obtain the data that were not presented in the articles, we e-mailed the authors at least 3 times, 2 wk apart.

Risk of bias in individual studies

The risk of bias of each study was assessed by 2 reviewers (NM and AS-A) with the Cochrane Collaboration Risk of Bias tool (25). The factors regarded as contributing to study quality were the generation of the allocation sequence, allocation concealment, blinding, blinding outcome data, incomplete outcome data, and selective reporting. We classified these factors as low risk of bias, high risk of bias, or unclear. Because blinding is not possible in clinical trials with dietary interventions, we judged the quality of the studies on the basis of the other 5 items (generation of the allocation sequence, allocation concealment, blinding outcome data,

incomplete outcome data, and selective reporting). Studies with a low risk of bias for at least 3 items were regarded as good quality; studies with a low risk of bias for 2 items were regarded as fair; and studies with a low risk for no items or only 1 item were regarded as poor (25).

Statistical analysis

The mean difference (MD) between the intervention (nut intake period or group) and control groups in change in SBP and DBP and its SD was used as the effect size for the meta-analysis. Summary weighted means and their corresponding SDs were estimated following DerSimonian and Laird (41) and by using the random-effects model, which takes the variability among studies into account. Subgroups were analyzed to check for a specific source of heterogeneity. Statistical heterogeneity among studies was evaluated with Cochran's Q test and the I^2 statistic (I^2) (42). In fact, heterogeneity was assessed in all analyses. We assessed the heterogeneity of all of the studies once and also verified the heterogeneity for each nut category subgroup. Then, we examined the same effects (including the summary effect and heterogeneity) for the studies that recruited participants without type 2 diabetes and analyzed the nut-type subgroups. Subsequently, we reported the summary effect and its heterogeneity for each subgroup. Diet interventions might affect participants with type 2 diabetes differently, so to reduce heterogeneity, we removed the studies that recruited participants with type 2 diabetes. To explore the extent to which inferences might depend on one study or one group of studies, sensitivity analysis was performed by excluding the studies one by one or by excluding studies conducted in a group of subjects with the same disease. Publication bias was assessed by visual inspection of funnel plots (43), and the funnel plot asymmetry was statistically assessed by using Egger's regression asymmetry test and adjusted rank correlation test (44). Statistical analyses were conducted by using STATA, version 11.2 (Stata Corp.). P values <0.05 were considered to be significant.

RESULTS

The literature search retrieved 1572 articles. After screening, 239 articles were identified for full-text revision. Of these, we excluded 218 studies after applying the inclusion and exclusion

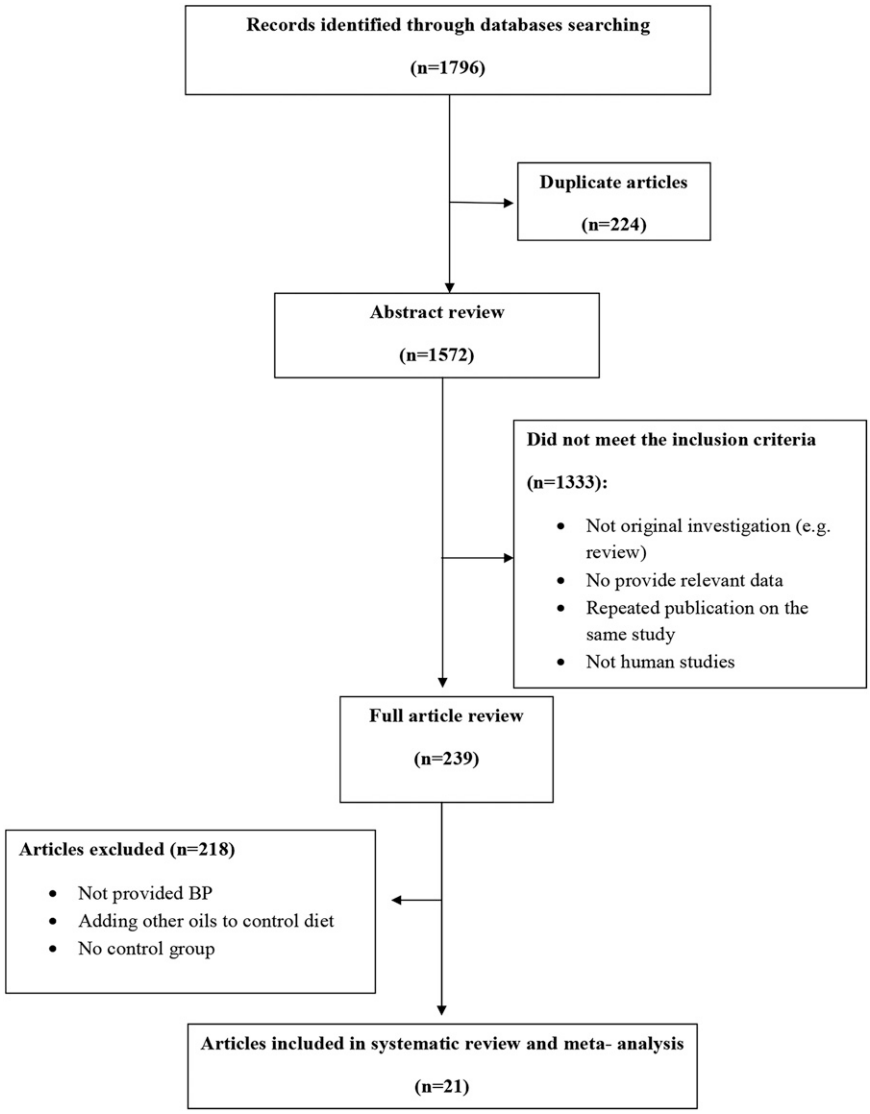

FIGURE 1 Flowchart of the study selection process.

TABLE 1
RCTs eligible for inclusion in the systematic review and meta-analysis[1]

First author, year (ref)	Sex: no. of participants	Country	Study design	Age,[2] y	Diet type[3]		Duration, wk	Notes on follow-up	No. randomized/no. analyzed and results
					Intervention	Control			
Bakhtiary, 2012 (13)	F: 50	Iran	RCT, parallel	60–70 (64.2 ± 2.9[4])	Control + 35 g soy nuts (not reported whether salted or unsalted); baseline: SBP, 127.3 ± 4.4; DBP, 79.4 ± 6.5	Control diet; baseline: SBP, 127.4 ± 4.6; DBP, 81.4 ± 6.1	12	Adherence to intervention assessed by 3-d DR; no biomarker; no reported baseline diet; no run-in period	75/75 No significant reduction in SBP and DBP
Foster, 2012 (28)	M/F: 123	USA	RCT, parallel	18–75	Low-calorie diet + 56 g almonds (raw and roasted); baseline: SBP,123.8 ± 15.0; DBP, 72.2 ± 9.9	Low-calorie diet; baseline: SBP, 122.4 ± 17.6; DBP, 69.6 ± 9.6	72	1-wk run-in period; no reported baseline; method of adherence to intervention not detectable	123/— (ITT) No significant reduction in SBP and DBP
West, 2012 (39)	M/F: 28	USA	RCT, crossover	35–61 (48 ± 1.5[5])	Low-fat diet + 30 g pistachios Low-fat diet + 60 g pistachios (50% raw and 50% roasted and salted) Baseline: SBP, 121.5 ± 13.2; DBP, 74.4 ± 6.3	Low-fat diet; baseline: SBP, 121.5 ± 13.2; DBP, 74.4 ± 6.3	4	Meal provided; 2-wk run-in period	28/28 Significant reduction in SBP
Casas-Agustench, 2011 (26)	M/F: 50	Spain	RCT, parallel, single-blind	18–65 (51.7 ± 8.4[4])	Healthy diet + 30 g mixed nuts (raw); baseline: SBP, 145 ± 15; DBP, 86 ± 8	Healthy diet; baseline: SBP, 137 ± 19; DBP, 82 ± 10	12	Adherence to intervention assessed by 3-d DR every 4 wk; plasma α-Linolenic acid as biomarker of walnut intake; no reported baseline diet	52/50 No significant reduction in SBP and DBP
Jenkins, 2011 (31)	M/F: 117	Canada	RCT, parallel	62 ± 9[4]	1.Therapeutic lifestyle diet + half dose of muffins + 37 g mixed nuts; baseline: SBP, 123 ± 12.6; DBP, 71 ± 6.3 2. Therapeutic lifestyle diet + 73 g mixed nuts (unsalted and mostly raw); baseline: SBP, 121 ± 9.7; DBP, 70 ± 9.7	Therapeutic lifestyle diet + full dose of muffins; baseline: SBP, 125 ± 12.6; DBP, 71 ± 9.6	12	Adherence to intervention assessed by 3-d DR every 2 wk; no biomarker; no reported baseline diet	117/— (ITT) Significant reduction in DBP in full-dose nuts vs. muffins and significant reduction in SBP and DBP in full dose vs. half dose of nuts
Li, 2011 (33)	M/F: 20	China	RCT, crossover	58 ± 2[5]	Step II + 56 g almonds (20% of daily calories; unsalted); baseline: SBP, 131.8 ± 16.5; DBP, 73.1 ± 11.5	Step II; baseline: SBP, 131 ± 16.5; DBP, 73.1 ± 11.5	4	Meal provided; 2-wk run-in period; 2-wk washout; adherence to intervention assessed by 3-d DR; no biomarker; no reported baseline diet	22/20 No significant reduction in SBP and DBP

(Continued)

TABLE 1 (*Continued*)

First author, year (ref)	Sex: no. of participants	Country	Study design	Age,[2] y	Diet type[3]		Duration, wk	Notes on follow-up	No. randomized/no. analyzed and results
					Intervention	Control			
Ghadimi Nouran, 2010 (29)	M: 54	Iran	RCT, crossover	25–65 (54 ± 6)	Regular diet + 75 g peanuts (20% of energy; roasted and lightly salted); baseline: SBP, 120.1 ± 18.3; DBP, 80.6 ± 10.8	Regular diet; baseline: SBP, 120 ± 15; DBP, 87.2 ± 12.5	4	Adherence to intervention assessed by three 24-h dietary recalls in each period; 2-wk run-in period; 2-wk washout; MUFAs as biomarker of peanut intake; no reported baseline diet	60/54 No significant reduction in SBP and DBP
Ma, 2010 (34)	M/F: 24	USA	RCT, crossover	30–75 (58 ± 6)	Ad libitum diet + 56 g walnuts (unsalted); baseline: SBP, 133.2 ± 14; DBP, 77.7 ± 7.3	Ad libitum diet; baseline: SBP, 133.2 ± 14; DBP, 77.7 ± 7.3	8	Adherence to intervention assessed by 3-d DR in each diet period; 4-wk run-in period; 8-wk washout; no biomarker; no reported baseline diet	24/21 (but analyses based on ITT) Significant increase in SBP and DBP
Sari, 2010 (36)	M: 32	Turkey	RCT, crossover	21–24 (22 ± 6)	Mediterranean diet + 60–100 g pistachios (20% of daily energy; roasted and unsalted); baseline: SBP, 117 ± 8; DBP, 73 ± 8	Mediterranean diet; baseline: SBP, 117 ± 8; DBP, 73 ± 8	4	Meal provided and supervised by dietitian to ensure complete intake; no biomarker; no reported baseline diet	33/32 Significant reduction in SBP and DBP
Wien, 2010 (24)	M/F: 54	USA	RCT, parallel	(53.5 ± 10[4])	American Diabetic Association diet + 56 g almonds (raw or dry roasted); baseline: SBP, 117 ± 8; DBP, 73 ± 8	American Diabetic Association diet; baseline: SBP, 117 ± 8; DBP, 73 ± 8	16	Adherence to intervention assessed by 3-d DR before intervention, at the beginning and every 4 wk; Plasma α-tocopherol as biomarker of almond intake; no differences between MUFA and PUFA intake at baseline	65/53 No significant reduction in SBP and DBP
Wu, 2010 (19)	M/F: 283	China	RCT, parallel	25–65 (48.4 ± 8.2[4])	Low-fat diet + 30 g walnuts; baseline: SBP, 135 ± 16.2; DBP, 86.5 ± 9.9	Low-fat diet; baseline: SBP, 133.7 ± 14.6; DBP, 85.4 ± 9.0	12	Adherence to intervention assessed by asking to bring unused bread; erythrocyte α-linolenic acid as biomarker of walnut intake; no reported baseline diet	283/277 (but analyses based on ITT) No significant reduction in SBP and DBP
Claesson, 2009 (27)	M/F: 25	Sweden	RCT, parallel	18–30 (23.4 ± 2.7[4])	Regular diet + 75 g peanuts (20% of daily energy; salted); baseline: SBP, 117 ± 8.5; DBP, 69.2 ± 8.1	Regular diet + candy; baseline: SBP, 116.5 ± 8.2; DBP, 71.6 ± 8.3	2	Adherence to intervention assessed by 3-d DR; MUFAs and PUFAs at baseline diet did not differ; no biomarker	26/25 No significant reduction in SBP and DBP

(Continued)

TABLE 1 (*Continued*)

First author, year (ref)	Sex: no. of participants	Country	Study design	Age,[2] y	Diet type[3]		Duration, wk	Notes on follow-up	No. randomized/no. analyzed and results
					Intervention	Control			
Spaccarotella, 2008 (38)	M: 21	USA	RCT, crossover	47–75	Average American diet + 75 g walnuts; baseline BP: not reported	Average American diet; baseline BP: not reported	8	Adherence to intervention assessed by 3-d DR at baseline and every 4 wk of each diet; 2-wk washout period; plasma α-tocopherol measurement as biomarker of walnut intake; no reported baseline diet	22/21 No significant reduction in SBP and DBP
Azadbakht, 2007 (12)	F: 42	Iran	RCT, crossover		DASH diet +30 g soy nuts (unsalted); baseline: SBP, 116 ± 4.5; DBP, 87 ± 1.3	DASH diet; baseline: SBP, 116 ± 4.5; DBP, 87 ± 1.3	4	Adherence to intervention assessed by 3-d DR at baseline and after 1 mo; 4-wk washout period; no biomarker; no reported baseline diet	42/42 No significant reduction in SBP and DBP
Mukudden-Petersen, 2007 (23)	M/F: 64	South Africa	RCT, parallel	21–65 (45 ± 10[4])	Control diet +63–108 g walnuts (20% of daily energy); baseline: SBP, 128 ± 5.8; DBP, 78.7 ± 5.5 Control diet +63–108 g cashews daily (20% of daily energy; unsalted); baseline: SBP, 131 ± 10.5; DBP, 77 ± 7	Control diet; baseline: SBP, 131 ± 14; DBP, 79.2 ± 7.3	8	Adherence to intervention assessed by control feeding protocol (lunch in the metabolic ward) and breakfast and dinner were provided (food was weighed and complete intake ensured by dietitian) and complete dairy questionnaire; 2-wk run-in period; no biomarker; no reported baseline diet	68/64 No significant reduction in SBP and DBP
Sheridan, 2007 (37)	M/F: 15	USA	RCT, crossover	36–75 (60 ± 11.6[4])	Regular diet + 30–90 g pistachios (15% of daily energy; not reported whether salted or unsalted); baseline: SBP, 129 ± 14.3; DBP, 84 ± 10.4	Regular diet; baseline: SBP, 129 ± 14.3; DBP, 84 ± 10.4	4	Adherence to intervention assessed by 1-d food diary questionnaire every 1 wk; no biomarker; MUFAs did not differ and increased in intervention group compared with baseline diet	20/15 No significant reduction in SBP and DBP
Estruch, 2006 (11)	M/F: 515	Spain	RCT, parallel	55–80 (69 ± 6[4])	Mediterranean diet + 30 g mixed nuts; baseline BP: not reported	Low-fat diet; baseline BP: not reported	12	Biomarker: linolenic acid plasma content by gas chromatography as a measure of adherence to mixed nut intake	772/769 (but analyses based on ITT) Significant reduction in SBP and DBP

(Continued)

TABLE 1 (*Continued*)

First author, year (ref)	Sex: no. of participants	Country	Study design	Age,[2] y	Diet type[3]		Duration, wk	Notes on follow-up	No. randomized/no. analyzed and results
					Intervention	Control			
Ros, 2004 (35)	M/F: 21	Spain	RCT, crossover	25–75	Mediterranean diet + 40–65 g walnuts (32% of daily energy); baseline: SBP, 131 ± 17; DBP, 80 ± 9	Mediterranean diet; baseline: SBP, 131 ± 17; DBP, 80 ± 9	4	Adherence to intervention was assessed by measuring plasma α-tocopherol, as biomarker of walnut intake and 7-d dietary recall; 4-wk run-in period; baseline diet was reported	21/20 Significant increase in DBP
Wien, 2003 (40)	M/F: 65	USA	RCT, parallel	27–79 (55 ± 2[4])	Low-calorie diet + 84 g almonds (salted and unblanched); baseline: SBP, 143 ± 17; DBP, 77 ± 11.3	Low-calorie diet; baseline: SBP, 140 ± 17.2; DBP, 78 ± 11.5	24	Adherence to intervention was assessed by completing detailed daily food questionnaire; 2 groups had different concentrations of MUFAs and PUFAs at baseline but were equally balanced on total calories, protein, cholesterol, and SFAs; no biomarker	65/52 Significant reduction in SBP
Iwamoto, 2002 (30)	M: 10	Japan	RCT, single-blind crossover	20–36 (23.8 ± 0.7[4])	Average Japanese diet + 58 g walnuts (12.5% of daily energy); baseline: SBP, 117 ± 13; DBP, 73 ± 11	Average Japanese diet; baseline: SBP, 117 ± 13; DBP, 73 ± 11	4	Adherence to intervention assessed by control feeding protocol (lunch in the metabolic ward), breakfast and dinner were provided, tray checks after meals eaten on site and by self-report on standardized forms for packed meals; 5-d run-in period; no biomarker; MUFAs reduced and PUFAs increased in intervention diet compared with baseline diet	10/10 Significant reduction in SBP and increase in DBP

(Continued)

TABLE 1 (*Continued*)

First author, year (ref)	Sex: no. of participants	Country	Study design	Age,[2] y	Diet type[3]		Duration, wk	Notes on follow-up	No. randomized/no. analyzed and results
					Intervention	Control			
Iwamoto, 2002 (30)	F: 10	Japan	RCT, single blind crossover	20–36 (23.8 ± 0.7[4])	Average Japanese diet + 58 g walnuts (12.5% of daily energy); baseline: SBP, 109 ± 12; DBP, 66 ± 7	Average Japanese diet; baseline: SBP, 109 ± 12; DBP, 66 ± 7	4	Adherence to intervention assessed by control feeding protocol (lunch in the metabolic ward), breakfast and dinner were provided, tray checks after meals eaten on site and by self-report on standardized forms for packed meals; 5-d run-in period; no biomarker; MUFAs reduced and PUFAs increased in intervention diet compared with baseline diet	10/10 No significant reduction in SBP and DBP
Jenkins, 2002 (32)	M/F: 27	Canada	RCT, crossover	48–86 (64 ± 9[4])	Step II diet + half dose of whole-wheat muffin + 37 g almonds; baseline: SBP, 121 ± 15.6; DBP, 75 ± 10.4 Step II diet + half dose of whole-wheat muffin + 73 g almonds (raw and unblanched); baseline: SBP, 120 ± 10.4; DBP, 75 ± 10.4	Step II + full dose of whole-wheat muffin; baseline: SBP, 119 ± 15.6; DBP, 75 ± 10.4	4	Adherence to intervention assessed by 1-d DR and completing checklist on which subjects recorded supplements consumed and return of uneaten supplements, which were weighed and recorded; 2-wk washout period; no biomarker; no baseline reported	43/27 No significant reduction in SBP and DBP

[1]BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DR, dietary report; ITT, intention-to treat analysis; RCT, randomized controlled trial; ref, reference; SBP, systolic blood pressure.

[2]Values are ranges and/or means ± SDs or means ± SEs, as indicated.

[3]Values are means ± SDs. DBP and SBP values are given in mm Hg.

[4]Mean ± SD.

[5]Mean ± SE.

TABLE 2
Inclusion and exclusion criteria of studies[1]

First author, year (ref)	Inclusion criteria	Exclusion criteria
Bakhtiary, 2012 (13)	MetS based on ATP-III	Currently or previously using estrogen therapy; taking soy products or supplements; treatment with aspirin; taking antibiotics; history of CVD; hyper- and hypothyroidism; kidney, liver, breast, or any cancer; vegetarian diet; smoking; and allergic reaction to soy consumption
Foster, 2012 (28)	Obese [BMI (kg/m^2): 27–40]	Uncontrolled hypertension (defined as a BP >180/100 mm Hg), established CVD or an inflammatory condition (e.g., lupus), type 2 diabetes or use of antihyperglycemic medications, dyslipidemia requiring prescription drug therapy as defined by the ATP-III, or any known allergy or sensitivity to nuts
West, 2012 (39)	Healthy, nonsmoker, high LDL, normal or mild hypertension	BP- or TC-lowering medication; use of nut supplement; pregnancy; weight loss >10% of body weight in the previous 6 mo; vegetarian or weight-loss diets; liver, kidney, autoimmune, or vascular disease
Casas-Agustench, 2011 (26)	MetS based on ATP-III	Nut allergy; history of alcohol abuse/drug dependence; type 2 diabetes; endocrine disorders; BMI >35; acute/chronic infection; chronic inflammatory disease; history of cancer; treatment with anti- inflammatory, corticosteroid, hormonal, or antibiotic agents; a restrictive diet or weight change >5 kg during the 3 mo before study, as assessed by medical history, a complete physical examination, and laboratory tests
Jenkins, 2011 (31)	Type 2 diabetes and postmenopausal women	CVD or renal or liver disease (alanine aminotransferase > 3 times the upper normal limit) or a history of cancer; after surgery or myocardial infarction <6 mo
Li, 2011 (33)	Type 2 diabetes, hyperlipidemia	Insulin therapy; medications or supplementations known to alter lipid metabolism; stable blood lipid and sugar concentrations within 3 mo before study; CVD; hepatic, gastrointestinal, or renal disease; alcoholism; smoking
Ghadimi Nouran, 2010 (29)	Hypercholesterolemic men	Type 2 diabetes, kidney, liver, and thyroid diseases; cancer; the presence of inflammatory or infectious disease; vitamin supplements; hormone therapy or medications that might have influenced the study variables (e.g., antihypertensive and antilipidemic agents administered in the 4 mo before the study); recent history of weight gain or loss (≥9 kg) in past 6 mo; very atypical diet; rigorous exercise; allergy or aversion to nuts; habitual consumption of nuts >70 g/wk; cigarette smokers; first-degree family history of CAD
Ma, 2010 (34)	Type 2 diabetes, nonsmokers	Vasoactive medications or supplement, current eating disorder, known atherosclerosis, sleep apnea, pregnancy, restricted diet, nut allergy, use of lipid-lowering or antihypertensive medications <3 mo
Sari, 2010 (36)	Acute and chronic medical disorders	Smoking, frequent nut consumption (>1/wk), nut or food allergy, regular use of any drugs or vitamin supplement, history of any known disease, inflammatory diseases (infections, recent surgical procedures), dyslipidemia
Wien, 2010 (24)	Prediabetic	Self-reported allergy to almonds, history of irritable bowel disease or diverticulitis, use of corticosteroids or immunosuppressant medications, or presence of liver disease, renal disease, and/or severe dyslipidemia (TGs >400 or TC >300 mg/dL)
Wu, 2010 (19)	MetS based on ATP-III	History of allergy or high consumption of nuts, flaxseed, or sesame seeds (120 g/wk); clinically diagnosed renal, liver, heart, pituitary, thyroid, or mental diseases or alimentary tract ulceration or diseases affecting absorption; history of CVD, cancer, or mental disorders; current or previous (in the preceding 6 mo) use of antidepressants, estrogen, or steroid therapy; pregnancy or lactation
Claesson, 2009 (27)	Healthy subjects	Nonobese (BMI: 27) and free from current diseases, including eating disorders

(Continued)

TABLE 2 (*Continued*)

First author, year (ref)	Inclusion criteria	Exclusion criteria
Spaccarotella, 2008 (38)	Healthy, nonsmoking men	Allergies to nuts; use of prescription and nonprescription preparations known to alter PSA, hormone concentrations, BP or blood lipids; men taking vitamin E supplement were eligible if they discontinued use 2 mo before entering the study
Azadbakht, 2007 (12)	MetS based on ATP-III; postmenopausal women	Any secondary cause of hyperglycemia, current or previous (in the preceding 6 mo) use of estrogen therapy, treatment with insulin or oral hypoglycemic agents, untreated hypothyroidism, smoking, kidney or liver diseases, breast malignancy or breast cancer
Mukudden- Petersen, 2007 (23)	MetS based on ATP-III	Pregnancy or lactation, thiazide (>25 mg/d) and β-blocker (nonspecific, β1 and β2) use, nut allergies, type 2 diabetes
Sheridan, 2007 (37)	Moderate hypercholesterolemia	Treated for hyperlipidemia, hypertension, type 2 diabetes kidney or liver disease, food allergies, smokers, consuming >3 alcoholic drinks/wk, women receiving hormone therapy
Estruch, 2006 (11)	Type 2 diabetes or 3 CVD risk factors	CVD or any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or low predicted likelihood of changing dietary habits according to the stages-of change model
Ros, 2004 (35)	Nonsmokers, moderate hypercholesterolemia	Chronic illnesses or secondary hypercholesterolemia, allergy to nuts, vitamin supplements, hormone replacement therapy, medications known to affect lipid metabolism
Wien, 2003 (40)	Obese (BMI: 24–55)	Patients taking lipid-lowering medications and women receiving hormone replacement therapy
Iwamoto, 2002 (30)	Healthy subjects	Frequent nut consumption, food allergies, cigarette smoking, history of hypertension or atherosclerotic or metabolic disease, regular medication, or considered unable to comply with the study protocol
Jenkins, 2002 (32)	Healthy hyperlipidemic and postmenopausal women	Food allergies, abdominal discomfort, type 2 diabetes, liver or renal disease, hyperlipidemic or BP medications, hormone replacement therapy

[1]ATP-III, Adult Treatment Panel III; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; MetS, metabolic syndrome; ref, reference; TC, total cholesterol; TG, triglyceride.

criteria. Finally, 21 RCTs, which studied a total of 1652 adults aged 18–86 y, were selected for the present systematic review and meta-analysis. **Figure 1** shows the study selection process.

Table 1 presents the characteristics and the main outcomes of the 21 RCTs included in the systematic review (11–13, 19, 23, 24, 26–40). In brief, the intervention period in these RCTs ranged between 2 and 16 wk. Some studies used a randomized crossover design (12, 26, 29, 30, 32–39), 2 of which were also single blind (26, 30). Six studies reported having a washout period (12, 29, 32–34, 38), and 8 studies reported a run-in period (23, 28–30, 33–35, 39). The others had no run-in or washout periods or did not report this. Table 1 shows the studies that had run-in and washout periods, although these variables were not used in the analysis. Seven studies were conducted in the United States (24, 28, 34, 37–40), 3 in Spain (11, 26, 35), 1 in South Africa (23), 3 in Iran (12, 13, 29), 2 in Canada (31, 32), 2 in China (19, 33), and 1 each in Japan (30), Sweden (27), and Turkey (36). The effect of walnuts was examined in 6 studies (19, 23, 30, 34, 35, 38), almonds in 5 studies (24, 28, 32, 33, 40), pistachios in 3 studies (36, 37, 39), peanuts in 2 studies (27, 29), soy nuts in 2 studies (12, 13), and mixed nuts in 3 studies (11, 26, 31). The effect of 2 dosages of nut consumption on BP was evaluated in 3 studies (31, 32, 39), and the effect of 2 different types of nuts was examined in 1 study (23). Iwamoto et al. (30) also reported the effect of nut consumption among men and women separately; 2 effect sizes were therefore extracted from these studies and were included as separate studies in the meta-analysis. In 5 studies, the analyses were based on the intention-to-treat principle (11, 19, 28, 31, 34) and the others were based on per protocol analysis (12, 13, 23, 24, 26, 27, 29, 30, 32, 33, 35–40). **Table 2** shows the inclusion and exclusion criteria, including health and disease status and medication.

Risk of bias

Table 3 shows the methodologic quality of the studies. Briefly, none of the studies was suitable for all of the 6 items considered for the methodologic quality assessment because none of them were blind. Approximately 42% of studies were rated as appropriate (11, 13, 19, 23, 24, 28, 31, 38, 40), whereas the method used to generate the allocation sequence was unclear in the others (12, 21, 26, 27, 29, 30, 32–37, 39). Allocation concealment and blinding of outcome were appropriate in only 9% (11, 24) and 5% (31) of studies, respectively. In contrast, 86% and 81% of studies had a low risk of bias for incomplete outcome data (12, 13, 23, 24, 26–38, 40) and selective reporting (11–13, 23, 24, 26, 28, 29, 31–37, 39, 40), respectively. Thus, these categories provide the lowest risk of bias. The overall quality was assessed and rated as "good" (low risk of bias) for 6 studies (13, 19, 23, 28, 31, 40), "fair" for 12 studies (11, 12, 26, 29, 32–39), and "poor" for 3 studies (19, 27, 30).

TABLE 3
Study quality and risk of bias assessment[1]

First author, year (ref)	Sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Bakhtiary, 2012 (13)	+	?	−	?	+	+	Good
Foster, 2012 (28)	+	?	−	?	+	+	Good
West, 2012 (39)	?	?	−	?	?	+	Fair
Casas-Agustench, 2011 (26)	?	?	−	?	+	+	Fair
Jenkins, 2011 (31)	+	−	−	+	+	+	Good
Li, 2011 (33)	?	?	−	?	+	+	Fair
Ghadimi Nouran, 2010 (29)	?	?	−	?	+	+	Fair
Ma, 2010 (34)	?	?	−	?	+	+	Fair
Sari, 2010 (36)	?	?	−	?	+	+	Fair
Wien, 2010 (24)	+	+	−	?	+	+	Good
Wu, 2010 (19)	+	?	−	?	−	−	Poor
Claesson, 2009 (27)	?	?	−	?	+	−	Fair
Spaccarotella, 2008 (38)	+	?	−	?	+	−	Fair
Azadbakht, 2007 (12)	?	?	−	?	+	+	Fair
Mukudden-Petersen, 2007 (23)	+	?	−	?	+	+	Good
Sheridan, 2007 (37)	?	?	−	?	+	+	Fair
Estruch, 2006 (11)	+	+	−	?	−	+	Fair
Ros, 2004 (35)	?	?	−	?	+	+	Fair
Wien, 2003 (40)	+	?	−	?	+	+	Good
Iwamoto, 2002 (30)	?	?	−	?	+	−	Poor
Jenkins, 2002 (32)	?	?	−	?	+	+	Fair

[1]ref, reference; +, low risk; −, high risk; ?, unclear.

Effect of nut consumption on SBP

Our preliminary analysis in a total of 1652 adults from 21 RCTs indicated that all-type nut intake had no significant reducing effect on SBP (MD: −0.91; 95% CI: −2.18, 0.36; $P = 0.16$). However, there was significant heterogeneity among studies (Cochran's Q test = 95.31, $P < 0.001$, $I^2 = 73.8\%$) (**Figure 2**). Subgroup analyses stratified by specific types of nut suggested that pistachios had a significant reducing effect on SBP (MD: −1.82; 95% CI: −2.97, −0.67; $P = 0.002$). On the contrary, analyses suggested that almonds, walnuts, cashews, mixed nuts, peanuts, and soy nuts do not have a significant reducing effect on SBP (Figure 2). No significant heterogeneity was observed among studies examining the effect of pistachios, peanuts, and soy nuts. On the other hand, heterogeneity was found among studies on almonds (Cochran's Q test = 15.97, $P = 0.007$, $I^2 = 68.7\%$), walnuts (Cochran's Q test = 39.34, $P < 0.001$, $I^2 = 84.7\%$) and mixed nuts (Cochran's Q test = 14.21, $P = 0.003$, $I^2 = 78.9\%$) (Figure 2).

When only the studies that recruited participants without type 2 diabetes were considered, a significant overall reducing effect on SBP was observed (MD: −1.29; 95% CI: −2.35, −0.22; $P = 0.018$) and the heterogeneity among studies was significant (Cochran's Q test = 44.93, $P = 0.002$, $I^2 = 53.3\%$). The subgroup analysis showed that the effect of different types of nut intake on lowering SBP did not change after participants with type 2 diabetes were removed from the analysis (**Figure 3**). However, heterogeneity disappeared in each category except for almonds (Cochran's Q test = 15.97, $P = 0.007$, $I^2 = 68.7\%$).

Effect of nuts on DBP

According to our analysis in 1652 adults, overall nut consumption had no significant effect on DBP (MD: 0.21; 95% CI: −0.54, 0.97; $P = 0.58$). There was significant heterogeneity among the studies (Cochran's Q test = 82.31, $P < 0.001$, $I^2 = 69.6\%$) (**Figure 4**). The subgroup analysis based on the type of nut revealed that pistachios (MD: −0.80; 95% CI: −1.43, −0.17; $P = 0.01$) and mixed nuts (MD: −1.19; 95% CI: −2.35, −0.03; $P = 0.04$) lowered DBP significantly, whereas other types did not (Figure 4). Heterogeneity was significant among studies that assessed the effect of walnuts on DBP (Cochran's Q test = 28.89, $P < 0.001$, $I^2 = 79.2\%$) but not for other types of nut (Figure 4). Our analysis of subjects without type 2 diabetes showed that only pistachios decrease DBP (MD: −0.80; 95% CI: −1.43, −0.17; $P = 0.01$) and that there was no heterogeneity among the studies (Cochran's Q test = 2.68, $P = 0.44$, $I^2 = 0.0\%$) (**Figure 5**).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the removal of any of the studies from the whole sample or subgroups did not considerably change the effect of nut consumption on SBP and DBP. Exclusion of the trials with soy nuts from the overall analysis did not significantly change our previous findings on the effect of nuts on SBP and DBP in all studies or in those studies that focused only on participants without type 2 diabetes (data not shown). Although a slight asymmetry was seen in funnel plots, there was no evidence of publication bias for studies examining the effect of nut consumption on SBP (Begg's test, $P = 0.29$; Egger's test, $P = 0.99$) and DBP (Begg's test, $P = 0.23$; Egger's test, $P = 0.77$).

DISCUSSION

In the present systematic review and meta-analysis of 21 studies involving 1652 participants, we found that overall nut consumption had no significant effect on SBP. Subgroup analyses based on the type of nut suggest that pistachios significantly

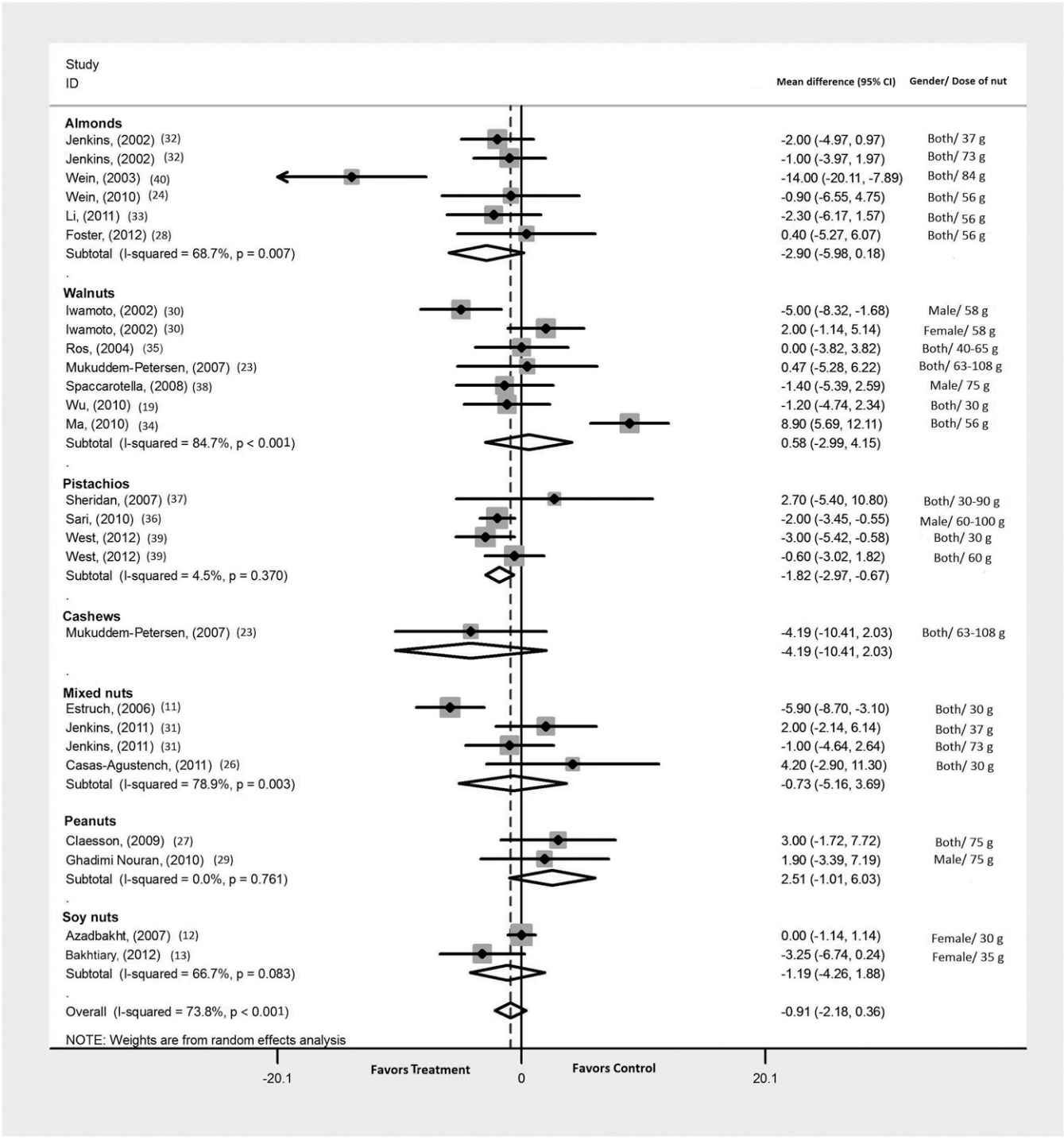

FIGURE 2 Forest plot showing the overall effect of nut consumption on systolic blood pressure and analysis of nut-type subgroups. Note: weights are from random-effects analysis.

reduce both SBP and DBP, whereas mixed nuts reduce only DBP. Sensitivity analysis for participants without type 2 diabetes showed an overall reduction only in SBP. Furthermore, by removing participants with type 2 diabetes from the analysis, only pistachios significantly reduced both SBP and DBP. To the best of our knowledge, the present study is the first systematic review and meta-analysis to analyze the effect of nut consumption on BP.

Two prospective cohort studies investigated the association between nut consumption and incident hypertension as the primary outcome (9, 10). They both included healthy subjects and showed controversial results. The first, conducted in 15,966 subjects from the cohort of the Physicians' Health Study I, showed that men who consumed nuts ≥7 times/wk had an 18% lower risk of developing hypertension than did those who did not consume nuts. However, this association was mainly observed

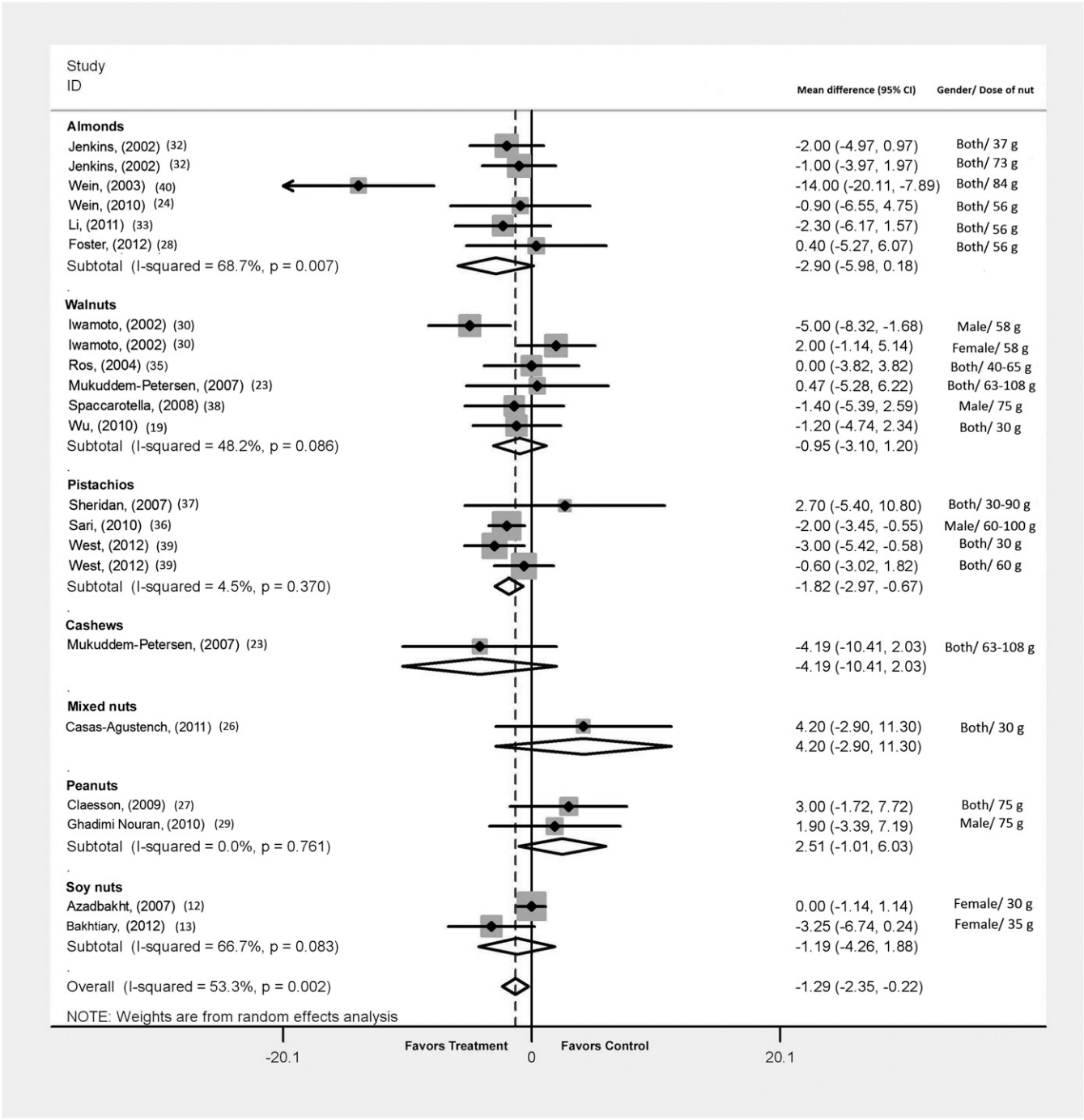

FIGURE 3 Forest plot showing the overall effect of nut consumption on systolic blood pressure and analysis of nut-type subgroups by using sensitivity analysis in participants without type 2 diabetes. Note: weights are from random-effects analysis.

in lean, not obese, individuals (10). The second was the SUN (Seguimiento Universidad de Navarra) study, which included 9919 Spanish university graduates followed up for a median of 4.3 y. After adjustment for potential confounders, no association was found between nut consumption and the incidence of hypertension (9).

The RCTs in this systematic review that investigated the effect of mixed nuts, almonds, pistachios, walnuts, and cashews also reported conflicting findings on SBP and DBP (11, 19, 23, 24, 26, 28, 30–40). These nuts are of very similar nutritional composition and, as reported, most of them tended to reduce BP. However, RCTs on soy nuts and peanuts, which, botanically, are considered to be legumes, found no significant effect on BP (12, 13, 27, 29). It should be pointed out that the nutritional composition of soy nuts is quite different to that of the other nuts. Soy nuts are rich in carbohydrate and protein and less rich in vegetable unsaturated fatty acid, and this may explain their lack of effect on BP. However, we found no difference in overall effect of nuts on BP when we excluded the soy nut studies (12, 13).

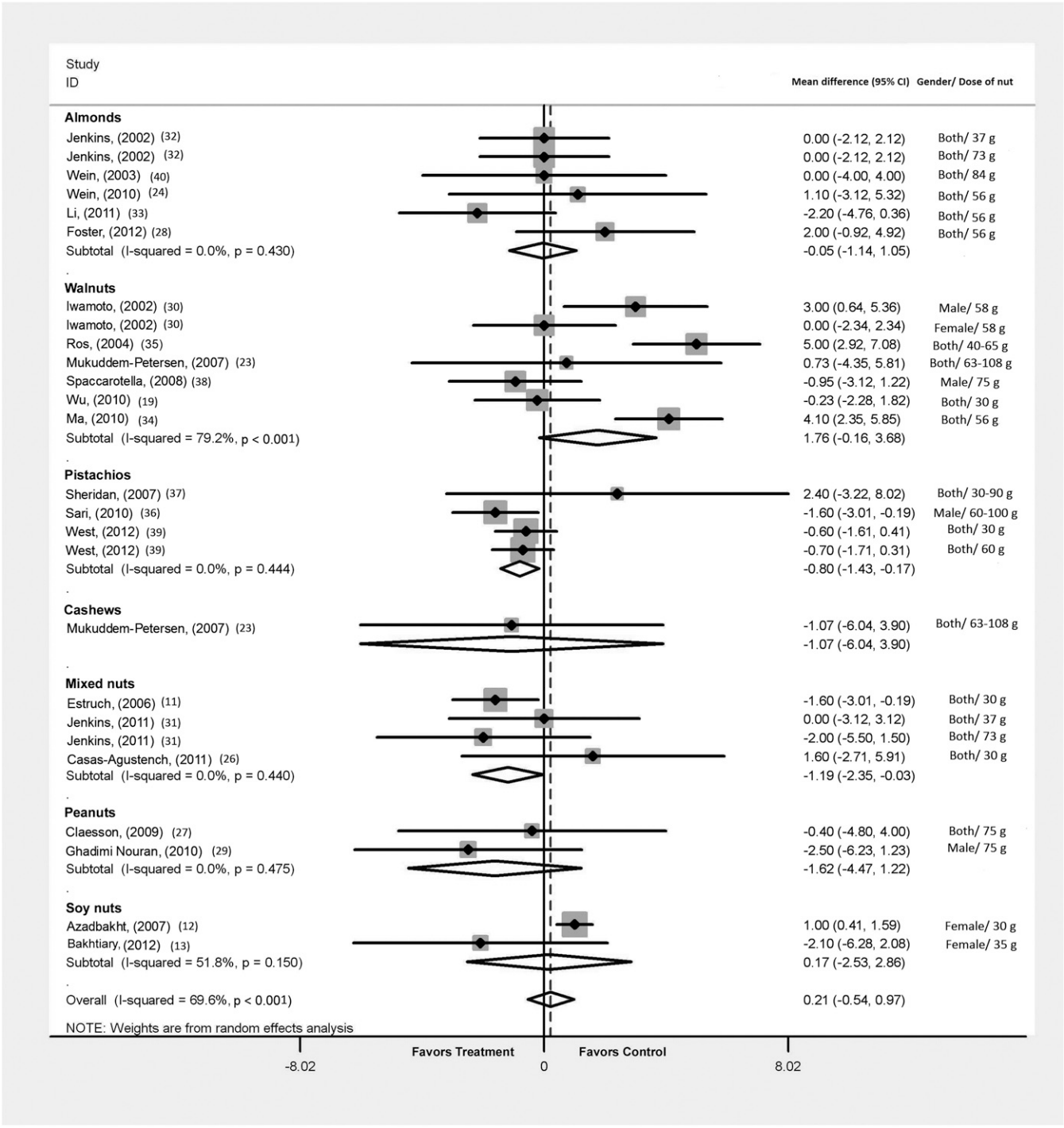

FIGURE 4 Forest plot showing the overall effect of nut consumption on diastolic blood pressure and analysis of nut-type subgroups. Note: weights are from random-effects analysis.

Our results are in agreement with various recent systematic reviews and meta-analyses that showed that nut consumption is inversely associated with the incidence of several diseases related to BP, such as hypertension (45, 46) and ischemic heart disease (46–48), and with all-cause mortality (47). A pooled analysis of clinical trials by Salas-Salvadó et al. (49) also reported that nuts had a protective effect on metabolic syndrome, of which hypertension is one of the main components.

CVD-protective dietary patterns, including the DASH and Mediterranean diets, recommend frequent nut consumption, because nuts contain little SFA and 40–60% unsaturated fatty acids, mostly PUFAs in walnuts and MUFAs in almonds, hazelnuts, macadamia nuts, pecans, pistachios, and peanuts. However, the antihypertensive effect of nuts probably depends on non–fatty acid compounds such as dietary fiber, plant proteins, antioxidants, and bioactive substances such as flavonoids

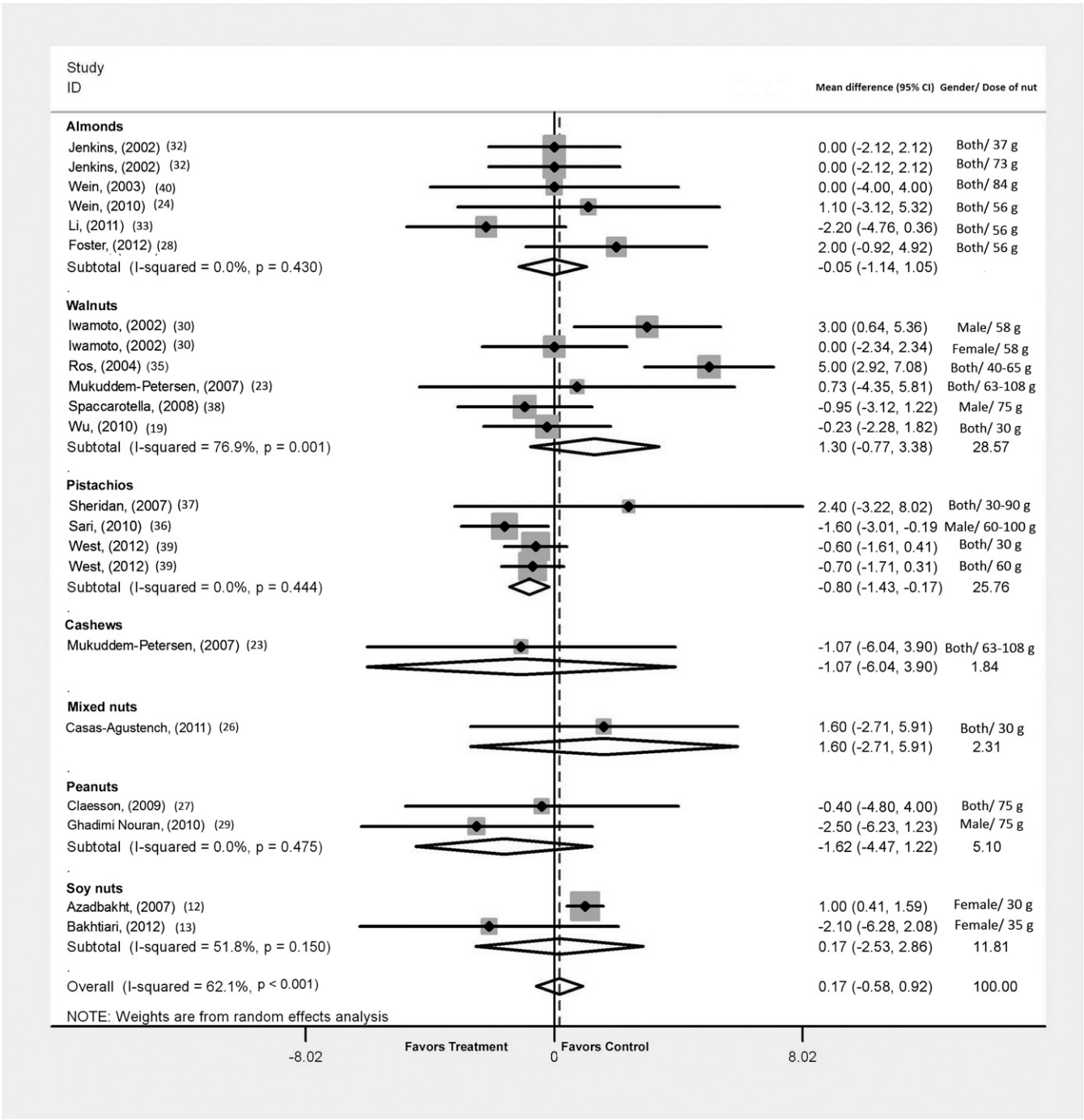

FIGURE 5 Forest plot showing the overall effect of nut consumption on diastolic blood pressure and analysis of nut-type subgroups by using sensitivity analysis in participants without type 2 diabetes. Note: weights are from random-effects analysis.

or phytosterols, vitamins, and minerals (mainly potassium and magnesium) (50).

In the present study, our data suggest that pistachio consumption significantly reduces SBP and DBP. Pistachios contain MUFAs and high amounts of phytosterols, which may have beneficial effects on lowering BP. Because of their specific composition and richness in lutein, β-carotene and γ-tocopherol, pistachios are prone to affect the inflammatory and oxidative state, C-reactive protein, and circulating IL-6, leading to a reduction in oxidized LDL cholesterol and improved the total antioxidant status, all recognized factors mediating the endothelial function. Nuts are also very rich in arginine (51), a precursor of endogenous nitric oxide, which is a potent vasodilator acting via second intracellular cyclic guanosine-5'-monophosphate (52). These might be the main reasons for the significant lowering effect of these types of nuts on BP in our meta-analysis (21, 37).

The current meta-analysis has some limitations, which must be taken into account when the results are interpreted. Six trials

(53–58) were not included in our meta-analysis because they lacked essential data. The reasons for the observed heterogeneity may be due to the differences in the duration of interventions, inclusion criteria (including age range and health situation), exclusion criteria (including disease status and medication use), nut dosages, sample size, and type of recommendation given to the subjects. Consequently, we used the random-effects model, which takes into account heterogeneity among studies. In addition, the nuts consumed in some of the RCTs were roasted (24, 28, 29, 36, 39) and in 1 study they were salted (39). However, in the latter study the other sources of salt intake were limited in the intervention group, and sodium intake was equivalent to that of the control group. Finally, the extent to which participants complied with the intervention was evaluated in 19 studies by using 24-h recalls and 3-d dietary records (11–13, 19, 23, 24, 26, 27, 29–38, 40), although we acknowledge the limitations of these methods for validating nut intake. Only 7 of the studies (11, 19, 24, 26, 29, 35, 38) used biochemical biomarkers as a proxy for nut consumption. The results of the present work should be interpreted taking into account the methods used in the original studies.

In conclusion, our systematic review and meta-analysis of RCTs revealed that nut consumption can reduce BP, and particularly SBP. Of the different types of nuts studied, pistachios seem to have the strongest SBP- and DBP-reducing effect. Although some pharmacologic treatments and exercise appear to be effective at reducing BP, healthy diets that include the consumption of tree nuts may help to enhance their effectiveness and even reduce the required dosages of antihypertensive medications.

The authors' responsibilities were as follows—NM: designed the study and wrote the first draft of the manuscript; NM and AS-A: identified and extracted relevant articles and analyzed the data; AS-A, JS-S, MG-F, KH, and NS: read and commented on the manuscript; and all of the authors: read and approved the final manuscript. None of the authors declared a conflict of interest.

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