Nut intake and adiposity: meta-analysis of clinical trials[1–3]

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ABSTRACT

Background: Epidemiologic studies have shown an inverse association between the frequency of nut consumption and body mass index (BMI) and risk of obesity. However, clinical trials that evaluated nut consumption on adiposity have been scarce and inconclusive.

Objective: We performed a systematic review and meta-analysis of published, randomized nut-feeding trials to estimate the effect of nut consumption on adiposity measures.

Design: MEDLINE and the Cochrane Central Register of Controlled Trials databases were searched for relevant clinical trials of nut intake that provided outcomes of body weight, BMI (in kg/m^2), or waist-circumference measures and were published before December 2012. There were no language restrictions. Two investigators independently selected and reviewed eligible studies. The weighted mean difference (WMD) between nut or control diets was estimated by using a random-effects meta-analysis with 95% CIs.

Results: Thirty-three clinical trials met our inclusion criteria. Pooled results indicated a nonsignificant effect on body weight (WMD: –0.47 kg; 95% CI: –1.17, 0.22 kg; $I^2 = 7\%$), BMI (WMD: –0.40 kg/m^2; 95% CI: –0.97, 0.17 kg/m^2; $I^2 = 49\%$), or waist circumference (WMD: –1.25 cm; 95% CI: –2.82, 0.31 cm; $I^2 = 28\%$) of diets including nuts compared with control diets. These findings were remarkably robust in the sensitivity analysis. No publication bias was shown.

Conclusion: Compared with control diets, diets enriched with nuts did not increase body weight, body mass index, or waist circumference in controlled clinical trials. *Am J Clin Nutr* 2013;97: 1346–55.

INTRODUCTION

Nuts are energy-dense foods because they contain ≥50% fat, most of which is in the form of MUFAs, except walnuts, in which PUFAs predominate (1). Nuts are also rich in dietary fiber (2) besides many other bioactive nutrients and phytochemicals, and there is increasing scientific evidence that the incorporation of nuts into healthy diets is beneficial for heart health (3). Results from observational studies have consistently shown that frequent nut consumption relates inversely to fatal and nonfatal coronary heart disease and sudden cardiac death (4). Recent findings from epidemiologic studies suggested that frequent nut consumption is associated with lower mortality rates (5, 6). Limited evidence from observational studies has also suggested that nut consumption protects against the development of diabetes in women (7, 8) or hypertension in men (9). A recently published pooled analysis of 25 feeding clinical trials that used different types and amounts of nuts supported a consistent cholesterol-lowering effect of nut consumption (10). In addition, clinical trials have shown that diets supplemented with nuts have beneficial effects on other cardiovascular risk factors, reducing inflammation, and oxidative stress (11) and ameliorating insulin resistance or endothelial dysfunction (12). Recently, nut supplementation has also been shown to improve glycemic control in patients with type 2 diabetes (13).

Despite these findings, because nuts are energy-dense foods with a high-fat content (1), there is still a widespread perception that their consumption leads to unwanted increases in body weight and higher long-term risk of developing overweight or obesity. This perception poses a constraint to the recommendation of nut consumption as a strategy to help prevent cardiovascular diseases. However, different cross-sectional and prospective epidemiologic studies indicated an inverse association between the frequency of nut consumption and BMI (in kg/m^2) and risk of obesity (7, 14–16). In addition, several metabolic studies and short-term controlled feeding trials have supported that the addition of nuts to usual diets does not induce weight gain, despite an expected increase in energy intake (17). Because the magnitude of the effect of nut consumption on adiposity measures has not been comprehensively evaluated previously, we systematically reviewed all scientific literature published before December 2012 for results of randomized clinical trials in which nut-rich diets were compared with different control diets and adiposity measures such as body weight, BMI, or waist circumference were reported.

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METHODS

Search strategy

We searched MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) and the Cochrane Central Register of Controlled Trials (http://www.thecochranelibrary.com/view/0/index.html) that reported the effects of nut diets compared with control diets on weight change by using the free-text and Medical Subject Headings terms nuts, hazelnut, walnut, almond, pecan, macadamia, peanut, pistachio, cholesterol, hypercholesterolemia, dyslipidemia, triglycerides, hypertension, blood pressure, diabetes mellitus, glucose, obesity, overweight, body mass index, waist circumference, and metabolic syndrome. The search period was all-inclusive until December 2012. There were no language restrictions. In addition, we manually reviewed reference lists from relevant original research and review articles.

Study selection

We included all clinical trials with either a parallel or a crossover design that were conducted in adults aged ≥18 y that assessed a nut-enriched diet and reported anthropometrical outcomes (body weight, BMI, or waist circumference). Exclusion criteria were as follows: *1*) no original research (reviews, editorials, or nonresearch letters); *2*) case reports and case series; *3*) data on body weight, BMI, or waist circumference not clearly reported; and *4*) the absence of a comparator diet. Ethical approval was not required because only published data were analyzed in this review. The study-selection process is summarized in **Figure 1**.

Data extraction and quality assessment

Two investigators (DR-R and GF-M) independently abstracted articles that met the selection criteria and resolved discrepancies by consensus. Study outcomes included means (±SDs) for body weight, BMI, and waist circumference. These values were captured as mean changes from baseline to the end of intervention (with variations reported as SDs, SEs, or 95% CIs). When there were several publications from the same cohort, the study with the longest follow-up was selected; when the follow-up was equivalent, we selected the study with the largest number of cases, the publication that used internal comparisons, or the most recent study. For study assessment, one of the investigators abstracted data on the study design, setting, country of origin, sex, average age of participants, number of participants, type and amount of nuts consumed, length of the intervention, and number of individuals who consumed nut-enriched diets and control diets. To assess study quality, we used the Cochrane quality assessment of randomized controlled trials (18). Each of the criteria was categorized as clearly yes, not sure, or clearly no. Criteria for which there were differences between the 2 evaluators were discussed until a joint decision was reached. A score between 0 and 24 was given to perform a subgroup

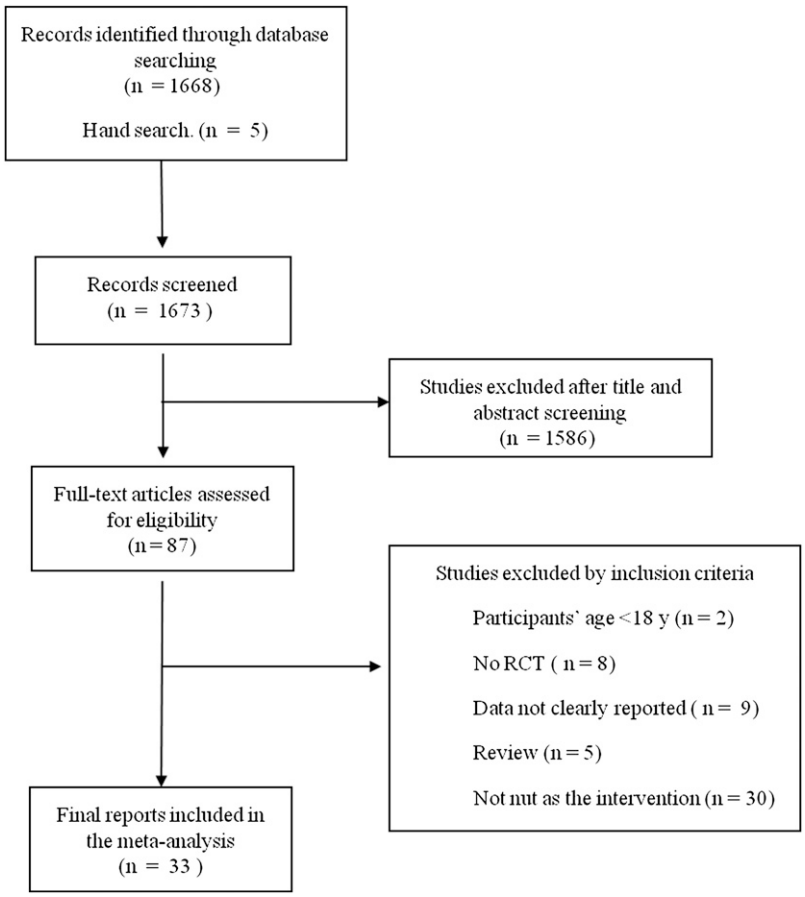

FIGURE 1. Flow diagram of the study-selection process. RCT, randomized controlled trial.

TABLE 1
Characteristics of included clinical trials[1]

First author, year of publication, country (reference)	Study design	Participants	Men	Age[2]	Diet period	Type of nut	Nut-enriched diets	Control diet	Quality score[3]
		n	%	*y*	*wk*				
Jenkins, 1997, Canada (20)	Randomized crossover	10	70	33	2	Almonds, cashews, and peanuts	60–120 g/d	Habitual diet	16
O'Byrne, 1997, United States (21)	Quasiexperimental study with a control group	25	0	50–65	24	Peanuts	35–68 g/d	Low-fat diet	10
Spiller, 1998, United States (39)	Randomized, controlled, parallel	30	27	53	4	Almonds	Supplementation with 100 g raw unblanched almonds/d	Cheddar cheese (85 g), butter (28 g), and rye crackers (21 g) were added to the Background diet	13
Zambón, 2000, Spain (22)	Randomized crossover	49	53	56	6	Walnuts	Walnuts partially replaced olive oil and other fatty foods (41–56 g walnuts/d)	Mediterranean diet	10
Morgan, 2000, United States (40)	Randomized, controlled, parallel	23	22	45	2	Pecans	Supply of 68 g pecans/d	Habitual diet	17
Almario, 2001, United States (41)	Randomized crossover	18	28	60	6	Walnuts	Supplementation with 48 g walnuts/d	Habitual diet	17
Alper, 2002, United States (42)	Randomized crossover	15	55	33	8	Peanuts	50% of dietary fat energy supplied by peanuts	Habitual diet	18
Jenkins, 2002, Canada (23)	Randomized crossover	25	55	64	4	Almonds	Supplementation with 73 g almonds/d	NCEP Step II	10
Sabaté, 2003, United States (38)	Randomized crossover	25	56	41	4	Almonds	Replaced 20% of energy of the Step I diet with 68 g almonds/d	NCEP Step I	14
Jenkins, 2003, Canada (24)	Randomized, controlled, parallel	25	64	60	4	Almonds	Portfolio diet, which included 16.6 g unblanched whole almonds/d per 1000 kcal of diet	NCEP Step II	10
Wien, 2003, United States (25)	Randomized, controlled, parallel	65	43	27–79	24	Almonds	Whole, unblanched, unsalted almonds (84 g/d)	Low-fat diet	18
Ros, 2004, Spain (26)	Randomized crossover	21	40	55	4	Walnuts	40–65 g/d	Mediterranean diet	14
Tapsell, 2004, Australia (27)	Randomized, controlled, parallel	58	68	59	24	Walnuts	Adding 30 g walnuts/d	Low fat diet	15
Lamarche, 2004, Canada (43)	Randomized crossover	12	50	65	4	Almonds	2.9 g raw, unblanched almonds/4.2 MJ	Low fat diet	12
Sabaté, 2005, United States (44)	Randomized crossover	90	54	55	24	Walnuts	Supplement of 28 g walnuts/d	Habitual diet	14
Chisholm, 2005, New Zealand (51)	Randomized crossover	28	18	48	6	Combination of nuts	Supplement of a daily serving of nuts	Habitual diet plus cereal	14
Schutte, 2006, South Africa (35)	Randomized, controlled, parallel	62	45	45	8	Walnut or cashews	63–108 g cashews/d	Habitual diet	8

(Continued)

TABLE 1 (*Continued*)

First author, year of publication, country (reference)	Study design	Participants	Men	Age[2]	Diet period	Type of nut	Nut-enriched diets	Control diet	Quality score[3]
Kocyigit, 2006, Turkey (52)	Randomized, controlled, parallel	44	54	33	3	Pistachios	Pistachio nuts contributing 20% of the total daily energy intake	Habitual diet	13
Canales, 2007, Spain (36)	Randomized crossover	22	60	54	5	Walnut-enriched frozen meat	150 g walnut paste/wk	Habitual diet and meat without walnut paste	10
Hollis, 2007, United States (28)	Randomized crossover	24	No data	24	10	Almonds	To eat a 1440-kJ portion of raw, unsalted almonds each day	Habitual diet	12
Sheridan, 2007, United States (29)	Randomized crossover	15	73	60	4	Pistachios	15% of daily energy	Habitual diet	14
Mukuddem-Petersen, 2007, South Africa (30)	Randomized, controlled, parallel	43	45	45	8	Walnuts or cashews	20% of the total energy came from nuts	Habitual Diet	11
Mercanligil, 2007, Turkey (45)	Randomized crossover	15	No data	48	8	Hazelnuts	40 g hazelnuts/d	Low-fat, low-cholesterol, high-carbohydrate diet	12
Olmedilla-Alonso, 2008, Spain (31)	Randomized crossover	25	60	54	5	Walnut-enriched frozen meat	20% of walnuts added	Habitual diet and meat without walnut paste	10
Gebauer, 2008, United States (32)	Randomized crossover	28	35	48	4	Pistachios	20% of daily energy	Low-fat diet	14
Spaccarotella, 2008, United States (46)	Randomized crossover	22	100	66	8	Walnuts	Supplement of 75 g walnuts/d	Habitual diet	14
Tapsell, 2009, Australia (33)	Randomized, controlled, parallel	50	No data	54	48	Walnuts	30 g walnuts/d	Low-fat diet	17
Razquin, 2010, Spain (34)	Randomized, controlled, parallel	737	45	55–80	156	Walnuts, hazelnuts, and almonds	Supplement of raw nuts (15 g/d)	Low-fat diet	20
Wien, 2010, United States (47)	Randomized, controlled, parallel	65	21	54	16	Almonds	ADA diet with 20% of energy from almonds	ADA diet	18
Ma, 2010, United States (48)	Randomized crossover	24	42	58	8	Walnuts	Supplement of 56 g walnuts/d	Habitual diet	18
Li, 2011, Taiwan (54)	Randomized crossover	20	45	58	8	Almonds	Almonds replaced 20% of calories	NCEP Step II	16
Casas-Agustench, 2011, Spain (37)	Randomized, controlled, parallel	50	56	52	12	Walnuts, almonds, and hazelnuts	Supplement of raw nuts (30 g/d)	Habitual diet	16
Foster, 2012, United States (50)	Randomized, controlled, parallel	123	6.5	47	72	Almonds	Supplement of 28 g almonds/d	Low-calorie diet	18

[1] ADA, American Diabetes Association; NCEP, National Cholesterol Education Program.
[2] All values are means or ranges.
[3] Quality criteria were from http://bjmtg.cochrane.org/resources-review-authors.

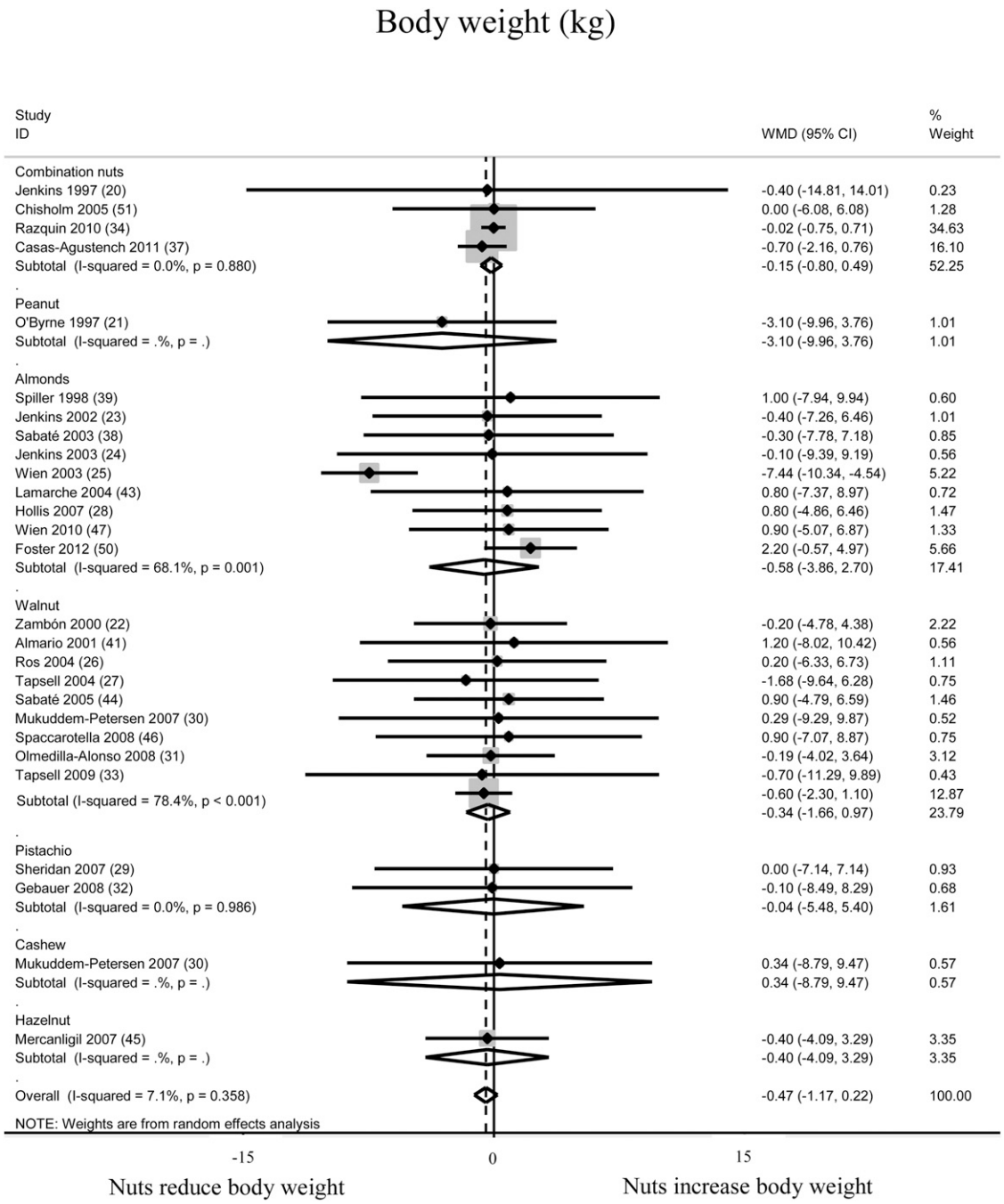

FIGURE 2. Meta-analysis of the net change (kg) in body weight associated with nut-enriched diets expressed as the change during the intervention with nut products minus the change during the control diet. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from inverse-variance–weighted random-effects models. ID, identification; WMD, weighted mean difference.

analysis of quality (0 denoted noncompliance with any criteria, and 24 denoted the fulfillment of all criteria).

Statistical methods

The estimate of the principal effect was defined as the mean difference (net change in kilograms, kilograms per meter squared, or centimeters) in body weight, BMI, or waist circumference between participants assigned to nut-enriched and control diets. SE and CIs were converted to SDs for analyses. Clinical trials were analyzed according to the intention-to-treat principle. Weighted mean differences (WMDs) were estimated by using random-effects models because high heterogeneity was shown.

Heterogeneity was quantified with the I^2 statistic, which describes the proportion of total variation in study estimates as a result of heterogeneity (19). To explore sources of heterogeneity, we performed subgroup analyses and metaregression to evaluate whether results were different by the duration of intervention ($\geq$24 or $<$24 wk), including energy restriction (yes or no), study design (parallel or crossover trial), quality of the study, and type

TABLE 2
Stratified WMD for body weight, BMI, and waist circumference[1]

	Body weight				BMI				Waist circumference			
	n	WMD (95% CI)	I^2	*P*	*n*	WMD (95% CI)	I^2	*P*	*n*	WMD (95% CI)	I^2	*P*
		kg	*%*			kg/m^2	*%*			*cm*	*%*	
Time of follow-up												
<24 wk	20	–0.39 (–1.29, 0.51)	0	—	9	–0.18 (–0.66, 0.31)	0	—	3	–0.65 (–2.44, 1.14)	0	—
≥24 wk	8	–1.24 (–3.85, 1.36)	0	0.788	5	–0.78 (–2.19, 0.63)	84	0.904	2	–2.47 (–7.10, 2.12)	83	0.282
Study focus												
Energy restriction	2	–2.61 (–12.1, 6.84)	0	—	1	–2.50 (–3.32, –1.67)	—	—	1	–5.00 (–8.22, –1.78)	—	—
No energy restriction	26	–0.18 (–0.76, 0.37)	0	0.046	13	–0.08 (–0.45, 0.28)	0	0.004	4	–0.49 (–1.81, 0.83)	0	0.031
Study design												
Randomized parallel	11	–1.65 (–4.13, 0.83)	0	—	7	–0.19 (–0.76, 0.38)	0	—	—	—	—	—
Randomized crossover	17	–0.03 (–0.62, 0.56)	0	0.282	7	–0.55 (–1.48, 0.37)	70	0.801	5	–1.25 (–2.82, 0.31)	28	—
Quality												
<14 points	15	–0.17 (–1.70, 1.36)	1	—	7	–0.14 (–0.93, 0.64)	0	—	1	0.511 (–5.29, 6.31)	0	—
≥14 points	13	–0.76 (–2.21, 0.69)	61	0.582	7	–0.49 (–1.36, 0.39)	74	0.987	4	–1.46 (–3.37, 0.45)	54	0.372
Intervention diet												
Supplementation with nuts	17	–0.08 (–0.65, 0.48)	0	—	7	–0.08 (–0.47, 0.32)	0	—	3	–0.54 (–1.90, 0.81)	0	—
Replacement with nuts	11	–1.68 (–4.01, 0.65)	0	0.08	7	–0.66 (–1.70, 0.37)	45	0.924	2	–2.93 (–6.84, 0.98)	26	0.480

[1] *P* values were obtained by using metaregression. WMD, weighted mean difference.

of nut diet (nuts added to diet or nuts that partially replaced other fatty foods). We assessed the relative influence of each study on pooled estimates by omitting one study at a time. Finally, we assessed the publication bias by using Egger's test and funnel plots. Statistical analyses were performed with STATA software (version 11; StataCorp LP).

RESULTS

Study selection

The search strategy retrieved 1668 articles from different sources. We excluded 1586 publications on the basis of titles and abstracts and 54 articles after a full-text review, which left 33 clinical trials for final inclusion in the meta-analysis (20–52) (Figure 1) (**Table 1**). One study contributed with 2 articles (31, 36). We used body weight data from the study of Olmedilla-Alonso et al (31), but because this report did not include BMI measurements, we took BMI data from the publication of Canales et al (36). In most of the studies, nuts were used in isocaloric diets to replace other food items with high energy density. Only 2 studies included energy restriction (25, 53). The length of follow-up ranged from 2 (20) to 156 (34) wk.

Meta-analysis of nut intake and adiposity changes

Body weight

Data from a total of 1806 participants were analyzed in 28 clinical trials (20–34, 37–39, 41–48, 51). There was no significant difference in body weight changes between nut-enriched and control diets (WMD: –0.47 kg; 95% CI: –1.17, 0.22 kg; I^2 = 7%) (**Figure 2**).

A metaregression and subgroup analysis (**Table 2**) showed that energy restriction (P = 0.046) significantly influenced pooled estimates. A nonsignificant reduction in body weight in the nut group was shown in studies that imposed an energy restriction (WMD: –2.61 kg; 95% CI: –12.1, 6.84 kg; I^2 = 0%) (Table 2). Furthermore, in studies without an energy restriction, no significant effect of nut-enriched diets was observed (WMD: –0.18 kg; 95% CI: –0.70, 0.37 kg; I^2 = 0%).

Other sources of heterogeneity investigated, such as the follow-up of the study (P = 0.788), study design (P = 0.282), trial quality (P = 0.582), and type of intervention (P = 0.080), did not influenced pooled estimates. Funnels plot showed reasonable symmetry and a nonsignificant Egger's test for publication bias (P = 0.609), which suggested no evidence of publication bias in clinical trials of nut-enriched diets and body weight (*see* Figure S1 under "Supplemental data" in the online issue). In the sensitivity analysis, the exclusion of individual studies did not substantially modify estimates.

BMI

Data from a total of 1057 participants were analyzed in 14 clinical trials (21, 25, 27, 29, 34–36, 40, 41, 45, 47, 48, 52, 54). Pooled results indicated a nonsignificant reduction in BMI when subjects consumed a nut-rich diet compared with a control diet (WMD: –0.40 kg/m^2; 95% CI: –0.97, 0.17 kg/m^2; I^2 = 49%) (**Figure 3**). We performed a metaregression and subgroup analysis to explore sources of heterogeneity (Table 2). Nut consumption had greater effect on BMI (−2.50 compared with −0.08) when assessed

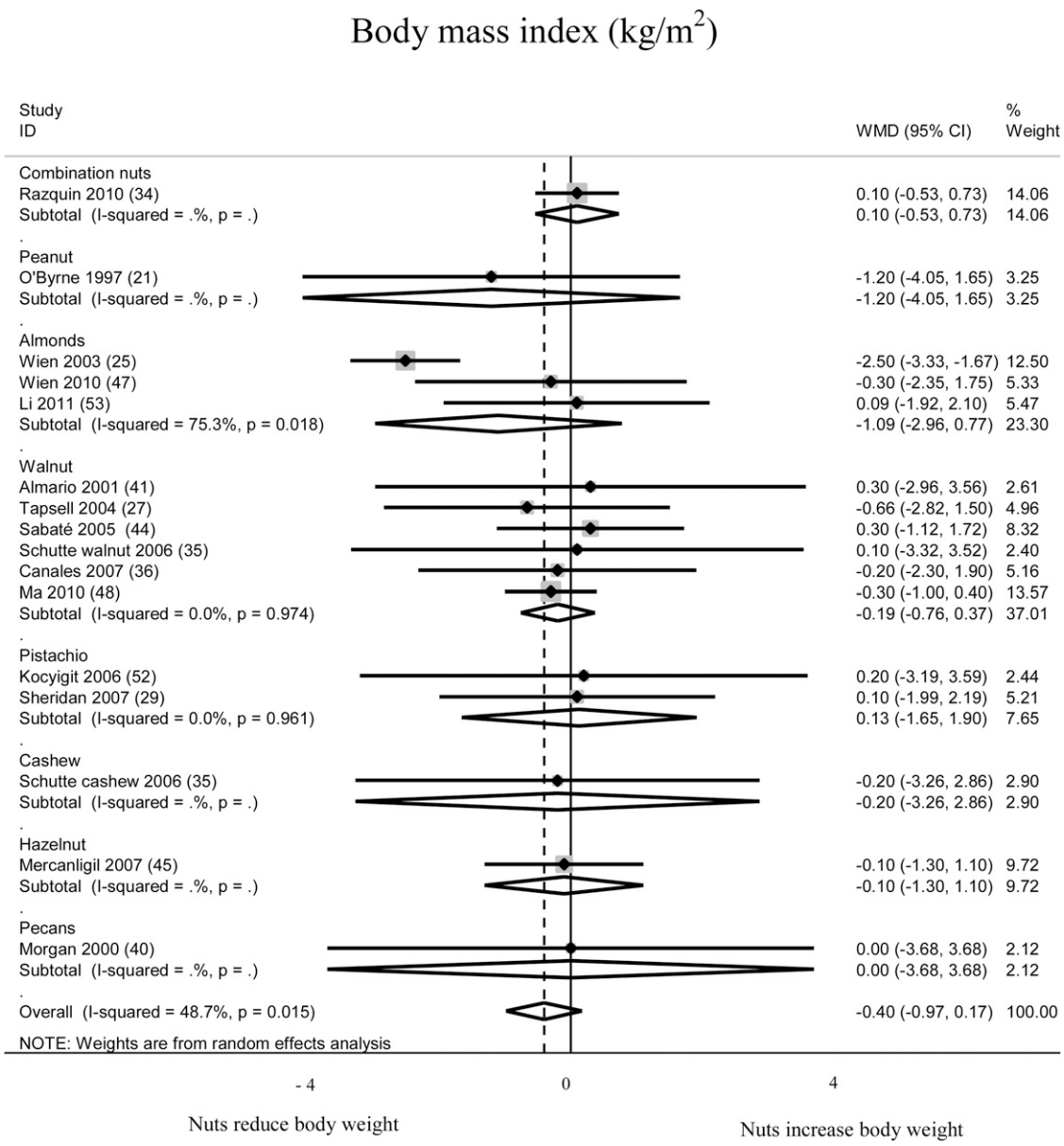

FIGURE 3. Meta-analysis of the net change in BMI (in kg/m^2) associated with nut-enriched diets expressed as the change during the intervention with nut products minus the change during the control diet. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from inverse-variance–weighted random-effects models. ID, identification; WMD, weighted mean difference.

studies focused on intervention that imposed energy restriction were compared with studies that focused on weight maintenance, respectively ($P = 0.05$). The duration of intervention ($P = 0.904$), study design ($P = 0.801$), trial quality ($P = 0.987$), or type of nuts tested ($P = 0.552$) did not modify effects on BMI.

The funnel plot showed reasonable symmetry and a non-significant Egger's test for publication bias ($P = 0.461$), which suggested no evidence of publication bias in clinical trials of nut-enriched diets and BMI (*see* Figure S1 under "Supplemental data" in the online issue). In the sensitivity analysis, the exclusion of individual studies did not modify estimates.

Waist circumference

Data from 681 participants were analyzed in 5 clinical trials (25, 34, 35, 37, 48). Compared with control diets, nut-enriched diets had no significant effect on waist circumference (WMD: –1.25 cm; 95% CI: –2.82, 0.31 cm; $I^2 = 28\%$) (**Figure 4**). The estimated effect of nut consumption on waist circumference was greater for studies that imposed energy restriction than for studies that focused on weight maintenance (-5.00 compared with -0.49; $P = 0.031$). The time of follow-up ($P = 0.282$), quality of study ($P = 0.372$), or intervention diet ($P = 0.480$) did not modified effects on waist circumference (Table 2).

DISCUSSION

To our knowledge, the current study is the first meta-analysis to summarized the evidence to date regarding effects of nut-enriched diets compared with various control diets on changes of body weight, BMI, or waist circumference. Overall, the

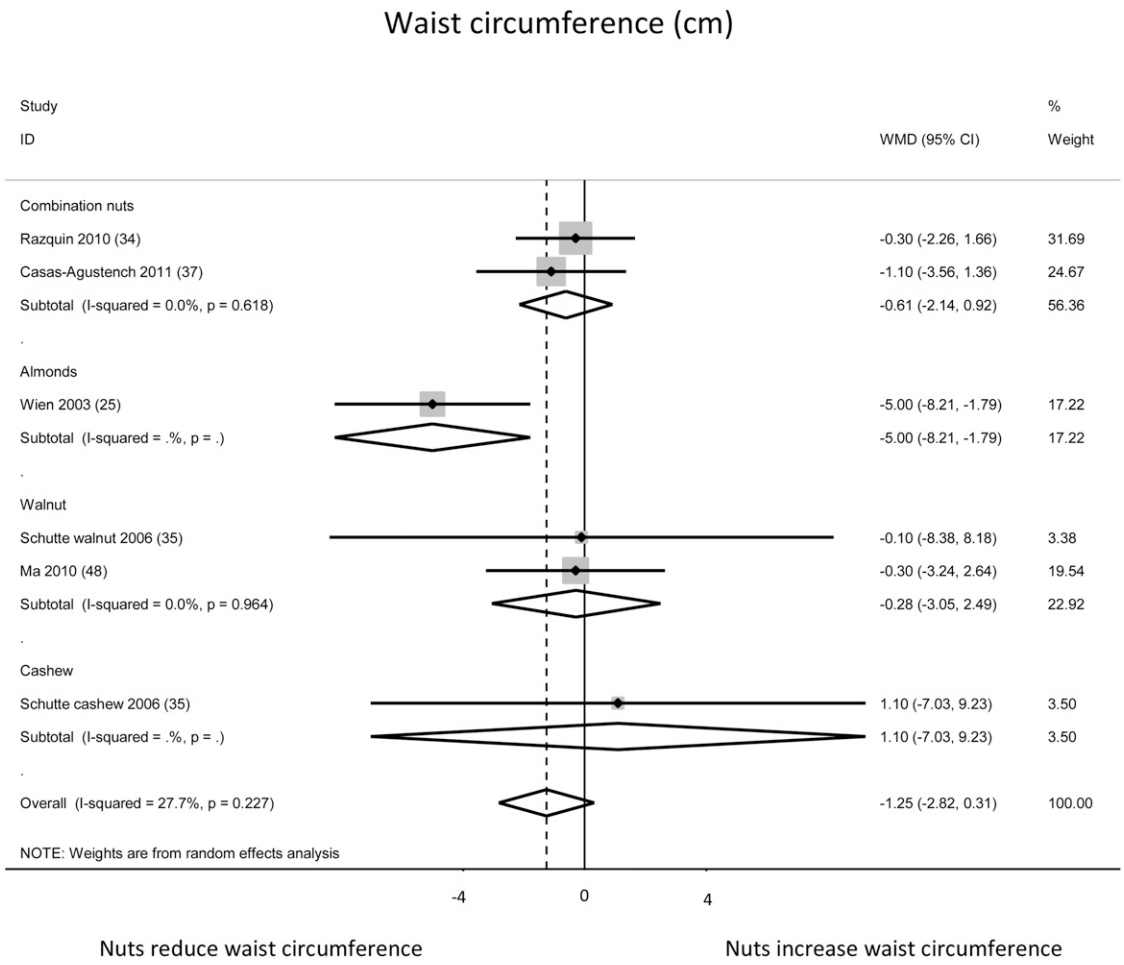

FIGURE 4. Meta-analysis of the net change (cm) in waist circumference associated with nut-enriched diets expressed as the change during the intervention with nut products minus the change during the control diet. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from inverse-variance–weighted random-effects models. ID, identification; WMD, weighted mean difference.

summarized WMD for all of studies suggested that nut-enriched diets do not increase adiposity measures.

A significant heterogeneity in studies existed, and subgroup analyses and the metaregression identified the study focus (energy restriction compared with weight-loss maintenance) as a potential source of heterogeneity. As expected with this type of intervention, for energy-restriction studies, the weight loss was more pronounced than for non–energy-restriction studies.

Comparison of current results with those of epidemiologic studies

Our findings confirmed the results of epidemiologic studies that suggested an inverse association between the frequency of nut consumption and BMI and risk of obesity. Cross-sectional studies showed either that nut consumption was associated with lower BMI (16), or there was no relation between the frequency of nut consumption and BMI (55). Two large, prospective cohort studies (the Adventist Health Study and Nurse's Health Study II) showed significant inverse associations between the frequency of nut consumption and BMI (56, 57), whereas no relation was reported in the Physicians' Health Study (58). Frequent nut consumption was also associated with reduced risk of weight gain in the Seguimiento University of Navarra cohort of young university graduates (15).

Biological plausibility

Several biological mechanisms may explain the results of the current meta-analysis regarding the effect of nut consumption on adiposity. Nuts are very rich in unsaturated fatty acids, and evidence has suggested that MUFAs and PUFAs are more readily oxidized (59) and have a greater thermogenic effect (60) than do saturated fatty acids, which can lead to less fat accumulation. Because of their energy density and abundance of unsaturated fatty acids, fiber, and protein, nuts are a highly satiating food, and thus, after the consumption of nuts, hunger is suppressed and subsequent food intake is curtailed (61). The physical structure of nuts may also contribute to their satiety effect because they must be mechanically reduced to particles small enough for swallowing. Mastication activates mechanical, nutrient, and sensory signaling systems that may modify appetitive sensations (62). Furthermore, a small degree of fat malabsorption occurs after nut intake because fat is contained within walled cellular structures that are incompletely digested in the gut (63), which is an effect that can be compounded by incomplete mastication (64). It has been shown recently that Atwater factors,

when applied to almonds (65) or pistachios (66), resulted in an overestimation of their measured energy contents.

Strengths and limitations

We aimed to avoid heterogeneity by including only randomized clinical trials with control diets. However, heterogeneity was present for all outcomes, which was only partly explained in subgroup analyses. Publication bias is another concern in meta-analyses that only include studies that are actually published. With tests and visual inspections, such as Egger's methods used in this review, we were able to exclude publication bias with some confidence. Finally, we did not observe any change in waist circumference in the 681 participants for whom such data were available. Weight changes observed in this type of analyses were probably too small to identify any such changes. Thus, it is necessary to design high-quality clinical trials aimed to detect the effect of nut-enriched diets on waist circumference.

One advantage of pooling data from clinical trials to investigate this important clinical issue was better generalizability, because this analysis combined data from heterogeneous populations. Another advantage was the high quality of studies included in the analysis. The lengthy follow-up and comprehensive surveillance in many of the clinical trials, as well as the large number of participants, also provided sufficient power to detect the chosen effect. Also, to our knowledge, no previous meta-analysis of clinical trials has summarized the effects of nut consumption on body weight, BMI, or waist circumference.

Clinical implications

Our meta-analysis of clinical trials showed that nut consumption was associated with a nonsignificant decrease in body weight of 0.47 kg, BMI of 0.40, and waist circumference of 1.25 cm. Although the magnitude of these effects was modest, the results allay the fear that nut consumption may promote obesity. This message should not be lost to dietitians, caregivers in general, and subjects at risk of cardiovascular disease who can then freely consume nuts as cardioprotective foods.

In conclusion, this meta-analysis of clinical trials shows that nut-rich diets compared with different control diets do not increase body weight, BMI, or waist circumference. Our findings support the inclusion of nuts in healthy diets for cardiovascular prevention.

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The authors' responsibilities were as follows—GF-M and DR-R: conceived the study, carried out the literature search, and assessed the quality of included studies; and all authors: contributed to the study conception and design, analysis and interpretation of data, writing of the manuscript, critical revision of manuscript drafts for important intellectual content, and approval of the final version of the manuscript submitted for publication. JS is a nonpaid member of the Scientific Advisory Committee of the International Nut and Dried Fruit Foundation, and ER is a nonpaid member of the Scientific Advisory Committee of the California Walnut Commission. None of the other authors had a conflict of interest.

REFERENCES

1. Ros E, Mataix J. Fatty acid composition of nuts–implications for cardiovascular health. Br J Nutr 2006;96(suppl 2):S29–35.
2. Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. Br J Nutr 2006;96(suppl 2):S46–51.
3. Ros E, Tapsell LC, Sabaté J. Nuts and berries for heart health. Curr Atheroscler Rep 2010;12:397–406.
4. Sabaté J, Ang Y. Nuts and health outcomes: new epidemiologic evidence. Am J Clin Nutr 2009;89:1643S–8S.
5. van den Brandt PA. The impact of a Mediterranean diet and healthy lifestyle on premature mortality in men and women. Am J Clin Nutr 2011;94:913–20.
6. Baer HJ, Glynn RJ, Hu FB, Hankinson SE, Willett WC, Colditz GA, Stampfer M, Rosner B. Risk factors for mortality in the nurses' health study: a competing risks analysis. Am J Epidemiol 2011;173:319–29.
7. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA 2002;288:2554–60.
8. Parker ED, Harnack LJ, Folsom AR. Nut consumption and risk of type 2 diabetes. JAMA 2003;290:38–9.
9. Djoussé L, Rudich T, Gaziano JM. Nut consumption and risk of hypertension in US male physicians. Clin Nutr 2009;28:10–4.
10. Sabaté J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. Arch Intern Med 2010;170:821–7.
11. López-Uriarte P, Bullo M, Casas-Agustench P, Babio N, Salas-Salvado J. Nuts and oxidation: a systematic review. Nutr Rev 2009;67:497–508.
12. Kendall CW, Josse AR, Esfahani A, Jenkins DJ. Nuts, metabolic syndrome and diabetes. Br J Nutr 2010;104:465–73.
13. Jenkins DJ, Kendall CW, Banach MS, Srichaikul K, Vidgen E, Mitchell S, Parker T, Nishi S, Bashyam B, de Souza R, et al. Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes Care 2011;34:1706–11.
14. Bes-Rastrollo M, Sabaté J, Gomez-Gracia E, Alonso A, Martinez JA, Martinez-Gonzalez MA. Nut consumption and weight gain in a Mediterranean cohort: The SUN study. Obesity (Silver Spring) 2007;15:107–16.
15. Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change, and obesity risk in women. Am J Clin Nutr 2009;89:1913–9.
16. Casas-Agustench P, Bullo M, Ros E, Basora J, Salas-Salvado J. Cross-sectional association of nut intake with adiposity in a Mediterranean population. Nutr Metab Cardiovasc Dis 2011;21:518–25.
17. García-Lorda P, Megias Rangil I, Salas-Salvadó J. Nut consumption, body weight and insulin resistance. Eur J Clin Nutr 2003;57(suppl 1):S8–11.
18. Higgins J, Green S (eds). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www/cochrane-handbook.org/2011.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
20. Jenkins DJ, Kendall CW, Popovich DG, Vidgen E, Mehling CC, Vuksan V, Ransom TP, Rao AV, Rosenberg-Zand R, Tariq N, et al. Effect of a diet high in vegetables, fruit, and nuts on serum lipids. Metabolism 1997;46:530–7.
21. O'Byrne DJ, Knauft DA, Shireman RB. Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein profiles. Lipids 1997;32:687–95.
22. Zambón D, Sabaté J, Muñoz S, Campero B, Casals E, Merlos M, Laguna JC, Ros E. Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. A randomized crossover trial. Ann Intern Med 2000;132:538–46.
23. Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, Haight JS, Faulkner D, Vidgen E, Lapsley KG, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. Circulation 2002;106:1327–32.
24. Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, et al. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. Metabolism 2003;52:1478–83.
25. Wien MA, Sabaté JM, Ikle DN, Cole SE, Kandeel FR. Almonds vs complex carbohydrates in a weight reduction program. Int J Obes Relat Metab Disord 2003;27:1365–72.
26. Ros E, Núñez I, Pérez-Heras A, Serra M, Gilabert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in

hypercholesterolemic subjects: a randomized crossover trial. Circulation 2004;109:1609–14.
27. Tapsell LC, Gillen LJ, Patch CS, Batterham M, Owen A, Baré M, Kennedy M. Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. Diabetes Care 2004;27:2777–83.
28. Hollis J, Mattes R. Effect of chronic consumption of almonds on body weight in healthy humans. Br J Nutr 2007;98:651–6.
29. Sheridan MJ, Cooper JN, Erario M, Cheifetz CE. Pistachio nut consumption and serum lipid levels. J Am Coll Nutr 2007;26:141–8.
30. Mukuddem-Petersen J, Stonehouse OW, Jerling JC, Hanekom SM, White Z. Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: a controlled feeding trial. Br J Nutr 2007;97:1144–53.
31. Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blazquez-Garcia S, Perez-Sacristan B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. J Am Coll Nutr 2008;27:342–8.
32. Gebauer SK, West SG, Kay CD, Alaupovic P, Bagshaw D, Kris-Etherton PM. Effects of pistachios on cardiovascular disease risk factors and potential mechanisms of action: a dose-response study. Am J Clin Nutr 2008;88:651–9.
33. Tapsell L, Batterham M, Tan SY, Warensjo E. The effect of a calorie controlled diet containing walnuts on substrate oxidation during 8-hours in a room calorimeter. J Am Coll Nutr 2009;28:611–7.
34. Razquin C, Martinez JA, Martinez-Gonzalez MA, Fernández-Crehuet J, Santos JM, Marti A. A Mediterranean diet rich in virgin olive oil may reverse the effects of the -174G/C IL6 gene variant on 3-year body weight change. Mol Nutr Food Res 2010;54(suppl 1):S75–82.
35. Schutte AE, Van Rooyen JM, Huisman HW, Mukuddem-Petersen J, Oosthuizen W, Hanekom SM, Jerling JC. Modulation of baroreflex sensitivity by walnuts versus cashew nuts in subjects with metabolic syndrome. Am J Hypertens 2006;19:629–36.
36. Canales A, Benedi J, Nus M, Librelotto J, Sanchez-Montero JM, Sanchez-Muniz FJ. Effect of walnut-enriched restructured meat in the antioxidant status of overweight/obese senior subjects with at least one extra CHD-risk factor. J Am Coll Nutr 2007;26:225–32.
37. Casas-Agustench P, López-Uriarte P, Bullo M, Ros E, Cabre-Vila JJ, Salas-Salvado J. Effects of one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. Nutr Metab Cardiovasc Dis 2011;21:126–35.
38. Sabaté J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. Am J Clin Nutr 2003;77:1379–84.
39. Spiller GA, Jenkins DA, Bosello O, Gates JE, Cragen LN, Bruce B. Nuts and plasma lipids: an almond-based diet lowers LDL-C while preserving HDL-C. J Am Coll Nutr 1998;17:285–90.
40. Morgan WA, Clayshulte BJ. Pecans lower low-density lipoprotein cholesterol in people with normal lipid levels. J Am Diet Assoc 2000;100:312–8.
41. Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. Am J Clin Nutr 2001;74:72–9.
42. Alper CM, Mattes RD. Effects of chronic peanut consumption on energy balance and hedonics. Int J Obes Relat Metab Disord 2002;26:1129–37.
43. Lamarche B, Desroches S, Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, et al. Combined effects of a dietary portfolio of plant sterols, vegetable protein, viscous fibre and almonds on LDL particle size. Br J Nutr 2004;92:657–63.
44. Sabaté J, Cordero-MacIntyre Z, Siapco G, Torabian S, Haddad E. Does regular walnut consumption lead to weight gain? Br J Nutr 2005;94:859–64.
45. Mercanligil SM, Arslan P, Alasalvar C, Okut E, Akgül E, Pinar A, Geyik PO, Tokgözoğlu L, Shahidi F. Effects of hazelnut-enriched diet on plasma cholesterol and lipoprotein profiles in hypercholesterolemic adult men. Eur J Clin Nutr 2007;61:212–20.
46. Spaccarotella KJ, Kris-Etherton PM, Stone WL, Bagshaw DM, Fishell VK, West SG, Lawrence FR, Hartman TJ. The effect of walnut intake on factors related to prostate and vascular health in older men. Nutr J 2008;7:13.
47. Wien M, Bleich D, Raghuwanshi M, Gould-Forgerite S, Gomes J, Monahan-Couch L, Oda K. Almond consumption and cardiovascular risk factors in adults with prediabetes. J Am Coll Nutr 2010;29:189–97.
48. Ma Y, Njike VY, Millet J, Dutta S, Doughty K, Treu JA, Katz DL. Effects of walnut consumption on endothelial function in type 2 diabetic subjects: a randomized controlled crossover trial. Diabetes Care 2010;33:227–32.
49. Li Z, Song R, Nguyen C, Zerlin A, Karp H, Naowamondhol K, Thames G, Gao K, Li L, Tseng CH, et al. Pistachio nuts reduce triglycerides and body weight by comparison to refined carbohydrate snack in obese subjects on a 12-week weight loss program. J Am Coll Nutr 2010;29:198–203.
50. Foster GD, Shantz KL, Vander Veur SS, Oliver TL, Lent MR, Virus A, Szapary PO, Rader DJ, Zemel BS, Gilden-Tsai A. A randomized trial of the effects of an almond-enriched, hypocaloric diet in the treatment of obesity. Am J Clin Nutr 2012;96:249–54.
51. Chisholm A, Mc AK, Mann J, Williams S, Skeaff M. Cholesterol lowering effects of nuts compared with a Canola oil enriched cereal of similar fat composition. Nutr Metab Cardiovasc Dis 2005;15:284–92.
52. Kocyigit A, Koylu AA, Keles H. Effects of pistachio nuts consumption on plasma lipid profile and oxidative status in healthy volunteers. Nutr Metab Cardiovasc Dis 2006;16:202–9.
53. Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, Niaz MA. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. BMJ 1992;304:1015–9.
54. Li SC, Liu YH, Liu JF, Chang WH, Chen CM, Chen CY. Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. Metabolism 2011;60:474–9.
55. Soriguer FJ, González-Romero S, Esteva I, García-Arnés JA, Tinahones F, Ruiz de Adana MS, Olveira G, Mancha I, Vazques F. Does the intake of nuts and seeds alter the appearance of menarche? Acta Obstet Gynecol Scand 1995;74:455–61.
56. Fraser GE, Sabaté J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. Arch Intern Med 1992;152:1416–24.
57. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, Speizer FE, Hennekens CH, Willett WC. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ 1998;317:1341–5.
58. Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. Arch Intern Med 2002;162:1382–7.
59. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. The influence of the type of dietary fat on postprandial fat oxidation rates: monounsaturated (olive oil) vs saturated fat (cream). Int J Obes Relat Metab Disord 2002;26:814–21.
60. Casas-Agustench P, López-Uriarte P, Bullo M, Ros E, Gomez-Flores A, Salas-Salvado J. Acute effects of three high-fat meals with different fat saturations on energy expenditure, substrate oxidation and satiety. Clin Nutr 2009;28:39–45.
61. Jaceldo-Siegl K, Sabaté J, Rajaram S, Fraser GE. Long-term almond supplementation without advice on food replacement induces favourable nutrient modifications to the habitual diets of free-living individuals. Br J Nutr 2004;92:533–40.
62. Mattes RD, Dreher ML. Nuts and healthy body weight maintenance mechanisms. Asia Pac J Clin Nutr 2010;19:137–41.
63. Ellis PR, Kendall CW, Ren Y, Parker C, Pacy JF, Waldron KW, Jenkins DJ. Role of cell walls in the bioaccessibility of lipids in almond seeds. Am J Clin Nutr 2004;80:604–13.
64. Cassady BA, Hollis JH, Fulford AD, Considine RV, Mattes RD. Mastication of almonds: effects of lipid bioaccessibility, appetite, and hormone response. Am J Clin Nutr 2009;89:794–800.
65. Novotny JA, Gebauer SK, Baer DJ. Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. Am J Clin Nutr 2012;96:296–301.
66. Baer DJ, Gebauer SK, Novotny JA. Measured energy value of pistachios in the human diet. Br J Nutr 2012;107:120–5.