Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP)

A systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background: The effects of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP) are not well established. We aimed to undertake a systematic review and meta-analysis of prospective studies to determine the effect of nut consumption (tree nuts, peanuts, and soy nuts) on serum CRP.

Method: PubMed-Medline, Web of Science, Cochrane Database, and Google Scholar databases were searched (up until April 2016) to identify prospective studies evaluating the impact of tree nut, peanut, and soy nut consumption on serum CRP. Random effects models meta-analysis was used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Heterogeneity was quantitatively assessed using the I² index. Systematic review registration: CRD42016038044.

Results: From a total of 844 entries identified via searches, 20 studies were included in the final selection. The meta-analysis indicated a nonsignificant increase in serum CRP concentrations following nut consumption (weighted mean difference [WMD] 0.17 mg/L, 95% CI: 0.67 to 0.33, I² 52.1%). The WMDs for IL6 was -0.06 (mg/dL), (95% CI: -0.69 to 0.56, I² 9.6%), -0.71 (mg/dL), (95% CI: -1.11 to -0.30, I² 6.3%) for leptin, and -0.60 (mg/dL), (95% CI: -1.88 to 0.68, I² 5.6%) for adiponectin, and -0.18 (mg/dL), (95% CI: -1.24 to 0.88, I² 9.3%) for IL10 and -0.37 (pg/mL), (95% CI: -0.90 to 0.16, I² 7.9%) for TNF-α. These findings were robust in sensitivity analyses.

Conclusions: This meta-analysis suggests that nut consumption significantly decreases leptin while having no significant effect on CRP, IL6, adiponectin, IL10, and TNF-α.

Abbreviations: CCTR = Cochrane Central Register of Controlled Trials, CDSR = Cochrane Database of Systematic Reviews, CI = confidence interval, CMA = comprehensive meta-analysis, CRP = C-reactive protein, CVD = cardiovascular disease, ICAM-1 = intracellular adhesion molecule-1, IL-6 = interleukin-6, PRISMA = systematic reviews and meta-analyses, RCT = randomized control trials, SD = standard deviation, SEM = standard error of the mean, VCAM-1 = vascular cell adhesion molecule-1, [WMD] = weighted mean difference.

Keywords: C-reactive protein, meta-analysis, peanut, tree nut
1. Introduction

Inflammation play a crucial role in the progress of cardiovascular disease (CVD) and type 2 diabetes (T2D). Inflammatory and endothelial markers such as serum C-reactive protein (CRP), Interleukin-6 (IL-6), fibrinogen, vascular cell adhesion molecule-1 (VCAM-1) and Intracellular adhesion molecule-1 (ICAM-1) have been recognized as independent predictors of CVD or (T2D). Serum CRP is a indicator of general inflammation and is raised in the existence of chronic situation such as CVD, obesity, (T2D), and components of metabolic syndrome; hypertension, increased waist circumference, fasting hyperglycemia, low serum high-density lipoprotein cholesterol, and hypertriglyceridemia. Recently, mostly the focuses of dietary components were on interaction between diet and inflammation. Clinical and epidemiologic surveys proposed that dietary factors including-3 polyunsaturated fatty acids (PUFA), antioxidant vitamins, dietary fiber, and L-arginine might play an curial role in regulating inflammation. Nuts are full of unsaturated fatty acids and have non lipid components including antioxidant vitamins (especially vitamin E), dietary fiber, magnesium, plant protein have a lot of arginine and numerous phytochemicals.

Earlier experiments reported that the cardio protective properties of nuts consumption might be credited to the amended insulin sensitivity, endothelial function, or anti-inflammatory role of nuts. Studies suggested that common nuts consumption is related with improvements stages of inflammatory factors including CRP, IL-6, and fibrinogen, even after adjustment for covariates. Though the action of nuts which are high in monounsaturated fat, including almonds, has not been formally explained in association with inflammation, some of the constituents of nuts including arginine, magnesium, fiber, and vitamin E have confirmed an anti-inflammatory effect. A randomized clinical trial verified that a filtered palmitoleic acid (16:1; omega-7) can make a weighty decreases in serum CRP following administration for a month. In this regard, Jiang et al. reported the reverse association between nut consumption and the inflammatory factors such as CRP, fibrinogen, and IL-6. In same line, it has been reported that the administration of almonds made a substantial decrease in serum CRP.

As of yet, no systematic review and meta-analysis is available on the impact of different types of tree nut, peanut, and soy nut consumption serum CRP. Consequently, in this survey, we aimed to perform a systematic review and meta-analysis of published randomized control trials (RCTs) to review the data on impacts of nuts (pistachios, cashews, hazelnuts, almonds, pecans, macadamia nuts, peanuts, and soy nuts) on serum CRP. Via meta-analysis we computed the impact of before selected articles being regained (a flowchart is available in Fig. 1).

2. Materials and methods

2.1. Literature search strategy

The current study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. Furthermore, this systematic reviewed meta-analysis protocol is registered in the International Prospective Register of Systematic Reviews (registration no: CRD42016038044). The primary exposure of interest was to evaluate the effect of tree nut, peanut, and soy nut consumption on serum CRP. We searched multiple databases including PUBMED/ Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Google scholar, and Web of Science; until April 2016 using a combination of search term shown in the supplementary Table 1, http://links.lww.com/MD/B367. The wild-card term “*” was used to surge the sensitivity of the search strategy .No language restriction was applied. This was completed by hand search of the reference list of eligible articles, and email correspondences to authors for additional data where relevant.

2.2. Selection criteria

We included all prospective studies which assessed the effect of nut consumption on our outcomes of interested. Eligible studies had to meet the following criteria: (1) being a controlled trial with either parallel or crossover design, (2) prospective studies of patients treated with nut consumption compared to control group (either no nut or placebo), (3) presentation of sufficient information on primary outcome at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were: (i) nonclinical studies; (ii) observational studies with case–control, cross-sectional or cohort design; and (iii) studies that did not provide mean (or median) serum or plasma concentrations of our interested outcomes at baseline and/or at the end of trial. Abstracts, narrative reviews, comments, opinion pieces, methodological, editorials, letters, or any other publications lacking primary data and/or explicit method explanations, were excluded. Study selection began with the removal of duplicates; next, 2 reviewers (MM and EK) excluded some papers based on titles and abstracts only. To avoid bias, they were blinded to the names, qualifications, or the institutional affiliations of the study authors. The agreement between the reviewers was excellent (Kappa index: 0.88; P < 0.001). Disagreements were fixed at a meeting between reviewers prior to selected articles being regained (a flowchart is available in Fig. 1).

2.3. Data extraction and management

The full text of studies meeting inclusion criteria was recovered and screened to determine eligibility by 2 reviewers (MM, EK). Following assessment of methodological quality, the 2 reviewers extracted data onto a purpose-designed data extraction form and independently summaries what they consider to be the most important results from each study. Descriptive data extracted included the First author, year of publication, country, total sample size, study design; age range, male (%), follow-up duration (week), nut dose, and type of nut were summarized in Table 1. An independent reviewer confirmed all data entries.

2.4. Quality assessment

An assessment of bias in the included manuscript was performed by the Cochrane criteria. The objects used for the assessment of manuscripts were including: acceptability of random sequence generation, distribution concealment, blinding of subjects, employees and consequence assessment, talking of drop-outs, selective outcome reporting, and additional possible causes of bias.

2.5. Quantitative data synthesis

Based on recommendation of Cochrane Handbook the mean change from baseline in the concentrations and SD of the variables of interest for both intervention and control groups were used to calculate the effect size. In brief, net changes in
measurements (change scores) were calculated as follows: measure at end of follow-up − measure at baseline. Hozo et al.[27] method was used in the case of the median and range (or 95% confidence interval [CL]). Moreover, standard deviation = standard error of the mean × square root (n), where n is the sample size.[25] Blood lipid and glucose levels were collated in mmol/L. A multiplication factor of 0.0259, 0.0113, or 0.0555 was used to convert cholesterol (total cholesterol, high-density
lipoprotein (HDL-C) or low-density lipoprotein (LDL-C), triglycerides and glucose levels respectively from mg/dL to mmol/L as appropriate.\(^{[25]}\)

A random effects model (using the DerSimonian–Laird method) and the generic inverse variance method were used.\(^{[28]}\) Heterogeneity was quantitatively assessed using the \(I^2\) index.\(^{[25]}\) Effect sizes were stated as weighed mean difference (WMD) and 95% CL. Sensitivity analysis was performed using the leave-one-out method, that is, removing 1 study each time and repeating the analysis.\(^{[29,30]}\)

### 2.6. Publication bias

Publication bias was discovered using visual inspection of Begg’s funnel plot asymmetry, Begg’s rank correlation, and Egger’s weighted regression tests. Duval & Tweedie “trim and fill” and “fail-safe N” methods were used to adjust the analysis for the effects of publication bias.\(^{[13]}\) Meta-analysis was performed using the comprehensive meta-analysis (CMA) V3 software (Biostat, NJ).\(^{[32]}\)

### 3. Results

#### 3.1. Flow of studies

Briefly, after multiple database searches, 844 published studies were identified and the abstracts reviewed. In total, 695 records remained after removing duplicates. However, 643 did not meet the inclusion criteria and were excluded. Also, 52 articles remained for further evaluation, of which, 32 were excluded for the inclusion criteria and were excluded. Also, 52 articles remained after removing duplicates. However, 643 did not meet the inclusion criteria and were excluded. The study selection process is shown in Figure 1.

#### 3.2. Risk of bias assessment

There is unclear risk of bias in some of items including allocation concealment, blinding of participants and personnel, incomplete outcome data, and other biases. Four studies have moderate risk of bias.\(^{[33–36]}\) The other studies that were included had a low risk of bias according to selective outcome reporting. Details of the quality of bias assessment are shown in supplementary Table 2, [http://links.lww.com/MD/B367].

#### 3.3. Characteristics of included studies

The 22 trials were all published between 2002 and 2015 (most of the studies were published in 2014) (Table 1). The clinical trials used different types and doses of nuts. Four studies investigated soy at an intake of 35,\(^{[37]}\) 70,\(^{[38]}\) or 30 g/day,\(^{[39,40]}\) 6 studies investigated walnuts at an intake of 48,\(^{[41,42]}\) 40 to 65,\(^{[43]}\) 30,\(^{[36]}\) 43,\(^{[44]}\) 42.5 g/day,\(^{[45]}\) 2 studies investigated almonds at an intake of 73 ± 3,\(^{[46]}\) 34 and 68 g/day,\(^{[47]}\) 5 studies investigated pistachio at an intake of 59–128,\(^{[47]}\) 50,\(^{[48]}\) 75,\(^{[49]}\) 80,\(^{[49]}\) 49 g/day,\(^{[50]}\) 2 studies investigated mixed nuts; walnut (15 g/day), almond (7.5 g/day), hazelnut (7.5 g/day), and another walnut (15 g/day), peanut (7.5 g/day), pine (7.5 g/day)\(^{[51]}\) 1 study investigated Brazilian nut 0.5, 20 and 50,\(^{[52]}\) Peanut 56,\(^{[52]}\) hazelnut 30 and 60 g/day,\(^{[53]}\) respectively. The range of intervention periods was from 4 day\(^{[41]}\) up to 1 year.\(^{[36]}\) The study designs of included studies were cross-over, open label, parallel-group \(^{[33,36,37,49–53]}\) and double-blinded.\(^{[42]}\) Selected trials enrolled subjects with metabolic syndrome,\(^{[33,37,41,42,50,51]}\) postmenopausal and metabolic Syndrome,\(^{[38,39]}\) type 2 diabetestes,\(^{[35,36,47]}\) overweight/obese,\(^{[52,53]}\) healthy subjects,\(^{[21,34,48]}\) healthy hyperlipidemic men and postmenopausal women,\(^{[46]}\) hypercholesterolemic,\(^{[43]}\) healthy men and postmenopausal women,\(^{[44]}\) mild dyslipidemia\(^{[45]}\) and mild hyperlipidemic.\(^{[45]}\)

The number of participants included in studies ranged from 10\(^{[34]}\) to 107,\(^{[53]}\) The range of ages of the participants was from 18\(^{[52,53]}\) to 86.\(^{[46]}\) Three of these studies were carried out on female subjects only.\(^{[37,39,51]}\) Moreover, details each of these studies are listed in Table 1.

#### 3.4. Pooled estimate of the effect of nuts consumption

Pooled estimate of the effect of nuts consumption on inflammatory and anti-inflammatory factors are shown in Fig. 2. Our results showed that nut consumption have no significant effect on serum CRP level 0.17(mg/L) (95% CI –0.67 to 0.33); subgroup analysis is also shown in Fig. 2. We also found no significant effects of nut consumption on other inflammatory and anti-inflammatory factors apart from leptin 0.71 pg/mL (95% CI –1.11 to –0.30). We have failed to find a significant effect on
serum markers of endothelial function (shown in Fig. 3). Our analysis showed that nut consumption improved HDL-c, LDL-c, total cholesterol, ApoAl, and fasting blood glucose significantly (Fig. 4).

3.5. Sensitivity analysis

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar across all studies and within subgroups (Table 2).

3.6. Publication bias

Visual inspection of funnel plot symmetry suggested no potential publication bias for the comparison of CRP levels between nuts consumed group and placebo (Fig. 5). That is in line with Begg’s rank correlation test (tau with continuity correction = −0.03, z-value = 0.24, P-value = 0.809) and Egger’s linear regression (intercept = −1.25, standard error = 2.96, 95% CI = −7.45 to 4.94, t-value = 0.423, df = 9, 2-tailed P = 0.676). After adjustment of effect size for potential publication bias using the Duval and Tweedie “trim and fill” correction, no potentially missing studies were imputed in the funnel plot (WMD 0.17 (mg/L), 95% CI = −0.67, 0.33) (Fig. 6).

4. Discussion

As far we are aware, this is the first meta-analysis of randomized controlled trials specifically considered to evaluate the effects of nuts consumption on inflammatory markers and endothelial function parameters. Meta-analysis presented consuming variable doses of nuts significantly improved inflammatory and anti-inflammatory indexes compared with baseline. However, we found that nut consumption did not have a significant effect on serum CRP levels, though it was associated with a small nonsignificant increase. Other serum markers of inflammation and anti-inflammatory that we reviewed were not influenced by the nut consumption, except leptin which was associated with a significant increase with nut consumption. We surveyed several endothelial markers too in this study such as plasma fibrinogen, and E-selectin, ICAM and VCAM; our analysis did not reveal any significant changes in their serum concentration after nut consumption. Although we did not find a significant association between nut and seed consumption with most inflammatory indexes independently previously, various components of nuts and seeds it possible have anti-inflammatory properties. Numerous cross-sectional studies revealed lower concentrations of circulating levels of pro-inflammatory cytokines or endothelial cell adhesion molecules in subjects consuming nuts, for example, it has been described that α-linolenic acid (18:3(n-3)), resulting from nuts was inversely related with levels of CRP, IL-6, soluble tumor necrosis factor receptors 1 and 2, and fibrinogen in healthy individuals and/or patients with stable coronary artery disease. Moreover, it has been reported individuals with healthy individuals and/or patients with stable coronary artery disease.

### Table 2

| Variables | Result of the leave-one-out sensitivity analyses |
|-----------|-----------------------------------------------|
| CRP       | 0.17 mg/L (95% CI = −0.67 to 0.33)            |
| Pistachios| −0.96 mg/L (95% CI = −2.14 to 0.22)           |
| Almond    | 1.29 mg/L (95% CI = 0.12–2.46)                |
| IL6       | −0.06 pg/mL (95% CI = −0.69 to 0.56)          |
| Leptin    | −0.71 pg/mL (95% CI = −1.11 to −0.30)         |
| Adiponectin| −0.60 pg/mL (95% CI = −1.88 to 0.68)         |
| IL10      | −0.18 pg/mL (95% CI = −1.24 to 0.88)         |
| TNF-α     | −0.37 pg/mL (95% CI = −0.90 to 0.16)         |
| Fibrinogen| −0.13 pg/mL (95% CI = −1.43 to 1.70)         |
| HDL-c     | 0.54 (mg/dL) (95% CI = 0.17–0.90)             |
| LDL-c     | −0.69 (mg/dL) (95% CI = −1.32 to −0.07)       |
| TC        | −0.82 (mg/dL) (95% CI = −1.53 to −0.11)       |
| TG        | −0.66 (mg/dL) (95% CI = −1.34 to 0.01)        |
| ApoAl     | 1.38 (g/L) (95% CI = 0.15–2.61)               |
| ApoB100   | −1.50 (g/L) (95% CI = −2.43 to 0.57)          |
| FBG       | −1.45 (mg/dL) (95% CI = −2.20 to −0.70)       |
| CRP       | −0.69 mm Hg (95% CI = −1.34 to −0.03)         |
| DBP       | −0.14 mm Hg (95% CI = −0.54 to −0.25)         |

Q = confidence interval, CRP = C-reactive protein, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL = high-density lipoprotein, ICAM = Intracellular Adhesion Molecule-1, IL-6 = Interleukin-6, LDL = low-density lipoprotein, PRISMA = Systematic Reviews and Meta-Analyses, RCT = Randomized control trials, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, VCAM-1 = Vascular Cell Adhesion Molecule-1.
to the configuration of nuts, which is recognized by a greater level of MUFAs, lesser saturated fatty acids, no cholesterol, and a suitable amount of proteins, fiber, phytosterols, antioxidants, and numerous minerals and vitamins.\[^{[59,60]}\] Soy also have a fiber, PUFA, and phytoestrogens, which are separately related with lesser concentration of inflammatory parameters and improved endothelial function factors.\[^{[61]}\] In this meta-analysis, we focused on these types of nuts. In contrast with our findings, some other individual studies showed different effects of nuts on inflammatory and endothelial markers. One study reported that a high Isoflavone soy diet augmented IL-6 in women.\[^{[62]}\] Also, a long-term observational study stated that nuts consumption is related with greater adiponectin level.\[^{[63]}\] It might be supposed that a mechanism relating between different effect of nuts and seed intake on elements involved in the procedure of inflammation and endothelial function is certain diseases at the baseline, various ethnicity, and various doses of nuts.

Interestingly, some studies examined how quickly after beginning of walnut consumption promising effects on factors of inflammation can be seen.\[^{[41,42]}\] In this regard, it has been stated that intake of walnuts (48g per day for 4 days) was associated with a substantial enhance in the apolipoprotein level, nevertheless did not alter the concentration of CRP, IL-6, IL-8, and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)).\[^{[42]}\] It might be concluded that >4 days are essential for detecting the beneficial effects of the walnut consumption on inflammatory factors and different results between investigations of short- and long-term walnut consumption are perhaps attributing to the length of the intervention (\(\leq 4\) days vs to \(\geq 4\) weeks).

Additionally, though it has been stated that there was no significant alterations in LDL, HDL, total cholesterol, or triglyceride levels on walnut consumption in 4 days period,\[^{[41]}\] but it has been reported that that short-term intake of walnuts have beneficial effects on lipid profile and lipid metabolism even within 4 days of intake.

Some limitations of this meta-analysis should be noted. First, most of the included studies had a moderately small sample size, theoretically causing unstable estimates of treatment effects.\[^{[64,65]}\] Another point would that we have used some studies which they did not count the leptin level as an end point which may be affect
our results. Potential explanations for the heterogeneity in the results, might be because each study had its own follow-up periods, inclusion criteria, basic health condition, gender, varied periods of life, drug usage, amount of the nut. Accordingly, because of the heterogeneity, we have performed our analysis by using the random-effects model. Moreover because the original studies we have used were lack of the real composition of the nuts and hence may be our finding is somehow biased. As we all know that even there are differences in composition of same nuts in different part of the world and even different part of the same country.

5. Conclusion
This meta-analysis suggests that while nut consumption appears to be associated with a reduction in serum leptin in our selected publications, it had no significant effect on serum CRP, IL6, adiponectin, IL10, and TNF-α.

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