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Effects of nut consumption on selected inflammatory markers: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Several randomized controlled trials (RCTs) have assessed the effects of nut consumption on inflammatory markers. However, the results have been inconsistent. The aim of this meta-analysis of RCTs was to quantitatively evaluate the effects of nut consumption on selected inflammatory markers.
Methods: PubMed, Embase, Cochrane Library database, and Google Scholar were searched for published RCTs that reported the effects of nuts on inflammatory markers as primary or secondary outcomes in an adult population (aged ≥18 y). Summary estimates of weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated using random-effects meta-analysis.
Results: Twenty-three RCTs met the inclusion criteria. Overall, nut consumption significantly reduced the levels of intercellular adhesion molecule (ICAM)-1 (WMD, –0.17; 95% CI, –0.32 to –0.03; $P = 0.01$), but had no significant effect on other inflammatory markers. In the subgroup analyses by nut types, mixed nuts had a significant effect on ICAM-1 reduction. The significant effect of nuts on ICAM-1 reduction was only observed in parallel, but not crossover RCTs. Additionally, nut consumption significantly reduced ICAM-1 and vascular cell adhesion molecule-1 levels in long-term (≥12 wk), but not short-term (<12 wk) RCTs. No significant heterogeneity or publication bias was observed in the studies included.
Conclusions: Nut consumption significantly reduced ICAM-1 levels, but had no effect on other inflammatory markers. More studies are needed to assess the effects of nuts on inflammation.

Introduction

Inflammation is a complex biological response of human body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, resulting in a disruption of tissue homeostasis [1]. Inflammation over a prolonged period that usually lasts weeks to months with the presence of lymphocytes and macrophages, vascular proliferation, fibrosis, and tissue destruction is called chronic inflammation. Inflammation plays an essential role in the development of many chronic and non-chronic diseases of major global disease burden, including atherosclerotic cardiovascular disease (CVD), cancer, diabetes, Alzheimer's disease, rheumatoid arthritis, asthma, and infectious diseases [2]. Vascular inflammation is activated by proinflammatory stimuli, such as saturated fat intake, hypercholesterolemia, hyperglycemia, obesity, and smoking, which induce the secretion of inflammatory cytokines. These cytokines in turn promote the generation of endothelial adhesion molecules and other chemoattractants [3]. It has been proposed that a prolonged overproduction of inflammatory cytokines without regulation might lead to several

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chronic diseases. It has been found that elevated levels of interleukin (IL)-6 and C-reactive protein (CRP) are associated with the development of atherosclerosis and type 2 diabetes [4]. Therefore, research on these cytokines as biomarkers in inflammation-related diseases is of great relevance for prevention of these diseases.

Since the first report of an association between nut consumption and lower risk for coronary heart disease in 1992 [5], extensive research has been conducted to investigate the effects of nuts on various health outcomes. Nuts are rich in unsaturated fatty acids and bioactive compounds, such as dietary fiber, vitamin E, and phytochemicals [6]. Epidemiologic studies have consistently observed that diets rich in a variety of nuts, such as the Mediterranean diet, are associated with a reduced all-cause mortality, incidence and mortality of CVD and cancer, and a reduced risk for type 2 diabetes [7–10]. Potential mechanisms of CVD risk reduction include antiinflammatory, antioxidant, and antiatherogenic properties of compounds such as tocopherols, folic acids, and phytochemicals rich in nuts. Nut consumption has been found to have beneficial effects on CVD and diabetes risk factors, such as reducing low-density lipoprotein cholesterol (LDL-C) [11–13], blood pressure [11,14], and visceral adiposity [15], and improving hyperglycemia and insulin resistance [16,17] in previous randomized controlled trials (RCTs). Furthermore, nuts may play important anticarcinogenic roles, for instance, regulation of cell differentiation and proliferation, reduction of tumor initiation or promotion, DNA protection, and regulation of immunologic and inflammatory response [18].

Clinical and epidemiologic evidence also indicate that nut consumption improves profiles of inflammatory markers, with a daily dose of 30 g being able to confer benefits [19]. Mediterranean diets, in which walnuts, mixed nuts, or pistachios replaced olive oil, demonstrated improvements in one or more of inflammatory markers in some studies [13,19,20]. However, other studies showed no benefits on inflammatory markers, likely due to the relatively small sample size, insufficient intake of nuts or duration of intervention, and different types of nuts or subject groups of these trials [21–23]. Therefore, results of RCTs have not been consistent in showing the antiinflammatory benefit, and the precise effect of nut consumption on inflammation has not been well established.

Because inflammation plays an important role in the development of many diseases and health conditions, the protective effect of nuts against these diseases may be at least partially attributed to their antiinflammatory effect. In the present study, a meta-analysis of RCTs was performed to comprehensively assess the evidence and quantitatively estimate the effect of nut consumption on selected inflammatory markers.

Methods

Data sources and search strategy

The current meta-analysis was performed following the PRISMA criteria guidelines [24]. The relevant articles were identified by searching the databases of PubMed, Embase, the Cochrane Library database, and Google Scholar through April 2017. No language or other restrictions were set in literature search. Three groups of medical subject headings (MeSH) and non-MeSH keywords were used to search the databases: keyword group 1: "nut," "almond," "pistachio," "cashew," "macadamia," "pecan," "hazelnut," "walnut," "peanut"; keyword group 2: "inflammation," "inflammatory," "CRP," "C-reactive protein"; "IL," "interleukin," "endothelial," "adhesion molecules," "TNF," "tumor necrosis factor," "selectin," or "cytokines"; and keyword group 3: "randomized," "intervention," "controlled trial," "random," and "placebo." We searched the relevant literature using keyword group 1 in combination with both keyword groups 2 and 3. Bibliographies of included studies and recent reviews were also screened to ensure a complete study list.

Study selection

The inclusion criteria were as follow:

(1) Studies were RCTs.
(2) The RCTs investigated the effect on inflammatory markers (CRP, vascular cell adhesion molecule [VCAM]-1, ICAM-1, tumor necrosis factor [TNF]-α, ILs, or E-selectin) as primary or secondary outcomes.
(3) The RCTs examined consumption of either a single or mixed type of nuts, including walnuts, almonds, pistachios, cashews, hazelnuts, macadamia nuts, pecans, and peanuts.
(4) The RCTs explicitly reported baseline and follow-up values of inflammatory markers, the mean changes from baseline to follow-up or the values of postintervention for each comparison group, or the mean differences between intervention and control groups.
(5) The RCTs were conducted in adult samples ≥18 y of age.
(6) The minimum intervention period of the RCTs was 4 wk.

The titles and abstracts were screened by two investigators (Y.X. and S.W.) to identify potentially relevant articles, and full texts of the articles that appeared to meet the inclusion criteria were then retrieved for further screening. The references of related articles were reviewed for any missing articles. In the case of multiple publications from the same trial, only the most recent or informative one was selected.

Studies were excluded, if they evaluated only postprandial and acute effects for <2 wk; they did not assess inflammatory markers as a primary or secondary outcome; or they reported redundant results of the same clinical trial.

Data collection and quality assessment

Literature search and screening, data extraction, and quality assessment were completed independently by two reviewers (Y.X. and S.W.) according to the inclusion criteria. Discrepancies in data extraction between reviewers were resolved by consensus discussion. The following information was recorded for each of the included studies: last name of the first author, year of publication, country of the studies, study design (crossover or parallel), whether participants having relevant comorbidities (including hypercholesterolemia, dyslipidemia, diabetes, overweight or obesity, metabolic syndrome, and coronary artery disease), mean (range) age of participants, the total number of participants by sex, details of the intervention (including the exact amount of nuts consumed (g/d, and/or % of total daily energy consumption)), the kind of diet or any other intervention carried out in the control group, the duration of treatment, the run-in and washout periods, baseline and follow-up values or percentage changes in outcome parameters (inflammatory markers), and the inclusion and exclusion criteria of study participants.

The quality of each included study was assessed by two reviewers (Y.X. and S.W.) using the Cochrane Collaboration Risk of Bias tool [25]. The items contributing to study quality included the generation of the allocation sequence, allocation concealment, blinding, blinding of outcome assessment, incomplete outcome data, and selective reporting. We classified the studies as low risk of bias, high risk of bias, or unclear in these aspects. Because blinding is difficult in RCTs with dietary interventions, we judged the quality of the studies mainly on the basis of the other five items. Studies with a low risk of bias for at least three items were considered good quality; studies with a low risk of bias for two items were regarded as fair; and studies with a low risk for no items or only one item were considered poor quality.

Statistical analysis

The primary outcome was the mean difference in inflammatory markers from baseline to final follow-up by nut consumption. If the mean difference in inflammatory markers was not reported in the study, we calculated it according to the Cochrane Handbook for Systematic Review and Follman et al.'s theory for overview of clinical trials with continuous variables [26]. We assumed equal variance between intervention and control groups in each trial and among different trials. Standard errors and confidence intervals were converted to SD for analyses. For studies with more than one comparison group, we included the control diet most similar to the nut diet other than the nut intake. Studies that did not report any SD, SE, confidence interval (CI), or P value accompanying the mean values were excluded from the analysis.

Summary estimates of weighted mean differences (WMDs) and 95% CIs were obtained by using random-effects meta-analysis [27]. Statistical heterogeneity of treatment effects across studies was formally tested with Cochran's test ($P < 0.1$). The I^2 statistic was examined, and an I^2 value >50% indicated significant heterogeneity among the trials [28,29]. Subgroup analyses were performed to further identify the possible sources of heterogeneity, including trial design (parallel versus crossover), intervention duration, nut types and dosages, and baseline levels of