

The Role of Tree Nuts and Peanuts in the Prevention of Coronary Heart Disease: Multiple Potential Mechanisms^{1,2}

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Abstract

Epidemiologic and clinical trial evidence has demonstrated consistent benefits of nut and peanut consumption on coronary heart disease (CHD) risk and associated risk factors. The epidemiologic studies have reported various endpoints, including fatal CHD, total CHD death, total CHD, and nonfatal myocardial infarct. A pooled analysis of 4 U.S. epidemiologic studies showed that subjects in the highest intake group for nut consumption had an ~35% reduced risk of CHD incidence. The reduction in total CHD death was due primarily to a decrease in sudden cardiac death. Clinical studies have evaluated the effects of many different nuts and peanuts on lipids, lipoproteins, and various CHD risk factors, including oxidation, inflammation, and vascular reactivity. Evidence from these studies consistently shows a beneficial effect on these CHD risk factors. The LDL cholesterol-lowering response of nut and peanut studies is greater than expected on the basis of blood cholesterol-lowering equations that are derived from changes in the fatty acid profile of the diet. Thus, in addition to a favorable fatty acid profile, nuts and peanuts contain other bioactive compounds that explain their multiple cardiovascular benefits. Other macronutrients include plant protein and fiber; micronutrients including potassium, calcium, magnesium, and tocopherols; and phytochemicals such as phytosterols, phenolic compounds, resveratrol, and arginine. Nuts and peanuts are food sources that are a composite of numerous cardioprotective nutrients and if routinely incorporated in a healthy diet, population risk of CHD would therefore be expected to decrease markedly. J. Nutr. 138: 1746S–1751S, 2008.

Introduction

Cardiovascular disease (CVD)⁷ is the leading cause of death in developed countries. Progress has been made in reducing death from CVD over the past 25 y. For example, in the United States, CVD mortality rate has decreased 41% since the early 1980s (1). This reduction is associated with progress that has been made with treatments as well as prevention. Related to treatment is the rise in the number of hospital discharges for CVD since the 1970s related in part to more angioplasties and bypasses being performed (2). Furthermore, there has been an increase in the incidence of heart failure (i.e. more people are living with progressive heart disease), which reflects advances made in treatment efforts (3). With respect to prevention, the population-based decrease in LDL cholesterol (LDL-C) from the mid-1970s to 2002 is a good metric of the progress that has been made in decreasing CVD risk. Despite the “progress” that has been made in decreasing the prevalence of CVD, the American College of Cardiology recently predicted that by 2050, the number of Americans diagnosed with CVD will double to 25 million (2). Consequently, treatment

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⁷ Abbreviations used: ALA, α -linolenic acid; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; LA, linoleic acid; LDL-C, LDL cholesterol; MUFA, monounsaturated fatty acids.

activities will rise to an all-time high. This projection is troubling, because it is predictive of what likely will occur worldwide. Thus, despite the progress that has been made in reducing CVD death, a focus on prevention is key to a long-term decrease in CVD and the monetary burden associated with contemporary health care.

It is clear that lifestyle practices can have a marked impact on the prevention of CVD. Diet remains the cornerstone of prevention efforts and impressive progress has been made in understanding how individual dietary factors, including nutrients and foods, and dietary patterns modulate multiple CVD risk factors. In recent years, tree nuts and peanuts have been shown to have cardioprotective effects and there is a large body of consistent evidence from epidemiologic and controlled clinical studies demonstrating their multiple beneficial effects on CVD. This has been the impetus for research to determine the biological mechanisms that account for the cardiovascular benefits reported for nuts and peanuts. The purpose of this article is to review the epidemiologic and clinical trial evidence and to discuss some of the mechanistic research that appears to explain how tree nuts and peanuts elicit remarkable effects on CVD risk reduction. Studies that are ongoing also will be described.

Cardioprotective nutrients and dietary factors in nuts

Nuts are rich in unsaturated fatty acids and most contain substantial amounts of monounsaturated fatty acids (MUFA); walnuts are especially rich in both (n-6) [linoleic acid (LA)] and (n-3) [α -linolenic acid (ALA)] PUFA. Healthy fats (i.e. unsaturated fatty acids) in nuts contribute to the beneficial associations of frequent nut intake observed in epidemiologic studies [prevention of coronary heart disease (CHD), diabetes, and sudden death], effects in short-term feeding trials (cholesterol lowering), and decreases in other CVD risk factors. However, nuts are complex food matrices that also are sources of other bioactive compounds, namely: macronutrients, such as vegetable protein and fiber; other nutrients, such as potassium, calcium, magnesium, and tocopherols; and phytochemicals, such as phytosterols and phenolic compounds, among other bioactive compounds, such as resveratrol and arginine (4). Collectively, the individual nutrients and composite of cardioprotective nutrients explain the beneficial effects of nuts on CVD. However, much remains to be learned about the underlying mechanisms of action that mediate the multiple effects reported to date.

Epidemiologic evidence

All epidemiologic studies conducted in the U.S. have reported a beneficial relationship of nut consumption to CHD incidence. A pooled analysis of 4 U.S. studies showed that subjects in the

highest intake group for nut consumption had an ~35% reduced risk of CHD incidence (Fig. 1) (5–8). The relative risk for total CHD based on a multivariate analysis was 0.65 (CI: 0.47–0.89). The relative risk of fatal CHD for individuals consuming nuts 5+ times per week was 0.61 (CI: 0.35–1.05). For nonfatal myocardial infarction, the relative risk was 0.68 (CI: 0.47–1.00) (6). Importantly, a dose-response relationship was reported for all relative risks of CHD and nut consumption. Of particular note is the study conducted by Albert et al. (8) with subjects in the Physicians' Health Study. A reported inverse association between nut consumption and total CHD death was due primarily to a reduction in sudden cardiac death. Compared with men who rarely or never consumed nuts, those who consumed nuts 2 or more times per week had a 47% reduced risk of sudden cardiac death (relative risk, 0.53; CI: 0.30–0.92).

Peanut consumption also was associated with lower relative risk of CHD (6). Subjects who consumed peanuts 2+ times per week had a relative risk of CHD of 0.66 (CI: 0.46–0.94). For tree nuts, the relative risk for consumption 2+ times per week was 0.79 (CI: 0.50–1.25). One mechanism by which tree nut and peanut consumption may decrease risk of CHD is by decreasing inflammatory markers, thereby improving inflammatory status. Inflammation is a key process in atherogenesis, among other diseases. In a cross-sectional study conducted by Jiang et al. (9) using data from the Multi-Ethnic Study of Atherosclerosis, consumption of nuts and seeds was inversely associated with levels of inflammatory markers, C-reactive protein (CRP), interleukin (IL)-6, and fibrinogen. This is important because inflammation contributes to all phases of atherosclerotic disease, ranging from initial recruitment of circulating leukocytes to inducing endothelial dysfunction and to plaque rupture.

Clinical studies

The epidemiologic evidence reporting benefits of nut consumption on CHD risk was the impetus for clinical studies designed to assess the effects on risk factors for CVD and to begin building an understanding of the underlying mechanisms that explained the observational data. The first study was the Loma Linda University walnut study (10). Sabate et al. (10) evaluated a blood cholesterol-lowering diet that provided 20% of energy from walnuts and 31% of energy from fat, of which 6% came from SFA and 16% from PUFA compared with a standard Step-I diet that provided 30% of energy from fat, of which 10% was from SFA and 10% from PUFA. Total cholesterol and LDL-C decreased 12 and 18%, respectively, in the normocholesterolemic subjects studied. Since then, over 25 clinical studies have been conducted evaluating the effects of nut consumption on serum lipids and

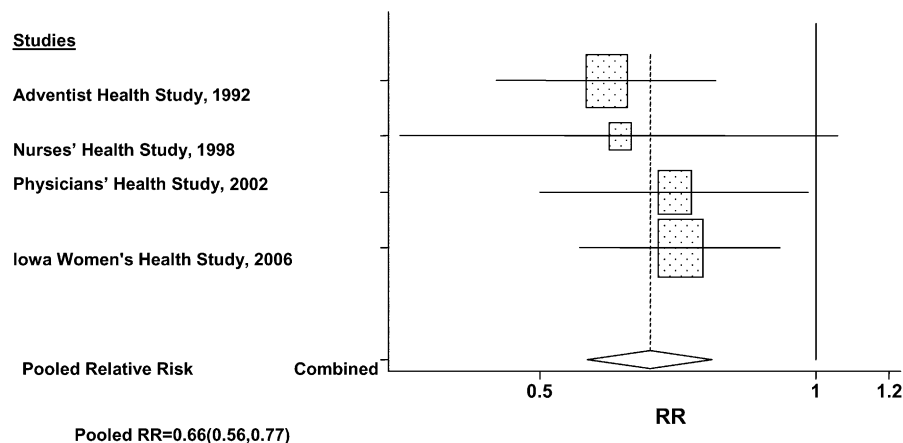


FIGURE 1 Pooled analysis of epidemiologic studies on nut consumption and CHD risk.

lipoproteins. The most studied nuts have been walnuts and almonds. Some research has been conducted on peanuts, pecans, macadamia nuts, hazelnuts, and pistachios. To date, there have been no clinical studies with Brazil nuts, cashews, or pine nuts. The diets that contained nuts were compared with the following control diets: low in total fat and high in carbohydrate; high in saturated fat; a Mediterranean diet; or subjects' usual diet. Although the degree of dietary control has been variable, ranging from being tightly controlled to simply providing dietary advice, the results have been consistent in showing a cholesterol-lowering effect of regular nut intake (11). These studies have evaluated lipids, lipoproteins, and apolipoproteins. More recently, the effects of nuts on other emerging CVD risk factors have been evaluated in clinical trials, including oxidative stress and inflammation.

Because nut consumption decreases total cholesterol and LDL-C, the question emerged whether the response agreed with that expected on the basis of the fatty acid profile of the nut diets. The reasoning was that if the response were greater, there were other bioactive factors with cholesterol-lowering properties in nuts. In a review published by Griel and Kris-Etherton (11), 10 of 17 controlled feeding studies with nuts demonstrated a decrease in LDL-C that was greater than that predicted using blood cholesterol-predictive equations (Fig. 2). The predicted average decrease in LDL-C for these 17 studies was -0.23 mmol/L, with an observed decrease of -0.29 mmol/L when comparing the tree nut-rich diet to the control diet (10,12–26). It has been speculated that other nut constituents such as plant protein, and possibly other factors (that remain to be identified), could account for this effect.

The rather large database of clinical studies conducted with nuts is a valuable resource for a pooled analysis designed to evaluate the cholesterol-lowering response of dietary patterns that incorporate nuts. Controlling for many factors that could affect the diet response, a pooled analysis could provide important information about the magnitude of the cholesterol-lowering response due to nuts and identify factors that contribute to the response. This data analysis is being conducted and will contribute key information that will assist in the translation of nut messages to different population groups.

Effects of nuts on oxidation, inflammation, and vascular reactivity

By virtue of their unique fat and nonfat composition, nuts are likely to affect oxidative stress, inflammation, and vascular reactivity. In nut feeding trials, effects on these markers of atherogenesis have been studied less than the lipid and lipoprotein CVD

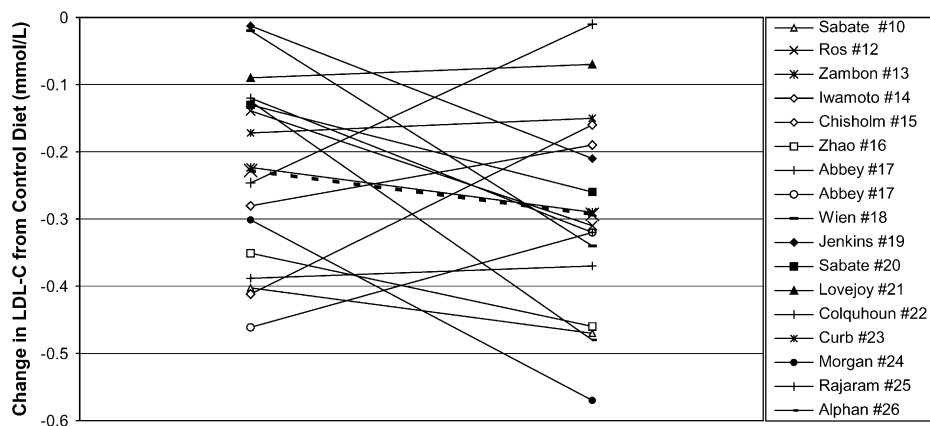
risk factors. Nonetheless, the emerging picture is that frequent nut consumption has beneficial effects on CVD risk factors beyond cholesterol lowering.

Nut intake and oxidative stress. Nuts are important sources of tocopherols and phenolic antioxidants and protective effects of these dietary constituents on LDL oxidation have been well documented in human and animal studies (27). Recently, walnuts were shown to contain substantial amounts of melatonin, which contributed a significant antioxidant effect in an experimental rat model (28). In addition, because a substantial fraction of fat contained in most nuts comes from MUFA, which is not a substrate for oxidation (29), they are not susceptible to oxidation. Nuts also are a source of PUFA, especially walnuts. Whereas research has shown that PUFA are more susceptible to oxidation than MUFA (29), nuts are a rich source of many antioxidants that protect the PUFA in vivo against oxidative modification.

Oxidative markers after feeding of MUFA-rich nuts have been examined in several clinical trials. Results have been inconsistent in studies involving almonds. Berry et al. (30) showed that oxidation of plasma and LDL lipids in healthy volunteers was less after an almond diet compared with a low-fat diet. Jenkins et al. (19), in a dose-response study comparing 2 doses of almonds with a low-fat diet in hyperlipidemic subjects, observed a 14% reduction in plasma oxidized LDL levels after the higher dose (average 73 g/d). However, Hyson et al. (31) did not show any improvement in the susceptibility of LDL to an oxidative stress above the baseline level after feeding either whole almonds or almond oil to healthy individuals, even though SFA intake was lower during the almond diets. Single feeding trials with diets enriched in hazelnuts (32), pistachios (33), and macadamia nuts (34) have shown an improved oxidation status, but the results must be interpreted with caution because in these studies the SFA content of the nut diets was lower than that of the comparison diets. Diets enriched in peanut oil or peanuts plus peanut butter also improved LDL oxidizability compared with an average American diet rich in fat, but not compared with a low-fat diet (35).

In studies with PUFA-rich nuts, resistance of LDL to an in vitro oxidative stress was a secondary outcome in 3 feeding trials that compared walnut diets with other healthy diets (matched for SFA content) (12–14). There were no diet differences in oxidative susceptibility. As discussed, tocopherols and other antioxidants present in walnuts likely prevented the potentially adverse effects of increasing the LDL content of PUFA. In a recent parallel feeding trial with higher statistical power than usual clinical studies with nuts, the PREDIMED study (36), a Mediterranean diet enriched with 1 ounce raw nuts (1.5 g walnuts, 7.5 g almonds,

FIGURE 2 Predicted vs. observed changes in LDL-C in select tree nut studies. Reprinted with permission from the British Journal of Nutrition.



and 7.5 g hazelnuts) given daily for 3 mo to older subjects at high cardiovascular risk resulted in a lower oxidized LDL level [-7.3 U/L (95% CI, -11.2 to -3.3)] compared with a control diet of similar SFA content [-2.9 U/L (-7.3 to 1.5)]. A recent study examined postprandial oxidation after consumption of a high-fat, high-SFA meal enriched with either walnuts or olive oil (37). Neither meal affected oxidative status, as measured by the susceptibility of LDL to an in vitro oxidative challenge and circulating oxidized LDL levels.

Remarkably, in all nuts, most of the antioxidants are located in the pellicle or outer soft shell, and $\geq 50\%$ of them are lost when the skin is removed (27). This fact, rarely taken into consideration in prior feeding trials with nuts, should not be overlooked in future studies. Walnuts are an exception, because they are almost always consumed as the raw product with skins. Recent studies have shown that almond (38,39) and peanut (40) skins are very high in antioxidants.

Nut intake and inflammation. Plasma high-sensitivity CRP, an accepted measure of systemic low-grade inflammation, was a secondary outcome in several controlled nut feeding trials carried out in hypercholesterolemic subjects with almonds (17,41,42) or walnuts (12,16). Three studies, 2 with almonds (41,42) and 1 with walnuts (16), demonstrated a CRP-lowering effect. However, 2 other studies reported no significant decrease in CRP (12,19). The more statistically powered PREDIMED trial (43) also did not show an effect of the Mediterranean diet enriched with mixed nuts on circulating CRP levels. However, the plasma level of IL-6, a potent inflammatory cytokine, decreased after the Mediterranean diet with nuts compared with the control diet (43).

In the Portfolio Diet Studies (41,42), a dietary combination (portfolio) of cholesterol-lowering foods that was very low in SFA, based on milled whole-wheat cereals and low-fat dairy products, also included plant sterols (1.0 g/1000 kcal), soy protein (21.4 g/1000 kcal), viscous fibers (9.8 g/1000 kcal), and almonds (14 g/1000 kcal) and was compared with the same diet without plant sterols, soy protein, viscous fiber, and almonds given with 20 mg/d of lovastatin and without statin therapy. Reductions in CRP were 33% in the statin group and 28% in the dietary portfolio groups (42). In a more recent study (41), when subjects with CRP levels >75 th percentile (>3.5 mg/L) were excluded from the analysis, CRP levels were reduced similarly on both statin (-16.3%) and dietary portfolio (-23.8%) treatments. Inclusion of almonds in the dietary portfolio might have contributed to the antiinflammatory response observed. Obviously, the specific dietary constituent that contributed to CRP lowering cannot be determined because of the multiple dietary changes that were made.

Zhao et al. (16,44) used walnuts and walnut oil to enrich the diet in PUFA and, specifically, ALA to compare effects on inflammatory markers (16) and proinflammatory cytokine production by blood mononuclear cells (44). In the feeding study (16), 2 high-PUFA diets were fed, 1 being higher in LA, which provided 12.6% of energy from LA and 3.6% of energy from ALA, and another diet high in ALA, which provided 17% of energy from PUFA (10.5% LA and 6.5% ALA). Compared with an average American diet, CRP levels decreased 75% in subjects consuming the ALA diet ($P < 0.01$) and $\sim 45\%$ ($P = 0.08$) in subjects consuming the LA diet (16). In addition, tumor necrosis factor- α , IL-6, and IL-1 β production by cultured mononuclear cells from subjects fed the ALA-enriched diet was significantly decreased (44). The beneficial changes might be due to a decrease in SFA; however, because the high-ALA and -LA diets in these

studies provided a similar amount of SFA, the responses appear to be due to ALA and also eicosapentaenoic acids (EPA), derived from the conversion of ALA.

Based on the data for marine-derived (n-3) PUFA, ALA would be expected to have antiinflammatory properties. This has been assessed in relatively few clinical studies (45) with small or no effects noted. Interestingly, there is evidence from a study in which human monocytic cells (THP-1) were cultured with the individual fatty acids palmitic acid, ALA, LA, or docosahexaenoic acid (DHA) in the presence of lipopolysaccharide (46). Secretion of IL-6, IL-1 β , and tumor necrosis factor- α was significantly decreased after treatment with LA, ALA, and DHA vs. palmitic acid ($P < 0.01$ for all). ALA and DHA elicited more favorable effects. These findings suggest that ALA in walnuts evokes an antiinflammatory response. Because of gaps in our knowledge from clinical studies and cell culture studies and because of clinical studies that have not been designed specifically to evaluate the effects of nuts on inflammatory response, more research is needed to conclusively resolve the question about the antiinflammatory effects of nuts.

Nut intake and vascular reactivity. Endothelial dysfunction is a critical event in atherogenesis that is implicated both in early disease and in advanced atherosclerosis, where it relates to perfusion abnormalities and the causation of ischemic events (47). It is characterized by a decreased bioavailability of nitric oxide, the endogenous vasodilator synthesized from the amino acid L-arginine (48), and increased expression of proinflammatory cytokines and cellular adhesion molecules. Endothelial injury caused by cardiovascular risk factors or atherosclerotic vascular disease reduces nitric oxide production, which is followed by arterial wall abnormalities, both functional (inhibition of vasodilatation or paradoxical vasoconstriction) and structural (smooth muscle cell growth and blood cell adhesion), that are responsible for the initiation, development, and progression of atherosclerosis (47).

Food has important effects on vascular reactivity. Short-term feeding studies have shown consistently that diets rich in SFA impair endothelial function (49–51). In addition, a single fatty meal rich in SFA usually is followed by transient endothelial dysfunction in association with elevated triglyceride-rich lipoproteins (52). Whether acute or chronic, these detrimental effects can be counteracted by the administration of (n-3) PUFA and other nutrients present in nuts, such as antioxidant vitamins and L-arginine, the precursor of nitrous oxide (4).

Walnuts are the only nuts that have been evaluated for effects on vascular reactivity, as assessed by brachial artery vasodilatation following ischemic occlusion of the forearm. A recent feeding trial showed that, compared with an isoenergetic Mediterranean diet with similar SFA content, a walnut diet attenuated the endothelial dysfunction associated with hypercholesterolemia (12). In a follow-up of this study, Cortes et al. (37) showed that adding walnuts to a high-fat, high-SFA meal counteracted ensuing postprandial endothelial dysfunction compared with the same meal with added olive oil. By analogy with the improvement of endothelial function observed after supplementation of marine (n-3) PUFA (49–51), this beneficial effect of walnuts may be ascribed in part to their high ALA content. L-Arginine and antioxidants in walnuts also might have played a role. Of note, supplementing a high-fat meal with ALA from canola oil also was shown to improve postprandial endothelial function in subjects with diabetes (53).

Endothelial dysfunction also may be evaluated by changes in circulating levels of cellular adhesion molecules critical to leukocyte recruitment to the arterial wall (47). Recent clinical

studies have shown that diets enriched with ALA from walnuts (12,16,43) or other foods (16,54) reduce endothelial activation, as assessed by decreased plasma cellular adhesion molecules levels. Walnut feeding also reduced the expression of endothelin-1, a potent endothelial activator, in an animal model of accelerated atherosclerosis and this effect could be attributed to the fat component of walnuts (55). Indeed, there is increasing evidence suggesting that ALA is a potent antiatherosclerotic agent (56). Although no vascular reactivity studies have been performed after consumption of diets enriched with nuts other than walnuts, they might be expected also to show beneficial effects, because all nuts contain substantial quantities of bioactive compounds that can favorably influence vasoactivity, such as L-arginine and antioxidants. This is a key area for further research with nuts.

The role of nuts and peanuts in a healthful dietary pattern for reduced risk of CHD

A healthy dietary pattern is high in fruits, vegetables, nuts, legumes, whole grains, and lean protein sources and low-fat dairy products (57). Nuts are a popular and important protein source in vegetarian diets (58). In a cohort of Seventh Day Adventists, Fraser (58) reported that in vegetarians, after soft margarine on bread and green salads, nuts were next on the list of foods most frequently consumed. In fact, nuts were consumed more than meat substitutes. As discussed by Sabaté (59), a well-balanced diet that includes nuts and peanuts can markedly benefit health, and in the context of this article, reduce CVD risk.

In summary, there is impressive evidence from epidemiological and clinical trials and in vitro studies of beneficial effects of nut consumption and their constituents on the risk of CVD, including sudden death, as well as on major and emerging CVD risk factors. The evidence to date is convincing that including nuts in a heart-healthy diet extends cardioprotective effects beyond those defined for a contemporary heart-healthy dietary pattern. Importantly, these effects target multiple CVD risk factors and mechanisms, which help explain why nuts so potently reduce risk for CVD. Understanding the underlying biological mechanisms that explain the effects nuts have on multiple CVD risk factors may help in the design of the next generation of diets that include nuts to maximally reduce CVD risk.

Other articles in this supplement include references (60–65).

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