Original Article

Nuts, blood lipids and cardiovascular disease

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The aim of this paper is to evaluate nut-related epidemiological and human feeding study findings and to discuss the important nutritional attributes of nuts and their link to cardiovascular health. Frequent nut consumption has been found to be protective against coronary heart disease in five large epidemiological studies across two continents. A qualitative summary of the data from four of these studies found an 8.3% reduction in risk of death from coronary heart disease for each weekly serving of nuts. Over 40 dietary intervention studies have been conducted evaluating the effect of nut containing diets on blood lipids. These studies have demonstrated that intake of different kinds of nuts lower total and LDL cholesterol and the LDL: HDL ratio in healthy subjects or patients with moderate hypercholesterolaemia, even in the context of healthy diets. Nuts have a unique fatty acid profile and feature a high unsaturated to saturated fatty acid ratio, an important contributing factor to the beneficial health effects of nut consumption. Additional cardioprotective nutrients found in nuts include vegetable protein, fiber, α-tocopherol, folic acid, magnesium, copper, phytosterols and other phytochemicals.

Key Words: nuts, fatty acids, cardiovascular disease, blood lipids, cholesterol

INTRODUCTION

During the past two decades, a multitude of human feeding studies have investigated the effect of nut consumption on blood lipids and other cardiovascular disease (CVD) outcomes.[1,2] The findings of these trials have supported the epidemiologic evidence that frequent nut intake is associated with a reduced risk of coronary heart disease (CHD).[3,4] In light of the consistency across several lines of scientific inquiry, the United States Food and Drug Administration issued a health claim for nuts in the context of reducing the risk of heart disease.[5] The aim of this paper is to evaluate the epidemiological and human feeding study findings and to discuss the important nutritional attributes of nuts and their link to cardiovascular health.

NUT CONSUMPTION AND EPIDEMIOLOGICAL STUDIES

There has been a remarkable consistency among four prospective epidemiological studies in the United States regarding the increased frequency of nut intake and reduced risk of heart disease. We were the first group to discover the association between frequent nut consumption and the reduced risk of CHD among the 31,208 participants enrolled in the Adventist Health Study (AHS).[6] The AHS cohort is homogeneic for potential confounders (e.g. non-smoking, little alcohol use) and half consumes a vegetarian diet, which makes the cohort valuable for exploring dietary relationships and risk of chronic diseases. A validated 65 item food frequency questionnaire (FFQ) was administered to this cohort to assess dietary intake at baseline. During six years of follow-up (1977 to 1982), nuts had the strongest inverse relationship for non-fatal myocardial infarction (MI) and fatal CHD. An additional analysis showed that this protective effect of nuts occurred in both vegetarians and non-vegetarians[7] and in the oldest subjects (over 84 years of age).[8]

Three other large epidemiological studies have investigated the link between nut consumption and risk of CHD. The Iowa Women's Health Study (IWHS)[9] enrolled 34,111 postmenopausal women and explored the relationship between diet and CHD using a 127 item FFQ. The initial findings were similar to the AHS and, after 15-years of follow-up, there were substantial reductions in total CHD mortality for those frequently consuming nuts and peanut butter. Additionally, the findings from the 86,016 women enrolled in the Nurses' Health Study (NHS)[10] and the 22,071 men enrolled in the Physician's Health Study[11] have been consistent with the AHS results regarding the inverse relationship between nut intake and specific CHD outcomes.

A qualitative summary of the data from the aforementioned prospective cohort studies was performed using the median of each category of nut consumption associated with the relative risk of fatal CHD.[12] A clear dose-response gradient was present in each study and approximately 70% of the variance in the relative risk among the studies was explained by the linear relationship between the relative risk and frequency of nut consumption. Across the studies, an 8.3% reduction in risk of CHD death was observed for each weekly serving of nuts. A

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clinically and statistically significant cardioprotective effect exists from frequent nut consumption and the average risk reduction for CHD mortality is 37% (RR = 0.63, 95% CI: 0.51-0.83) (Figure 1).[12] A very similar estimate has been recently reported[13] on a pooled analysis of the four US cohort studies,[6,9-11] which showed a relative risk of 0.65 (CI: 0.47-0.89). Hence, subjects in the highest nut intake group had an approximate 35% reduced risk of CHD compared to those in the lowest intake group.[13]

The European Prospective Investigation into Cancer and Nutrition (EPIC) study has provided an opportunity to explore the association between frequency of nut intake and risk of CHD mortality among 520,000 adults consuming a variety of different background diets.[14] In this large European cohort representing 10 countries, a higher intake of nuts appears to be associated with a reduction in risk of CHD death. More specifically, an intake of two servings of nuts per week (8 g/d) may reduce the risk of CHD mortality by 16%.[15]

Although these epidemiological findings are consistent across studies and the studies controlled for potential confounders, residual confounding cannot be completely excluded. Thus, randomized controlled feeding trials that could identify factors related to causality were warranted.

HUMAN FEEDING TRIALS OF NUTS AND BLOOD LIPIDS

The epidemiological findings on nuts and CHD fueled a body of research surrounding the effects of nuts on blood lipids, lipoproteins and apolipoproteins, which are major risk factors for CHD. Over 40 human nutrition studies have been conducted to date that have evaluated the effect of nut containing diets on blood lipids, lipoproteins and/or their corresponding apolipoproteins. Most studies with nuts have been short-term and have compared diets supplemented with nuts to control diets for outcomes on blood lipid changes in healthy subjects or patients with moderate hypercholesterolaemia.

Studies have varied in length from two weeks to six months duration and have compared nut containing diets with a high saturated fat diet, a low fat/high carbohydrate diet, or, against the subject's usual diet. The seminal study was the Loma Linda University walnut study, which featured a crossover design to evaluate the effects of walnut consumption on serum lipids and lipoprotein levels.[16] Eighteen healthy males consumed two diets for four weeks duration. Both diets conformed to the NCEP Step 1 diet except that 20 percent of the calories of the walnut diet were derived from walnuts (offset by lesser amounts of fats [oils, margarine, and butter]). With the walnut diet, the mean total and LDL cholesterol levels were, respectively, 22.4 mg/dL and 18.2 mg/dL lower than the reference diet. These lower values represented reductions of 12.4 and16.3 % in the levels of total and LDL cholesterol, respectively. The LDL:HDL ratio was also lowered 12.0 % by the walnut diet. Others have also shown that nut intake reduces TC, LDL, apolipoprotein B (ApoB), LDL:HDL, and ApoB:ApoA1, which are favorable outcomes for CHD prevention and management.[2]

Two groups of investigators have shown similar findings from studies designed to evaluate if a serum lipid dose-response relationship exists when subjects consume a graduated enrichment of a NCEP Step 1 diet with nuts. First, Sabate et al.[17] provided 10% (low-almond) and 20% (high-almond) of energy from almonds within a Step 1 diet in healthy and mildly hypercholesterolemic adults. Using a randomized crossover design, 25 healthy subjects (14 men, 11 women) with a mean (±SD) age of 41±13 y were fed 3 isoenergetic diets for 4 weeks each. Significant inverse relationships were observed between the percentage of energy in the diet from almonds and the subject's TC, LDL, and ApoB concentrations and the ratios for LDL:HDL and ApoB:ApoA1 (all $p<0.001$). Compared with the Step I diet, the high-almond diet significantly reduced TC 4.4%, LDL 7.0%, and ApoB 6.6%, and, the LDL:HDL ratio decreased 8.8% (all $p< 0.01$). In a separate randomized crossover design study, Jenkins et al.[18] evaluated the dose-response effects of whole almonds

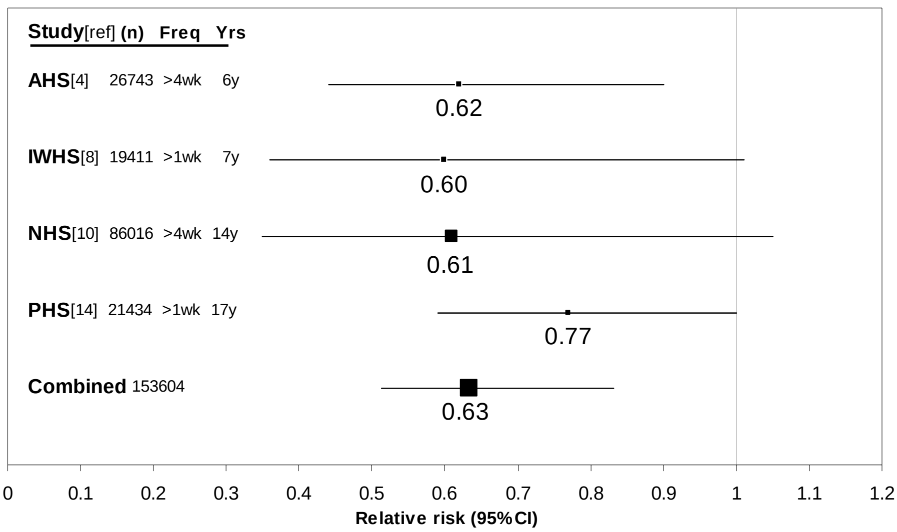

Figure 1. Summary of epidemiological studies on the frequency of nut intake and relative risk of coronary heart disease mortality. Relative risk and 95% confidence intervals (CI) derived by comparing the highest and lowest frequency of nut intake, adjusted for similar risk factors across studies. Size of marker represents the study sample size. AHS, Adventist Health Study (Fraser *et al*, 1992[6]); IWHS, Iowa Women's Health Study (Kushi *et al*, 1996[9]); NHS, Nurses Health Study (Hu *et al*, 1998[10]); PHS, Physician's Health Study (Albert *et al,* 2002[11]).

Table 1. Fat composition of nuts and common foods of animal origin (per 100 g of food)†

		Percentage of Total Fat			
	Total fat (% of weight)	SFA	MUFA	PUFA	UFA/SFA ratio
Almonds	49	8	62	24	11.5
Cashews	44	20	60	20	4.1
Hazelnuts	61	8	79	14	11.6
Macadamia	76	17	81	2	4.9
Pecans	72	9	59	32	10.1
Pistachios	44	13	55	32	6.7
Walnuts	65	10	14	76	9.0
Peanuts	49	15	52	33	5.7
Beef, T-bone (trimmed)	16	38	45	4	1.3
Chicken, roasted	13	28	40	22	2.2
Whole milk	3	57	25	6	0.5
Eggs	10	31	38	14	1.7
Cheddar cheese	33	64	28	3	0.5

†Values taken from US Department of Agriculture Nutrient Data Base Release 22 at http://www.ars.usda.gov/ba/bhnrc/ndl (accessed 16 November 2009).

compared with low-saturated fat (<5% energy) whole-wheat muffins in the diets of 27 hyperlipidemic subjects for one month periods. Subjects consumed snacks that provided 22.2% of daily energy and consisted of full-dose almonds (73+/-3 g/d), half-dose almonds plus half-dose muffins, and, full-dose muffins. Significant reductions from baseline were seen on both the half- and full-dose almonds for LDL (4.4±1.7% and 9.4±1.9%, respectively) and LDL:HDL (7.8±2.2% and 12.0±2.1%, respectively).

Over 40 dietary intervention trials have been conducted to date assessing the effects of nut consumption on serum lipids and lipoproteins.[19] While some studies have used peanuts, pecans, macadamia nuts, hazelnuts, pistachios, and cashews, the most studied nuts have been walnuts and almonds. From the published results of the main human feeding trials of walnuts and almonds, Ros[20] estimated an average decrease of LDL cholesterol of 9 and 6 percent, respectively. We recently completed a pooled analysis of 25 nut studies with different types of nuts including peanuts.[21] This pooled analysis was capable of providing a more precise quantitative estimate of the effects of nuts on blood lipids, as the dataset included approximately 1300 observations contributed by 600 unique participants. The mean estimated reductions of total cholesterol and LDL cholesterol were 11 mg/dL (5%) and 10 mg/dL (7%), respectively. Different types of nuts had similar effects on serum lipids. The estimated reductions on TC and LDL in this pooled analysis are consistent with those obtained by a recent meta-analysis of walnut studies.[22]

The decreases in total and LDL cholesterol observed in many nut studies are greater than expected on the basis of the dietary fatty acid and cholesterol exchange between nut diets and control diets.[19] This suggests that nut constituents other than fatty acids, such as protein, fiber and/or phytosterols may also contribute to the blood cholesterol lowering effect of nuts.

COMPOSITION OF NUTS AND THEIR CARDIOPROTECTIVE EFFECT

Nuts are an energy dense food as they contain between 44 and 76% total fat by weight (Table 1). However, they have a unique fatty acid profile and feature a proportionally higher content of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) versus saturated fatty acids (SFA) (range 83 to 93% and 8 to 20%, respectively).[1] Thus, a beneficial unsaturated fatty acid (UFA) to SFA ratio of 4.1 to 11.6 results and is likely to be an important[20] contributing factor to the beneficial health effects of frequent nut consumption. Additionally, walnuts contain significant levels of n-3 fatty acids, which are known to be cardioprotective due to reduced platelet aggregation and vasoconstriction[23] and inflammation.[24] It is important to highlight that walnuts are the whole food with the highest level of α-linolenic acid of all edible plants.[25]

Several nutritional attributes that are found in most nuts that are specifically linked to cardioprotective effects are shown in Table 2, and Table 3 provides nutritional information on the nonfat components of select nuts and common foods of animal origin (per 100 g of food). Nuts are a good source of protein (10-25 g/100 g of nut) and include a favorable amino acid profile. More specifically, most nuts are rich in L-arginine,[26] the dietary precursor of the endogenous vasodilator known to improve vascular reactivity, nitric oxide. Further, this high level of L-arginine yields a preferentially low arginine to lysine amino acid ratio (range 0.01 to 0.57) that can contribute to reducing blood LDL concentrations.[27,28] Most nuts are good sources of dietary fiber (range 3 to 12 g per 100g) and a standard serving size provides up to 5 to 10% of one's daily fiber requirements.[29] Nuts also contain notable levels of folic acid, magnesium, and copper.[30] Folic acid plays an essential role in detoxifying the sulfur-containing amino acid homocysteine, which has atherothrombotic properties and accumulates in plasma when folic acid levels are subnormal.[31] Magnesium and copper are associated with improved insulin resistance, reduced arterial hypertension and prevention of ventricular arrhythmias.[32,33] Almonds, hazelnuts and peanuts are excellent natural sources of the antioxidant α-tocopherol, whereas walnuts contain significant levels of its isomer γ-tocopherol, which is emerging as a relevant anti-atherogenic molecule.[34] In addition to containing the aforementioned cardioprotective vita-

Table 2. Constituents of nuts linked to cardiovascular health

Nut Constituent	Mechanism
High in monounsaturated and polyunsaturated fatty acids	Lower total serum cholesterol and improve lipoprotein and apoliprotein profile
Vegetable protein (amino acids): High in arginine and low in lysine	Low arginine to lysine ratio reduces serum LDL levels Arginine is a precursor of nitric oxide (endothelium derived relaxing factor)
Dietary fiber	Lowers serum LDL levels
Tocopherols	Increase LDL oxidative resistance
Folic acid	Decreases blood homocysteine levels
Magnesium	Prevents ventricle arrhythmia
Copper	Reduces blood cholesterol and blood pressure
Phytochemicals: Ellagic acid, flavonoids, phenolic compounds, luteolin, tocotrienols, resveratrol, tannins, plant sterols	Antioxidant potential

LDL, low density lipoprotein

Table 3. Nonfat components of select nuts and common foods of animal origin (per 100 g of food)†

	Protein (g)	Lysine (g)	Arginine (g)	Lysine/ Arginine ratio	Fiber (g)	α-tocopherol (mg)	Folic acid (μg)	Mg (mg)	Cu (mg)	Cholesterol (mg)
Almonds	21.2	0.58	2.44	0.24	12.2	26.2	50	268	1.0	0
Cashews	18.2	0.93	2.12	0.44	3.3	0.9	25	292	2.2	0
Hazelnuts	15.0	0.42	2.21	0.19	9.7	15.0	113	163	1.7	0
Macadamia	7.9	0.02	1.40	0.01	8.6	0.5	11	130	0.8	0
Pecans	9.2	0.29	1.18	0.25	9.6	1.4	22	121	1.2	0
Pistachios	20.3	1.14	2.01	0.57	10.3	2.3	51	121	1.3	0
Walnuts	15.2	0.42	2.28	0.18	6.7	0.7	98	158	1.6	0
Peanuts	25.8	0.09	3.08	0.03	8.5	8.3	240	168	1.1	0
Beef, T-bone (trimmed)	24.2	2.26	1.62	1.40	0	0.2	7	24	0.1	0
Chicken, roasted	24.0	1.94	1.51	1.28	0	N/A‡	5	20	0	76
Whole milk	3.2	0.14	0.07	2.00	0	0.1	5	10	0	97
Eggs	12.6	0.91	0.82	1.11	0	1.0	47	12	0.1	423
Cheddar cheese	24.9	2.07	0.94	2.20	0	0.3	18	28	0	105

†Values taken from US Department of Agriculture Nutrient Data Base Release 22 at http://www.ars.usda.gov/ba/bhnrc/ndl (accessed 16 November 2009)

‡N/A, not available

mins and minerals, nuts contain many bioactive constituents such as phytosterols, phytoestrogens and phytochemicals (e.g. ellagic acid, flavonoids, phenolic compounds, luteolin, tocotrienols).[35] Phytosterols are nonnutritive components of all nuts and they compete with dietary cholesterol absorption, which may be partially responsible for their cholesterol lowering effects.[20]

A comparison of several of the macronutrients and micronutrients found in nuts and in other common high fat foods of animal origin is shown in Tables 1 and 3. The contrast between meats and nuts is very dramatic as nuts have a distinctly lower lysine to arginine ratio, higher UFA to SFA ratio, zero cholesterol, and higher levels of fiber, α-tocopherol, folic acid, magnesium and copper. Nuts are currently found in the meats/beans category of the United States Department of Agriculture food pyramid, however we,[36] and others,[37] have categorized nuts more appropriately with seeds and legumes in the context of framing public health dietary recommendations.

There is general consensus that the Therapeutic Lifestyle Change (TLC) Diet is an essential component of the National Cholesterol Education Program Adult Treatment Panel III guidelines[38] and is a necessary adjunct for the prevention and management of CVD. The TLC diet has the potential to reduce CVD risk through several mechanisms beyond lowering low density lipoprotein (LDL) cholesterol. The nutrient composition of the TLC includes up to 10% of total calories from PUFA, up to 20% of total calories from MUFA, less than 7% of total calories from SFA and trans fatty acids, and less than 200mg/day cholesterol. Thus, nuts are an appropriate fit for persons seeking to improve the quality of their diet for CVD risk reduction.

In conclusion, frequency of nut consumption has been found to be protective against CHD in five large epidemiological studies across two continents. Human nutrition studies with almonds and walnuts have shown marked cholesterol lowering and favorable modification of lipoproteins and apolipoproteins in both normal and hyperlipidemic subjects. Peanuts, macadamia nuts, hazelnuts, pistachios and pecans have also shown some of these effects, although there have been fewer studies.

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AUTHOR DISCLOSURES

The authors disclose no conflicts of interest.

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Original Article

Nuts, blood lipids and cardiovascular disease

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核果類與血脂質以及心血管疾病

這篇論文的目的是評估與核果類相關的流行病學及人體給食研究的結果，並且討論核果類和相關的心血管健康的重要營養特性。在兩大洲的五個大型流行病學研究中指出，經常攝取核果類具有預防冠心病的效用。綜整其中四個研究的定性資料，發現每週攝取一份的核果類，可減少 8.3%因為冠心病而死亡的風險。有超過 40 個飲食介入的研究，針對血脂質來進行飲食中包含核果類的效果評估。這些研究顯示攝取不同種類的核果類，甚至是健康飲食中含有核果類，可降低健康者以及患有中度高膽固醇血脂症患者的總膽固醇、低密度脂蛋白膽固醇以及低密度脂蛋白膽固醇與高密度脂蛋白膽固醇比值。核果類具有特殊的脂肪酸組成，而且有較高的不飽和脂肪酸與飽和脂肪酸比例，這是攝取核果類有益健康效果的一個重要因子。核果類保護心血管的營養成分還包括植物性蛋白、纖維、維生素 E、葉酸、鎂、銅、植物固醇以及其他植化素等。

關鍵字：核果、脂肪酸、心血管疾病、血脂質、膽固醇