

Nuts and health outcomes: new epidemiologic evidence¹⁻³

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ABSTRACT

This article reviews recent epidemiologic evidence on nut intake and health outcomes. It focuses on studies in which nut consumption is directly assessed or when nuts are included in a dietary score or pattern. Epidemiologic studies have been remarkably consistent in showing an association between nut consumption and a reduced risk of coronary heart disease (CHD). Some evidence has emerged recently to suggest health-protective benefits of nuts other than CHD. Frequent nut intake probably reduces risk of diabetes mellitus among women, but its effects on men are unknown. Evidence on the anticarcinogenic effects of nuts is somewhat limited because studies in the past 2 decades have examined only 3 tumor sites, and the benefits appear to be manifested only in women. However, the protective benefits of frequent nut consumption on gallstone diseases are observed in both sexes. Long-term nut consumption is linked with lower body weight and lower risk of obesity and weight gain. A dietary pattern or score that includes nuts is consistently related with beneficial health outcomes, and this provides an indirect evidence of the salutary benefits of nut consumption. More longitudinal studies are needed to clarify the possible effects of nuts on diseases other than CHD. *Am J Clin Nutr* 2009;89(suppl):1643S-8S.

INTRODUCTION

When a landmark epidemiologic study reported that a higher frequency of nut consumption was associated with a lower risk of coronary heart disease (CHD) (1), nuts were brought from obscurity to prominence as an important health food. In the 15 y since this first epidemiologic observation, scientific evidence on the health effects of nuts has not only accumulated in the area of CHD and its risk factors but also extended to other areas of health. Scores of human dietary intervention studies were conducted that investigated the effect of nuts on blood lipids and other biological markers of heart disease. Much less research has been conducted on other health outcomes, and only a few of those studies were epidemiologic in nature. The purpose of this article is to review epidemiologic studies on nut intake and any health outcome, focusing on the research performed since the previous edition of the International Congress on Vegetarian Nutrition 6 y ago (2).

One of the challenges in interpreting epidemiologic data about nut consumption and health outcome lies in the fact that nuts, seeds, and legumes are frequently presented together. Such groupings make independent analyses difficult. In epidemiologic studies, nut exposure has been assessed and analyzed in 3 ways: 1) nut intake is directly measured, 2) a food group (eg, the plant group) or a dietary pattern (eg, the Mediterranean diet) is as-

essed when nuts are included, and 3) a nutrient in nuts is measured (eg, fiber) instead of nuts themselves, making the nutrient a surrogate of nut consumption. This review primarily covers epidemiologic studies that used the first 2 measures of nut exposures.

NUTS, CHD, AND RISK FACTORS

Epidemiologic studies have been remarkably consistent in showing a cardioprotective effect associated with increased nut intake. The 4 major cohort studies—Adventist Health Study (1), the Iowa Women's Health Study (3), the Nurses' Health Study (4), and the Physicians' Health Study (5)—all show a clear dose-response gradient between nut consumption and reduced CHD risk. Taken together, these 4 epidemiologic studies exhibited an average risk reduction of CHD death by 37% [relative risk (RR): 0.63; 95% CI: 0.51, 0.83] or an average of 8.3% reduction in risk of CHD death for each weekly serving of nuts (6). The beneficial effects of nut consumption are observed to be similar for different clinical outcomes: nonfatal myocardial infarction, fatal CHD, and sudden cardiac death. The effects are evident across sex, age, different locations, and subjects' occupations (6). The risk of CHD death by frequency of nut consumption from 4 prospective epidemiologic studies is depicted in **Figure 1**. Collectively, these findings provide strong and compelling evidence of the cardioprotective benefit of nut consumption.

Many clinical studies have consistently shown a hypocholesterolemic effect of regular nut intake, which explains in part the lower cardiovascular risk (7). Besides the lipid hypothesis of atherosclerosis, firm evidence suggests that inflammatory processes are implicated in the cause or pathophysiology or both of cerebral ischemia or CHD (8-10). These findings have led to the investigation of several novel risk factors for CHD, beyond blood lipids, such as markers of inflammation and endothelial function and the effects of nut consumption. Nonetheless, few of those studies are epidemiologic in nature (11). The Multi-Ethnic Study of Atherosclerosis is the only large-scale cohort study in the past 6 y that examines the direct health effects of nut consumption on

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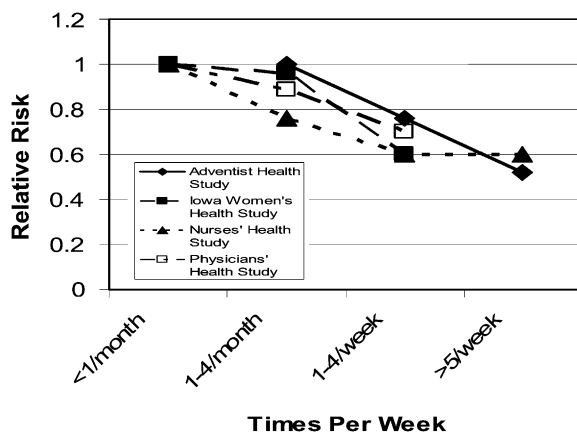


FIGURE 1. Frequency of nut consumption and coronary heart disease risk reduction in a dose-response manner. *P* for trend: crude odds ratio = 0.058; adjusted odds ratio = 0.026. Results are from 4 epidemiologic studies adapted from Kelly and Sabaté (6).

inflammatory markers relating to atherosclerosis (12). The results showed a significant inverse association between selected inflammatory markers such as C-reactive protein, interleukin-6, fibrinogen, and frequent total nut and seed consumption among ≈ 6000 men and women aged 45–84 y. When nuts, seeds, peanuts, and peanut butter were examined individually, the inverse associations with inflammatory markers persisted, although they were not always significant (12).

A cohort study in France reported an inverse relation between the intake of fiber from nuts and seeds and several CHD risk factors (13). That cross-sectional study examined the dietary fiber intake of a cohort of 2532 men and 3429 women and reported that fiber from nuts and seeds was associated with decreased body mass index (BMI; in kg/m^2) [odds ratio (OR): 0.78; 95% CI: 0.65, 0.95; $P = 0.01$], decreased waist-to-hip ratio (OR: 0.72; 95% CI: 0.66, 0.88; $P = 0.001$), decreased apolipoprotein B (OR: 0.78; 95% CI: 0.62, 0.99; $P = 0.03$), and decreased fasting glucose (OR: 0.57; 95% CI: 0.37, 0.90; $P = 0.002$).

NUTS AND DIABETES

The association of nut consumption and diabetes is not as consistent as with CHD. Only 3 major epidemiologic studies have evaluated nut consumption and its effect on incidence of diabetes—the Nurses' Health Study (14), the Iowa Women's Health Study (15), and the Shanghai Women's Health Study (16)—and they were all studies in women.

The Nurses' Health Study (14) was the first large-scale cohort study ($n = 83,818$) that directly assessed the effects of nut consumption and risk of diabetes. That prospective study with 16 y of follow-up provided strong evidence that consumption of both nuts (which included peanuts) and peanut butter were inversely associated with risk of diabetes, independent of several known risk factors for type 2 diabetes. However, in the Iowa Women's Health Study (15), the association with the risk of diabetes was less clear. In the 11 y of follow-up, the postmenopausal women who ate nuts often had no reduced risk of diabetes compared with those who ate nuts occasionally after adjusting for multiple factors, including diet. However, a significant reduction in risk (OR: 0.57; 95% CI: 0.37, 0.90; $P = 0.002$) was observed between the highest (≥ 5 times/wk) and

lowest (<1 time/wk) frequency of consuming peanut butter when the analysis was adjusted for age only. It could be argued that the lack of effect in the separate analysis of the Iowa Women's Health study is in part due to dietary overadjustment. Nutrients such as fiber, magnesium, monounsaturated fat, or polyunsaturated fat are considered to be the bioactive compounds responsible, at least to some degree, for the health benefits conferred by nuts. In addition, the null findings in the Iowa Women's Study could be due to a smaller sample size ($n = 1800$).

A recent population-based study was performed among a Chinese cohort in Shanghai (16). Approximately 64,000 women were followed for an average of 4.6 y. The study showed an inverse association between peanut consumption and risk of diabetes in both pre- and postmenopausal women. Similar to the Nurses' Health Study, the association with diabetes risk among the Chinese women remained significant after controlling for BMI or waist-to-hip ratio. A strong and significant risk reduction of 20% was observed between the first quintile (0.1 g/d) and upper quintile (3.1 g/d) of peanut consumption (RR: 0.80; 95% CI: 0.68, 0.95) even after multiple adjustment for dietary and nondietary variables. The results of the Shanghai Women's Health Study relating peanut consumption to risk of developing type 2 diabetes are summarized in **Table 1**.

In summary, epidemiologic evidence on the effects of nuts on the risk of diabetes is limited to women. Two studies reported a protective effect against risk of diabetes with consumption of nuts, whereas one reported either no or a weak association. It is not known whether nut consumption is associated with a reduced risk of diabetes in men.

NUTS AND BODY WEIGHT

Obesity is now considered a major public health problem of epidemic proportion that threatens millions of lives in the United States (17) and worldwide (18). Obesity is linked to a number of chronic diseases (19). Because nuts are high-fat, energy-dense foods, it is a reasonable concern that frequent ingestion of nuts may lead to weight gain and, consequently, increase the risk of many chronic degenerative diseases. A recent review on nut intervention trials in both controlled and free-living conditions did not show any adverse effect of nut consumption on energy balance or body weight (20). Those types of studies provide strong evidence in the causal link between nut consumption and body weight. Findings from past epidemiologic studies similarly

TABLE 1

Association between type 2 diabetes and quintile (Q) of intake of peanuts in the Shanghai Women's Health Study¹

	Peanut intake	Relative Risk	95% CI
	<i>g/d</i>		
Q1	0.1	1.00	(reference)
Q2	0.4	0.80	0.69, 0.94
Q3	0.7	0.95	0.82, 1.11
Q4	1.4	0.79	0.68, 0.92
Q5	3.1	0.80	0.68, 0.95

¹ Data from Villegas et al (16). Analysis adjusted for age, energy intake, BMI, waist-to-hip ratio, smoking, alcohol consumption, vegetable intake, fiber intake, physical activity, income level, education level, occupation, and hypertension. *P* for trend not available.

disputed the concern that frequent nut consumption would lead to weight gain (1, 4, 5).

Recently, the prospective Seguimiento Universidad de Navarra (SUN) study (21), with extended follow-up of a Mediterranean cohort, continued to support the observation that frequent nut intake is not associated with weight gain. The SUN Study is the only epidemiologic study that has examined the direct effect of nut consumption on body weight in a prospective fashion. That study, involving ≈ 8800 adult men and women, found that those who ate nuts frequently (≥ 2 times/wk) had a 40% reduced risk of weight gain (OR: 0.61; 95% CI: 0.47, 0.79; P for trend < 0.001); even after adjusting for baseline BMI, which was the strongest confounder, the OR was 0.69 (95% CI: 0.53, 0.90; P for trend: 0.006). Specifically, those frequent nut consumers gained 350 g less weight than did those who never ate nuts during a follow-up period of 28 mo (Figure 2). In that cohort, those who consumed nuts ≥ 2 times/wk reduced their odds of becoming overweight or obese by 43% (OR: 0.57; 95% CI: 0.39, 0.83; P for trend: 0.007), after age and sex were adjusted, compared with those not consuming nuts. The inverse association was attenuated and became nonsignificant (OR: 0.73; 95% CI: 0.49, 1.10; P for trend: 0.206) after adjustment for body weight and physical activity. The SUN Study provides evidence that frequent nut consumption is not associated with increase in body weight, change in body weight, or incidence of overweight or obesity over time.

NUTS AND CANCER

Nuts are rich in compounds that are believed to have antioxidant, antiinflammatory, or anticarcinogenic properties such as tocopherols, folic acids, selenium, magnesium, and several phytochemicals (22–24). The relation between nut intake and cancer has been previously reviewed (25). Notably, past epidemiologic evidence on the role of cancer prevention and nut consumption was insufficient and inconclusive (26–28). In the past 6 y, 3 prospective studies from different population groups were published (29–31), and collective findings suggested that protective effects of nuts on colorectal and endometrial cancers were possible. A summary of those 3 studies in terms of foods evaluated, tumor sites, and findings is presented in Table 2.

Results from the European Prospective Investigation into Cancer and Nutrition cohort suggest a sex difference in the

protective effects of nuts on colon cancer (29). No significant association was observed between higher intake of nuts and seeds and risk of colorectal, colon, and rectal cancers in combined analysis for men and women. However, when the subgroup of women was analyzed separately, a significant inverse association was detected between the highest quintile (>6.2 g/d) compared with the lowest quintile (nonconsumers; OR: 0.69; 95% CI: 0.50, 0.95).

Remarkably, a significant sex discrepancy was also reported in the risk of colorectal cancer associated with peanut consumption in a different ethnic group in Asia (30). That population-based cohort study of $\approx 24,000$ people in Taiwan reported an anticarcinogenic effect from peanuts—a relatively common nut in the Asian population. In the 10-y follow-up period, women consuming peanuts had a remarkable risk reduction of 58% compared with nonconsumers (RR: 0.42; 95% CI: 0.21, 0.84; $P = 0.01$). However, the protective effect was not observed in men. That epidemiologic study provided a rare examination of the independent health effects of peanuts on the risk of cancer.

A Mediterranean study in Greek women appears to support the role of a diet rich in nuts in reducing the risk of endometrial cancer (OR: 0.63; 95% CI: 0.44, 0.88) (31). Interpretation of results in that case-control study, however, needs to be made with caution because that study involved a small sample group (84 cases and 84 controls) in a population that is known for low risk of endometrial cancer. Furthermore, seeds and legumes were grouped with nuts as one category in the analysis.

The relation between nuts and cancer warrants further study because research in this area is insufficient. However, there are some challenges, opportunities, and limitations. First, the issue of sex difference should be considered in future studies on the cause of colorectal cancer. The anticarcinogenic benefits appear to be evident only in women and not men. Notably, only 3 cancer types (colorectal, prostate, and endometrial) have been studied in relation to the effects of nut intake in epidemiologic studies in the past 2 decades. Hence, there are no data to draw conclusions about nut effects on other tumor sites. In addition, some of the analyses did not separate the effects of nuts from seeds or legumes. The bioactive ingredients responsible for the postulated anticarcinogenic effects of nuts remain to be further defined because some of the health-conferring phytonutrients found in nuts are also present in fruit, vegetables, and legumes. Finally, more epidemiologic studies are required to clarify the possible effects of nuts on different types of cancer.

OTHER HEALTH OUTCOMES: GALLSTONE DISEASE

Because nuts are rich in unsaturated fat and fiber, the protective effects against the development of gallstones are plausible. Two separate reports by the same investigators, on 2 different populations, provide some insight into the relation of frequent nut intake and risk of gallstone formation. After following 80,718 women for 20 y (1980–2000), data from the Nurses' Health Study (32) showed that frequent nut consumers (≥ 5 times/wk) had a 25% reduced risk of needing cholecystectomy (RR: 0.75; $P < 0.0001$). Similar findings were also observed among $\approx 43,000$ men in the Health Professionals Follow-up Study (33). During 457,305 person-years of follow-up, men who consumed ≥ 5 servings/wk of nuts (the frequent nut consumers) showed a risk of developing gallstone disease that was 30% lower than for

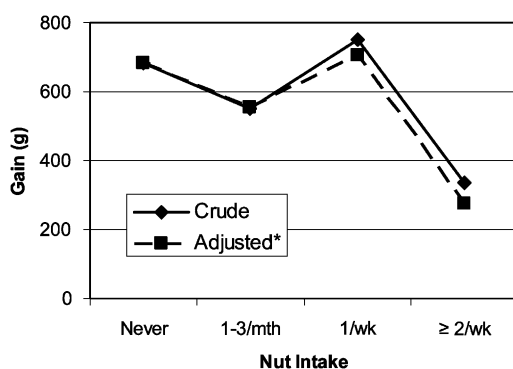


FIGURE 2. Estimated weight gain in 2 y according to frequency of nut intake (50 g serving) in the Seguimiento Universidad de Navarra (SUN) Study. *Adjusted for age, sex, BMI, physical activity, smoking status, snacking, and watching television. Crude odds ratio P for trend, 0.068; adjusted OR P for trend, 0.026. Adapted from Bes-Rastrollo et al (21).

TABLE 2Cohort and case-control studies on nuts and cancer in the past 6 y: information on tumor sites, foods evaluated, and results¹

Study	Country	Study type	Tumor sites	Foods evaluated	Results
Jenab et al, 2004 (29)	10 European countries	European cohort	Colorectal	Nuts and seeds	OR: 0.69; 95% CI: 0.50, 0.95; significant only in colon cancer and in women; no association in men
Yeh et al, 2006 (30)	Taiwan	Chinese cohort	Colorectal	Peanut products	≥2 Times/wk: (OR: 0.42; 95% CI: 0.21, 0.84); significant only in women; no association in men
Petridou et al, 2002 (31)	Greece	Case-control (women only)	Endometrial	Nuts, seeds, and legumes	OR: 0.64; 95% CI: 0.47, 0.86

¹ OR, odds ratio.

those who did not eat nuts at all (RR: 0.70; 95% CI: 0.60, 0.86; $P < 0.001$). Thus, it appears that the frequency of nut consumption is equally protective of gallstone disease in both sexes.

NUTS IN DIETARY SCORES AND PATTERNS

An increasing body of literature in recent years has related dietary patterns rather than individual nutrients to health outcomes. Certain dietary patterns are associated with positive health outcomes more so than others. Nuts are commonly found in those dietary patterns linked with health benefits. Nuts are now recognized by nutritionists not just as a food item with many

different bioactive constituents but also as a food item that can make an important contribution to a healthy dietary pattern. As such, a number of recent nutrition epidemiologic studies included nuts in the dietary scores or as a component of a dietary pattern (34–40). Relating these nut-containing dietary scores or patterns to health outcomes provides an opportunity to indirectly assess the health effects of nuts.

Several health outcomes from 6 studies that included nuts as a component of a dietary score or pattern are summarized in **Table 3**. Three observational studies featured nuts as a prominent food group in a Mediterranean diet (34–36). Overall, those 3 studies in 2 continents, Europe and North America, presented

TABLE 3Summary of studies in the past 6 y in which nuts were included as a component of dietary scores or pattern¹

Study	Country	Population	Study type	Scores or pattern	Health outcome	Results
Mitrou et al, 2007 (34)	United States	Elderly men ($n = 214,284$) and women ($n = 166,012$), aged 50–71 y	Prospective 10-y follow-up	Nuts along with vegetables, fruit, legumes, grains, and fish were considered as healthy components in the Mediterranean diet.	All-cause mortality	Conformity with Mediterranean dietary pattern associated with decreased mortality.
Schroder et al, 2004 (35)	Spain	Spanish men ($n = 1547$) and women ($n = 1615$), aged 25–74 y	Cross-sectional	Nuts were given same weight as cereals, vegetables, fruit, legumes, and fish in Mediterranean diet.	BMI	Increased adherence to Mediterranean dietary pattern associated with decreased prevalence of obesity.
Salas-Salvado et al, 2008 (36)	Spain	Elderly men ($n = 339$) and women ($n = 433$), aged 55–80 y	Cross-sectional analysis of a 3-mo clinical trial	Nuts were part of a component in the beneficial food group of the Mediterranean diet.	Inflammation markers	Conformity with Mediterranean dietary pattern associated with decreased concentration of ICAM-1.
Estruch et al, 2006 (37)	Spain	Elderly men ($n = 339$) and women ($n = 433$), aged 55–80 y	3-mo clinical trial	Nuts were part of enriched Mediterranean diet.	Cardiovascular risk factors	Conformity with nut-enriched Mediterranean dietary pattern associated with decreased blood glucose, systolic blood pressure, and total-to-HDL-cholesterol ratio.
Nettleton et al, 2006 (39)	United States	5089 Men and women, aged 45–84y; multiethnic groups: whites, blacks, Hispanics, and Asians	Cross-sectional	Nuts were grouped in the dietary pattern that included whole grains, fruit, green leafy vegetables.	Inflammation markers	Consumption of dietary pattern that included nuts inversely associated with CRP, IL-6, homocysteine, and ICAM-1.
Steffen et al, 2005 (40)	United States	Young adults: black and white men and women ($n = 4304$), aged 18–30 y	Prospective 15-y follow-up	Nuts were grouped as part of plant-food group that included fruit, vegetables, legumes, and whole and refined grain.	Blood pressure	Consumption of plant foods inversely associated with incidence of blood pressure in black and white men and women.

¹ ICAM-1, intercellular adhesion molecule 1; CRP, C-reactive protein; IL-6, interleukin-6.

consistent evidence that the closer the diet conforms to the Mediterranean pattern in which nuts are a key food item, the better are the ensuing health outcomes.

The US study included a large cohort of 380,000 men and women and offered a longitudinal perspective of a nut-rich diet on all-cause mortality: among those elderly men and women who consumed a nut-rich, Mediterranean-style diet, a reduced risk of all-cause mortality was observed over a 10-y follow-up period (34). The other 2 studies supported the evidence of health benefits of nut consumption from a cross-sectional perspective (35, 36). In a study of 3000 Spanish men and women, those who showed good adherence to the Mediterranean diet experienced a lower prevalence of obesity (35). A study in Spain (36), a cross-sectional analysis of the PREDIMED (PREvención con DIeta MEDiterránea) nutrition intervention trial, found that among the 772 elderly men and women enrolled in the study, those with the highest consumption of nuts and virgin olive oil had the lowest concentration of selected inflammatory markers. Even when nuts were analyzed independently, the inverse association of frequency of nut intake and one inflammatory marker (ie, intercellular adhesion molecule-1) persisted. In the same PREDIMED trial, in a separate published report of the same study population, more cardiovascular benefits of nut consumption were observed (37). The subgroup of individuals on a Mediterranean diet supplemented with mixed nuts, as opposed to those on a low-fat diet, experienced significant reductions in blood pressure, plasma glucose concentrations, insulin resistance, the total cholesterol-to-HDL cholesterol ratio, triglycerides, and several inflammatory biomarkers over a 3-mo dietary intervention (37). A recent report of the PREDIMED study with intervention for 1 y in 1224 participants showed that participants assigned a Mediterranean diet supplemented with nuts experienced a 14% reduction in prevalence of the metabolic syndrome, compared with a 2% reduction in the group assigned a low-fat diet (38). Of note, the beneficial effect of the nut diet on metabolic syndrome status was mainly due to increased rates of reversal of central obesity despite the lack of weight changes (38).

Dietary patterns other than the Mediterranean diet have also been examined. A whole-grain and fruit diet pattern in which nuts were a part was associated with a reduced CHD risk through its favorable effects on selected biomarkers (39). This cross-sectional study examined 4 dietary patterns in a multiethnic group in North America, and the dietary pattern that exerted a reduction in several inflammatory biomarkers, endothelial function, and homocysteine was one that included nuts.

Finally, one cohort study provided further evidence of a long-term health effects of a plant food group pattern that includes nuts. Approximately 4300 young men and women aged between 18 and 30 y showed improved blood pressure over a 15-y period with increased consumption of a plant food group in which nuts were a major component (40). The long-term protective benefits were evident in both white and black cohorts in that study. In summary, dietary patterns that include nuts have been consistently associated with beneficial health outcomes in cross-sectional or longitudinal studies.

CONCLUSIONS

Epidemiologic evidence is compelling for the protective effects of nuts on risk of CHD. Nuts improve serum lipids and

perhaps other indexes of CHD risk. Nuts probably lower the risk of diabetes in women, but the effect remains unknown in men. Although nuts are high in fat, the fear about nut consumption leading to weight gain may be assuaged because epidemiologic and clinical evidence so far showed that frequent nut consumption is not related to obesity. The association between nut consumption and cancer risk is not adequately studied. Nuts are commonly included in dietary scores or patterns associated with positive health outcomes. More longitudinal population-based studies are needed to clarify the possible effects of nuts on diseases other than CHD. (Other articles in this supplement to the Journal include references 11 and 41–67.)

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