

Dose Response of Almonds on Coronary Heart Disease Risk Factors: Blood Lipids, Oxidized Low-Density Lipoproteins, Lipoprotein(a), Homocysteine, and Pulmonary Nitric Oxide

A Randomized, Controlled, Crossover Trial

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Background—Although recent studies have indicated that nut consumption may improve levels of blood lipids, nuts are not generally recommended as snacks for hyperlipidemic subjects because of their high fat content. Furthermore, the effective dose is still unknown.

Methods and Results—The dose-response effects of whole almonds, taken as snacks, were compared with low-saturated fat (<5% energy) whole-wheat muffins (control) in the therapeutic diets of hyperlipidemic subjects. In a randomized crossover study, 27 hyperlipidemic men and women consumed 3 isoenergetic (mean 423 kcal/d) supplements each for 1 month. Supplements provided 22.2% of energy and consisted of full-dose almonds (73±3 g/d), half-dose almonds plus half-dose muffins, and full-dose muffins. Fasting blood, expired air, blood pressure, and body weight measurements were obtained at weeks 0, 2, and 4. Mean body weights differed <300 g between treatments. The full-dose almonds produced the greatest reduction in levels of blood lipids. Significant reductions from baseline were seen on both half- and full-dose almonds for LDL cholesterol (4.4±1.7%, $P=0.018$, and 9.4±1.9%, $P<0.001$, respectively) and LDL:HDL cholesterol (7.8±2.2%, $P=0.001$, and 12.0±2.1%, $P<0.001$, respectively) and on full-dose almonds alone for lipoprotein(a) (7.8±3.5%, $P=0.034$) and oxidized LDL concentrations (14.0±3.8%, $P<0.001$), with no significant reductions on the control diet. No difference was seen in pulmonary nitric oxide between treatments.

Conclusions—Almonds used as snacks in the diets of hyperlipidemic subjects significantly reduce coronary heart disease risk factors, probably in part because of the nonfat (protein and fiber) and monounsaturated fatty acid components of the nut. (*Circulation*. 2002;106:1327-1332.)

Key Words: hypercholesterolemia ■ lipids ■ lipoproteins ■ diet ■ antioxidants

Studies over the last decade have demonstrated favorable effects of nuts in modifying lipid risk factors for coronary heart disease (CHD).¹⁻¹¹ However, their use is not yet part of standard advice for patients with hyperlipidemia,^{12,13} despite recognized health benefits for the general population.¹³ There is also concern that high-fat foods may cause weight gain.^{13,14} Furthermore, there are no dose-response data on nuts, and their advantage in a low-saturated fat therapeutic diet is uncertain. Nevertheless, almond consumption fits well with current American Heart Association guidelines¹³ to replace saturated fats with unsaturated fats and with the National Cholesterol Education Program (NCEP) guidelines to liber-

alize total fat intake, specifically from monounsaturated fat (MUFA),¹² related to its ability to increase HDL cholesterol.¹⁵ Although replacing dietary carbohydrate with MUFA does not result in large changes in serum LDL cholesterol, the addition of MUFA to the diet as almonds reduces the LDL:HDL cholesterol ratio.² Further benefits of almonds may result from their high polyunsaturated:saturated fatty acid (PUFA:SFA) ratio, nut protein, plant sterols, fiber, and associated phenolic substances.^{14,16} We therefore assessed the effects of whole unblanched almonds at 2 doses on the blood lipids of hyperlipidemic subjects when provided as supplements to their self-selected therapeutic diets.

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Methods

Study Protocol

Three 1-month diet phases taken in a randomized crossover design, with each phase separated by a minimum 2-week washout period, were completed by 27 subjects. The 3 phases consisted of a muffin phase (control) and 2 almond phases, 1 full-dose almond and the other half-dose almond plus half-dose muffin. During all study phases, subjects followed their own self-selected low-fat therapeutic diets to which they included the supplement. Subjects were counseled on strategies to facilitate weight maintenance.

After overnight fasts (12 to 14 hours), body weight, blood samples, and blood pressure measurements were obtained at the start and at weeks 2 and 4 of each 4-week diet phase. Expired air was also collected through a modified Haldane-Priestley tube for nitric oxide (NO) measurement at weeks 0 and 4 of each phase. Seven-day weighed diet records were obtained before and at week 4 of each phase. All subjects were instructed to weigh all foods consumed with the self-taring electronic food scales provided during the weeks when diets were recorded. After the study, subjects assessed palatability of the supplements on a semantic scale of zero to 10 (0, very distasteful; 5, neutral; and 10, very appetizing).

The Ethics Committee of the University of Toronto and St Michael's Hospital approved the study. All subjects gave informed consent.

Subjects

Healthy hyperlipidemic men and postmenopausal women were recruited by newspaper advertisement and from patients attending the Risk Factor Modification Center, St Michael's Hospital. Of the 43 subjects who started the study, 16 withdrew during or after completion of 1 to 2 study phases. Three quit for reasons directly related to the study (food allergies, $n=2$; abdominal discomfort, $n=1$). The majority ($n=13$) withdrew for unrelated reasons. Twenty-seven subjects completed all 3 phases: 15 men and 12 postmenopausal women; mean \pm SD age 64 \pm 9 years (range 48 to 86 years; 4 subjects \geq 75 years, healthy and interested in the study); body mass index 25.7 \pm 3.0 kg/m² (range 20.5 to 31.5 kg/m²); baseline LDL cholesterol 4.32 \pm 0.63 mmol/L (range 2.77 to 5.32 mmol/L). All subjects had elevated LDL cholesterol levels on initial assessment at recruitment (>4.1 mmol/L) and triglyceride concentrations <4.0 mmol/L. None had clinical or biochemical evidence of diabetes, liver, or renal disease. Three men and 5 women were taking the following medications: a hypolipidemic agent (statin; $n=2$), β -blocking agents ($n=3$), ACE inhibitors ($n=3$), angiotensin II ATI receptor blockers ($n=1$), thiazide diuretics ($n=2$), levothyroxine ($n=2$), and hormone replacement therapy ($n=2$). Medication dosages were held constant throughout the study. Subjects were asked to maintain their habitual level of physical activity throughout the study.

Diets

At recruitment, 14 subjects were following therapeutic NCEP Step 2 diets ($<7\%$ energy from saturated fat and <200 mg/d dietary cholesterol). Those who were not were given appropriate instruction at least 1 month before commencing the study. All subjects took all 3 supplements: whole raw unblanched almonds (73 \pm 3 g/d), muffins (147 \pm 6 g/d), and half portions of almonds (37 \pm 2 g/d) plus muffins (75 \pm 3 g/d). The level of supplement intake was based on subjects' estimated daily energy requirement.¹⁷ For individuals requiring <1600 kcal/d, the full portions of almonds and muffins were 50 g (1 package) and 100 g (2 muffins), respectively (287 kcal/d supplement). The respective figures for the 1600 to 2400 kcal/d energy requirement were 75 g of almonds and 150 g of muffins (3 muffins; 430 kcal/d supplement) and for the >2400 kcal/d energy requirement, 100 g of almonds and 200 g of muffins (4 muffins; 574 kcal/d supplement). On the half-almond plus half-muffin phase, subjects consumed each supplement at half the full amount. The muffins were made from whole-wheat flour with corn oil sufficient to provide the same amount of SFA, PUFA, and fiber as the almonds and skim milk powder and egg white to provide a similar level of protein, although

the muffin protein was 46% of animal origin. This balance allowed comparison of the effects of MUFA from almonds with starch from muffins, although the effect would be modified by the different nature of the other components of nuts (eg, vegetable protein and fiber).

The macronutrient composition of the muffins as a percentage of energy was 14.7% protein, 53.3% available carbohydrate, 32.1% fat, 4.3% SFA, 7.6% MUFA, and 18.9% PUFA with 18 g/1000 kcal dietary fiber and 6 mg/1000 kcal cholesterol. Muffin supplements, provided at biweekly intervals, were stored in the freezer until the day before use. Subjects were instructed on reducing total food intake, especially starchy foods (breads, bagels, nonstudy muffins, and breakfast cereals) to allow supplements to be taken as snacks without increasing total energy intake. The background diet was kept constant across all 3 phases to allow direct comparison between the supplements. To minimize changes in body weight and diet composition, detailed dietary counseling was undertaken before and at weeks 1 and 2 of each phase. During the study, subjects were asked not to consume any additional nuts or nut products or alter consumption of dietary fiber or vegetable protein foods. Compliance was assessed from 7-day diet records, a supplement checklist on which subjects recorded supplements consumed, and return of uneaten supplements, which were weighed and recorded.

Analyses

Serum was analyzed according to the Lipid Research Clinics protocol¹⁸ for total cholesterol, triglyceride, and HDL cholesterol after dextran sulfate-magnesium chloride precipitation. All samples from a given individual were analyzed in the same batch. LDL cholesterol was calculated.³ Serum apolipoprotein A-I and B were measured by nephelometry,³ lipoprotein(a) [Lp(a)] by a commercial ELISA (Macra Lp(a) Kit, Trinity Biotech USA), and C-reactive protein by end-point nephelometry (Behring BN-100, N high-sensitivity C-reactive protein reagent, Dade-Behring). Plasma total L-homocysteine was analyzed with a fluorescence polarization immunoassay (IMx homocysteine assay, Axis-Shield).

Exhaled NO samples were collected by an offline method¹⁹ with fixed-flow expired air (6 L/min), stored at -20°C in plastic syringes with 3-way valves, and measured by a rapid-response chemiluminescent NO analyzer (Sievers, model 280). Oxidized LDL was measured as conjugated dienes in the LDL fraction after isolation of LDL particles by precipitation with buffered heparin at their isoelectric point.²⁰ The results were expressed as total serum conjugated dienes (oxidized lipids) in the LDL fraction.

Study supplements were analyzed by Association of Official Analytical Chemists methods for fat, protein, and fiber, with available carbohydrate calculated by difference.³ Fatty acid composition was determined by gas chromatography. Dietary macronutrient

TABLE 1. Calculated Macronutrient Intakes on the Control, Half-Almond, and Full-Almond Treatment Periods

	Control	Half-Almond Dose	Full-Almond Dose
Energy, kcal/d	1900 \pm 89	1951 \pm 94	2034 \pm 98
Total protein, %	17.5 \pm 0.5	17.6 \pm 0.5	17.4 \pm 0.4
Vegetable protein	7.2 \pm 0.3	7.8 \pm 0.3	8.7 \pm 0.3
Available carbohydrate, %	54.5 \pm 1.1	48.4 \pm 1.1	44.8 \pm 1.2
Total dietary fiber, g/1000 kcal	16.3 \pm 1.1	16.5 \pm 0.9	16.4 \pm 0.9
Total fat, %	26.3 \pm 1.0	32.1 \pm 1.0	36.0 \pm 1.0
SFA	7.0 \pm 0.4	7.5 \pm 0.4	7.2 \pm 0.4
MUFA	9.0 \pm 0.5	14.5 \pm 0.5	18.9 \pm 0.6
PUFA	8.0 \pm 0.3	8.0 \pm 0.3	8.2 \pm 0.2
Dietary cholesterol, mg/1000 kcal	89.7 \pm 7.3	96.8 \pm 6.2	79.3 \pm 5.3
Alcohol, %	1.8 \pm 0.5	1.9 \pm 0.5	1.8 \pm 0.6

$n=27$. Values are mean \pm SEM.

TABLE 2. Body Weight, Blood Lipid, and Blood Pressure Data on the Control, Half-Dose, and Full-Dose Almond Diet Periods

	Control		Half-Dose Almond		Full-Dose Almond	
	Week 0	Treatment*	Week 0	Treatment*	Week 0	Treatment*
Body weight, kg†	71.0±2.4	71.2±2.5	71.1±2.4	70.9±2.4‡	71.2±2.5	71.0±2.5
Cholesterol, mmol/L						
Total	6.54±0.16	6.44±0.15	6.47±0.15	6.25±0.15§	6.60±0.16	6.21±0.15‡
LDL	4.34±0.14	4.22±0.13	4.30±0.12	4.10±0.12	4.45±0.13	4.01±0.12‡
HDL	1.43±0.09	1.41±0.08	1.38±0.08	1.43±0.08	1.40±0.08	1.45±0.09§
Triglycerides, mmol/L	1.69±0.13	1.80±0.12	1.75±0.16	1.58±0.11	1.66±0.13	1.64±0.11
Apolipoproteins, g/L						
ApoA-1	1.74±0.07	1.73±0.06	1.71±0.06	1.73±0.06	1.74±0.06	1.76±0.07
ApoB	1.30±0.03	1.27±0.03	1.27±0.03	1.23±0.03	1.31±0.03	1.21±0.03‡
Ratios						
Total:HDL cholesterol	4.95±0.28	4.89±0.24	5.07±0.28	4.68±0.24§	5.00±0.22	4.58±0.23
LDL:HDL cholesterol	3.32±0.22	3.23±0.18	3.40±0.22	3.11±0.20	3.40±0.18	2.99±0.19
ApoB:ApoA-1	0.78±0.04	0.76±0.03	0.77±0.04	0.74±0.04	0.77±0.03	0.71±0.03
Oxidized LDL†						
LDL conjugated dienes, μmol	64±3	60±2	65±3	53±3‡	62±3	51±2‡
LDL conjugated dienes/LDL, μmol/mmol	14.8±0.6	14.3±0.5	15.3±0.8	13.4±0.6	14.1±0.6	12.9±0.5§
Homocysteine, μmol/L†	8.9±0.5	8.6±0.4	8.9±0.5	8.7±0.5	8.4±0.4	8.7±0.5
Lp(a), mg/dL	15.3±3.0	15.5±3.2	15.4±3.3	15.4±3.2	16.3±3.4	14.2±2.9§
C-reactive protein, mg/L†	3.21±1.39	2.37±0.45	1.81±0.27	1.77±0.27	1.62±0.25	2.27±0.69
Pulmonary nitric oxide, ppm†	25.4±3.2	18.2±1.3	15.3±1.8	19.2±1.8	22.3±2.8	17.4±1.4
Blood pressure, mm Hg						
Systolic	119±3	121±2	121±3	121±2	120±2	121±3
Diastolic	75±2	76±2	75±2	76±2	75±2	76±2
Estimated CHD risk, 10 y, %¶	10.7±1.2	11.0±1.1	11.2±1.1	10.4±4.1	11.1±1.1	10.1±1.1§

Values are mean±SEM. n=27.

To convert cholesterol and triglycerides and mg/dL, multiply by 38.67 and 88.57, respectively. To convert apolipoprotein A-I and B values to mg/dL, multiply by 100.

Treatment values represent the mean of: *Weeks 2 and 4 or †Week 4 alone.

‡P≤0.01; §P<0.050; or ||P≤0.001, significance of the difference of half- and full-almond dose vs control treatment using the least squares method with Tukey adjustment in SAS. No significant differences were seen between the half- and full-dose almonds.

¶CHD risk was estimated using the Framingham cardiovascular risk equation (21).

intakes (Table 1) were assessed on the 7-day diet records with a computer program based on US Department of Agriculture data. The percentage figures for soluble and insoluble fiber were derived from published data.³

Statistical Analysis

Results are expressed as mean±SEM. The response variable was the mean of the week 2 and 4 values for each dietary treatment. Absolute differences between treatments were assessed by the method of least squares means within the mixed model procedure (PROC MIXED/SAS) with a Tukey adjustment for multiple means comparisons. The statistical model included diet, the interaction term of diet by sex and sequence, a random term that represented the individual (nested within sex by sequence), and baseline as a covariate. To test for the overall effect of the diet-sex interaction, ANCOVA (PROC GLM/SAS) was used with the same model specification. Student's *t* test for paired data (2-tailed) was used to assess the significance of percentage changes across diets. CHD risk was calculated with the total: HDL cholesterol ratio and systolic blood pressure in the Framingham cardiovascular disease risk assessment equation.²¹ SAS software was used throughout (SAS/STAT version 8, 1997; SAS Institute).

Results

Compliance was good. Percentages of the prescribed supplements consumed during the 3 phases were as follows: control muffins, 98.1±0.8%; half-dose almonds plus half-dose muffins, 99.5±0.6%; and full-dose almonds, 97.8±0.7%, with no significant differences between treatments. The full-dose almonds were perceived as more palatable than the control muffin (control 6.5±0.4 on a scale of 0 to 10; almond 8.4±0.3 on a scale of 0 to 10; P<0.001). There was virtually no effect of any of the supplements on body weight change across the treatment periods (muffins, 0.1±0.1 kg; half-dose almonds, -0.3±0.2 kg; and full-dose almonds, -0.2±0.1 kg; Table 2).

Baseline blood lipid values did not differ among the 3 treatments (Table 2). On the muffin control diet, the only significant change from baseline was the increase in triglycerides (10.8±4.7%, P=0.031). Almonds tended to reduce blood lipids in a dose-dependent manner (Figure 1). Compared with baseline values, half- and full-dose almond sup-

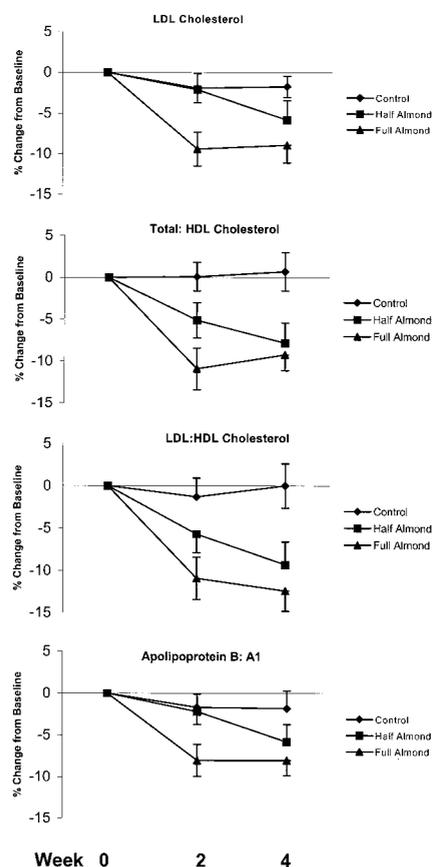


Figure 1. Change from baseline at weeks 2 and 4 in blood lipids and their ratios on control, half-dose almonds, and full-dose almonds. Values are mean \pm SEM.

plements, respectively, significantly reduced total cholesterol ($3.1 \pm 1.5\%$, $P=0.043$; $5.6 \pm 1.4\%$, $P<0.001$), LDL cholesterol ($4.4 \pm 1.7\%$, $P=0.018$; $9.4 \pm 1.9\%$, $P<0.001$), apolipoprotein B ($3.0 \pm 1.5\%$, $P=0.057$; $7.3 \pm 1.6\%$, $P<0.001$), total:HDL cholesterol ($6.6 \pm 2.1\%$, $P=0.004$; $8.4 \pm 1.7\%$, $P<0.001$), LDL:HDL cholesterol ($7.8 \pm 2.2\%$, $P=0.001$; $12.0 \pm 2.1\%$, $P<0.001$), and apolipoprotein B:A-I ($4.3 \pm 1.6\%$, $P=0.01$; $8.2 \pm 1.7\%$, $P<0.001$), with increases in HDL cholesterol ($4.6 \pm 2.0\%$, $P=0.034$; $3.8 \pm 1.8\%$, $P=0.047$). There was also a significant reduction in Lp(a) on the full-dose almond supplement ($7.8 \pm 3.5\%$, $P=0.034$).

No significant differences were seen between week 2 and 4 blood lipid values (Figure 1). Comparison of the absolute treatment values for full-dose almonds with the respective

control values (Table 2) confirmed the significantly lower blood lipid concentrations for total cholesterol ($P=0.006$), LDL cholesterol ($P=0.002$), and apolipoprotein B ($P=0.002$); the ratios of total:HDL cholesterol ($P<0.001$), LDL:HDL cholesterol ($P<0.001$), and apolipoprotein B:A-1 ($P<0.001$); and higher HDL cholesterol levels ($P=0.041$; Figure 2). Lp(a) values were lower on the full-dose almond phase than for control ($P=0.026$). The 2 subjects taking statins responded similarly to the rest of the group, and the reduction in lipoprotein ratios in the 4 subjects aged ≥ 75 years was similar to that for the younger subjects.

Conjugated dienes in the LDL fraction as a marker of LDL oxidation were also significantly reduced on almonds compared with baseline values (control, $3.1 \pm 4.2\%$, $P=0.466$; half-dose almonds, $15.0 \pm 4.0\%$, $P<0.001$; full-dose almonds, $14.0 \pm 3.8\%$, $P<0.001$). The difference between almond and control treatments was confirmed with absolute values (half-dose almonds, $P=0.007$; full-dose almonds, $P=0.001$). No treatment differences were seen in homocysteine, C-reactive protein, blood pressure, or pulmonary NO (Table 2). Calculated CHD risk for the full dose of almonds was significantly reduced compared with baseline ($9.2 \pm 3.5\%$, $P=0.015$) and compared with the control value ($P=0.029$; Table 2).

Discussion

Consumption of 73 g of almonds daily as a supplement in the diets of hyperlipidemic subjects reduced LDL cholesterol from baseline by 9.4%, whereas 37 g/d almonds (a "hand full") reduced LDL cholesterol by 4.4%. These data suggest a dose response in which ≈ 7 g of almonds per day reduces LDL cholesterol by $\approx 1\%$, which translates into a 2% risk reduction for CHD.²² The full-dose of almonds was also associated with a significant reduction in calculated CHD risk based on the total:HDL cholesterol and blood pressure data.²¹ The Adventist²³ and Nurses' Health Study²⁴ data have demonstrated that nut consumption is associated with reduced CHD risk. The nut consumption in those studies (<20 g/d) was below the half dose of almonds in the present study.

Our findings are in line with previous studies of almonds and other types of nuts. For almonds, reductions of 15% have been noted in LDL cholesterol per 100 g/d (1% reduction for 7 g/d),² 12% for 100 g/d (1% reduction for 8 g/d),²⁵ and 10% for 84 g/d (1% reduction for 8 g/d).²⁶ One-percent reductions in LDL cholesterol for walnuts, pecans, peanuts (an oil seed legume), macadamias, and pistachios would be achieved with daily intakes of 4, 11, 4, 10, and 4 g, respectively.^{1,4-11}

In the present study, the main macronutrient difference between the almond and muffin diets was the higher MUFA and lower carbohydrate intake with almonds. The SFA and PUFA contents of the almonds and muffins were the same. In general, exchanging carbohydrate for MUFA does not appear to result in large changes in LDL cholesterol levels.^{15,27,28} The meta-analysis by Mensink and Katan²⁹ indicated a coefficient for LDL cholesterol reduction by MUFA that was less than half that for PUFA. Application of the equation²⁹ to the present data indicated that the MUFA exchange for carbohydrate accounted for 29% of the reduction in LDL cholesterol seen with almonds. The difference in LDL cholesterol between the control and full-dose almonds remained significant

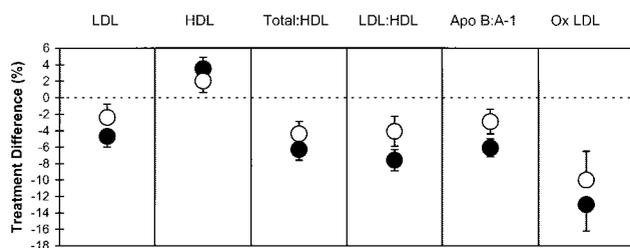


Figure 2. Percentage treatment difference from control in LDL, HDL, total and LDL:HDL cholesterol, apolipoprotein B:A1, and oxidized LDL on full-dose (●) and half-dose (○) almonds. Values are mean \pm SEM.

after adjustment for MUFA ($P=0.011$). MUFA has, however, been associated with higher HDL cholesterol concentrations,^{15,30} reflected in lower total:HDL cholesterol and LDL:HDL cholesterol ratios, as potentially important predictors of cardiovascular risk.²¹ Higher SFA intakes in exchange for carbohydrate in the DELTA (Dietary Effects on Lipoproteins and Thrombogenic Activity) study were associated with a lower Lp(a) level,³¹ an effect associated in the present study with higher MUFA intakes. This lipid risk factor for CHD is not altered by most dietary and pharmacological treatments, and the effect of almonds is therefore notable.

Another study with almonds also assessed the dose response in metabolically controlled conditions. In that study, 10% and 20% of energy of a background NCEP Step 1 diet was isoenergetically replaced with almonds for 4 weeks. A 1% reduction in LDL cholesterol was noted for every 10 g of almonds consumed (Joan Sabaté, MD, DrPH, unpublished data, 2002).

The present study addressed a somewhat different question of the effect of nuts plus their constituent monounsaturated fats in diets that were low in saturated fats. The data indicated an advantage of the higher-fat diet in the context of increased monounsaturated fat from nuts.

Almonds also reduced oxidized LDL. Similar reductions and other evidence of antioxidant activity, including lower urinary isoprostane outputs, have been reported after feeding soy and other vegetable protein diets.^{20,32} The proteins and other components of nuts may therefore share properties with legumes, especially soy, that contribute additionally to the cardioprotective effect of nuts.^{23,24} In addition, the full-dose almonds add 18 mg of the antioxidant vitamin E to the diet per day. Finally, an increased intake of monounsaturated fat in the diet has been associated with reduced susceptibility of LDL to oxidation.³³ There are therefore a number of components of almonds that may reduce LDL oxidation.

We conclude that almonds substituted for whole-wheat flour muffins of similar calories and SFA, PUFA, and protein content reduce lipid risk factors for CHD even in diets already low in saturated fat. The macronutrient profile of the muffins in the present study is likely to have reduced the contrast that would have been seen had nuts been compared with commercial muffins high in saturated and trans fatty acids. The dose response to almonds appears linear in the acceptable range of intake, with a 1% reduction in LDL cholesterol resulting from each 7-g portion of almonds. These data support epidemiological studies that suggest that nut consumption may reduce the risk of CHD and the suggestion that nuts should be considered for inclusion in lipid-lowering diets.¹³

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