Critical Review

A Systematic Review of the Effects of Nuts on Blood Lipid Profiles in Humans

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ABSTRACT The inverse association of nut consumption and risk markers of coronary heart disease (lipids) has sparked the interest of the scientific and lay community. The objective of this study was to conduct a systematic review to investigate the effects of nuts on the lipid profile. Medline and Web of Science databases were searched from the start of the database to August 2004 and supplemented by cross-checking reference lists of relevant publications. Human intervention trials with the objective of investigating independent effects of nuts on lipid concentrations were included. From the literature search, 415 publications were screened and 23 studies were included. These papers received a rating based upon the methodology as it appeared in the publication. No formal statistical analysis was performed due to the large differences in study designs of the dietary intervention trials. The results of 3 almond (50–100 g/d), 2 peanut (35–68 g/d), 1 pecan nut (72 g/d), and 4 walnut (40–84 g/d) studies showed decreases in total cholesterol between 2 and 16% and LDL cholesterol between 2 and 19% compared with subjects consuming control diets. Consumption of macadamia nuts (50–100 g/d) produced less convincing results. In conclusion, consumption of ~50–100 g (~1.5–3.5 servings) of nuts ≥5 times/wk as part of a heart-healthy diet with total fat content (high in mono- and/or polyunsaturated fatty acids) of ~35% of energy may significantly decrease total cholesterol and LDL cholesterol in normo- and hyperlipidemic individuals. J. Nutr. 135: 2082–2089, 2005.

KEY WORDS: • *lipids* • *lipoprotein* • *nuts* • *triacyglycerol*

It is undisputed that dietary habits affect coronary risk factors and hence the risk of a coronary event. In the search for bioactive components in foods that favorably affect cardiovascular disease (CVD)[2] risk, nuts have begun to attract attention (1).

Epidemiologic studies have consistently demonstrated an association between nut consumption and coronary heart disease (CHD) morbidity and mortality in different population groups (2). Compared with people who ate nuts <1 time/wk, those who ate them 1–4 times/wk had a 25% reduced risk of dying from CHD; people who ate nuts ≥5 times/wk experienced an ~50% reduction in risk (3). Nut consumption may not only offer protection against heart disease, but also increase longevity (4). Recently, the benefits of nuts were acknowledged by the U.S. FDA when they approved a qualified health claim that eating nuts (1.5 oz/d, ~42.8 g/d) may reduce the risk of CHD (5).

There is substantial evidence that nuts may have favorable effects on CHD through a variety of mechanisms. The most extensively studied mechanism involves the lipid-lowering effects. Nuts are good sources of unsaturated fatty acids [monounsaturated fatty acids (MUFA) and PUFA] (**Fig. 1**), known for their favorable effects on blood lipids. Furthermore, evidence suggests that components in nuts further reduce total cholesterol (TC) and LDL cholesterol (LDL-C) concentrations beyond the effects predicted by equations based solely on fatty acid profiles (6,7). In particular, the magnitude of the cholesterol-lowering effect was shown to be 25% greater than would be predicted based on the fatty acid profiles of the test diets studied (2). Therefore, the possible mechanisms whereby nuts may improve lipid profiles do not rely exclusively on the beneficial action of unsaturated fatty acids (PUFA and MUFA) but may include the effects of fiber, micronutrients such as vitamin E and C, folic acid, copper, magnesium, plant protein (e.g., arginine), plant sterols, and phenolic components (2).

The aim of this systematic review was to evaluate the scientific evidence that is related to the effects of nut consumption on lipid profiles.

SUBJECTS AND METHODS

Subjects

Dietary intervention studies with 186 healthy or diseased (216 hypercholesterolemic, 66 hyperlipidemic, 30 type 2 diabetic) or mixed (95) subjects (312 men and 281 women) were included in this systematic review.

Studies

Studies were included if the objective was to investigate the independent effect of nuts on lipid concentrations and the study was

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[2] Abbreviations used: AAD, average American diet; CHD, coronary heart disease; CHO, carbohydrate; CVD, cardiovascular disease; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MUFA, monounsaturated fatty acid; TC, total cholesterol; TF, total fat; TG, triacylglycerol.

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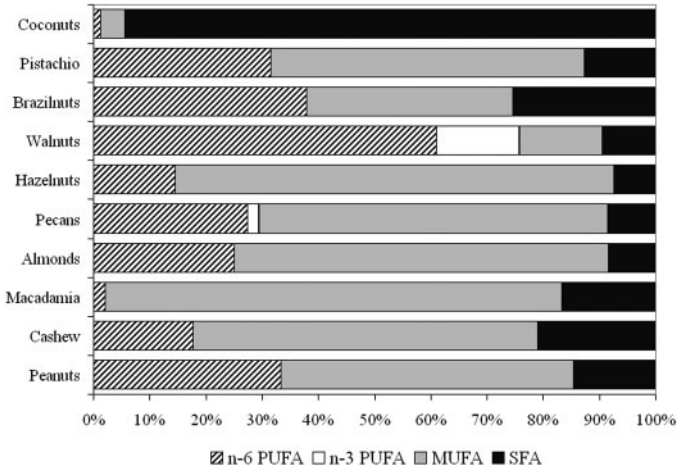

FIGURE 1 Fatty acid composition of nuts [based on data from (38)].

conducted among humans. Trials were excluded when these independent effects could not be assessed and studies had incomplete or missing data.

Outcome measures

The main outcome measures were percentage differences between treatment and control groups for blood TC, LDL-C, HDL cholesterol (HDL-C), and triacyglycerols (TG).

Data sources

Dietary intervention trials with the primary objective of determining the effects of nuts on lipid concentrations were identified through Medline (8) (since inception to August 2004) and Web of Science (9) (from 1994 to August 2004) research databases, supplemented by contact with authors of papers and reference lists of relevant publications. Search terms used included MeSH terms (Medline): Nuts [MeSH] AND ("Lipoproteins"[MeSH] OR "Cholesterol"[MeSH]) OR "Triacylglycerol"[MeSH]) and key words (Web of Science): (nuts OR walnut* OR almond* OR pecan* OR macadamia* OR hazelnut* OR peanut* OR pistachio*) AND (cholesterol OR triacylglycerol OR lipoprotein).

Study selection and data extraction

Two reviewers independently assessed studies to determine eligibility, executed data extraction by using a prepiloted standardized form, and determined the quality of all of the identified intervention studies. Differences in data extracted or quality score were adjudicated by a third reviewer and then finalized in discussion among the 3 authors.

Data synthesis

After careful scrutiny of selected studies, they received a rating based upon the methodology as it appeared in the publication. The following criteria for quality assessment of the dietary intervention trials were used (adapted from Verhagen et al.) (10): *1*) the study was controlled; *2*) randomization was performed; *3*) justified sample size (20 participants or <20 with power calculation for TC or LDL-C); *4*) good compliance; *5*) single-blind study; *6*) groups were similar at baseline for the most important prognostic indicators or differences in baseline characteristics were controlled for statistically; and *7*) no order of treatment effect (applicable to crossover trials)

The following quality scores were assigned: 1 = if all of the above criteria were present; 2 = if controlled and two criteria were missing; 3 = if not controlled or ≥3 criteria were missing. Furthermore, the letter *a* was assigned for controlled feeding trials and *b* for studies conducted under free-living conditions. In addition, the nut studies that received a 3 rating were not considered when conclusions were drawn. No formal statistical analysis was performed due to large differences in study designs of the dietary intervention trials.

RESULTS

Of the 415 articles screened (titles and abstracts, original research and review papers), 71 were considered in depth for inclusion. Of these, 48 were excluded due to incomplete or missing data and because the independent effects of nuts could not be assessed. Consequently, from this comprehensive literature search, 23 original research papers were identified that were suitable for inclusion in this systematic review. Of the 23 studies, 16 received a 1 or 2 rating. In **Table 1** (11–33) all the dietary intervention trials investigating the effects of nut consumption on lipid profiles are summarized. The experimental designs of these studies were variable; subject characteristics differed (normolipidemic, hypercholesterolemic, and diabetic), as did the degree of dietary control, the type and amount of fat (ranging from 20 to 45%), dose/mode of nuts consumed, duration of the studies, the control diets, and sample sizes. In this systematic review, most of the nut intervention diets were diets low in SFA, *trans* fatty acids, and dietary cholesterol and high in unsaturated fatty acids and dietary fiber (**Table 2**). Only studies with a 1 or 2 rating will be discussed. The majority of the studies were short (4–6 wk); only 1 study lasted 6 mo (21). Most of the studies (12 of 16) included >20 subjects/group. This is sufficient to detect clinically significant changes in TC and LDL-C. However, according to power calculations (80% power at a level of 5% significance) based on data from several studies (14–16,27,33), it was clear that not all of the studies had adequate power to detect clinically significant changes in HDL-C and TG. At least 109 participants/treatment group are required to detect an increase in HDL-C of 0.13 mmol/L, which might reduce the risk of CVD by 10% (34). For TG, at least 67 participants per treatment group are required to detect a decrease in TG of 0.31 mmol/L, which in turn may decrease the risk of CVD by 10% (35). For the latter effect, it is important to consider the large (12.9–40.8%) intraindividual variation (36,37) in TG concentrations.

In Table 1, 3 of 4 highly rated almond studies showed that a diet containing 50–100 g of almonds/d significantly decreased TC (between 4 and 16%) and LDL-C (between 7 and 19%) in hypercholesterolemic (13,14) and normocholesterolemic (16) subjects compared with subjects consuming a control diet (control, low-fat, and Step I diet). The intervention diets that provided <50 g of almonds/d did not affect LDL-C concentrations (14,16). The lipid profile did not improve in subjects consuming the almond intervention diet compared with the olive oil–based diet (13). In the study by Jenkins and investigators (14), in which hyperlipidemic subjects consumed 50–100 g of almonds/d, there was a significant 2% increase in HDL-C compared with those consuming a low-fat control diet (26 vs. 36% fat provided by the almond diet). Lovejoy and collaborators (15) showed that 57–113 g of almonds/d did not affect the lipid profile of diabetic subjects compared with high- and low-fat control groups. In that study, there was a significant decrease in HDL-C concentrations compared with the aforementioned control groups. In the 4 almond studies, TG concentrations were not affected in a comparison of consumption of the nut intervention diet with that of the respective control diet (13–16).

Two macadamia nut studies with higher quality scores are summarized in Table 1. Consumption of this nut diet signifi-

TABLE 1

Effects of nuts on the blood lipid profile in human dietary intervention trials[1]

Reference and subjects	Study design	Comparison made	Mean amount of nuts/d	Duration of intervention	% Total fat from		Nut diet end vs. control diet end[2]				Quality score of publication
					Nut diet	Control diet	TC	LDL-C	HDL-C	TG	
							%				
Almonds											
(11) n = 26: 13M, 13W (hypercholesterolemic)	Single intervention	Baseline diet	100 g/d	9 wk	36.9	28.5	−8.9 $P < 0.05$	−12.4 $P < 0.01$	NS	−4.4 NS	3*b*
(12) n = 16M (normolipidemic)	Sequential intervention periods	Control	84 g/d	3 wk	35.9	35.7	−7 $P < 0.01$	−10 $P < 0.001$	NS NS	+1.4	3*b*
(13) n = 45: 12M, 33W (hypercholesterolemic)	Randomized, controlled, parallel design	Control	100 g/d	4 wk	39	35	−15.6 $P < 0.001$	−19 $P < 0.001$	NS	NS	2*b*
		Olive oil-based diet	100 g/d	4 wk	39	35	−8.7 NS	−9.8 NS	NS	NS	
(14) n = 27: 15M (hyperlipidemic), 12 W (postmenopausal, hyperlipidemic)	Randomized, crossover design	Muffins-control	25–50 g/d (half almond dose)	4 wk	32.1	26.3	−2[3] $P < 0.05$	−1.9[3] NS	2.2[3] NS	−3.2[3] NS	2*b*
		Muffins-control	50–100 g/d (full almond dose)	4 wk	36	26.3	−4.4[3] $P \leq 0.01$	−7.1[3] $P \leq 0.01$	2.2[3] $P < 0.05$	−5.3[3] NS	
(15) (Study 2) n = 30: 13M, 17W (type 2 diabetes)	Randomized, double-blind, crossover design	High-fat control	57–113 g/d	4 wk	39	36.8	−1.3 NS	−2.7 NS	−3.4 $P = 0.002$	5.4 NS	1*a*
		Low-fat control	57–113 g/d	4 wk	27.2	26	NS	NS	−2.6 $P = 0.002$	5 NS	
(16) n = 25: 14M, 11W (healthy)	Randomized crossover design,	Step I diet	±27 g/d (10% of total energy, low almond diet)	4 wk	35	30	−0.9 NS	−1.1 NS	−0.9 NS	NS	2*a*
		Step I diet	±54 g/d (20% of total energy, high almond diet)	4 wk	39	30	−4.4 $P < 0.05$	−7 $P < 0.05$	1.7 NS	−3.3 NS	
Hazelnut											
(17) n = 30: 18M, 12W (healthy)	Single intervention	Baseline diet	1 g/kg BW/d	1 mo	NR	NR	−6.1 $P < 0.005$	−18.7 $P < 0.001$	7.2 $P < 0.05$	24.8 $P < 0.001$	3*b*
Macademia											
(18) n = 14: 7M, 7W (hypercholesterolemic)	Dietary advice, randomized, crossover design	Low-fat high-complex CHO diet	50–100 g/d (20% of total energy)	4 wk	42.4	21.3	0.2 NS	−0.3 NS	9.1 NS	−13.3 NS	2*b*
(19) n = 30: 15M, 15W (normo- and hyperlipidemic)	Randomized, controlled, crossover design	Step I diet	NR	4 wk	35	30	−0.8 NS	0.3 NS	2.2 NS	−16 NS	1*a*
		AAD	NR	4 wk	35	35	−4.8 $P < 0.01$	−4.5 $P < 0.05$	−4.2 $P < 0.01$	−9.2 $P < 0.05$	
(20) n = 17M (hypercholesterolemic)	Single intervention	Baseline diet	40–90 g/d (15% of total energy)	4 wk	37.6	31.2	−3.2 $P < 0.05$	−6 $P < 0.05$	6.7 $P < 0.05$	−2.8 NS	3*b*
Peanuts											
(21) n = 25W (hypercholesterolemic, postmenopausal)	Controlled parallel design	Low-fat diet	35–68 g/d	6 mo	26	17	−7.4[3] $P \leq 0.01$	−9.1[3] $P \leq 0.01$	−0.3[3] $P \leq 0.01$	−11[3] NS	2*b*
(22) n = 22: 9M, 13W (normocholesterolemic)	Randomized, double-blind controlled, crossover design	AAD	NR	24 d	36	34	−10.9 $P < 0.05$	−13.9 $P < 0.05$	−2.3 NS	−12.8 $P < 0.05$	1*a*
		Step II diet	NR	24 d	36	25	−2 $P < 0.05$	0.7 NS	1.61 NS	−21.6 $P < 0.05$	
		Olive oil-based diet	NR	24 d	36	34	0.6 NS	1.7 NS	−1.6 NS	0.9 NS	

TABLE 1 *(continued)*

Effects of nuts on the blood lipid profile in human dietary intervention trials[1]

Reference and subjects	Study design	Comparison made	Mean amount of nuts/d	Duration of intervention	% Total fat from		Nut diet end vs. control diet end[2]				Quality score of publication
					Nut diet	Control diet	TC	LDL-C	HDL-C	TG	
Pecans											
(23) n = 19: 4M, 15W (normolipidemic)	Randomized, controlled, parallel design	Control	68 g/d	8 wk	20	17	−10.7[3] $P < 0.05$	−16.3[3] $P < 0.05$	1.2[3] $P < 0.05$	−9.3[3] NS	3*b*
(24) n = 23: 14M, 9W (normal-high cholesterol)	Single-blind, randomized, controlled, crossover design	Step I diet	72 g/d	4 wk	39.6	28.3	−6.7 $P \leq 0.01$	−10.4 $P \leq 0.01$	5.6 $P \leq 0.01$	−11.1 $P \leq 0.01$	1*a*
Pistachio nuts											
(25) n = 10: 4M, 6W (hypercholesterolemic)	Controlled, randomized, crossover design	Habitual diet	20% of total energy	3 wk	39	37	−3.7 $P < 0.04$	−6.1 NS	8 $P < 0.09$	−5.3 NS	3*b*
Walnuts											
(26) n = 18M (healthy)	Randomized, controlled, single-blind, crossover design	Step I diet	84 g/d (20% of total energy)	4 wk	31.3	29.3	−12.4 $P < 0.001$	−16.3 $P < 0.001$	−4.9 $P = 0.009$	−8.3 NS	2*a*
(12) n = 16M (normolipidemic)	Consecutive supplemental periods	Control	68 g/d	3 wk	36.5	35.7	−5 $P < 0.01$	−9 $P < 0.001$	3.13 NS	4.3 NS	3*b*
(27) n = 21M (hyperlipidemic)	Randomized, crossover design	Low-fat diet	78 g/d	4 wk	38	30	−2 NS	−3.9 NS	2.5 NS	7.5 NS	2*b*
(28) n = 49; 26M, 23W (hypercholesterolemic)	Randomized, crossover design	Mediterranean diet	41–56 g/d (18% of total energy)	6 wk	33.2	31.2	−4.1 $P < 0.001$	−5.9 $P < 0.001$	3.2 NS	−6.1 NS	2*b*
(29) n = 18: 5M (hyperlipidemic), 13W (hyperlipidemic, postmenopausal)	Sequential intervention periods	Habitual diet (4 wk)	48 g/d	6 wk	37.2	31.4	−3 NS	−1.7 NS	−10.2 $P < 0.01$	−10.1 NS	3*b*
		Low-fat diet	48 g/d	6 wk	33.7	19.7	−7.7 $P < 0.01$	−12.3 $P < 0.01$	1.8 NS	−1.3 NS	
(30) n = 10M subset of the Zambon study (polygenic hypercholesterolemic)	Randomized, crossover design	Mediterranean diet	41–56 g/d	6 wk	31.8	30.9	−4.2 NS	−6 NS	0 NS	−5.1 NS	2*b*
(31) n = 42: 17M, 25W (borderline hypercholesterolemic)	Randomized, crossover design	Step I	64 g/d	6 wk	45	33	−3.3 NS	−3 NS	6.7 NS	−6.3 NS	2*b*
(32) n = 40; 20M, 20W (healthy)	Randomized crossover design	Japanese diet	44–58 g/d (12.5% of total energy)	4 wk	26	24	−4.5 $P = 0.001$	−9.8 $P = 0.001$	−1.3 NS	0 NS	1*a*
(33) n = 20: 8M, 12W (hypercholesterolemic)	Randomized, crossover design	Mediterranean diet	40–65 g/d (18% of total energy)	4 wk	33	33.2	−4.3 $P = 0.02$	−6.7 $P = 0.01$	−1.3 NS	8.3 NS	1*b*

[1] Abbreviations used: M, men; W, women; NR, not reported; NS, nonsignificant; Step I, American Heart Association/National Cholesterol Education Program Step I diet with 30% of energy from fat; Step II, American Heart Association/National Cholesterol Education Program Step II diet with 25% of energy from fat.

[2] In cases in which the percentage difference was not indicated, we used the formula: (End value nut diet − End value control diet)/End value control diet × 100. When baseline values were compared to nut intervention end values the formula was: (End value nut diet − Baseline value)/Baseline value × 100. In cases in which no values were given, the changes were not reported.

[3] In cases in which baseline values were different, change from baseline to end with the nut diet was compared with the change from baseline to end in the control diet.

cantly lowered TC (5%), LDL-C (5%), and TG (9%) concentrations compared with consumption of the average American diet (AAD) (19), but not compared with a low-fat high complex carbohydrate (CHO) (18) or Step I diet (19). The HDL-C concentration was not affected compared with those consuming a Step I diet or a low-fat high complex CHO diet (18,19). Compared with the AAD, consumption of the macadamia nut diet significantly decreased HDL-C concentrations (4%) (19).

In 2 studies of peanut consumption, there was a significant

TABLE 2

Nutrient composition of diets used in dietary intervention trials investigating the blood lipid-lowering potential of nuts[1,2]

Nut diet (reference)	TF	SFA	MUFA	PUFA	Chol	CHO	Fiber	Control diet	TF	SFA	MUFA	PUFA	Chol	CHO	Fiber
			%		mg/d	%	g/d				%		mg/d	%	g/d
Almonds															
(13)	39	5	28	7	72	47	25	Control	35	17	15	3	269	47	26
	39	5	28	7	72	47	25	Olive oil-based diet	35	6	27	3	119	48	29
(14)															
Half-dose	32	8	15	8	189	48	32	Muffins control	26	7	9	8	170	55	31
Full-dose	36	7	19	8	161	45	33	Muffins control	26	7	9	8	170	55	31
(15)															
High fat	39	7	23	11	226	46	31	High-fat control	37	7	21	9	270	49	17
Low fat	27	5	16	8	167	57	31	Low-fat control	26	5	15	7	257	60	17
(16)															
Low-dose	35	8	17	8	163	51	30	Step I	30	8	12	6	202	56	28
High-dose	39	8	19	9	140	46	32	Step I	30	8	12	6	202	56	28
Macademia															
(18)	42	11	27	4	189	39	31	Low-fat complex CHO	21	9	8	5	218	57	33
(19)	35	9	20	6	300	48	NR	Step I	30	9	15	7	297	54	NR
	35	9	20	6	300	48	NR	AAD	35	14	12	9	305	48	NR
Peanuts															
(21)	26	5	14	2	130	55	22	Low-fat diet	17	5	6	2	129	63	17
(22)	36	8	18	10	200	47	NR	AAD	34	16	11	7	400	50	NR
	36	8	18	10	200	47	NR	Step II	25	7	12	6	200	59	NR
	36	8	18	10	200	47	NR	Olive oil-based diet	34	7	21	6	200	50	NR
Pecans															
(24)	40	8	19	11	175	47	30	Step I	28	8	11	6	210	57	25
Walnuts															
(26)	31	6	7	17	125	54	37	Step I	29	9	9	10	237	56	36
(27)	38	10	10	16	230	40	30	Low-fat diet	30	12	10	5	320	46	30
(28)	33	6	14	12	166	48	9[3]	Mediterranean	31	7	18	5	221	50	8[3]
(30)	32	6	13	11	167	49	8[3]	Mediterranean	31	6	18	4	223	49	7[3]
(31)	45	13	NR	NR	213	41	NR	Step I	33	13	NR	NR	NR	50	NR
(32)	26	5	7	15	252	60	22	Japanese diet	24	7	10	7	279	62	20
(33)	33	5	14	12	147	49	8[3]	Mediterranean	33	6	20	4	183	49	8[3]

[1] Abbreviations: See Table 1.
[2] Only clinical trials that received a 1 or 2 rating were included in this table.
[3] Grams (g) of soluble fiber/d.

decrease in TC and LDL-C concentrations compared with consumption of a low-fat control diet (7%) (21) and with the AAD (11%) and Step II diet (2%; only for TC) (22), and there was a significant decrease in HDL-C concentrations compared with the low-fat diet (0.3%) (21). In the latter study (21), the modest reduction in HDL-C concentration was due to changes in the cholesterol content of the HDL_3 subfraction. The ratio of TC:HDL-C and LDL-C:HDL-C decreased by 0.05–0.11 in the peanut intervention group compared with the low-fat control group (21). The TG concentrations decreased in both studies but this was significant only compared with the AAD (13%) and Step II diet (22%) (22). The lipid profile did not differ when consumption of the peanut diet was compared with the olive oil diet (22).

A feeding trial conducted by Rajaram et al. (24) showed that intakes of 72 g of pecans/d by subjects with normal-to-high cholesterol concentrations decreased serum TC (7%), LDL-C (10%), TG (11%) and increased HDL-C (6%), beyond that seen in the Step I diet (Table 1).

Walnuts are unique compared with other nuts because they contain predominantly (n-6) (linoleic acid) and (n-3) (α-linolenic acid) PUFAs rather than the MUFAs that predominate in most other nuts (Fig. 1) (38). In 4 of 7 studies of walnut consumption (40–84 g/d), there was a significant decrease in TC (4–12%) and LDL-C (6–16%) compared with consumption of Step I (26), Mediterranean (28,33), and Japanese (32) diets. Three studies showed no significant change in the lipid profile of hyperlipidemic subjects who followed a walnut intervention diet (41–78 g/d) compared with low-fat (27), Mediterranean (30), and Step I diets (31). In 1 study of walnut consumption, the HDL-C concentrations decreased significantly compared with consumption of a Step I diet (26). Despite the aforementioned significant decrease in HDL-C (26), the mean ratio of LDL-C:HDL-C was 2.5 $\pm$ 0.6 during consumption of the reference diet and decreased to 2.2 $\pm$ 0.7 during the walnut diet ($P < 0.001$). The ratio of TC:HDL-C also decreased from 4.0 $\pm$ 1.0 during consumption of the reference diet to 3.7 $\pm$ 1.0 during the walnut diet ($P < 0.001$) (26). In most of the walnut studies HDL-C was not significantly affected, as seen in the other nut studies. In addition, TG was not significantly affected by consumption of the walnut diets compared with their respective control diets.

No conclusions can be drawn from the studies performed using hazel and pistachio nuts because of insufficient reporting of data.

DISCUSSION

A lipid-lowering (decrease in TC and LDL-C) effect was documented in experimental studies with almonds (13,14,16) peanuts (a legume) (21,22), pecan nuts (24), and walnuts

(26,28,32,33) (Table 1). However, the evidence for macadamia nuts (19) is not sufficiently convincing.

The length of the dietary intervention periods of the clinical trials in this systematic review was sufficient to achieve stabilization of blood lipids (2–3 wk) (39). The sustainability of the outcomes cannot be evaluated, however, with duration periods of 4–6 wks (40).

Inconsistent trial results could possibly be explained in a number of ways. The lack of significant change in the lipid profile when the almond diet was compared with the olive oil–based diet could be the result of the similarities in fatty acid composition of these 2 diets (13) (Table 2). The possible explanation for the increase in HDL-C in the Jenkins study (14) could be the low-fat (26%) content of the control diet compared with the intervention diet (36%). Consumption of low-fat diets was shown to decrease HDL-C concentrations (22). The absence of an effect in the study of Lovejoy et al. (15) may be linked to the similarities in fatty acid distribution of the almond and control diets (MUFA provided by olive and canola oil) as seen in the study of Spiller et al. (13). Also, it was the only nut study with diabetic subjects (15), which may suggest that other mechanisms came into play. Notably, almond consumption in the 2 aforementioned almond studies did not differ from consumption of the olive oil control diets (13,15). Thus, we speculate that like the nut diets, the olive oil control diets may also have additional cholesterol-lowering effects that may extend beyond their fatty acid composition (e.g., phytosterols and flavonoids).

In the macadamia nut intervention, which was compared with consumption of the AAD, there were significant decreases in the lipid profile (19). This nut diet and the AAD diet had the same percentage of total fat (35% TF); however, the control diet was high in SFA (14 vs. 9%) and low in MUFA (12 vs. 20%) (Table 2). The absence of a beneficial lipid effect when comparing consumption of the macadamia nut diet with the low-fat high complex CHO (18), or Step I diet (19) may be due in part to the high concentration of palmitoleic acid (16:1) (38). A study by Nestel et al. (41) showed that palmitoleic acid behaves like an SFA, not a MUFA in its effect on LDL-C in hypercholesterolemic men. The lack of effect of the nut diet intervention by Colquhoun and researchers (18) may be explained by the large contrast between the very high concentration of TF (42%), SFA (11%), and low concentrations of CHO (39%) compared with the low-fat high complex CHO control diet (21% TF, 9% SFA, and 57% CHO) (Table 2). Curb and collaborators (19) concluded that the interpretation of the decrease in HDL-C may be difficult, and further investigation of HDL-C effects in longer-term macadamia nut studies with close attention to other dietary components is warranted.

It is evident from the 2 peanut intervention studies (21,22) that the TC and LDL-C concentrations of both hyper- and normocholesterolemic subjects were significantly improved except in comparison with an olive oil control diet (22). Epidemiologic and clinical data indicate that the inverse relation between HDL-C and premature atherosclerosis is stronger for HDL_2-C than for HDL_3-C (42,43), although HDL_3-C decreased the concentration of HDL_2-C, and apolipoprotein A-1 did not change in O'Byrne's study. The resultant ratio of LDL-C:HDL-C was lower and the protective role of HDL-C was, therefore, not compromised (21). The significant decrease in TG could be ascribed to consumption of the Step II control diet, which caused a significant increase in TG concentrations (22).

Pecan consumption decreased TC and LDL-C concentrations compared with a Step I diet. The increase in HDL-C and decrease in TG concentrations may be ascribed in part to the decreasing effect of the HDL-C and increasing effect of TG with consumption of the low-fat Step I diet (28 vs. 40% provided by the pecan diet) (Table 2).

It is clear from the walnut interventions that the decreasing effect on TC and LDL-C concentrations extended beyond the cholesterol-decreasing effect that occurs with the consumption of Step I (26), Mediterranean (28,33), and Japanese (32) diets. We speculate that subjects in the study by Sabate and investigators (26) had the greatest improvement because the intervention had the largest dosage of walnuts (i.e., 84 g/d). In 2 walnut intervention trials (64–78 g/d) compared with consumption of low-fat (27) and Step I diets (31), the lipid profiles were not affected, possibly because of the large difference in the percentage of fat between the nut diet (38 and 45% respectively) and the control diets (30 and 33%, respectively). Also, it is evident from all of the walnut studies that the significantly favorable change in the lipid profile did not occur when the total percentage of fat in the diet was >37% (27,31). Nevertheless, the beneficial results in TC and LDL-C concentrations were evident when consumption ranged from ~40 to 84 g walnuts/d. In the study by Munoz et al. (30), consumption of the walnut diet compared with the Mediterranean diet did not affect the lipid profile, probably as a result of the small sample size (n = 10). Generally, most of the walnut diets did not affect HDL-C concentrations compared with the aforementioned control diets (27,28,30–33). In a study by Sabate and investigators (26), there was a significant decrease in HDL-C, even though the TC:HDL-C and LDL-C:HDL-C ratios were favorable. The decrease in HDL-C may be ascribed to the high PUFA (17 vs. 10%), low SFA (6 vs. 9%) and MUFA (7 vs. 9%) content of the walnut diet compared with the control diet. SFA and MUFA increase HDL-C, whereas high intakes of PUFA (>10%) decrease HDL-C (44).

The inclusion of nuts altered the fatty acid composition of the diet (45), which may in turn favorably affect lipid concentrations. Similar to what has been done by other authors (1), we compared the actual observed changes with the predicted changes in LDL-C and TC concentrations (**Fig. 2**) based on differences in the dietary fatty acid composition in the individual nut and control diets; we used the predictive equation of Mensink and Katan ($\Delta TC = 1.51\Delta$%energy from SFA/d -0.12Δ%energy from MUFA/d -0.60Δ%energy from PUFA) (6). There were significantly greater reductions in LDL-C and TC concentrations of 0.11 and 0.12 mmol/L, respectively, with the nut diets combined compared with the predicted changes.

Although the fatty acid profile of the nuts contributes to the hypocholesterolemic effect, other components in nuts also have favorable effects on the lipid profile (1). Nuts are comprised of ~7 g/100 g of dietary fiber, of which ~25% is soluble fiber (46). Brown et al. (46) conducted a meta-analysis of 67 controlled trials to quantify the cholesterol-lowering effect of major dietary fibers. They concluded that 2–10 g/d of soluble fiber was associated with small but significant decreases in TC. Rimm and Stampfer (47) suggested that plasma α-tocopherol concentrations ≥27.5 μmol/L may be necessary to reduce cardiovascular risk by a dietary intake of ~15–30 mg of vitamin E. Arginine, the second most abundant amino acid found in nut proteins, may account for the hypocholesterolemic effect observed in animal studies (48). In addition, this effect was seen in human intervention trials when the dosage of arginine in the diet appeared to be very high (6–21 g/d of arginine) (49). Nuts are also sources of phytosterols (38) and other phytochemical compounds such as polyphenols and ellagic acid, with possible serum cholesterol–modulating effects

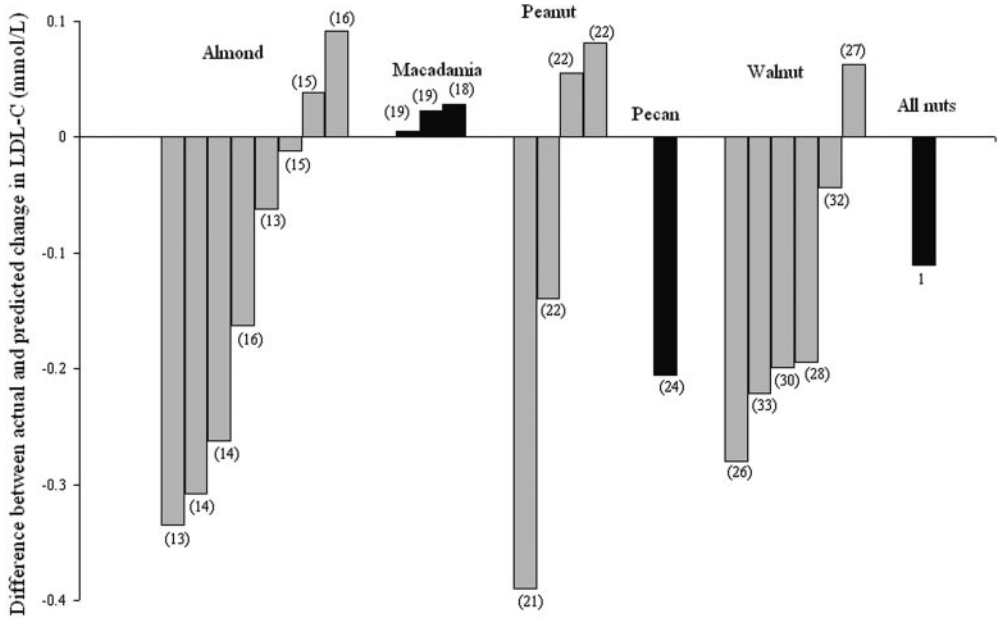

FIGURE 2 The difference between the actual and predicted changes (based on fatty acid distribution and using the predictive equation of Mensink and Katan) (6) in blood LDL-C when nut diets compared with control diets were consumed. Only clinical trials that received a 1 or 2 were included in this figure. Reference numbers for trials in which there was a reduction are shown below the bars; those that had an increase are cited above the bars. 1. Actual change was significantly different from the predicted change, $P < 0.05$ (Wilcoxon matched pairs test).

(50–54). In particular, studies showed that 2 g of plant sterols/d significantly reduces cholesterol absorption, which in turn decreases plasma TC and LDL-C concentrations (50,52). It is apparent that fiber, vitamin E, arginine, phytosterols, and phenolic components from realistic amounts of nuts are not sufficient to exert individual hypocholesterolemic effects (55). In essence, it is possible that there are multiple small effects that contribute, and these are mediated by more than the lipid-lowering fatty acid composition.

Some of the limitations of this review include the fact that the independent effects of the type of nut diets and the type of control diets may mask some potential effects or accentuate others. There were also differences in the study populations whose lipid profile may be altered due to underlying disease, poorly designed studies (sample size, control, duration, size of intervention), publication bias, and insufficient reporting of results.

This systematic review highlights the evidence from well-designed nut intervention studies. As alluded to previously, most of these nut intervention diets are in fact heart healthy diets. In this regard, consumption of moderate-fat diets (35% of energy) containing ~50–100 g/d of nuts, especially almonds, peanuts, pecan nuts, or walnuts, significantly lowered TC (2–16%) and LDL-C (2–19%) concentrations to a greater degree than observed for consumption of lower-fat, cholesterol-lowering diets without nuts or changes in dietary fatty acid profiles. At this stage, the evidence for macadamia nuts is less convincing. On the basis of the results of these nut intervention studies, it is appropriate to recommend that normo- and hyperlipidemic individuals consume a variety of nuts (~50–100 g) at least 5 times/wk. Therefore, future food-based dietary strategies for improving plasma lipid concentrations should consider the lipid-lowering effect of nuts.

Future research should use quality feeding studies with larger sample sizes and longer duration to investigate the effects of nuts on HDL-C and TG concentrations. In particular, this should apply to mixed nuts and those individual nuts not yet considered. The unique nutrient and nonnutrient composition of nuts requires further research to elucidate the possible mechanisms responsible for the LDL-C–lowering effect.

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LITERATURE CITED

1. Kris-Etherton, P. M., Yu-Poth, S., Sabate, J., Ratcliffe, H. E., Zhao, G. & Etherton, T. D. (1999) Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. Am. J. Clin. Nutr. 70: 504S–511S.

2. Kris-Etherton, P. M., Zhao, G., Binkoski, A. E., Coval, S. M. & Etherton, T. D. (2001) The effects of nuts on coronary heart disease risk. Nutr. Rev. 59: 103–111.

3. Dreher, M. L., Maher, C. V. & Kearney, P. (1996) The traditional and emerging role of nuts in healthful diets. Nutr. Rev. 54: 241–245.

4. Sabate, J. (1999) Nut consumption, vegetarian diets, ischemic heart disease risk, and all-cause mortality: evidence from epidemiologic studies. Am. J. Clin. Nutr. 70: 500S–503S.

5. Brown, D. (2003) FDA considers health claim for nuts. J. Am. Diet. Assoc. 103: 426.

6. Mensink, R. P. & Katan, M. B. (1992) Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler. Thromb. 12: 911–919.

7. Hegsted, D. M., Ausman, L. M., Johnson, J. A. & Dallal, G. E. (1993) Dietary fat and serum lipids: an evaluation of the experimental data. Am. J. Clin. Nutr. 57: 875–883.

8. Pubmed [Online], U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed [accessed May 9, 2005].

9. Web of Science [Online], Thomson Scientific. http://isi02.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame [accessed May 9, 2005].

10. Verhagen, A. P., de Vet, H. C., de Bie, R. A., Kessels, A. G., Boers, M., Bouter, L. M. & Knipschild, P. G. (1998) The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J. Clin. Epidemiol. 51: 1235–1241.

11. Spiller, G. A., Jenkins, D. J., Cragen, L. N., Gates, J. E., Bosello, O., Berra, K., Rudd, C., Stevenson, M. & Superko, R. (1992) Effect of a diet high in monounsaturated fat from almonds on plasma cholesterol and lipoproteins. J. Am. Coll. Nutr. 11: 126–130.

12. Abbey, M., Noakes, M., Belling, G. B. & Nestel, P. J. (1994) Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol. Am. J. Clin. Nutr. 59: 995–999.

13. Spiller, G. A., Jenkins, D. A., Bosello, O., Gates, J. E., Cragen, L. N. & Bruce, B. (1998) Nuts and plasma lipids: an almond-based diet lowers LDL-C while preserving HDL-C. J. Am. Coll. Nutr. 17: 285–290.

14. Jenkins, D. J., Kendall, C. W., Marchie, A., Parker, T. L., Connelly, P. W., Qian, W., Haight, J. S., Faulkner, D., Vidgen, E., et al. (2002) 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. Circulation 106: 1327–1332.

15. Lovejoy, J. C., Most, M. M., Lefevre, M., Greenway, F. L. & Rood, J. C. (2002) Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. Am. J. Clin. Nutr. 76: 1000–1006.

16. Sabate, J., Haddad, E., Tanzman, J. S., Jambazian, P. & Rajaram, S. (2003) Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. Am. J. Clin. Nutr. 77: 1379–1384.

17. Durak, I., Koksal, I., Kacmaz, M., Buyukkocak, S., Cimen, B. M. & Ozturk, H. S. (1999) Hazelnut supplementation enhances plasma antioxidant potential and lowers plasma cholesterol levels. Clin. Chim. Acta 284: 113–115.

18. Colquhoun, D. M., Humphries, J. A., Moores, D. & Somerset, S. M. (1996) Effects of a macadamia nut enriched diet on serum lipids and lipoproteins compared to a low-fat diet. Food Aust. 48: 216–222.

19. Curb, J. D., Wergowske, G., Dobbs, J. C., Abbott, R. D. & Huang, B. (2000) Serum lipid effects of a high-monounsaturated fat diet based on macadamia nuts. Arch. Intern. Med. 160: 1154–1158.

20. Garg, M. L., Blake, R. J. & Wills, R. B. (2003) Macadamia nut consumption lowers plasma total and LDL cholesterol levels in hypercholesterolemic men. J. Nutr. 133: 1060–1063.

21. O'Byrne, D. J., Knauft, D. A. & Shireman, R. B. (1997) Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein profiles. Lipids 32: 687–695.

22. Kris-Etherton, P. M., Pearson, T. A., Wan, Y., Hargrove, R. L., Moriarty, K., Fishell, V. & Etherton, T. D. (1999) High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. Am. J. Clin. Nutr. 70: 1009–1015.

23. Morgan, W. A. & Clayshulte, B. J. (2000) Pecans lower low-density lipoprotein cholesterol in people with normal lipid levels. J. Am. Diet. Assoc. 100: 312–318.

24. Rajaram, S., Burke, K., Connell, B., Myint, T. & Sabate, J. (2001) A monounsaturated fatty acid-rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. J. Nutr. 131: 2275–2279.

25. Edwards, K., Kwaw, I., Matud, J. & Kurtz, I. (1999) Effect of pistachio nuts on serum lipid levels in patients with moderate hypercholesterolemia. J. Am. Coll. Nutr. 18: 229–232.

26. Sabate, J., Fraser, G. E., Burke, K., Knutsen, S. F., Bennett, H. & Lindsted, K. D. (1993) Effects of walnuts on serum lipid levels and blood pressure in normal men. N. Engl. J. Med. 328: 603–607.

27. Chisholm, A., Mann, J., Skeaff, M., Frampton, C., Sutherland, W., Duncan, A. & Tiszavari, S. (1998) A diet rich in walnuts favourably influences plasma fatty acid profile in moderately hyperlipidaemic subjects. Eur. J. Clin. Nutr. 52: 12–16.

28. Zambon, D., Sabate, J., Munoz, S., Campero, B., Casals, E., Merlos, M., Laguna, J. C. & Ros, E. (2000) Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. A randomized crossover trial. Ann. Intern. Med. 132: 538–546.

29. Almario, R. U., Vonghavaravat, V., Wong, R. & Kasim-Karakas, S. E. (2001) Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. Am. J. Clin. Nutr. 74: 72–79.

30. Munoz, S., Merlos, M., Zambon, D., Rodriguez, C., Sabate, J., Ros, E. & Laguna, J. C. (2001) Walnut-enriched diet increases the association of LDL from hypercholesterolemic men with human HepG2 cells. J. Lipid Res. 42: 2069–2076.

31. Morgan, J. M., Horton, K., Reese, D., Carey, C., Walker, K. & Capuzzi, D. M. (2002) Effects of walnut consumption as part of a low-fat, low-cholesterol diet on serum cardiovascular risk factors. Int. J. Vitam. Nutr. Res. 72: 341–347.

32. Iwamoto, M., Imaizumi, K., Sato, M., Hirooka, Y., Sakai, K., Takeshita, A. & Kono, M. (2002) Serum lipid profiles in Japanese women and men during consumption of walnuts. Eur. J. Clin. Nutr. 56: 629–637.

33. Ros, E., Nunez, I., Perez-Heras, A., Serra, M., Gilabert, R., Casals, E. & Deulofeu, R. (2004) A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation 109: 1609–1614.

34. Gordon, D. J., Probstfield, J. L., Garrison, R. J., Neaton, J. D., Castelli, W. P., Knoke, J. D., Jacobs, D. R., Jr., Bangdiwala, S. & Tyroler, H. A. (1989) High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 79: 8–15.

35. Austin, M. A., Hokanson, J. E. & Edwards, K. L. (1998) Hypertriglyceridemia as a cardiovascular risk factor. Am. J. Cardiol. 81: 7B–12B.

36. Demacker, P. N., Schade, R. W., Jansen, R. T. & Van't, L. A. (1982) Intra-individual variation of serum cholesterol, triglycerides and high density lipoprotein cholesterol in normal humans. Atherosclerosis 45: 259–266.

37. Warnick, G. R. & Albers, J. J. (1976) Physiological and analytical variation in cholesterol and triglycerides. Lipids 11: 203–208.

38. USDA Nutrient Database for Standard Reference, Release 17 [Online], U.S. Department of Agriculture, Agricultural Research Service. http://www.nal.usda.gov/fnic/foodcomp [accessed May 9, 2005].

39. Ginsberg, H. N., Kris-Etherton, P., Dennis, B., Elmer, P. J., Ershow, A., Lefevre, M., Pearson, T., Roheim, P., Ramakrishnan, R., et al. (1998) Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. Arterioscler. Thromb. Vasc. Biol. 18: 441–449.

40. Feldman, E. B. (2002) The scientific evidence for a beneficial health relationship between walnuts and coronary heart disease. J. Nutr. 132: 1062S–1101S.

41. Nestel, P., Clifton, P. & Noakes, M. (1994) Effects of increasing dietary palmitoleic acid compared with palmitic and oleic acids on plasma lipids of hypercholesterolemic men. J. Lipid Res. 35: 656–662.

42. Assmann, G. & Funke, H. (1990) HDL metabolism and atherosclerosis. J. Cardiovasc. Pharmacol. 16 (suppl. 9): S15–S20.

43. Tribble, D. L. & Krauss, R. M. (1993) HDL and coronary artery disease. Adv. Intern. Med. 38: 1–29.

44. Riccardi, G., Rivellese, A. A. & Williams, C. M. (2003) The cardiovascular system. In: Nutrition and Metabolism (Gibney, M. J., Macdonald, I. A. & Roche, H. M., eds.), pp. 224–246. Blackwell Science, Oxford, UK.

45. Jaceldo-Siegl, K., Sabate, J., Rajaram, S. & Fraser, G. E. (2004) Long-term almond supplementation without advice on food replacement induces favourable nutrient modifications to the habitual diets of free-living individuals. Br. J. Nutr. 92: 533–540.

46. Brown, L., Rosner, B., Willett, W. W. & Sacks, F. M. (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am. J. Clin. Nutr. 69: 30–42.

47. Rimm, E. B. & Stampfer, M. J. (1997) The role of antioxidants in preventive cardiology. Curr. Opin. Cardiol. 12: 188–194.

48. Kurowska, E. M. & Carroll, K. K. (1994) Hypercholesterolemic responses in rabbits to selected groups of dietary essential amino acids. J. Nutr. 124: 364–370.

49. Maxwell, A. J., Anderson, B., Zapien, M. P. & Cooke, J. P. (2000) Endothelial dysfunction in hypercholesterolemia is reversed by a nutritional product designed to enhance nitric oxide activity. Cardiovasc. Drugs Ther. 14: 309–316.

50. Anderson, K. J., Teuber, S. S., Gobeille, A., Cremin, P., Waterhouse, A. L. & Steinberg, F. M. (2001) Walnut polyphenolics inhibit in vitro human plasma and LDL oxidation. J. Nutr. 131: 2837–2842.

51. Mojzisova, G. & Kuchta, M. (2001) Dietary flavonoids and risk of coronary heart disease. Physiol Res. 50: 529–535.

52. Law, M. (2000) Plant sterol and stanol margarines and health. Br. Med. J. 320: 861–864.

53. Vorster, H. H., Raal, F. J., Ubbink, J. B., Marais, A. D. & Rajput, M. C. (2003) Phytosterols—a new dietary aid for the treatment of hypercholesterolaemia. S. Afr. Med. J. 93: 581–582.

54. Richelle, M., Enslen, M., Hager, C., Groux, M., Tavazzi, I., Godin, J. P., Berger, A., Metairon, S., Quaile, S., et al. (2004) Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. Am. J. Clin. Nutr. 80: 171–177.

55. Lampe, J. W. (1999) Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am. J. Clin. Nutr. 70: 475S–490S.