

## Possible Benefit of Nuts in Type 2 Diabetes<sup>1,2</sup>

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### Abstract

Nuts, including peanuts, are now recognized as having the potential to improve the blood lipid profile and, in cohort studies, nut consumption has been associated with a reduced risk of coronary heart disease (CHD). More recently, interest has grown in the potential value of including nuts in the diets of individuals with diabetes. Data from the Nurses Health Study indicates that frequent nut consumption is associated with a reduced risk of developing diabetes and cardiovascular disease. Randomized controlled trials of patients with type 2 diabetes have confirmed the beneficial effects of nuts on blood lipids also seen in nondiabetic subjects, but the trials have not reported improvement in A1c or other glycosylated proteins. Acute feeding studies, however, have demonstrated the ability of nuts, when eaten with carbohydrate (bread), to depress postprandial glycemia. Furthermore, there was evidence of reduced postprandial oxidative stress associated with nut consumption. In terms of dietary composition, nuts have a good nutritional profile, are high in monounsaturated fatty acids (MUFA) and PUFA, and are good sources of vegetable protein. Incorporation of nuts in the diet may therefore improve the overall nutritional quality of the diet. We conclude that there is justification to consider the inclusion of nuts in the diets of individuals with diabetes in view of their potential to reduce CHD risk, even though their ability to influence overall glycemic control remains to be established. *J. Nutr.* 138: 1752S–1756S, 2008.

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### Introduction

The prevalence of type 2 diabetes is increasing rapidly in the US and worldwide. The toll of diabetes on health and the economy is enormous and will continue to rise. In Western nations, the incidence of diabetes is likely to increase by ~40–45% (from 51 to 72 million people) from 1995 to 2025 (1). Diabetes is also the major cause of blindness and renal transplantation and the presence of diabetes increases the risk of cardiovascular disease 2- to 5-fold, especially for women (2,3). There is even greater concern now that the increase in diabetes incidence is occurring on the Indian subcontinent, China, Central and South America, and Africa, with particularly rapid growth in the Middle East (4).

The burden of ill health related to diabetes is far broader than that resulting from diabetes complications alone. It extends to the metabolic syndrome and associated disorders as the common soil from which type 2 diabetes rises. Thus, hypertension and stroke, cancers including colon, breast, and prostate, and even gallstone disease form part of this complex.

The resulting burden of the so-called chronic diseases of lifestyle has already overextended the health systems of Western nations and will pose an insurmountable challenge for nations with limited resources. Because there is no currently available cure for diabetes, primary prevention through diet and lifestyle modification is of paramount importance.

In this respect, the news is far from bleak. Diabetes prevention trials in groups of high risk individuals have shown repeatedly that 45–60% reductions in the incidence of diabetes can be achieved over a 3- to 6-y period (5) by application of

modest dietary change, weight loss, and exercise (5–7). Furthermore, an assessment of the Nurses Health Study between 1980 and 1996 suggested that 91% of type 2 diabetes in this cohort could be prevented by a good diet, BMI < 25 kg/m<sup>2</sup>, moderate to vigorous exercise ≥30 min/d, not smoking, and modest alcohol intake ≥5 g/d (8). The only problem with these seemingly simple choices was that as few as 3.4% of the population in the study were complying with all components of this lifestyle (8).

There is therefore urgent need to identify and develop additional diet and lifestyle approaches that will support a comprehensive diabetes prevention strategy. One part of this strategy may be an increase in dietary vegetable protein and fat in the form of nuts. As well as providing vegetable protein and unsaturated [monounsaturated fatty acids (MUFA)<sup>9</sup> and PUFA] fatty acids, nuts provide other nutrients that may improve lipid risk factors for heart disease and also glucose and insulin homeostasis.

### Nut consumption and diabetes incidence

Many studies have indicated that nut and peanut consumption are associated with an apparent protection from coronary heart disease (CHD). These data, together with evidence that nut consumption is also associated with reduced LDL cholesterol concentrations and possibly raised HDL cholesterol levels (9,10), have reversed the proscription against nut consumption for those at risk of CHD. Nuts were formerly regarded as high-fat foods and were therefore contraindicated for those for whom caloric restriction was required. The current acceptance that nuts are no longer detrimental and may now be recommended for individuals at risk of heart disease has prompted a reevaluation of the possible role of nuts in the diabetic diet.

The one study that has addressed this issue directly is the evaluation of nut and peanut butter consumption and risk of type 2 diabetes is the Nurses Health Study (11). In this study, nut consumption was inversely associated with risk of type 2 diabetes after adjustment for age, BMI, family history of diabetes, physical activity, smoking, and alcohol and total energy intake. Also, peanut butter consumption was associated with a lower risk of developing diabetes. The relative risk (RR) of developing diabetes was reduced 27% in those who ate nuts 5 or more times per week compared with those who rarely or never ate nuts. The effect seemed the most marked in those with a normal body weight in whom the RR was reduced further to 45% in the ≥5 servings/wk group. High intake of peanut butter, >5 times/week, also appeared protective (RR = 0.79) (11). High intake of nuts was not associated with overweight, and among the nurses diagnosed with diabetes, nut consumption ≥5 times per week tended to reduce the RR of CHD (multivariate RR = 0.53; 95% CI 0.24–1.41; *P*-trend = 0.07) (12).

Furthermore, gallstone disease, as an associated metabolic syndrome disease, also appears to be influenced favorably by nut consumption in both men and women. Gallstone disease is associated with all the individual components of the metabolic syndrome, e.g. low HDL, high triglycerides, high blood pressure, insulin resistance, and impaired glucose tolerance or type 2 diabetes. Recent data suggest that the prevalence of gallstone disease is markedly elevated among subjects with the metabolic syndrome, increased insulin resistance, or fatty liver (even after taking BMI into account) (13,14). Recently, nut consumption (peanuts, other nuts, and peanut butter) was studied prospectively in relation to the risk of cholecystectomy, a surrogate of

symptomatic gallstone disease, in the Nurses Health Study and Health Professionals' Follow-up and showed that higher consumption of nuts was associated with lower risk of gallstone disease in both men and women (15,16).

There is, however, one rather important consideration with respect to nutrient bioavailability and bioaccessibility from whole nuts vs. ground nuts (e.g. almonds vs. almond butter). Studies have shown that several dietary components from whole nuts, including lipids, are poorly absorbed, possibly due to the cell wall structures in the almond kernel (17). Thus, one would expect ground nuts to have a higher bioaccessibility of nutrients. The decreased bioavailability and accessibility of nutrients from nuts may have biological consequences; however, to our knowledge, no data exist documenting different health outcomes in head-to-head comparisons of nutrient absorption from whole nuts vs. ground nuts. Nevertheless, although some valuable nutrients may be lost, the excretion of lipid may explain other literature demonstrating that daily incorporation of nuts does not contribute to weight gain over time (9,18,19).

### Intervention studies in metabolic syndrome and diabetes

In general, intervention studies with nuts have not demonstrated considerable benefits in terms of glycemic control. Lovejoy et al. (20) assessed the effect of diets supplemented with almonds on measures of insulin sensitivity, glycemic control, and serum lipids. Two 4-wk studies were conducted with subjects with normoglycemia or type 2 diabetes, respectively. In study 1, 100 g/d of almonds was supplied as a dietary supplement to free-living individuals and study 2 compared 4 diets in a randomized crossover design. These diets were: high fat, high almond; low fat, high almond; high-fat control (olive or canola oil); low-fat control. Results showed that insulin sensitivity across the almond treatment did not change in study 1; however, despite a modest weight increase, serum total cholesterol (21%) and LDL cholesterol (29%) concentrations decreased (*P* < 0.05). In study 2, the high-fat, high-almond diet had the greatest decrease in total cholesterol (−4.46 ± 0.14 mmol/L); however, no diet affected glycemia (20). Of note, glycemia was measured by fasting glucose, postprandial glucose, and A1c. The lack of a glycemic effect may have been due in part to the short duration of the study in which A1c did not seem to change over a 4-wk period (20).

Furthermore, a study by Scott et al. (15) in patients with either metabolic syndrome or type 2 diabetes demonstrated a similar effect to that in the study by Lovejoy et al. (20). Subjects were randomized to a standard AHA diet (15% protein, 30% fat, 15% MUFA) vs. a higher protein (25%), high-MUFA (22%) diet for 42 wk. To replace other high-MUFA foods, almonds were given during the last 24 wk to the high-MUFA group (21). Blood lipids and fasting glucose did not differ between the groups. However, patients in both groups improved their glycemic control, possibly related to the weight loss observed with both treatments (21).

More recently, a 6-mo randomized, controlled, parallel study was undertaken in type 2 diabetes (10). Fifty-eight subjects were randomized to 3 treatment arms of different dietary advice; a conventional low-fat control diet, a low but modified-fat diet higher in eicosapentanoic acid and docosahexanoic acid PUFA, and a low-fat plus 30 g/d walnut diet high in  $\alpha$ -linolenic acid PUFA. Each diet had <30% energy from fat. Biomarker data from this study indicated that the plasma HDL cholesterol:total cholesterol ratio and HDL cholesterol increased (*P* = 0.049 and *P* = 0.046, respectively) and plasma LDL cholesterol (*P* = 0.032) decreased by 10% in the walnut group compared with the other 2 groups. Body weight, percent body fat (assessed by

<sup>9</sup> Abbreviations used: CHD, coronary heart disease; MUFA, monounsaturated fatty acid; RR, relative risk.

**TABLE 1** Dietary and plasma lipid variables at baseline and after 6 mo intervention with 30 g/d of walnuts in subjects with type 2 diabetes mellitus<sup>1</sup>

Variable	Control		Modified fat		Walnut		P-value
	0 mo	6 mo	0 mo	6 mo	0 mo	6 mo	
Energy intake							
kcal/d	2054 ± 686	2146 ± 432	2091 ± 504	1978 ± 500	2025 ± 665	2007 ± 376	NS
kJ/d	8594 ± 2870	8979 ± 1807	8748 ± 2109	8276 ± 2092	8473 ± 2782	8397 ± 1573	
Dietary P:S ratio <sup>2</sup>	0.6 ± 0.2	0.6 ± 0.3	0.8 ± 0.6	1.3 ± 0.5	0.7 ± 0.4	1.8 ± 0.5	0.001 <sup>3</sup>
Body fat, %	31.2 ± 8.0	32.4 ± 8.2	35.1 ± 10.2	35.5 ± 10.0	34.5 ± 9.1	34.0 ± 9.0	NS <sup>4</sup>
HDL-C, <sup>2</sup> mmol/L	1.11 ± 0.22	1.25 ± 0.27	1.11 ± 0.24	1.34 ± 0.21	1.10 ± 0.24	1.30 ± 0.62	0.046
HDL-C:TC <sup>2</sup>	0.24 ± 0.06	0.26 ± 0.06	0.25 ± 0.07	0.29 ± 0.07	0.27 ± 0.08	0.33 ± 0.10	0.049
LDL-C, <sup>2</sup> mmol/L	2.70 ± 1.56	2.69 ± 1.49	2.58 ± 1.30	2.73 ± 1.20	2.17 ± 1.31	1.95 ± 0.75	0.032 <sup>5</sup>
Triglycerides, mmol/L	2.18 ± 0.82	2.13 ± 0.71	1.76 ± 0.82	1.55 ± 0.73	1.90 ± 0.74	1.70 ± 0.68	NS

<sup>1</sup> Values are means ± SD, n = 58. Adapted with permission from (10).

<sup>2</sup> HDL-C, HDL cholesterol; TC, total cholesterol; LDL-C, LDL cholesterol.

<sup>3</sup> Significant effect due to treatment over time (repeated-measures ANOVA control vs. walnut group).

<sup>4</sup> Repeated measures analysis adjusted for sex. NS = P > 0.05.

<sup>5</sup> Significant group effect (univariate analysis demonstrated significant reduction in walnut group over time, P = 0.036).

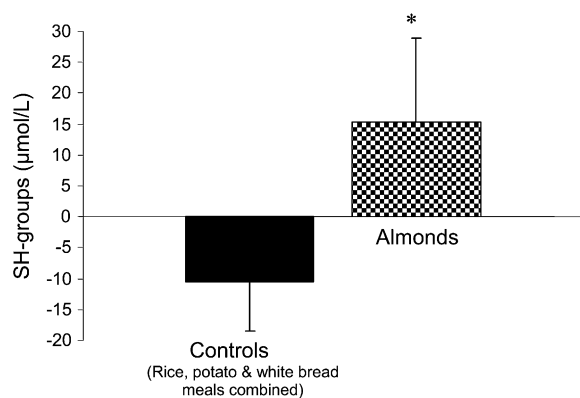
bioelectrical impedance analysis), plasma total antioxidant capacity, and A1c(10) did not differ in this study. The effect on lipids was attributed to changes achieved in the dietary PUFA:SFA ratio shown to have been largely due to walnut consumption in an otherwise low-fat diet (Table 1).

Although these studies did not show a glycemic effect after subjects consumed both MUFA- and PUFA-rich nuts, even in the shorter term, benefits were still seen, including lower levels of serum total cholesterol, LDL cholesterol, and the HDL cholesterol:total cholesterol ratio, thus reducing the risk factor status for subsequent heart disease.

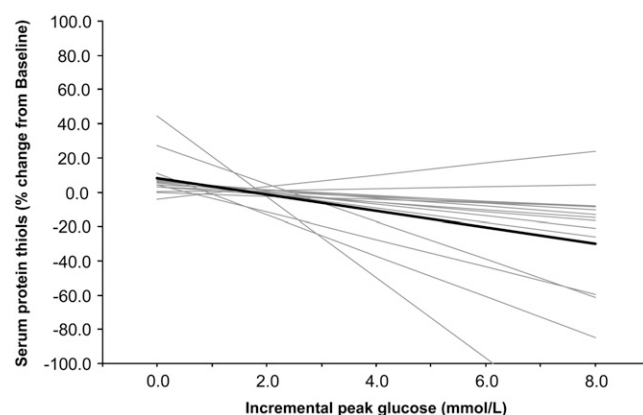
### Acute effects of nuts on postprandial glycemia

Nuts in general contain very little available carbohydrate and therefore contribute little to the postprandial glycemic response. However, by virtue of the content of fat and protein, and possibly of related phytochemicals (e.g. phytates and phenolics

in the skin), nuts depress the glycemic response to a standard carbohydrate load in a dose-dependent fashion (22). The effect of nuts on postprandial events may not be confined to reducing glycemia and insulinemia but may also influence postprandial oxidative damage. When almonds were fed with bread, the destruction (i.e. oxidation) of serum protein thiols, as a maker of oxidative stress, was less than when bread was taken alone or when potato and rice were both fed with butter and cheese to equalize the fat and protein in the almond plus bread meal (Fig. 1). Moreover, the whole-blood glycemic excursions related negatively to protein thiol losses, suggesting that any dietary change that reduces postprandial glycemia may have a benefit by reducing meal-induced oxidative damage (Fig. 2) (23). Longer-term studies to assess these effects of nuts are required to determine the extent to which fasting serum concentrations are altered and whether the changes are likely to have overall physiological or pathological importance.



**FIGURE 1** Postprandial change over 4 h from baseline in serum protein thiol concentrations in 15 healthy subjects [7 men and 8 women; age 26.3 ± 8.6 y (range, 19–52 y); BMI, 23.4 ± 3.4 kg/m<sup>2</sup> (range, 17.4–29.5 kg/m<sup>2</sup>)] after consumption of 60 g almonds plus white bread compared with the 3 control meals combined (mashed potatoes plus cheese and butter, parboiled rice plus cheese and butter, and control white bread) using a statistical CONTRAST statement. \*P = 0.021 for the comparison. The reduction in the combined control group indicates increased oxidative breakdown in serum protein thiols.



**FIGURE 2** Percent change from baseline in mean postprandial serum protein thiol concentration vs. incremental peak blood glucose concentration for the 15 healthy subjects after consumption of 4 meals: white bread control; 60 g almonds plus white bread; mashed potatoes plus cheese and butter; parboiled rice plus cheese and butter. A negative mean gradient is shown by the thick black line (slope = -4.8; n = 15; P = 0.014). The higher the incremental peak blood glucose concentration, the greater the damage (i.e. reduction) in protein thiols [previously published in (23)].

## Nuts as part of the diet

In many ways, nuts have the ideal macronutrient profile for chronic disease risk reduction. They are an excellent source of MUFA and PUFA, with some nuts also being good sources of (n-3) fatty acids (Table 2), which may contribute to high-sensitivity C-reactive protein reduction (24). Many nuts are also a good source of vegetable protein. A recent assessment of the Nurses Health Study indicated that higher intakes of vegetable oils and protein, but not of animal fats and protein, were protective for CHD (25). Such data support the effect of nuts as cardioprotective and indicate that food-based recommendations, in addition to macronutrient recommendations, may be most helpful in producing diets aimed at reducing chronic disease risk. Thus, it has been shown that including walnuts in an overall dietary plan for the management of type 2 diabetes mellitus assured that the

**TABLE 2** Macronutrient and micronutrient composition of 1 ounce (28 g) of whole, natural nuts<sup>1</sup>

	Almonds	Walnuts	Hazelnuts	Pistachios	Macadamias
<b>Nutrient</b>					
Water, g	1.5	1.2	1.5	1.1	0.4
Energy, kcal	163.9	185.4	178.0	157.9	203.6
Protein, g	6.0	4.3	4.2	5.9	2.2
Total lipid, g	14.4	18.5	17.2	12.6	21.5
Carbohydrates, by difference, g	5.6	3.9	4.7	7.9	3.9
Fiber, total dietary, g	3.3	1.9	2.8	2.9	2.4
Sugars, total, g	1.4	0.7	1.2	2.2	1.3
<b>Minerals, mg</b>					
Calcium	70.3	27.8	32.3	30.3	24.1
Iron	1.2	0.8	1.3	1.2	1.0
Magnesium	78.0	44.8	46.2	34.3	36.9
Phosphorus	134.4	98.1	82.2	138.9	53.3
Potassium	206.4	125.0	192.8	290.6	104.3
Sodium	0.3	0.6	0.0	0.3	1.4
Zinc	1.0	0.9	0.7	0.6	0.4
Copper	0.3	0.5	0.5	0.4	0.2
Manganese	0.7	1.0	1.8	0.3	1.2
Selenium	1.2	1.3	1.1	2.0	1.0
<b>Vitamins,<sup>2</sup> mg</b>					
Vitamin C	0.0	0.4	1.8	1.4	0.3
Thiamin	0.1	0.1	0.2	0.2	0.3
Riboflavin	0.2	0.0	0.0	0.0	0.0
Niacin	1.1	0.6	0.5	0.4	0.7
Pantothenic acid	0.1	0.2	0.3	0.1	0.2
Vitamin B-6, $\mu$ g	0.0	0.2	0.2	0.5	0.1
Folate, total, $\mu$ g	8.2	27.8	32.0	14.5	3.1
Vitamin B-12, $\mu$ g	0.0	0.0	0.0	0.0	0.0
Vitamin A	0.8	3.5	3.4	47	0.0
Vitamin E	7.4	0.8	4.3	1.3	0.2
$\alpha$ -Tocopherol	7.3	0.2	4.3	0.7	0.2
<b>Lipids</b>					
SFA	1.1	1.7	1.3	1.5	3.4
MUFA	9.1	2.5	12.9	6.6	16.7
PUFA	3.5	13.4	2.2	3.8	0.4
Phytosterols	34.0	20.4	27.2	60.7	32.9
<b>Amino acids</b>					
Lysine	0.2	0.1	0.1	0.3	0.0
Arginine	0.7	0.6	0.6	0.6	0.4

<sup>1</sup> Adapted from (31).

<sup>2</sup> Mg unless otherwise stated.

targeted fatty acid profile that lead to the desired changes in lipid biomarkers of disease risk was achieved (10,26,27). Studying the effect of a food component, such as fat, in the context of whole foods has the advantage that the results are immediately interpretable for practice. Furthermore, there may be synergies in the food matrix that help to maximize the benefits or deliver additional benefits (28). The latter suggests there is still much to be uncovered, given that whole foods such as nuts contain a number of potentially beneficial bioactive components simultaneously (Table 2). Incorporating nuts into the overall diet may provide nutritional benefit on more than one level, especially in a disease such as diabetes. Studies of biomarkers of a variety of physiological and pathological mechanisms and events are beginning to explain the relationship between nut consumption and risk for disease. Research that addresses these new frontiers may lead to a better appreciation of food in its own right, which in turn translates into more effective practice in diabetes management.

Evidence suggests that nut consumption, including peanuts, protects against not only CHD but also against diabetes and the CHD associated with diabetes, and other metabolic syndrome diseases, notably gallstone disease. The exact mechanisms are not known but may relate to beneficial changes in blood lipids and reduction in oxidative damage and inflammatory biomarkers (24). Beneficial changes in blood lipids have been seen both in studies of nondiabetic, hyperlipidemic subjects (9,29,30) and in type 2 diabetes (10,20,21). But, intervention studies of nuts and type 2 diabetes have not demonstrated improvement in glycemic control (10,20,21). However acute, postprandial studies suggest that meal composition may be important and that nuts should be combined with the carbohydrate portion of the meal to reduce postprandial glycemia (22,23). In this respect, nuts have many potential advantages in allowing recommended macronutrient test targets to be met while fitting well into a heart-healthy diet. More intervention studies are required to demonstrate the therapeutic potential of nuts to complement data indicating their preventive potential against CHD and diabetes.

Other articles in this supplement include references (32–37).

## Literature Cited

- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414–31.
- Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, et al. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol*. 1986;123:504–16.
- Barrett-Connor E, Wingard DL. Sex differential in ischemic heart disease mortality in diabetics: a prospective population-based study. *Am J Epidemiol*. 1983;118:489–96.
- Adeghate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. *Ann N Y Acad Sci*. 2006;1084:1–29.
- Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537–44.
- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–50.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.

8. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345:790-7.
9. Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, Haight JS, Faulkner D, Vidgen E, et al. 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*. 2002;106:1327-32.
10. Tapsell LC, Gillen LJ, Patch CS, Batterham M, Owen A, Bare M, Kennedy M. Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. *Diabetes Care*. 2004;27:2777-83.
11. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002;288:2554-60.
12. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, Speizer FE, Hennekens CH, Willett WC. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *BMJ*. 1998;317:1341-5.
13. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol*. 2006;20:981-96.
14. Nervi F, Miquel JF, Alvarez M, Ferreccio C, Garcia-Zattera MJ, Gonzalez R, Perez-Ayuso RM, Rigotti A, Villarreal L. Gallbladder disease is associated with insulin resistance in a high risk Hispanic population. *J Hepatol*. 2006;45:299-305.
15. Tsai CJ, Leitzmann MF, Hu FB, Willett WC, Giovannucci EL. A prospective cohort study of nut consumption and the risk of gallstone disease in men. *Am J Epidemiol*. 2004;160:961-8.
16. Tsai CJ, Leitzmann MF, Hu FB, Willett WC, Giovannucci EL. Frequent nut consumption and decreased risk of cholecystectomy in women. *Am J Clin Nutr*. 2004;80:76-81.
17. Ellis PR, Kendall CW, Ren Y, Parker C, Pacy JF, Waldron KW, Jenkins DJ. Role of cell walls in the bioaccessibility of lipids in almond seeds. *Am J Clin Nutr*. 2004;80:604-13.
18. Wien MA, Sabate JM, Ikle DN, Cole SE, Kandeel FR. Almonds vs complex carbohydrates in a weight reduction program. *Int J Obes Relat Metab Disord*. 2003;27:1365-72.
19. Jaceldo-Siegl K, Sabate J, Rajaram S, Fraser GE. Long-term almond supplementation without advice on food replacement induces favourable nutrient modifications to the habitual diets of free-living individuals. *Br J Nutr*. 2004;92:533-40.
20. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. 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*. 2002;76:1000-6.
21. Scott LW, Balasubramanyam A, Kimball KT, Aherns AK, Fordis CM Jr, Ballantyne CM. Long-term, randomized clinical trial of two diets in the metabolic syndrome and type 2 diabetes. *Diabetes Care*. 2003;26:2481-2.
22. Josse AR, Kendall CW, Augustin LS, Ellis PR, Jenkins DJ. Almonds and postprandial glycemia: a dose-response study. *Metabolism*. 2007;56:400-4.
23. Jenkins DJ, Kendall CW, Josse AR, Salvatore S, Brighenti F, Augustin LS, Ellis PR, Vidgen E, Rao AV. Almonds decrease postprandial glycemia, insulinemia, and oxidative damage in healthy individuals. *J Nutr*. 2006;136:2987-92.
24. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr*. 2004;134:2991-7.
25. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. *Am J Epidemiol*. 2005;161:672-9.
26. Gillen LJ, Tapsell LC, Patch CS, Owen A, Batterham M. Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with type 2 diabetes mellitus. *J Am Diet Assoc*. 2005;105:1087-96.
27. Tapsell LC, Gillen LJ, Patch CS. Walnuts and dietary approaches to the prevention and management of abnormal lipid profiles in type 2 diabetes mellitus. *Future Cardiol*. 2005;1:809-14.
28. Jacobs DR Jr, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. *Am J Clin Nutr*. 2003;78:S508-13.
29. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290:502-10.
30. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E, et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. *Am J Clin Nutr*. 2005;81:380-7.
31. Almonds ABC. A nutrition and health perspective. Modesto (CA): Almond Board of California; 2003.
32. King JC, Reckemmer G, Geiger CJ. Second international nuts and health symposium, 2007: introduction. *J Nutr*. 2008;138:1734S-5S.
33. King JC, Blumberg J, Ingwersen L, Jenab M, Tucker KL. Tree nuts and peanuts as components of a healthy diet. *J Nutr*. 2008;138:1736S-40S.
34. Mattes RD, Kris-Etherton PM, Foster GD. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J Nutr*. 2008;138:1741S-5S.
35. Kris-Etherton PM, Hu F, Ros E, Sabate J. The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. *J Nutr*. 2008;138:1746S-51S.
36. Davis PA, Jenab M, Vanden Heuvel JP, Furlong T, Taylor S. Tree nut and peanut consumption in relation to chronic and metabolic diseases including allergy. *J Nutr*. 2008;138:1757S-62S.
37. Allen LH. Priority areas for research on the intake, composition and health effects of tree nuts and peanuts. *J Nutr*. 2008;138:1763S-5S.