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#1

Walnut and Coronary Heart Disease Health Claim

Submitted by Alice H. Lichtenstein, D.Sc., Stanley N. Gershoff Professor of Nutrition Science and Policy and Senior Scientist and Director, Cardiovascular Nutrition Laboratory, Gerald J. & Dorothy R. Friedman School of Nutrition Science & Policy and Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts Univeristy.

"What is your conclusion with regards to the adequacy of the quality and quantity of publicly available scientific evidence to establish a causal relationship between consumption of walnuts and reduced risk of heart disease in the general US population? On what do you base this conclusion?"

Quality of evidence;

The quality of the evidence is variable depending on the specific outcome assessed. Issues related to the validity of the biochemical measures do not appear to be of concern.

Limitations in methodologies for assessing food intake may be important and confound interpretation of the data. For example, reported increased caloric intake in the absence of weight gain is difficult to reconcile unless uncertainties related to accuracy of self-reported data are taken into consideration. This factor, combined with limitations imposed by small sample size and short duration of intervention (see next section, quantity of evidence), limit an actuate assessment of the independent effect of walnuts relative to other changes in the diet. It should be noted that in the two controlled randomized trails available, both reported that changes in body weight were not related to specific diet.

Lack of specificity with regard to the actual foods displaced by walnuts from the diet also limit an actuate assessment of the independent effect of walnuts versus, for example, changes in the fatty acid and cholesterol content of the diet. In some cases it appears that walnuts displaced foods not only high in saturated fatty acids but also high in *trans* fatty acids. Were this the case and without information on the *trans* fatty acid intake it is difficult to attribute outcomes to walnuts, per se, rather than other changes in the diet.

Quantity of evidence;

The amount of evidence from the intervention studies is limited to date. The study periods are relatively short (4 to 6 weeks), the number of subjects small (30 males and 10 females) and the lipid characteristics of subjects narrow (nomocholesterolemic).

The amount of evidence from the supplementation studies is also limited to date. The study periods are relatively short (3-6 weeks), the number of

subjects studied small, especially when the total is subdivided into normocholesterolemic and hypercholesterolemic subjects, and female and male subjects.

The study designs range from crossover to sequential. The background diets were both low and high in fat. This later point is an important issue because within one of the studies (Almario et al.) a significant effect of walnuts was observed after subjects consumed the low fat but not higher fat diet.

The actual level of compliance is questionable in some of the studies because substitution of walnuts for other fat containing foods in the diet appeared, in practice, to result in additions to the diet in some of the studies but not all. This inconsistency in the contribution of walnuts among the supplementation studies further taxes interpretation of the limited amount of data.

Summary

The evidence from the "walnut" studies appears to supports a relationship between decreasing the saturated fat and increasing the polyunsaturated fat content of the diet with relatively large quantities of walnuts and more favorable total and LDL cholesterol levels, hence decreased predicted risk of developing heart disease. It would appear at this time that this response is the result of alterations in the fatty acid profile of the diet, independent of whether walnuts were used to accomplish this end. The study comparing almonds and walnuts (Abbey et al.) directly underscores this point. In a few cases it was reported that the response observed was somewhat greater than might have been predicted from standardized equations. However, it is not clear the equations used to make this assessment were developed for use with the small sample sizes available. In addition, they do not take *trans* fatty acids into consideration. If walnuts displaced *trans* fatty acid containing foods from the diet, which seems to be the case in a least some of the studies that actually reported specific food substitutions, the predictive equations may have underestimated the actual effect of the diet.

It should also be noted that the levels of polyunsaturated fatty acids in the "walnut" diets are relatively high and exceed current recommendations (National Cholesterol Education Program [NCEP]). It is difficult to predict the physiological consequences of these high intakes. One issue of potential concern, increased susceptibility of LDL to oxidation, was addressed in some of the studies and reported not to change. Available data are limited. Guidance on this issue of diets very high polyunsaturated fatty acid diets will likely be available in the near future from the Dietary Reference Intakes Report issued by the National Academy of Sciences.

In all the available studies the contribution of walnuts to the total energy intake of the diet was high and unlikely attainable by most Americans on a

regular basis. Data available on a dose dependent relationship are inadequate to extrapolate beneficial effects for the casual use of walnuts or even doubling current walnut intakes. This limitation needs to be taken into consideration if a generic recommendation is made to increase walnut consumption in the absence of absolute guidance on quantity of walnuts.

Summarized below are the available studies to date and the points considered when formulating the aforementioned.

Controlled randomized trials:

Sabate et al. NEJM 1993:328;603-607

Subjects:	18 male subjects normocholesterolemic males (mean cholesterol 183+/-23 mg/dl after consuming reference diet)
Design:	randomized cross-over design
Duration:	4 weeks/ diet phase
Diet perturbation:	20% energy walnuts displaced "...portions of fatty foods, such as potato chips and meat.....and the amount of visible fat (oils, margarine, and butter)..." ....." The total fat content of the diets were similar at about 30% of energy
Body weight:	maintained constant
Outcome:	12% lower total cholesterol and 16% lower LDL cholesterol when the walnut diet is compared to the reference diet.
Assessment:	Well controlled study, total energy from walnuts extremely high (55% total fat in diet).
Comment:	The authors state the Keys et al. equation (Lancet 1957;2:959) predicted a smaller response than observed and suggested "..the type of dietary fiber and the very low ratio of lysine to arginine...." may have accounted for the discrepancy. This is still theoretical with respect to walnuts because there are no human data to date to support this statement. There are two other explanations for the discrepancy noted between the observed and predicted changes. First, the predictive equation does not take *trans* fatty acids into consideration. Given that potato chips, margarine, meat and "other foods" were displaced by walnuts it would be presumed that the *trans* fatty acid content of the walnut diet was lower than the reference diet. Second, the predictive equations may not be appropriate for estimating predicted changes for such a small sample size.

Iwamoto et al. Eur J Clin Nutr; in press; originally published in J Nutr 2000;130:171-176 and retracted in J Nutr 2000;130:2407 due to copyright infringement of Sabate et al NEJM article.

Subjects:	20 male and 20 female normocholesterolemic subjects (mean baseline cholesterol for males 184+/-73 mg/dl and for females 175+/-6 mg/dl)
Design:	randomized cross-over design study
Duration:	4 weeks/ diet phase
Diet perturbation:	"...substituted two servings of walnuts per day walnuts for portions of some foods in the reference diet. The portion size of fatty foods, such as meat, were reduced, and the amounts of visible fat (oils, margarine, and butter) were decreased....." The total fat content of the diets were similar at about 25% of energy.
Body weight:	assumed to be maintained constant
Outcome:	4.5% lower total cholesterol and 9.8% lower LDL cholesterol
Assessment:	Well controlled study, total energy from walnuts relatively high (55% total fat in diet).
Comment:	The saturated fat content and possibly the *trans* fatty acid content, of the walnut diet was lower, and the polyunsaturated fat content of the diet was higher. These differences could have accounted for the changes in lipids reported.

Supplementation trials;

Abbey et al. Am J Cin Nutr 1994;59:995

Subjects:	16 normocholesterolemic male subjects (mean cholesterol 200+/-9 mg/dl after consuming reference diet)
Design:	sequential design
Duration:	3 weeks/ diet phase, reference, almond, walnut
Diet perturbation:	"...background diet provided 18% of energy as fat from meat, dairy products, vegetable oils, and fat spreads. An additional 18% of energy from fat (half of the total dietary fat) was provided by a daily supplement of nuts [almonds and walnuts]." The total fat content of the diets were similar at about 36% of energy.
Body weight:	assumed to be maintained constant
Outcome:	approximately 7% and 5% lower total cholesterol and 10% and 9% lower LDL cholesterol, almond and walnut diets, respectively
Assessment:	Well conducted supplementation study, total energy from almonds or walnuts is relatively high (50% total fat in diet).
Comment:	These data provide a comparison between an equal amount of walnuts and another nut, almonds. Walnuts are high in polyunsaturated fatty acids, almonds are high in monounsaturated fatty acids. The fiber content of the walnut diet was a little lower than the almond diet. There was little

difference in response between the two groups. More favorable lipids after either the nut diets relative to the reference diet likely due to the dramatic decrease in saturated fat intake (16% to 8-9%).

Chisholm et al. Eur J Cin Nutr 1998;52:12

Subjects:	21 hypercholesterolemic male subjects (mean cholesterol 254+/-23 mg/dl at screening); 16 subjects completed the study
Design:	randomized crossover
Duration:	4 weeks/ diet phase
Diet perturbation:	"....subjects were asked to consume two low fat diets (fat 30% total energy), one containing, on average, 78g/d walnuts." "Walnuts contributed 20% of the total energy and 55% of energy from fat...." "During the Low Fat diet all fat came from a variety of foods other than nuts."
Body weight:	remained constant
Outcome:	Apo B was significantly lower after subjects consumed the walnut relative to the low fat diet, this difference was not reflected in a significant effect on total or LDL cholesterol levels.
Assessment:	Total energy from walnuts relatively high (20% total energy).
Comment:	These data raise an interesting issue. The subjects were counseled to consume a low fat (30% of energy) diet. The authors state that their "...intention was for participants to replace various other fat sources with the nuts provided." They further state that "Regrettably, despite detailed dietary instructions and regular reinforcement throughout the experimental period total energy from fat was higher on the walnut diet" (38% v 30% energy) and "...instead of replacing other high fat foods with walnuts the participants were consuming the raw nuts in addition to their usual food." Interestingly, body weight appeared to remain constant so the intake of other foods was likely reduced but not reflected in the food records. It was reported that walnuts were used to displace meat, dairy products, bakery products and fruit from the diet. This study raises issues related to how a recommendation to increase walnut consumption, or for that matter any nut consumption, would be interpreted by the American public.

Zambon et al. Ann Intern Med 2000;132:538 (Munoz et tal. J Lipid Res 2002;42:2069 was a subset of 10 male subjects from the Zambon et al. study)

Subjects:	55 hypercholesterolemic males and females (mean cholesterol 279+/-32 mg/dl at screening); 49 subjects completed the study
Design:	randomized crossover
Duration:	6 weeks/ diet phase
Diet perturbation:	Reference diet – "Red meat and eggs were limited, vegetable products and fish were emphasized, olive oil was indicated for culinary use....The walnut diet was similar to the control diet, but walnuts partially replaced olive oil and other fatty foods." "In the walnut diet, walnuts contributed approximately 18% of the total energy and 35% of the total fat."
Body weight:	remained constant
Outcome:	Total and LDL cholesterol decreased by 4.1% and 5.9% between the control and walnut diets.
Assessment:	Total energy from walnuts relatively high (18% total energy).
Comment:	The authors indicate that "...the hypolipidemic effect of the walnut diet can be explained in part by its fatty acid profile". This assessment appears to be accurate because the saturated fatty acid intake was slightly lower in the walnut diet. The subjects reported consuming more calories on the walnut diet but did not increase body weight. This discrepancy is likely attributable to the difficultly in getting accurate self reported data and should not detract from the study. No strong evidence was reported that the changes in total and LDL cholesterol are attributable to a unique characteristic of walnuts. The total walnut intake was relatively high for such a modest improvement in cholesterol levels. The increased caloric intake is of concern because, if real, over the long term it could result in weight gain.

Almario et al. Am J Cin Nutr 2001;74:72

Subjects:	16 postmenopausal females and 7 males with combined hypercholesterolemia (mean cholesterol 231+/-11 mg/dl on the habitual diet). 13 postmenopausal females and 5 males completed the study.

Design:	sequential - habitual diet, habitual diet plus 48 g walnuts, low-fat diet, low-fat diet plus walnuts 48 g walnuts.
Duration:	6 weeks/ diet phase except habitual diet, 4 weeks
Diet perturbation:	"During the habitual diet and habitual diet + walnut periods, the participants received no nutrition education…..". "During the low-fat phase the subjects were given intensive group education to decrease fat intake".
Body weight:	body weight on low-fat diets lower than habitual diets
Outcome:	There was no significant effect on total or LDL cholesterol of adding walnuts to the habitual diet. The total fat content of the habitual diet increased from 31% to 37% of energy but palmitic acid intake decreased. Caloric intake was reported to have increased although body weight did not change. There was a significant decrease in total and LDL cholesterol, 8% and 12%, respectively, when walnuts were added to the low-fat diet. The total fat content of the diet increased from 31% to 34% of energy but again the palmitic acid intake decreased. The increase in total energy intake reported was not reflected in a change in body weight.
Assessment:	Total energy from walnuts was 48g (about 314 kcal). The percent contribution to the diet was variable because the reported caloric intakes ranged from 1592 kcal to 2337 kcal among the four diets.

Comment: There was no significant effect of walnuts when added to the habitual diet but a positive effect when added to the low-fat diet. Given the reported changes in the fatty acid profile of the diets with respect to saturated fatty acids these data are difficult to reconcile. As with the Chisholm et al. these data raise an interesting practical issue. When walnuts were added to the diet there was a self reported increase in the total fat and energy. There was no change in body weight so some of the discrepancy may have been due to difficultly in accurately assessing food intake. This may also explain why it is difficult to interpret the lipid responses in light of the dietary data and again raises the issue of how a recommendation to increase walnut consumption will be interpreted by the American public.

"Would any meaningful public health benefit with respect to heart disease incidence be derived from consumers increasing walnut consumption?"

At this point it would appear that there would be little public health benefit with respect to heart disease incidence from consumers increasing walnut consumption without ensuring that increased walnut consumption would a) be accomplished by a displacement of saturated fat, *trans* fatty acid and cholesterol containing foods from the diet and b) not result in a net increase in total caloric intake. Weight gain can increase heart disease risk.

In considering any question related to potential public health benefit, it would appear important to know how and in what context walnuts are currently being consumed in the U.S. diet. For example, what percent of U.S. walnut consumption is represented by raw walnuts? Were adults to increase walnut consumption in what context would that occur? Similarly, how would an increase in walnut consumption affect the intake of total energy? What percent of calories from walnuts could reasonably and habitually be contributed within the context of current U.S. dietary intake patterns? How would a message to increase walnut intake be interpreted?

The total walnut intake in all the current studies was relatively high. It should be noted that in some cases, when subjects were instructed to increase walnut intake by displacing other foods from the diet, they did not accomplish this successfully but appeared to add them to the diet.

"How do think your conclusions, with respect to a casual relationship of walnut consumption and reduced risk of heart disease, would compare to a consensus opinion of other qualified experts evaluating the same evidence?"

It is my opinion that my assessment would be consistent with that of other qualified experts carefully evaluating the same evidence.

"If you conclude that the available evidence does support a relationship between walnut consumption and reduced heart disease risk, what is the daily walnut intake required to derive such a benefit? Can available intervention trail data be extrapolated to lower consumption levels than those of the intervention trials, or to less frequent consumption?"

Not applicable, see responses to prior questions.

"FDA health claim regulations require that the claim specify, in most situations, the daily dietary intake necessary to achieve the claimed benefit. This petition asserts that such reference to daily walnut intake is an unjustified limit on the expression of the walnut claim. Would any meaningful public health benefit be derived from labeling statements regarding walnut/heart disease relationship without indicating the effective daily consumption level?

In general, for any food or nutrient, it is unlikely that meaningful public health benefit would be derived from general widespread labeling statements without indicating the effective daily consumption level. At best, if inadequate quantities were consumed to induce a physiologically significant effect the outcome would be null. At worst, if inadequate quantities were consumed to induce a physiologically significant effect but the consumer assumed a benefit it might convey a false sense of security and cause people to be less vigilante about other aspects of their diet and/or lifestyle or cause excess caloric intake.

"For all previously authorized 'reduced heart disease risk' claims, the significant scientific agreement evaluation of the nutrient – disease relationship was based on the efficacy of the dietary substance, as part of a diet low in total fat, saturated fat and cholesterol, in reducing serum total and LDL-cholesterol. Do extenuating considerations (e.g., relatively short intervention trials of 3 – 6 weeks; small sample sizes of 10-49 subjects; an intervention that is a high fat food, and adds ca. 40 g fat and 400 kcal per day, to the diet) impact upon the predictive value of the surrogate marker for heart disease risk?"

The surrogate markers for heart disease risk, total and LDL cholesterol levels, are appropriate criteria for evaluating the nutrient-disease relationship. However, the data need to be relatively consistent among studies, show a dose-response relationship and be demonstrated in a wide range of people. For walnuts, this does not appear to be the case. In addition, diets low in saturated fat and cholesterol result in lower total and LDL cholesterol levels. An individual food may be high or low in saturated fat and cholesterol, however, its contribution to total and LDL cholesterol levels needs to be considered within the context of the entire diet. In the case of walnuts there is concern because of the data suggesting that subjects may add rather than substitute walnuts in their diet. The current data were collected over a relatively short period of time. Were the increased caloric intakes resulting from walnut supplementation real it might result in increased body weight. Increased body weight would result in increased risk of developing heart disease. The data are inadequate to evaluate this scenario.

"The health claim provisions of the FFD&C Act restrict health claims to foods that do not contain any nutrients in amounts which increase the risk of a disease which is diet related, taking into account the significance of the food in the total daily diet, except that FDA may permit a claim on such a food based on a finding that the claim would assist consumers in maintaining health dietary practices. Under this restriction, FDA has established a disqualifying level for total fat of 13 g per 50 g food. Walnuts contain approximately 32g fat/50 g. What consideration might lead to a conclusion that a walnut/heart disease claim would assist consumers in maintain health dietary practices, and justify waiving the disqualifying fat level?"

1. Dietary recommendations with respect to restricting total fat intake (i.e. Dietary Guidelines, NECP, American Heart Association) refer specifically to the total diet, not individual foods. Pairing high and low fat foods within a meal or day can result in total fat intakes that are consistent with current recommendations. Therefore, it would not appear that the total fat content of any individual food, in this case specifically walnuts, when consumed as part of a diet, would necessary be predicted to increase heart disease risk. It would be expected that the fatty acids profile of a food, whether high or low in total fat, would impact on heart disease risk.

2. Since formulation of the health claim provisions of the FFD&C Act there has been a shift in recommendations for total fat intake. In 2000 the Dietary Guidelines for Americans was revised and the guideline "Choose a diet low in fat, saturated fat, and cholesterol" (1995) was changed to "Choose a diet that is low in saturated fat and cholesterol and moderate in total fat" (2000). In 2000 the American Heart Association published revised guidelines (Circulation 2000;102:2284-2299) and the recommendation for a Step 1 and Step 2 diets (<30% calories as fat) was changed to a more general statement; "Include a variety of fruits, vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry, leans meats". In 2001 the Adult Treatment Panel III of the NCEP published revised guidelines (JAMA 2001:285;2486-2497) and the recommendations for a Step 1 and Step 2 diets (<30% calories as fat) was changed to a Therapeutic Lifestyle Change (TLC) diet with a total fat recommendation of 25%-30% of calories as fat. These changes are consistent with data suggesting the putative factor in the diet/heart disease relationship is saturated fat, not total fat.