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Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr. 2015;102(6):1347–56.

What We Know, Think We Know, or Are Starting to Know

Arguably one of the most well-established facts in nutrition science is that the replacement of saturated fat with unsaturated fat reduces blood cholesterol levels and cardiovascular disease risk [1-3]. This historic single-nutrient focus has, however, been expanded into a much more nuanced position in which the whole food matrix is considered as an exposure of interest. In this paradigm, it is acknowledged that multiple components of a given food may act synergistically to influence health [4,5]. And viewing food as the relevant exposure inherently is more applicable in daily life, as people eat food, not isolated nutrients.

For cardiovascular disease, within the broad definition of 'unsaturated fat' falls a number of specific food sources which have attracted particular research attention: oily fish, extra-virgin olive oil and other vegetable oils, seeds, and nuts. Oily fish and extra-virgin olive oil do, however, receive a lions share of the attention. While oily fish is lauded for its content of essential marine omega-3 fatty acids, and olive oil for its fatty acid composition and polyphenol content, nuts are a rich source not of both monounsaturated and polyunsaturated fats [which differs depending on the type of nut], phytosterols*, fibre, and also provide a source of protein. Thus, it could be the particular nutrient constituents of this food group which underscore their health effects.

Somewhat under the radar, extensive research in both epidemiology and controlled interventions have investigated the effects of nuts on various short-term intermediate risk factors and long-term disease outcomes. In the original Adventist Health Study, the Iowa Women's Health Study, the Nurses Health Study, and the Physicians Health Study, consumption of >4 servings nuts per week was associated, respectively, with a 38%, 40%, 39%, and 23% reduction in risk of death from heart disease [6].

In one of the few interventions to directly compare food sources of unsaturated fats, the Spanish PREDIMED trial [7] compared two intervention groups enriched in unsaturated fats to a control diet: one intervention group consumed 4-tablespoons extra-virgin olive oil per day, while the other group consumed 30g of mixed nuts (almonds, hazelnuts, walnuts) per day. While both olive oil and nut diets resulted in similar 30% risk reduction for overall cardiovascular disease events, interestingly the added nuts diet displayed a greater reduction in risk for stroke and myocardial infarction [heart attack].

By what mechanism might nuts reduce cardiovascular risk? The study we look at today conducted a meta-analysis of trials investigating the effects of nuts on blood lipid and blood pressure levels.

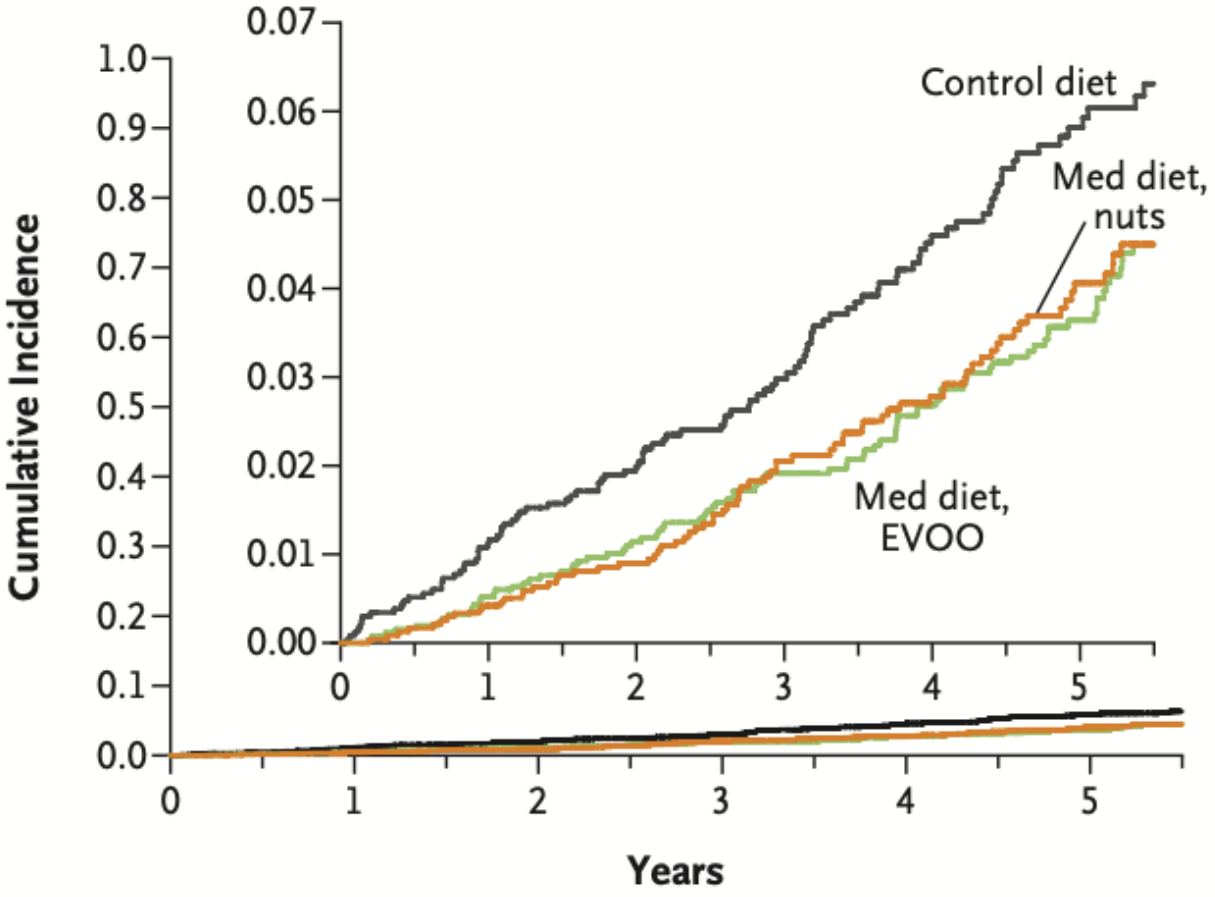

***Figure** from the PREDIMED trial [(7)] illustrating the relative risk reduction for cardiovascular disease events in from the olive oil diet **(green line)** and mixed nuts diet **(orange line)** compared to the control diet **(black line)**. This type of graph, known as a Kaplan-Meier Curve, is also known as a 'survival analysis'. The graph depicts the probability of surviving from the incidence of a specified endpoint, for example heart attack or stroke, over a given period of time (in this study it was 5yrs).*

*Geek Box: Phytosterols

Phytosterols comprise both plant stanols and plant sterols, but there is no clinical or statistically relevant difference between the two regarding their cholesterol-lowering effects. Phytosterols are cholesterol-like molecules found in all plant foods, that act by inhibiting intestinal absorption of cholesterol; they also inhibit recirculating endogenous biliary cholesterol, which is a key step in cholesterol elimination. Phytosterols have very low systemic absorption, and act by displacing dietary cholesterol from intestinal micelles, in turn decreasing the absorbable pool of cholesterol. In addition, phytosterols are taken up by enterocytes (intestinal cells) and increase the expression of ATP-binding cassette A1 transporter (ABCA1). ABCA1 is a cell membrane transport protein, responsible for the transport of cholesterol and phospholipids across the cell membrane; it also has been shown to have a role in determining plasma HDL levels. By increasing the clearance of cholesterol from macrophages (immune cells implicated in atherosclerosis and oxidation of cholesterol), and generating HDL particles, ABCA1 has an important role in mediating the secretion of excess cholesterol from the cell into HDL pathways, to be cleared by HDL. There is a final pathway by which phytosterols may decrease cholesterol levels: transintestinal cholesterol secretion, or TICE, which is an important pathway in cholesterol excretion. In animal models it has been shown that phytosterols stimulate cholesterol secretion via TICE. It should be noted that to date there are no human studies regarding the role of TICE; however, TICE has been detected in human jejunal explants, so future work may confirm that phytosterols influence this pathway in humans. Nonetheless, significant cholesterol lowering effects can be obtained from 2g per day of phytosterols, with no adverse effects noted at this dose in long-term human studies.

The Study

The study was conducted as a systematic review and meta-analysis of intervention studies on nut consumption and cardiovascular risk factors. To be included in the study, a primary trial had to meet the following criteria:

- Controlled study [randomised or non-randomised]
- Whole nuts as the intervention [excluding nut oils, nut butters, etc.]
- Blood lipids [LDL-cholesterol, HDL-cholesterol, triglycerides, ApoB (a marker for all atherogenic lipoproteins in circulation)], blood pressure, and inflammation [measured as C-reactive protein (CRP)] as outcomes
- Reported mean outcomes together with confidence intervals or standard errors

The results from each included study were standardised to a 28g [1oz] daily serving of nuts. To investigate dose-responses, the absolute level of nut intake in grams per day was analysed against the absolute change in the outcomes.

A meta-analysis was conducted for randomised trials only together, non-randomised trials only together, and all trials combined together.

Results: 61 trials - 42 randomised and 18 non-randomised - met the inclusion criteria and were included in the study, encompassing a total of 2,582 participants with a mean age of 45yr. 41 trials included both men and women. Participants in each trial were provided with nuts to consume daily. 21 trials investigated walnuts, and 16 investigated almonds, others included pistachios [n=7], hazelnuts [n=6], macadamia nuts [n=4], Brazil nuts [n=1], and 2 investigated mixed nuts. The average dose was 56g/d, with a range from 5-100g.

Statistically significant findings were observed for the following outcomes per 28g serving of nuts a day:

- ***Total Cholesterol:*** -4.7mg/dL [95% CI -5.3 to -4.0mg/dL]
- ***LDL-C:*** -4.8mg/dL [95% CI -5.5 to -4.2mg/dL]
- ***ApoB:*** -3.7mg/dL [95% CI -5.2 to -2.3mg/dL]
- ***Triglycerides:*** -2.2mg/dL [95% CI -3.8 to -0.5mg/dL]

For total and LDL cholesterol, the magnitude of effect was significantly greater in non-randomised trials. No significant difference between randomised and non-randomised trials was evident for ApoB or triglycerides.

There were no significant differences observed for any of the other lipid outcomes, blood pressure, or inflammation, either from all trials combined or separately analysing randomised and non-randomised trials.

The Critical Breakdown

Pros: A large number of trials met the inclusion criteria, providing more power to detect associations across a range of possible mediating factors [i.e., randomised vs. non-randomised, trial duration, and background diet]. Including trials where nuts were specifically provided to participants, rather than dietary advice alone to consume nuts, may have allowed for more precise quantification of the daily dose and the dose-response. The analysis was conducted using a standardised dose, rather than the usual “high vs. low” comparison used in nutrition meta-analysis, which often results in distortive lumping of studies with different levels for “high” and different levels for “low”.

Cons: Compliance in the included studies was self-reported, and misreporting cannot be ruled out. Only a handful of included studies examined certain nut types, and therefore it was not possible to robustly compare the effects of the different types of nut against each other. Weight loss was not considered from the included studies, so it is not known what effect (if any) weight loss may have had on the outcomes in the primary studies, and therefore ultimate analysis.

Key Characteristic

Including controlled trials allowed for a large pool of intervention studies to be included, however, it also illustrates the importance of randomisation. The benefit to randomisation has previously been described as "control in expectation" [8], i.e., the expectation in the effect size and in the margin or error. This apt description is illustrated well in the present study. For example, let' s take LDL-C. In randomised trials the magnitude of effect was an average of a 4.2mg decrease, with a range of -5.0mg to -3.4mg decreases as lower and upper limits, respectively. In non-randomised trials the mean was 6.0mg decrease with a range of -7.1mg to -4.9mg. As you can see, the lower limit range of the non-randomised trials [4.9mg] is practically the same as the upper limit range of the randomised trials [5.0mg]. And the mean effect size of 6.0mg in non-randomised trials is significantly greater than the mean effect size of 4.2mg in randomised trials. Were we to look only at non-randomised trials, we could expect the 'true' effect of nuts on LDL-C was significantly greater than it may be. The balancing of variables between randomising the intervention and control group, repeated over multiple studies [41 randomised in the present study], helps achieve "control in expectation" of the actual effect size. Importantly, it should be noted that confining the analysis to only randomised trials, the reduction in total cholesterol, LDL-C, and ApoB, were all significant.

Interesting Finding

The dose-response analysis indicated a minimum dose of ~60g nuts per day beyond which linear reductions in total cholesterol and LDL-C were observed. Further, the primary factor in the reduction of LDL-C appeared to be the total dose of nuts, rather than any specific type of nuts. However, higher doses of nuts would imply higher doses of the constituents in nuts: could this explain some of the findings?

The investigators published a separate analysis [9], which specifically examined the relationship between nut phytosterols and LDL-C. Because the analysis was based on a standardised 28g/d of nuts, phytosterol levels were determined by multiplying the amount of nuts by the phytosterol content of the different nut types. They then analysed the effects of phytosterol levels on LDL-C, with and without adjusting for the total content of nuts. Total phytosterol dose was associated with a significant reduction in LDL-C, but after adjusting for the total nuts intake the independent effect of phytosterols was no longer evident. However, total phytosterol content was highly correlated with total nut intake, so it may be that individual type of nuts are less relevant for phytosterol intake than higher total intake of nuts.

Thus, while the heart health benefits of nuts are often attributed to unsaturated fat and fibre content, it would appear that phytosterol content of higher nut intakes is a factor in reducing LDL-C levels.

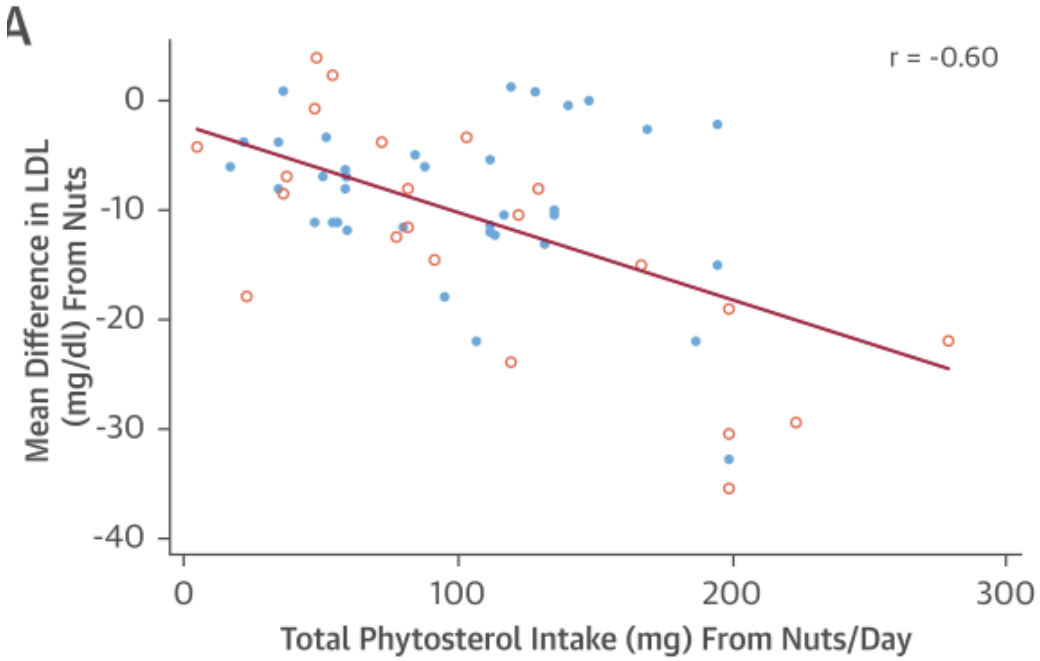

***Figure** from [9] of the regression analysis demonstrating the relationship between increasing dose of nut phytosterols (**x-axis on bottom, increasing from left to right**) and difference in LDL-C (**y-axis on left, decreasing from top to bottom**), demonstrating that as the phytosterol content from nuts increases, LDL-C decreases, evident in the red slope line running through the graph with individual study's plotted in circles (blue for randomised trials, red for non-randomised trials).*

Relevance

Dietary strategies to protect against cardiovascular disease remains a focal of nutrition science, and the evidence supporting a benefit to replacing saturated with unsaturated fats goes back to the 1950' s [1-3]. Initially, however, monounsaturated fats were deemed to be rather neutral in their effects, with polyunsaturated fats having a more clear and pronounced benefit for reducing cholesterol and CVD risk [1]. Interest in the Mediterranean diet brought more focus on to the food sources of monounsaturated fats, with an emphasis on plant sources of this fat subtype. Indeed, one feature of the PREDIMED intervention was that it occurred in the context of a high total fat diet, ~47% energy, which was predominantly monounsaturated [7].

The consistent finding of reductions of risk for heart disease from high nut intake in epidemiology has some biological plausibility in the effects of nuts on cholesterol levels observed in intervention studies. Although the magnitude of effect may not be enormous, it may be clinically relevant in the context of a wider heart-health promoting dietary pattern. In support of this, the supplementary data of the present study indicates that the greatest reduction of LDL-C observed in randomised controlled trials was against the background American Heart Association diet, an average of 6.9mg/dL reduction.

It is plausible that the contribution of higher nut intake to daily phytosterol intake underpins this effect, given their inhibition of cholesterol uptake and reabsorption [10,11] [see **Geek Box**, above]. The most effective dose of phytosterols for cholesterol reduction is ~2g/d, and the maximum level in the present study was ~275mg - could greater nut phystosterol intake result in a greater reduction in LDL-C? Perhaps. And, it is important to bear in mind that other constituents of nuts, unsaturated fats and fibre, may also exert beneficial effects. Nonetheless, the evidence indicates that nuts are a beneficial food group for cardiovascular health, potentially mediated by the contribution to phytosterol intake.

Application to Practice

First: Please check for allergies! Caveat aside, nuts are quite a defined nutritional exposure, and relatively small amounts in the 30-100g range are easily added to the diet, requiring no preparation. The minimum effective dose appears to be 30g, but perhaps intakes of >60g/d would confer an additional benefit for lowering blood cholesterol levels.

References

1. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ. 1997;314(7074):112-112.
2. Mensink R, Zock P, Kester A, Katan M. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. The American Journal of Clinical Nutrition. 2003;77(5):1146-1155.
3. Hodson L, Skeaff C, Chisholm W. The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults. European Journal of Clinical Nutrition. 2001;55(10):908-915.
4. Jacobs D, Gross M, Tapsell L. Food synergy: an operational concept for understanding nutrition. The American Journal of Clinical Nutrition. 2009;89(5):1543S-1548S.
5. Jacobs D, Tapsell L. Food, Not Nutrients, Is the Fundamental Unit in Nutrition. Nutrition Reviews. 2008;65(10):439-450.
6. Kelly J, Sabaté J. Nuts and coronary heart disease: an epidemiological perspective. British Journal of Nutrition. 2006;96(S2):S61-S67.
7. Estruch R, Ros E, Salas-Salvadó J, Covas M. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378(e34).
8. Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Social Science & Medicine. 2018;210:2-21.
9. Del Gobbo L, Falk M, Feldman R, Lewis K, Mozaffarian D. Are Phytosterols Responsible for the Low-Density Lipoprotein–Lowering Effects of Tree Nuts?. Journal of the American College of Cardiology. 2015;65(25):2765-2767.
10. MacKay D, Jones P. Phytosterols in human nutrition: Type, formulation, delivery, and physiological function. European Journal of Lipid Science and Technology. 2011;113(12):1427-1432.
11. Ostlund R. Phytosterols and cholesterol metabolism. Current Opinion in Lipidology. 2004;15(1):37-41.