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Fleming JA, Kris-Etherton PM, Petersen KS, Baer DJ. Effect of varying quantities of lean beef as part of a Mediterranean-style dietary pattern on lipids and lipoproteins: a randomized crossover controlled feeding trial. Am J Clin Nutr. 2021 Apr 7:nqaa375.

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

Nutrition science has evolved away from a purely reductionist focus on the effects of an isolated nutrient, or a single food, to a paradigm oriented around dietary patterns. From a research perspective, two characteristics that have important influence on the effect of any diet have become more evident:

- The substitution effect of replacing a given nutrient(s) or food(s) with others, and;
- The effect of 'food synergy', i.e., the interaction of different nutrients and bioactive compounds in a total diet pattern.

In 2001, Professor David Jacobs was one of the first researchers in the field to call for a reevaluation of the methodological focus for nutrition science, to one which emphasised a "top down" approach that focused on total diet patterns, followed by foods [(1)]. Jacobs and Professor Linda Tapsell published on the concept of 'food synergy', and the relevance of considering the potential interaction between nutrients and other compounds in the diet, that may add up to health-promoting effects [(2,3)].

For example, in the food-based intervention PREDIMED trial, supplementing a background Mediterranean diet with 30g per day of mixed almonds, hazelnuts, and walnuts, led to an 30% relative risk reduction in cardiovascular disease risk over 5-years [(4)]. While nominally the effect is attributable to increasing unsaturated fat intake, we cannot say that for certain. The nuts intervention provided vitamin E, alpha-linoleic acid, fibre, phytosterols and polyphenolic compounds, in addition to monounsaturated fats. In the context of a 'food first' intervention, however, where the exposure of interest is the nuts themselves, not the constituent nutrients, any food synergy is inherently accounted for.

These concepts - of substitution effects and food synergy - may also be extended to foods which have primarily been associated with adverse health outcomes, in particular red meat. One of the earliest studies to investigate this effect was the Beef in an Optimally Lean Diet [BOLD] trial, where ~150g/d lean red meat was added against a background DASH dietary pattern [(5)]. The saturated fat content of the diet was 6% energy, and the diet was high in fruit, vegetables, legumes, and wholegrain servings per day. In the context of this total dietary pattern, the red meat group had a reduction in LDL-cholesterol [LDL-C] similar to the original DASH diet [(5)].

Recent interventions have looked at other comparisons between different meat types and 'plant meat' for effects on cardiovascular risk factors [(6)]. The present study examined three different levels of daily red meat intake in the context of a Mediterranean dietary pattern for effects on blood cholesterol levels.

The Study

The study recruited healthy adults aged between 30-70yrs, with blood cholesterol levels and other cardio-metabolic markers all within normal healthy ranges. The study involved 4 different diet periods, each 4-weeks in duration. The diets were as follows:

- Med diet with 14g lean beef per day [“MED14”]
- Med diet with 71g lean beef per day [“MED71”]
- Med diet with 156g lean beef per day [“MED156”]
- Average American Diet with 71g lean beef per day [“AAD”]

Each of the Mediterranean diets had the same macronutrient profiles, which differed only to the AAD:

- Med diets: 41% fat [8% saturated, 26% monounsaturated, 8% polyunsaturated], 42% carbohydrate, 17% protein
- AAD: 33% fat [12% saturated, 13% monounsaturated, 8% polyunsaturated], 52% carbohydrate, 15% protein

The Med diets contained an average of 250mg per day EPA/DHA, had <300mg dietary cholesterol, and <2,300mg sodium. In terms of food-based targets, the Med diets contained ~30ml olive oil, 3-6 servings of fruit, and >6 servings of vegetables, per day. Both the Med14 and Med71 diets had similar amounts of plant-proteins from nuts and legumes, however, these foods were replaced by lean beef to reach the target daily intake in the Med156 group.

All diets were prepared in the metabolic kitchen at the research centres involved, and comprised 3 main meals and 2 snacks. The meals and snacks were part of a 7-day menu, which rotated for each week of the 4-week diet period. The nutrient content of the diets were verified by laboratory analysis of sample meals.

Blood samples were taken at the start of the study [baseline] and at the end of each diet period. The primary outcome was blood lipids, including total cholesterol, LDL-C, apolipoprotein B*, triglycerides, etc.

*Geek Box: Apolipoprotein B

Known as ‘ApoB’, this marker has emerged as a refined measure of all atherogenic lipoproteins in circulation. Historically, LDL-cholesterol has been the focus of assessing cardiovascular risk, given this atherogenic lipoprotein has been established as causal in the process of atherosclerosis. However, there are other lipoproteins with atherogenic potential; very-low density lipoprotein [VLDL]., intermediate density lipoprotein [IDL]., and lipoprotein(a) [Lp(a)], all of which have the potential to penetrate the arteries, become trapped, and generate the processes of atherosclerosis. This pool of atherogenic lipoproteins has not historically been measured with any accuracy; ’non-HDL cholesterol’ was a crude measure, taken by subtracting HDL out of the measure of total cholesterol. However, each atherogenic lipoprotein particle contains one molecule of ApoB; consequently, measuring ApoB provides a direct measure of the exact number of atherogenic lipoproteins in circulation. From 2019, the European Atherosclerosis Society have recommended a direct measure of ApoB to assess cardiovascular risk, where circumstances allow for it.

Results: 59 participants completed the intervention, with a mean age of 49yrs, BMI of 27m/kg2, and baseline total cholesterol of 5.0mmol/L [193mg/dL] and LDL-C of 2.8mmol/L [109mg/dL].

Compared to the AAD, all MED diets resulted in significant reductions in total cholesterol and other blood lipids. The most relevant findings in relation to blood lipids are set out below.

LDL-C: Compared to the AAD, the MED diets lowered LDL-C as follows:

- MED14: 0.26mmol/L [10.3mg/dL] decrease
- MED71: 0.23mmol/L [9.1mg/dL] decrease
- MED14: 0.17mmol/L [6.9mg/dL] decrease

ApoB: Compared to the AAD, the MED diets lowered LDL-C as follows:

- MED14: 6.3% decrease
- MED71: 5.9% decrease
- MED14: 3.9% decrease

LDL Particle Number: Compared to the AAD, the MED diets lowered LDL-C as follows:

- MED14: 91.2nmol/L decrease
- MED71: 85.3nmol/L decrease
- MED14: 73.8nmol/L decrease

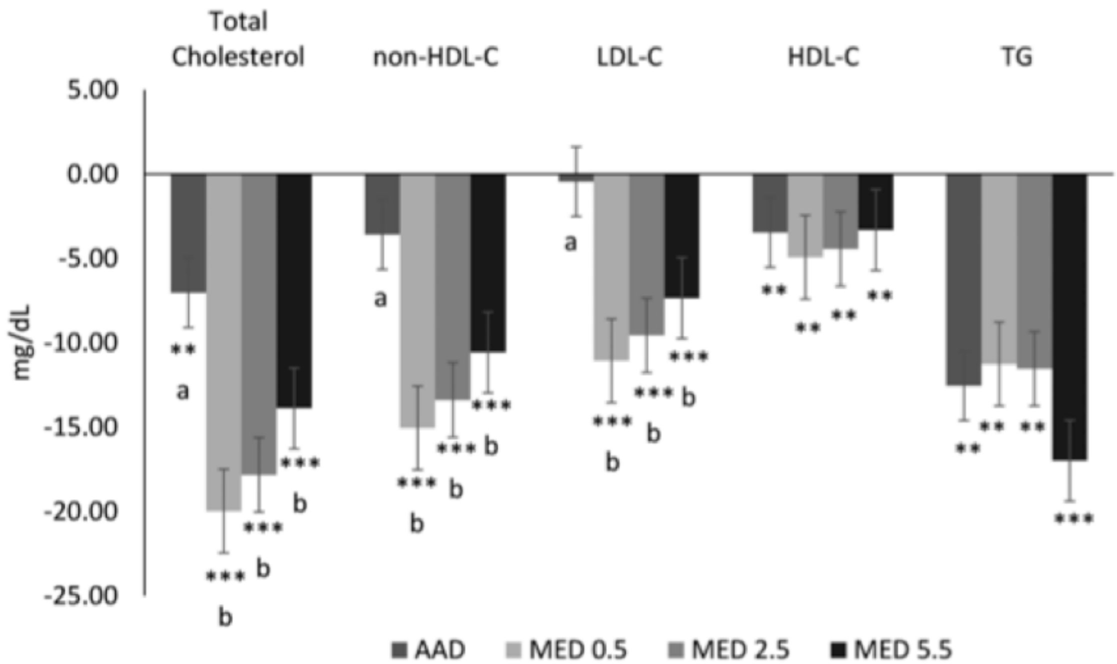

***Figure** from paper illustrating the reductions in different cholesterol measures and triglycerides [TG], with the AAD diet the far-left bar in each group, followed [from left to right] by the MED14, MED71, and MED156 diets. You'll note the paper described the diets as MED0.5, etc. This reflects the ounce amount of red meat, and while it may look cleaner than my metric adaptation, I can't think in ounces and neither does the rest of the world, so I presented each diet with their gram amount in this Deepdive.*

The Critical Breakdown

Pros: Randomisation was appropriate and fully described. The investigators and statisticians were blinded for outcome assessments and statistical analysis. The study participants were well matched and balance for male and female participants. The trial was preregistered and the description and outcomes reflect the register. The study rigorously controlled for the composition of each diet, including a biochemical analysis of the nutrient contents of diets. The intervention was designed to maintain weight in participants, such that the observed effects may be considered independent of weight loss.

Cons: Given the fact that there clearly were differences between diets, and the importance of potential modifiers, the lack of more detail on the Med diets in terms of amounts per day of legumes, nuts, fish, and other foods which made up the diets. In addition, no data on fibre was provided in the paper, another potentially important effect modifier. In light of previous recent research, it would have been useful to have a no-meat comparison group [although this is nitpicking as the AAD served as an informative control]. Notwithstanding the rigorous preparation of diet, the diets were consumed in free-living contexts and relied on self-reported adherence, thus some non-compliance cannot be ruled out. The participant demographic was predominantly Caucasian, limiting generalisability to the wider US population.

Key Characteristic

The level of control over the diets, i.e., one where participants are consuming the meals in their own day-to-day life, provides confidence to the findings. The only level up from this is if the participants were in-patients, residing in the research centre for the duration of the study: this level of control has, for example, been characteristic of Kevin Hall’ s metabolic ward studies where participants remain as in-patients for the entire four-week duration of the intervention. However, I’ m sure you could appreciate this isn’ t always feasible for many reasons. In the present study, all meals were prepared in the research facilities, and provided to participants. Further, the nutrient composition of each diet was verified through a laboratory analysis of sample foods from each rotating menu, for different calorie levels. Finally, the diets were designed to maintain weight in participants, mitigating against the potential confounder of weight loss. Overall, for a free-living dietary intervention this level of control over diet composition is as good as it gets.

Interesting Finding

Notwithstanding that all diets reduced blood lipids, the magnitude of effect was greater in the MED14 and MED71 diets, compared to the MED156 diet. Now, the tempting conclusion would be that this difference is obviously explained by red meat alone, right? But we can' t say that: the MED156 diet had twice the daily red meat as the control Average American Diet [the AAD diet had the same daily red meat as the MED71 diet], yet resulted in significantly lower LDL-C levels and other blood lipid outcomes compared to this diet.

Thus, the results more likely reflect the total dietary pattern and differences in dietary fat composition, vegetable and fruit intake, and specific food sources of protein. And it is the latter point that is potentially where an explanation lies. The Med diets were matched overall for major variables we could expect to influence blood lipids: saturated fat, polyunsaturated fat, dietary cholesterol, etc.

In fact, the primary difference between the diets related to the ratio of beef to other protein sources, in particular sources like nuts and legumes: as the amount lean beef increased to facilitate the 156g/d in the highest lean beef diet group, the amount of nuts, legumes, and fish, decreased. The paper states that both the MED14 and MED71 groups had similar amounts of these foods, i.e., nuts and legumes, despite their differing beef amounts.

Previous research investigating the cardiovascular benefits of nuts has attributed their cholesterol-lowering effects to phytosterols [(7)], for which legumes are also a rich source. Another potential explanation could be differences in soluble fibre between diets [(8)], but inexplicably for the level of dietary control in the study, no data on fibre was presented. With other aspects of the diet controlled for, we are left to infer that perhaps differences in compounds like phytosterols and/or fibre explained the slight advantage to the MED14 and MED71 diets, but we can' t be certain.

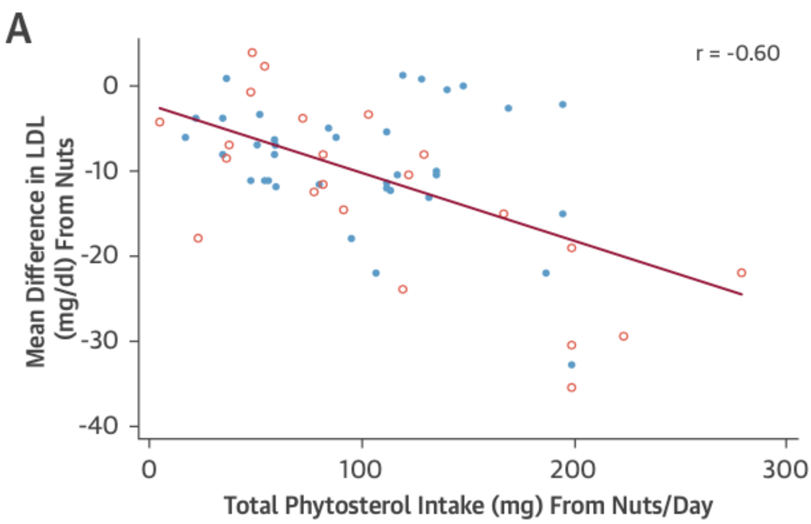

Figure *from* [(7)] *of the regression analysis demonstrating the relationship between increasing dose of nut phytosterols (**x-axis on bottom, increasing from left to right**) and difference in LDL-C (**y-axis on left, decreasing from top to bottom**), demonstrating that as the phytosterol content from 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

First, credit where credit is due: overall this a really high quality study, short of a metabolic ward study in overall execution from a dietary perspective. The Mediterranean diet is a reference health-promoting dietary pattern, that has transcended the region and found its way into dietary guidelines well beyond the Balearics. But it also heavily co-opted: depending on who you speak to, the Med diet may be described as "plant-based" [implying exclusion of animal products] or "low-carb" [implying a diet pattern resembling Twitter Keto]. And while it may be rich in foods of plant origin, and may be higher in total fat than other reference healthy diet patterns, it is neither of the two narrow latter definitions often claimed for it.

The primary relevance of the findings, particularly with high dietary control, is that the differences observed between diets must be attributable to compositional differences in the total dietary pattern, over the presence of a single food in the diet. Foods are the fundamental unit in nutrition, and have primacy in the interface between diet and health; in this regard it is more likely the cumulative and interactive effects of multiple constituents of diet that coalesce to influence health and disease (1-3). This study lends weight to the concepts of food synergy and the 'top down' focus on dietary patterns as elucidated by Jacobs and Tapsell (2,3).

However, we are still left to speculate on the what, as it is clear from recent interventions that some aspect of dietary composition modifies the effects of red meat on cardiovascular risk factors, but what that something is remains to be fully determined. For example, a study we covered in a previous Deepdive compared the effects of red meat, white meat, and 'plant meat', the red and white meat diets resulted in higher LDL-C levels independent of saturated fat content (7). In the present study, it is unclear what factors mediated the small differences between diets. We are left to speculate that it may be compounds from the foods which differed between diets: nuts, legumes, and fish. Whether factors like phytosterols and fibre [or marine omega-3's] modify any effect of red meat will require addressing directly in future research.

The diets in the present study were highly controlled and designed to cover as many bases as possible: they had saturated fat levels ~50% lower than current population averages, were replete with vegetables, fruits, legumes, and nuts, have a dietary fat composition conducive to cardiovascular health. This isn't a limitation per se, for those who can achieve such a dietary pattern; it is a reminder that neither the diet nor the characteristics of the participants are generalisable to the wider population. However, diet pattern research may have more translational relevance for contemporary dietary guidelines. While historically dietary guidelines have been nutrient-focused ['eat more fibre', 'reduce saturated fat'], little guidance has been provided on actual food intake which would yield such dietary characteristics. This study suggests that, at current average levels of red meat intake in the population [76g/d for men and 48g/d for women], focusing on *adding* to the diet in the context of Med diet characteristics may yield greater return on investment.

Application to Practice

In individuals at low risk, i.e., with normal cardiovascular risk factors, a healthy Mediterranean dietary pattern with low saturated fat and enriched in vegetables and fruit may include lean red meat and yield overall improvements in risk factors. There isn' t necessarily anything new here, in light of recent findings. However, the data does clearly indicate that the magnitude of any such improvement may relate to the lower side of moderate. Whether this effect may be compensated for by increasing intakes of other beneficial compounds remains to be fully elucidated. Overall, and this may come as a surprise to some, but public health recommendations for red meat consumption are valid.

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