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

Ah, the Mediterranean diet. There is no more popular dietary pattern in modern nutrition research, and indeed in the wider nutritional populism debates. Yet, there are some operational definitions that are often misleading. In the first instance, the term itself is offered as a homogenous representation of a diet that in reality is a very diverse region, encompassing diets from Morocco to the Dalmatian coast to Lebanon.

In fact, if you look more closely at the broad term "Mediterranean diet" as it is used in nutrition science terms, in fact this primarily represents the diets of Greece and southern Italy. This is because the genesis for identifying a specific "Mediterranean" dietary pattern was the Seven Countries Study [SCS; the most recent Research Lecture was on this study], which included three cohorts from Italy, two from Greece, and also one from Dalmatia on the Croatian Adriatic Sea coast, which each exhibited similar dietary characteristics.

If there is one unifying feature of the generic term "Mediterranean diet", it is olive oil, as the diet ties to traditional regions of olive tree cultivation [(1)]. Some other characteristics may also be similar: emphasis on legumes, cereal grains, and vegetables, is evident across the region [(1)]. However, what we in nutrition generically term the "Mediterranean diet" is mostly derived from the Greek and Italian iterations, with the Dalmatian broadly similar.

Nevertheless, one aspect in which the diet may vary is in relation to the total fat content of the diet [(1)]. For example, in the Montegiorgio (Italy) and Crevalcore (Italy) cohorts of the SCS total dietary fat was ~30% energy; in the Corfu (Greece) cohort total fat was ~32-33% energy; and in the Dalmatian (Croatia) and Crete (Greece) cohorts' total dietary fat was nearly 40% [(2)].

The lower observed rates in coronary heart disease in this dietary pattern have long attracted interest from the nutrition research community [(3,4)]. Yet the number of more robust intervention studies on the Mediterranean diet is far less than you might think from the hyperbole about the diet [(5,6)]. The present intervention trial may just have changed that.

The Study

The CORDIOPREV study was conducted at a single-centre hospital in Córdoba, Spain. The trial was a randomised intervention comparing the effects of two diets in patients with established CHD. Participants were randomised to either:

- Mediterranean Diet [MD]: Minimum 35% total fat [22% monounsaturated, 6% polyunsaturated, <10% saturated; 15% protein; 50% carbohydrates.
- Low-fat Diet [LFD]: <30% total fat [12-14% MUFA, 6-8% PUFA, <10% SFA]; 15% protein, minimum 50% carbohydrates.

The MD emphasised extra-virgin olive oil, while the LFD emphasised complex, wholegrain carbohydrate sources. Dietary cholesterol was <300mg/d in both groups. There was no restriction on daily energy intake, and physical activity targets were not promoted.

Participants in both groups had individual dietary counselling every 6-months, group sessions every 3-months, and phone calls from study dietitians every 2-months. Adherence to the diets was assessed using a points system for each diet.

The primary outcome was a composite endpoint of major CVD events [including myocardial infarction, coronary revascularisation, ischaemic stroke, peripheral artery disease, and death]. The analysis adjusted for age, sex, family history of early CHD, smoking, BMI, LDL-cholesterol, diabetes, hypertension, statin therapy, changes in weight, physical activity, and order of randomisation [the “fully adjusted model”]. Differences between groups were calculated as the time to an event* over 7-years of the study.

*Geek Box: Kaplan-Meier "Survival Analysis" and Cox Proportional Hazard Ratios

In cohort studies, you will commonly see what is known as a "survival analysis", which is data that measure the time from the beginning of a study to the occurrence of a specific event. For example, you could be interested in the effect of a type of knee surgery on the time to a further injury, i.e., the surgery would be the starting time point and a subsequent injury would be the event.

Survival analyses allow you to look at the probability of 'survival' [in this example, staying injury-free] past specified time points. However, you can also compare two groups for their respective survival times. Staying with our knee surgery example, you could compare participants who underwent one type of surgery vs. another type, or one type of surgery vs. a sham surgery.

Two common methods to estimate survival are the Kaplan-Meier method and the Cox proportional hazards model, also known as a Cox regression. These methods produce what is known as the "hazard ratio", or HR, and should be presented with 95% confidence intervals around the estimated HR. With Kaplan-Meier analysis, both the probability of surviving over a total specified time period [e.g., 5-years], and the cumulative proportion of participants surviving a specific time within the overall timeframe [e.g., each year within the 5-year overall period], are calculated. Staying with our knee surgery example, if the total study period was 5yrs, Kaplan-Meier analysis would allow you to look at the probability of having further knee surgery at 1yr, 2yrs, 3yrs, etc.

The Cox proportional hazards model differs to the Kaplan-Meier method as it allows the differences in survival times between groups to be tested while including other factors. This is why it is also known as 'Cox regression' because it is analogous to a multiple regression model, where multiple variables are entered into the model to see whether the levels of these variables predict a change in the outcome. To continue with our knee surgery example, we might want to know whether type of activity [running vs. resistance training] or type of rehabilitation [active vs. passive] influence the association between type of surgery [the exposure] and risk of a further knee injury [the outcome].

In a Cox regression, the HR's produced from the analysis do not depend on time, i.e., the hazard is 'proportional' between the groups being compared over time. Therefore, the difference in risk for an outcome is the difference at any given time, not a specific time like with the Kaplan-Meier method. The main attractive of Cox regression is that additional predictor variables can be included in the model in order to account for potential confounders.

Results: 1,002 participants were randomised and began the intervention; 502 in the MD group and 500 in the LFD group. 82.5% were male and the average age was 59.5yrs.

- ***Major CVD Events*:** In total, the primary outcome of major CVD events occurred in 87 participants in the MD group and 111 participants in the LFD group. Thus, in the fully adjusted model, there was a 29% [HR 0.71, 95% CI 0.54 to 0.97] lower risk of CVD events in the MD group compared to the LFD group.

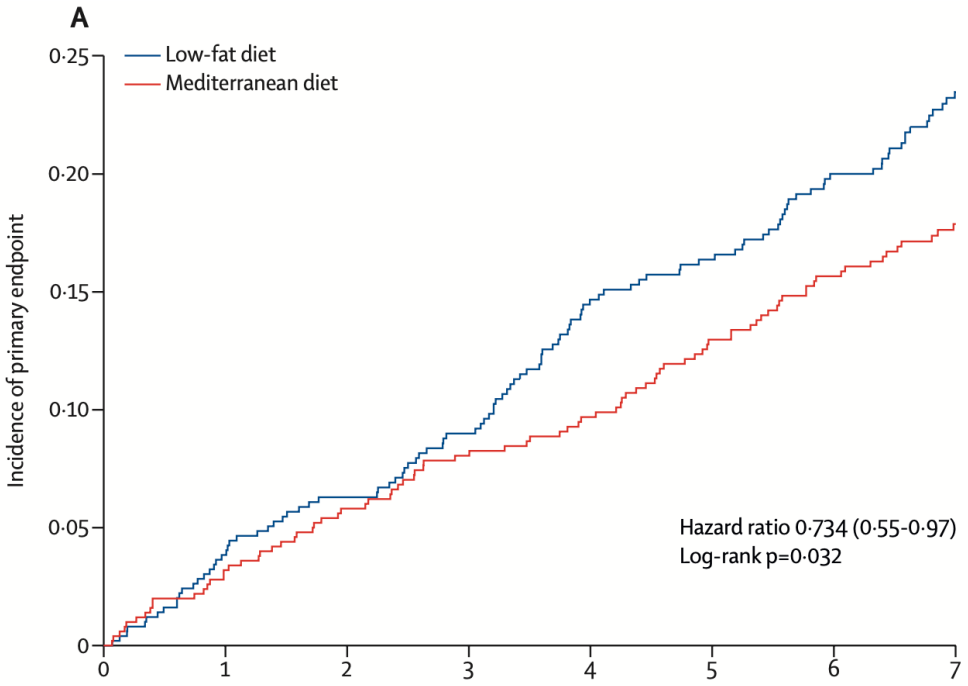

***Figure** from the paper of the Kaplan-Meier survival curve for the MD and LFD. The bottom X-axis is each year of the intervention; the left Y-axis is the incidence of the primary endpoint of major CVD events. Recall from the ***Geek Box**, above, that the estimates from a Kaplan-Meier analysis do not include additional variables; therefore this is what is known as the 'crude rate' difference between groups, which is why the HR is different. However, as you'll note from the primary findings above, adjusting for all of the additional variables using the Cox regression analysis strengthened the findings, albeit overall the difference between the crude rate HR for the MD and the fully adjusted HR was minimal [HR 0.73 and HR 0.71, respectively].*

- ***Subgroup Analysis – Effect of Sex*:** There was no significant difference between groups in women [HR 1.27, 95% CI 0.64 to 2.49], however, in men there was a significant 32% [HR 0.68, 95% CI 0.50 to 0.94] lower risk of CVD events in the MD group compared to the LFD group.
- ***Subgroup Analysis – Effect of Age*:** There was a significant 28% [HR 0.72, 95% CI 0.53 to 0.97] lower risk in participants under 70yrs of age, but no significant difference in those older than 70yrs.
- ***Subgroup Analysis – Effect of LDL-C*:** There was a significant 36% [HR 0.64, 95% CI 0.43 to 0.90] lower risk in participants with LDL-C of <100mg/dL [2.5mmol/L], but no significant difference in those with LDL-C >100mg/dL [more under ***Interesting Finding***, below].

The Critical Breakdown

Pros: Randomisation was stratified according to sex, age, and previous myocardial infarctions. Stratified block randomisation of this type ensures that these factors are balanced between both diet groups. Only the study dietitians knew the assignment of participants; physicians, investigators, and statisticians remained blinded to the participants diet group. Participants in both groups were provided with the same intensity of dietary counselling. The statistical analysis was conducted including all participants using the intention-to-treat principle [ITT], i.e., all participant included whether they completed the trial or not [using the last data point if not], to maintain balance between groups and reduce risk of bias. The study had a sufficient sample size for statistical power to detect significant differences between groups. The fully adjusted analysis adjusted for multiple relevant variables. The 7-year follow-up period is the longest follow-up for a nutrition intervention comparing diets in secondary CVD prevention.

Cons: More participants dropped out of the LFD [n = 86] compared to the MD [n = 46]. Further, adherence to the diets [based on points scales] also differed with 62% and 42% in the MD and LFD groups, respectively. Both findings indicate that, despite the same intensity of counselling, the LFD group was less acceptable in some ways. The fact that the significant difference between groups reflected a significant difference in men, but not women, indicates that the low numbers of women in the trial [17.5%] may have lacked statistical power to detect effects in women separately.

Key Characteristic

Recall in our previous Research Lecture on the SODIUM-HF trial, we introduced this heuristic to think through a study: Exposure, Mechanism, Outcome, Population ['EMOP']. On this point, it is important to bear in mind the participant characteristics, both in terms of region and health status, i.e., south of Spain and secondary prevention patients already treated for CHD. The point here is that even at baseline, the LFD group and MD group were relatively similar in already exhibiting beneficial dietary characteristics: ~25g/d fibre, ~8% saturated fat, ~16% oleic acid, and >600g/d combined vegetables and fruits.

In fact, in trying to tease out the differences between groups, it becomes clear that there were not that many substantial differences in many food-based intakes. Eggs, poultry, dairy, red and processed meats, and wholegrain cereals were all largely similar between diet groups. The main food-based differences that were higher in the MD were total and extra-virgin olive oils, vegetables, fruits, total seafood and oily fish. Thus, it is possible that the minimal changes in total fat and carbohydrate in the LFD group did not add any meaningful difference to the quality of the LFD dietary pattern, which was actually a good dietary pattern overall anyway.

Another possibility to consider is whether the effect size was influenced by differences in dietary compliance, e.g., the LFD group never achieved their targets for total fat and carbohydrate over the 7yrs of the intervention. However, this does not appear to be the case from the data. If we look at the supplementary materials, we can see that they conducted a sensitivity analysis confined to only participants with >80% adherence. In this analysis, the effect was *stronger* again, with a 41% [HR 0.59, 95% CI 0.37 to 0.92] lower risk in the MD group.

All of this points to the fact that in this group of participants already with CHD, and even with an LFD diet that was a good quality dietary pattern overall, the apparently subtle differences in macronutrient composition [potentially] and/or specific foods [more plausibly] in the MD, influence underlying processes of CVD in clinically meaningful ways [more under ***Relevance***, below].

Interesting Finding

The finding of the subgroup analysis which stratified participants based on their levels of LDL-C is striking, for two related reasons. The first is that in the context of disease management, usually, diet is considered the adjuvant treatment to drugs/surgery. In this context, when patients are treated with drugs to target levels of specific risk factors, e.g., LDL-C or blood pressure, then we would not expect to see a major additive effect of diet, but potentially more modest effect sizes. The second related reason is that where there are differences in risk factors, we would expect the direction of effect to favour those patients with higher levels of that risk factor.

Let' s think about this in the context of the present study. Overall, baseline LDL-C was ~90mg/dL [2.3mmol/L], a reflection of the fact that 86% of all participants were on statins at baseline [equal between groups]. In both groups, LDL-C decreased by ~11mg/dL [0.28mmol/L], and there was no significant difference between groups in any blood lipid or blood glucose parameters before or after the intervention.

In the MD and LFD groups, the numbers of participants with LDL-C under 100mg/dL was 355 and 353, respectively, and with >100mg/dL was 147 and 147 in the MD and LFD groups, respectively. Could lower numbers drive the lack of significance, once stratified by LDL-C level? This is always arguable.

However, the difference in the crude event rate is striking. In participants with LDL >100mg/dL, the event rate was 27 out of 147 participants in the MD group and 30/147 in the LFD: practically no difference. However, in participants with <100mg/dL LDL-C, the event rate was 57/355 and 84/353 in the MD and LFD groups, respectively, a crude difference of 27 major CVD events. And this analysis was fully adjusted for potential confounders.

Thus, in effect we have a significantly lower risk in the MD group that is additive to already low LDL-C, when compared with the LFD. The whys and wherefores of this, at this point, I think we can only speculate on. A sub-study of the CORDIOPREV intervention showed significantly greater improvements in endothelial function, including flow-mediated dilation, repair mechanisms, and reduce damage to the vascular endothelium [(7)]. It is possible that this might explain the additive effect of the MD even in the context of low LDL-C levels, but we will need future research to confirm this.

Relevance

So here we are. Recall in the What We Know section at the outset, we highlighted that despite the hyperbole for the Mediterranean diet in the nutrition community, the number of interventions showing reductions in CVD endpoints is quite limited.

What is often considered the first, the Lyon Diet-Heart Study [LDHS], showed a whopping 75% [HR 0.35, 95% 0.15 to 0.83] lower risk of cardiac death and nonfatal MI in patients in secondary prevention [6]. However, consistent with the overly generic application of the term "Mediterranean diet", the LDHS was not quite an MD; rapeseed oil [aka canola oil in North America] was the primary added oil, and the diet was more "resembles Med diet in macronutrient composition" rather than in food-based terms.

Then PREDIMED came along, and everyone lost their Med-minded minds; a multi-centre primary prevention diet trial with a 30% reduction in risk of CVD events with a "true" Med diet, where the exposures of interest in two the intervention groups were extra-virgin olive and nuts, respectively [8]. However, questions were raised over the potential for bias from the randomisation procedure, in which several of the centres were randomised, rather than individuals. The initial 2013 paper was retracted, the data reanalysed, and ultimately republished in 2018 with similar findings [5].

But PREDIMED left questions: how reliable were Mediterranean diet interventions for CVD? One way to think about reliability of research findings is to look beyond *p*-values and 'statistical significance' to consider the Fragility Index [FI] [9]. The FI is based on the fact that a change in a very small number of events in a study could shift statistically significant findings to non-significant [9]. Using the FI identifies the number of events that would be required to change the results, i.e., it is a tool to consider how robust the findings are [9].

While I' m not a huge fan of the FI because it repackages the binary "statistically significant/non-significant" way of thinking about scientific findings [10,11], it can be useful to think about robustness. For example, a recent analysis of Mediterranean diet trials using the FI found that as little as 1 to 4 further events in the intervention group eliminated the statistical significance of the findings [12]. For example, the authors calculated that 5 more events in the intervention groups in PREDIMED would have eradicated the significant difference between groups [12]. Conversely, 17 more would be required to have the same effect on the findings of the LDHS, indicating a more robust outcome for that trial.

How reliable are the findings of CORDIOPREV? Arguably they add the best available evidence to date for the effects of a Mediterranean diet on CVD, bolstering the LDHS in showing substantial reductions in secondary prevention of patients with existing CHD/CVD. The crude rate difference was not just observed for the primary endpoint of major CVD events, but for each component of that composite endpoint. Nevertheless, only the composite endpoint was 'statistically significantly' different between groups.

However, when we factor in the methodological quality of the trial and the findings as a whole: the fact that the strength of the primary outcome remained after fully adjusting for relevant variables, the strengthening of the finding with higher adherence to the Mediterranean diet, and the fact that these benefits were independent of medications and already low and controlled levels of key risk factors – blood lipids and blood glucose – and, unlike LDHS, a more representative Mediterranean diet, CORDIOPREV is the best-in-class to date for Mediterranean diet intervention studies.

Application to Practice

I think the LDHS actually gives us a really point: the idea the a “Mediterranean diet” could be some ubiquitous, homogenous entity applied in all populations is a little absurd. For example, if you lived in Estonia, why would you opt for trying to copy a Mediterranean diet when the Nordic and Baltic Sea dietary recommendations are just as good? I think we need to think hard about external validity, i.e., the wider generalisability of the findings of these studies before assuming that if you’ re working with someone in Seattle, Singapore, or Slough, that the food-based characteristics of the Mediterranean diet are replicable anywhere.

The reason I’m referring to LDHS here is because it is instructive that the Mediterranean diet doesn’t need to be perfectly replicated. What arguably matters more is the nutritional composition that such a dietary pattern facilitates: low saturated fat, enriched unsaturated fat content, primarily derived from plant and marine sources; increased vegetable and fruit intake; adequate dietary fibre; adequate dietary protein; wholegrain carbohydrates. At the level of those characteristics, these can be achieved in the context of a much broader palate of dietary patterns. For example, oats are not a habitual aspect of the Mediterranean diet, but you’ re hardly going to stop considering them for that reason.

That said, is there cause for considering specific food-based aspects of the Mediterranean diet? Arguably the polyphenol and oleic acid enrichment of extra-virgin olive oil places it atop a pyramid of oil quality. Thankfully this is available anywhere in the world. But for the wider characteristics, there is plenty of scope to achieve the nutritional composition with foods more habitual to regional dietary patterns.

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