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

For the long history of interest in the role of diet in cardiovascular disease [CVD], the question over the total fat content of a diet has loomed large [(1)]. In his 1952 review paper on the role of diet in atherosclerosis published in the journal *Circulation*, Ancel Keys stated that, although the evidence was weak, it suggested:

"a substantial measure of control of the development of atherosclerosis in man may be achieved by control of the intake of calories and of all kinds of fats..."

This was before the elegant 1950's metabolic ward feeding studies, to which he contributed, demonstrated that the composition of fat in the diet, in particular the relationship between saturated and unsaturated fats, was the most important determinant of blood cholesterol levels [(2–4)].

Nevertheless, it did appear that both total fat content *and* fat composition were somewhere related in those years [(5)]. For example, in the Seven Countries Study [SCS], the highest total fat intakes were observed in the East Finnish [38.5%], West Finnish [34.3%], Dutch [38.0%], and American [38.0%] cohorts [(6)]. These cohorts also exhibited the highest intakes of saturated fats at between 16–24%.

However, in the Greek cohorts [Corfu and Crete] total fat intake was 33–36%, but saturated fat comprised 6–7% energy [(6)]. In the 15-year follow-up of the SCS, high intake of monounsaturated fats [MUFA] was associated with lower risk of coronary heart disease [CHD] [(6)]. Yet what was particularly interesting in this paper was the differences in CHD risk between the different levels of MUFA intakes across cohorts was explained by differences in oleic acid [(6)]. Because the Seven Countries Study conducted laboratory analysis of food samples, they were able to identify that ~80% of the oleic acid in the diets consumed in the Italian, Greek, and Dalmatian [Croatian] cohorts was from olive oil [(6)].

In the context of prevailing public health advice to lower total fat intake to <30–35% [depending on country], it has been common for research to investigate low-fat diets for CVD/CHD risk. In PREDIMED, comparing a higher fat [~45%] Mediterranean diet to a "low-fat" diet showed a 30% lower risk of major CVD events over 5-years [(7)]. However, the "low-fat diet" was 37.5% energy, which is a mischaracterisation of the diet, even if it was intended for the control group to consume a low-fat diet.

We have previously covered the primary publication from the CORDIOPREV trial in a Deepdive, which compared a Mediterranean diet to a low-fat diet in Spanish participants

with CHD, i.e., in secondary prevention. Over 7-years of follow-up, the risk of experiencing a further CVD event was 29% lower in the Mediterranean diet group.

What mechanism might explain the effects of the Med diet over the low-fat diet? The present study was part of the secondary objectives of the CORDIOPREV trial, to investigate the effects of the diets on atherosclerosis progression using measurements of intima-media thickness of the carotid arteries.

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.

In food-based terms, the primary recommendations for both diets were as follows:

- **MD**: ≥4/day tablespoons extra-virgin olive oil, ~200g/d vegetables [with one of which raw veg], ≥3/d units' fresh fruit, ≥3/week servings legumes, ≥3/week servings of seafood [with one of which oily fish], ≥3/week servings nuts and seeds.
- **LFD**: 6–11/day servings of wholegrains/legumes/potatoes, ≥200g/d vegetables [one raw, but without any added fat, sauce, or oil], ≤2/d tablespoons of sunflower or non-virgin olive oil, ≤1/week serving oily fish, ≤1/week serving nuts and seeds.

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 present study was a secondary objective of the overall CORDIOPREV trial, to assess changes in intima-media thickness [IMT] of the carotid arteries* [see **figure** below], a marker of subclinical atherosclerosis. This analysis used measures of both left and right side carotid arteries [IMT-CC], expressed as the average of both in millimetres. Measurements were taken at baseline, 5yrs, and 7yrs follow-up.

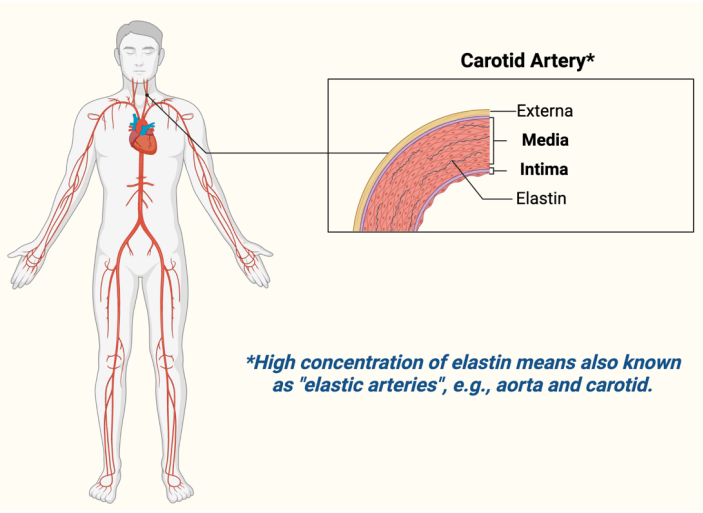

***Figure** illustrating the location of the media and intima of the carotid arteries. The carotid arteries are elastic arteries located on either side of the neck which deliver blood to the brain.*

Results: 939 participants had IMT-CC scans at baseline, of which 731 completed IMT-CC scans at 5 and 7yrs follow-up, respectively. Average age of participants at baseline was 59.6yrs, and 82.4% of participants were male. Carotid plaque was present in 82.3% of participants at baseline, and 85.7% were treated with statins.

Changes in Diet*:** Mediterranean diet adherence scores [range: 0–14] were similar at baseline in both groups, 8.7 and 8.9 in the LFD and MD, respectively. In the MD group, average adherence scores had increased by 2.5 and 2.3 after 5yrs and 7rys follow-up, respectively. In the LFD group, average Mediterranean diet adherence scores had decreased by 1.1 and 0.9 after 5yrs and 7rys follow-up, respectively [more under ***Key Characteristic, below].

***Effect of Diet on IMT-CC Plaques*:** The MD group showed a significant decrease in IMT-CC of 0.027mm and 0.031mm after 5yrs and 7rys follow-up, respectively, compared to the LFD [see **figure** below]. The maximum carotid plaque height was also significantly reduced in the MD group by 0.09mm and 0.10mm after 5yrs and 7rys follow-up, respectively.

In a multi-variable regression analysis to determine the independent effects of different factors which may have influenced changes in IMT-CC over time, the strongest predictor was baseline levels of IMT-CC, i.e., those with higher IMT-CC at baseline had greater reductions in IMT-CC over time [discussed further under ***Interesting Finding***, below].

The Critical Breakdown

Pros: The aims and objectives of the study were clearly stated. Randomisation was stratified according to sex, age, and previous myocardial infarctions, which 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. Further, the IMT ultrasound scans were also performed by technicians blinded to the dietary allocation of participants. The characteristics of the participants who dropped out were similar to those who completed follow-up scans, which may minimise bias from dropouts. The statistical analysis adjusted for multiple relevant covariates, e.g., sex, energy intake, medications, smoking, etc. The study was sufficiently powered to detect changes in IMT-CC over time, and between groups. IMT-CC was determined according to best practice recommendations. The 7yr follow-up period is the longest follow-up for a nutrition intervention comparing diets in secondary CVD prevention.

Cons: No hypothesis was stated. Participants were not well matched for sex and the study contained only 17.6% female participants. This is important given sex differences in CVD risk and management [8]. The LFD was not in reality a "low-fat diet", with an average of 32.1% fat over the follow-up period. The food-based instructions differed substantially, despite the participants all having a background diet that was overall of good quality and "Mediterranean" in dietary characteristics at baseline [more under ***Key Characteristic***, below]. There were also differences in adherence, with more dropouts from the LFD group compared to the MD, and lower adherence to the overall respective dietary recommendations in the LFD group.

Key Characteristic

One of the clear challenges for valid inferences and conclusions in large nutrition trials of "low-fat diets" and CVD/CHD is that the construction of the diets often leaves a lot to be desired, e.g., lowering fat by replacement with refined carbohydrates [9].

Or they are simply not "low-fat diets", e.g., PREDIMED with its "low-fat" control group that consumed ~37% total fat. Which is the same issue as the present study, in which the LFD failed to reach the target intakes for both carbohydrate and total fat.

In the present study, the MD was characterised by positive steps, i.e., *adding* to the diet in the context of a population consuming a background diet that is relatively "Mediterranean" in composition. Conversely, the LFD was characterised by instructions to "minimise" or "avoid"; recall that the instructions in this group was not to add any oils to raw veg...yummy! Thus, the MD group had the benefit of more culturally compatible dietary changes, which the LFD did not.

Both diet groups, for the general population, had relatively good diet quality at baseline. However, if we look at food-based changes over time, the MD had greater increases in veg, fruit, legumes, and wholegrains compared to the LFD [although the LFD still had decent diet quality overall]. The MD emphasised extra-virgin olive oil, while the LFD instead was instructed to have sunflower or non-virgin olive oil. It may have been a more instructive intervention to test similar total fat intakes, but different food sources of fats and oils.

We are thus presented with some ambiguous inferences from this study. First, the LFD was not a "low-fat diet", so we should not mischaracterise it as such. Second, because the actual changes in macronutrient intakes and foods between diets were relatively modest, it is challenging to infer *what* explains the difference between groups.

Nevertheless, there were some obvious increases in the MD compared to the LFD that we could infer might explain differences, in particular extra-virgin olive oil, veg and fruit, and nuts. The question that arises is to what extent is there an independent contribution of diet to the reduction in IMT-CC, which leads us to our Interesting Finding...

Interesting Finding

The study conducted two separate analyses to investigate the changes in IMT-CC over the course of the study. The first tested the effects of each diet at each time point [see the **figure** above in the **Results** section]. This showed that the MD group had significant reductions in IMT-CC at 5yrs and 7yrs follow-up, while the LFD did not show any overall change.

However, this type of statistical analysis does not necessarily allow us to determine the strength of contribution of different variables to the outcome, which a multi-variable regression analysis does. Thus, in addition to their analysis of changes over time, the authors also conducted a regression analysis to determine whether the baseline level of IMT-CC, diet, or other factors [i.e., age] predicted changes in IMT-CC over the course of the study.

The outputs of a regression analysis are reported as "unstandardised coefficients" or "standardised coefficients". The difference is that unstandardised coefficients are interpreted in the unit of measurement that was analysed. For example, in the present study the unstandardised coefficient for the effect of the MD was -0.027; you would interpret this as indicating that allocation to the MD was associated with a 0.027mm decrease in IMT-CC, compared to the LFD. This is consistent with the primary analysis.

However, with a standardised coefficient, the unit of measurement is removed, because the aim is to rank the relative importance of each variable included in the regression in terms of their strength of influence on the outcome. For example, the standardised coefficients for factors associated with reduced IMT-CC were –0.678 for baseline IMT-CC and –0.117 for diet.

This tells us that the baseline level of IMT-CC was much more strongly independently associated with subsequent changes in IMT-CC during the study than diet was. Importantly for our interpretation, it does not appear that any specific macronutrient changes, i.e., SFA, MUFA, or PUFA, were independently associated with lower IMT-CC. Thus, we are left only with a broad inference for the overall MD.

In the **table** from the paper, below, I've added the differences in what unstandardised and standardised coefficients communicate to us in red; unit of measurement [i.e., unstandardised] on the left, and ranking of relative strength of importance [i.e., standardised] on the right.

Independent variables	Unstandardized coefficients		Standardized coefficients	
	B	SE		*P* value
Age, y	0.002	4.5×10^{-5}	0.154	7.0×10^{-6}
Allocation into Mediterranean diet (vs low-fat diet)†	–0.027 mm	0.007	–0.117 No.2	2.7×10^{-4}
BMI at baseline, kg/m^2	0.002	0.001	0.076	0.020
Energy intake at baseline, kcal/d	1.5×10^{-5}	7.0×10^{-7}	0.073	0.024
T2DM at baseline, yes	0.017	0.008	0.074	0.029
IMT-CC at baseline, mm	–0.521 mm	0.027	–0.678 No.1	3.1×10^{-66}
Carotid plaque number at baseline, n	0.008	0.003	0.085	0.010

Relevance

In our previous Deepdive of the primary CORDIOPREV findings, we stated that this study was the "best-in-class to date for Mediterranean diet intervention studies". In terms of the overall quality of the trial, and its duration of follow-up, this is a statement that we can stand over; the trial provides a more advanced study of secondary prevention compared to the Lyon Diet-Heart Study [LDHS], which was published in 1999 [10].

CORDIOPREV also has the advantage over PREDIMED in terms of total duration of follow-up [7yrs vs. 5yrs], and is more highly powered than the PREDIMED sub-study of IMT progression which was conducted over 1-year in 187 participants [11]. That PREDIMED sub-study showed that the extra-virgin olive oil and nut-enriched Mediterranean diets lowered IMT-CC compared to the control, but only in participants with baseline IMT-CC of >0.9mm [11].

This is somewhat instructive for interpretation of CORDIOPREV, which suggested that participants with a high plaque burden at baseline exhibited the greatest reduction in IMT-CC, and that the MD was the dietary allocation that was independently associated with this reduction in carotid plaque.

Bear in mind that previous research has shown that progression in carotid IMT of between 0.018mm to 0.033mm per year was associated with a 130% higher odds of a further coronary event [12]. Thus, the reduction of 0.027mm associated with the MD in the present study may be clinically meaningful in the overall picture of risk reduction in secondary prevention.

Application to Practice

The CORDIOPREV study has shown a 29% lower risk of incidence of further CVD events in secondary prevention patients, and the present study expands on this analysis by demonstrating reductions in IMT-CC in the MD group.

However, this research does leave us with some open questions about what aspects of the diet composition differences may explain the benefit to the MD. Nevertheless, of this we can be certain based on current evidence; the total fat content of the diet is not a relevant consideration, but the composition of fat is.

In the present study, the MD group consumed 41.5% total fat, of which 8.1% was SFA, 22% MUFA, and 7.5% PUFA. The majority of the increase in MUFA was explained by the emphasis on high daily extra-virgin olive oil intake. Overall, the echoes of the Seven Countries Study ring through in the CORDIOPREV trial. Although we can't make confident inferences about that specific food, the overall MD dietary changes that include the increase in nuts, veg and fruit, and oily fish, are consistent with the health effects of this dietary pattern.

If we think about these findings relative to the LDHS, collectively these two secondary prevention trials suggest that dietary changes in high-risk patients that are already managed with medications, may in fact yield meaningful benefits to risk of further CVD events.

References

1. Keys A. Human Atherosclerosis and the Diet. Circulation. 1952 Jan;5(1):115–8.
2. Keys A, Anderson JT, Grande F. Prediction of Serum-Cholesterol Responses of Man to Changes in Fats in the Diet. The Lancet. 1957;Nov 16(73(7003)):959=966.
3. Bronte-Stewart B, Antonis A, Eales L, Brock JF. Effects of Feeding Different Fats on Serum-Cholesterol Level. The Lancet. 1956;April 28(270(6922)):521–6.
4. Ahrens EH, Blankenhorn DH, Tsaltas TT. Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet. Proc Soc Exp Biol Med. 1954;Aug-Sep(86(4)):872–8.
5. Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, et al. Dietary Saturated and transFatty Acids and Cholesterol and 25-Year Mortality from Coronary Heart Disease: The Seven Countries Study. Prev Med (Baltim). 1995 May;24(3):308–15.
6. Keys A, Menott A, Karvonen MJ, Aravanjs C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. Am J Epidemiol. 1986;124(6):903–15.
7. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. New England Journal of Medicine. 2018;378(25):e34.
8. de Miguel-Yanes JM, Jiménez-García R, Hernandez-Barrera V, de Miguel-Díez J, Muñoz-Rivas N, Méndez-Bailón M, et al. Sex Differences in the Incidence and Outcomes of Acute Myocardial Infarction in Spain, 2016–2018: A Matched-Pair Analysis. J Clin Med. 2021 Apr 20;10(8):1795.
9. Howard B V., Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, et al. Low-Fat Dietary Pattern and Risk of Cardiovascular Disease. JAMA. 2006;295(6):655.
10. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779–85.
11. Murie-Fernandez M, Irimia P, Toledo E, Martínez-Vila E, Buil-Cosiales P, Serrano-Martínez M, et al. Carotid intima-media thickness changes with Mediterranean diet: A randomized trial (PREDIMED-Navarra). Atherosclerosis. 2011 Nov;219(1):158–62.
12. Haberka M, Bałys M, Matla M, Kubicius A, Maciejewski Ł, Gąsior Z. Carotid artery stenosis and ultrasound vascular indexes predict the coronary revascularization in patients with high cardiovascular risk scheduled for coronary angiography. Kardiol Pol. 2019 Nov 22;77(11):1028–33.