ALINEA

NUTRITION

JANUARY 2022

www.alineanutrition.com

TABLE OF

CONTENTS

Delgado-Alarcón JM, Hernández Morante JJ, Aviles FV, Albaladejo-Otón MD, Morillas-Ruíz JM. Effect of the Fat Eaten at Breakfast on Lipid Metabolism: A Crossover Trial in Women with Cardiovascular Risk. Nutrients. 2020;12(6):1695.

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

What you may not know is that cardiovascular disease [CVD] has, since the late 1970' s, been considered by some to be a "post-prandial phenomenon" [(1)]. The digestion, absorption, and metabolism of fat following a meal influences circulating levels of lipoproteins* capable of penetrating the artery [(2)]. So, let' s have a brief recap on what we know about fat metabolism…

There are two main pathways relevant to fat metabolism: the exogenous [dietary] and endogenous [liver] pathways [see ***Figure***, below]. The exogenous pathway reflects fat taken in through the diet, the primary vehicle for which are chylomicrons. The endogenous pathway reflects fat synthesis in the liver, the primary vehicle for which is very-low-density lipoproteins [VLDL].

First, the exogenous pathway. Triglycerides [TG] are the primary form of fat consumed in the diet, which are packaged in intestinal cells into chylomicrons [CM], the largest of all lipoproteins. As the fat content of a meal increases, CM increase in their size, i.e., in their TG content, rather than increase in number [(3)]. The size and composition of CM after a meal containing fat is determined by both the total fat content, and the types of fat, in a meal [(3)].

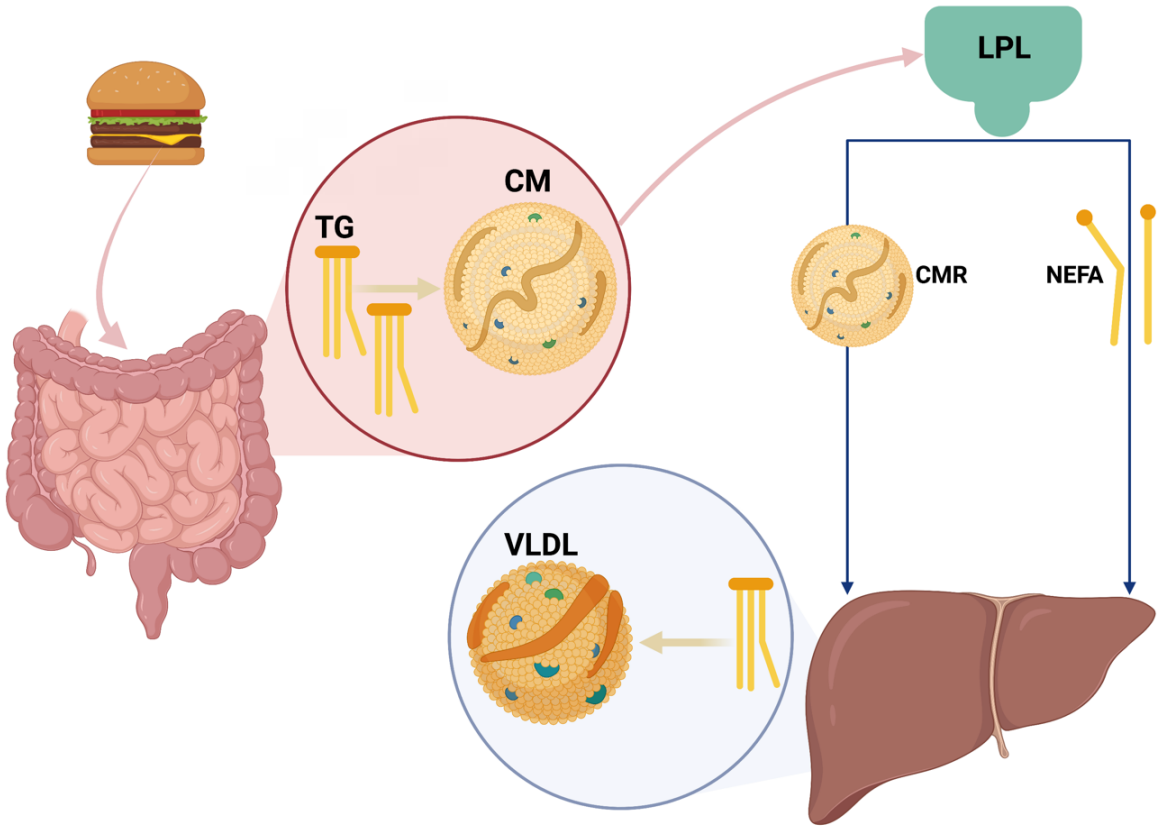


Figure *illustrating the exogenous [dietary] and endogenous [liver] fat metabolism pathways.*

As CM then enter the circulation, the TG on board are broken down by an enzyme, known as lipoprotein lipase [LPL]. The fatty acids [known as 'non-esterified fatty acids', or NEFA] released from this breakdown of TG can be used for energy production, taken up by fat tissue, or taken up by the liver, where they are often repackaged into new TG [see ***Figure***, above] [(2)]. With the breakdown of the TG, CM become smaller, more cholesterol-rich particles, known as "chylomicron remnants" [CMR]. These CMR may also be taken up by the liver [see ***Figure***, above] [(3)].

For the endogenous pathway, VLDL is synthesised in response to the delivery of fatty acids to the liver [and also the conversion of carbohydrates to fatty acids] and the creation of new TG. These fatty acids may be derived from 'spill over' from the diet, as noted above with CMR and NEFA, and from mobilisation from fat tissue during the fasted state. VLDL is released in two sizes, larger and smaller. The TG in larger VLDL are also broken down by LPL, which creates VLDL remnants. As the TG in smaller VLDL are broken down, it become intermediate-density lipoprotein [IDL] and ultimately low-density-lipoprotein [LDL] [(3)].

For some more on lipoproteins, check out the Geek Box, below. With all of that in mind, it should be clear that the amount and type of dietary fat may be important in determining the levels of these fat transporters in the circulation. Let's get to the study…

*Geek Box: Atherogenic Lipoproteins

The size and density of lipoproteins is crucial to understanding the capacity of these compounds to enter into the artery. The following are the major classes of lipoproteins classified according to their size and their density:

1. *Chylomicrons (CM): 75-1,200 nanometers [nm] in diameter*
2. *Very-low-density lipoprotein (VLDL): 30-80nm*
3. *Intermediate density lipoprotein (IDL): 25-35nm*
4. *Low-density lipoprotein (LDL): 18-25nm*
5. *High-density lipoprotein (HDL): 5-12nm*
6. *Lipoprotein(a) or Lp(a) - technically a sub-type of the LDL class: 25-30nm*

'Density' refers to the amount of lipid relative to protein (known as 'apolipoprotein') of the particle. For example, the composition of VLDL is roughly 92% lipids and 8% protein. Because lipids are large compounds, this means that VLDL are large lipoproteins, but with low-density. Conversely, the composition of HDL is roughly 58% lipids and 42% protein; this high protein composition makes HDL quite 'dense', and the smallest of all lipoprotein subclasses. Thus, more lipid and less protein means a larger, less dense particle. On the other hand, less lipid and more protein means a smaller, more dense particle. All of these lipoproteins except for HDL are wrapped in apolipoprotein-B, or ApoB. A key feature of 'forward cholesterol transport' is the progressive breakdown of triglycerides carried in chylomicrons and VLDL, leading in turn to the formation of chylomicron remnants, IDL, and LDL. With less lipid in the form of triglycerides, these lipoproteins become characterised by their enrichment with cholesterol. The capacity of cholesterol-enriched lipoproteins to penetrate the arteries is a function of their size. Lipoproteins with a diameter of >75nm are too large to penetrate the artery; thus, chylomicrons and large VLDL particles are not atherogenic ('atherogenic' meaning capable of forming fatty deposits in the arteries). The smaller particles, namely: VLDL, IDL, LDL, and Lp(a), are all pro-atherogenic lipoproteins. Thus, any ApoB-containing lipoprotein of a size <75nm can penetrate the artery and deposit cholesterol. LDL is the primary carrier of cholesterol in circulation, and thus the primary causal lipoprotein in atherosclerosis.

The Study

A total of 60 women were enrolled into a study investigating the effects of 3 different fat compositions consumed at breakfast on post-prandial fat metabolism. The three breakfasts were:

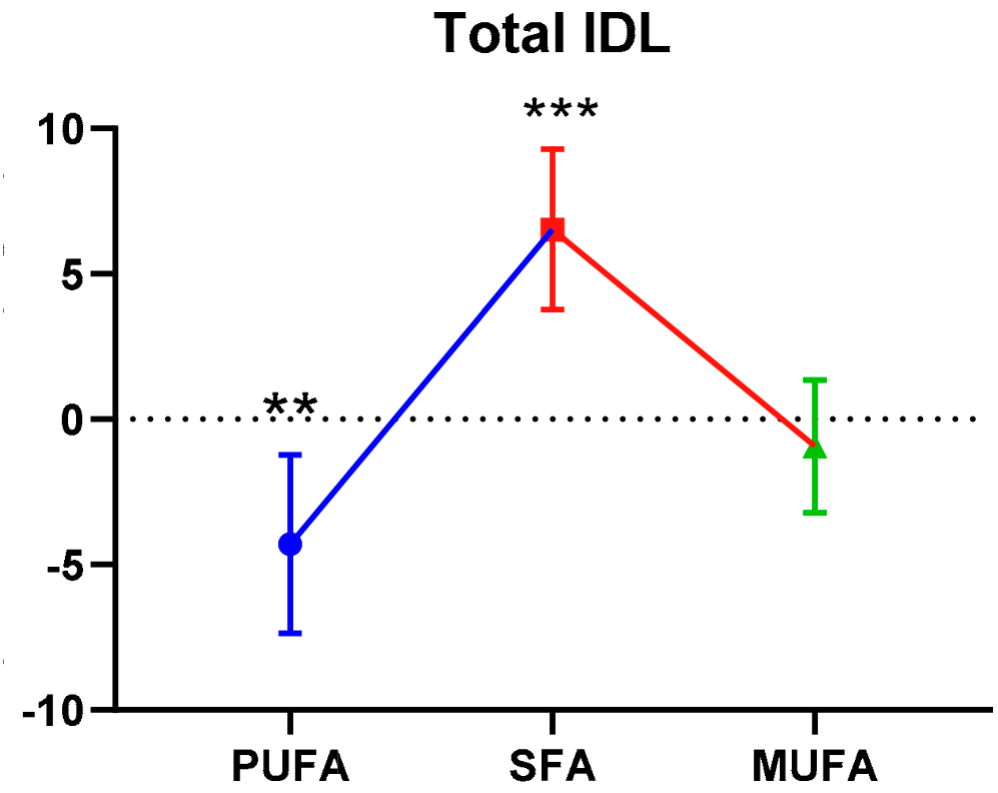
- 20g butter [saturated fat rich breakfast, SFA-B]
- 20g margarine [polyunsaturated fat rich breakfast, PUFA-B]
- 20g olive oil [monounsaturated fat rich breakfast, MUFA-B]

The study used a randomised, crossover design. Women were randomised to begin the study consuming one breakfast type, then crossed over in subsequent phases to consume each of the other two breakfast types. Each breakfast was consumed for 30-days, and each breakfast phase was separated by a 45-day washout period. Except for the type of fat consumed at breakfast, the remaining diet was identical during each phase in energy intake and macronutrient composition.

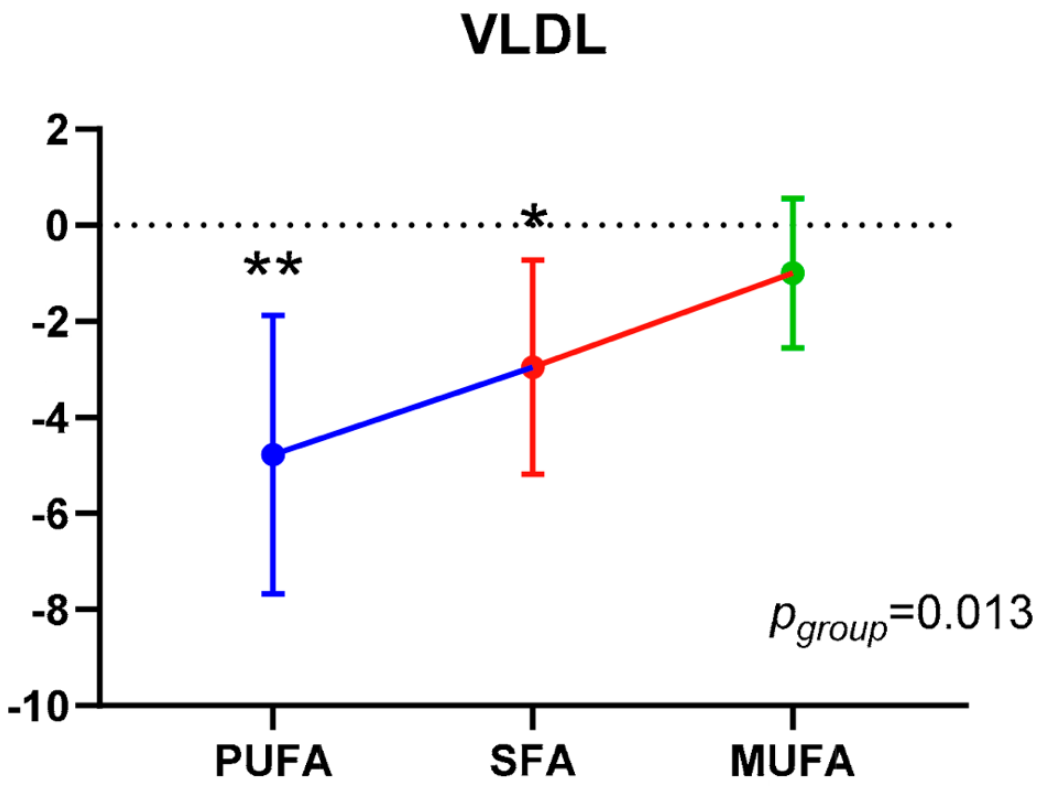
The primary outcome was plasma lipoproteins, measured at baseline and after each intervention period. The study measured VLDL, IDL, LDL, HDL, and ApoB.

Results: 53 women completed the study. Participants average age was 63.5yrs, and BMI of 27.7kg/m2. Baseline LDL and HDL levels were within normal ranges.

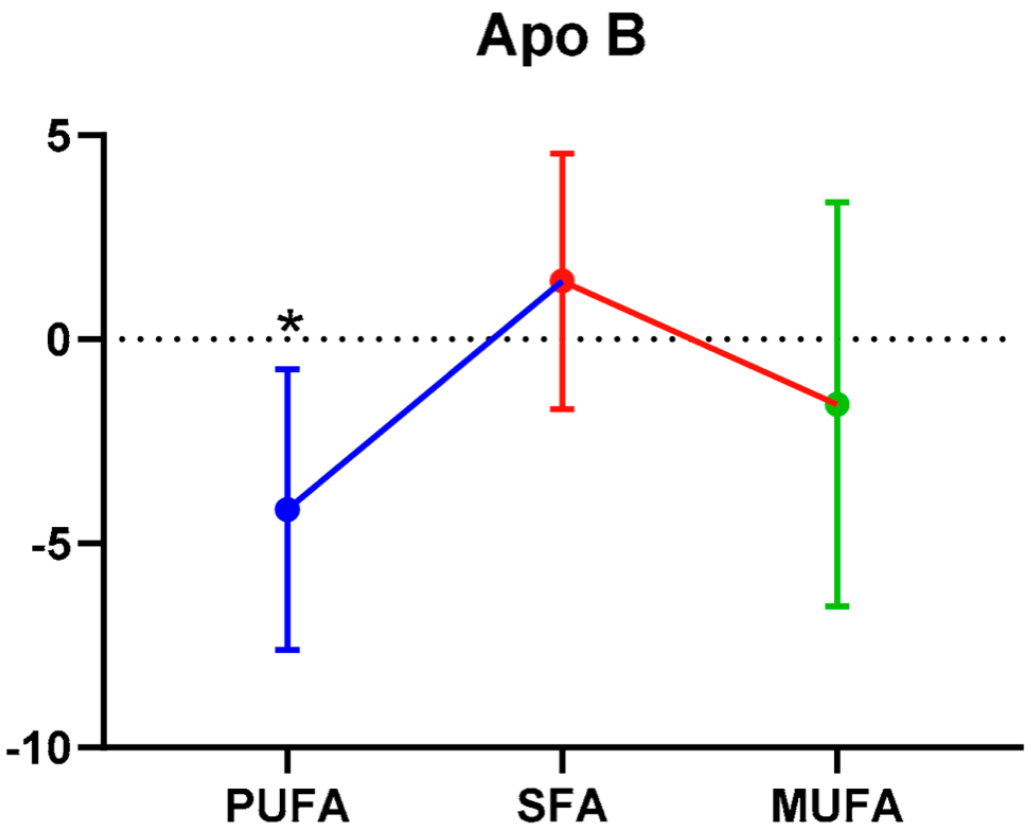
- ***SFA-B*:** The butter breakfast led to significant increases in beta-lipoproteins, isolated IDL, HDL, and significant decreases in VLDL.



- ***PUFA-B*:** The margarine breakfast led to significant decreases in VLDL, IDL, and Lp(a), and significant increases in HDL. There was also a reduction in chylomicrons and in ApoB.



- ***MUFA-B*:** The olive oil breakfast led to significant increases in HDL, and a reduction in chylomicrons.



The Critical Breakdown

Pros: The study was a food-based intervention and has more general applicability as such to commonly consumed foods in the population. The remaining diet appears to have been controlled for energy and macronutrient content, so the only variable changing between diets was the fat composition of the breakfast meals. Each diet lasted for 30-days, which negates the potential for short-term post-prandial fat responses to influence the findings. The washout period was also long, thus we would not expect to see any carryover effects from the previous intervention period. The crossover design meant that each participant acted as their own control for the other diet periods, minimising potential for between-person variation to influence the results.

Cons: The paper says that the participants *"lived in the same institution"* but doesn't state what this institution is. At a mean age of 63, it's hard to imagine it is residential care. But who knows? This is a major oversight. The study was also very underpowered, as 45 per group was estimated for the sample size, and ~20 per group completed the study. The baseline LDL levels were well within normal ranges, so the applicability of the study to more high-risk population groups is limited. The actual reporting of the results is poor; only *p*-values are reported.

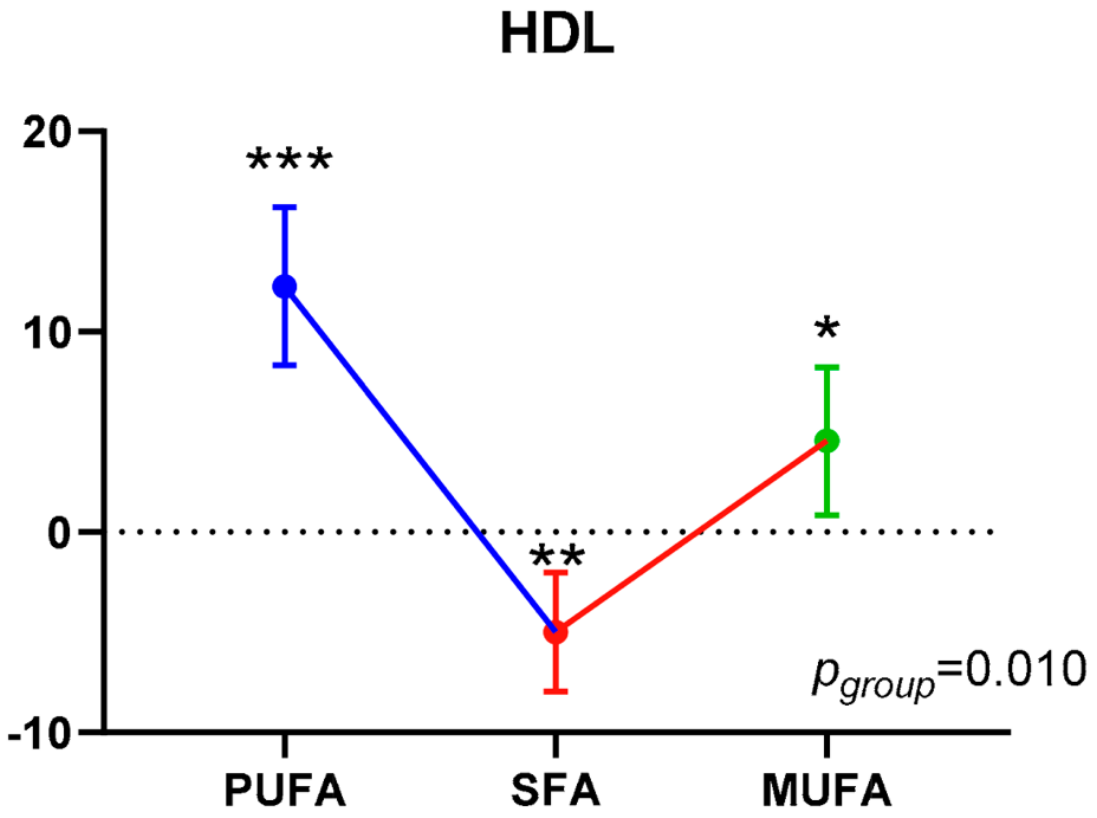
Key Characteristic

The study undertook extensive measurements of blood lipids, which allowed for a more refined analysis than if only LDL, HDL, and total cholesterol had been analysed [which is often the case in studies investigating blood lipids]. This allowed for a comprehensive assessment of lipid metabolism associated with each breakfast.

And what we ultimately saw was yet another vindication of the protective role of PUFA: lower chylomicrons, lower VLDL, lower IDL, lower beta-lipoproteins [a measured which includes LDL-C and IDL-C], and lower ApoB. This latter finding is particularly important, because ApoB as a measure reflects *all* circulating atherogenic lipoproteins [4]. Thus, PUFA improve almost every relevant measure of fat metabolism, from both the exogenous [dietary, chylomicron] pathway, and endogenous [liver, VLDL] pathway, and the total burden of circulating lipoproteins with the potential to penetrate the artery.

Interesting Finding

The effects of the different breakfasts on HDL is, well, odd. The MUFA-B was shown to increase HDL levels, which is the one finding we would expect from previous research on the effects of MUFA [5,6]. But then it gets odd…the PUFA-B was shown to *increase* HDL and the SFA-B *decreased* HDL, neither of which we would expect from the volumes of available, tightly controlled studies on these respective fat types [5,7].



This is particularly interesting given the SFA-B used butter as the intervention food, which has previously been shown to result in increased HDL concomitant to increasing LDL [8]. There is some evidence that HDL may increase in response to PUFA intake [7], however, this may be observed where PUFA replace carbohydrate in the diet [5]. And this may provide a clue, because during the washout period the participants consumed a primarily carb-based breakfast. However, in this case we would still expect to see SFA increase HDL when replacing carbohydrate, which was not observed.

Overall, it should be noted that HDL generally has been difficult to predict responsiveness to dietary fats. In their 1993 paper, which updated the available metabolic ward studies on dietary fat and blood cholesterol levels from Ancel Keys to that date, Hegsted *et al*. stated that *"little reliance can be placed on the equation describing HDL changes"* [7]. While people like emphasising HDL because of its role as "good cholesterol", it is more probable that we are looking at a degree of noise in this finding.

Relevance

This study has some important limitations which can't be overlooked: small sample size, ambiguous context of the study setting, and baseline blood lipid levels all in low ranges. This latter fact may explain why there was little observed effect on LDL itself, notwithstanding improvements in other lipoprotein classes.

However, there is 70yrs of wider context within which the findings fit. Nearly 400 metabolic ward experimental studies have constantly demonstrated the cholesterol-lowering effects of PUFA, particularly compared to SFA [7,9,10].

The effects of dietary fat on post-prandial fat metabolism are important in influencing the burden of circulating lipoproteins. One reason PUFA appear to influence the overall picture of circulating lipids is due to their structure; having >2 double bonds means these unsaturated fats are quite large and occupy a lot of space when packaged into CM or VLDL [3]. The larger PUFA TGs are more easily broken down by LPL, resulting in greater clearance of fat after a meal [3].

There is also a diurnal variation in fat metabolism, which is more effective during the day compared to the later evening and night [11,12]. The fact that this study investigated fat intake at breakfast also means we could be looking at a time-of-day effect, in addition to the effect of fat composition.

Nevertheless, from the perspective of dietary fat and its impact on blood lipids, it is clear which type of fat exerts the most favourable effects.

Application to Practice

Make Margarine Great Again! You need to understand that polyunsaturated fats *love you*. And all they ask is that you love them back. How would you feel if you were called "toxic" and "inflammatory", when all you were trying to do was help? We all have a higher purpose, and PUFA's higher purpose is stopping your arteries getting clogged.

Ok, glibness aside, simple modifications to the fat composition of your clients' diet can be easily achieved with food-based swaps and changes; these small changes may go a long way as far as healthy blood cholesterol profiles go.

References

1. Zilversmit DB. Atherogenesis: a postprandial phenomenon. Circulation. 1979 Sep;60(3):473–85.
2. Lambert JE, Parks EJ. Postprandial metabolism of meal triglyceride in humans. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2012;1821(5):721–6.
3. Griffin BA. Lipid metabolism. Surgery (United Kingdom). 2013;31(6):267–72.
4. Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, et al. Apolipoprotein B Particles and Cardiovascular Disease: A Narrative Review. JAMA Cardiology. 2019;4(12):1287-1295
5. Mensink RP, Zock PL, Kester ADM, Katan MB. 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. American Journal of Clinical Nutrition. 2003;77(5):1146–55.
6. Joris PJ, Mensink RP. Role of cis-Monounsaturated Fatty Acids in the Prevention of Coronary Heart Disease. Current Atherosclerosis Reports. 2016;18(7):38.
7. Hegsted MD, Ausman LM, Johnson JA, Dallal GE. Fat and Serum Lipids: The American Journal of Clinical Nutrition. 1993;57(6):875–83.
8. Griffin BA, Lovegrove JA. Butter Increases High-Density Lipoprotein Functional Capacity: Is This Compensation for Its Adverse Effect on Serum Low-Density Lipoprotein Cholesterol? The Journal of Nutrition. 2018;(June):1–2.
9. Keys A, Anderson JT, Grande F. Prediction of Serum-Cholesterol Response of Man to Changes in Fat in the Diet. The Lancet. 1957;73(7003):959-966.
10. Clarke R, Frost C, Collins R, Appleby PN, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ. 1997;314:112–7.
11. Gooley JJ, Chua EC-P. Diurnal Regulation of Lipid Metabolism and Applications of Circadian Lipidomics. Journal of Genetics and Genomics. 2014;41(5):231–50.
12. Grant LK, Czeisler CA, Lockley SW, Rahman SA. Time-of-day and Meal Size Effects on Clinical Lipid Markers. The Journal of Clinical Endocrinology & Metabolism. 2021;106(3):e1373–9.