

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Effects of Linoleic Acid Consumption on Lipid Risk Markers for Cardiovascular Disease

Erik Froyen

Abstract

Cardiovascular disease (CVD) is the number one contributor to death in the United States and worldwide. Lipid risk markers for CVD include high serum concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), lipoprotein (a), and triglycerides, as well as low serum concentrations of high-density lipoprotein cholesterol (HDL-C). Additional factors to assess CVD risk include apolipoprotein A (associated with HDL) and apolipoprotein B (associated with LDL). A suggested dietary strategy to decrease these risk factors is to replace a portion of saturated fatty acids with unsaturated fatty acids – especially polyunsaturated fatty acids (PUFAs). One PUFA, in particular, is the essential omega-6 PUFA linoleic acid, which has been demonstrated to affect these CVD risk markers. Therefore, this chapter will discuss the effects of linoleic acid consumption on lipid risk markers for CVD in healthy individuals, the associated mechanisms, and dietary recommendations to decrease CVD risk.

Keywords: linoleic acid, fatty acids, lipid risk markers, cardiovascular disease, humans

1. Introduction

Cardiovascular disease (CVD) (includes heart disease and stroke) is the leading cause of death in the United States [1] and worldwide [2]. In the United States, heart disease is the number one contributor to death, causing 647,457 deaths (23% of total deaths), while stroke is the fifth leading cause of death, contributing to 146,383 deaths (5.2% of total deaths) in 2017 [1]. Worldwide, heart disease is the leading cause of death, leading to 8.9 million deaths, or 16% of the total deaths globally in 2019. Stroke is the second leading contributor to deaths worldwide, causing more than 6 million deaths, or 11% of the deaths, worldwide [2].

A suggested dietary strategy to decrease the risk factors for CVD is to replace a portion of saturated fatty acids (SFAs) with monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) [3–10]. For example, the Nurses' Health Study [11] demonstrated that replacing 5% of energy from SFAs with equivalent

energy from MUFAs, PUFAs, or carbohydrates from whole grains, decreased the risk for coronary heart disease (CHD). A meta-analysis of randomized controlled trials reported that replacing saturated fat with polyunsaturated fat reduced CHD events [12].

However, certain authors and publications are not in agreement with these recommendations to decrease the risk factors for CVD, cardiovascular events, and/or mortality [13–22]. The PURE prospective cohort study concluded that intakes of total, saturated, and unsaturated fats were not significantly associated with the risk of myocardial infarction or CVD mortality [23]. Meta-analyses of prospective cohort studies demonstrated that consumption of saturated fat was not associated with an increased risk of CVD [24]. Interestingly, there was an inverse association between saturated fat intake and the risk of stroke [25]. Additionally, a meta-analysis of randomized controlled trials reported that replacing saturated fat with primarily polyunsaturated fat is “unlikely” to reduce CVD events or mortality [26]. Hooper et al. [27], in a review of randomized controlled trials, stated that there is “little or no effect of reducing saturated fat on all-cause mortality or cardiovascular mortality.”

As noted, there is controversy regarding the effects of the consumption of fatty acids on CVD risk. One such controversy is the recommendation of linoleic acid, which is the essential omega-6 (or n-6) PUFA [28–30]. For example, it has been found that replacing saturated fat with linoleic acid lowers serum cholesterol, but does not lower the risk of death from CHD [21, 22]. Furthermore, there is concern regarding whether linoleic acid increases the risk for inflammation [31].

An analysis of prospective observational studies demonstrated that higher tissue and serum concentrations of linoleic acid decreased the risk for cardiovascular events [32]. The Cardiovascular Health Study, a prospective cohort study, discovered that higher circulating linoleic acid concentrations reduced total and CHD mortality [33]. A meta-analysis of prospective cohort studies found that decreased consumption of omega-6 PUFAs and increased intakes of saturated and trans-fatty acids increased CHD mortality [34]. Linoleic acid consumption reduced the risk of CHD events and death, according to another meta-analysis of prospective cohort studies [35]. A systematic review of randomized controlled trials, in which there was a replacement of dietary saturated and monounsaturated fatty acids with omega-6 fatty acids, concluded that omega-6 fatty acids lowered the risk of myocardial infarction. Additionally, the intake of omega-6 fatty acids reduced total serum cholesterol, but not “other blood fat fractions”. It was also highlighted that “the benefits of omega-6 fats remain to be proven” [36].

According to the diet-heart hypothesis, a high consumption of saturated fat and cholesterol – and a low intake of polyunsaturated fat – increase the build-up of cholesterol and plaques in artery walls; these developments, therefore, increase the risks for atherosclerosis, cardiovascular disease, and myocardial infarction [18, 21, 37]. However, the diet-heart hypothesis has been evolving, and thus, some individuals recommend focusing more on overall dietary patterns, rather than individual fatty acids [37]. Moreover, there are a variety of factors that contribute to increasing the risk for CVD, such as high blood pressure, arrhythmia, inflammation, thrombosis, insulin resistance, endothelial dysfunction, obesity, cigarette smoke, genetics, the microbiome, a lack of exercise, a high alcohol consumption, and overall dietary patterns [14, 18, 37–42].

Lipid levels have also been proposed to be “strong” risk factors for CVD and mortality. These lipid risk factors include the following: high serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), lipoprotein(a), and very-low-density lipoprotein cholesterol (VLDL-C), as well

as low serum concentrations of high-density lipoprotein cholesterol (HDL-C). In addition, apolipoprotein A1 (associated with HDL) and apolipoprotein B (associated with LDL) have been used as CVD risk markers [18, 43]. Interestingly, LDL particle size has also been utilized as a risk marker for CVD. The small, dense LDL subclass, compared to large, buoyant LDL particles, has been reported to be more atherogenic [44–50].

Therefore, this chapter will focus on the consumption of linoleic acid on lipid risk markers for CVD in healthy individuals, such as total cholesterol, triglycerides, LDL-C, LDL particle size, lipoprotein(a), VLDL-C, HDL-C, apolipoprotein A1, and apolipoprotein B. The associated mechanisms of action will also be covered. The chapter will conclude with recommendations to decrease the risk factors for CVD. Significant dietary sources of linoleic acid are presented in **Tables 1** and **2**. The chemical structure of linoleic acid is illustrated in **Figure 1**.

Oils	Linoleic acid (grams)
Corn oil	53.5
Cottonseed oil	51.9
Grapeseed oil	69.6
Peanut oil	32.0
Safflower oil	12.7
Sesame oil	41.3
Soybean oil	51.0
Sunflower oil	65.7
Walnut oil	52.9

Table 1.
Oil sources of linoleic acid (per 100 grams) [51, 52].

Nuts and seeds	Linoleic acid (grams)
Almonds	3.49
Brazil nuts	6.82
Pecans	5.85
Pine nuts	9.4
Pistachios	4.0
Pumpkin seeds	5.55
Sesame seeds	5.78
Sunflower seeds	9.29
Walnuts	10.8

Table 2.
Linoleic acid content in nuts and seeds (per 1 ounce or 28.3495 grams) [51, 52].

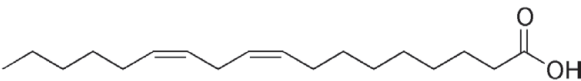


Figure 1.
The chemical structure of linoleic acid [53].

2. The effects of linoleic acid consumption on lipid risk markers for cardiovascular disease in healthy individuals

The consumption of linoleic acid has been demonstrated to affect lipid risk markers for cardiovascular disease. The discussed studies include intervention trials that investigated the effects of linoleic acid consumption, in grams or percentage of energy, on CVD lipid risk markers in healthy individuals. Therefore, epidemiological, postprandial, and animal studies are not covered. The results are organized by the respective CVD lipid risk marker.

2.1 Total cholesterol

The consumption of linoleic acid decreased total cholesterol compared to a usual U.S. diet (high in saturated fat and cholesterol) [54], and diets high in SFAs [55] (including stearic acid [56] and palmitic acid [57]), MUFAs [58], or medium-chain fatty acids [59]. A high intake of alpha-linolenic acid, the essential omega-3 fatty acid, decreased cholesterol concentrations compared to the control diet with the same percentage of linoleic acid [60]. In contrast, no significant differences in total cholesterol were observed after linoleic acid consumption compared to diets containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 fatty acids) [61, 62], alpha-linolenic acid [63], high and low amounts of linoleic acid [64], oleic acid (a MUFA) [65, 66], or stearic acid [66]. Interestingly, intakes of SFA- or linoleic acid-rich diets – both supplemented with EPA and DHA – produced no significant differences in cholesterol concentrations [67].

2.2 Triglycerides

The consumption of linoleic acid decreased triglycerides compared to diets with significant amounts of oleic acid [58], stearic acid [56], or medium-chain fatty acids [59]. Intakes of linoleic acid, supplemented with EPA and DHA, reduced triglyceride concentrations versus a linoleic acid diet rich in oleic acid [62]. A SFA-rich diet and a diet high in linoleic acid, both with added EPA and DHA, lowered triglyceride concentrations, with no significant differences between diets [67]. In contrast, diets supplemented with EPA and DHA decreased triglycerides compared to linoleic acid intakes [55, 61]. No significant differences were observed regarding triglyceride concentrations between lower and higher linoleic acid intakes [54, 60, 64], and diets rich in linoleic acid versus diets high in alpha-linolenic acid [63], oleic acid [65], or stearic acid [66].

2.3 Low-density lipoprotein cholesterol (LDL-C)

Intakes of linoleic acid decreased LDL-C versus diets rich in oleic acid [58], SFAs [55], palmitic acid [57], stearic acid [56, 68], trans-fatty acids [68], or medium-chain fatty acids [59]. Furthermore, higher amounts of linoleic acid more significantly lowered LDL-C concentrations [54, 57]. There were mixed results or no significant differences in comparison to oleic acid [62, 65, 66, 68]. Additionally, there were no significant differences when comparing linoleic acid consumption to alpha-linolenic acid [63] or stearic acid [66]. Consuming low and high amounts of linoleic acid – along with significant amounts of alpha-linolenic acid [64] or EPA and DHA [62] – also did not differ. Moreover, no significant differences were observed with respect to LDL-C after following a SFA-rich diet or a diet high in linoleic acid – both supplemented with EPA and DHA [67].

2.4 LDL particle size

There were no significant differences in LDL particle size after consumption of low and high amounts of linoleic acid [60, 69], and intakes of linoleic acid compared to oleic acid or stearic acid [66]. Interestingly, there were decreases in large and small LDL particle concentrations after 10 days of a linoleic acid-rich diet compared to a diet high in SFAs, with both diets supplemented with EPA and DHA [70]. In contrast, no significant differences were observed in LDL particle size after 6 weeks of a linoleic acid-rich diet compared to a SFA-rich diet (both supplemented with EPA and DHA) [67].

2.5 Very-low-density lipoprotein cholesterol (VLDL-C)

Following consumption of diets rich in linoleic acid, there were decreases in VLDL-C concentrations compared to diets containing significant amounts of oleic acid [58] or medium-chain fatty acids [59]. In contrast, intakes of a SFA- or linoleic acid-rich diet (both containing significant amounts of EPA and DHA) resulted in no significant differences between diets; however, both diets decreased VLDL-C concentrations [67].

2.6 High-density lipoprotein cholesterol (HDL-C)

HDL-C increased following consumption of linoleic acid compared to stearic acid [56]. In contrast, intakes of linoleic acid decreased HDL-C compared to EPA and DHA [61] or palmitic acid [57]. However, most studies noticed no significant differences regarding HDL-C concentrations after consuming low and high amounts of linoleic acid [54, 60, 62, 64], and linoleic acid compared to oleic acid [58, 65, 66], alpha-linolenic acid [60, 63], or stearic acid [66]. Interestingly, intakes of SFAs or linoleic acid (both diets supplemented with EPA and DHA) displayed no significant differences in HDL-C concentrations [67].

2.7 Lipoprotein(a)

Linoleic acid consumption reduced lipoprotein(a) concentrations compared with a diet high in trans-fatty acids [68]. However, linoleic acid intake increased lipoprotein(a) compared to a diet rich in SFAs [55]. In contrast, no significant differences were found after consuming linoleic acid compared to SFAs, oleic acid, or stearic acid [68].

2.8 Apolipoproteins A1, A2, and B

The consumption of linoleic acid increased apolipoprotein A1 compared to a typical U.S. diet [54]. Additionally, linoleic acid increased apolipoprotein A2 compared to EPA and DHA [55]. In contrast, apolipoproteins A1 and A2 decreased after following a diet rich in linoleic acid compared to a diet high in oleic acid [65]. Apolipoprotein A1 concentrations did not differ when comparing low and high linoleic acid intakes [60], and consumption of linoleic acid compared to diets containing high amounts of stearic acid or oleic acid [66]. There were decreases in apolipoprotein B concentrations after linoleic consumption compared to a typical U.S. diet [54], stearic acid, elaidic acid (a trans-fatty acid) [56], or SFAs [55]. There were no significant differences with respect to apolipoprotein B after intakes of linoleic acid compared with oleic acid [65, 66] or stearic acid [66].

3. The mechanisms by which linoleic acid affects lipid risk markers for cardiovascular disease

Linoleic acid (or PUFAs) has been demonstrated to affect CVD lipid risk markers. The mechanisms involved in altering these risk markers will be discussed in this section.

3.1 Total cholesterol

PUFAs have been shown to increase liver X receptor alpha (LXR α) gene expression [71, 72] via peroxisome proliferator activated receptors (PPARs) [71]. LXR α stimulates the expression of cholesterol 7 α -hydroxylase (CYP7), thereby converting cholesterol to bile acids. Therefore, by increasing CYP7 activity, PUFAs participate in cholesterol catabolism [73].

3.2 Triglycerides

PUFAs interact more strongly with PPAR α compared to SFAs [74]. PPAR α binds to peroxisome proliferator response elements (PPREs) located in the promotor regions of genes, such as apoC-III and lipoprotein lipase (LPL) [75]. It has been proposed that LPL may demonstrate increased activity towards VLDL triglycerides containing polyunsaturated fatty acids, thereby leading to increased breakdown of triglyceride-rich lipoproteins (chylomicrons and VLDL particles) [73, 76, 77]. LPL activity is inhibited by apoC-III, and thus, increases triglyceride concentrations [78]. It has been reported that PUFAs decrease apoC-III, thereby increasing LPL activity and, indeed, VLDL catabolism [73]. Moreover, omega-3 PUFAs have been shown to reduce triglycerides by lowering diacylglycerol acyltransferase, fatty acid synthase, and acetyl coenzyme A (CoA) carboxylase [79–84].

3.3 LDL-C

Intakes of linoleic acid [85] or PUFAs [73] have been demonstrated to increase LDL receptor activity, protein, and mRNA compared to SFAs. Furthermore, PUFAs increase membrane fluidity [73, 85, 86], which increases LDL receptor activity, and thus, increases LDL catabolism [87–89].

3.4 LDL particle size

It has been reported that consumption of SFAs increases large, buoyant LDL particles compared to lower SFA-containing diets [69, 90], whereas consumption of diets rich in PUFAs decreases large, buoyant LDL particles versus diets high in SFAs [70, 91]. It has been suggested that SFAs increase LPL and hepatic lipase activities [92, 93]. As such, LPL increases large, buoyant LDL particles, whereas hepatic lipase may stimulate the catabolism of triglyceride-rich lipoprotein remnants [92]. However, additional research is needed in this area regarding the mechanisms by which individual fatty acids affect LDL particle size.

3.5 VLDL-C

The sterol regulatory element-binding protein-1 (SREBP-1) is associated with lipogenesis and cholesterol synthesis in the liver [94, 95]. PUFAs have been shown to inhibit SREBP-1 gene transcription and/or protein [96], thereby lowering VLDL secretion from the liver [73, 96]. In addition, intakes of PUFAs increase VLDL catabolism and uptake [59, 81].

3.6 HDL-C

Replacing SFAs with MUFAs and/or PUFAs generates lower total cholesterol and LDL-C concentrations, with modest HDL-C reductions; however, a lower total cholesterol: HDL-C ratio results [4, 97]. It is thought that dietary fat increases the “transport rate” and decreases the “fractional catabolic rate” of HDL cholesterol ester and apolipoprotein A1 [98]. However, more research is needed to describe the mechanisms by which individual fatty acids impact HDL-C.

3.7 Lipoprotein(a)

Lipoprotein(a) is synthesized in the liver and contains apolipoprotein A, which is bound to apolipoprotein B-100 [99–101]. The biological activity of lipoprotein(a) is unknown [102]; however, high concentrations have been associated with CVD [101, 103, 104]. Genetics seem to be the primary determinant of lipoprotein(a) [105]. Hence, diet and exercise do not appear to be significant contributors to lipoprotein(a) concentrations. There have also been inconsistent findings of fatty acid consumption (including PUFAs) on lipoprotein(a) concentrations [106]. However, it has been suggested that fatty acids may affect liver apolipoprotein(a) synthesis, thereby impacting lipoprotein(a) [106–108]. As such, more research is needed to determine the effects of dietary composition on lipoprotein(a) concentrations.

3.8 Apolipoprotein A1

HDL particles contain apolipoprotein A1, which interacts with the ATP-binding cassette transporter on the surface of cells. Furthermore, apolipoprotein A1 is a cofactor for lecithin cholesterol acyl transferase, which generates mature HDL particles [43, 109]. Plasma apolipoprotein A1 concentration typically coincide with HDL-C concentrations [43]. The significance of apolipoprotein A2 is less clear [110]. Interestingly, PPAR α also interacts with PPREs in the promoter region of the apolipoprotein A1 gene in the liver [75]. Hence, PUFAs may exert their effects on apolipoprotein A1 via PPAR α [73].

3.9 Apolipoprotein B

Apolipoprotein B also occurs in two forms: apolipoprotein B-48 and apolipoprotein B-100. The intestine synthesizes apolipoprotein B-48, which is a component of chylomicrons. The liver produces apolipoprotein B-100, which is associated with VLDL and LDL particles. Apolipoprotein B is necessary for the binding of lipoproteins to the LDL receptor. Apolipoprotein B plasma concentrations are significantly associated with LDL-C concentrations [43, 111]. It has been reported that high apolipoprotein B concentrations increase the risk for CVD, whereas apolipoprotein A1 concentrations decrease CVD risk [43, 112]. As mentioned previously, PUFAs increase LDL catabolism, thereby reducing apolipoprotein B [87].

4. Linoleic acid recommendations

The adequate intake (AI) values for linoleic acid for males and females (19-50 years) are 17 grams/day and 12 grams/day, respectively. Regarding males and females ages 51-70 years, the AI values for linoleic acid are 14 grams/day and 11 grams/day, respectively. The American Heart Association recommends consuming 5 to 10% of energy as

linoleic acid to decrease CVD risk [29, 31]. Additionally, the World Health Organization recommends consuming 2.5 to 9% of energy from linoleic acid to decrease LDL and total cholesterol concentrations, and thus, lower the risk for CVD [113]. It is not recommended to consume more than 10% of energy as linoleic acid due to limited research.

5. Fat recommendations

In addition to linoleic acid recommendations, there are fat recommendations to reduce CVD risk, cardiovascular events, and/or mortality. For example, it has been suggested to replace approximately 5% of energy from SFAs with MUFAs and/or PUFAs [4, 8–12, 38, 113], and to consume less than 10% of energy as SFAs [113, 114]. On the other hand, certain studies do not coincide with these recommendations [14–17, 21–27, 115]. In addition, low-fat, and in-turn, high-carbohydrate diets, decrease LDL-C; however, there is also a reduction in HDL-C and increased concentrations of VLDLs or triglycerides [37, 97, 116–118], which may produce higher amounts of small, dense LDL particles [41, 119, 120]. It has been reported that higher-fat versus lower-fat diets increase large, buoyant LDL and/or decrease small, dense LDL particles [69, 92, 121–123]. Interestingly, higher SFA intakes also increase large LDL and/or decrease small LDL particles [69, 90, 124–126]. These small, dense LDL particles may increase the risk for CVD in the following ways: 1) increased transport into arterial walls [127]; 2) increased attachment to proteoglycans [128]; 3) increased oxidation [129, 130]; and 4) reduced binding to the LDL receptor [127, 131, 132].

Various organizations have published dietary recommendations to decrease the risk factors for CVD. The American College of Cardiology/American Heart Association Task Force suggests consuming a diet rich in fruits, vegetables, whole grains, nuts, legumes, lean animal or plant protein sources, and fish. Additionally, it is recommended to decrease the consumption of red and processed meats, refined carbohydrates, trans-fatty acids, sodium, cholesterol, and sugar-sweetened drinks [38]. The Dietary Guidelines for Americans suggest consuming vegetable oils to replace sources rich in SFAs, such as butter, shortening, lard, palm oil, palm kernel oil, coconut oil, full-fat dairy products, and high-fat meats [114]. The World Health Organization also recommends replacing SFAs with unsaturated fatty acids, such as sunflower, safflower, corn, soybean, canola, and olive oils, as well as nuts, avocado, and fish [113].

It has been recently proposed, however, that guidelines to lower the risk for CVD should focus on overall dietary patterns, rather than individual fatty acids [14, 133]. The consumption of low-fat diets, for example, did not reduce CVD risk [134, 135]. Furthermore, certain individuals with higher intakes of saturated fat and cholesterol do not possess high CVD mortality rates, as they have an increased consumption of plant foods – in addition to MUFAs and PUFAs [15]. Furthermore, some foods that are higher in SFAs have not been demonstrated to increase the risk for CVD. A proposed explanation for these outcomes is the food matrix of these items, such as macro- and micronutrients, phytochemicals, and probiotics [14, 37].

6. Conclusions

This chapter focused on the effects of linoleic acid consumption on lipid risk markers for CVD in healthy individuals. Interestingly, linoleic acid reduced total cholesterol and LDL-C compared to diets that were lower in PUFAs and/or higher in

SFAs. In contrast, linoleic acid generated inconsistent outcomes regarding triglycerides, whereas EPA and DHA more significantly reduced triglyceride concentrations. In limited studies, linoleic acid decreased VLDL-C compared to diets containing oleic acid or medium-chain fatty acids, and decreased HDL-C compared to palmitic acid or EPA and DHA; however, linoleic acid increased HDL-C compared with stearic acid. Additionally, linoleic acid reduced apolipoprotein B in comparison to a typical U.S. diet, SFAs, or trans-fatty acids. Interestingly, there were inconsistent

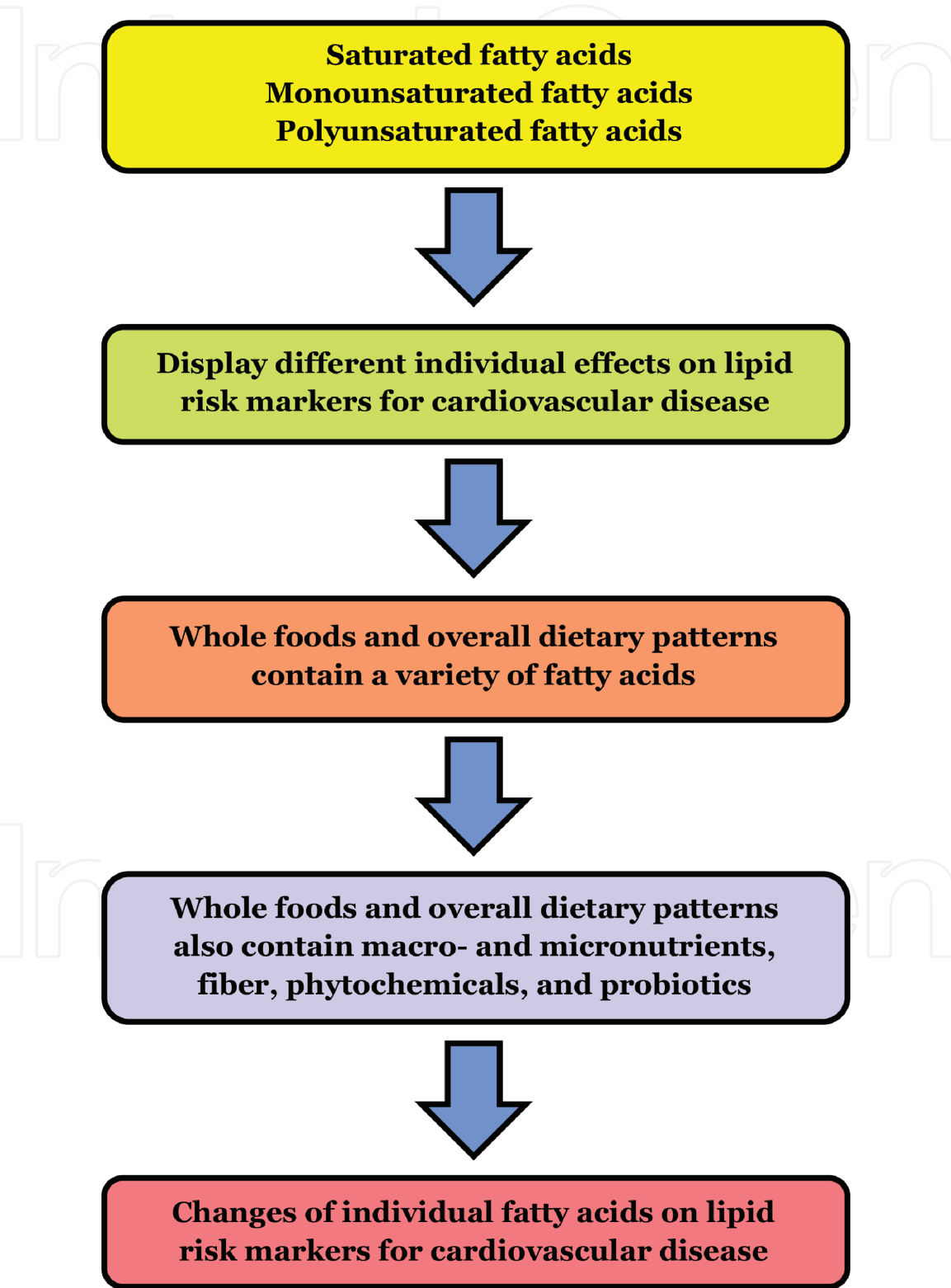


Figure 2.
The progression from individual fatty acids to whole foods and overall dietary patterns on lipid risk markers for cardiovascular disease.

results or no significant differences for selected CVD lipid risk markers – particularly when comparing linoleic acid to oleic acid. Therefore, additional research is needed regarding the effects of fatty acids on markers that increase the risk for CVD – in addition to the associated mechanisms.

The development of CVD is a complex process which involves many factors that influence the discussed lipid risk markers, such as exercise patterns, overweight/obesity, cigarette smoke, hypertension, high alcohol consumption, and genetics. To add to this complexity is our dietary patterns. As discussed, there are mixed results regarding the consumption of linoleic acid on CVD lipid risk markers. One such dietary explanation is the complex food matrices of these items, which may, therefore, influence CVD risk markers. In other words, we do not consume individual fatty acids; we consume food. For example, individual saturated and unsaturated fatty acids have differing effects on CVD risk markers; however, these individual effects may be diminished when these fatty acids are components of whole food items. This attribute may explain, in part, for the differing outcomes of saturated and unsaturated fat on CVD risk, events, and/or mortality. Perhaps, therefore, we should focus on whole foods and overall dietary patterns when providing guidelines to reduce the risk for CVD.

It is recommended that future studies investigate the effects of various dietary patterns on CVD risk markers, such as lower-carbohydrate versus higher-carbohydrate diets, lower-fat versus higher-fat diets, and plant-based versus meat-based diets. Based on the heterogeneity of the reviewed studies on the effects of linoleic acid consumption on lipid risk markers for CVD, future studies should be longer in duration – with more participants. Moreover, it should be clarified, in future publications, whether the discussed CVD lipid risk markers exist as strong and independent risk factors for CVD.

It is clear that the consumption of fat is a critical component to a healthy diet; consuming too much or too little can have detrimental effects on one's health. Therefore, moderation is an important factor to keep in mind regarding fat consumption. It seems, however, that certain dietary recommendations focus on decreasing the intakes of saturated fatty acids, and increasing the consumption of monounsaturated and polyunsaturated fatty acids. These recommendations may not be optimal in the following ways: 1) foods consist of individual fatty acids, which have different effects on CVD lipid risk markers; 2) overall dietary patterns and food components may offset the effects of specific fatty acids; and 3) individuals may not be familiar with significant food sources of saturated, monounsaturated, and polyunsaturated fatty acids. Therefore, it seems that dietary guidelines to lower the risk for CVD should focus on overall dietary patterns, rather than individual fatty acids (**Figure 2**).

Acknowledgements

No funding was used for this project.

Conflict of interest

The author declares no conflict of interest.

IntechOpen

IntechOpen

Author details

Erik Froyen
California State Polytechnic University, Pomona, USA

*Address all correspondence to: ebfroyen@cpp.edu

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Deaths: Leading Causes for 2017 [Internet]. Available from: <https://www.cdc.gov/nchs/nvss/leading-causes-of-death.htm> [Accessed: 2021-05-16].
- [2] World Health Organization. The top 10 causes of death [Internet]. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> [Accessed: 2021-05-16].
- [3] Anton SD, Heekin K, Simkins C, Acosta A. Differential effects of adulterated versus unadulterated forms of linoleic acid on cardiovascular health. *J Integ Med*. 2013 Jan;11(1):2-10.
- [4] Wang DD, Hu FB. Dietary Fat and Risk of Cardiovascular Disease: Recent Controversies and Advances. *Annu Rev Nutr*. 2017 Aug 21;37:423-46.
- [5] Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *Jama*. 2002 Nov 27;288(20):2569-78.
- [6] Zock PL, Blom WA, Nettleton JA, Hornstra G. Progressing Insights into the Role of Dietary Fats in the Prevention of Cardiovascular Disease. *Curr Cardiol Rep*. 2016 Nov;18(11):111.
- [7] Millen BE, Wolongevicz DM, de Jesus JM, Nonas CA, Lichtenstein AH. 2013 American Heart Association/ American College of Cardiology Guideline on Lifestyle Management to Reduce Cardiovascular Risk: practice opportunities for registered dietitian nutritionists. *J Acad Nutr Diet*. 2014 Nov;114(11):1723-9.
- [8] Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation*. 2017 Jul 18;136(3):e1-e23.
- [9] Clifton PM, Keogh JB. A systematic review of the effect of dietary saturated and polyunsaturated fat on heart disease. *Nutr Metab Cardiovasc Dis*. 2017 Dec;27(12):1060-80.
- [10] Wang DD, Li Y, Chiuve SE, Stampfer MJ, Manson JE, Rimm EB, et al. Association of Specific Dietary Fats With Total and Cause-Specific Mortality. *JAMA Intern Med*. 2016 Aug 1;176(8):1134-45.
- [11] Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. *J Am Coll Cardiol*. 2015 Oct 6;66(14):1538-48.
- [12] Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010 Mar 23;7(3):e1000252.
- [13] Harcombe Z, Baker JS, Cooper SM, Davies B, Sculthorpe N, DiNicolantonio JJ, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. *Open Heart*. 2015;2(1):e000196.
- [14] Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, et al. Saturated Fats and Health: A Reassessment and Proposal for Food-Based Recommendations: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020 Aug 18;76(7):844-57.
- [15] Artaud-Wild SM, Connor SL, Sexton G, Connor WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. A paradox. *Circulation*. 1993 Dec;88(6):2771-9.

- [16] de Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR, Jr., et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr.* 2012 Aug;96(2):397-404.
- [17] de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *Bmj.* 2015 Aug 11;351:h3978.
- [18] Willett WC. Dietary fats and coronary heart disease. *J Intern Med.* 2012 Jul;272(1):13-24.
- [19] Whelan J. The health implications of changing linoleic acid intakes. *Prostaglandins Leukot Essent Fatty Acids.* 2008 Sep-Nov;79(3-5):165-7.
- [20] Kris-Etherton PM, Krauss RM. Public health guidelines should recommend reducing saturated fat consumption as much as possible: YES. *Am J Clin Nutr.* 2020 Jun 3;112(1):13-8.
- [21] Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). *Bmj.* 2016 Apr 12;353:i1246.
- [22] Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *Bmj.* 2013 Feb 4;346:e8707.
- [23] Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet.* 2017 Nov 4;390(10107):2050-62.
- [24] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr.* 2010 Mar;91(3):535-46.
- [25] Kang ZQ, Yang Y, Xiao B. Dietary saturated fat intake and risk of stroke: Systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis.* 2020 Feb 10;30(2):179-89.
- [26] Hamley S. The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials. *Nutr J.* 2017 May 19;16(1):30.
- [27] Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev.* 2020 Aug 21;8:CD011737.
- [28] Jandacek RJ. Linoleic Acid: A Nutritional Quandary. *Healthcare (Basel).* 2017 May 20;5(2):25.
- [29] Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation.* 2009 Feb 17;119(6):902-7.
- [30] Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: dietary fatty acids for healthy

adults. *J Acad Nutr Diet*. 2014 Jan; 114(1):136-53.

[31] Whelan J, Fritsche K. Linoleic acid. *Adv Nutr*. 2013 May 1;4(3):311-2.

[32] Marklund M, Wu JHY, Imamura F, Del Gobbo LC, Fretts A, de Goede J, et al. Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality. *Circulation*. 2019 May 21;139(21):2422-36.

[33] Wu JH, Lemaitre RN, King IB, Song X, Psaty BM, Siscovick DS, et al. Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality: the Cardiovascular Health Study. *Circulation*. 2014 Oct 7;130(15):1245-53.

[34] Wang Q, Afshin A, Yakoob MY, Singh GM, Rehm CD, Khatibzadeh S, et al. Impact of Nonoptimal Intakes of Saturated, Polyunsaturated, and Trans Fat on Global Burdens of Coronary Heart Disease. *J Am Heart Assoc*. 2016 Jan 20;5(1):e002891.

[35] Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, et al. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation*. 2014 Oct 28;130(18):1568-78.

[36] Hooper L, Al-Khudairy L, Abdelhamid AS, Rees K, Brainard JS, Brown TJ, et al. Omega-6 fats for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018 Nov 29;11:CD011094.

[37] Forouhi NG, Krauss RM, Taubes G, Willett W. Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. *Bmj*. 2018 Jun 13;361:k2139.

[38] Arnett DK, Blumenthal RS, Albert MA, Buroker AB,

Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019 Sep 10;74(10):e177-e232.

[39] Xu LB, Zhou YF, Yao JL, Sun SJ, Rui Q, Yang XJ, et al. Apolipoprotein A1 polymorphisms and risk of coronary artery disease: a meta-analysis. *Arch Med Sci*. 2017 Jun;13(4):813-9.

[40] Austin MA. Triglyceride, small, dense low-density lipoprotein, and the atherogenic lipoprotein phenotype. *Curr Atheroscler Rep*. 2000 May;2(3):200-7.

[41] Kwiterovich PO, Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol*. 2002 Oct 17;90(8A):30i-47i.

[42] Krauss RM. Dietary and genetic effects on low-density lipoprotein heterogeneity. *Annu Rev Nutr*. 2001;21:283-95.

[43] Florvall G, Basu S, Larsson A. Apolipoprotein A1 is a stronger prognostic marker than are HDL and LDL cholesterol for cardiovascular disease and mortality in elderly men. *J Gerontol A Biol Sci Med Sci*. 2006 Dec;61(12):1262-6.

[44] Carr MC, Ayyobi AF, Murdoch SJ, Deeb SS, Brunzell JD. Contribution of hepatic lipase, lipoprotein lipase, and cholesteryl ester transfer protein to LDL and HDL heterogeneity in healthy women. *Arterioscler Thromb Vasc Biol*. 2002 Apr 1;22(4):667-73.

[45] Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. *J Lipid Res*. 1982 Jan;23(1):97-104.

- [46] Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002 Oct 8;106(15):1930-7.
- [47] Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease. *J Am Coll Cardiol*. 2020 May 5;75(17):2122-35.
- [48] Williams PT, Superko HR, Haskell WL, Alderman EL, Blanche PJ, Holl LG, et al. Smallest LDL particles are most strongly related to coronary disease progression in men. *Arterioscler Thromb Vasc Biol*. 2003 Feb 1;23(2):314-21.
- [49] Coresh J, Kwiterovich PO, Jr., Smith HH, Bachorik PS. Association of plasma triglyceride concentration and LDL particle diameter, density, and chemical composition with premature coronary artery disease in men and women. *J Lipid Res*. 1993 Oct;34(10):1687-97.
- [50] DiNicolantonio JJ, O'Keefe JH. Effects of dietary fats on blood lipids: a review of direct comparison trials. *Open Heart*. 2018;5(2):e000871.
- [51] U.S. Department of Agriculture (USDA). Food Data Central [Internet]. Available from: <https://fdc.nal.usda.gov/> [Accessed: 2021-05-26].
- [52] Froyen E, Burns-Whitmore B. The Effects of Linoleic Acid Consumption on Lipid Risk Markers for Cardiovascular Disease in Healthy Individuals: A Review of Human Intervention Trials. *Nutrients*. 2020 Aug 4;12(8).
- [53] Chemical structure of linoleic acid [Internet]. Available from: https://commons.wikimedia.org/wiki/File:Linoleic_acid.png [Accessed: 2021-05-26].
- [54] Iacono JM, Dougherty RM. Lack of effect of linoleic acid on the high-density-lipoprotein-cholesterol fraction of plasma lipoproteins. *Am J Clin Nutr*. 1991 Mar;53(3):660-4.
- [55] Sanders TA, Oakley FR, Miller GJ, Mitropoulos KA, Crook D, Oliver MF. Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. *Arterioscler Thromb Vasc Biol*. 1997 Dec;17(12):3449-60.
- [56] Zock PL, Katan MB. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res*. 1992 Mar;33(3):399-410.
- [57] French MA, Sundram K, Clandinin MT. Cholesterolaemic effect of palmitic acid in relation to other dietary fatty acids. *Asia Pac J Clin Nutr*. 2002;11 Suppl 7:S401-7.
- [58] Wagner KH, Tomasch R, Elmadfa I. Impact of diets containing corn oil or olive/sunflower oil mixture on the human plasma and lipoprotein lipid metabolism. *Eur J Nutr*. 2001 Aug;40(4):161-7.
- [59] van Schalkwijk DB, Pasman WJ, Hendriks HF, Verheij ER, Rubingh CM, van Bochove K, et al. Dietary medium chain fatty acid supplementation leads to reduced VLDL lipolysis and uptake rates in comparison to linoleic acid supplementation. *PLoS One*. 2014;9(7):e100376.
- [60] Goyens PL, Mensink RP. The dietary alpha-linolenic acid to linoleic acid ratio does not affect the serum lipoprotein profile in humans. *J Nutr*. 2005 Dec;135(12):2799-804.

- [61] Sanders TA, Hochland MC. A comparison of the influence on plasma lipids and platelet function of supplements of omega 3 and omega 6 polyunsaturated fatty acids. *Br J Nutr.* 1983 Nov;50(3):521-9.
- [62] Damsgaard CT, Frokiaer H, Andersen AD, Lauritzen L. Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men. *J Nutr.* 2008 Jun;138(6):1061-6.
- [63] Pang D, Allman-Farinelli MA, Wong T, Barnes R, Kingham KM. Replacement of linoleic acid with alpha-linolenic acid does not alter blood lipids in normolipidaemic men. *Br J Nutr.* 1998 Aug;80(2):163-7.
- [64] Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. *J Nutr.* 2007 Apr;137(4):945-52.
- [65] Sola R, La Ville AE, Richard JL, Motta C, Bargallo MT, Girona J, et al. Oleic acid rich diet protects against the oxidative modification of high density lipoprotein. *Free Radic Biol Med.* 1997;22(6):1037-45.
- [66] Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. *Am J Clin Nutr.* 2005 Sep;82(3):510-6.
- [67] Dias CB, Amigo N, Wood LG, Correig X, Garg ML. Effect of diets rich in either saturated fat or n-6 polyunsaturated fatty acids and supplemented with long-chain n-3 polyunsaturated fatty acids on plasma lipoprotein profiles. *Eur J Clin Nutr.* 2017 Nov;71(11):1297-302.
- [68] Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary cis and trans fatty acids on serum lipoprotein[a] levels in humans. *J Lipid Res.* 1992 Oct;33(10):1493-501.
- [69] Dreon DM, Fernstrom HA, Campos H, Blanche P, Williams PT, Krauss RM. Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. *Am J Clin Nutr.* 1998 May;67(5):828-36.
- [70] Dias CB, Amigo N, Wood LG, Mallol R, Correig X, Garg ML. Improvement of the omega 3 index of healthy subjects does not alter the effects of dietary saturated fats or n-6PUFA on LDL profiles. *Metabolism.* 2017 Mar;68:11-9.
- [71] Tobin KA, Steineger HH, Alberti S, Spydevold O, Auwerx J, Gustafsson JA, et al. Cross-talk between fatty acid and cholesterol metabolism mediated by liver X receptor-alpha. *Mol Endocrinol.* 2000 May;14(5):741-52.
- [72] Ide T, Shimano H, Yoshikawa T, Yahagi N, Amemiya-Kudo M, Matsuzaka T, et al. Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. II. LXRs suppress lipid degradation gene promoters through inhibition of PPAR signaling. *Mol Endocrinol.* 2003 Jul;17(7):1255-67.
- [73] Fernandez ML, West KL. Mechanisms by which dietary fatty acids modulate plasma lipids. *J Nutr.* 2005 Sep;135(9):2075-8.
- [74] Ferre P. The biology of peroxisome proliferator-activated receptors: relationship with lipid metabolism and insulin sensitivity. *Diabetes.* 2004 Feb;53 Suppl 1:S43-50.
- [75] Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator-activated receptor (PPAR) in mediating

the effects of fibrates and fatty acids on gene expression. *J Lipid Res.* 1996 May;37(5):907-25.

[76] Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S, et al. PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *Embo J.* 1996 Oct 1;15(19):5336-48.

[77] Vasandani C, Kafrouni AI, Caronna A, Bashmakov Y, Gotthardt M, Horton JD, et al. Upregulation of hepatic LDL transport by n-3 fatty acids in LDL receptor knockout mice. *J Lipid Res.* 2002 May;43(5):772-84.

[78] Shachter NS. Apolipoproteins C-I and C-III as important modulators of lipoprotein metabolism. *Curr Opin Lipidol.* 2001 Jun;12(3):297-304.

[79] Cottin SC, Sanders TA, Hall WL. The differential effects of EPA and DHA on cardiovascular risk factors. *Proc Nutr Soc.* 2011 May;70(2):215-31.

[80] Mozaffarian D, Wu JH. (n-3) fatty acids and cardiovascular health: are effects of EPA and DHA shared or complementary? *J Nutr.* 2012 Mar;142(3):614S-25S.

[81] Ooi EM, Watts GF, Ng TW, Barrett PH. Effect of dietary Fatty acids on human lipoprotein metabolism: a comprehensive update. *Nutrients.* 2015 Jun 2;7(6):4416-25.

[82] Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol.* 2011 Nov 8;58(20):2047-67.

[83] Grimsgaard S, Bona KH, Hansen JB, Nordoy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects

but divergent effects on serum fatty acids. *Am J Clin Nutr.* 1997 Sep;66(3):649-59.

[84] Allaire J, Couture P, Leclerc M, Charest A, Marin J, Lepine MC, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. *Am J Clin Nutr.* 2016 Aug;104(2):280-7.

[85] Mustad VA, Ellsworth JL, Cooper AD, Kris-Etherton PM, Etherton TD. Dietary linoleic acid increases and palmitic acid decreases hepatic LDL receptor protein and mRNA abundance in young pigs. *J Lipid Res.* 1996 Nov;37(11):2310-23.

[86] Tripodi A, Loria P, Dilengite MA, Carulli N. Effect of fish oil and coconut oil diet on the LDL receptor activity of rat liver plasma membranes. *Biochim Biophys Acta.* 1991 Jun 3;1083(3):298-304.

[87] Fernandez ML, Lin EC, McNamara DJ. Differential effects of saturated fatty acids on low density lipoprotein metabolism in the guinea pig. *J Lipid Res.* 1992 Dec;33(12):1833-42.

[88] Caviglia JM, Gayet C, Ota T, Hernandez-Ono A, Conlon DM, Jiang H, et al. Different fatty acids inhibit apoB100 secretion by different pathways: unique roles for ER stress, ceramide, and autophagy. *J Lipid Res.* 2011 Sep;52(9):1636-51.

[89] Shepherd J, Packard CJ, Grundy SM, Yeshurun D, Gotto AM, Jr., Taunton OD. Effects of saturated and polyunsaturated fat diets on the chemical composition and metabolism of low density lipoproteins in man. *J Lipid Res.* 1980 Jan;21(1):91-9.

- [90] Bergeron N, Chiu S, Williams PT, S MK, Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. *Am J Clin Nutr.* 2019 Jul 1;110(1):24-33.
- [91] Ulven SM, Christensen JJ, Nygard O, Svardal A, Leder L, Ottestad I, et al. Using metabolic profiling and gene expression analyses to explore molecular effects of replacing saturated fat with polyunsaturated fat-a randomized controlled dietary intervention study. *Am J Clin Nutr.* 2019 May 1;109(5):1239-50.
- [92] Campos H, Dreon DM, Krauss RM. Associations of hepatic and lipoprotein lipase activities with changes in dietary composition and low density lipoprotein subclasses. *J Lipid Res.* 1995 Mar;36(3):462-72.
- [93] Wang CS, Weingand KW, Anthony MS. Effect of atherogenic diet on lipoprotein lipase activity in cynomolgus monkeys. *Atherosclerosis.* 1987 Oct;67(2-3):173-80.
- [94] Xu J, Nakamura MT, Cho HP, Clarke SD. Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. A mechanism for the coordinate suppression of lipogenic genes by polyunsaturated fats. *J Biol Chem.* 1999 Aug 13;274(33):23577-83.
- [95] Shimomura I, Bashmakov Y, Ikemoto S, Horton JD, Brown MS, Goldstein JL. Insulin selectively increases SREBP-1c mRNA in the livers of rats with streptozotocin-induced diabetes. *Proc Natl Acad Sci U S A.* 1999 Nov 23;96(24):13656-61.
- [96] Field FJ, Born E, Mathur SN. Fatty acid flux suppresses fatty acid synthesis in hamster intestine independently of SREBP-1 expression. *J Lipid Res.* 2003 Jun;44(6):1199-208.
- [97] Mensink RP, Zock PL, Kester AD, 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. *Am J Clin Nutr.* 2003 May;77(5):1146-55.
- [98] Hayek T, Ito Y, Azrolan N, Verdery RB, Aalto-Setälä K, Walsh A, et al. Dietary fat increases high density lipoprotein (HDL) levels both by increasing the transport rates and decreasing the fractional catabolic rates of HDL cholesterol ester and apolipoprotein (Apo) A-I. Presentation of a new animal model and mechanistic studies in human Apo A-I transgenic and control mice. *J Clin Invest.* 1993 Apr;91(4):1665-71.
- [99] Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol.* 2017 Feb 14;69(6):692-711.
- [100] Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res.* 2016 Aug;57(8):1339-59.
- [101] Malaguarnera M, Vacante M, Russo C, Malaguarnera G, Antic T, Malaguarnera L, et al. Lipoprotein(a) in cardiovascular diseases. *Biomed Res Int.* 2013;2013:650989.
- [102] Tholstrup T, Marckmann P, Vessby B, Sandstrom B. Effect of fats high in individual saturated fatty acids on plasma lipoprotein[a] levels in young healthy men. *J Lipid Res.* 1995 Jul;36(7):1447-52.
- [103] Gudbjartsson DF, Thorgeirsson G, Sulem P, Helgadóttir A, Gylfason A, Saemundsdóttir J, et al. Lipoprotein(a) Concentration and Risks of Cardiovascular Disease and Diabetes. *J Am Coll Cardiol.* 2019 Dec 17;74(24):2982-94.

- [104] Ljungberg J, Holmgren A, Bergdahl IA, Hultdin J, Norberg M, Naslund U, et al. Lipoprotein(a) and the Apolipoprotein B/A1 Ratio Independently Associate With Surgery for Aortic Stenosis Only in Patients With Concomitant Coronary Artery Disease. *J Am Heart Assoc.* 2017 Dec 15;6(12):e007160.
- [105] Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest.* 1992 Jul;90(1):52-60.
- [106] Enkhmaa B, Petersen KS, Kris-Etherton PM, Berglund L. Diet and Lp(a): Does Dietary Change Modify Residual Cardiovascular Risk Conferred by Lp(a)? *Nutrients.* 2020 Jul 7;12(7).
- [107] Brousseau ME, Ordovas JM, Nicolosi RJ, Schaefer EJ. Effects of dietary fat saturation on plasma lipoprotein(a) and hepatic apolipoprotein(a) mRNA concentrations in cynomolgus monkeys. *Atherosclerosis.* 1994 Mar;106(1):109-18.
- [108] Azrolan N, Gavish D, Breslow JL. Plasma lipoprotein(a) concentration is controlled by apolipoprotein(a) (apo(a)) protein size and the abundance of hepatic apo(a) mRNA in a cynomolgus monkey model. *J Biol Chem.* 1991 Jul 25;266(21):13866-72.
- [109] Fielding CJ, Shore VG, Fielding PE. A protein cofactor of lecithin:cholesterol acyltransferase. *Biochem Biophys Res Commun.* 1972 Feb 25;46(4):1493-8.
- [110] Gao X, Yuan S, Jayaraman S, Gursky O. Role of apolipoprotein A-II in the structure and remodeling of human high-density lipoprotein (HDL): protein conformational ensemble on HDL. *Biochemistry.* 2012 Jun 12;51(23):4633-41.
- [111] Kuyl JM, Mendelsohn D. Observed relationship between ratios HDL-cholesterol/total cholesterol and apolipoprotein A1/apolipoprotein B. *Clin Biochem.* 1992 Oct;25(5):313-6.
- [112] Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet.* 2001 Dec 15;358(9298):2026-33.
- [113] World Health Organization. Interim Summary of Conclusions and Dietary Recommendations on Total Fat & Fatty Acids [Internet]. Available from: https://www.who.int/nutrition/topics/FFA_summary_rec_conclusion.pdf?ua=1 [Accessed: 2021-06-05].
- [114] Dietary Guidelines for Americans 2020-2025 [Internet]. Available from: <https://www.dietaryguidelines.gov/> [Accessed: 2021-07-02].
- [115] Schwingshackl L, Hoffmann G. Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression. *BMJ Open.* 2014 Apr 19;4(4):e004487.
- [116] Krauss RM. Dietary and genetic probes of atherogenic dyslipidemia. *Arterioscler Thromb Vasc Biol.* 2005 Nov;25(11):2265-72.
- [117] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. *Am J Clin Nutr.* 2010 Mar;91(3):502-9.
- [118] Parks EJ, Krauss RM, Christiansen MP, Neese RA, Hellerstein MK. Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production, and clearance. *J Clin Invest.* 1999 Oct;104(8):1087-96.
- [119] Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL

heterogeneity. *J Lipid Res.* 2002 Sep;43(9):1363-79.

[120] Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care.* 2004 Jun;27(6):1496-504.

[121] Krauss RM, Dreon DM. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am J Clin Nutr.* 1995 Aug;62(2):478S-87S.

[122] Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res.* 2010 Nov;51(11):3324-30.

[123] Guay V, Lamarche B, Charest A, Tremblay AJ, Couture P. Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. *Metabolism.* 2012 Jan;61(1):76-83.

[124] Egert S, Kratz M, Kannenberg F, Fobker M, Wahrburg U. Effects of high-fat and low-fat diets rich in monounsaturated fatty acids on serum lipids, LDL size and indices of lipid peroxidation in healthy non-obese men and women when consumed under controlled conditions. *Eur J Nutr.* 2011 Feb;50(1):71-9.

[125] Wang L, Bordi PL, Fleming JA, Hill AM, Kris-Etherton PM. Effect of a moderate fat diet with and without avocados on lipoprotein particle number, size and subclasses in overweight and obese adults: a randomized, controlled trial. *J Am Heart Assoc.* 2015 Jan 7;4(1):e001355.

[126] Kratz M, Gulbahce E, von Eckardstein A, Cullen P, Cignarella A, Assmann G, et al. Dietary mono- and polyunsaturated fatty acids similarly affect LDL size in healthy men and women. *J Nutr.* 2002 Apr;132(4):715-8.

[127] Griffin BA. Lipoprotein atherogenicity: an overview of current mechanisms. *Proc Nutr Soc.* 1999 Feb;58(1):163-9.

[128] Anber V, Millar JS, McConnell M, Shepherd J, Packard CJ. Interaction of very-low-density, intermediate-density, and low-density lipoproteins with human arterial wall proteoglycans. *Arterioscler Thromb Vasc Biol.* 1997 Nov;17(11):2507-14.

[129] Taskinen MR. LDL-cholesterol, HDL-cholesterol or triglycerides--which is the culprit? *Diabetes Res Clin Pract.* 2003 Jul;61 Suppl 1:S19-26.

[130] DeJager S, Bruckert E, Chapman MJ. Dense low density lipoprotein subspecies with diminished oxidative resistance predominate in combined hyperlipidemia. *J Lipid Res.* 1993 Feb;34(2):295-308.

[131] Nigon F, Lesnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. *J Lipid Res.* 1991 Nov;32(11):1741-53.

[132] Galeano NF, Milne R, Marcel YL, Walsh MT, Levy E, Ngu'yen TD, et al. Apoprotein B structure and receptor recognition of triglyceride-rich low density lipoprotein (LDL) is modified in small LDL but not in triglyceride-rich LDL of normal size. *J Biol Chem.* 1994 Jan 7;269(1):511-9.

[133] Liu AG, Ford NA, Hu FB, Zelman KM, Mozaffarian D, Kris-Etherton PM. A healthy approach to dietary fats: understanding the science and taking action to reduce consumer confusion. *Nutr J.* 2017 Aug 30;16(1):53.

[134] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Supplemented with Extra-Virgin Olive
Oil or Nuts. N Engl J Med. 2018 Jun
21;378(25):e34.

[135] Howard BV, Van Horn L, Hsia J,
Manson JE, Stefanick ML,
Wassertheil-Smoller S, et al. Low-fat
dietary pattern and risk of
cardiovascular disease: the Women's
Health Initiative Randomized
Controlled Dietary Modification Trial.
Jama. 2006 Feb 8;295(6):655-66.