Lipids
DOI 10.1007/s11745-015-4113-x

REVIEW

Current Evidence Supporting the Link Between Dietary Fatty Acids and Cardiovascular Disease

Shatha Hammad[1] · Shuaihua Pu[1] · Peter J. Jones[1]

Received: 27 September 2015 / Accepted: 4 December 2015

Abstract Lack of consensus exists pertaining to the scientific evidence regarding effects of various dietary fatty acids on cardiovascular disease (CVD) risk. The objective of this article is to review current evidence concerning cardiovascular health effects of the main dietary fatty acid types; namely, trans (TFA), saturated (SFA), polyunsaturated (PUFA; n-3 PUFA and n-6 PUFA), and monounsaturated fatty acids (MUFA). Accumulating evidence shows negative health impacts of TFA and SFA; both may increase CVD risk. Policies have been proposed to reduce TFA and SFA consumption to less than 1 and 7 % of energy intake, respectively. Cardiovascular health might be promoted by replacing SFA and TFA with n-6 PUFA, n-3 PUFA, or MUFA; however, the optimal amount of PUFA or MUFA that can be used to replace SFA and TFA has not been defined yet. Evidence suggests of the potential importance of restricting n-6 PUFA up to 10 % of energy and obtaining an n-6/n-3 ratio as close as possible to unity, along with a particular emphasis on consuming adequate amounts of essential fatty acids. The latest evidence shows cardioprotective effects of MUFA-rich diets, especially when MUFA are supplemented with essential fatty acids; namely, docosahexaenoic acid. MUFA has been newly suggested to be involved in regulating fat oxidation, energy metabolism, appetite sensations, weight maintenance, and cholesterol metabolism. These favorable effects might implicate MUFA as the preferable choice to substitute for other fatty acids, especially given the declaration of its safety for up to 20 % of total energy.

✉ Shatha Hammad
hammads@myumanitoba.ca

Peter J. Jones
Peter.Jones@umanitoba.ca

[1] Richardson Centre for Functional Foods and Nutraceuticals, University of Manitoba, 196 Innovation Drive, Winnipeg, MB R3T 6C5, Canada

Keywords Unsaturated fatty acids · Saturated fatty acids · Chronic disease · Cardiovascular disease risk · Lipid profile · Dietary lipids

Abbreviations

ARA	Arachidonic acid
ALA	Alpha-linolenic acid
Apo	Apo-lipoprotein
CHO	Carbohydrate
COMIT	The Canola Oil Multicenter Intervention Trial
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
LNA	Linoleic acid
LDL-C	Low density lipoprotein cholesterol
MUFA	Monounsaturated fatty acid
n-3 PUFA	Omega-3 polyunsaturated fatty acid
n-6 PUFA	Omega-6 polyunsaturated fatty acid
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
TC	Total cholesterol
TFA	Trans fatty acid
VLDL-C	Very low density lipoprotein cholesterol
TAG	Triacylglycerol
WHO	World Health Organization

Introduction

An important health concern is to identify and control modifiable risk factors for prevention of cardiovascular disease (CVD) [1, 2]. Modulating dietary fat intake plays an integral role in preventing and controlling CVD risk [3, 4].

Published online: 30 December 2015

Observational and clinical data suggest that the amount and quality of dietary fat exist as main foci of dietary guidelines targeting reduced morbidity and mortality related to such diseases [2, 4–9]. This interest has been particularly directed towards four main types of fatty acids in food; trans fatty acids (TFA), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), or the two types of polyunsaturated fatty acids (n-3 PUFA and n-6 PUFA) [2]. These fatty acids are classified depending on the number, location, and configuration of double bonds contained within the fatty acid chains [2, 10]. Higher intakes of SFA (~12 % of total energy), TFA (~2 % of total energy), and an offset n-6 PUFA:n-3 PUFA ratio (>10:1) characterize current dietary patterns in industrialized countries [8, 11]. Until now, international guidelines have been considerably varied in term of recommended amounts and types of fatty acids for optimization of cardiovascular health [2, 8, 10]. This variation might be partially attributable to lack of conclusive scientific evidence for several possible reasons [10, 12–14]. Firstly, inaccuracy may exist in the means of measurement of dietary fatty acid intake using self-reported dietary assessment tools in observational studies. Secondly, in controlled trials, differences in trial length, diet composition, and trial power may also be responsible [10, 12]. The controversy might be attributed to the diversity in design and/or tested parameters between different trials; trials have either studied effects of dietary fatty acids on intermediate risk markers, such as blood lipids, or studied effects of heterogeneous dietary fatty acids on heterogeneous combinations of cardiovascular outcomes, which indeed limit our ability to compare between study results [13]. Additionally, inter-individual genetic variation might, in part, also explain the inconsistency in existing scientific evidence; heterogeneity in genetic regulation of lipid metabolism may result in different metabolic responses to a given dietary fat [14]. In this review, the objective is to review and assess current evidence regarding cardiovascular effects of the four principal dietary fatty acid categories. Specifically, search procedures for studies and reviews in this particular field were performed using the PubMed database, and targeted recent publications from 2000 through 2015.

Trans Fatty Acids

TFA are unsaturated fatty acids with one or more double bonds in *trans* configurations [1, 15, 16]. Two sources of dietary TFA exist; one is ruminant-derived TFA, but is found naturally only in trace amounts, while the second and main source is through the industrial hydrogenation of vegetable oils [1, 15, 17, 18]. The process of hydrogenation converts liquid vegetable oils into semi-solid fats, characterized by longer shelf life as well as greater stability and solidity for their use in commercial cooking and manufacturing processes [1, 15, 18]. Margarines, deep-fried fast foods, bakery products, and packaged foods are the main sources of TFA in North American diets [15, 17].

TFA from partially hydrogenated vegetable oils are known for their independent associations with cardiovascular events [1, 3, 19]. Results from meta-analysis of cohort studies on TFA show that high intakes (2.5–6.3 % total energy) of TFA significantly increase relative risk of CVD deaths by more than 30 % and CVD events by 25 %, as compared with low (<1–2.4 % total energy) TFA intake [3]. In the United States alone, 600,000 myocardial infarctions and 451,300 deaths related to coronary heart disease are reported yearly, which might be related, in part, to high intakes (2–3 % of total energy) of TFA [1]. A 2 % increase in TFA consumption was associated with a 23 % higher incidence of CVD [20]. TFA consumption has been recently suggested to be a causative factor for metabolic dysfunction, abnormal lipid profile, systemic inflammation, endothelial dysfunction, increased visceral adiposity and higher body weight, as well as risk of type 2 diabetes mellitus [1].

The impact of TFA on lipid parameters has been thoroughly studied [15–17, 19, 21]. Increasing evidence has documented that consumption of TFA is associated with significant elevations in plasma total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triacylglycerol (TAG), very low density lipoprotein cholesterol (VLDL-C), lipoprotein-a, and ratios of TC: high density lipoprotein cholesterol (HDL-C) and LDL-C:HDL-C, as well as a reduction in HDL-C concentrations [15, 17, 19, 21]. On a metabolic basis, these alterations might occur due to decreased particle size and catabolic rates of apolipoprotein (apo) B-100 [15, 16] and/or increased catabolic rates of apo A-I [15]. Additionally, it has been found that consumption of TFA increases the transfer of cholesterol esters from HDL-C to LDL-C and VLDL-C, due to an increase in plasma activity of cholesteryl ester transfer protein levels [15].

A meta-analysis of 60 controlled trials concluded that replacing TFA with unsaturated fatty acids efficiently improved blood lipid profiles, and especially the ratio of TC:HDL-C [5]. The TC:HDL-C ratio was found to be reduced by 0.022, 0.054 and 0.067 after replacing 1 % of energy of TFA by carbohydrate (CHO), oleic acid or linoleic acid (LNA), respectively [21]. Over a 1-year period, for every 1 % reduction in consumption of TFA, an independent and significant reduction of 27 nmol/L in LDL-C particle number was observed [20]. The Centers for Disease Control and Prevention of the United States estimate prevention of 20,000 coronary events and 7000 deaths from coronary causes each year in the United States as a result of complete elimination of dietary TFA [22].

Beyond altering plasma lipid profiles, consumption of TFA results in their incorporation into phospholipids within cellular membranes which in turn might alter membrane fluidity, as well as responses of membrane receptors [23]. It has also been suggested that TFA might be able to regulate gene expression, and therefore, affect CVD-related metabolic abnormalities such as inhibiting the normal metabolism of essential fatty acids [24]. TFA may decrease the amount of arachidonic acid (ARA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels, possibly by interfering with the desaturation and elongation of n-3 and n-6 fatty acids [25].

TFA intake has also been associated with other CVD risk factors, such as obesity, inflammatory biomarkers, and endothelial dysfunction [26, 27]. A substitution of 2 % of total energy of either PUFA or CHO with TFA was associated with a 0.77 cm waist gain [26]. Additionally, consumption of TFA was found to adversely affect endothelial function, and was found to elevate C-reactive protein, interleukin-6 (IL-6), soluble tumor necrosis factor receptor 2, E-selectin, as well as soluble intercellular and vascular cell adhesion molecules [27].

Therefore, different policies were proposed at national and international levels to reduce/eliminate TFA consumption. For example, several jurisdictions have banned partially hydrogenated oils starting in 2003 [22]. In addition, mandatory labelling has been adopted by many countries. Indeed, the recent recommendation of World Health Organization (WHO) is to restrict TFA intake to less than 1 % of dietary energy intake [18]. Additionally, the United States Food and Drug Administration has not only allowed for only small amounts (1–2 % of energy) of TFA to be used in foods in the United States, but further declared a notice proposing that partially hydrogenated oils are no longer considered "generally recognized as safe" [22]. However, such policies have not been not successful enough to reflect a reduction in TFA intake in all countries [18]. Further education and more restrictive policies, especially at the industrial level, are needed to completely eliminate partially hydrogenated TFA from foods.

Saturated Fatty Acids

SFA have no double bonds between carbon atoms of the fatty acid chain [2, 10]. Major sources of dietary SFA are meat and dairy products, as well as certain plant fats such as palm oil [2, 28]. One of the most frequently stated dietary recommendations for a healthier cardiovascular system is to reduce SFA intake [4, 13]. In the US, the current daily dietary intake of SFA is high, reaching 11–12 % of total energy [8]. Based on data from controlled trials, intervention studies, and prospective cohort studies, the U.S. Department of Agriculture and U.S. Department of Health and Human Services in 2010 recommended consumption of less than 10 % of energy from SFA [29]. Furthermore and more recently, according to the American Heart Association's Diet and Lifestyle Recommendations, SFA intake should be less than 7 % of total energy [2].

Studies on animals and humans have shown positive associations between dietary SFA intake and plasma cholesterol concentrations as well as CVD risk [12, 30]. For instance, Jakobsen et al. found a 36 % greater risk of CVD among women who consumed 5 % higher level of energy from SFA [31]. SFA intake has been suggested to inhibit LDL-C receptor activity and to enhance apo B production, thus elevating plasma LDL-C and TC levels, as well as the LDL-C:HDL-C ratio [14, 21]. Consumption of SFA is associated with increased body weight, insulin resistance, abnormal glycemic response, and inflammatory capacity of adipose tissue [28, 32]. Consumption of SFA diet (8 % of total energy of stearic acid), compared with CHO, was found to elevate fibrinogen concentrations by 4.4 %, which is thought to raise the risk of myocardial infarction by 7 % [33]. Trials of longer duration might be required to detect a potentially important reduction in CVD risk with reduction or modification of SFA; indeed, reducing SFA intake in longer-term trials, by either simply reducing its quantity or substituting a certain amount with unsaturated fatty acids and/or CHO, resulted in a 17 % risk reduction of cardiovascular events [7]. A systematic review and meta-analysis of randomized controlled trials replacing SFA with PUFA found that the incidence of CVD events decreased by 19 %; with 10 % reduction in CVD risk with each 5 % (of energy) replacement of SFA [13]. When either MUFA or CHO were used as replacements for SFA, reductions in plasma TC, LDL-C, and HDL-C levels were observed [14]. Similarly, LDL-C concentrations were significantly decreased in response to replacing 7 % of SFA with either MUFA or CHO [14].

On the other hand, more recent studies examining the association of dietary SFA with CVD morbidity and/or mortality have revealed inconclusive results; varied between either positive [31, 34], inverse [12, 37], or even no association [35, 36]. Different meta-analysis studies have argued that no association exists between SFA intake and increased risk of CVD [10, 12]. This controversy has raised a claim, by Chowdhury et al., that the current cardiovascular guidelines of reducing SFA intake are not supported by strong evidence; they found, in their meta-analysis, that the relative risk for coronary disease was 1.02 for SFA intake [10].

The debate has been extended further to question whether the beneficial effect of replacing SFA results from adding more of the replaced nutrient or from eliminating SFA from diet [14]. It has been argued that protective

effects of replacing SFA with PUFA observed in intervention trials were detected at PUFA:SFA ratios ranging from 1.4 to 2.4, which greatly exceed the threshold of 0.49 above which CVD risk reduction has been previously reported [12]. This finding might indicate that a high level of PUFA is required to counteract SFA effects on CVD. However, in a randomized, controlled, parallel-group dietary intervention, about 9.5 % energy of SFA was replaced with either MUFA or n–6 PUFA [38]. This replacement of SFA with MUFA induced a reduction in plasma levels of TC by 8.4 % and LDL-C by 11.3 %, while PUFA replacement reduced plasma TC and LDL-C levels by 9.2 and 13.6 %, respectively. A 17–20 % reduction in CVD mortality has been estimated to be induced due to changes in LDL-C level of this magnitude [38].

This discrepancy among the available sources of scientific evidence might be, in part, explained by dissimilarities in the impact of different SFA on CVD risk. Plasma LDL-C levels were found to be differentially affected by myristic acid (C14:0) followed by lauric (C12:0) and palmitic (C16:0) acids [39]. On the other hand, no significant effects have been detected for stearic acid (C18:0) on plasma TC or LDL-C or TC:HDL-C ratio as compared with CHO [14, 21]. Dietary intakes of different populations have diverse SFA compositions; this possibly affects the consistency between studies conducted across different countries [39]; Western diets mainly supply fats consisting of myristic and lauric acid, while palmitic acid is the major SFA in the diet of Latin America, Asia, and Europe. In addition to the effect of different SFA types, it has been proposed that TAG structure plays a role in inducing cholesterolemia [30]. Additionally, the effect of SFA intake on CVD risk might be influenced by the source of SFA. Plant sources of palmitic acid failed to elevate plasma TC and LDL-C levels in contrast to animal sources [21]. Similarly, cheese consumption failed to elevate LDL-C concentrations as much as did butter [14]. Furthermore, the LDL-C raising effect of SFA has been suggested to be affected by the presence of other dietary components. Plasma LDL-C concentrations were the greatest when the intake consisted of SFA containing the highest level of dietary cholesterol, while the intake of SFA had a negligible effect when cholesterol was absent and PUFA was adequate (5–10 % of energy) [14]. In the MultiEthnic Study of Atherosclerosis, higher intakes of SFA from dairy were associated with a lower CVD risk, which might be attributable to increased fecal fat excretion and the calcium content of dairy foods [40]. The inconsistency in results within the available literature is probably either due to using different nutrients for replacing dietary SFA, or to diversity in types of SFA. For instance, palm oil substitution for myristic and lauric acid significantly lowered serum concentrations of TC, HDL-C, and apo A-I, and showed a trend for significant reduction of LDL-C levels [30].

Notwithstanding these inconsistencies in the current scientific evidence, professional authorities such as WHO, American Dietetic Association, Dietitians of Canada, American Heart Association, and others all around the world advise on the positive association between SFA consumption and CVD risk, and all underscore the importance of reducing SFA intake for a healthier cardiovascular system [2, 41]. SFA must be restricted at least to less than 10 % of total energy, and to less than 7 % for high-risk group.

Polyunsaturated Fatty Acids

PUFA are fatty acids that contain more than one double bond in their backbone [42]. Two classes of PUFA are well known for their nutritional relevance; n-6 and n-3 PUFA, based on the position of their double bonds [43]. LNA (C18:2n-6) and alpha-linolenic acid (C18:3n-3; ALA), the two essential fatty acids [42, 43], can both be further elongated and desaturated to longer chain PUFA in human body. LNA is considered the precursor of ARA (C20:4n-6), and ALA is the precursor of both EPA (C20:5n-3) and DHA (C22:6n-3) [25]. Dietary Guidelines for Americans recommend an intake of 5–10 % of energy from n-6, and 0.6 to 1.2 % of energy from n-3 PUFA [2]. Additionally, the American and European heart associations have recommended sufficient intake of these long-chain PUFA (1 g/day of EPA and DHA) for preventing cardiovascular events [42].

During the past few decades, the Western dietary pattern has been changing toward increasing consumption of PUFA-rich vegetable oils and decreasing animal fats. For example, the daily consumption of LNA and ALA has increased by about 50 and 100 %, respectively, in the last 20 years in Europe [42]. Results from randomized controlled trials indicate that consumption of total (n-6 and n-3) PUFA at 10–21 % energy reduces the risk of CVD by 17 %, as compared with lower intakes [44]. Compared to CHO or any other major class of fatty acids, consumption of PUFA has the most beneficial effect on TC:HDL-C, mainly by reducing LDL-C levels [13]. For each 5 % (of energy) short-term increment in total PUFA consumption, plasma LDL-C was reduced by 0.26 mmol/l without significant reductions in HDL-C concentrations [5]. The 13–15 % LDL-C reduction effect was associated with a 25–43 % reduction in CVD events [45]. PUFA may also contribute to cardiovascular health by improving insulin resistance and reducing systemic inflammation [46, 47]. These favorable effects of PUFA highlight the possibility of using PUFA for replacing dietary SFA; however, the extent of this replacement might be limited to a certain extent, by subsequent evidence that shows possible negative

effects of high PUFA intake on cardiovascular health. For instance, consumption of more than 10 % of energy from PUFA has been suggested to increase CVD risk [13]. Further, increases in the development of new arterial lesions were significantly associated with consumption of 9.7 % energy of total PUFA [45]. This discrepancy might in part be attributable to higher intake of n-6 relative to n-3, as discussed later in this chapter.

The two classes of PUFA, n-3 and n-6 fatty acids, have different roles and effects on cardiovascular health. The n-3 fatty acids may contribute to the cardiovascular benefits by decreasing TAG and VLDL-C levels, as well as apo B production, blood pressure, platelet aggregation and moderate elevating HDL-C levels [42, 48, 49]. Furthermore, n-3 fatty acids may promote vasodilation, anti-inflammatory response, improvements in endothelial function, and neutralize oxidative damage as well as restore free radical homeostasis, among other functions [42, 48, 50]. The beneficial effect of reducing TAG and VLDL-C levels has been found to be induced mostly by n-3 PUFA compared to other fatty acid classes [45]. This effect is well established, and is induced by controlling TAG uptake and synthesis in the liver [48]. Supplementing 4 g/day of DHA and EPA for 6 weeks was found to reduce VLDL-C and TAG levels by 20 and 18 %, respectively, as compared to 4 g/day of corn oil [49]. Adding n-3 PUFA sources to the diet has been shown to lead to a 30–50 % reduction in CVD-related morbidity and mortality [42, 48]. However, scientific evidence shows inconsistent results regarding cardiovascular effects of n-3 PUFA consumption. A recent review indicated no strong effects of n-3 PUFA in lowering blood lipids or fibrinolysis and plasminogen activator inhibitor-1 [42]. Based on a large body of clinical trial data, no effect of 5 years of supplementation with 1.8 g/d EPA was found on plasma TC, LDL-C, or HDL-C levels [50]. Further, 3 g/d of fish oil supplementation, as a major source of n-3 fatty acids, for 3 months was shown to increase TC and LDL-C levels [50]. n-3 PUFA enhance the catabolism of VLDL-C, which, therefore, might result in increase in the production of intermediate-density lipoprotein and LDL-C [49]. In addition, scientists have been increasingly concerned regarding the higher risk of hemorrhagic complications following prolonged supplementation with n-3 PUFA [48]. Even the antioxidant ability of n-3 fatty acids has been questioned, especially at high doses where these fats have been suggested to act as a pro-oxidants [50].

Regarding cardiovascular effects of n-6 PUFA, epidemiological evidence has revealed a beneficial effect of n-6 fatty acids on plasma LDL-C, TC, and HDL-C levels, as well as the TC: HDL-C ratio [42–45]. A replacement of 10 % of calories from SFA with n-6 PUFA was found to decrease LDL-C by 0.46 mmol/l [44]. Diets rich in LNA (12 % energy PUFA, 11 % SFA, 16 % MUFA, 0.1 % TFA) were found to lower serum TC concentrations by 0.15 mmol/l and LDL-C by 0.17 mmol/l when compared to diets rich in stearic acid (4.2 % PUFA, 10 % SFA, 23 % MUFA, 7.7 % TFA) [45]. Improvements in insulin resistance and reductions in blood pressure have also been identified as favorable effects of n-6 fatty acids consumption [44]. Similar to n-3 fatty acids, controversy exists in the literature regarding the role of n-6 fatty acids in CVD prevention. A diet containing in excess of 10 % n-6 fatty acids has been evoked to induce adverse effects against CVD, mostly due to their proinflammatory and oxidation effects [11, 42]. It is suggested that dietary n-6 fatty acids may increase oxidation susceptibility of LDL-C and VLDL-C [42]. High intake of n-6 PUFA might also be associated with increased vasospasm, vasoconstriction, and blood viscosity [11]. ARA is a substrate for the synthesis of a diversity of vasoconstrictive, proinflammatory, and proaggregatory molecules; therefore, this category of fats might induce atherosclerosis, high blood pressure, and thus increase risk of CVD and obesity [11, 44, 51]. Higher concentrations of proinflammatory interleukin-6, tumor necrosis factor alpha, and C-reactive protein levels were evidenced with higher intakes of n-6 PUFA [11, 51]. These adverse effects were maximized when n-6 PUFA intake was accompanied with low dietary n-3 PUFA intakes [11]. It is worth mentioning that most interventional trials that failed to detect cardiovascular protective effects of higher n-6 PUFA consumption, ranging between 4 and 15 % more PUFA in treatment than in control group, were insufficiently powered, while corresponding meta-analyses have shown protective effects [13]. Additionally, a systematic review of randomized, controlled intervention studies among healthy, non-infant humans concluded that an absence of evidence exists regarding the adverse effects of LNA on inflammatory markers [52].

In fact, numerous studies have highlighted the importance of the n-6/n-3 FA ratio, rather than the amount of each single fatty acid individually, on health status [25, 42]. It has been documented that a high ratio of n-6/n-3 fatty acids is related to the pathogenesis of CVD, whereas protective effects appear when the ratio is close to unity [42]. Lower ratios of n-6/n-3 fatty acids have been found to be associated with suppressed levels of vascular endothelial growth factor and inflammatory biomarkers, as well as with reduced rates of platelet aggregation [25]. During the past few decades, this ratio has increased in the Western diet to reach a range of 10:1 to 20:1 [11]. When such a high n-6/n-3 ratio was reduced, in a prospective prevention trial, to reach 4:1, it was found to be associated with 70 % reduction in all-cause mortality [42]. However, this ratio does not distinguish among different classes of PUFA, or whether the consumption of essential fatty acids is sufficient [42].

Also the preferable strategy to obtain the desirable n-6/n-3 fatty acid ratio has not been presently defined [53].

The majority of evidence is highly supportive of the beneficial effects of PUFA on cardiovascular morbidity and mortality risk when the population intake is low and as long as the increase does not exceed the upper acceptable level [45]. Until the discrepancy in the existing evidence is resolved, the Dietary Guidelines for Americans recommend an intake of 5–10 % of energy from n-6, and 0.6 % to 1.2 % of energy from n-3 [2]. Most importantly, PUFA intake should be directed to obtain an n-6/n-3 ratio as close as possible to unity, while ensuring an adequate intake of essential fatty acids.

Monounsaturated Fatty Acids

MUFA are fatty acids that possess one double bond in the carbon chain, with the remaining carbon atoms being single-bonded. Oleic acid (C18:1n-9) is the predominant dietary MUFA, accounting for up to 92 % of dietary MUFA [43]. With the extensive evidence regarding eliminating TFA, reducing SFA, and limiting PUFA intake to about 10 % of energy, scientific interest has been directed toward emphasizing the cardioprotective effect of MUFA consumption. Dietary MUFA consumption has been suggested as inducing a 20 % reduction in the risk of CVD events, as evidenced by a large body of prospective cohort studies [8]. While the American Heart Association sets a limit of MUFA consumption at 20 % of total energy [54], recent recommendations of the American Diabetes Association and Dietitians of Canada allow for consuming almost 25 % of energy of MUFA [8, 54]. These recommendations have been derived based on a body of evidence that shows favorable effects of MUFA on CVD risk reduction, and are also supported by the absence of reported side effects of MUFA-rich diet in the literature, compared to other fatty acids [8, 54].

Among the numerous dietary sources of MUFA, olive and canola oil are the most commonly consumed [8]. The Mediterranean diet is characterized by its high MUFA content, 16–29 % of energy as MUFA out of 33-40 % of energy as total fat, with olive oil being the predominant source of fat, and SFA as low as 8 % [8, 50]. The Mediterranean dietary pattern is associated with a low prevalence of chronic disease among its consumers [55, 56], more specifically, the cardioprotective effects of this dietary pattern have been extensively reported in epidemiological studies and randomized clinical trials [8, 50]. For instance, the prevalence of metabolic syndrome in the United States is almost threefold compared to the prevalence in Mediterranean countries [8], most likely attributable to difference on their dietary patterns [56]. Even though the total levels of fat in Mediterranean and Western diets are similar, massive differences are found in the type of fat [8]. In the United States, SFA might reach 11–12 % of energy with low intake of MUFA (13–14 % energy), while oleic acid, usually is the main source (92 %) of MUFA [8]. For more than a decade, and in an attempt to reduce CVD risk, high-oleic canola oil with higher stability has been commercially produced in North America, making this healthy vegetable oil suitable for use in food preparation and processing as well as a replacement for dietary SFA and TFA [57].

The beneficial effect of MUFA on cardiovascular health was proposed to be induced by modulating several parameters, Table 1 shows newly identified effects/mechanisms. MUFA-rich diet reduces cardiovascular effects by lowering plasma TC and LDL-C levels as well as elevating the HDL-C:TC ratio [21, 50]. MUFA-rich diets have variously been found to increase HDL-C more than do PUFA- or CHO-rich diets [8, 58]. Regular consumption of dietary MUFA among myocardial infarction patients was shown to induce a significant 24 % reduction in mortality risk [50]. One previous study showed that feeding a diet rich in high-oleic canola oil reduced plasma TC and LDL-C levels by 3.5 and 7.4 %, respectively, whereas more favorable effects were induced when canola oil was enriched with ALA; −11 % in TC and −15.1 % in LDL-C. However, feeding the blended oil (canola with ALA) resulted in 8.5 % reduction in HDL-C level [6]. In contrast, HDL-C levels did not change following consumption of moderate fat weight-maintenance diets (33 % energy) with high MUFA content in overweight and obese subjects, while this diet decreased TAG and TC:HDL-C and non-HDL-C:HDL-C ratios [59]. These favorable effects of MUFA on lipid profile have been suggested to be induced via ability of dietary MUFA to stimulate acyl-CoA: cholesterol acyltransferase in the liver, which leads to an augmented cholesterol ester formation, decreased sterol pool, and higher expression of the LDL receptor in the liver [60]. Moreover, low cholesterol content of high MUFA diet may result in degradation of insulin-induced gene-1 protein, and therefore, inactivation of the transcription factor sterol regulatory element binding protein which regulates cholesterol synthesis, cellular LDL uptake, and fat oxidation. This inactivation inhibits the biosynthesis and cellular uptake of cholesterol and promotes fat oxidation [60].

Evidence from clinical trials and meta-analysis has shown a beneficial effect of MUFA-rich diets on blood pressure in hypertensive and pre-hypertensive subjects as well as among metabolic syndrome patients, as compared to CHO- or PUFA-rich diets [58, 61, 62]. Further, providing a MUFA-rich diet for 6 months was found to markedly reduce the daily requirement of anti-hypertensive medication [58].

Table 1 Newly identified cardiovascular effects/mechanisms of action for dietary MUFA

Cardiovascular effect	Suggested mechanism	References
Lipid profile	Via ability of dietary MUFA to stimulate acyl-CoA: cholesterol acyltransferase in the liver, which leads to an augmented cholesterol ester formation, decreased sterol pool, and higher expression of the LDL receptor in the liver	Kien et al. [60]
	Low cholesterol content of high MUFA diet may result in degradation of insulin-induced gene-1 protein, and therefore, inactivation of the transcription factor sterol regulatory element binding protein (which regulates cholesterol synthesis, cellular LDL uptake, and fat oxidation); this inactivation inhibits the biosynthesis and cellular uptake of cholesterol and promotes fat oxidation	
Energy metabolism, body composition and body weight	High oxidation rate of MUFA	Krishnan and Cooper [9]
	Increment in fat oxidation rate, diet-induced thermogenesis, and energy expenditure	
Energy intake	Elevated post-prandial oleoylethanolamide level that regulated food intake by influencing metabolic and reward systems; therefore reducing energy intake	Mennella et al. [69]
Cholesterol metabolism	Decline in Proprotein convertase subtilisin/kexin type 9 levels (a novel circulating protein that reduces the burden of atherosclerotic CVD by significantly contributing in regulation of cholesterol metabolism)[a]	Pu et al. [72]
	Via lowering LDL-proteoglycan binding	

[a] The MUFA diet was supplemented with DHA

Additionally, dietary substitution of MUFA for SFA has been shown to improve beta-cell function and reduce insulin resistance in participants with normal fasting glucose and normal glucose tolerance [63]. MUFA intake improves insulin sensitivity, which might be increased by 8.8 % with MUFA-rich diets [8, 9]. Results from nine long-term (≥6 months) randomized controlled intervention trials showed that feeding diets high (>12 % of total energy) in dietary MUFA, as compared to the low-MUFA diets (≤12 % of total energy), significantly reduced hemoglobin A1c (HbA1c) by 0.21 % [64]. More recent parallel randomized trials have demonstrated that consumption of diets rich in canola oil for 3 months reduced HbA1c by 0.47 % and improved the glycemic response in type 2 diabetic patients [65]. A meta-analysis of randomized controlled trials indicated an improvement in the glycemic control of patients with either type one or two diabetes in response to high MUFA diet, as compared to a CHO-rich diet [8]. While 6 months of Western (>15 % energy of SFA and 35 % of energy as total fat) and low-fat (20–30 % of energy) diets worsened glucose homeostasis biomarkers, high dietary MUFA (>20 % of energy and total fat: 35–45 % energy) induced 3.0 and 9.4 % reductions in fasting glucose and insulin levels, respectively, and improved insulin sensitivity by 12.1 % [66]. These results showed an even more favorable effect of a MUFA-rich diet than the previously recommended low fat diet (<30 % of energy; according to Dietary guidelines for Americans, 2005), where the low fat diet elevated fasting glucose by 1.4 % and insulin levels by 13.1 %. High MUFA diets seem to have favorable effects on glucose metabolism and may hold the promise for glycemic control.

Existing scientific evidence exploring the effect of different types of long chain fatty acids on fat oxidation and energy metabolism has been recently reviewed by Krishnan and Cooper [9]. Considerable data show that the oxidation rate of unsaturated fatty acids is higher than SFA, and among the two, unsaturated and SFA, the highest oxidation rate is from MUFA sources in the diet [9, 67]. An increasing body of evidence indicates an increment in fat oxidation rate, diet-induced thermogenesis, and energy expenditure, specifically with higher dietary MUFA levels [9]. The beneficial effects of different types of fatty acids on energy metabolism, body composition, and weight maintenance were demonstrated to be equally induced by unsaturated fatty acids and mostly by MUFA (MUFA ≥ PUFA > SFA) [8, 9, 59]. Nimptsch et al. found an inverse association between oleic acid intake and weight gain, while SFA, ARA, as well as ALA intakes were linearly associated with weight gain [68]. Furthermore, high-oleic MUFA diets may promote weight loss in both diabetic and non-diabetic obese patients [43].

A recent randomized intervention trial found that the oleic acid content of a meal is associated with reduced appetite and suppression of energy intake after subsequent meals in humans [69]. The high-oleic acid content

of diet was found to elevate post-prandial oleoylethanolamide (OEA) levels. Oleoylethanolamide, a member of the recently identified group of fatty acid ethanolamide group of metabolic regulators, regulates food intake by influencing metabolic and reward systems. OEA controls appetite sensation, and therefore, reduces energy intake. This finding is novel in humans and might hold promise toward the use of oils rich in oleic acid as new food ingredients for controlling energy intake [69].

Novel modified vegetable oils are designed to contain the balanced proportions of SFA, MUFA and n-6/n-3 PUFA; they provide opportunities to prevent CVD events. The knowledge gaps are how to evaluate the efficacy of those vegetable oils with various combinations of n-9, n-6, and n-3 fatty acids on common risk factors in human clinical trials. The previous clinical intervention study conducted by our group [6] has demonstrated that consumption of novel high-oleic canola oil is cardioprotective through lipid-lowering effects compared to a typical Western diet (high in SFA). Thus, our research team recently completed the Canola Oil Multicenter Intervention Trial (COMIT) where the purpose was to examine specific beneficial effects of consumption of different dietary oil varying unsaturated fat contents on a comprehensive range of metabolic responses that are important in the development of CVD. The COMIT study was a randomized controlled crossover weight-maintenance full-feeding study focused on exploring metabolic actions of unsaturated fatty acids. Full details of this study have been published by Senanayake et al. [70]. The goal of the study was to examine effects of different dietary oil/oil blends on a comprehensive range of metabolic responses that are important in the development of CVD. COMIT was recently conducted across three centers in Canada and the United States to investigate the cardiovascular effects of five diets that provided different oils and/or oil blends in 130 participants with abdominal obesity. These five oils and oil blends were selected to test the effect of major fatty acids; MUFA, n-3 PUFA and n-6 PUFA at different levels. The five treatments were: (1) a conventional canola, (2) high-oleic canola oil, (3) high-oleic canola and 15 % DHA blend, (4) 60 % flax oil and 40 % safflower oil blend, and (5) 25 % corn oil and 75 % safflower oil blend. The importance of this study is not only that it investigated various dietary fatty acid blends in a crossover design, but also it comprehensively evaluated the effects of these fatty acids on biomarkers of CVD, where it went beyond blood lipids and/or lipoproteins, which are theconventional biomarkers most used by other studies [70–75].

One of the most important findings of the COMIT study was that the DHA enriched high oleic canola oil treatment produced a 19 % risk reduction at Framingham 10-y coronary heart disease risk score the greatest risk reduction among the 5 regimens [71]. Significant reductions in plasma LDL-C and TC levels from baseline to endpoint were detected following each diet, whereas the greatest reductions in TAG (−20.7 %) and systolic blood pressure (−3.3 %) were induced following the feeding of the diet high in oleic-acid–rich canola/DHA. Furthermore, high-oleic canola/DHA was the only diet that increased HDL-C from baseline, but at the same time, the increase in LDL-C level was the highest following this diet [71]. However, the effect of increased LDL-C level following high-oleic canola/DHA blend might have been counteracted by the detected decline in proprotein convertase subtilisin/kexin type 9 levels, a novel circulating protein that reduces the burden of atherosclerotic CVD by significantly affecting the regulation of cholesterol metabolism [72]. Additionally, the COMIT data suggested that high-oleic canola oil consumption may reduce atherosclerosis risk in humans by lowering LDL-proteoglycan binding [73]. Among the results of this study, oleic-acid–rich diets were found to elevate cholesterol absorption biomarkers while n-3 PUFA, namely DHA, resulted in higher circulating cholesterol levels possibly due to its ability to accelerate cholesterol synthesis [74]. The effects of COMIT diets on pro-inflammatory biomarkers were also assessed. Results indicated that the canola oil diet reduced high-sensitivity C-reactive protein concentrations, whereas feeding canola oil increased plasma adiponectin concentrations and decreased the relative expression of levels of interleukin 1B after feeding high-oleic canola/DHA diet [75]. The COMIT study also demonstrated that a negative correlation exists between plasma oleoylethanolamide levels and android fat mass change in a subgroup of 27 subjects after canola-oil–rich diets, indicating the potential benefits of high MUFA intake on energy regulation [76].

In summary, the primary outcomes from the COMIT study demonstrate that dietary oils low in SFA, high in MUFA and PUFA can significantly lower predicted CVD risks. Optimal balance among daily intake of MUFA, n-3 PUFA and n-6 PUFA can effectively improve the health condition for individuals who are consuming a Western diet daily in North America. These desirable changes on pro-inflammatory biomarkers may consequently improve glucose and lipid metabolism, ameliorate atherosclerotic and inflammatory status, and further reduce cardiovascular morbidity and mortality.

Conclusion

The latest evidence shows the favorable effects of MUFA-rich diets, especially if supplemented with essential fatty acids. Promoting health may be achieved by eliminating TFA from diet, restricting SFA and n-6 PUFA to less than 7 % of energy and 10 % of energy, respectively, and

obtaining an n-6/n-3 fatty acid ratio as close as possible to unity with adequate intakes of essential fatty acids. Furthermore, considering the emerging science promising favorable effects of MUFA, it might be the best choice to substitute for other dietary fatty acids, especially with the declaration of its safety for up to 20 % of total energy [8, 54]. The Mediterranean dietary pattern is an excellent example of the association between adherence of high MUFA intakes (up to 29 %) and the low prevalence of chronic disease among those adopting this dietary paradigm. Given the newly identified health advantages of MUFA, such as regulating fat oxidation, energy metabolism, appetite sensations, weight maintenance and cholesterol metabolism, it might be beneficial to increase the upper limit for intakes of MUFA even beyond 20 %.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Micha R, Mozaffarian D (2009) Trans fatty acids: effects on metabolic syndrome, heart disease and diabetes. Nat Rev Endocrinol 5(6):335–344
2. Kris-Etherton PM, Innis S, Ammerican Dietetic Assocition, Dietitians of Canada (2007) Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. J Am Diet Assoc 107(9):1599–1611
3. Skeaff CM, Miller J (2009) Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. Ann Nutr Metab 55(1–3):173–201
4. Committee American Heart Association Nutrition, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J (2006) Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 114(1):82–96
5. Mensink RP, Zock PL, Kester AD, Katan MB (2003) 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 77(5):1146–1155
6. Gillingham LG, Gustafson JA, Han SY, Jassal DS, Jones PJ (2011) High-oleic rapeseed (canola) and flaxseed oils modulate serum lipids and inflammatory biomarkers in hypercholesterolaemic subjects. Br J Nutr 105(3):417–427
7. Hooper L, Martin N, Abdelhamid A, Davey Smith G (2015) Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev 6:CD011737
8. Gillingham LG, Harris-Janz S, Jones PJ (2011) Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. Lipids 46(3):209–228
9. Krishnan S, Cooper JA (2014) Effect of dietary fatty acid composition on substrate utilization and body weight maintenance in humans. Eur J Nutr 53(3):691–710
10. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E (2014) Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 160(6):398–406
11. Patterson E, Wall R, Fitzgerald GF, Ross RP, Stanton C (2012) Health implications of high dietary omega-6 polyunsaturated Fatty acids. J Nutr Metab 2012:539426
12. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr 91(3):535–546
13. Mozaffarian D, Micha R, Wallace S (2010) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic reviewand meta-analysis of randomized controlled trials. PLoS Med 7(3):e1000252
14. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM (2010) Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. Curr Atheroscler Rep 12(6):384–390
15. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC (2006) Trans fatty acids and cardiovascular disease. N Engl J Med 354(15):1601–1613
16. Mauger JF, Lichtenstein AH, Ausman LM, Jalbert SM, Jauhiainen M, Ehnholm C, Lamarche B (2003) Effect of different forms of dietary hydrogenated fats on LDL particle size. Am J Clin Nutr 78(3):370–375
17. Matthan NR, Welty FK, Barrett PH, Harausz C, Dolnikowski GG, Parks JS, Eckel RH, Schaefer EJ, Lichtenstein AH (2004) Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-densitylipoprotein apoB-100 catabolism in hypercholesterolemic women. Arterioscler Thromb Vasc Biol 24(6):1092–1097
18. Downs SM, Thow AM, Leeder SR (2013) The effectiveness of policies for reducing dietary trans fat: a systematic review of the evidence. Bull World Health Organ 91(4):262H–269H
19. Lamarche B, Couture P (2015) Dietary fatty acids, dietary patterns, and lipoprotein metabolism. Curr Opin Lipidol 26(1):42–47
20. Garshick M, Mochari-Greenberger H, Mosca L (2014) Reduction in dietary trans fat intake is associated with decreased LDL particle number in a primary prevention population. Nutr Metab Cardiovasc Dis 24(1):100–106
21. Sanders TA (2009) Fat and fatty acid intake and metabolic effects in the human body. Ann Nutr Metab 55(1–3):162–172
22. Brownell KD, Pomeranz JL (2014) The trans-fat ban—food regulation and long-term health. N Engl J Med 370(19):1773–1775
23. Roach C, Feller SE, Ward JA, Shaikh SR, Zerouga M, Stillwell W (2004) Comparison of cis and trans fatty acid containing phosphatidylcholines on membrane properties. Biochemistry 43(20):6344–6351
24. Vanden Heuvel JP (2004) Diet, fatty acids, and regulation of genes important for heart disease. Curr Atheroscler Rep 6(6):432–440
25. Simopoulos AP (2008) The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood) 233(6):674–688
26. Koh-Banerjee P, Chu NF, Spiegelman D, Rosner B, Colditz G, Willett W, Rimm E (2003) Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. Am J Clin Nutr 78(4):719–727
27. Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, Willett WC, Hu FB (2005) Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. J Nutr 135(3):562–566
28. Kennedy A, Martinez K, Chuang CC, LaPoint K, McIntosh M (2009) Saturated fatty acid-mediated inflammation and insulin

resistance in adipose tissue: mechanisms of action and implications. J Nutr 139(1):1–4
29. USDA and UDHHS (2010) Report of the Dietary Guidelines Advisory Committee on the dietary guidelines for Americans. http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm. Accessed 15 June 2010
30. Fattore E, Bosetti C, Brighenti F, Agostoni C, Fattore G (2014) Palm oil and blood lipid-related markers of cardiovascular disease: a systematic review and meta-analysis of dietary intervention trials. Am J Clin Nutr 99(6):1331–1350
31. Jakobsen MU, Overvad K, Dyerberg J, Schroll M, Heitmann BL (2004) Dietary fat and risk of coronary heart disease: possible effect modification by gender and age. Am J Epidemiol 160(2):141–149
32. Lee JS, Pinnamaneni SK, Eo SJ, Cho IH, Pyo JH, Kim CK, Sinclair AJ, Febbraio MA, Watt MJ (2006) Saturated, but not n-6 polyunsaturated, fatty acids induce insulin resistance: role of intramuscular accumulation of lipid metabolites. J Appl Physiol 100(5):1467–1474
33. Baer DJ, Judd JT, Clevidence BA, Tracy RP (2004) Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr 79(6):969–973
34. Xu J, Eilat-Adar S, Loria C, Goldbourt U, Howard BV, Fabsitz RR, Zephier EM, Mattil C, Lee ET (2006) Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. Am J Clin Nutr 84(4):894–902
35. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC (2005) Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol 161(7):672–679
36. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL, Baltimore Longitudinal Study of Aging (2005) The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. J Nutr 135(3):556–561
37. Mozaffarian D, Rimm EB, Herrington DM (2004) Dietary fats, carbohydrate, and progression of coronary atherosclerosis in postmenopausal women. Am J Clin Nutr 80(5):1175–1184
38. Vafeiadou K, Weech M, Altowaijri H, Todd S, Yaqoob P, Jackson KG, Lovegrove JA (2015) Replacement of saturated with unsaturated fats had no impact on vascular function but beneficial effects on lipidbiomarkers, E-selectin, and blood pressure: results from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. Am J Clin Nutr 102(1):40–48
39. Sacks FM, Katan M (2002) Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins andcardiovascular disease. Am J Med 113(Suppl 9B):13S–24S
40. Lamarche B, Couture P (2014) It is time to revisit current dietary recommendations for saturated fat. Appl Physiol Nutr Metab 39(12):1409–1411
41. Joint WHO/FAO Expert Consultation (2003) Diet, nutrition and the prevention of chronic diseases (WHO technical report series 916) (PDF). World Health Organization, pp 81–94. ISBN 92-4-120916-X. Retrieved 3 Nov 2011
42. Russo GL (2009) Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. Biochem Pharmacol 77(6):937–946
43. Poudyal H, Brown L (2015) Should the pharmacological actions of dietary fatty acids in cardiometabolic disorders be classified based on biological or chemical function? Prog Lipid Res 59:172–200
44. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F (2009) 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 119(6):902–907
45. Kris-Etherton P, Hecker K, Binkoski A (2008) Polyunsaturated fatty acids and cardiovascular health. Nutr Rev 62(11):414–426
46. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB (2003) Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation 108(2):155–160
47. Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN (2002) Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improvesinsulin sensitivity. Diabetologia 45(3):369–377
48. Lavie CJ, Milani RV, Mehra MR, Ventura HO (2009) Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol 54(7):585–594
49. Chan DC, Watts GF, Mori TA, Barrett PH, Redgrave TG, Beilin LJ (2003) Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity. Am J Clin Nutr 77(2):300–307
50. Venturini D, Simão AN, Urbano MR, Dichi I (2015) Effects of extra virgin olive oil and fish oil on lipid profile and oxidative stress in patients with metabolic syndrome. Nutrition 31(6):834–840
51. James MJ, Gibson RA, Cleland LG (2000) Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr 71(1 Suppl):343S–348S
52. Johnson GH, Fritsche K (2012) Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. J Acad Nutr Diet 112(7):1029–1041
53. Harris WS (2006) The omega-6/omega-3 ratio and cardiovascular disease risk: uses and abuses. Curr Atheroscler Rep 8(6):453–459
54. Schwingshack L, Hoffmann G (2012) Monounsaturated fatty acids and risk of cardiovascular disease: synopsis of the evidence available from systematic reviews and meta-analyses. Nutrients 4(12):1989–2007
55. Potenza MV, Mechanick JI (2009) The metabolic syndrome: definition, global impact, and pathophysiology. Nutr Clin Pract 24(5):560–577
56. Bergouignan A, Momken I, Schoeller DA, Simon C, Blanc S (2009) Metabolic fate of saturated and monounsaturated dietary fats: the Mediterranean diet revisited from epidemiological evidence to cellular mechanisms. Prog Lipid Res 48(3–4):128–147
57. Tarrago-Trani MT, Phillips KM, Lemar LE, Holden JM (2006) New and existing oils and fats used in products with reduced trans-fatty acid content. J Am Diet Assoc 106(6):867–880
58. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello Russo A, Marotta T (2000) Olive oil and reduced need for antihypertensive medications. Arch Intern Med 160(6):837–842
59. Pelkman CL, Fishell VK, Maddox DH, Pearson TA, Mauger DT, Kris-Etherton PM (2004) Effects of moderate-fat (from monounsaturated fat) and low-fat weight-loss diets on the serum lipid profile in overweight and obese men and women. Am J Clin Nutr 79(2):204–212
60. Kien CL, Bunn JY, Stevens R, Bain J, Ikayeva O, Crain K, Koves TR, Muoio DM (2014) Dietary intake of palmitate and oleate has broad impact on systemic and tissue lipid profiles in humans. Am J Clin Nutr 99(3):436–445
61. Shah M, Adams-Huet B, Garg A (2007) Effect of high-carbohydrate or high-cis-monounsaturated fat diets on blood pressure: a meta-analysis of intervention trials. Am J Clin Nutr 85(5):1251–1256

62. Muzio F, Mondazzi L, Harris WS, Sommariva D, Branchi A (2007) Effects of moderate variations in the macronutrient content of the diet on cardiovascular disease risk factors in obese patients with the metabolic syndrome. Am J Clin Nutr 86(4):946–951
63. López S, Bermúdez B, Pacheco YM, Villar J, Abia R, Muriana FJ (2008) Distinctive postprandial modulation of beta cell function and insulin sensitivity by dietary fats: monounsaturated compared with saturated fatty acids. Am J Clin Nutr 88(3):638–644
64. Schwingshackl L, Strasser B, Hoffmann G (2011) Effects of monounsaturated fatty acids on glycaemic control in patients with abnormal glucose metabolism: asystematic review and meta-analysis. Ann Nutr Metab 58(4):290–296
65. Jenkins DJ, Kendall CW, Vuksan V, Faulkner D, Augustin LS, Mitchell S, Ireland C, Srichaikul K, Mirrahimi A, Chiavaroli L, Blanco Mejia S, Nishi S, Sahye-Pudaruth S, Patel D, Bashyam B, Vidgen E, de Souza RJ, Sievenpiper JL, Coveney J, Josse RG, Leiter LA (2014) Effect of lowering the glycemic load with canola oil on glycemic control and cardiovascular risk factors: a randomized controlled trial. Diabetes Care 37(7):1806–1814
66. Due A, Larsen TM, Hermansen K, Stender S, Holst JJ, Toubro S, Martinussen T, Astrup A (2008) Comparison of the effects on insulin resistance and glucose tolerance of 6-mo high-monounsaturated-fat, low-fat, and control diets. Am J Clin Nutr 87(4):855–862
67. Kien CL, Bunn JY (1999) Gender alters the effects of palmitate and oleate on fat oxidation and energy expenditure. Obesity 16:29–33
68. Nimptsch K, Berg-Beckhoff G, Linseisen J (2010) Effect of dietary fatty acid intake on prospective weight change in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition. Public Health Nutr 13(10):1636–1646
69. Mennella I, Savarese M, Ferracane R, Sacchi R, Vitaglione P (2015) Oleic acid content of a meal promotes oleoylethanolamide response and reduces subsequent energy intake in humans. Food Funct 6(1):204–210
70. Senanayake VK, Pu S, Jenkins DA, Lamarche B, Kris-Etherton PM, West SG, Fleming JA, Liu X, McCrea CE, Jones PJ (2014) Plasma fatty acid changes following consumption of dietary oils containing n-3, n-6, and n-9 fatty acids at different proportions: preliminary findings of the Canola Oil Multicenter Intervention Trial (COMIT). Trials 15:136–147
71. Jones PJ, Senanayake VK, Pu S, Jenkins DJ, Connelly PW, Lamarche B, Couture P, Charest A, Baril-Gravel L, West SG, Liu X, Fleming JA, McCrea CE, Kris-Etherton PM (2014) DHA-enriched high-oleic acid canola oil improves lipid profile and lowers predicted cardiovascular disease risk in the canola oil multicenter randomized controlled trial. Am J Clin Nutr 100(1):88–97
72. Pu S, Rodríguez-Pérez C, Ramprasath V, Segura-Carretero A (2015) Dietary high oleic canola oil supplemented with DHA oil attenuates plasma PCSK9 levels in humans. FASEB 29(1 Suppl):743.12S
73. Jones PJ, MacKay DS, Senanayake VK, Pu S, Jenkins DJ, Connelly PW, Lamarche B, Couture P, Kris-Etherton PM, West SG, Liu X, Fleming JA, Hantgan RR, Rudel LL (2015) High-oleic canola oil consumption enriches LDL particle cholesteryl oleate content and reduces LDL proteoglycan binding in humans. Atherosclerosis 238(2):231–238
74. Jones P, Pu S, Rodríguez-Pérez C, Ramprasath V, Khaloufi K, Sabra A, Segura-Carretero A (2015) DHA-enriched high oleic canola oil diet may accelerate the cholesterol synthesis in humans. FASEB 29(1 Suppl):248.4S
75. Baril-Gravel L, Labonté ME, Couture P, Vohl MC, Charest A, Guay V, Jenkins DA, Connelly PW, West S, Kris-Etherton PM, Jones PJ, Fleming JA, Lamarche B (2015) Docosahexaenoic acid-enriched canola oil increases adiponectin concentrations: a randomized crossover controlled intervention trial. Nutr Metab Cardiovasc Dis 25(1):52–59
76. Jones PJ, Lin L, Gillingham LG, Yang H, Omar JM (2014) Modulation of plasma N-acylethanolamine levels and physiological parameters by dietary fatty acid composition in humans. J Lipid Res 55(12):2655–2664