Review

Diverse Mechanisms of Saturated Fatty Acids in Cardiovascular Disease

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Abstract: For many years, excessive intake of SFAs has been recognized as a principal cause of cardiovascular disease (CVD). Despite the prevalence of guidelines recommending the restriction of SFAs intake, particularly among patients with atherosclerotic cardiovascular disease and dyslipidemia, some researchers have pointed out a new connection between SFAs intake and cardiovascular health. This review explores the sources of SFAs in humans and the controversy surrounding the link between different chain lengths of SFAs and CVD risk by analyzing the available evidence, focusing on the effects of SFAs carbon chain heterogeneity. Based on the latest mechanistic studies and epidemiological data, it offers evidence-informed recommendations for clinical practice and dietary guideline amendments. In the authors' view, the cardiovascular effects of SFAs depend not only on chain length but also on the food matrix in which they are consumed and the nutrients they displace.

Keywords: saturated fatty acids; cardiovascular diseases

1. Introduction

Cardiovascular disease (CVD) is a syndrome involving disorders in the structure or function of the heart and blood vessels [1,2]. Among these, the primary manifestations include myocardial infarction, angina pectoris, stroke, heart failure, accompanied by hypertensive heart disease, atherosclerosis, and other pathological processes [3,4]. CVD is a serious threat to global health, accounting for the highest number of deaths from non-communicable diseases (NCDs) worldwide [5,6]. Predictions indicate that the number of deaths from CVD worldwide will increase to 23 million by 2030. The burden of disease has shifted significantly toward younger demographics, primarily in low- and middle-income countries [7]. Therefore, optimizing the treatment strategies of CVD based on mechanism research and precision medicine exploration has become a key issue that needs to be urgently addressed in the global public health field.

Circulating saturated fatty acids (SFAs), as the main components of dietary fats, are essential for the construction of tissues and the normal functioning of cells in the human body. The quantity and quality of dietary fat intake reflect the levels of SFAs and influence endogenous lipid metabolism [8]. SFAs constitute one-fifth of the general population's total daily energy intake, and approximately one-third of the total fatty acids [9,10]. A diet with a high proportion of SFAs has been identified as potentially influencing the development of CVD due to its ability to increase low-density lipoprotein cholesterol (LDL-C) levels [11].

This review provides a systematic critical evaluation of the latest scientific evidence revealing the mutual influence between dietary SFAs intake and CVD. It focuses on the mechanism of action of SFAs with even carbon chains (carbon chain lengths C2–C26), which account for over 99% of total human plasma fatty acid concentrations [10]. By integrating molecular mechanisms, population studies, and nutritional epidemiological evidence, we reveal the differences in the origins of SFAs with different carbon chain lengths and their potential roles in CVD populations. Meanwhile, a meticulous SFAs dietary strategy is proposed to provide a novel perspective on the scientific management of dietary fat.

2. The Classification and Sources of SFAs

2.1. The Classification of SFAs

SFAs are a class of fatty acids without double bonds in their carbon chain [12,13], which have a molecular structure characterized by a preponderance of carbon atoms interconnected by single bonds, with methyl (CH_3) and carboxylic acid (COOH) groups at both extremities [14]. The classification of SFAs, as determined by the length of their carbon chains, can be categorized into four distinct groups (Table 1) [15,16].

Table 1. The classification of SFAs.

Classification	Characterization	Type
Short-chain saturated fatty acids (SCSFAs)	$C \leq 6$	Acetic Acid (C2:0), propionic Acid (C3:0）, butyric acid (C4:0), valeric acid (C5:0), hexanoic acid (C6:0).
Medium-chain saturated fatty acids (MCSFAs)	$8 \leq C \leq 12$	Caprylic Acid (C8:0), capric Acid (C10:0), undecanoic acid (C11:0), lauric Acid (C12:0).
Long-chain saturated fatty acids (LCSFAs)	$13 \leq C \leq 21$	Tridecanoic acid (C13:0), myristic Acid (C14:0), pentadecanoic acid (C15:0), palmitic Acid (C16:0), heptadecanoic acid (C17:0), stearic Acid (C18:0), arachidic Acid (C20:0), henicosanoic acid (C21:0)
Very-long-chain saturated fatty acids (VLCSFAs)	≥C22	Behenic Acid (C22:0), tricosanoic acid (C23:0), lignoceric Acid (C24:0).

2.2. The Sources of SFAs in Humans

2.2.1. SCSFAs

SCSFAs have carbon chains shorter than 6, the most representative of which are acetic acid, propionic acid, and butyric acid [17]. The production of endogenous SCSFAs in the human body relies on two primary pathways: direct dietary intake and anaerobic fermentation of undigested carbohydrates by the gut microbiota, which accounts for approximately 95% of SCSFAs (Figure 1) [18,19]. Specifically, the process of converting dietary fiber to pyruvate via the glycolytic and pentose phosphate pathways is catalyzed by specific microbial enzyme systems, resulting in the production of SCSFAs. Acetic acid (C2:0) is produced via two pathways: the acetyl-CoA pathway, which is catalyzed by the pyruvate dehydrogenase system, and the Wood Ljungdahl Pathway (WLP), which involves one-carbon unit conversion. Propionic acid (C3:0) is produced via the succinate intermediate pathway. Within this pathway, succinyl-CoA, via the intermediate methylmalonyl-CoA, ultimately yields propionic acid through decarboxylation [20]. Propionic acid is primarily metabolized by β-oxidation in the liver [21]. Butyric acid (C4:0) can be synthesized through the condensation of two acetyl-CoA molecules. This is followed by a two-step reaction involving the reduction of butyryl-CoA by butyryl-CoA synthetase and the dephosphorylation of butyryl-CoA by phosphotransbutyrylase-butyrate (PTB-BK) kinase. [22,23]. Butyric acid's metabolism primarily occurs in the mitochondria of colonic epithelial cells [24]. Notably, the spectrum and yield of SCSFAs are regulated by two factors: the structure of the intestinal flora (e.g., the ratio of thick-walled bacteria to anthrobacteria) and the properties of the substrate (e.g., the type of dietary fiber and resistant starch content) [19,25]. This dynamic balance is imperative for sustaining intestinal homeostasis and systemic immune metabolism.

2.2.2. MCSFAs

MCSFAs are saturated fatty acids with carbon chain lengths of C6–C12, mainly including octanoic acid, decanoic acid and lauric acid [26]. MCSFAs are poorly synthesized endogenously. Thus, the human body primarily derives them exogenously [27] (Figure 1). The core sources of MCSFAs are MCFA-rich vegetable oils, with lauric acid content ranging from 45% to 50% [28,29]. Although trace amounts of MCSFAs can be generated by the liver via fatty acid elongase (ELOVL) using SCSFAs as precursors, the contribution of this endogenous pathway is negligible and contingent on specific metabolic conditions, such as a high-carbohydrate diet or excessive fat oxidation [30,31]. Furthermore, some gut microbiota can synthesize modest quantities of MCSFAs through carbohydrate fermentation [32]. However, the physiological relevance of this process remains unclear [33,34]. In general, MCFA production is significantly influenced by dietary structure.

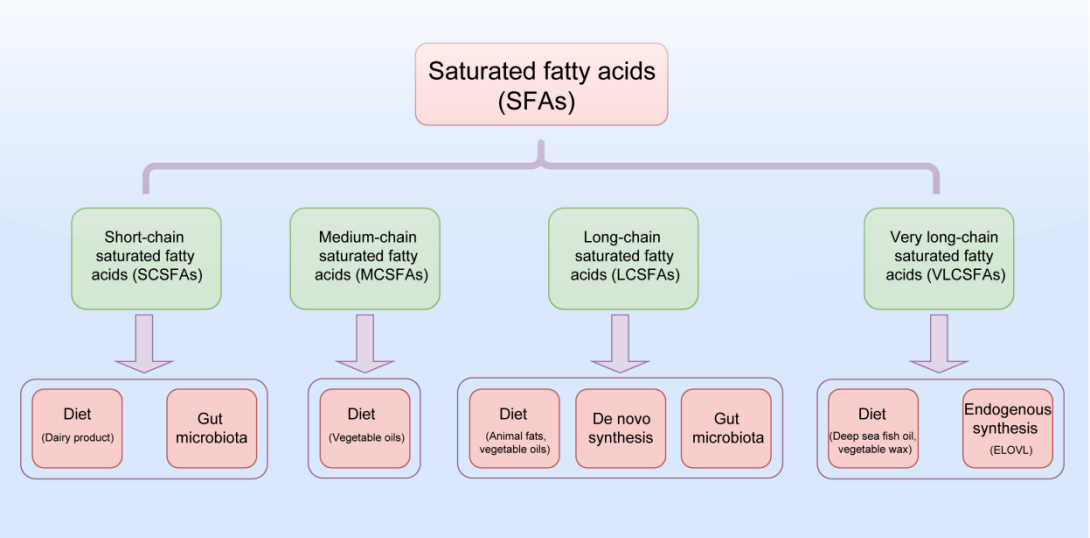

Figure 1. The source of SFAs in humans. The synthesis of endogenous SCSFAs in the human body relies on two primary pathways: direct dietary intake and anaerobic fermentation by the gut microbiota. MCSFAs are sourced from the dietary intake of certain vegetable oils. LCSFAs can be acquired from dietary sources, and they can also be synthesized within the body and produced by gut flora. VLCSFAs are primarily sourced from dietary intake, with a smaller contribution from endogenous synthesis.

2.2.3. LCSFAs

LCSFAs are saturated fatty acids with carbon chain lengths of 13–20 carbon atoms [35]. The synthesis of LCSFAs is a product of endogenous metabolism that is significantly influenced by dietary intake (Figure 1) [36]. The human body can synthesize LCSFAs from carbohydrate or ethanol metabolites in the liver, which occurs in a series of steps via the fatty acid synthase (FASN) complex [36,37]. The final product of this process is palmitic acid (PA), and the subsequent step involves the elongation of the carbon chain to produce stearic acid (SA), which is catalyzed by the ELOVL [38]. The regulatory signal for this process originates from sterol regulatory element-binding protein 1c and is significantly enhanced The regulatory signal for this process originates from sterol regulatory element-binding protein 1c (SREBP-1c) and is significantly enhanced under conditions of high-sugar or high-calorie diets [39]. Evidence has been demonstrated that dietary intake constitutes a major source of LCSFAs [40]. LCSFAs are predominantly found in animal fats (such as red meat and butter) and certain vegetable oils (such as cocoa butter containing 34% SA and palm oil containing 44% PA) [41]. Industrial trans fats (TFAs), which are found in margarine, are also present in processed foods alongside LCSFAs [42]. Additionally, some gut microbes have been found to produce LCSFAs [43,44].

2.2.4. VLCSFAs

VLCSFAs are saturated fatty acids with carbon chains of at least 22 atoms [45]. VLCSFAs are primarily synthesized through endogenous extended pathways and dietary intake (Figure 1). The metabolism of VLCSFAs involves complex enzymatic reactions and organelle collaboration [46]. VLCSFAs, such as SA (C18:0), are used as precursors in the synthesis of LCFA. This process is catalyzed by an elongase complex (ELOVL1-7) in the endoplasmic reticulum (ER), which extends the carbon chain one step at a time by adding two carbon atoms (derived from malonyl-CoA) in each round of the cycle [47,48]. Furthermore, dietary sources of VLCSFAs can enter the circulatory system directly through digestion and absorption. For instance, certain animal fats (e.g., beef tallow) contain trace amounts of C24:0 [49].

3. The Effect of SFAs on CVD

The pathogenesis of CVD is multifactorial, involving a combination of genetic predisposition, environmental exposure, and lifestyle factors [50]. Traditional risk factors for CVD include [51,52]: (1) Hypertension, which has a global prevalence of more than 30% and is a leading cause of stroke. (2) Dyslipidemia, which is characterized by elevated LDL-C, is directly and positively correlated with atherosclerosis. (3) Type 2 diabetes mellitus, which elevates the CVD risk by two to four times. (4) Obesity, which elevates the heart failure risk by 2.5 times in people with a BMI $\geq$ 30. CVD is a multifactorial condition, meaning it is caused by numerous factors, some of which are modifiable. Poor dietary habits represent a significant modifiable risk factor [53,54]. Numerous studies have

indicated that dietary interventions reduce the risk of developing CVD by approximately 50%, suggesting a key role for dietary management as a modifiable factor [55,56]. Notably, recent nutritional epidemiology studies have revealed new aspects of the metabolic effects of SFAs.

There has been a significant paradigm shift in research on the association of SFAs with CVD. In the 1970s, Ancel Keys first suggested that consuming SFAs was significantly associated with an increased risk of CVD. The study indicated that the primary mechanism by which SFAs contribute to atherosclerosis is by increasing serum LDL-C [57]. This finding provided the basis for the recommendation in various countries' dietary guidelines to limit SFAs to below 10% of daily total energy. However, a Prospective Urban and Rural Epidemiology Study challenged this traditional perception [58]. The cohort analysis based on 154,000 subjects from 18 countries demonstrated that total SFAs intake (particularly from dairy sources) was not statistically correlated with CVD risk. Instead, mortality was reduced by 14% in the high SFAs intake group (13–15% of energy supply). Conversely, an elevated carbohydrate intake, defined as a percentage of energy supply exceeding 60%, shows a correlation with a 28% increased risk of total mortality. Subsequent molecular mechanism studies revealed significant heterogeneity in the effects of SFAs on CVD, with these effects are contingent upon the carbon chain and the metabolic pathways [59,60]. Consequently, a thorough investigation into the pathophysiological mechanisms via which SFAs of different lengths contribute to CVD would be a more effective way to transition from the current approach of limiting the total amount of SFAs to optimizing the sources of SFAs. This would provide a solid foundation for re-evaluating dietary guidelines with the aim of reducing the prevalence of CVD.

3.1. SCSFAs

Consistent findings from epidemiological and mechanistic studies indicate a significant negative correlation between circulating SCSFAs levels and CVD risk, suggesting their potential value in CVD prevention [61]. The core members of the SCSFAs family exhibit protective effects in the progression of atherosclerosis, heart failure, and hypertension through multi-targeted mechanisms of action. These mechanisms include modulating inflammation, improving the intestinal barrier, regulating lipid and glucose metabolism, and regulating blood pressure (Figure 2).

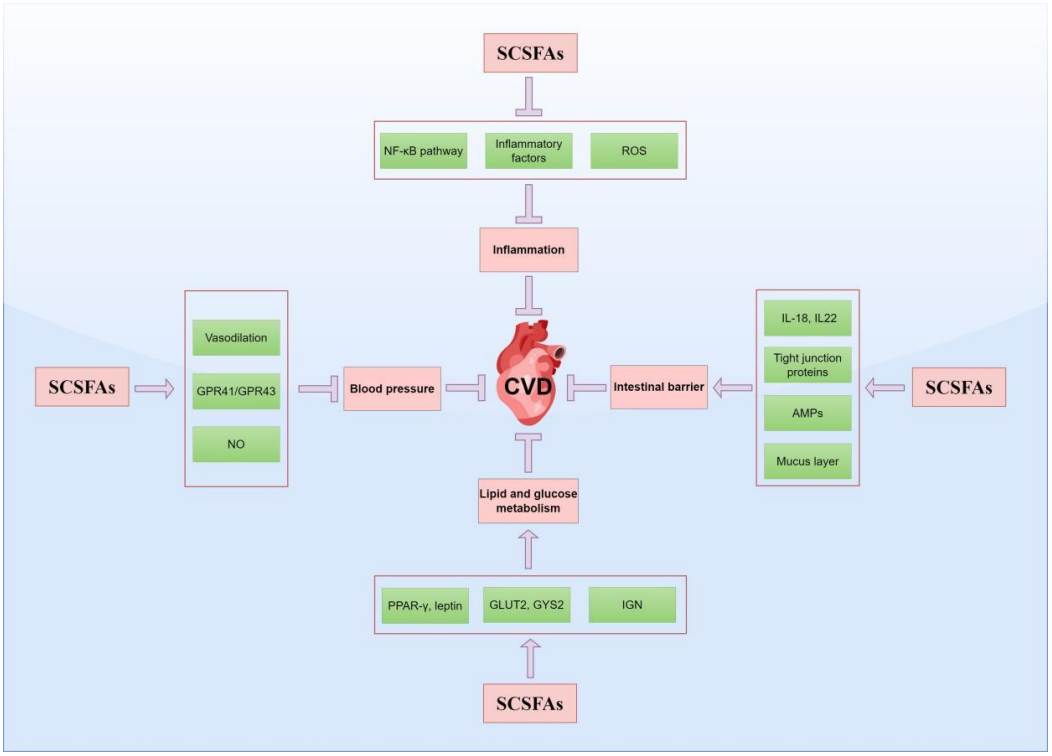

Figure 2. The effect of SCSFAs on CVD. SCSFAs have beneficial effects on CVD by modulating inflammation, improving the intestinal barrier, regulating lipid and glucose metabolism, and regulating blood pressure. SCSFAs suppress inflammation by inhibiting the NF-κB pathway and the generation of inflammatory factors and ROS. SCSFAs improve the intestinal barrier by stimulating the production of IL-18/IL-22, tight junction proteins and antimicrobial peptides (AMPs), and by protecting the intestinal mucus layer. SCSFAs can regulate lipid and glucose metabolism by promoting the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), leptin, glucose transporter protein 2 (GLUT2), glycogen synthase 2 (GYS2) and intestinal gluconeogenesis (IGN). SCSFAs

contribute to the regulation of blood pressure by inducing vasodilation and promoting the level of G protein-coupled receptors (GPR41/GPR43) and nitric oxide (NO).

3.1.1. Anti-Inflammation

SCSFAs have anti-inflammatory properties that act through multiple molecular mechanisms. Acetate inhibits the NF-κB pathway and decreases the release of IL-6 and IL-8 [62]. The inhibition of histone deacetylase (HDAC) activity by butyrate and propionate serves as the mechanism for promoting histone acetylation of the FoxP3 gene. This drives the differentiation of regulatory T cells, decreasing the secretion of TNF-α and IL-6, while increasing IL-10 expression [63,64]. In Dendritic cells (DCs), butyrate and propionate significantly inhibited lipopolysaccharide (LPS)-induced secretion of IL-6, IL-12, and down-regulated the levels of chemokines such as CXCL11, CXCL10, and CCL5, effectively blocking the transmission of inflammatory signals to the adaptive immune system [65]. Additionally, butyric acid inhibited the production of reactive oxygen species (ROS) mediated by NADPH oxidase 2 (NOX2) in endothelial cells by activating the peroxisome proliferator-activated receptor delta (PPARδ)/microRNA-181b (miR-181b) pathway. This resulted in decreased expression of vascular cell adhesion molecule-1 (VCAM-1) and reduced mononuclear cell infiltration, consequently delaying the development of atherosclerotic plaques [66,67].

3.1.2. Improve Intestinal Barrier

SCSFAs can regulate intestinal barrier function through multiple mechanisms, thereby reducing chronic inflammation caused by increased intestinal permeability and CVD caused by endothelial dysfunction [68]. SCSFAs stimulate potassium efflux and hyperpolarization in intestinal epithelial cells. This results in the activation of the inflammatory protein NOD-like receptor family 3 (NLRP3), which subsequently promotes the release of IL-18. IL-18 contributes to maintaining intestinal barrier integrity and restoring intestinal homeostasis [69]. Meanwhile, SCSFAs strengthened the physical barrier between intestinal epithelial cells by elevating the levels of claudin-1, claudin-7, and ZO-1 [70]. IL-22 enhances epithelial barrier function by controlling the growth and permeability of epithelial cells, mucus secretion, as well as the synthesis of antimicrobial proteins (AMPs) and complement [71]. The inhibition of class I and II histone deacetylases (HDACs) by butyrate leads to the acetylation of the hypoxia-responsive element (HRE) within the IL-22 promoter region. This acetylation enhances the binding affinity of hypoxia-inducible factor 1 alpha, promoting IL-22 secretion [72,73]. Additionally, SCSFAs induce the production of antimicrobial peptides via activating the mTOR and STAT3 pathways, which directly inhibit the colonization of pathogenic bacteria [74]. The maintenance of gut structural integrity and the safeguarding of the mucus layer are crucial components for achieving intra-symbiotic homeostasis. Butyrate promotes the secretion of mucin (MUC2) by cup cells, which reinforces the mucus layer's isolation from pathogens [75].

3.1.3. Regulate Lipid and Glucose Metabolism

Disorders of lipid metabolism and imbalances in glucose metabolism have been demonstrated to have a significant impact on the CVD risk. These conditions contribute to atherosclerotic plaque formation, chronic inflammation, and endothelial dysfunction. SCSFAs account for approximately 10% of the body's caloric requirements and play an important role in modulating lipid and glucose metabolic pathways [76,77]. SCSFAs have been shown to regulate lipid metabolism in both in vitro and in vivo. A study revealed that 3T3-L1 mouse embryonic fibroblasts (preadipocytes) treated with acetate and propionate exhibited increased expression of GPR43, peroxisome proliferator-activated receptor-γ (PPAR-γ) and leptin, which promoted lipolysis [78]. Meanwhile, in the mouse model that was fed a diet supplemented with SCSFAs, the GPR43 and GPR41 in adipose tissue increased. This elevated activity promoted the breakdown of triglycerides, enhanced the oxidation of free fatty acids in fat tissue to generate brown fat, and resulted in weight loss [79]. Similarly, SCSFA promotes the levels of glucose transporter protein 2 (GLUT2) and glycogen synthase 2 (GYS2) in the liver, thereby regulating hepatic glucose metabolism [80]. In mice fed a high-fat diet, butyrate supplementation improved insulin sensitivity [81]. Consumption of soluble dietary fiber generates SCSFAs, which stimulate intestinal gluconeogenesis (IGN) via complementary pathways. Activation of IGN contributes to beneficial regulation of glucose and energy balance, supporting metabolic health and helping to control body weight and blood glucose [80]. Malonate can alter the metabolic profile of adult mouse hearts following myocardial infarction, shifting energy utilization from oxidative phosphorylation toward increased glucose metabolism. These findings indicate that malonate could be a promising metabolic target for treating cardiac infarcts [82].

3.1.4. Regulate Blood Pressure

SCSFAs regulate blood pressure through complex interactions among metabolic, immune, and neuroendocrine pathways, thereby influencing vascular function and cardiovascular health. In 1928, acetate was initially identified as a vasodilator capable of lowering blood pressure by inducing vasodilation. Subsequent studies demonstrated dose-dependent vasodilation of acetate, propionate, and butyrate, promoting hypotension [83,84]. SCSFAs inhibit the renin-angiotensin system and reduce the effects of vasoconstriction by activating G protein-coupled receptors [85]. They also stimulate the release of nitric oxide, thereby enhancing vascular endothelial function and promoting better diastolic relaxation of blood vessels. Numerous clinical studies and animal experiments have demonstrated that supplementation with SCSFAs can markedly lower systolic blood pressure in hypertensive animals and stabilize blood pressure fluctuations in individuals with salt-sensitive hypertension. Furthermore, prebiotic and probiotic interventions that enhance endogenous SCSFAs production have been shown to effectively reduce blood pressure in both genetic and diet-induced models of hypertension [86,87].

3.2. MCSFAs

Compared to other fatty acids, MCSFAs are more easily hydrolyzed and converted to ketone bodies, which enter the liver for energy supply, rather than being stored as fat [88,89]. MCSFAs contain slightly lower in calories than other fats, though this difference has little practical impact [90]. Overall, moderate amounts of MCSFAs can modulate lipid metabolism and inhibit inflammation and oxidative stress (Figure 3).

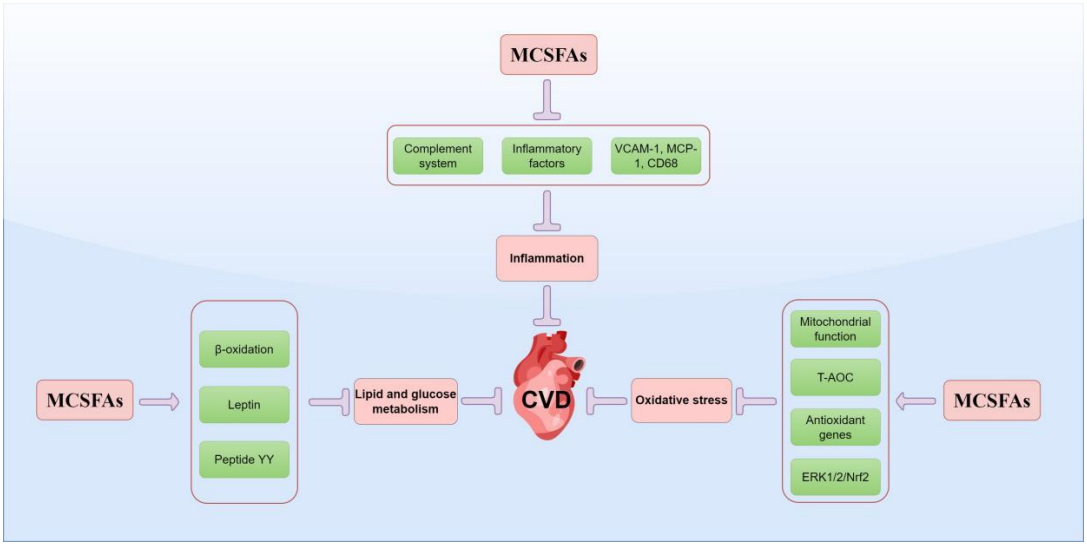

Figure 3. The effect of MCSFAs on CVD. MCSFAs have beneficial effects on CVD by modulating inflammation, inhibiting oxidative stress, and regulating lipid and glucose metabolism. MCSFAs suppress inflammation by inhibiting the complement system and the generation of inflammatory factors and VCAM-1, MCP-1, and CD68. MCSFAs inhibit oxidative stress by improving mitochondrial function, enhancing T-AOC, increasing the level of antioxidant-related genes, and influencing ERK1/2/Nrf2 pathway. MCSFAs improve lipid and glucose metabolism by facilitating the β-oxidation and elevating levels of leptin and peptide YY.

3.2.1. Anti-Inflammation

The current study suggests that MCSFAs modulate inflammation and oxidative stress through their unique metabolic pathways, achieved through the inhibition of pro-inflammatory factor release [91]. It can be hypothesized that these effects are related to the anti-inflammatory properties of their metabolite, ketone bodies. A high MCSFAs diet also down-regulates the complement system and the expression of inflammatory genes [92]. These results suggest that MCSFAs may have a beneficial effect on atherosclerosis. Supplementation with MCSFAs can downregulate the expression of VCAM-1, monocyte chemoattractant protein-1 (MCP-1), and CD68 in aortic tissue, all of which are markers of inflammation. Furthermore, the supplementation of MCSFAs can also reduce the dimensions of atherosclerotic lesions in ApoE$^{-/-}$ mice [93].

3.2.2. Inhibit Oxidative Stress

In addition, the rapid oxidative properties of MCSFAs may reduce free radical generation, thus alleviating oxidative stress damage. Incubating starved human endothelial cells with monocytes MCSFAs revealed that MCSFAs can act as a potential energy source and improve mitochondrial function under inflammatory conditions [94]. As Wang D's study observes, three MCSFAs have been executed to assess the protective efficacy of the agents for hepatocytes under H_2O_2 challenge. Results indicated that the administration of MCSFAs enhanced cell viability and total antioxidant capacity (T-AOC). Furthermore, treatment with MCSFAs led to a substantial enhancement in Nrf2 levels and an increase in the phosphorylation levels of ERK1/2. Additionally, linoleic acid (LA) notably facilitated the nuclear translocation of Nrf2. In summary, MCSFAs treatment positively influences the protection of AML12 cells from oxidative stress [95].

3.2.3. Regulate Lipid and Glucose Metabolism

MCSFAs have many unique metabolic properties and distinctive transport systems, and they are rapidly metabolized in vivo [96]. MCSFAs do not rely on membrane transporter proteins for cellular and mitochondrial uptake. Instead, medium-chain acyl-CoA synthetase in the mitochondrial matrix is responsible for their direct activation before β-oxidation [97]. Consequently, MCSFAs are quickly absorbed by cells, preferentially broken down through β-oxidation in mitochondria to generate energy, and have a limited tendency to be stored as adipose tissue [98]. Researchers investigated the combined impact of a diet rich in medium-chain triglycerides (MCTs) and exercise on fat reduction in rats. The results indicated MCTs consumption enhanced fat loss primarily by elevating thermogenesis, which increased the rats' overall energy expenditure and facilitated weight reduction [99]. Similarly, clinical studies have indicated that compared to LCTs, MCT consumption leads to greater fat oxidation, an effect observed in both healthy-weight and obese individuals [29,100]. MCTs can lead to elevated levels of leptin and peptide YY, while simultaneously reducing growth hormone-releasing peptide (GHRP) activity. Conversely, these hormonal changes were not observed in levels of GLP-1 or total growth hormone-releasing peptide, indicating a selective hormonal response to MCT intake [101]. Sophia Airhart et al. demonstrate that the MCSFAs diet enhances cardiac contractile function and modifies lipidomic profiles, which provide potential cardiac benefits to patients with type 2 diabetes mellitus [102]. A study that used microarrays to measure genome-wide changes in gene expression in the subcutaneous adipose tissue of 12 individuals with high or low dietary intake of monounsaturated fatty acids (MC-SFA) found that high MC-SFA intake resulted in the up-regulation of genes associated with the citric acid cycle and oxidative phosphorylation [92]. This indicates that the positive effects of MCSFAs on preventing fat accumulation are mediated by increased expression of genes involved in energy metabolism in adipose tissue.

3.3. LCSFAs

LCSFAs are the main source of circulating saturated fatty acids. Consequently, the association of them with CVD constitutes an important topic in nutritional and cardiovascular research. Conventionally, it was believed that the LCSFAs exhibited a positive correlation with CVD mortality (Figure 4).

3.3.1. Dyslipidemia

PA disrupts plasma lipid metabolism, which elevates the risk of CVD. Incubation of PA with HepG2 cells revealed an increase in lipid droplet accumulation and higher TG content in the cells [103]. PA increases the synthesis and secretion of hepatic apolipoprotein B-100 (ApoB-100) and promotes the assembly of very low-density lipoprotein (VLDL) [104,105]. The activity of SREBP-1c and the expression of FASN and acetyl-CoA carboxylase (ACC) were promoted by PA in the liver [106,107]. PA also inhibits adenylate-activated protein kinase (AMPK) activity and decreases fatty acid oxidation, resulting in a buildup of adipose tissue in the liver. In 3T3-L1 and HepG2 cells, PA can induce inflammation and glucose metabolism disorders by up-regulating KLF7 expression through the GPR40/120-NF-κB signaling pathway [108]. However, SA has a smaller effect on serum cholesterol or LDL cholesterol, and may even lower the rate of HDL cholesterol [26,109]. This is possibly attributable to the restricted activity of stearoyl-CoA desaturase (SCD) and the ability of SA to be incorporated into triacylglycerols (TGs) [110]. Research has indicated that SA may reduce total cholesterol levels by inhibiting key enzymes in the cholesterol synthesis pathway, such as HMG-CoA reductase [111].

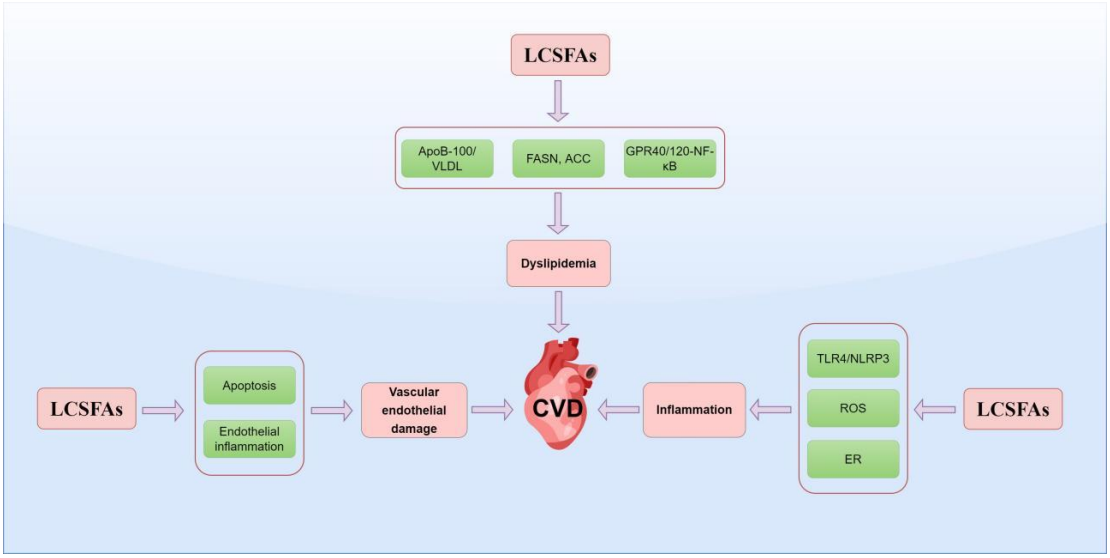

Figure 4. The effect of LCSFAs on CVD. LCSFAs promote CVD by inducing dyslipidemia, promoting inflammation and damaging vascular endothelial cells. LCSFAs disrupt lipid metabolism by elevating apolipoprotein B-100 (ApoB-100) and very low-density lipoprotein (VLDL), upregulating the expression of FASN and ACC and activating GPR40/120-NF-κB signaling pathway. LCSFAs promote inflammation by stimulating TLR4 and NLRP3 pathways, increasing the generation of reactive ROS and inducing endoplasmic reticulum (ER) stress. LCSFAs damage vascular endothelial cells by inducing apoptosis and triggering endothelial inflammation.

3.3.2. Promote Inflammation

The pro-inflammatory effects of PA have been thoroughly documented, involving mechanisms such as the activation of the TLR4/NLRP3/NF-κB pathway, the stimulation of reactive ROS production, and the triggering of ER stress. PA activates NF-κB signaling, releasing pro-inflammatory factors through Toll-like receptor 4 (TLR4) and NLRP3 pathways. The knockdown of TLR4 has been demonstrated to result in a substantial reduction in NF-κB activation and IL-8 expression induced by PA [112]. Previous studies have shown that PA can increase the generation of reactive oxygen species in different types of cells, including monocytes, adipocytes, cardiomyocytes, RAW264.7 cells, and vascular endothelial cells [113,114]. SA can induce inflammation by activating macrophages and producing pro-inflammatory cytokines [115]. Prolonged exposure to high concentrations of free fatty acids, especially LCSFAs, induces ER stress and cell death in many cell types. After 24 h of exposure, the mitochondria and ER dilate and lipid droplets and organelles are observed in autophagosomes [116]. Increased levels of oxidative stress, ER stress, and apoptosis have been noted in H9c2 cells treated with PA [117]. Meanwhile, the intracellular accumulation of SA in malignant pleural mesothelioma (MPM) activates inflammatory signaling, leading to ER stress-mediated apoptosis [118]. In H4IIE hepatocytes and primary hepatocytes, 6-h exposure to PA and SA depleted thapsigargin-sensitive calcium stores and significantly elevated biochemical markers associated with ER stress. These changes occurred prior to cell death and were only observed at the 16-h time point.

3.3.3. Damage Vascular Endothelial

A variety of studies have indicated that LCSFAs, particularly PA and SA, promote the development of CVD by inducing apoptosis in various vascular cells [119,120]. The vascular endothelial functions as a biological barrier, preventing direct interaction with circulating free fatty acids. It is an essential component of the physiological process underlying pathological phenomena associated with metabolic vascular diseases, coronary artery disease, and diabetes mellitus [121]. Notably, PA and SA trigger endothelial inflammation by activating signaling pathways, such as NF-κB. They also induce endothelial cell apoptosis, which decreases the stability of atherosclerotic plaques and increases the risk of plaque erosion [122]. Together, these findings reveal that LCSFAs play a regulatory role in the pathophysiology of CVD.

3.4. VLCSFAs

Due to their unusually long chain length, VLCSFAs possess unique functions that distinguish them from other SCSFAs. In contrast to LCSFAs, VLCSFAs demonstrate the possibility of positive effects on CVD, healthy aging, diabetes and heart failure. A cohort study has demonstrated that individuals with higher circulating levels

of C22:0 and C24:0, relative to total serum fatty acid levels, have a lower risk of mortality [123,124]. In addition, research has demonstrated that individuals within hyperlipidemic and hypertensive populations who present with elevated proportions of circulating C22:0 and C24:0 as a fraction of total serum fatty acid levels demonstrate a reduced risk of CVD mortality [125]. Lemaitre and King described the benefits of VLCSFAs in relation to CVD. They found that C22:0, and C24:0 were associated with a lower risk of CVD, including coronary artery disease, heart failure, atrial fibrillation, and cardiac arrest [126]. Meta-analyses of prospective cohort studies have indicated that a particular group of saturated fatty acids, namely C22:0 and C24:0, are linked to a reduced incidence of type 2 diabetes and CVD [127,128]. Furthermore, well-characterized prospective cohort studies have indicated that 22:0 and 24:0 predict a healthier aging process and lower mortality [129]. Although epidemiological evidence indicates a possible link between VLCSFAs and CVD risk, the underlying mechanism of action remains unclear [130]. The potential benefits of VLSCFA on CVD may be associated with their role in regulating lipid metabolism and sphingolipid levels [126].

4. Food Matrix Effects and CVD

4.1. Dairy Products

Dairy products, one of the most widely consumed foods globally, are a major source of dietary SFAs, accounting for 20% of saturated fat intake in the United States and 17% to 41% in Europe [131,132]. A meta-analysis of existing randomized controlled trials aimed to examine the influence of various dairy products (milk, butter, cheese, yogurt) on major cardiovascular risk factors [133]. The observational results of this study suggest that maintaining a daily dairy intake below 200 g has no significant association with an increased incidence of coronary heart disease. A subsequent meta-analysis that quantified dairy intake in terms of daily servings, as opposed to grams, demonstrated that a daily intake of three or more servings of dairy products was significantly negatively correlated with the incidence of CVD [134]. Numerous studies have explored the connection between milk consumption and health outcomes. A meta-analysis of these studies revealed a neutral relationship between daily consumption of up to 200 g of low-fat milk and health outcomes. However, consumption of the same amount of whole milk was associated with a significantly higher risk of 8% [135]. The ingestion of fermented dairy products (i.e., yogurt, yogurt products, and cheese) has been demonstrated to exhibit a negative correlation with mortality and CVD risk. Specifically, high yogurt intake (≥200 g/day) has been associated with a reduced CVD risk, while moderate cheese intake (50 g/day) has been associated with a reduced CVD risk [136,137].

4.2. Red Meat

Red meat is named for its red color, which is due to its high concentration of myoglobin (>1.5 mg/g) and heme iron (2.5–4.5 mg/100 g). A positive correlation has been demonstrated between the consumption of red meat, particularly processed red meat (e.g., sausage and bacon), and a substantial increase in CVD risk [138,139]. According to a meta-analysis on dose-response relationships, increasing daily processed red meat intake by 50 g was associated with higher CVD mortality, while a daily increase of 100 g in red meat intake was correlated with an elevated risk of CVD mortality [140]. This association is attributable not only to the high content of SFAs in red meat, which leads to elevated levels of low-density lipoprotein cholesterol (LDL-C), but more fundamentally, it is attributed to the unique food matrix effect of red meat [141,142]: High concentrations of heme iron have been shown to catalyze lipid peroxidation, thereby promoting the formation of oxidized LDL and the accumulation of foam cells. L-carnitine, when metabolized by gut microbiota, produces trimethylamine-N-oxide (TMAO), which has been observed to exacerbate vascular inflammation and cholesterol deposition. Nitrites and polycyclic aromatic hydrocarbons (PAHs) have been demonstrated to directly impair endothelial function and inhibit the bioavailability of NO.

5. Intervention Strategies of CVD Based on SFAs

5.1. Distinguishing the Metabolic Effects of Carbon Chain Length

The metabolic pathways of SFAs and CVD risk were significantly influenced by the carbon chain length (C2–C26). SCSFAs (C2–C6) are mainly produced by fermentation of gut microbiota, which have anti-inflammatory and immunomodulatory effects [143]. MCSFAs (C8–C12) are rapidly oxidized for energy and do not significantly elevate blood lipids, which possibly improves metabolic disorders [144]. LCSFAs (C13–C20) increase the risk of CVD by promoting dysregulation of lipid metabolism, inflammation with insulin resistance, and endothelial damage [145]. VLCSFAs (≥C22) are cardio-protective at physiological concentrations [125]. This

chain-specific effect indicates a shift in focus from limiting the total intake of SCSFAs to optimizing the composition of those carbon chains. This can be achieved by combining dietary sources with metabolic context to develop intervention strategies.

5.2. Optimizing the Selection of SCSFAs from Dietary Sources

In precision dietary interventions, food choices should be based on the metabolic effects of SFAs and accompanying nutrients for scientific decision-making. Dairy products that are rich in SCSFAs and MCSFAs, such as full-fat yogurt, are given priority [146]. These SFAs have a unique metabolic pathway that provides rapid energy and reduces the likelihood of lipid deposition. The combined effects of calcium, conjugated linoleic acid, and probiotics found in dairy products can enhance insulin sensitivity and promote a balanced gut microbiota [88,89]. Intake of processed red meat and hydrogenated vegetable oils should be restricted, as they are high in long-chain fatty acids that have been demonstrated to promote chronic inflammation and atherosclerosis [138,147]. Concurrently, replacing SFAs with foods rich in polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), such as nuts, deep-sea fish and olive oil, effectuates a reduction in the total SFAs supply ratio. Furthermore, the capacity of PUFA to mitigate the potential adverse effects of SFA through their anti-inflammatory properties lends further support to this notion [148,149].

The Limitations of Current Epidemiological Studies

While extant epidemiological studies have yielded salient insights into the impact of SFAs intake and CVD risk, their conclusions are constrained by key methodological limitations. Firstly, residual confounding bias is a prevalent phenomenon. Individuals with high red meat consumption frequently exhibit unadjusted risk behaviors, such as smoking, low physical activity, and excessive consumption of refined carbohydrates [150]. Conversely, dairy consumers tend to adhere to healthier lifestyles, characterized by higher fiber intake [151]. This discrepancy in lifestyle patterns can result in a systematic overestimation or underestimation of the independent effect of SFAs. Furthermore, reverse causality interference is inevitable. For instance, individuals with a high CVD risk may actively reduce their red meat intake and increase their consumption of dairy products, resulting in an overestimation of the protective effects of dairy products. Finally, masking key differences in food matrix effects may lead to oversimplified conclusions, such as “red meat increases the CVD risk “, which may be due to the confounding effects of matrix components, such as heme iron in red meat and calcium in dairy products, rather than SFAs themselves. These limitations underscore the necessity for additional research to ascertain the causal role of SFA. When combined with food matrix-specific mechanism analysis, they can provide biological evidence for precision nutrition interventions.

6. Conclusions and Future Outlook

The relationship between SFAs and CVD has evolved from a simplistic understanding to a more nuanced interpretation. Conventional theories emphasize that SFAs promote atherosclerosis by elevating LDL-C. However, recent studies indicated that the pathogenicity of SFAs must be assessed based on a combination of inflammatory activation, endothelial dysfunction, and insulin resistance. A number of large-scale studies, for example the PURE, study have challenged the classic assumption that total SFAs intake is positively correlated with CVD, leading to a shift in perspective from “limiting the total intake” to “optimizing the source”. Future research should prioritize the following areas: first, verifying the intervention effect of alternative nutrients on CVD risk in different populations through long-term randomized controlled trials, and the clarification of the dose-effect of the length of the SFA carbon chain and the substitution ratio. Secondly, it is essential to enhance the application of precision nutrition, which entails integrating host genotype information, gut microbiota profiling, and metabolomic markers. Concurrently, to enhance the translation of extant evidence into clinical practice, future research must prioritize the development of biomarkers of exposure to SFAs from particular food sources (e.g., TMAO in red meat) to objectively capture food matrix effects beyond dietary questionnaires. Consequently, dietary patterns should be restructured based on food sources and the long-term cardiovascular safety of extreme diets should be evaluated.

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