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REVIEW
Cardiovascular disease

Saturated fat: villain and bogeyman in the development of cardiovascular disease?

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See the editorial comment for this article 'Saturated fatty acids: should really be considered as dietary cardiovascular risk factors or it is time to change perspective?', by F. Cortese, https://doi.org/10.1093/eurjpc/zwac206.

Aims Cardiovascular disease (CVD) is the leading global cause of death. For decades, the conventional wisdom has been that the consumption of saturated fat (SFA) undermines cardiovascular health, clogs the arteries, increases risk of CVD, and leads to heart attacks. It is timely to investigate whether this claim holds up to scientific scrutiny. The purpose of this paper is to review and discuss recent scientific evidence on the association between dietary SFA and CVD.

Methods and results PubMed, Google scholar, and Scopus were searched for articles published between 2010 and 2021 on the association between SFA consumption and CVD risk and outcomes. A review was conducted examining observational studies and prospective epidemiologic cohort studies, randomized controlled trials (RCTs), systematic reviews and meta-analyses of observational studies and prospective epidemiologic cohort studies, and long-term RCTs. Collectively, neither observational studies, prospective epidemiologic cohort studies, RCTs, systematic reviews, and meta-analyses have conclusively established a significant association between SFA in the diet and subsequent cardiovascular risk and coronary artery disease, myocardial infarction, or mortality nor a benefit of reducing dietary SFAs on CVD rick, events, and mortality. Beneficial effects of replacement of SFA by polyunsaturated or monounsaturated fat or carbohydrates remain elusive.

Conclusion Findings from the studies reviewed in this paper indicate that the consumption of SFA is not significantly associated with CVD risk, events, or mortality. Based on the scientific evidence, there is no scientific ground to demonize SFA as a cause of CVD. SFA naturally occurring in nutrient-dense foods can be safely included in the diet.

Keywords cardiovascular disease • mortality • saturated fat • clogged arteries

Introduction

Cardiovascular disease (CVD) [it is a pathological condition affecting the heart and cerebral and blood vessels and includes coronary heart disease (CHD), also called coronary artery disease (CAD), heart failure, stroke. and cardiomyopathy[1–3]] is the leading cause of death worldwide, and deaths have been steadily climbing for the decades.[1,4–11] It has been projected that by 2030 nearly 23.6 million people will die from cardiovascular disorders.[12] Hence, CVD is a major global public health problem.

For decades, the conventional wisdom has been that the consumption of saturated fat (SFA) undermines cardiovascular health, clogs the arteries, increases CVD risk and leads to heart attacks.[13–19] This misconception, vilification and condemnation of SFA arose from the most comprehensive epidemiological population study, the Seven Country Study (SCS), by physiologist Ancel Keys who claimed that SFA was the cause of CHD.[20] The SCS was not a scientifically robust study (The Seven Countries study classified ultra-processed foods as SFAs, but these are primarily refined carbohydrates. There were no comments on causation and no attempt was made to consider association until 25 years post study completion,[21]) yet resulted in the 'diet-heart hypothesis' (Diet-heart hypothesis was first proposed by nutritionist Ancel Keys in the early 1950s. The hypothesis postulates that a fatty diet elevates serum cholesterol levels, leading to atherosclerosis and myocardial infarction, whereas reducing dietary saturated fat reduces serum cholesterol, thereby reducing the risk of cardiovascular disease.[22] The focus of the hypothesis soon shifted from the total fat consumed in the diet to the idea that saturated

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fats should be replaced by polyunsaturated fats and the benefits of replacing animal fats with vegetable fats were advocated.[6]) that gained widespread acceptance in the 1970s and 1980s.[23–25] The message that doctors have conveyed to their patients since the 1980s, and many of them still do,[25] is:

> *Eating too much fat is bad for us. Fatty food intake causes a build-up of fat in our arteries, which clog up and give us heart attacks.*

This 'fat is deadly' message propagated in the media spread around the world, and fat, particularly SFA, was demonized since the SCS.[2,5,24,25] This misguided public health message led to confusion and doubt among patients, their physicians and the public.[5,10,23,26–29]

Populations worldwide were led to believe that dietary fat, especially SFA is the cause of CAD.[30] Populations were recommended to avoid foods high in SFA and to limit dietary SFA intake to prevent CVD.[11,22,31–33] Consequently, consumers started restricting SFA in their diet.[18]

Current dietary recommendations advise reducing the intake of SFAs to reduce CVD and CHD risk and mortality, but recently, the role of SFA has been increasingly called into question.[13,21] Continued prioritization of SFA reduction relies on selected evidence, primarily effects on LDL-cholesterol alone (discounting the other, complex lipid and lipoprotein effects) and expedient comparisons with polyunsaturated fat (PUFA).[8] There is mounting rigorous scientific evidence from systematic reviews (SRs) and meta-analyses (MAs) of randomized controlled trials (RCTs) and observational studies that have found no beneficial effects of reducing SFA intake on CVD and total mortality.[31]

Nevertheless, within the medical and scientific community, the 'diet-heart hypothesis' remains controversial, with scientists having vitriolic debates and the literature is still full of articles arguing opposing positions.[6,34] Various studies that have reported divergent findings and have come to discordant conclusions about the relationship between dietary SFA and CVD.[10,17,35–38] These conflicting findings and conclusions warrant scrutinization of the current evidence on the association between SFA and CVD risk, events and mortality. A reappraisal of the evidence may help resolve this controversy around the 'diet-heart hypothesis'. Therefore, this review considers controversies and analyses and discusses new evidence on the association between SFA and CVD to either support of refute claims that SFA causes CVD.

This paper attempts to answer the following research questions:

> *Are SFAs as bad as we have been led to believe?*
>
> *Are SFAs 'villains,' are they benign, or are they even 'heroes' that could help us consume better overall quality diets and promote cardiovascular health?*
>
> *Is there an evidence-based rationale for dietary recommendations to maximally reduce dietary SFAs?*

The purpose of this comprehensive review paper is to address these important questions by critically evaluating recent scientific evidence on the association between dietary SFA intake and CVD, investigating the effect of its replacement by other types of fats and carbohydrates.

Establishing the relationship between SFA and CVD is important for clinicians in order to provide evidence-based dietary recommendations to patients to reduce CVD risk and events.

This paper contributes to the scientific literature in the following ways: Firstly, by demystifying the common allegations and misconceptions about SFA and the association with CVD in order to overcome consumers' confusion and to guide them in making heart-healthy dietary choices. Secondly, by proposing an evidence-based recommendation for a healthy intake of different SFA food sources in order to promote cardiovascular health.

Methods

An integrative review was undertaken to identify, critically analyse, and synthesize the literature on the association between SFA and CVD risk, incidence, and mortality.

To this end, Google Scholar (scholar.google.com) and PubMed (www.ncbi.nlm.nih.gov/pubmed) were searched for studies that investigated the link between SFA and CVD risk, events and mortality in the general population. Search terms used were 'fat', 'saturated fat', 'nutrition', 'diet', or 'dietary guidelines' in combination with 'cardiovascular disease', 'coronary heart/artery disease', 'atherosclerosis', or 'heart'. References in articles were examined for additional relevant studies. This search generated epidemiological studies, long-term, nation-specific and multiple country-specific prospective cohort studies and well-controlled RCTs assessing multiple clinical end points, such as myocardial infarction (MI) and death from cardiovascular causes. The search also generated review papers/reports, narrative reviews, umbrella reviews, systematic reviews (SRs) and meta-analyses (MAs) offering the possibility to synthesize a wealth of data, to unravel inconsistencies or inconclusiveness, and to draw valid and reliable conclusions based on scientific evidence (cf. 38).

Studies were included that examined a reduction in SFA intake or swapping SFA out and PUFA and carbohydrates in, reporting CVD risk, events and hard clinical endpoints, such as CVD/CHD events, mortality and total mortality. Studies that arrived at conclusions by examining exclusively changes in serum LDL-C as a primary outcome, but no other outcomes, such as changes in total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, fasting plasma glucose and C-reactive protein- risk factors for CVD, were excluded. Studies were also excluded if they were published as letters, conference abstracts, perspectives, editorials, observations or opinion pieces.

The identified studies for inclusion in this review were published between 2010 and 2021. This timeframe was selected since studies on the association between SFA and CVD, investigating the 'diet-heart hypothesis', largely increased throughout this time period. The large number of articles published within this timeframe has not been subjected to a comparable review. The final article selection included 4 observational studies, 3 RCT and 25 (narrative) reviews, reports, systematic reviews and metanalyses.

Taken together, these studies provide the most recent scientific evidence on the association between SFA and CVD in order to answer the aforementioned research questions.

Results

Scientific evidence on the association between SFA and CVD

Several epidemiologic studies and clinical trials, SRs and MA of RCTs have aimed to test the 'diet-heart hypothesis', i.e. the association between SFA and CVD. *Table 1* provides an overview of these studies, assessing the impact of SFA on CVD events and CVD mortality in particular. Findings will be described in consecutive sections.

Table 1 Studies on the association between SFA and CVD

Study	Research methodology	Cardiovascular disease	Cardiovascular heart disease mortality
Praagman *et al.* (2016)[39]	Observational epidemiological	Evidence of no effect	Not applicable
Praagman *et al.* (2016)[34]	Observational epidemiological	Positive impact	Not applicable
Dehghan *et al.* (2017);[40] Spector (2020a)[25]	Observational epidemiological	Evidence of no effect	Positive impact
Ho *et al.* (2020)[28]	Observational epidemiological	Evidence of no effect	Not applicable
Estruch *et al.* (2013, 2018)[41,42]	Randomized controlled clinical trial	Positive impact	Not applicable
Khaw *et al.* (2018)[43]	Randomized controlled clinical trial	Inconclusive association	Not applicable
Vijayakumar *et al.* (2016)[19]	Randomized controlled clinical trial	Evidence of no effect	Not applicable
Mozaffarian *et al.* (2010)[38]	Systematic reviews and meta-analyses	Negative impact	Evidence of no effect
Siri-Tarino *et al.* (2010)[17]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
Chowdhury *et al.* (2014)[35]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
Farvid *et al.* (2014)[36]	Systematic reviews and meta-analyses	Not applicable	Not applicable
Schwingshackl and Hoffmann (2014)[44]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
Siri-Tarino *et al.* (2015)[18]	Systematic reviews and meta-analyses	Inconclusive association	Not applicable
Harcombe *et al.* (2015)[45]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
De Souza, Mente, Maroleanu *et al.* (2015)[46]	Systematic reviews and meta-analyses	Inconclusive association	Inconclusive association
Hooper *et al.* (2015)[37]	Systematic reviews and meta-analyses	Negative impact	Evidence of no effect
Guo *et al.* (2017)[7]	Systematic reviews and meta-analyses	Positive impact	Positive impact
Gholami *et al.*, 2017)[1]	Systematic reviews and meta-analyses	Positive impact	Not applicable
Harcombe *et al.* (2016)[26]	Systematic reviews and meta-analyses	Not applicable	Evidence of no effect
Pimpin *et al.* (2016)[33]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Ramsden, Zamora, Majchrzak-Hong *et al.* (2016)[47]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Sacks *et al.* (2017)[10]	Systematic reviews and meta-analyses	Negative impact	Evidence of no effect
Harcombe *et al.* (2016)[26]	Systematic reviews and meta-analyses	Not applicable	Evidence of no effect
Harcombe (2017)[48]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Zhu *et al.* (2019)[11]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Nettleton *et al.* (2017)[15]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Hamley (2017)[49]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Heileson (2019)[27]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
Hooper *et al.* (2020)[50]	Systematic reviews and meta-analyses	Evidence of no effect	Evidence of no effect
Astrup *et al.* (2021)[14]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable
Astrup *et al.* (2020)[31]	Systematic reviews and meta-analyses	Positive impact	Not applicable
DuBroff and De Lorgeril (2021)[22]	Systematic reviews and meta-analyses	Evidence of no effect	Not applicable

Evidence from epidemiolocal, observational studies

The Prospective Urban Rural Epidemiology study (it is important to note that this study is still ongoing to assess hard outcomes related to the consumption of fat and carbohydrates, notably CHD risk and mortality and other causes of death) is the largest-ever epidemiological study observing 135 335 individuals from 337 communities in 18 countries on 5 continents. Findings showed that all types of fat were not associated with CVD, MI or CVD mortality, whereas high carbohydrate intake was associated with higher risk of total mortality.[14,25,31,40] This study contradicts the 'diet-heart hypothesis'.

In 2020, the UK Biobank observational study of 195 658 participants who were followed up for 10.6 years found no evidence that SFA intake was associated with incident CVD. In contrast, the substitution of PUFA for SFA was associated with higher CVD risk. For dietary carbohydrate, higher consumption, mainly from starchy carbohydrates and sugar, was associated with a higher risk of CVD and mortality.[10,28,31]

In a prospective cohort study including 35 597 Dutch men and women, a higher intake of total SFAs was associated with a lower risk of incident IHD.[39]

Another prospective cohort study including 4722 Dutch men and women (≥55 years) found that total SFA was not associated with incident CHD risk, and differentiation of SFA intake according to food sources had no conclusive effect on the association.[34] Overall, longitudinal cohort studies have demonstrated largely neutral effects of overall SFA intake on CHD.[8]

Evidence from clinical trials

RCTs are higher on evidence hierarchies than observational studies as these can demonstrate *cause and effect*, thereby providing the most rigorous kind of data. RCTs can assess the impact on long-term

clinical outcomes, i.e. 'hard endpoints', such as heart attacks and death.[14,25,49]

In the Prevencion con Dieta Mediterranea (PREDIMED) study, 7447 participants (55 to 80 years of age, 57% women) who were at high cardiovascular risk, but with no CVD at enrolment, were assigned in a multicentre trial in Spain to one of three diets: (i) a Mediterranean diet supplemented with extra-virgin olive oil; (ii) a Mediterranean diet supplemented with mixed nuts; (iii) a control diet (advised to reduce dietary fat). The primary end point was a major cardiovascular event (MI, stroke, or death from CVD). Results showed that participants assigned to an energy-unrestricted Mediterranean diet, supplemented with polyphenol-rich extra-virgin olive oil or nuts, had a lower rate of major cardiovascular events than those assigned to a low-fat diet.[41,42] These results were confirmed by a MA of 45 reports of prospective studies, including 4 RCTs and 32 independent observational cohorts. The results showed that better conformity with the traditional Mediterranean diet is associated with reductions in rates of CHD, ischaemic stroke, and total CVD as well as well as non-fatal MI.[16]

A RCT on the effects of different dietary fats was conducted in which participants from the population in Cambridgeshire, UK, were randomized to extra virgin coconut oil, extra virgin olive oil or unsalted butter. Participants were asked to consume 50 g daily of one of these fats for 4 weeks, which they could incorporate into their usual diet or consume as a supplement. Conclusions drawn from the RCT were that effects of different dietary fats on lipid profiles, metabolic markers and health outcomes may vary not just according to the general classification of their main component fatty acids as saturated or unsaturated, but possibly according to different profiles in individual fatty acids, processing methods as well as the foods and dietary patterns in which they are consumed.[43] The authors concluded that this short-term trial does not provide evidence to modify existing prudent recommendations to reduce SFA in the diet as emphasized in most consensus recommendations.

Another clinical trial on the effects of different dietary fats—a single centre randomized study in India—, patients with stable CAD on standard medical care were assigned to receive coconut oil (Group I) or sunflower oil (Group II) as cooking media for 2 years. This study found that coconut oil, even though rich in SFA, in comparison to sunflower oil, when used as cooking oil media over a period of 2 years, did not change the lipid-related cardiovascular risk factors and events.[19]

Taken together, the results from the totality of RCTs constituting the largest and longest experimental tests of the 'diet-heart hypothesis' in the past 60 years, do not provide support for the hypothesis.[14]

Evidence from reviews, systematic reviews and meta analyses

Research on the large body of evidence on the association between SFA and CVD gained momentum from 2010 with a MA of 21 epidemiologic prospective cohort studies involving 347 747 participants. Results revealed that there is insufficient evidence to conclude that dietary SFA is associated with an increased risk of CHD, stroke, or CVD.[17]

A systematic review and meta-analysis of observational and cohort studies, including studies undertaken on over 300.000 healthy people followed up over 20 years, reported no association between the highest and lowest intakes of SFA and CHD mortality. "Furthermore, no association was reported between the intake of SFA and total CHD.[16,48]

SRs and MA of prospective cohort studies and RCTs where a dietary fat intervention had been made found no statistically significant results to implicate total or SFA in CHD mortality.[21,48,51] Furthermore, dietary fat guidelines were introduced with the intention of reducing CHD mortality, yet even in people who have already suffered a MI, evidence does not support dietary recommendations to reduce SFA intake.[21]

Various studies attempted to elucidate whether CVD risks and events are likely to be influenced by the specific nutrients used to replace SFA, notably PUFA, MUFA, or carbohydrates.

The National Institute of Clinical Excellence (NICE) reported that dietary energy derived from SFA tends to be related to mortality from CHD and emphasized that the reduction of dietary SFA is crucial to the prevention of CHD. NICE claimed that 30 000 lives could be saved annually by replacing SFAs with PUFAs.[26]

Several MA of prospective cohort studies and controlled clinical trials suggested similar benefits by demonstrating that reducing intake of SFA and replacing it by PUFA is more beneficial to preventing CVD. Findings provided evidence that consuming PUFA in place of SFA reduces CHD events and suggested that a shift toward greater population PUFA consumption in place of SFA would significantly reduce rates of CHD.[36,38]

A Cochrane systematic review of 15 RCTs analysing CVD events and CVD mortality suggested that replacing SFA with PUFA appears to be a useful strategy, replacement with carbohydrates appears less useful and replacement with MUFA was uncertain. Yet, when a sensitivity test was undertaken on the RCTs that actually significantly reduced SFA intake (as opposed to having the aim of reducing SFA intake), the CVD events finding (for >52,000 participants) reduced from 17% to 9% and was no longer statistically significant.[36] This implies that there is adequate evidence of no effect of SFA intake on CHD events. Regarding PUFA, one study reported that replacing SFA by cis-PUFA was associated with significant CHD risk reduction, which was confirmed by RCTs.[15] Another study reported that increased consumption of PUFA-rich vegetable oils is an evidence-based strategy to lower CHD risk and, in place of saturated animal fats, reduces CHD events.[8]

By contrast, several studies have reported that replacing SFA by PUFA might not be beneficial to reducing CVD. An examination of the traditional 'diet-heart hypothesis' through recovery and analysis of previously unpublished data from the Minnesota Coronary Experiment and the Sydney Diet Heart Study was undertaken through a SR and MA of clinical trials. Findings showed no support for replacement of SFA with linoleic acid (found in abundance in corn oil, sunflower oil, safflower oil, cottonseed oil, or soybean oil) to significantly reduce CHD events or deaths.[47]

In fact, the rise in deaths from CHD coincided with the time when the use of these ultra-processed seed oils became commercially and domestically available.[5] Studies have highlighted potential harms of replacing SFA with PUFA in these seed oils, e.g. vascular inflammation, increased risk of CHD, cardiovascular events and mortality.[2,23,43]

Another study examine evidence for all-cause mortality, CVD mortality, CVD events and MIs for both reduced fat intake and

modified fat intake with a systematic review and meta-analysis of RCTs. This study concluded that "the present systematic review provides no evidence (moderate quality evidence) for the beneficial effects of reduced/modified fat diets in the secondary prevention of coronary heart disease. Recommending higher intakes of polyunsaturated fatty acids in replacement of saturated fatty acids was not associated with risk reduction".[41]

A consecutive MA of RCTs investigating the effect of replacing SFA with mostly n-6 PUFA on CHD concluded that the available evidence from adequately controlled RCTs suggest replacing SFA with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality or total mortality.[49] The author argued that the suggestion of benefits reported in earlier MAs is due to the inclusion of inadequately controlled trials, i.e. many of these 'diet-heart hypothesis' trials had substantial dietary or non-dietary differences between the intervention groups that were not related to SFA or mostly n-6 PUFA intake.[49]

Other MAs of clinical studies concluded that the evidence does not support current recommendations to replace SFA with PUFA since there was no effect on CHD mortality and total/all-cause mortality.[21,48,51]

Overall, dietary recommendations to replace SFA with carbohydrates or Ω-6 PUFA do not reflect the current evidence in the literature and its benefits are severely challenged.[8,23]

Various studies have investigated the role of SFA vs. TFA in assessing CVD risk and events. A SR and MA of prospective, observational studies and RCTs examining SFA, PUFA, MUFA and trans fatty acids (TFAs) found no association of dietary SFA intake, nor of circulating SFA, with CHD. It was TFA intake that was positively associated with CHD.[35] These findings were corroborated by other studies that found a robust association of higher TFA intake, particularly industrially-produced TFA in partially hydrogenated vegetable oils, with elevated CHD risk and sudden death.[2,8,10]

A study investigating the effect of dietary total fat and fatty acid intake on CVDs risk based on dose-response MA of prospective cohort studies found no significant association between dietary SFA intake and CVD risk.[11] The MA found it is TFA intake that can increase risk of CHD mortality and incidence, because TFA intake may impair insulin sensitivity and C-reactive protein concentrations and increase inflammation, all associated with CVD. Notably, this MA did not support the popular viewpoint that dietary SFA intake increases CVD risk. The authors argued that this viewpoint might be based on selective emphasis on some studies, but ignore other studies that do not support these conclusions.[11]

Other studies investigated the replacement of SFA by carbohydrates and found that replacement of SFA with carbohydrates increased the risk of non-fatal MI.[36,38] Moreover, overall cardiometabolic health seems to improve to a greater extent when carbohydrate is restricted rather than fat.[23] These findings were partially supported by a later study that reported that the evidence supports increasing vegetable oils rich in PUFA and phenolics, in place of refined grains, starches, and added sugars, but, notably, not necessarily in place of SFA.[8] In fact, it has been reported in the literature that greater intake of SFA is associated with less progression of atherosclerosis whereas carbohydrate and PUFA intake are associated with greater progression.[3] A recent study found that if lowering SFA intake is achieved by consuming more carbohydrates, there is likely to be an adverse effect on CVD risk, whereas higher SFA intake in the context of a low-carbohydrate diet improved cardiometabolic risk status.[14]

Results of a SR and MAs suggested that health effects of foods high in SFA should be considered against the alternative choice, such as TFA, refined grains, starches, and sugars that have clear harmful effects on CVD.[13,33]

Several studies have investigated the role of dairy foods -high in SFA- and the effects on CVD. The findings of one MA investigating the role of dairy in CVD showed that total dairy intake can lower the risk of CVD by 10% while it has no relationship with CHD. This study showed the protective role of dairy consumption on stroke and CVD; the intake of dairy products can lower the blood pressure, which is an important risk factor of CVD.[1]

Random-effect MAs of 29 prospective cohort studies with summarized dose–response data for total (high-fat/low-fat) dairy, milk, fermented dairy, cheese, and yogurt established neutral associations of total, high-, and low-fat dairy, milk, and yogurt with risk of all-cause mortality, CHD, and CVD. This study also showed that total fermented dairy and cheese intake was marginally inversely associated with CVD risk and mortality. Conclusions were that the effect of dairy fat on CVD is complex and findings, especially on the association of fermented dairy products with CVD risk, different sub-types of CVD events and mortality, need confirmation in further studies.[7] Findings of these studies are consistent with previous research[8] that found that dairy, a leading source of SFA, has neutral or even beneficial effects on CHD.

Findings from the studies on the association between SFA and CVD in the early and mid-part of the past decade have been confirmed by recent studies. A narrative review of 19 MAs, RCTs, and observational studies found no significant associations between SFA consumption and CHD. The MAs of observational studies reported in the review found no association between SFA intake and CHD, while MAs of RCTs reported in the review were inconsistent, but tended to show a lack of association. The conclusion was that the strength of the evidence for the recommendation to limit SFA for CHD prevention may be overstated and is in need of re-evaluation.[27]

An updated SR by the Cochrane group in 2020[50] on SFA reported that reducing dietary SFA reduced CVD events, but had no effect on the remaining seven CVD end-points including total mortality, CVD mortality, CHD mortality, fatal heart attacks, non-fatal heart attacks, and CHD events. Even the significant effect of SFA on CVD events became non-significant when subjected to a sensitivity analysis that only included clinical trials, which had successfully reduced SFA consumption, while excluding those that intended to reduce SFA, but were not successful.

A review that critically evaluated the evidence from both cohort studies and RCTs of the health effects of dietary SFA found that the totality of the data on SFA and cardiovascular outcomes showed that SFA was found either to have no effect on CVD or CHD endpoints, or their consumption was associated with a lower risk.[14]

A review that examined the health effects of dietary SFA found SFA either to have no effect on CVD or CHD endpoints, or their consumption was associated with a lower risk.[31]

A review of 28 RCTs and 11 MAs that examined diet and CVD concluded that the preponderance of evidence indicates that low-fat diets do not reduce cardiovascular events or mortality.[22]

Chart 1 SFA impact on CVD

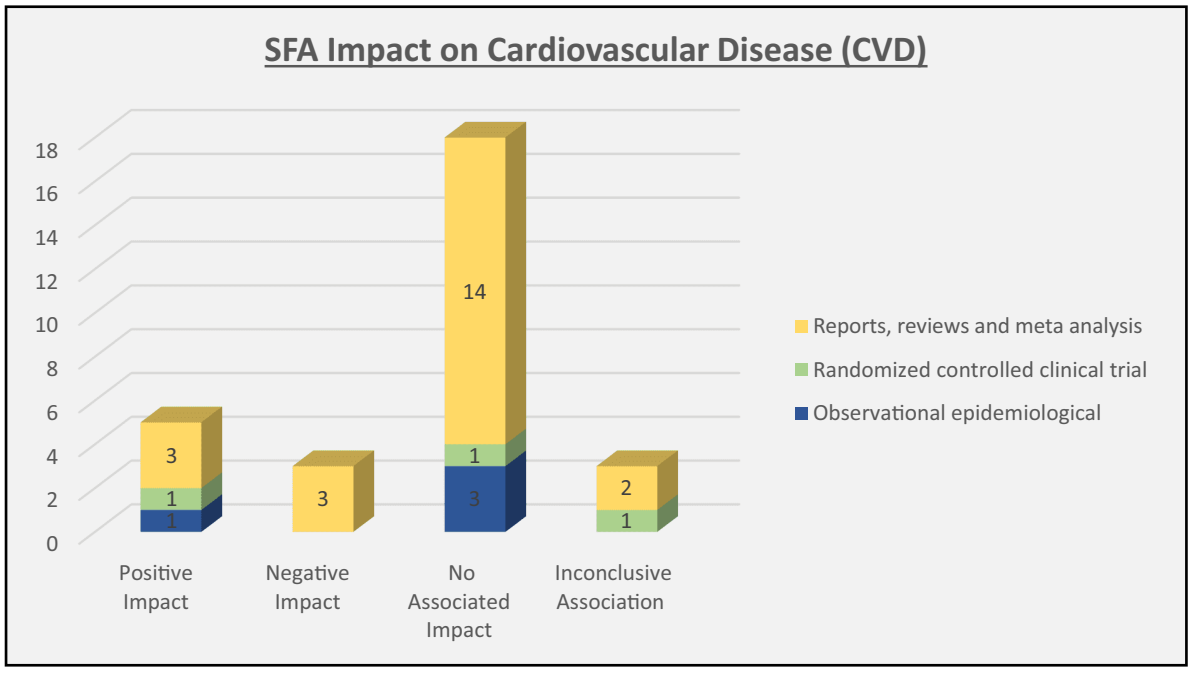

Chart 1 Saturated fat impact on cardiovascular disease.

Chart 2 SFA impact on CHD mortality (CHM)

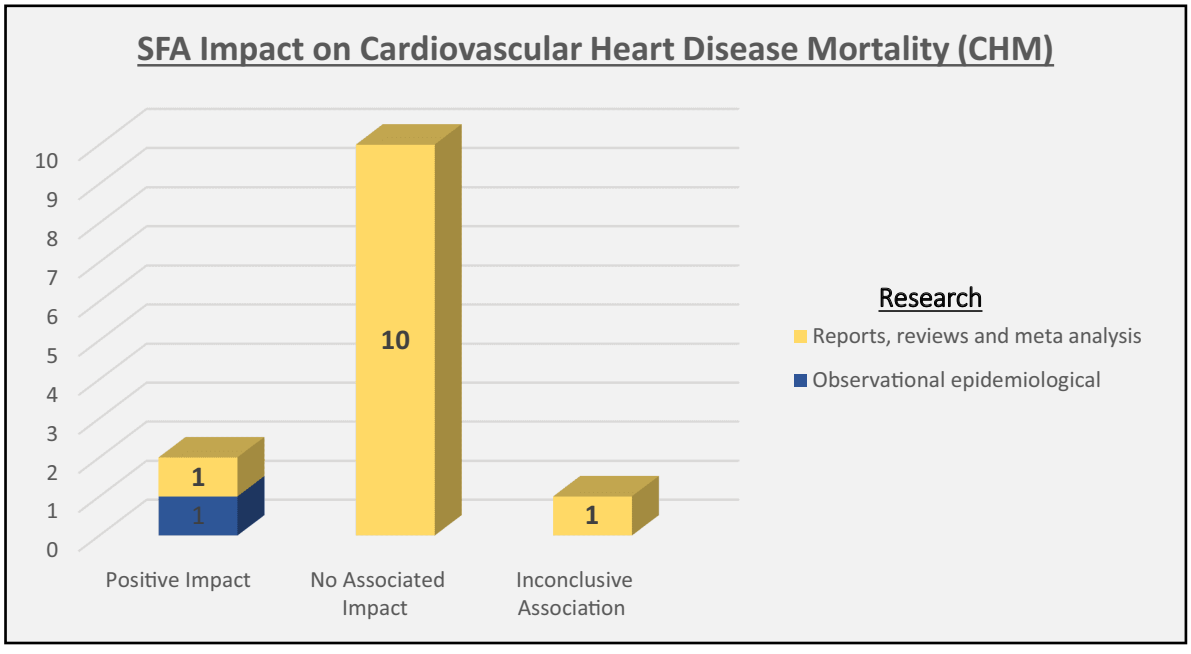

Chart 2 Saturated fat impact on coronary heart disease mortality.

Table 1 provides an overview of the reviewed studies and shows that out of the 32 studies, 3 found a negative (harmful) impact of SFA on CVD, whereas 5 found a positive impact (beneficial effect of SFA on CVD). 18 studies found 'Evidence of no effect, meaning that the studies found no statistically significant association between SFA and CVD. Two studies,[32,50] did not address CVD overall, but investigated deaths from CHD, hence were labelled as "Not studied" for CVD in Table 1. Only 3 studies,[16,47,48] were inconclusive. "Inconclusive association" means that no impact of SFA on CVD can be determined. This could be due do to other variables, such as different dietary fats and different profiles in individual fatty acids that impacted the studies' results. This implies that more nuanced studies are needed to better determine the relationship between different fat types and CVD and that carbohydrates possibly influence the outcomes.

Zooming in on the effect of SFA on CVD mortality (CHM), 2 studies showed a positive impact, 10 showed no associated impact, and 1 study established an inconclusive association. The remainder of the studies did not investigate CVD mortality (CHM), labelled as 'Not Applicable' in *Table 1*. *Chart 1* 'SFA impact on CVD' and *Chart 2* 'SFA impact on CHD mortality' (CHM) distinguish between CVD events and mortality. Making this distinction and capturing different CVD outcomes is important, because mortality is a clear 'hard endpoint' that is objectively measurable, whereas CVD risk and events are ambiguous. That is, what exactly constitutes CVD events? The definitions of CVD risks and events themselves are questionable. We contend that the meaning of the terminology needs to be defined. Yet, even if medical researchers and practitioners accept common definitions of CVD risk and events, but the mortality and CVD risks do not match up, then questions need to be asked. Finally, some studies reviewed in this paper addressed just one indicator, e.g. CVD events, but not mortality, while other studies address both CVD events and mortality, often with conflicting results. Such results do not allow for making conclusive inferences about SFA as a cause of CVD.

In sum, this review provides strong evidence for absence of observed cardiovascular harm of SFA. Collectively, neither observational and epidemiologic studies or RCTs or reviews, systematic reviews and meta analyses have conclusively established an evidence-based rationale for dietary recommendations to maximally reduce dietary SFAs to prevent CVD risk, events, outcomes and mortality. The evidence refutes the 'diet-heart hypothesis' and implies that it is timely that scientists, clinicians and the public reconsider this hypothesis.

Discussion

The purpose of this comprehensive review was to critically examine the currently available scientific evidence on the association between SFA and CVD, which will have implications for future dietary recommendations to reduce CVD risk, events, and mortality.

Our investigation expands upon prior studies investigating the association between SFA and CVD and adds to a growing body of evidence showing a lack of statistically significant impact of SFA on CVD risk and outcomes. The preponderance of evidence from reviews, meta-analyses of observational studies and clinical trials does not support the dietary recommendations to maximally limit SFA intake to reduce clinical cardiovascular risk and events on and mortality.[12,15,16,20,28,34,38,39,40,44] In fact, scientific evidence shows that the advice to remove SFA from the diet has, paradoxically, increased cardiovascular risks.[2] Therefore, this review supports the contention that continued recommendations to limit the consumption of SFA is based on weak and contradictory evidence and does not meet scientific standards for guidelines.[14]

It is evident that although the image of coronary arteries as kitchen pipes clogged with SFA causing heart attacks is simple, familiar, and evocative, it is also plain wrong.[3,24,30] The plumbing model—in which dietary fat is slowly deposited in arterial walls, leading to blockages—perpetuates misconceptions about fat consumption.[30] Despite popular belief among doctors and the public, what we now understand of the development of CVD, grounded in contemporary scientific evidence, is that the dietary dogma about SFA clogging a pipe is erroneous and has no scientific basis.[3,5,25]

This is captured well in the following statement: 'SFA does not clog the arteries: CHD is a chronic inflammatory condition, the risk of which can be effectively reduced from healthy dietary interventions'.[3]

The advancement of science requires us to consider new ideas and evidence even when they undermine or contradict the prevailing paradigm. A paradigm shift away from the single-nutrient paradigm,[8] is required in the prevention and treatment of CAD; it is time to shift the public health message away from reducing dietary SFA.[24]

This review lend support to the contention that there is a need to avoid making the mistake of reductionism, singling out scapegoats like SFA,[25] which takes our eyes and minds off the whole meal and dietary pattern that influences CVD risk and events. Indeed, a reductionist approach has plagued SFA research and demonstrates the hazards of isolating a single nutrient and failing to account for the overall nutrient composition, which leads to confusion and unintended deleterious consequences.[32] Not surprisingly, there is increasing controversy on the utility of focusing on isolated macronutrients, such as SFA, for determining CVD risk, because the effect of particular foods on CVD cannot be predicted solely by their content of SFAs.[13,33,53] Healthfulness of foods is not simply a function of their SFA content, but a result of various components in the food, often referred to as the 'food matrix'.[7,8,15,31,53] The food matrix and the overall dietary pattern captures the synergism and interactions between food sources and nutrients and may also influence the kinetics of SFA absorption.[8,15] Hence, in the diet, SFA should be viewed as part of the food and overall diet patterns rather than as a single isolated nutrient,[6,8,13,14,31] because cardiometabolic diseases are largely influenced not by a single nutrient, but by overall dietary patterns, which is of greater significance than SFA intake alone .[8,16,53]

Importantly, SFA represents a highly heterogeneous category, with ranging fatty acid chain lengths obtained from diverse foods, which are likely to have different cardiometabolic and physiological effects with different clinical manifestations, such as CVD.[6,8,16,43]

Therefore, complexities of health effects and benefits of SFA-containing foods, and possibly some specific SFAs, clarify why judging a person's diet as harmful, because it contains more SFA or beneficial and because it contains less, is unsound, and is likely to lead to erroneous conclusions.[8] Given that the cardiovascular health effects of SFA remain a controversial topic among scientists, an open discourse and debate among scientists and healthcare professionals is fundamental and encouraged. This might take away the

controversy among scientists, healthcare professionals, and the public about SFA recommendations to lower risk of CVD (cf. 30).

We hope the scientific evidence on the association between SFA and CVD presented in this paper provides a framework for such an open debate. This might take away the controversy among scientists, healthcare professionals and the confusion among the public about SFA recommendations to lower CVD risks (cf. 30).

Limitations and directions for future research

Potential limitations to this study should be considered when interpreting results. Observational or epidemiological studies can demonstrate associations with disease.

outcomes, but are unable to demonstrate causal connections.[14] Such studies have significant limitations, including confounding variables—such as concomitant changes in TFA, sugar, omega-3 fatty acids; potential bias– such as differences in care, adherence, attrition, and lack of blinding; measurement error in assessing habitual dietary consumption; social desirability bias; incomplete follow-up of participants, which pose considerable limitations that make interpretation of their results challenging[27] Furthermore, in most of the epidemiologic studies, diet was assessed using a Food Frequency Questionnaire. However, this method is subject to random and systematic measurement errors by the over- or under-reporting of the amounts of food usually eaten every day.[11,17,33,36,39]

Another limitation is publication bias, i.e. studies with significant large associations tend to be received more favourably for publication than small or null findings.[33,53]

Future research requires a more holistic approach to assess the effects of SFA from different food sources on CVD, because different food sources contain varying specific fatty acid profiles as well as other constituents that may result in distinct cardiometabolic effects.[13,33]

Another avenue for future research is to further investigate the role of SFA compared with other types of fat and types of carbohydrates in CVD risk and mortality in healthy individuals as well as those at high CVD risk. Well-designed RCTs that include appropriate controls, are adequately powered, and examine a range of CVD risk factors with sufficient follow-up to observe clinical events and deaths are required to further test the 'saturated fat-is bad' hypothesis. Together, such studies will aid in clarifying our current understanding of the relationship between SFA consumption and clinical endpoints, such as CVD events and MI (fatal and nonfatal). This is essential to building a stronger evidence base than currently exists on the association between SFA and CVD in order to provide evidence-based dietary fat recommendations to the public to reduce their CVD risk.

Social and public health implications

Whilst the health consequences of the COVID-19 virus pandemic are increasingly kept under control through vaccination, the cardiovascular epidemic is rapidly advancing in the world.[4,12] The global prevalence of diet-related cardiometabolic diseases, such as CVD, poses a major global public health crisis and present enormous health and economic burdens globally. Burdens are directly related to increased morbidity and mortality in affected individuals, which also translates into significant costs, including healthcare expenditures, reduced productivity, human cost in lost potential and lost capital, which are unsustainable in the future.[5,8,10] Unlike the COVID-19 virus, there currently is no vaccine for the prevention of CVD.[4] Therefore, prioritizing nutrition in clinical care, advocacy, research, and policy as preventive treatment can substantially reduce the number of people who develop CVD globally, thereby reducing the associated healthcare and economic costs.[5,8,10] Scientific advances on the association between dietary components, such as SFA, and CVD, presented in this paper, provide crucial new insights and best practices to reduce burdens of CVD.

Practical implications

First, enhance the public's understanding that many foods rich in SFA play an important role in meeting dietary and nutritional recommendations. A food-based translation of the recommendations for SFA intake would avoid unnecessary reduction or exclusion of foods that are key sources of important nutrients.

Second, make the public aware that diets high in SFA (whilst low in carbohydrates) may improve metabolic disease risk and 'hard endpoints', but emphasize that health effects of SFA depend on the amount, type and quality of food sources, degree of processing, etc.

Conclusions

This review has provided evidence on the association between SFA and CVD, showing that the consumption of SFA is not conclusively, significantly associated with CVD risk, events, or mortality. In so doing, this paper has demystified the common allegations and misconceptions about SFA being harmful to heart health. This helps to overcome consumers' confusion and guides them in making heart-healthy dietary choices including SFA. A key lesson from the scientific evidence presented in this paper is that SFAs are not bad as we have been led to believe, and SFAs are not "villains" in the development of CVD. There is no scientific ground to demonize SFA as a cause of CVD. SFA in nutrient-dense foods can be part of a healthy, quality diet, which will promote cardiovascular health.

Author contributions

R.V. and J.H. contributed to the conception and design of the work. R.V., J.H., and K.J.G. contributed to the acquisition, analysis, and interpretation of data for the work. R.V. and J.H. devised the table with an overview of the studies (epidemiological, randomized control trials, systematic reviews and meta-analysis) on the association between SFA and CVD. J.H. devised charts with data on CVD and CHD mortality per type of study (observational, RCT, systematic reviews and meta-analyses). R.V. and J.H. drafted the manuscript. R.V. critically revised the manuscript. JH and KJG reviewed the revised manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Disclaimer

The author affirms that the manuscript is an honest, accurate and transparent account of the research being reported.

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