


Dietary saturated fat and heart disease: a narrative review

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The American Heart Association (AHA) recently published a meta-analysis that confirmed their 60-year-old recommendation to limit saturated fat (SFA, saturated fatty acid) and replace it with polyunsaturated fat to reduce the risk of heart disease based on the strength of 4 Core Trials. To assess the evidence for this recommendation, meta-analyses on the effect of SFA consumption on heart disease outcomes were reviewed. Nineteen meta-analyses addressing this topic were identified: 9 observational studies and 10 randomized controlled trials. Meta-analyses of observational studies found no association between SFA intake and heart disease, while meta-analyses of randomized controlled trials were inconsistent but tended to show a lack of an association. The inconsistency seems to have been mediated by the differing clinical trials included. For example, the AHA meta-analysis only included 4 trials (the Core Trials), and those trials contained design and methodological flaws and did not meet all the predefined inclusion criteria. The AHA stance regarding the strength of the evidence for the recommendation to limit SFAs for heart disease prevention may be overstated and in need of reevaluation.

INTRODUCTION

The 2015 Dietary Guidelines for Americans (DGA) recommend consuming <10% of calories from saturated fat (SFA) for optimal health,¹ while the American Heart Association (AHA) recommends 5%–6% of total calories as SFA for those at risk of heart disease to reduce low-density lipoprotein cholesterol (LDL-c).² International food and nutrient guidelines tend to mirror the DGA recommendation.^{3–5} In contrast to this widespread acceptance, several recent meta-analyses have challenged the evidence and rationale supporting the current dietary recommendations on SFA.^{6–8} The consensus on SFA came into question after Siri-Tarino et al⁹ published a meta-analysis of 21 prospective cohort studies of over 347 000 subjects that found no evidence that saturated fat intake is associated with coronary heart disease (CHD) or cardiovascular disease (CVD). Two recent meta-analyses, which included unpublished data, have also challenged the advice to replace SFA

with polyunsaturated fat (PUFA).^{6,10} Despite the shift in the nutritional landscape, the AHA released a Presidential Advisory on dietary fats with a meta-analysis that provided evidence that re-established their nearly 6-decade-old dietary advice to reduce SFA and replace it with PUFA.¹¹

Except for the universally recognized detrimental role of trans fatty acids (TFAs), the dietary fat debate has led to extensive public confusion and questioned the credibility of the DGA.¹² In light of this, it is critical to objectively analyze the most recent meta-analytical evidence to determine the role of SFA in heart disease. However, at the outset, it is important to appreciate and understand the genesis and evolution of the current SFA guidelines.

Historical timeline of the current saturated fat guidelines

In the early 1900s, the relationship between diet and heart disease was first established when Anitschkow

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Key words: heart disease, low-density lipoprotein cholesterol, meta-analysis, polyunsaturated fat, saturated fat, trans fat.

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doi: 10.1093/nutrit/nuz091

Nutrition Reviews® Vol. 0(0):1–12

and Chalataw¹³ observed that rabbits fed high-cholesterol diets had elevated serum cholesterol and developed arterial lesions similar to atherosclerosis in humans. In contrast, humans fed high-cholesterol diets failed to elicit a significant increase in serum cholesterol levels.¹⁴ When dietary cholesterol appeared an unlikely driver of high serum cholesterol levels and heart disease, in 1950 Gofman et al¹⁵ presented data that showed restricting both dietary fat and cholesterol reduced LDL-c in 17 of 20 patients. In 1952, Kinsell et al¹⁶ replicated this finding by substituting vegetable oil for animal fat in participants' diets, dramatically decreasing their serum cholesterol. To explore this relationship further, in 1953 Keys¹⁷ compiled dietary and vital statistics from 6 countries and found a linear relationship between dietary fat intake and heart disease mortality. Subsequent epidemiological data indicated a correlation between total intake of dietary fat, serum cholesterol levels, and prevalence of heart disease.^{18,19} However, in 1970, Keys published the Seven Countries Study, which failed to show an association between total dietary fat and heart disease.²⁰ Rather, this study found that populations with the greatest SFA intake had the highest incidence of heart disease. Thus, the focus of dietary interventions to prevent heart disease shifted from total fat to saturated fat intake.

Results of these experimental and observational studies formed the framework for the theory known as the diet-heart hypothesis. This hypothesis postulates that heart disease risk is reduced by limiting saturated fat intake through its ability to lower LDL-c. The hypothesis quickly gained acceptance among clinicians at the time, leading to the AHA's official recommendation in 1961 to reduce total dietary fat and saturated fat and substitute dietary saturated fat with polyunsaturated fat.²¹ These recommendations were the foundation for the national dietary guidelines that advocated full-fat dairy products with low- or non-fat versions, fattier cuts of meat with lean meats, butter with margarine, and animal fats and tropical oils with vegetable oils. Recently, these long-standing dietary recommendations have been challenged. Compelling evidence aggregated since 2009 suggests a reevaluation of these recommendations may be warranted.^{9,22,23}

Despite the 2015 Dietary Guidelines for Americans Committee (DGAC) responding to current evidence by deemphasizing cholesterol as a nutrient of concern and removing their recommendation to limit total fat, they did not change their recommendations on SFA.^{24,25} In response, a panel of nutrition experts from the Academy of Nutrition and Dietetics called for consistent language among expert organizations regarding the DGA stance on SFAs, stating, "In the spirit of the 2015 DGAC's commendable revision of previous DGAC

recommendations to limit dietary cholesterol, the Academy suggests that HHS [the US Department of Health and Human Studies] and USDA [the US Department of Agriculture] support a similar revision deemphasizing saturated fat as a nutrient of concern."²⁶ More recently, a group of researchers challenged the World Health Organization's proposed saturated fat recommendation to reduce intake to less than 10% of total calories as this simplistic measure does not take into account the complexity of the food matrix.²⁷

This narrative review aims to provide a brief overview of the recent meta-analyses of dietary SFA and heart disease with special emphasis and review of the methodological approach used by the AHA's Presidential Advisory on dietary fats and cardiovascular disease (referred to here as the Advisory),¹¹ to include an in-depth review and critique of the 4 clinical trials included.

LITERATURE SEARCH STRATEGY

PubMed was searched using the terms "dietary saturated fat" AND "heart disease" from 2009 to April 2019. This timeframe was selected since meta-analytical evidence refuting the diet-heart hypothesis began to appear around this time, leading to an increase in meta-analyses of observational studies and randomized controlled trials (RCTs). The search yielded 5287 publications. Once filtered by the article type (meta-analysis and systematic review), 127 articles were available for review. Articles were screened and removed if they were duplicates or systematic reviews without a meta-analysis. Articles were retained if the meta-analysis included studies that compared dietary SFA (high vs low) intake or studies where SFA was replaced with polyunsaturated fat and included data on hard clinical endpoints such as total mortality, coronary heart disease mortality, and events; however, omega-3-PUFA-only meta-analyses were not included. Nineteen meta-analyses were identified: 9 observational and 10 randomized controlled trials. Additionally, reference lists from available meta-analyses, 2 Cochrane reviews,^{28,29} and the Advisory¹¹ were consulted to ensure all relevant studies were captured.

META-ANALYSES OF OBSERVATIONAL STUDIES

Since 2009, all 9 meta-analyses of observational studies related to dietary fat and heart disease found that SFA intake was not independently associated with heart disease (Table 1).^{7,9,23,30-35} Two of these studies concluded that replacement of SFA with PUFA was associated with a lower risk of heart disease.^{30,31}

Table 1 Findings from meta-analyses of observational studies of saturated fat and heart disease

Reference	Participants (no. of studies)	Author's conclusion
Jakobsen et al (2009) ³⁰	344 696 (11)	Replacement of SFA with PUFA decreased CHD events and mortality; however, replacement with MUFA or carbohydrates increased CHD events.
Mente et al (2009) ³⁴	160 673 (11)	Higher intake of SFAs were not associated with CHD events or mortality.
Skeaff et al (2009) ³³	159 433 (7)	Noted multiple methodological flaws in dietary fat research. They concluded that "the available evidence from cohort and randomized controlled trials is unsatisfactory and unreliable to make judgement about and substantiate the effects of dietary fat on risk of CHD."
Siri-Tarino et al (2010) ⁹	347 747 (16)	No significant evidence that SFAs are associated with increased risk of CHD.
Chowdhury et al (2014) ³²	283 963 (20)	No association with dietary or circulating SFAs with CHD.
Farvid et al (2014) ³¹	310 602 (13)	In prospective observational studies, dietary LA intake is inversely associated with CHD risk in a dose-response manner. These data provide support for current recommendations to replace saturated fat with polyunsaturated fat for primary prevention of CHD.
de Souza et al (2015) ⁷	145 922 (6)	SFAs are not associated with all-cause mortality or CHD.
Harcombe et al (2017) ²³	89 801 (7)	Meta-analysis of prospective cohort studies finds no significant association between CHD deaths and saturated fat consumption.
Zhu et al (2019) ³⁵	1 302 057 (56)	This current meta-analysis of cohort studies suggested that total fat, SFA, MUFA, and PUFA intake were not associated with the risk of cardiovascular disease.

Abbreviations: CHD, coronary heart disease; LA, linoleic acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

Jakobsen et al³⁰ conducted a pooled analysis of 11 cohort studies of 344 696 people that examined the effect of replacing saturated fat with monounsaturated fat (MUFA), PUFA, or carbohydrate on heart disease. Jakobsen et al³⁰ concluded that for every 5% replacement of SFA with PUFA there was an associated 13% reduction in CHD events (hazard ratio [HR] 0.87; 95% confidence interval [CI], 0.77–0.97). However, there was an increased risk with replacement of MUFA (HR 1.19; 95%CI, 1.00–1.41) or carbohydrates (HR 1.07; 95%CI, 1.01–1.14).³⁰ Although the study authors noted the dietary exposure as all PUFAs (omega-3 and omega-6), subsequent publications erroneously attributed the decreased risk solely to linoleic acid (LA).^{36–38} Despite the conflation of terms, the Farvid et al³¹ analysis of observational studies found that higher LA intake was independently associated with a decrease in CHD events (pooled relative risk [RR], 0.85; 95%CI, 0.78–0.92) and deaths (pooled RR, 0.79; 95%CI, 0.71–0.89), and, albeit weaker, replacement of SFA with LA also reduced CHD events (pooled RR, 0.91; 95%CI, 0.87–0.96).

Conversely, Chowdhury et al³² conducted a comprehensive analysis that included cohort and intervention studies, which analyzed omega-6 specifically, and found no significant association with decreased coronary events (RR, 0.98; 95%CI, 0.90–1.06). In agreement, the Mente et al³⁴ meta-analysis of prospective cohort studies found no association between PUFA intake and heart disease (RR, 1.03; 95%CI, 0.81–1.23). Interestingly, Skeaff and Miller³³ found that total intake of PUFA ($P=0.009$) and LA ($P=0.032$) were associated with a 25% increased risk in CHD mortality (RR, 1.25; 95%CI, 1.06–1.47 and RR, 1.25; 95%CI, 1.02–1.52,

respectively), but not CHD events (RR, 0.97; 95%CI, 0.74–1.27 – for PUFA).

A recent dose-response meta-analysis determined that total fat, MUFA, SFA, and PUFA were not associated with CVD risk.³⁵ Interestingly, in subgroup analysis, SFA intake was found to be significantly associated with reduced CVD risk in an Asian population (HR, 0.84; 95%CI, 0.73–0.97). Also during subgroup analysis, PUFA was inversely associated with CVD risk after 10 years; however, an incremental increase in PUFA (5 g/d) was associated with a 4% increased risk in CVD (HR, 1.04; 95%CI, 1.01–1.07; $P_{\text{linearity}}=0.030$). The authors speculated that this could be related to concomitant intake of mercury found in fatty fish. Although plausible, this finding would need to be confirmed, since the extant literature suggests an inverse association with fish consumption and myocardial infarction or cardiovascular mortality, especially in Asian populations.^{39,40}

It should be noted that the replacement of SFA for PUFA, or LA specifically, may not have been observed in the individual cohorts, but statistically determined by nutrient substitution analysis. While there are some benefits to this approach when nutrient replacement occurs isocalorically,⁴¹ the substitution analysis does not take into account the accompanying nutrient profile of the foods replaced. For example, a recent study determined that nutrient substitution – dairy fat for PUFA and MUFA – led to a decrease in the nutrient-rich food index; however, a food-level substitution led to an increase in the nutrient-rich food and the healthy eating index (for those with the highest dairy consumption) owing to a reduction in micronutrients such as calcium, vitamin A, vitamin D, and B12.⁴² Statistical modeling, at

the nutrient or food level, adds a new layer of complexity to nutritional epidemiology, but it does not alleviate observational studies of their limited ability to make causal inferences. To better understand whether a relationship exists between the replacement of SFA with PUFA and heart disease, the next section will briefly review the meta-analyses of RCTs.

META-ANALYSES OF RANDOMIZED CONTROLLED TRIALS

According to the hierarchy of evidence, RCTs offer a way to prove causation from associations determined by observational studies. The observational evidence seems to agree that no independent association exists between saturated fat and heart disease^{7,9,23,30–34,43}; however, 2 of the meta-analyses found an association with replacement of SFA with PUFAs.^{30,31} Since 2009, 10 meta-analyses of RCTs have been conducted (Table 2).^{6,8,10,11,22,28,29,44–46} None reported a significant increase in the hard points such as heart disease mortality or total mortality with SFA intake, although 3 found a significant decrease between groups for soft endpoints such as CHD or combined CVD disease events.^{11,29,44}

Mozaffarian et al⁴⁴ reviewed 8 RCTs from 7 cohorts to determine whether substitution of SFA with PUFA consumption would have an effect on CHD outcomes. The pooled risk reduction for CHD events was 19% (RR = 0.81; 95%CI, 0.70–0.95; $P = 0.008$). Unfortunately, their analysis included a nonrandomized controlled trial, the Finnish Mental Hospital Study (FMHS),^{47,48} and a multifactorial study, the Oslo Diet Heart Study (ODHS),⁴⁹ and excluded the only study that showed an increase in mortality with the degree of oil saturation – the Rose Corn Oil trial.⁵⁰ Mozaffarian et al⁴⁴ referred to the FMHS as a cluster-randomized crossover trial; however, a Cochrane systematic review available at the time excluded the FMHS since it was not a randomized trial.⁵¹ After 2010, all meta-analyses of randomized controlled trials excluded the FMHS from their analysis (Table 3),^{8,10,28,29,45,52} except the most recent Advisory.¹¹ Despite the inclusion of FMHS and ODHS, the authors noted that, “given these limitations of each individual trial, the quantitative pooled risk estimate should be interpreted with some caution.”⁴⁴

Hooper et al²⁹ reviewed RCTs examining the effects of saturated fat intake over 24 months. Fifteen trials involving 59 000 participants met the inclusion criteria. A reduction in SFA intake had no effect on all-cause, cardiovascular, or CHD mortality; myocardial infarctions; nonfatal myocardial infarctions; stroke; or CHD events; but there was a significant decline in combined CVD

events (RR, 0.83; 95%CI, 0.72–0.96). When analyzed by gender, this difference was observed in men (RR, 0.80; 95%CI, 0.69–0.93), but not in women (RR, 1.00; 95%CI, 0.88–1.14). The authors found no benefit to replacing SFA with carbohydrate or protein and found that the effects of replacing it with MUFA were unclear. Replacing SFA with PUFA had no impact on all-cause mortality, cardiovascular mortality, myocardial infarctions, nonfatal myocardial infarctions, stroke, or CHD mortality. There was a reduction in combined CVD events (RR, 0.73; 95%CI, 0.58–0.92). Interestingly, this substitution analysis differs from their earlier meta-analysis.²⁸ In 2012, the Cochrane Collaboration specifically excluded studies with a dietary difference, clear or unclear, in any variable other than fat intake, which excluded the ODHS and the St Thomas Atherosclerosis Regression Study.²⁸ Hooper et al²⁸ noted that both trials were at high risk of bias since the dietary differences—fiber intake from fruits and vegetables and omega-3 PUFAs from fish intake—may have impacted the primary outcomes; however, the most recent review did not exclude the trials despite their selection criteria stating that multifactorial trials would not be included.²⁹

Owing to the substantial between-study heterogeneity observed in the statistically significant findings for combined CVD events in the Hooper et al²⁹ meta-analysis ($I^2 = 65\%$), Thornley et al⁵³ reanalyzed the review using an inverse-variance heterogeneity method. This approach was selected in lieu of the random effects model as it maintained the weighted contribution of each trial, potentially reducing publication bias. The updated analysis yielded the same pooled relative risk for combined CVD events (RR 0.93; 95%CI, 0.74–1.16) as the fixed effects model, and was not statistically significant.

Only 3 of the 10 meta-analyses found any statistical difference in any CHD or CVD outcome. The divergent conclusions reached may be mediated by the studies included and excluded (Table 4).^{6,8,10,11,22,28,29,44–46} As discussed previously by Hamley,⁸ the most common diet-heart trials are the Rose Corn Oil trial, the Oslo Diet-Heart Study (ODHS), the Medical Research Council study, the Los Angeles Veterans Administration trial, the Finnish Mental Hospital Study (FMHS), the Sydney Diet Heart Study (SDHS), the Minnesota Coronary Study (MCS), the Diet and Reinfarction Trial, and the St Thomas Atherosclerosis Regression Study. Only 4 of the trials had an inclusion rate < 80%, most notably the FMHS, which had the lowest inclusion rate at 20% but was included in 2 of the 3 meta-analyses with negative findings on SFA and heart disease and is one of the 4 Core Trials in the Advisory.¹¹

Table 2 Findings from meta-analyses of randomized controlled trials exploring saturated fat and heart disease

Reference	Participants (no. of studies)	Intervention	Author's conclusion
Mozaffarian et al (2010) ⁴⁴	13 614 (8)	Replacement of SFA with PUFA	These findings provide evidence that consuming PUFA in place of SFA reduces CHD events in RCTs.
Ramsden et al (2010) ⁴⁵	11 275 (7)	Replacement of SFA with PUFA	Advice to increase n-6 PUFA intake is unlikely to provide the intended benefits and may increase the risks of CHD and death.
Hooper et al (2012) ²⁸	65 508 (24)	Reduced or modified fat	This review suggested that reducing saturated fat by reducing and/or modifying dietary fat reduced the risk of CV events.
Ramsden et al (2013) ¹⁰	13 308 (8)	Replacement of SFA with mostly LA	Selective substitution of n-6 LA for SFA is unlikely to be beneficial, particularly in patients with established CHD.
Schwingshackl and Hoffmann (2014) ⁴⁶	7150 (12)	SFA vs PUFA (secondary prevention)	In secondary CHD prevention, higher intakes of PUFA in replacement of SFA were not associated with risk reduction.
Hooper et al (2015) ²⁹	59 000 (15)	Reduced SFA	The findings are suggestive of a small but potentially important reduction in CV risk on reduction of SFA intake.
Ramsden et al (2016) ⁶	10 808 (5)	Replacement of SFA with LA	Replacement of SFA in the diet with LA lowers serum cholesterol but does not support the hypothesis that this lowers risk of death from CHD or all causes.
Harcombe et al (2016) ²²	62 421 (10)	Reduced or modified fat	Currently available RCT evidence does not support the current dietary fat guidelines.
Hamley (2017) ⁸	6045 (5)	Replacement of SFA with PUFA (mostly LA)	Available evidence from adequately controlled RCT suggest replacing SFA with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality, or total mortality.
Sacks et al (2017) ¹¹	2873 (4)	Replacement of SFA with PUFA	Lowering SFA and replacing it with vegetable oil rich in PUFA, primarily soybean oil, lowered CHD by 29%.

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; LA, linoleic acid; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; SFA, saturated fatty acids.

Table 3 The Finnish Mental Hospital Study (FMHS) design issues noted by meta-analysis authors

Reference	Author(s) comments
Ramsden et al (2010) ⁴⁵	"... patients were assigned by hospital and not randomized as individual patients ..."
Hooper et al (2012) ²⁸	"We did not include any cluster randomized trials in this review, and cross-over studies (such as the Finnish Mental Hospital Study, 1972) were excluded as this design would be inappropriate for assessing effects on cardiovascular events or mortality."
	"... inappropriate in a progressive condition such as cardiovascular disease."
Ramsden et al (2013) ¹⁰	"... was excluded because patients were assigned by hospital and not randomized as individual patients ..."
Hooper et al (2015) ²⁹	"Not randomized (cluster-randomized, but <6 clusters)."
Harcombe et al (2015) ⁵²	"... excluded, as they were not randomized. The Finnish study was also a cross-over trial. This is not appropriate for the examination of a long-term mortality, as deaths in the second phase may be due to conditions imposed during the initial phase."
Hamley (2017) ⁸	"Participants were allocated by hospital and were not individually randomized in FMHS, and while it has been suggested to be a cluster randomized trial, there would only have been 2 clusters and there is actually no mention of random allocation of the hospitals in the publications from the trial."

THE AMERICAN HEART ASSOCIATION PRESIDENTIAL ADVISORY ON DIETARY FATS AND CARDIOVASCULAR DISEASE

Despite a weak observational foundation, inconsistent RCTs, and 2 recent meta-analyses calling for reevaluation of the current SFA recommendations,^{6,8} in 2017 the AHA published a position statement that reestablished their 1961 stance on SFA and heart disease.¹¹ Based on 6 inclusion criteria, the AHA identified "4 trials that make up the core evidence on the basis of quality of study design, execution, and adherence" – also known as the 4 Core Trials (4CTs). The trials, listed in order of overall contribution (% weight), are the Finnish Mental Hospital Study (31.66%), the Oslo Diet Heart Study (27.95%), the Medical Research Council study (24.46%), and the Los Angeles Veterans Administration trial (15.93%).¹¹ Despite their inclusion into the Advisory meta-analysis, it appears that of the 4CTs, 3 did not meet the AHA's prescribed inclusion criteria for dietary control of intake for the intervention and control groups, while all 4 trials failed to meet the criteria for TFA intake (Table 5).^{47,49,54,55} The following section provides a discussion of the characteristics, designs, and limitations (primarily the lack of dietary control of the intervention and control groups and dominant confounding variables) of each of the

Table 4 The most common diet-heart clinical trials included in meta-analyses of randomized controlled trials exploring saturated fat and heart disease

Reference	RCO	ODHS	MRC	LA Vets	FMHS	SDHS	MCS	DART	STARS
Mozaffarian et al (2010) ⁴⁴		X	X	X	X		X	X	X
Ramsden et al (2010) ⁴⁵	X	X	X	X		X	X		X
Hooper et al (2012) ^{28,a}	X		X	X		X	X	X	
Ramsden et al (2013) ¹⁰	X	X	X	X		X	X		X
Schwingshackl and Hoffmann (2014) ⁴⁶	X	X	X			X		X	X
Hooper et al (2015) ²⁹	X	X	X	X		X	X	X	X
Ramsden et al (2016) ⁶	X	X	X	X		X	X	X	X
Harcombe et al (2016) ²²	X	X	X	X		X			
Hamley (2017) ⁸	X		X			X	X	X	
Sacks et al (2017) ¹¹		X	X	X	X				
Inclusion rate (%)	80	80	100	80	20	80	70	60	40

Abbreviations: DART, Diet and Reinfarction Trial; FMHS, Finnish Mental Hospital Study; LA Vets, Los Angeles Veterans Administration trial; MCS, Minnesota Coronary Study; MRC, Medical Research Council; ODHS, Oslo Diet-Heart Study; RCO, Rose Corn Oil trial; SDHS, Sydney Diet-Heart Study; STARS, St Thomas Atherosclerosis Regression Study; X, study included.

^aExcluded ODHS and STARS during sensitivity analysis.

Table 5 Inadequate control of confounding variables in the 4 Core Trials (4CTs)

4CTs (year)	TFA intake	Lack of control in diets and other variables
Turpeinen et al (1979) ⁴⁷	SFA group: consumed 9× more margarine	SFA group: more cardiotoxic medication, sugar intake, and smoking Overall: transient nature of the patient population led to less than 50% adherence to the trial
Leren (1970) ⁴⁹	PUFA group: “highly restricted” shortening, margarine, and hydrogenated oils	PUFA group: provided with counseling at hospital and in-home; consumed more fruits, vegetables, legumes, vitamin D, and omega-3
MRC (1968) ⁵⁴	PUFA group “forbidden” to use margarines and cakes	Adequately controlled trial
Dayton and Pearce (1969) ⁵⁵	PUFA group limited cakes, pastries, and biscuits	SFA group: more heavy smokers, fewer non-smokers, and consumed a vitamin E-deficient diet PUFA group: more than double the attrition; adherence was less than 50%

Abbreviations: MRC, Medical Research Council; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TFA, trans fatty acids.

4CTs, which undermines rather than supports their contention regarding the strength of their evidence for SFA recommendations.

Finnish Mental Hospital Study

The FMHS has been recognized as “one of the earliest and most convincing examples of the better efficacy of unsaturated than of saturated fat in reducing . . . heart disease.”⁵⁶ It was initiated in 1958 as a 12-year intervention trial that compared a diet high in PUFA with a diet high in SFA in 1222 patients from 2 psychiatric hospitals.^{47,48,57–59} The serum cholesterol-lowering diet (high PUFA) consisted of replacing milk with “filled milk,” switching butter for margarine (soft), and liberal use of vegetable oil (mostly soybean oil). The primary outcomes were coronary death and major or intermediate electrocardiograph changes. Serum cholesterol levels were consistently lower in the experimental group, by an average of 13% ($P < 0.001$). The pooled results of major and intermediate electrocardiograph changes plus CHD death were lower in men (47 in the control

vs 25 in the intervention)⁴⁷ than in women (46 in the control vs 27 in the intervention)⁴⁸; however, this finding was only statistically significant in men ($P < 0.008$).^{47,58}

One of the most unique features of the FMHS was the study design. It is the only diet-heart study to utilize a crossover design. The trial was carried out in 2 mental hospitals (N and K). During the first period (1959–1965), Hospital N served as the experimental group, whereas Hospital K served as the control group. The roles were reversed after 6 years. Although referred to as a randomized controlled trial or cluster-randomized trial in multiple publications,^{11,44,60,61} the FMHS is simply a crossover trial, as noted by the study authors,⁵⁸ and lacked randomization of the patients. Despite this common misconception, the FMHS was not included or specifically excluded from 8 of the 10 most recent meta-analyses of RCTs for lack of individual randomization, inadequate clusters, inappropriate design to study progressive diseases, and an inability to control for a carryover effect (Table 3).^{8,10,28,29,45,52} As a consequence of the transient nature of the study population,

only 36.4% of the men (246 of 676) and 20.6% of the women (122 of 591) completed both periods of the trial.^{47,48} Since the cluster design precluded participants acting as their own controls and the study was not randomized, multiple variables were uncontrolled and tended to disadvantage the control group, while benefiting the experimental group.

Parodi,⁴³ Ramsden et al,⁴⁵ and Hamley⁸ have previously detailed dominant confounders that likely contributed to the results of the FMHS. First, both control groups consumed more trans fat than the intervention groups. Ramsden et al⁴⁵ determined that Hospital K controls consumed 9 times, and Hospital N 3 times, more TFA than the experimental group. For Hospital K, this amounted to at least 2% more calories from TFA intake compared to the intervention group, which is associated with a 20%–32% increased risk of heart disease event or death.⁶² In a systematic review and meta-analysis of observational studies, de Souza et al⁷ found similar results for total trans fat but determined that industrial TFAs – the type used in the FMHS – were independently associated with a 42% increased risk of heart disease.

Second, psychotropic and antidepressant medication use was greater in the control groups. The Hospital N control group received 2.18 times more thioridazine. Thioridazine is cardiotoxic and can nearly double the risk of electrocardiograph abnormalities and sudden cardiac death,^{63,64} which were both endpoints in the study. Of note, the authors stated that electrocardiograph “was one of our principal means of detecting manifestations of CHD” ... and that “the most relevant changes in this respect are undoubtedly the Q (including QS) patterns.”⁴⁷ Specifically, thioridazine has been shown to increase QT-interval prolongation, ventricular arrhythmia, and sudden death to a greater extent than other antipsychotics.^{65,66} Furthermore, Ramsden et al⁴⁵ cited evidence that concurrent use of thioridazine with antidepressants can further exacerbate cardiac arrhythmias.

Third, in a 1972 Letter to the Editor, Rivers and Yudkin⁶⁷ noted that the Hospital K control group consumed 49% more sugar per day than the experimental group. Six years later, this disparity disadvantaged the Hospital N control group since they increased their sugar intake by 15%. Although not causal, 10%–24.9% of calories from added sugar have been associated with an increased risk of cardiovascular mortality (HR, 1.30; 95%CI, 1.09–1.55).⁶⁸

Lastly, the control group had 37 more smokers than the diet group (324 vs 287).⁴⁷ The authors believed the difference to be minimal; however, the smoking data was never considered during analysis. Furthermore, smoking data was not reported in

women participants – only the percentage of nonsmokers.⁴⁸

Oslo Diet Heart Study

The ODHS was conducted with 412 men aged 30–64 years with a previous myocardial infarction from 1956 to 1958. They were randomized 1–2 years later to a control group that consumed their normal diet or an intervention group that consumed a cholesterol-lowering diet low in animal fats and rich in vegetable oil.⁶⁹ After 5 years of intervention, serum cholesterol was 14% lower in the experimental group and there were significantly fewer major CHD relapses ($P=0.004$), but CHD mortality ($P=0.097$) and total mortality ($P=0.35$) did not reach statistical significance.^{69,70} When stratified by age, patients with high cholesterol and aged <60 years had greater risk of CHD mortality ($P=0.01$), whereas patients aged >60 years showed no association between higher cholesterol and CHD mortality.

The success of the ODHS cannot be attributed solely to the replacement of SFA by PUFA or the modification of either, as described by the Advisory.¹¹ According to Hooper et al,²⁸ the ODHS is at high risk for bias owing to an unclear blinding protocol, a systematic difference in care, and, most importantly, a distinct difference in other dietary factors.

Blinding is a well-established method for reducing bias in biomedical research. Knowledge can change behavior and blinding attempts to keep the participants, investigators, and outcome assessors unaware of the intervention and/or the outcome of concern. In Leren’s 1966 and 1970 publications,^{49,70} he acknowledged this lack of blinding and potential for bias, respectively: “In the diagnosis of acquired angina pectoris a personal bias may have been present” and “It should be remembered also that the classification of deaths was not carried out blindly, although it was performed according to precisely defined criteria.” Although speculative, the study author knew the patient assignments and made the determination that participants had experienced angina, the least objective measure, while criteria for sudden death, the most objective measure, remained the same in both groups.⁷⁰

Second, the experimental group benefited from continuous instruction and supervision by a dietitian, including home visits, letters, and phone calls.⁷⁰ This systematic difference in care can influence cardiovascular outcomes independent of other changes. A recent systematic review and meta-analysis of 34 studies with 5704 subjects determined that intervention by a registered dietitian compared to usual care improved typical measures of cardiovascular health, including total

cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, hemoglobin A1c, and body mass index.⁷¹

Lastly, the experimental group was counseled to make multiple dietary changes – to include increasing “salads, beans, peas, cabbage, carrots, fruits, and nuts” and “fish of all types, and all kinds of shell fish . . . whale beef” – while avoiding the use of sugar.⁷⁰ The experimental group was given sardines canned in cod-liver oil and soybean oil (15–30 g/d), which significantly increased vitamin D and omega-3 PUFA intake compared to the control group. Based on calculations by Ramsden et al,⁴⁵ this equates to at least 5 g/d of eicosapentaenoic acid + docosahexaenoic acid, which has been shown to independently reduce post-myocardial infarction sudden death. Most importantly, Leren⁷² noted that the typical Norwegian diet consisted of about 65 g/d of margarine, and since margarine intake was restricted in the experimental group, Ramsden et al⁴⁵ determined that the control group consumed up to 9.6% of total energy as TFA.

Medical Research Council Study

The Medical Research Council study involved 393 men (aged >60 years) recovering from a first myocardial infarction. They were randomly allocated to a normal diet or to an experimental diet characterized by low SFA and high PUFA.^{54,73} The experimental group were supplemented with 3 oz (85 g) of soybean oil and instructed to consume at least half unheated. The experimental diet reduced cholesterol by 22% after 6 months then slowly increased it over 5 years; however, cholesterol levels were at least 12% below baseline and at least 6% lower than in the control group. Fatal CHD events and major relapses were the same in both groups, but nonmajor relapses were lower in the experimental group (62 vs 74), albeit nonsignificant. Relapses were not associated with initial or follow-up serum cholesterol levels.

Similar to FMHS and ODHS, the Medical Research Council defined “forbidden foods” as “butter, other margarines, cooking fat, other oils, fatty meat, whole milk, cheese, egg yolk, and most biscuits and cakes.”⁵⁴ In practice, the experimental group decreased SFA, while unintentionally reducing TFA intake. Although the experimental group were allowed to have 14 g of “moderately unsaturated margarine” per day,⁵⁴ the control group most likely consumed more trans fat. Using margarine consumption as a surrogate marker of trans fat, Greaves and Hollingsworth⁷⁴ noted that margarine intake tripled from 1909 to 1953 (6lb [2.7 kg] vs 18lb [8.2 kg] per person per year) and slowly declined over the next 9 years. The average over this time was 15lb

(6.8 kg) per person per year or 4.6% of total calorie intake per day (average from 1953 to 1962). Since margarine contained 25%–40% TFA,⁷⁵ this would equate to 1.15%–1.84% of energy as TFA. This value most likely underestimates the total amount of TFA consumed, since shortening, breads, biscuits, and pastries are not included in this total.⁴⁵

Los Angeles Veterans Administration Trial

The LA Veterans trial is only one of 2 double-blind studies to test the diet-heart hypothesis. The trial lasted 8 years and the majority of the patients were enrolled for 6 years. In total, 846 male veterans were randomized to a control (n = 422) or experimental (n = 424) diet.⁵⁵ The control and experimental groups were fed in separate cafeterias from the rest of the hospital and each other.⁷⁶ The experimental diet was a high-PUFA diet characterized by replacing animal fats with vegetable oils, and butter with margarine (non-hydrogenated corn oil), using filled milk, and limiting eggs to 1 per day. The participants ranged from 55 to 89 years of age, with an average of 65.5 years. The primary endpoint was coronary artery disease as exhibited by sudden death or acute myocardial infarction. After about 8 years of intervention, serum cholesterol levels were reduced by approximately 13% in the experimental group, but there was no statistically significant difference in the primary endpoints of the study between the groups. However, when these data were pooled with secondary endpoints such as cerebral infarction, ruptured aneurysm, amputation, and others, statistical significance was reached. Deaths due to non-atherosclerotic causes were higher in the experimental group, so total mortality was similar in both groups.

As with the other AHA Core Trials, the LA Vets experimental group was instructed to reduce SFA and restrict TFA. Dayton and colleagues^{77,78} noted that animal fats, hydrogenated shortenings, and conventional margarines were replaced with equal amounts of unsaturated fat, to include un-hydrogenated corn oil-based margarine. Ramsden et al⁴⁵ estimated this difference in TFA intake to be about 2.1% of total energy. Despite randomization, other dominant confounders were present. For example, the control group included more heavy smokers (n = 25) and fewer nonsmokers (n = 17) and consumed only 16% of the recommended daily allowance for vitamin E compared to 149% in the experimental group, which is especially regrettable, since smoking increases vitamin E requirements⁷⁹; moreover, withdrawals were more than double in the experimental group, and adherence to the intervention diet was less than 50%.⁷⁷

In total, major confounding variables – such as concomitant changes in TFA, sugar, omega-3 fatty acids, smoking, and medication use – and potential bias – such as differences in care, adherence, attrition, and lack of blinding – introduced considerable limitations that make interpretation of their results challenging (Table 5).^{47,49,54,55} Based on the 4CTs alone, it is unclear whether the effects on heart disease were related to replacing SFA with PUFA and undermines the purported strength of this meta-analysis.

DISCUSSION

This narrative review aimed to provide an overview of the recent meta-analyses of dietary SFA and heart disease and provide a review and critique of the Advisory's 4 Core Trials leveraged as evidence for the AHA's dietary SFA recommendations. Meta-analysis, generally recognized as the pinnacle of the hierarchy of evidence,^{80,81} has become a popular statistical approach to systematically combine clinical trials. From 1995 to 2015, the United States published 16 581 meta-analyses – more than any other country.⁸² Since 2010, meta-analysis publications have increased by 132%⁸³ and comprise the most cited type of research.⁸⁴ The meteoric rise in meta-analysis publications has led the scientific community to scrutinize the quality and reliability of meta-analyses. Much of the criticism is related to the fact that meta-analyses evaluate the quantity, not the quality, of observations.^{83,85,86} A meta-analysis can only be as valid as the studies included in the review. In a 2017 editorial, Dr Milton Packer stated, "In the past, the favored approach was to depict these [patterns] in a narrative, but this task required insight into the details of each trial and a willingness to ask whether differences in design or execution might have contributed to differences in a study's findings. The current approach to meta-analysis requires no such intellectual effort; little knowledge is needed about any trial, except that it possesses certain minimum features."⁸⁵ Fagard et al⁸⁷ recommended that meta-analyses be approached with caution and meticulously evaluated to determine the risk of publication bias and the potential of malicious influence of inclusion and exclusion criteria. Two recent critiques of nutrition-related meta-analyses determined that individual studies were unreliable, did not meet predefined inclusion criteria, or lacked homogeneity.^{88,89} Most relevant to the discussion here, Leng⁹⁰ analyzed dietary fat and heart disease (secondary prevention) review publications from 1969 to 1984. It was determined that 82% (23/28) of reviews that presented supportive views of the diet-heart hypothesis underutilized and selectively cited available RCT evidence. Leng's analysis confirmed previous findings by Ravnskov.⁹¹ In

the earliest known review of publication or citation bias in cholesterol-lowering trials, Ravnskov determined that supportive trials were cited 40 times annually, whereas unsupportive trials were cited 7.4 times annually, despite having more trials published in a major journal.

To summarize, the Advisory¹¹ seemed to suffer from these same meta-analytical flaws. It only included 4 trials, 3 of the 4 trials did not meet 2 of their 6 inclusion criteria, all of the control/SFA groups in the 4CTs consumed greater TFA than the intervention/PUFA groups, and 3 of the 4CTs contained other major confounding factors (intermittent exposure to treatment diets, smoking, sugar intake, medication, and uncontrolled dietary factors such as vitamin D and omega-3 intake). Interestingly, the Advisory excluded 2 trials—the Minnesota Coronary Survey (MCS) and the Sydney Diet Heart Study (SDHS)—on account of TFA intake in the experimental group, even though 3 of the 4CTs exhibited this same flaw. However, in the Advisory, the disadvantage supported the diet-heart hypothesis. Eight of the 10 most recent meta-analyses included the SDHS, while 7 included the MCS (Table 4).^{6,8,10,11,22,28,29,44–46} Ramsden et al^{6,10} recovered data from the excluded trials and found that the SDHS and MCS provided evidence against the traditional diet-heart hypothesis. Despite a decrease in serum cholesterol for both studies (SDHS, 13.3%; MCS, 13.8%), all-cause mortality and CHD mortality were greater in the PUFA group (HR 1.62 and 1.74, respectively)¹⁰ or showed no benefit.⁶

Hamley⁸ accounted for the Advisory issues in his meta-analysis by differentiating trials as "adequately or inadequately controlled." His analysis included 5 adequately controlled trials, only 1 of which is included in the 4CTs from the Advisory Medical Research Council. Three of the 4CTs are listed as inadequately controlled for various reasons, including lack of randomization, multifactorial interventions, and lack of control of other variables such as trans fat, vitamin E, and the use of cardiotoxic medication.⁸ He concluded that adequately controlled trials failed to show a clear association between replacement of SFA with PUFA and CHD events, CHD mortality, or total mortality.

The preoccupation with the diet-heart hypothesis has led to an overemphasis of surrogate markers as the primary management tool in reducing heart disease, while neglecting the more meaningful clinical outcome measures such as total mortality, CHD mortality, and CHD events. For example, it is well established that SFA increases LDL-c, while replacing SFA with PUFA reduces LDL-c^{92,93}; however, SFA has not been causally linked to CHD events or mortality and recent evidence has also questioned the benefits of replacing SFA with PUFA (primarily LA).^{6,8,10} Focusing on surrogate

Table 6 Meta-analyses of studies of the effect of foods containing high saturated fat on cardiovascular health

Reference	Food product(s)	Main finding(s)
Soedamah-Muthu and de Goede (2018) ⁹⁶	Total dairy	Not associated with incidence of CHD
	Milk	Not associated with incidence of CHD and inversely associated with stroke
Guo et al (2017) ⁹⁷	High-fat dairy	Not associated with mortality, CVD, or CHD
Chen et al (2017) ⁹⁸	Cheese	Significantly associated with lower risk of CVD
Pimpin et al (2016) ⁹⁹	Butter	Not significantly associated with any CVD, CHD, or stroke
Alexander et al (2016) ¹⁰⁰	Eggs	Not associated with CHD and a reduced risk of stroke
O'Connor et al (2017) ¹⁰¹	Red meat	Does not negatively impact lipoprotein profiles or blood pressure
Wang et al (2015) ⁹⁴	Unprocessed red meat	Not associated with total mortality, CVD, or CHD
Khaw et al (2018) ⁹⁵	Coconut oil	Lowered LDL-c compared with butter; no difference in lipids compared with olive oil

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease, LDL-c, low-density lipoprotein cholesterol.

markers has, in turn, caused national agencies to concentrate on the overly simplistic model of single-nutrient recommendations as opposed to recognizing the complex nature of dietary behaviors. To underscore the lack of evidence supporting the link between dietary SFA intake and cardiovascular health, foods containing a high proportion of fat calories as SFA have largely failed to be associated with CVD outcomes (Table 6).^{94–101}

Despite the established recommendation to eliminate or reduce red meat, full-fat dairy products, butter, and eggs,²¹ recent meta-analyses have found that total dairy,⁹⁶ milk,⁹⁶ high-fat dairy,⁹⁷ cheese,⁹⁸ butter,⁹⁹ eggs,¹⁰⁰ and unprocessed red meat⁹⁴ are not associated with CVD outcomes.^{96–100} In 2 meta-analyses of RCTs, total red meat intake^{101,102} was not associated with cardiovascular risk factors. Coconut oil, which is the richest source of SFA at 92% of total fat, decreased LDL-c compared with butter and elicited no change in LDL-c compared with olive oil.⁹⁵ In the context of a healthy dietary pattern, saturated fat intake does not appear to be harmful. For example, a secondary analysis of a large randomized clinical trial (DIETFITS) found that participants with the greatest increase in the percentage of SFA intake experienced no detrimental effects to their lipid profile while consuming a diet of whole foods and low in refined carbohydrates.¹⁰³

CONCLUSION

This narrative review provides evidence from meta-analyses of observational studies and RCTs that saturated fat intake is not independently associated with the incidence of heart disease and that replacement of SFA with PUFA may not be beneficial despite reducing total- and low-density lipoprotein cholesterol. The clinical trials used by the AHA's Advisory to uphold their 1961 recommendation to reduce SFA and replace SFA with PUFA are plagued by design flaws, lacked dietary control of variables other than fat, and did not account for

trans-fat restriction in the high-PUFA groups. The Ramsden et al^{6,10} reanalysis of 2 sets of unpublished data, Hamley's⁸ meta-analysis of adequately controlled trials, the study selection bias in secondary trials noted by Leng,⁹⁰ and the Thornley et al⁵³ reanalysis and refutation of the Cochrane meta-analysis strongly challenge the traditional diet-heart hypothesis. The AHA stance regarding the strength of the evidence for the recommendation to limit SFAs to 5%–6% of kcal for those at risk of heart disease may be overstated and in need of reevaluation, especially since some foods with a high SFA profile may not exert LDL-c-elevating effects. The DIETFITS trial should serve as the primary example of the importance of focusing on whole foods instead of single nutrients.

Despite the evidence presented, the debate surrounding SFA and heart disease will continue. Whether SFA is a primary driver of heart disease or not, an evidence- and food-based model may be a more meaningful clinical approach to dietary recommendations. As described by Astrup et al,²⁷ recommendations from scientists and researchers to take the complex food matrix into consideration instead of individual nutrients are 9 years old. However, this whole-food approach has only been adopted by a few guideline-producing organizations. The most effective approach may be to provide a simple, straightforward message to the public on whole, unprocessed/minimally processed, nutrient-rich foods that is founded on the best available evidence. Meta-analyses are valuable tools for decision making; however, to determine the best available evidence, individual clinical trials need to be scrutinized to ensure design flaws and bias are adequately considered.

Acknowledgments

The author thank Dr Yunsuk Koh from the Robbins College of Health and Human Science at Baylor University; Dr Asma S. Bukhari from Walter Reed National Military Medical Center; Dr Julianna Jayne

from the Military Nutrition Division, US Army Research Institute of Environmental Medicine; Dr Adam Kieffer from the Army Medical Department Center and School, Health Readiness Center of Excellence; and William Konkright, doctoral student in the Neuromuscular Research Laboratory in the School of Health and Rehabilitation Sciences at the University of Pittsburgh, for encouragement and editorial services.

Author contributions. J.L.H. takes sole responsibility for the conceptual framework and content of this manuscript. The views and information presented are those of the author and do not represent the official position of the US Army Medical Center of Excellence, the US Army Training and Doctrine Command, the US Army Medical Command, or the Department of Army, Department of Defense, or US Government.

Funding. This research received no external funding.

Declaration of interest. The author declares no conflict of interest.

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