Annals of Nutrition and Metabolism

Systematic Review

Ann Nutr Metab 2021;77:4–15
DOI: 10.1159/000515058

Received: November 9, 2020
Accepted: February 3, 2021
Published online: March 31, 2021

Total Dietary Fat Intake, Fat Quality, and Health Outcomes: A Scoping Review of Systematic Reviews of Prospective Studies

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Keywords
Scoping review · Dietary fat · Fat quality · Systematic reviews · Health outcomes

Abstract
Introduction: We conducted a scoping review of systematic reviews (SRs) on dietary fat intake and health outcomes in human adults within the context of a position paper by the "International Union of Nutritional Sciences Task force on Dietary Fat Quality" tasked to summarize the available evidence and provide dietary recommendations. ***Methods:*** We systematically searched several databases for relevant SRs of randomized controlled trials (RCTs) and/or prospective cohort studies published between 2015 and 2019 assessing the association between dietary fat and health outcomes. ***Results:*** Fifty-nine SRs were included. The findings from SRs of prospective cohort studies, which frequently compare the highest versus lowest intake categories, found mainly no association of total fat, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), and saturated fatty acid (SFA) with risk of chronic diseases. SRs of RCTs applying substitution analyses indicate that SFA replacement with PUFA and/or MUFA improves blood lipids and glycemic control, with the effect of PUFA being more pronounced. A higher intake of total trans-fatty acid (TFA), but not ruminant TFA, was probably associated with an increased risk of mortality and cardiovascular disease based on existing SRs. ***Conclusion:*** Overall, the available published evidence deems it reasonable to recommend replacement of SFA with MUFA and PUFA and avoidance of consumption of industrial TFA.

Introduction

Worldwide, noncommunicable diseases, such as cardiovascular disease (CVD), cancer, and type 2 diabetes (T2D), account for over 70% of total deaths [1]. According to the Global Burden of Disease Study, suboptimal diet is the leading risk factor for about 50% of disabilities from CVDs [2].

In the past, recommendations to limit dietary fat intake to prevent chronic diseases were issued by many organizations and advisory bodies. For example, in 1980, the Dietary Guidelines for Americans (DGA) called for a limitation of dietary fat intake to <30% of total energy intake (TEI) [3] and changed to recommend "choose a diet

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that is low in saturated fat and cholesterol and moderate in total fat" to in 2000 and eliminated in 2015. The earlier recommendations were largely based on ecological studies and trials evaluating single intermediate disease markers, for example, serum total cholesterol (TC) levels. Compared to decades ago, the field of nutritional science now benefits from a richer repertoire of methodological approaches to assess diet-disease relationships, notably large, long-term prospective cohort studies and well-controlled randomized controlled trials (RCTs) which assess multiple clinical end points.

Systematic reviews (SRs) and meta-analyses (MAs) nowadays constitute the preferred methodology to summarize the body of available evidence for the development of dietary recommendations. They offer the possibility to synthesize a wealth of data, to explain inconsistencies or inconclusiveness, and to generate new knowledge by supporting valid and reliable conclusions based on scientific evidence. In the DGA 2015–2020, dietary recommendations were based on newly conducted SRs, existing SRs, and reports by federal agencies or leading scientific organizations [4]. However, the DGA have also been criticized for failing to take into account all available relevant scientific evidence (by omitting, e.g., available evidence on saturated fatty acid [SFA]) [5].

The scope of our review is to identify, describe, and summarize comprehensively the currently available evidence for total dietary fat or fat quality and risk of chronic diseases through collation and analysis of SRs of RCTs and prospective cohort studies published between 2015 and 2019. The rationale for focusing on this time frame was the large number of SRs of RCTs and cohort studies published between 2015 and 2019, which have not been subject to a comparable scoping review (ScR). Our ScR is the first in this research field and will serve as a basis for a position paper by the "International Union of Nutritional Sciences (IUNS) Task force on Dietary Fat Quality" that was tasked to summarize the available evidence and provide dietary recommendations.

Methods

We conducted this ScR in accordance with the methodology of the Joanna Briggs Institute's Reviewers' Manual [6]. For reporting, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for ScRs, the PRISMA-ScR statement [7].

Search Strategy

The databases MEDLINE (via Ovid), the Cochrane Database of Systematic Reviews, and Epistemonikos were searched from January 1, 2015 to December 31, 2019 for relevant articles (search conducted: February 19, 2020). The search strategy was developed and adapted for each database accordingly, and there was no restriction by language. The MEDLINE (Ovid), Cochrane Library, and Epistemonikos search strategy are presented in the online suppl. Appendix 1; see www.karger.com/doi/10.1159/000515058 for all online suppl. material. Moreover, forward citation tracking and reference checking from included documents were performed.

Selection of Studies

Inclusion Criteria

SRs fulfilling the following criteria were included in the ScR: (i) SRs of RCTs or prospective cohort studies, including nested case-control studies and case-cohort studies, involving adults as study participants published within the last 5 years (2015–2019). (ii) SRs focusing on interventions of or exposure to dietary fat (total fat) and/or fat quality, that is, SFA, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), trans-fatty acid (TFA) including industrial versus ruminant TFA, omega-6 (linoleic acid [LA] and conjugated linoleic acid [CLA]), omega-3 fatty acids (FAs) including eicosapentaenoic acid (EPA); docosahexaenoic acid (DHA); and α-linolenic acid (ALA), and dietary cholesterol. (iii) SRs reporting any of the following outcomes: all-cause mortality (ACM); chronic disease outcomes, such as CVD, coronary heart disease (CHD), and stroke; cancer, for example, breast, colorectal, gastric, endometrial, ovarian, pancreatic, and prostate cancer; T2D; hypertension; obesity; and intermediate disease markers, such as high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triacylglycerols (TG), systolic blood pressure, and diastolic blood pressure; glycemic control parameters, such as fasting glucose and glycosylated hemoglobin (HbA1c); C-reactive protein (CRP); and anthropometric outcomes, such as body weight (BW), fat mass, and waist circumference.

Exclusion Criteria

SRs that met any of the following criteria were excluded: (i) inclusion of solely critically ill and hospitalized patients, patients undergoing bariatric surgery, patients with eating disorders, or patients with T2D; inclusion of more than one-third of the patients/population suffering from CVD or cancer (due to the primary prevention focus of the IUNS Task force on Dietary Fat Quality position paper). (ii) Interventions/exposure with dietary supplements (for more than one-third of the population/patients); interventions/exposure including solely oils (e.g., olive oil) or solid fats (e.g., butter); or including circulating FAs as exposure. (iii) SRs of nonrandomized intervention trials, case-control, or cross-sectional studies.

Selection Process of Sources of Evidence

First, title and abstract screening was performed by 1 reviewer (J.Z.). Only clearly irrelevant references were excluded at this stage. Second, for all potentially relevant references, full-text publications were obtained and checked for final inclusion by 2 reviewers (J.Z. and L.S.) independently. Uncertainties were resolved through discussion with a third author (J.J.M.).

Data Extraction

For included SRs, 2 reviewers (J.B. and S.W.) extracted the study characteristics, and another reviewer cross-checked all extracted data (J.B., S.W., and L.S.). The following data were extract-

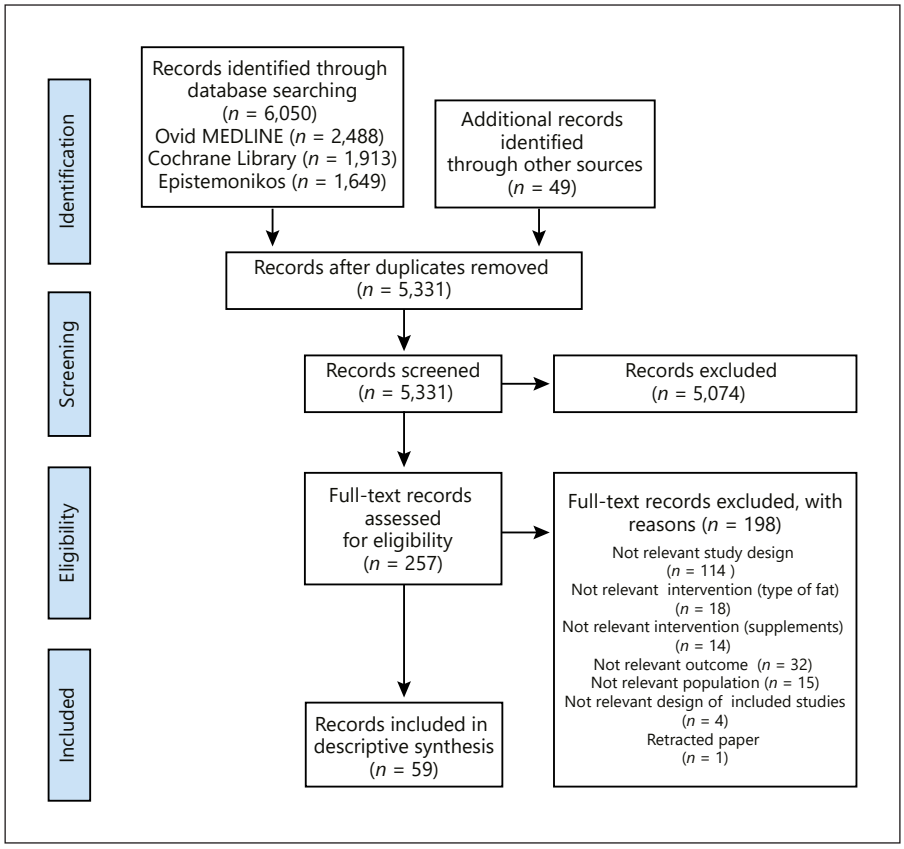

Fig. 1. Flow diagram showing study selection process.

ed: author, year of publication, aim of systematic review, design of included studies, number of included studies (for the corresponding outcomes), number of participants (for the corresponding outcome), description of participants/population, description of intervention/exposure, comparison parameter (e.g., high vs. low intake category), outcomes, direction of effect, certainty of evidence, search date of systematic review, and databases searched.

Data Categorization and Presentation

Besides a descriptive summary of the current research landscape on the effects and association of total dietary fat intake and fat quality with health outcomes, we visually displayed our results using a bubble plot. Bubble charts are used to highlight the main relationship between total dietary fat intake and fat quality by charting the intervention/exposure, the health outcomes assessed, and the study design.

Results

Out of 5,331 records identified by the literature searches, 257 records were assessed as full texts (Fig. 1; online suppl. Appendix 2). We excluded articles that failed to meet the required study design (RCTs and prospective cohort studies), which did not examine the interventions/exposures of interest, or that assessed outcomes or populations outside of the scope of this work. Finally, 59 SRs on total dietary fat intake and fat quality published in the last 5 years were included in the ScR [8–66].

Fifteen SRs included exclusively RCTs [18–20, 32, 34, 35, 45, 49–51, 53, 57, 60, 61, 63], 41 SRs solely prospective cohort studies [8, 10–14, 16, 17, 21–31, 33, 37–44, 46–48, 52, 54–56, 58, 59, 62, 64–66], and 3 SRs both study types [9, 15, 36]. The number of studies and participants for the outcomes in a SR varied between 1 [14, 31] and 99 [32] for studies and between 417 [51] and 1,786,537 [23] for participants. The types of participants varied across included SRs: whereas SRs of RCTs included mainly healthy and overweight/obese adults, SRs of prospective observational studies included mainly participants from the general population, whose characteristics were less well described. Types of interventions in the included SRs of RCTs encompassed low-fat diets (LFDs), diets rich in MUFA, PUFA, LA or dietary cholesterol, and diets replacing SFA by PUFA or MUFA. Types of total dietary fat intake and fat quality in the included SRs of prospective observational studies covered exposure intake of total fat, MUFA, PUFA, SFA, TFA (industrial, ruminant), ome-

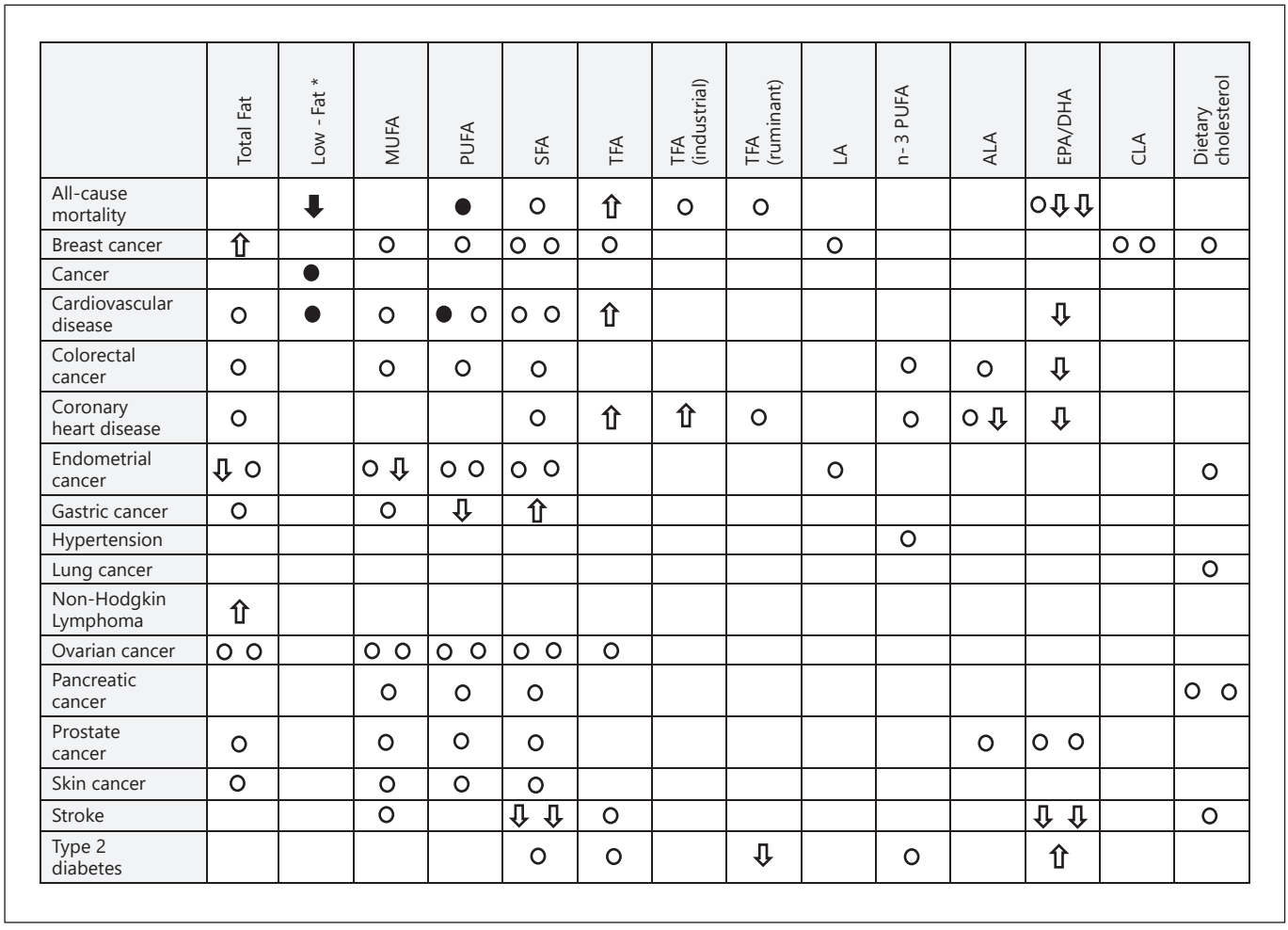

Fig. 2. Bubble plot showing the associations/effects between dietary fat/fat quality and patient relevant outcomes. Number of circles and arrows represent the number of studies. *As part of a weight-reducing diet vs. a control (nonweight reducing) diet. ALA, α-linolenic acid; CLA, conjugated linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acids SFA, saturated fatty acid; TFA, trans fatty acid; ACM, all-cause mortality; CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes; SRs, systematic reviews; RCTs, randomized controlled trials; CI, confidence interval. ⇧, SRs of prospective cohort studies: a positive association was shown (95% CI does not cross the null effect); ○, SRs of prospective cohort studies: there was no (significant) association; ⇩, SRs of prospective cohort studies: an inverse association was shown (95% CI does not cross the null effect); ●, SRs of RCTs: no (significant) effect (SRs of RCTs); ⬇, SRs of RCTs: a decreasing effect was shown (95% CI does not cross the null effect).

ga-6 (LA and CLA), omega-3 FA (EPA, DHA, and ALA), and dietary cholesterol. The majority of the included SRs conducted MAs comparing the highest versus lowest intake category.

Online suppl. Table 1 shows the general and specific characteristics of the included SRs. Associations and effects between health outcomes by study design and type of total dietary fat intake and fat quality are shown in Figures 2 and 3.

Health Outcomes Assessed in the Included Studies

In the SRs of RCTs, the investigated health outcomes included ACM, CVD, cancer, blood lipids, blood pressure, glycemic control, CRP, and anthropometric outcomes such as BW, fat mass, and waist circumference (Fig. 2, 3) [9, 15, 18–20, 32, 34–36, 45, 49–51, 53, 57, 60, 61, 63]. In the SRs of prospective observational studies, the investigated health outcomes included ACM, CVD (CHD and stroke), T2D, hypertension, and different types of cancer (breast, colorectal, endometrial, gastric,

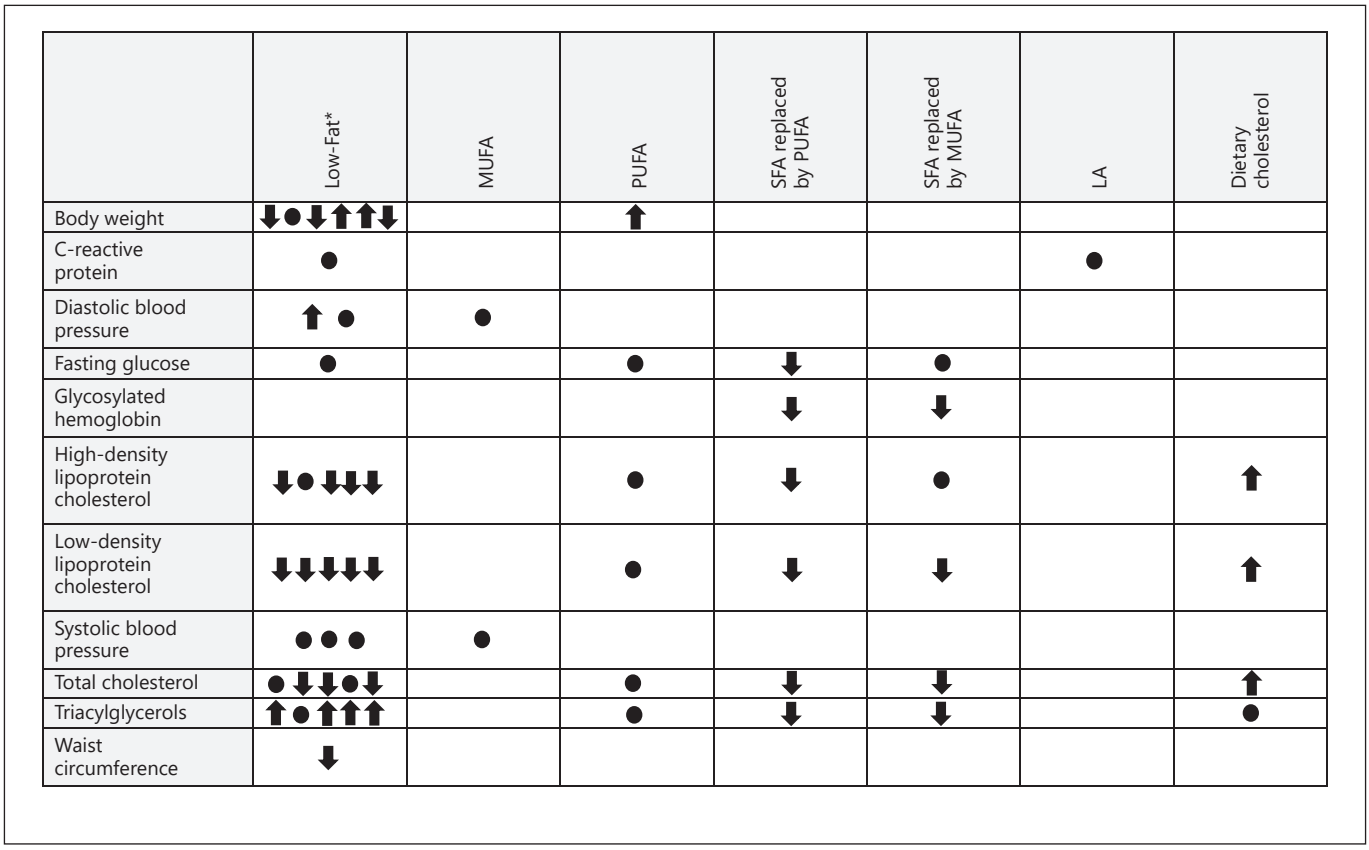

Fig. 3. Bubble plot showing the effects between dietary fat/fat quality and intermediate disease outcomes. Number of circles and arrows represent the number of studies. *Compared to lower carbohydrate/higher fat (presumably higher in SFA) diets.LA: linoleic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SRs, systematic reviews; RCTs, randomized controlled trials; CI, confidence interval; BW, body weight; CRP, C-reactive protein; FG, fasting glucose; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triacylglycerol; WC, waist circumference. ●, SRs of RCTs: no (significant) effect (SRs of RCTs); ⬇, SRs of RCTs: a decreasing effect was shown (95% CI does not cross null effect); ⬆, SRs of RCTs: a increasing effect was shown (95% CI does not cross null effect).

lung, ovarian, pancreatic, prostate, skin cancer, and non-Hodgkin lymphoma) [8–17, 21–31, 33, 36–44, 46–48, 52, 54–56, 58, 59, 62, 64–66].

Effects and Associations of Total Fatty Acids

In SRs of RCTs, MAs found that LFD (<30% dietary fat of TEI; and higher in carbohydrates) improves LDL-C and TC compared to lower carbohydrate/higher fat (presumably higher in SFA) diets, whereas a lower carbohydrate/higher fat diet performed better for HDL-C and TG [15, 19, 34, 57, 60]. In this regard in a SR of RCTs was shown that isocaloric replacement of carbohydrates by SFA raises TC, LDL-C, and HDL-C and reduces TG, whereas replacement of carbohydrates by MUFA and PUFA reduces TC, LDC, and TG and increases HDL-C [35]. The findings of LFD on anthropometric outcomes were inconsistent. One SR favored a LFD [15], whereas other SRs observed no significant differences [20, 57] or favored a lower carbohydrate/higher fat diet [19, 34]. One SR of RCTs found that weight reducing diets, usually low in fat and SFA, with or without exercise, may reduce premature ACM, but no effect on cancer and CVD risk in adults with obesity was observed [49] (Fig. 2, 3). In a majority of SRs of prospective observational studies, total fat intake was not associated with increased risk of ACM, CVD mortality, and several cancer types [14, 16, 17, 24, 27, 37, 39, 44, 46, 55, 62, 64] (Fig. 2).

Table 1. Available GRADE certainty of evidence ratings for total fat and fatty acids according to the investigated patient relevant outcomes and intermediate disease markers

	Total fat	MUFA	PUFA	SFA	Total TFA	TFA (industrial)	TFA (ruminant)
Patient relevant outcomes							
ACM	↓ high[†]	na	na	○ very low	↑ low	○ very low	○ very low
CVD (incidence/mortality)	○ high[†]	na	na	○ very low	na	na	na
CHD	na	na	na	na	↑ moderate	↑ very low	○ very low
Stroke	na	na	na	na	○ very low	na	na
T2D	na	na	na	○ very low	○ very low	na	↓ very low
Cancer (incidence/mortality)	○ very low[†]	na	na	na	na	na	na
Intermediate disease markers							
Blood lipids	na	↓ high[§]	↓ high[§]	na	na	na	na
BP	na	○ moderate	na	na	na	na	na
BW	↓ high[‡]	na	na	na	na	na	na
FG	na	na	○ moderate	na	na	na	na

na, not available; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TFA, trans-fatty acids; ACM, all-cause mortality; CVD, cardiovascular disease; CHD, coronary heart disease; T2D, type 2 diabetes; BW, body weight; BP, blood pressure; FG, fasting glucose; CI, confidence interval. [†] Weight loss interventions (usually low-fat diet and low SFA intake). [‡] Low-fat diet. [§] SFA replacement by MUFA and PUFA. ↑ A positive association was shown (95% CI does not cross the null effect); ↓ A inverse association was shown (95% CI does not cross the null effect); ○ there was no (significant) association.

Effects and Associations of MUFA

In SRs of RCTs, a higher MUFA (median: 20% of TEI) intake mainly substituting carbohydrates had no effect on blood pressure [61] (Fig. 3). In SRs of prospective observational studies, a higher overall MUFA intake was not associated with risk of CVD (and stroke) and several types of cancer [14, 16, 22, 24, 25, 27, 29, 37, 39, 55, 62, 64] (Fig. 2).

Effects and Associations of PUFA

In SRs of RCTs, a higher PUFA (≥6% of TEI) intake mainly substituting SFA and carbohydrates had little or no effect on ACM, CVD, blood lipids, and fasting glucose but leads to a slight increase in BW (0.76 kg) [53, 63] (Fig. 3). In SRs of prospective observational studies, a higher overall PUFA intake was not associated with risk of CVD, hypertension, and several cancer types [14, 16, 22, 24, 25, 27, 37–39, 55, 62, 64] (Fig. 2).

Effects and Associations of SFA

An isocaloric substitution (1 or 5% of TEI) of SFA with PUFA and MUFA improved TC, LDL-C, TG, and biomarkers of glycemic control [32, 35] (Fig. 3). Isocaloric replacement of carbohydrates with lauric acid, myristic acid, and palmitic acid raises TC, LDL-C, and HDL-C, and reduces TG [35]. Isocaloric replacement of carbohydrates with stearic acid did not affect blood lipids [35]. In a majority of SRs of prospective observational studies, a higher SFA intake was not associated with risk of ACM, CVD, T2D, and several cancer types [12, 14, 16, 22–25, 27, 36, 37, 39, 46, 62, 64]; however, it was inversely associated with risk of stroke [30, 65] (Fig. 2).

Effects and Associations of TFA

In SRs of prospective observational studies, a higher total TFA intake was associated with increased risk of ACM, CVD, and CHD but not with T2D, stroke, breast, and ovarian cancer [12, 37, 59, 64]. Higher industrial TFA intake was probably associated with CHD risk, whereas higher ruminant TFA intake showed no association with mortality and CVD and an inverse association with risk of T2D [12] (Fig. 2).

Effects and Associations of Omega-6 Fatty Acids

SRs of prospective cohort studies found no association between LA intake and risk of endometrial and breast cancer [39, 40] (Fig. 2). No effects were observed for CRP [50] (Fig. 3). We found no associations between risk for breast cancer and CLA intake [47, 59] (Fig. 2).

Effects and Associations of Omega-3 Fatty Acids

In SRs of prospective cohort studies, a higher intake of n-3 PUFA was not associated with CHD, hypertension, T2D, and colorectal cancer [38, 43, 48, 66]. Higher EPA/DHA intake was mainly inversely associated with risk of ACM, CVD, CHD, stroke, and colorectal cancer [11, 28,

41, 42, 48, 52, 55, 66] but had no effect on the risk for prostate cancer [8, 13] and was positively associated with T2D [43] (Fig. 2). We found no associations between risk for cancer and ALA intake [13, 55]. Higher ALA intake was inversely associated with risk of CHD [58] in one SR, whereas another SR observed no association [42].

Effects and Associations of Dietary Cholesterol

In SRs of RCTs, a higher dietary cholesterol intake was associated with raised blood lipid levels [9]. In SRs of prospective cohort studies, no association between higher dietary cholesterol intake and stroke or cancer risk was observed [10, 21, 31, 33, 54, 56].

Certainty of Evidence Ratings

Only 7 out of 59 SRs graded the certainty of the evidence [12, 15, 35, 42, 49, 61, 63] (Table 1). The beneficial effect of replacing SFA through MUFA and PUFA on blood lipid levels was rated as high certainty of evidence. The positive association between total TFA intake and CHD risk was rated as moderate certainty of evidence, whereas the positive association between total TFA intake and ACM was rated as low certainty of evidence.

Discussion

Summary of Findings

This ScR is the first to summarize the available SRs of RCTs and prospective observational studies on total dietary fat intake, fat quality, and health outcomes in human adults. Overall, 59 SRs published between 2015 and 2019 fulfilling our criteria were identified. The main SRs identified in our ScR found no evidence for an association of total fat intake with risk of ACM, CVD, and cancer. The findings from the included SRs of prospective cohort studies, which often compare the highest versus lowest intake categories, mainly found no association between MUFA, PUFA, and SFA intake and risk of chronic disease. However, SRs of RCTs applying substitution analyses indicate that SFA replacement with PUFA and/or MUFA improves blood lipids (high certainty of evidence) and glycemic control, with a more pronounced effect with PUFA replacement. Considering the types of SFA, isocaloric replacement of carbohydrates with lauric acid, myristric acid, and palmitic acid raises TC, LDL-C, and HDL-C and reduces TG, whereas stearic acid has little effect on blood lipids. Of note, the carbohydrate quality should be considered as well. Findings from cohort studies and RCTs showed that higher intakes of dietary fiber and whole grains indicate that the inverse relationships with several noncommunicable diseases could be causal [67, 68], whereas higher intakes of added sugar and refined starches have detrimental health effects [69–71].

A higher intake of total TFA was probably associated with an increased risk of ACM, CVD, and CHD. Higher industrial TFA intake was associated with CHD risk, whereas ruminant TFA intake showed no association with mortality and CVD and an inverse association with risk of T2D. In the past, evidence from RCTs has shown stronger detrimental effects of TFA on blood lipids than SFA [72]. A higher intake of EPA/DHA was inversely associated with risk of ACM, CVD, and stroke across SRs of prospective cohort studies. Unfortunately, only a few identified SRs graded the certainty of evidence. Moderate certainty of evidence suggests that a higher total TFA intake was associated with increased risk of CHD. High certainty of evidence suggests that SFA replacement by MUFA and PUFA improves blood lipid levels.

A Cochrane review that was excluded from our ScR due to the high number of secondary prevention trials included provides moderate certainty of evidence suggesting that a reduction of SFA and its replacement with PUFA reduces the risk of CVD [73]. Furthermore, the National Health and Nutrition Examination Survey showed that an isocaloric substitution (10% TEI) of SFA with PUFA or MUFA was inversely associated with overall mortality [74]. On the contrary, SFA intake was inversely associated with the risk of stroke in Asian populations [65, 75].

Global Fat Intake and Current Dietary Fat Recommendations

A systematic assessment of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group evaluating the consumption of dietary fat based on over 300 dietary surveys shows that the mean PUFA intake is approximately 6% and the mean SFA intake is approximately 10% worldwide [76]. In the European Prospective Investigation into Cancer and Nutrition cohort study, the mean total fat intake was ≥35% of TEI, among which ≥14% accounted for SFA, 10–13% accounted for MUFA, and 4–8% accounted for PUFA intake [77]. These data show that current intake of dietary fat exceeds dietary recommendations. Our ScR of 20 dietary guidelines shows that most of them recommend total fat intakes of 30–≤35% of TEI [78]. Most guideline organizations specified a quantitative range for SFA of between ≤7 (for patients with metabolic disorders) and ≤11% of TEI and further recommend replacement of SFA with MUFA and/or

PUFA [78]. Most organizations recommend complete avoidance of TFA or limit intake to ≤2% of TEI [78]. Only a few organizations give quantitative recommendations for MUFA or PUFA, which range between 10 and 25% for MUFA and between 5 and 11% for PUFA of TEI.

Comparison with Findings from Systematic Reviews on Oils and Solid Fats

The WHO guideline drafts on SFA and TFA have been recently criticized for not providing a food-based translation of the recommendations [79]. Analyzing the effects of SFA-rich foods on health outcomes, a MA of 16 intervention studies has recently shown that coconut oil consumption results in higher LDL-C than nontropical vegetable oils [80], whereas an SR of prospective observational studies found a relatively small or no associations of butter with mortality, CVD, and T2D [81]. An SR including both RCTs and prospective cohort studies observed that the intake of olive oil, which is a rich source of plant MUFA, could be beneficial for the prevention and management of T2D. Moreover, high phenolic olive oil may improve some cardiovascular risk factors stronger than refined olive oil [82, 83]. Higher consumption of canola oil results in a modest decrease in BW, whereas no significant effect was observed on other adiposity measures [84].

Finally, a network meta-analysis of 54 RCTs showed that, compared to butter, oils rich in unsaturated FAs such as safflower, sunflower, rapeseed, flaxseed, corn, olive, or soybean oil were more effective in reducing LDL-C. The network meta-analysis findings align with existing evidence on the metabolic effects of fat and support current recommendations to replace SFA-rich foods with unsaturated oils [85].

Another SR summarized the data related to foods high in SFA and risk of mortality [86]. Pooled risk estimates showed that higher intakes of milk, cheese, yogurt, and butter were not associated with risk of mortality than lower intakes. However, higher intakes of meat and processed meat were associated with an increased risk of ACM.

Strengths and Limitations

This ScR has several strengths. First, the inclusion criteria and the search strategy planned for this ScR enabled a broad, yet in-depth, view on the topic by taking into account both SRs of RCTs and prospective cohort studies based on an extensive search of 3 databases. We included a variety of dietary fats, including total fat, MUFA, PUFA, SFA, TFA, omega-3 and omega-6 FAs, and several health outcomes such as ACM, CVD, T2D, cancer, blood lipids, blood pressure, glycemic control, CRP, and anthropometric outcomes.

Limitations need to be considered as well. This review did not include studies focusing on dietary fat intake and health outcomes in vulnerable subgroups such as infant, children and adolescents, and pregnant and lactating women. A further limitation of our approach is its qualitative/nonquantitative findings. We did not evaluate the methodological quality of the identified SRs, and therefore, the methodological quality may vary substantially. Overall, the generalizability of our findings is limited because in our ScR: (i) SRs were only included if more than two-thirds of the included studies in an SR focused on dietary intake of fat rather than fat from dietary supplements and included less than one-third study participants with secondary prevention of CVD or T2D; (ii) SRs focusing on health outcomes such as metabolic syndrome, dementia, CKD, or respiratory diseases among others were omitted; (iii) we did not cover the full spectrum of possible dietary fat intake since we excluded SRs focusing on the consumption of omega-3 supplements, specific oils, and solid fat intake or other fatty foods. Several MAs of RCTs have shown either no effect or only very small benefits of omega-3 supplements on CVD risk [87, 88]. Focusing on foods rather than nutrients has been suggested recently also by Astrup and colleagues [89]. SR of prospective cohort studies has shown mainly no detrimental association between SFA-rich foods such as dairy or chocolate and risk of noncommunicable diseases [68, 90–95]. To improve the trustworthiness of such food-disease associations, rating the certainty of evidence [96, 97] and the use of novel statistical methods (e.g., substitution analyses or network MAs) is highly recommended [98, 99]; (iv) SR of prospective cohort studies frequently compared the highest versus lowest intake categories, whereas conducting dose-response (linear and nonlinear) MAs and substitution analyses would be more informative [100]. The SRs findings of RCTs also need to be interpreted with caution since not all primary studies were based on isocaloric substitution, and replacement with other dietary fats, carbohydrates, and/or protein might differ substantially between study arms.

Conclusion

SRs of prospective cohort studies mainly found little or no association of MUFA, PUFA, and SFA with risk of chronic disease but suggest to a positive association between higher intake of total TFA and an increased risk of ACM, CVD, and CHD but not ruminant TFA. Evidence

from RCTs has shown stronger detrimental effects of TFA on blood lipids than SFA. Substitution analyses indicate that SFA replacement with PUFA and/or MUFA improves blood lipids and glycemic control across bodies of evidence from RCTs. Overall, current recommendations to replace SFA with MUFA and PUFA and avoid the consumption of industrial TFA seems reasonable.

Acknowledgements

We are grateful to the members of the IUNS Task force on Dietary Fat Quality [Prof. Tom Brenna, Prof. Irina Kovalskys, Prof. Alice Lichtenstein, Prof. Ronald Mensink, Prof. Ladda Mo-Suwan, Prof. Marius Smuts, Prof. Shoichiro Tsugane, and Prof. Yang Yuexin] for their critical review of this article and insightful comments.

Statement of Ethics

Ethics Committee approval was not required since this paper is a systematic review, and no experimental procedure was performed in human beings.

Conflict of Interest Statement

L.S.: is a member of the GRADE working group; B.N.: is a member of the GRADE working group; J.J.M.: is a member of the WHO Nutrition Guidance Expert Advisory Group; Director, Freiburg GRADE Center. Other others declare that they have no conflict of interest to declare.

Funding Sources

International Union of Nutritional Sciences.

Author Contributions

L.S., J.Z., J.B., S.S.W., H.H., B.K., and J.J.M. designed the research. L.S., J.Z., and J.B. analyzed the data and wrote the first draft of the paper. L.S., J.Z., J.B., S.S.W., H.H., B.K., and J.J.M. interpreted the data, read the manuscript, and approved the final version. L.S. and J.J.M. are guarantors.

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