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Clinical Outcomes of Dietary Replacement of Saturated Fatty Acids with Unsaturated Fat Sources in Adults with Overweight and Obesity: A Systematic Review and Meta-Analysis of Randomized Control Trials

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Keywords
Obesity · Dyslipidemia · Dietary fat

Abstract
Background: Obesity and dyslipidemia are frequently treated with dietary interventions before pharmacotherapy is given. Diets high in unsaturated fat have proven advantageous to disease treatment. ***Aims:*** The purpose of this systematic review and meta-analysis was to assess the evidence of the effect of saturated fatty acids (SFA) replacement with unsaturated fatty acids (UFA) in metabolically healthy adults with overweight and obesity on markers of dyslipidemia and body composition. ***Methods:*** Keyword search was performed in PubMed, CINAHL, and Cochrane Library for randomized controlled trials (RCTs) evaluating the effects of fatty acid substitution in adults with overweight and obesity. Meta-analysis was performed on interventions assessing lipoprotein levels and body composition. Publication bias was assessed by funnel plot inspection, Begg's, and Egger's test. ***Results:*** Eight RCTs enrolling 663 participants were included in the review, with intervention durations between 4 and 28 weeks. Although nonsignificant ($p = 0.06$), meta-analysis found UFA replacement to reduce total cholesterol concentrations by 10.68 mg/dL (95%CI –21.90 to 0.53). Reductions in low-density lipoprotein cholesterol and triglycerides were statistically nonsignificant. ***Conclusions:*** Due to null results and a small number of studies included, there is no strong evidence that replacement of SFA with UFA may benefit lipid profiles in this population.

Introduction

In the United States, 35.5% of adults are currently affected by obesity [1], a condition linked to over 20 comorbidities such as cardiovascular disease (CVD), type 2 diabetes (T2DM), and hyperlipidemia [2]. Hyperlipidemia is defined by low levels of high-density lipoprotein cholesterol (HDL-C), or elevated concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) or triglycerides (TG). Lipid dysregulation affects 31.7% of adults living in the United States [3]. High cholesterol levels (both TC and LDL-C) are risk factors for the development of CVD and stroke due to their role in atherosclerotic progression [4].

The rise in the prevalence of obesity is partially attributed to decreased physical activity levels and poor dietary choices [5]. Research has linked a western diet, high in sat-

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urated fatty acids (SFA), commonly found in animal products such as red meat, butter, and dairy products, to weight gain and heightened metabolic risk [6]. The 2015–2020 Dietary Guidelines for Americans recommend obtaining no more than 10% of total daily energy from SFA [7]. An even lower percentage, 5–6%, is recommended by the American Heart Association for individuals with high TC [8]. This guidance is due to evidence linking a low-SFA diet with reduced risk of CVD. Serum cholesterol values are often used as a predictor for CVD risk, as high TC and LDL-C are strong predictors of CVD mortality [9]. Current strategies to manage cholesterol levels include a combination of pharmacotherapy and dietary modifications, the former being implemented after no benefit was achieved by the latter. Dietary patterns such as the Mediterranean and Dietary Approaches to Stop Hypertension diets have become increasingly popular with both practitioners who tailor dietary recommendations to their patients and individuals trying to lose weight and manage cholesterol levels [10, 11]. Among other recommendations, the Dietary Approaches to Stop Hypertension and Mediterranean diets emphasize SFA reduction with a concurrent increase in mono- and poly-unsaturated fatty acids (UFA) [12]. Monounsaturated (MUFA) and polyunsaturated fats (PUFA) are common in foods such as nuts, non-tropical plant oils, and cold-water fish. These UFA can lower CVD risk through the reduction of *de novo* cholesterol synthesis when consumption is increased [13]. Elevated UFA consumption may be more beneficial in reducing serum cholesterol levels than a low-fat diet alone [14]. It is standard practice for registered dietitians and health care providers to recommend diets high in UFA and low in SFA but often only after a patient has been diagnosed with dyslipidemia or CVD. Indeed, many studies and reviews confirm the effectiveness of SFA replacement with UFA for CVD risk reduction but these studies and reviews have been conducted among populations with preexisting diagnoses [15, 16].

A growing area of research focuses on persons with obesity who, despite excess adiposity, are considered to be metabolically healthy due to an absence of comorbidities [17–19]. In order to prevent weight gain and development of chronic disease, lifestyle modifications, such as changes in diet and exercise habits, are often the first recommendations given by health care professionals [20]. Behavioral changes are preferred over pharmacological or surgical interventions but can be difficult to implement and ensure compliance. However, interventions involving UFA replacement for SFA in individuals who are overweight and with obesity have been linked to both positive [21, 22] and null [23, 24] metabolic outcomes. To our knowledge, no systematic review has been conducted on the effect of dietary replacement of SFA with UFA in metabolically healthy individuals with excess body weight (BW). The purpose of this systematic review and meta-analysis was to evaluate the effectiveness of dietary modifications in the form of SFA replacement with UFA, in the forms of both MUFA and PUFA on serum cholesterol levels and body composition outcomes in metabolically healthy adults with overweight or obesity.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines [25]. The 2009 PRISMA checklist is available in the online supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000477216).

Study Eligibility Criteria

Studies that met the following criteria were included in the review: adults (≥18 years of age) meeting criteria for overweight and obesity (body mass index [BMI] ≥25 kg/m^2, or waist circumference [WC] ≥94 cm for men or ≥80 cm for women [26], or waist-to-hip ratio ≥0.96 for men or ≥0.81 for women) [27] without diagnosis of metabolic disease, enrolled in randomized control trial (RCT) interventions that included dietary replacement of SFA with UFA within the setting of a controlled feeding study or among free-living individuals. Interventions that focused on management of chronic conditions such as CVD or diabetes were excluded. Short-term studies with intervention duration less than 1 week were excluded.

Search Strategy

PubMed, CINAHL, and Cochrane Library were searched from database inception through June 24, 2016 using different combinations of keywords: saturated fat, unsaturated fat, obesity, overweight, and cholesterol. After acquiring initial search results, title and abstracts of articles were evaluated for suitability. Then, full-text articles were retrieved and assessed for inclusion. A cited reference search (forward reference search) and a reference list search (backward reference search) were also conducted based on the eligible articles identified through keyword search. Articles obtained through forward/backward reference search were screened and evaluated using the same study selection criteria. The reference search was repeated on all newly identified articles until no additional articles were found. Two authors (B.A.H. and S.V.T.) jointly determined the inclusion and exclusion of all articles retrieved for full text evaluation and resolved discrepancies through discussion. Interrater agreement was determined using Cohen's κ. The literature search was conducted following quality standards of Littell [28].

Data Extraction

The review team extracted the following information from each article included in the review: authors, year published, study design, dietary treatment information (specifically the percentages of SFA and UFA), intervention duration, participant characteristics (e.g., gender, age), number of participants who completed the study, and

pre- and post-intervention mean values and SDs of outcome measures. When needed, TC, LDL-C, and HDL-C were converted from mmol/L to mg/dL by multiplying by 38.67, and TG were converted from mmol/L to mg/dL by multiplying by 88.57 [29].

Meta-Analysis

Meta-analysis was performed on each outcome of interest, including TC, LDL-C, HDL-C, TG, BMI, body fat percentage (BFP), BW, fat mass (FM), and WC. Two studies [30, 31] included multiple intervention arms that were relevant to this review, but experimental groups were combined in meta-analysis. Heterogeneity between studies was assessed using the I^2 index. An I^2 index greater than 50% was considered to indicate substantial heterogeneity in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [32]. For studies with substantial heterogeneity, random effects models were used to estimate pooled effect sizes and 95% CIs. Fixed effects models were used when I^2 statistics was less than 50%. Subgroup analysis was performed within energy-restricted and energy-balanced diets. Meta-regression was conducted on TC, LDL-C, HDL-C, TG, and WC with intervention duration as the covariate. Publication bias was assessed by funnel plot inspection, Begg's test, and Egger's test. If necessary, SDs were imputed from standard error of CIs from the original publication. Statistical analyses were conducted using RevMan, version 5.3.5 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata, version 14.1 (StataCorp, College Station, Texas, USA).

Sensitivity Analysis

Study outliers were identified through sensitivity analysis of the four primary outcomes, where pooled effects were calculated after sequential removal of each article included in the meta-analysis. A study was considered to be an outlier if the resulting pooled effect size was ≥10% different from the overall pooled effect size.

Study Quality Assessment

Seven dichotomous questions (1 = yes, 0 = no) were used to assess individual study quality, adapted from Wu et al. [33]. The studies were given a score between 0 (lowest quality) and 7 (highest quality) based on a sum calculated for the following: (1) a control group was used, (2) statistically nonsignificant differences existed between baseline characteristics of control and treatment groups, (3) a high-SFA run-in period was used, where all participants were fed the same diet before randomization, (4) measurement tools for data collection were clearly explained in the methods section, (5) all potential confounders were controlled for, (6) study procedures were well defined, and (7) bias was adequately controlled. The Cochrane Risk of Bias tool was used to assess individual study bias. Each study was rated as low risk (listing of methods used to properly control bias), high (bias not controlled), or unclear (if methods were not explicitly stated) on the categories of randomization, blinding procedures, attrition reporting, incomplete outcome data, and selective reporting.

Results

Literature Search

The PRISMA flowchart describing the article selection process is presented in Figure 1. A total of 1741 articles (597 from PubMed, 871 from Cochrane Library, and 273 from CINAHL) were identified from keyword search, in which 1650 were excluded in title/abstract review. Common reasons for exclusion included studies conducted in animals, children, or adults with a chronic disease, or if dietary replacement did not involve UFA. The remaining 90 articles were selected for full-text review, during which 81 articles were excluded for not meeting study selection eligibility criteria. Reasons for exclusion included studies involving postprandial or acute outcomes, studies without an intervention, interventions that did not include SFA replacement, interventions that were not applicable to the review (i.e., behavioral or physical activity intervention), outcome measures were irrelevant to this review, or participants that did not meet the inclusion criteria. These are presented in online supplementary Table 1. Eight articles were determined to be eligible following full-text review. The interrater κ score was 0.93.

Characteristics of Included Studies and Participants

Table 1 summarizes characteristics of included studies. All 8 studies included in the review were RCTs, with intervention durations between 4 and 28 weeks. The included studies were published between 1999 and 2014, and involved a total of 663 participants. Three studies enrolled only men [31, 34, 35]. Three studies included ad libitum diets where compliance was monitored using food logs or communication with a registered dietitian or research staff [31, 34, 36]. The other 5 studies were controlled feeding studies, and all food was provided to the subjects over the course of the intervention [35, 37–40]. All studies enrolled a control group that was provided a diet high in SFA. Three studies included a high-SFA run-in period for all subjects [34, 37, 40]. Five studies utilized energy-restricted diets in both control and experimental conditions [31, 35, 36, 38, 39]. All 8 interventions were isocaloric between the control and experimental diets, and experimental diets contained an increased proportion of UFA in the form of a combination of MUFA and PUFA. MUFA were provided in the form of olive oil [37, 40], almonds, and canola oil-enriched biscuits [36], and both tree nuts and avocados were included [35]. PUFA were provided in the form of peanuts [31], sunflower seed oil [38], and encapsulated oils [39]. The high-SFA diets contained 14–24% of total energy from saturated fat. Replacement diets substituted SFA only for MUFA [34, 35, 38, 40], only for PUFA [39], or for a mixture of PUFA and MUFA [31, 36, 37]. All studies included a baseline measure of body composition and obtained serum lipid levels.

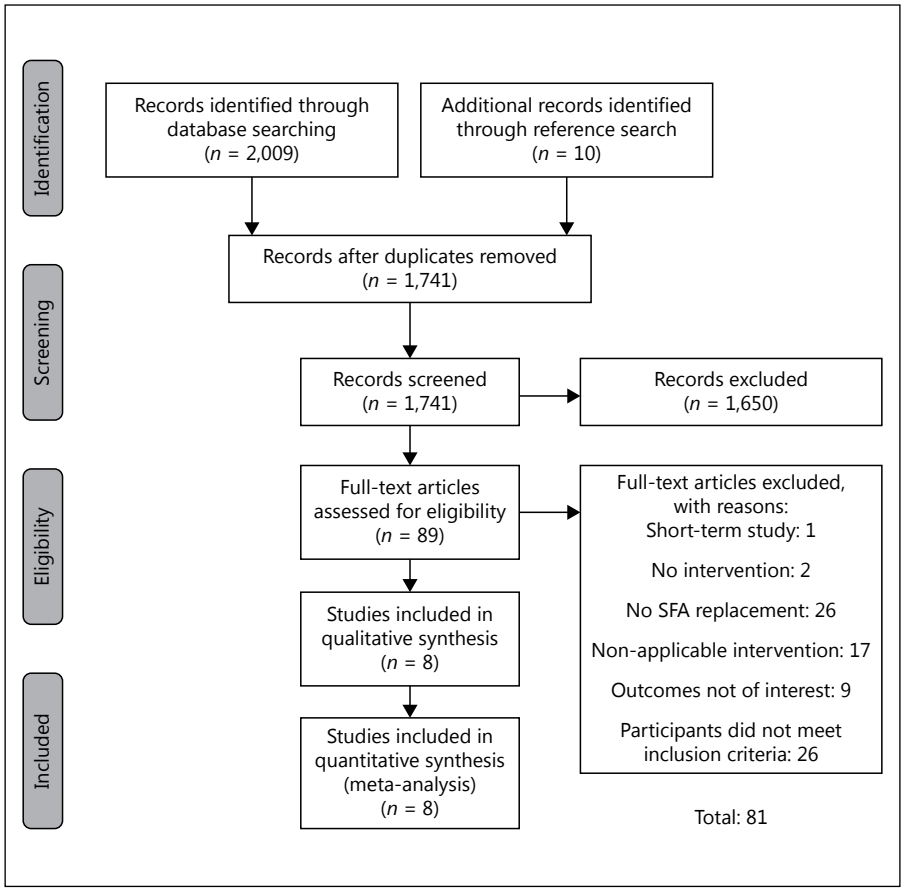

Fig. 1. PRISMA study search flowchart.

Eight studies reported significant reductions in TC, LDL-C, TG, and BW in the subjects consuming high-UFA diets. One study reported null results [39]. Piers et al. [35] reported a significant difference in TC and LDL-C reduction in the high-UFA diets compared to those rich in SFA.

Effects of SFA Replacement on Serum Cholesterol Levels

Table 2 reports results from meta-analysis on the effects of SFA replacement on serum cholesterol levels. Replacement of dietary SFA with UFA was found to reduce TC concentrations by 10.68 mg/dL (95% CI –21.90, 0.53, I^2 = 95%, p = 0.06). The pooled estimates of the effect of SFA replacement with UFA on serum concentrations of LDL-C (–8.70 mg/dL, 95% CI –19.17, 1.77, I^2 = 96%, p = 0.10), HDL-C (1.15 mg/dL, 95% CI –4.57, 6.86, I^2 = 98%, p = 0.69), and TG (–9.07 mg/dL, 95% CI –23.55, 5.42 I^2 = 96%, p = 0.22) were also statistically nonsignificant. Forest plots are presented in Figure 2.

Subgroup analysis for studies involving energy restriction found negative, although nonsignificant, pooled effect estimates for TC (–12.13 mg/dL, 95% CI –27.13, 2.88, I^2 = 97%, p = 0.11), LDL-C (–8.52 mg/dL, 95% CI –22.12, 5.08, I^2 = 97%, p = 0.22), HDL-C (–0.79, 95% CI –2.34, 0.77, I^2 = 71%, p = 0.32), and TG (–14.66 mg/dL, 95% CI –38.20, 8.87, I^2 = 95%, p = 0.22) in calorie-restricted studies. In energy-balanced studies, pooled effect sizes for TC (–10.48 mg/dL, 95% CI –27.28, 6.31, I^2 = 80%, p = 0.22) and LDL-C (–9.21 mg/dL, 95% CI –23.19, 4.76, I^2 = 75.4%, p = 0.2), HDL-C (5.84 mg/dL, 95% CI –10.74, 22.41, I^2 = 98%, p = 0.49), and TG (–2.12 mg/dL, I^2 = 95%, p = 0.74) were not significantly different between experimental groups. Subgroup effect sizes were not statistically different from the overall pooled effect sizes when tested at a significance level of 0.05. Forest plots for subgroup analysis are available in the online supplementary material.

Random-effect meta-regression calculations resulted in nonsignificant associations between intervention du-

Table 1. Characteristics of included studies

Reference	Participants, BMI kg/m^2	Study duration, weeks	Experimental groups	Fatty acid composition of diets	Energy restriction	Compliance assessment
Bos et al. [37], 2010	57 (42% M), 27.3	10	High SFA diet, high MUFA diet, mediterranean style diet	High SFA: 19.2% SFA, 10.7% MUFA, 5.4% PUFA; high MUFA: 10.9% SFA, 20.3% MUFA, 7.0% PUFA; Med: 10.7% SFA, 21.4% MUFA, 6.5% PUFA	No	Controlled feeding study
Hartwich et al. [38], 2009	99 (35% M), 34.6	12	High-fat SFA-rich diet, high-fat MUFA-rich diet All diets had 38% energy from fat	Not specified	Yes	Controlled feeding study
Krauss et al. [34], 2006	178 (M only), >25	12	High carb-low SFA diet, low carb-high MUFA diet, low carb-high SFA diet	High carb-low SFA: 7% SFA, 13% MUFA; low carb-high MUFA: 9% SFA, 27% MUFA, 5% PUFA; low carb-high SFA: 15% SFA, 20% MUFA, 6% PUFA	No	Participants given menus, compliance checked
Kriketos et al. [39], 2001	52 (35% M), 32.4 (M), 34.1 (F)	15	SFA-rich diet, omega-3 diet, omega-6 diet	SFA diet: ratio of polyunsaturated: saturated (P:S) of 0.25; omega-3 and omega-6 diet had (P:S) ratio of 1.0	Yes	Controlled feeding study
Moreira Alves et al. [31], 2014	65 (M only), 29.8	4	Control diet (CT), conventional peanut supplement (CVP), high-oleic peanut supplement (HOP)	CT: 22% SFA, 36% MUFA, 34% PUFA; CVP: 16% SFA, 51% MUFA, 32% PUFA; HOP: 13% SFA, 83% MUFA, 4% PUFA.* *Percentages as part of 30% total energy from fat in diets	Yes	Two 3-day food records
Noakes and Clifton [36], 2000	72 (7% M), 31.2	12	Very low fat diet (10% of energy from fat), High SFA diet (HSF) (32%), high-unsaturated fat diet (HUF) (32%)	VLF: 3% SFA, 3% MUFA, 2% PUFA; HSF: 17% SFA, 10% MUFA, 3% PUFA; HUF: 6% SFA, 17% MUFA, 7% PUFA	Yes	18 day food records
Piers et al. [35], 2003	8 (M only), >25	4	SFA-rich diet, MUFA-rich diet Both diets provided 40% energy from fat	SFA-rich: 24% SFA, 13% MUFA, 3% PUFA; MUFA-rich: 11% SFA, 23% MUFA, 6% PUFA	Yes	Controlled feeding study
van Dijk et al. [40], 2009	20 (50% M), 26.1 (SFA diet), 28.3 (MUFA diet)	10	SFA-rich diet or MUFA-rich diet with 31% total energy from fat	SFA-rich: 19% SFA, 11% MUFA; MUFA-rich: 11% SFA, 20% MUFA	No	Controlled feeding study

ration (in weeks) and serum lipid levels. The relevant regression coefficients for TC, LDL-C, HDL-C, and TG were 0.34 ($p = 0.75$), –0.73 ($p = 0.41$), –0.03 ($p = 0.94$), and 0.91 ($p = 0.09$), respectively.

Effects of SFA Replacement on Body Composition

Table 3 reports results from the meta-analysis on the effects of SFA replacement on BMI, BFP, BW, FM, and WC. No effect sizes were found to be statistically significant. Subgroup analysis revealed a significant effect size for WC in energy-restricted studies, in favor of the SFA diet (1.58 cm, $I^2 = 37\%$, $p = 0.02$). Forest plots are available in the online supplementary material.

Meta-regression found no significant associations between intervention duration (in weeks) and body composition measures. The relevant regression coefficients for BFP, BW, and WC were 0.17 ($p = 0.37$), 0.17 ($p = 0.46$), and 0.76 ($p = 0.62$), respectively.

Sensitivity Analysis

Sensitivity analysis revealed the pooled effect size changed by ≥10% following individual study omission for 7 out of 8 studies for TC, 6 out of 8 for LDL-C, 5 out of 8 for HDL-C, and 5 out of 8 for TG. However, none of the pooled effect sizes observed during sequential omission of studies were significantly different from the overall effect size for any of the 4 outcomes at a significance level of 0.05. The removal of Moreira Alves et al [31] resulted in a significant effect of the UFA diet over the SFA diet for TC ($p = 0.02$) and LDL-C ($p = 0.04$). Removal of

Table 2. Pooled estimate effect sizes for selected lipid outcomes

Study sample	Outcome, mg/dL	Studies included	Effect size	95% CI	I^2, %	*p* value
All	TC	8	−10.68	−21.90 to 0.53	95.0	0.06
All	LDL-C	8	−8.70	−19.17 to 1.77	96.0	0.10
All	HDL-C	8	1.15	−4.57 to 6.86	98.0	0.69
All	TG	7	−9.07	−23.55 to 5.42	96.0	0.22
ER	TC	5	−12.13	−27.13 to 2.88	97.0	0.11
ER	LDL-C	5	−8.52	−22.12 to 5.08	97.0	0.22
ER	HDL-C	5	−0.79	−2.34 to 0.77	71.0	0.32
ER	TG	5	−14.66	−38.20 to 8.87	93.0	0.22
EB	TC	3	−10.48	−27.28 to 6.31	80.0	0.22
EB	LDL-C	3	−9.21	−23.19 to 4.76	75.4	0.20
EB	HDL-C	3	5.84	−10.74 to 22.41	98.0	0.49
EB	TG	2	−2.05	−14.17 to 10.07	90.0	0.74

Random effects model used for all.

ER, energy restriction; EB, energy balance; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

4 studies resulted in a nonsignificant effect of the UFA diet for TG [31, 37–39]. Full results from the sensitivity analysis are presented in online supplementary Table 2. Study heterogeneity, shown by the I^2 value, was not substantially altered for any outcome.

Publication Bias

No evidence of publication bias was identified for any outcomes of this review using Begg's test. Egger's test, however, indicated an evidence for publication bias in the outcome of TG ($p = 0.037$).

Quality Assessment

Table 4 summarizes results from study quality assessment. All studies used a control group, reported no significant differences between groups at baseline, controlled for potential confounding variables, and clearly stated randomization procedures. Four studies did not employ blinding procedures [31, 35, 36, 38]. Seven studies documented attrition rates [31, 34–38, 40]. Results from the Cochrane Risk of Bias Tool report that all studies were at low risk of bias due to incomplete data reporting. The full Cochrane Risk of Bias tool is presented in the online supplementary material (Fig. 3). Three studies, Hartwich et al. [38], Kriketos et al. [39], and Piers et al. [35] showed high risk due to blinding procedures. Only one study, Piers et al. [35], was found to have high risk of bias due to randomization. The average quality assessment score was 5.3 out of 7 (SD = 0.75).

Discussion

This systematic review and meta-analysis assessed the effect of dietary replacement of SFA with UFA in metabolically healthy adults with overweight and obesity, and found no statistically significant effects on the modification of lipid profiles. However, the reductions in TC trended toward significance ($p = 0.06$). WC was significantly reduced in the SFA condition, solely in energy-restricted studies. However, as only two calorie restriction studies reported WC data, strong conclusions cannot be made from these findings. Intervention durations for the included studies were between 4 and 28 weeks. Despite this range, meta-regression calculations found no association between the duration and reduction in serum lipid levels.

A review published in 1997 [41] described the effects of different fatty acids on serum cholesterol levels, and established that SFA are associated with an increase of serum lipids, and that UFA decrease serum lipids. Another review examining the impact of SFA reduction on CVD risk observed a significant reduction in CVD events, an effect that was more pronounced when SFA was replaced with PUFA [42]. Schwingshackl et al. [43] found that high MUFA diets significantly reduced FM and blood pressure but had no effect on serum lipid values, which contrast the TG reduction described here. Studies involving increased MUFA intake have been primarily conducted in the context of the Mediterranean diet, which include large quantities of nontropical oils, and is considered to prevent heart disease to a great extent [44]. Adherence to the Mediterranean diet has

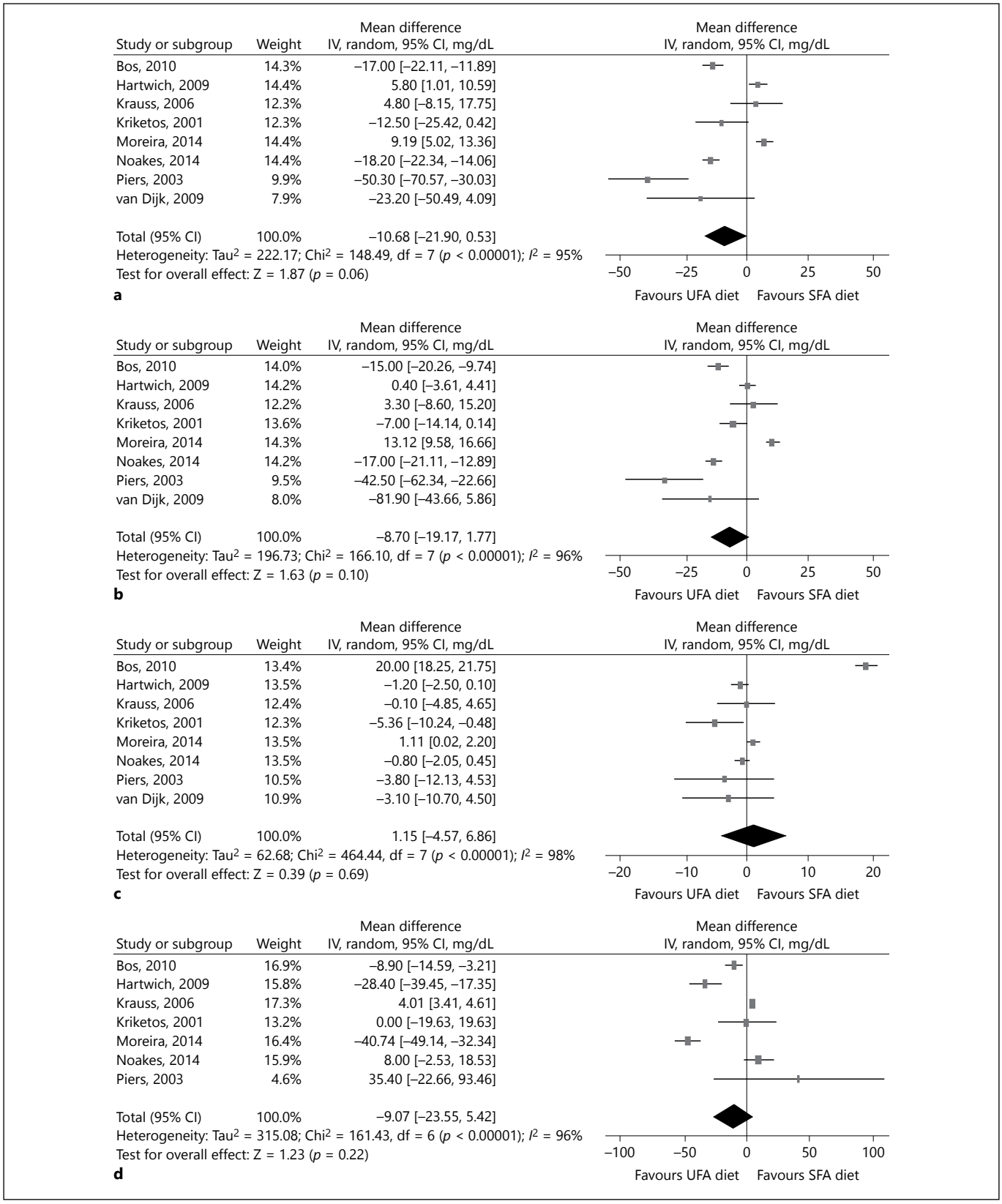

Fig. 2. Forest plots for primary outcomes. **a** Total cholesterol; **b** LDL-cholesterol; **c** HDL-cholesterol; **d** Triglycerides.

Table 3. Pooled estimate effect sizes for selected body composition outcomes

Study sample	Outcome	Studies included	Effect size	95% CI	I^2, %	*p* value
All	BFP, %	3	0.14	−0.86 to 1.14	27.0	0.79
All	BW, kg	6	−0.60	−2.10 to 0.91	0.0	0.44
All	FM, kg	2	0.84	−1.08 to 2.75	76.0	0.39
All	WC, cm	3	1.24	−0.15 to 2.64	0.0	0.08
ER	BFP, %	2	0.36	−0.87 to 1.59	58.0	0.57
ER	BW, kg**	3	−0.31	−2.77 to 2.15	27.0	0.80
ER	WC, cm	2	1.58	0.28 to 2.88	37.0	0.02*
EB	BW, kg**	3	0.12	−4.03 to 4.26	0.0	0.96

* $p < 0.05$.

Fixed effects model used unless denoted by ** for random effects.

ER, energy restriction; EB, energy balance; BMI, body mass index; BFP, body fat percentage; BW, body weight; FM, fat mass; WC, waist circumference.

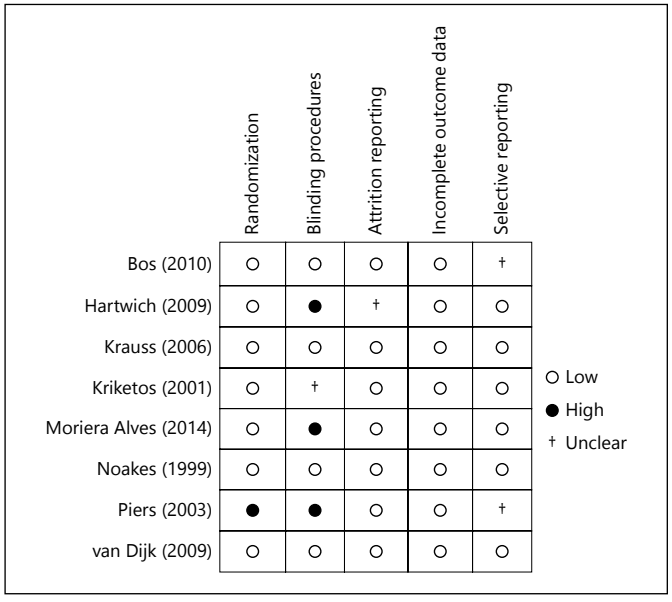

Fig. 3. Cochrane risk of bias tool for individual studies.

Table 4. Begg's and Egger's test results for all outcomes

Outcome	Included studies	Begg's test *p* value	Egger's test *p* value
TC, mg/dL	8	0.697	0.558
LDL-C, mg/dL	8	0.586	0.423
HDL-C, mg/dL	8	0.586	0.990
TG, mg/dL	7	0.788	0.037
BMI, kg/m^2	2	0.317	0.317
BFP, %	3	0.497	0.370
FM, kg	2	0.602	0.128
WC, cm	3	0.327	0.266
BW, kg	3	0.621	0.887

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BMI, body mass index; BFP, body fat percentage; BW, body weight; FM, fat mass; WC, waist circumference.

also been associated with lower serum TG concentrations in a previous meta-analysis of RCTs [45]. The incongruities could be related to the presence of other lipid-lowering components within a Mediterranean diet, such as fiber from fruits, vegetables, and whole grains, and higher intake of high-PUFA cold-water fish. It is therefore possible that increasing MUFA consumption alone may not produce as strong of a hypocholesterolemic effect as a diet that also contains elevated amounts of PUFA.

The mechanism by which UFA alters serum cholesterol levels has been examined both in vivo and in vitro. PUFA directly alter protein expression by upregulating mRNA levels and increasing the number of cellular LDL-receptors [46]. This increase in LDL-receptors occurs primarily in hepatocytes, resulting in a cholesterol influx increase. PUFA also decrease de novo lipogenesis and very low-density lipoprotein (VLDL) secretion by fatty acid synthase suppression [47]. These effects are not seen in

diets high in SFA or MUFA. The mechanism by which MUFA decrease serum cholesterol levels is less clear. Like PUFA, MUFA also have mechanistic effects at the mRNA level but act on hepatic apolipoproteins. MUFA have been linked to lower levels of apolipoprotein C-III mRNA [48], a protein present on LDL-C particles and precursor of VLDL. By downregulation of this protein, VLDL and LDL-C concentrations are reduced in circulation, and are therefore protective against CVD.

Dietary changes are consistently recommended for individuals at risk for obesity-related comorbidities prior to medication or surgery [49]. Common recommendations for weight loss include energy restriction, reduction of sugar intake, increased fruit and vegetable consumption, and a decrease in energy from SFA. The exact level of SFA energy restriction is clearly established. The American Heart Association recommends less than 7% of total energy from SFA, and the Dietary Guidelines Advisory Committee allows up to 10% of total calories [3, 7]. The acceptable macronutrient distribution range for fat is 20–35% of total calories, but evidence is currently lacking regarding the percentage of SFA versus UFA [50]. Additionally, more research is needed in both calorie-restricted and energy-balanced settings. This systematic review and meta-analysis demonstrates that there is not strong enough evidence to state that the replacement of SFA with UFA, in the form of MUFA and PUFA, may alter lipid profiles in adults with overweight and obesity. However, this dietary replacement, in conjunction with other health behaviors, may be beneficial. However, additional robustly designed trials are needed to confirm the effect of dietary fat modification for prevention of obesity-related comorbidities. Through controlled-feeding studies especially, researchers can manipulate the composition of dietary fat to achieve partial or total replacement of SFA with UFA to determine if there is an ideal balance of the 2 for protection against obesity-related chronic disease.

Reductions in WC were observed in the control and SFA condition in calorie-restricted studies only. Calorie restriction has been proven to induce weight and FM loss in patients with obesity [51]. The findings of this review may substantiate the notion that calorie restriction overall is more effective for central adiposity reduction than alterations in macronutrient distribution. Naude et al. [52] investigated differences in macronutrient distribution for weight loss and CVD risk, and found that, for participants who were overweight or with obesity, there were no significant differences in weight loss between low carbohydrate (<45% of total energy) and balanced carbohydrates (45–65% of total energy) diets within the first 6 months of treatment. These results were replicated in participants with T2DM. This review found no significant effects on any outcomes of interest using meta-analysis. The inconsistencies and null results here further emphasize the need for additional trials to inform future systematic reviews and meta-analyses so that conclusions may be drawn regarding effective macronutrient and dietary fat distributions for the management of obesity and chronic disease.

There were several limitations pertaining to this study. Only eight studies with small to moderate sample size were included in the meta-analysis. Many studies were rejected after full-text review, and the most common reason for exclusion was when participants were already diagnosed with disease, such as dyslipidemia or T2DM. Study findings are applicable only to adults with overweight and obesity and those who have not been previously diagnosed with a chronic disease. If this review included all participants with overweight and obesity, it is possible that more studies would have been included in the meta-analysis, perhaps resulting in different conclusions. Additional RCTs are warranted to determine the effects of diet on lipid concentrations and body composition among individuals with overweight and obesity. Another limitation was high study heterogeneity, but it did not appear that one study was driving this heterogeneity, as evidenced by sensitivity analysis. Though all studies were deemed to be at low risk of bias through the use of the Cochrane Risk of Bias tool, some included studies scored as high risk in certain categories. Piers et al. [35], which had high risk of bias for blinding and for randomization procedures, employed a crossover study design. Participants served as their own controls, and were recruited from an ongoing study conducted by the same authors. This causes concern for familiarity between researchers and participant characteristics; however, the sample size was only 8 individuals and was proven to not have a significant effect in the result of our sensitivity analyses. Kriketos et al. [39] reported adequate randomization procedures; however, it was not stated that the researchers were blinded to the condition the participants were enrolled for. Hartwich et al. [38] was not a blinded study and did not discuss randomization of participants. But, these biases did not prove to alter the results, as evidenced by sensitivity analysis. There was no evidence for publication bias in the meta-analysis as indicated in funnel plot inspection, Begg's, and Egger's tests. Funnel Plots are available in the online supplementary material. However, these tests are potentially underpowered due to a small number of

studies included. Publication of large-scale clinical trials of dietary interventions, including those reporting null results, are needed to add to the growing body of evidence-based nutritional guidance and practice [53]. Null studies are crucial to improve our understanding of nutritional therapies that are beneficial, but more importantly to identify which therapies are not. Though not all outcomes of this review were found to be statistically significant, this review and others of its kind will serve to direct future research studies on differences in fatty acid composition, on outcomes of circulating lipids, and body composition.

Conclusions

This review provides evidence that dietary replacement of SFA with UFA may be marginally effective in improving lipid profiles in metabolically healthy adults with overweight and obesity. Reductions in WC may be more effectively achieved by calorie restriction than modification of dietary fat alone. It is possible, however, that these results may be applicable only to adults without any diagnosis of chronic disease, and more research is warranted to strengthen the evidence that replacement of saturated fat for unsaturated fat improves hyperlipidemia. Well-designed replacement interventions should be conducted in these populations, as well as subgroups such as different ages, ethnicities, or genders, to better understand the impact of these dietary interventions on obesity and related metabolic disease prevention.

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