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Article

Published Version

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Sellem, L., Flourakis, M., Jackson, K. G. ORCID: <https://orcid.org/0000-0002-0070-3203>, Joris, P. J., Lumley, J., Lohner, S., Mensink, R. P., Soedamah- Muthu, S. S. and Lovegrove, J. A. ORCID: <https://orcid.org/0000-0001-7633-9455> (2022) Impact of replacement of individual dietary SFAs on circulating lipids and other biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials in humans. *Advances in Nutrition*, 13 (4). pp. 1200-1225. ISSN 2156-5376 doi: 10.1093/advances/nmab143 Available at <https://centaur.reading.ac.uk/102310/>

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To link to this article DOI: <http://dx.doi.org/10.1093/advances/nmab143>

Publisher: American Society for Nutrition

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Impact of Replacement of Individual Dietary SFAs on Circulating Lipids and Other Biomarkers of Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials in Humans

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ABSTRACT

Little is known of the impact of individual SFAs and their isoenergetic substitution with other SFAs or unsaturated fatty acids (UFAs) on the prevention of cardiometabolic disease (CMD). This systematic literature review assessed the impact of such dietary substitutions on a range of fasting CMD risk markers, including lipid profile, markers of glycemic control and inflammation, and metabolic hormone concentrations. Eligible randomized controlled trials (RCTs) investigated the effect of isoenergetic replacements of individual dietary SFAs for ≥ 14 d on ≥ 1 CMD risk markers in humans. Searches of the PubMed, Embase, Scopus, and Cochrane CENTRAL databases on 14 February, 2021 identified 44 RCTs conducted in participants with a mean $\pm$ SD age of 39.9 ± 15.2 y. Studies' risk of bias was assessed using the Cochrane Risk of Bias tool 2.0 for RCTs. Random-effect meta-analyses assessed the effect of ≥ 3 similar dietary substitutions on the same CMD risk marker. Other dietary interventions were described in qualitative syntheses. We observed reductions in LDL-cholesterol concentrations after the replacement of palmitic acid (16:0) with UFAs (-0.36 mmol/L; 95% CI: $-0.50, -0.21$ mmol/L; $I^2 = 96.0\%$, $n = 18$ RCTs) or oleic acid (18:1n-9) (-0.16 mmol/L; 95% CI: $-0.28, -0.03$ mmol/L; $I^2 = 89.6\%$, $n = 9$ RCTs), with a similar impact on total cholesterol and apoB concentrations. No effects on other CMD risk markers, including HDL-cholesterol, triacylglycerol, glucose, insulin, or C-reactive protein concentrations, were evident. Similarly, we found no evidence of a benefit from replacing dietary stearic acid (18:0) with UFAs on CMD risk markers ($n = 4$ RCTs). In conclusion, the impact of replacing dietary palmitic acid with UFAs on lipid biomarkers is aligned with current public health recommendations. However, owing to the high heterogeneity and limited studies, relations between all individual SFAs and biomarkers of cardiometabolic health need further confirmation from RCTs. This systematic review was registered at www.crd.york.ac.uk/prospero/ as CRD42020084241. *Adv Nutr* 2022;00:1–26.

Statement of Significance: This is the first systematic review and meta-analysis of randomized controlled trials that assessed the impact of individual SFAs and their isoenergetic substitution on a wide range of risk markers of cardiometabolic diseases (including lipid profile, markers of glycemic control, markers of inflammation, and metabolic hormones).

Keywords: palmitic acid, stearic acid, myristic acid, medium-chain fatty acids, saturated fatty acids, unsaturated fatty acids, lipoproteins, fasting lipid profile, glucose, insulin

Introduction

Cardiovascular diseases (CVDs) are the main cause of death worldwide with an estimated 17.9 million deaths from CVDs in 2019 (1). The etiology of CVD is complex and often results from a combination of risk factors, including the presence of other metabolic disorders and cardiometabolic diseases (CMDs) such as type 2 diabetes, hypertension, or hyperlipidemia (1). In particular, the fasting lipid profile and markers of glycemic control are routinely used as clinical biomarkers of risks of CVD and type 2 diabetes, but other risk factors such as markers of inflammation or blood hemostasis have been less extensively studied (2, 3). Changes in environmental and behavioral factors, such as dietary habits, tobacco use, and physical activity, have been identified as important strategies to help prevent CMD risk at a population level (4).

Among dietary factors, public health guidelines around the world advocate a reduction of dietary SFAs in favor of unsaturated fatty acids (UFAs), with a general consensus that dietary SFAs should not exceed ~10% total energy (%TE) intakes (5, 6). These recommendations are supported by systematic literature reviews (SLRs) and meta-analyses, such as the 2020 updated analysis of 12 randomized controlled trials (RCTs) from Hooper et al. (7) which reported a 17% decrease in CVD event risk associated with reduced dietary SFAs and showed an inverse linear relation between the amount of SFA removed from the diet and CVD risk. However, in the

context of isoenergetic dietary replacements, a reduction of SFAs can only be achieved with a concomitant increase in another type of dietary fat or another macronutrient. Current epidemiologic evidence suggests that replacing dietary SFAs with PUFAs might lead to a greater reduction of CMD risk than with other nutrients which have been less extensively studied (e.g., MUFAs or other nutrients like carbohydrates) (7, 8).

Importantly, dietary guidelines currently consider dietary SFAs as a whole group, but emerging evidence suggests that individual SFAs might have differential impacts on cardiometabolic health (9, 10). In a 2016 WHO SLR and regression analysis on the effect of SFAs on serum lipids and lipoproteins, Mensink (11) predicted that total cholesterol (TC), HDL-cholesterol, and LDL-cholesterol concentrations would increase when dietary carbohydrates were replaced with lauric (12:0), myristic (14:0), or palmitic (16:0) acids, but not stearic acid (18:0). This potential distinction of individual fatty acids (FAs) in the context of cardiometabolic health is reflected in current French dietary guidelines, which have recommended since 2011 that the sum of dietary lauric, myristic, and palmitic acids should not exceed 8%TE in adults (12), but this is not the case in other countries.

Despite the growing interest in the differential roles of individual SFAs in cardiometabolic health, to our knowledge there are no published SLRs or meta-analyses of well-controlled intervention studies investigating this research topic. Therefore, the objective of this SLR and meta-analysis was to address this knowledge gap. The hypothesis of this analysis was that the chronic consumption of individual dietary SFAs will have differential effects on circulating lipids and other markers of CMD risk.

Methods

This SLR and meta-analysis was conducted according to guidelines from the Cochrane Network and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42020084241.

Eligibility criteria and search strategy

This SLR included RCTs which investigated the impact of the dietary replacement of individual SFAs with other individual SFAs or UFAs on markers of cardiometabolic health. Eligible studies included in this SLR were defined as full-text, peer-reviewed, original research reports of RCTs published in the English language, which investigated food-based isoenergetic dietary fat interventions implemented for ≥ 14 d on humans aged >3 y old, and presented ≥ 1 fasting biomarker for circulating lipids, inflammation, glycemic control, hemostasis, or hormones. The groups considered for synthesis were defined as dietary interventions replacing 1 out of 8 groups of dietary SFAs defined by their carbon-chain length [i.e., medium-chain SFAs $< 12:0$, lauric acid, myristic acid, pentadecanoic acid (15:0), palmitic acid, heptadecanoic acid (17:0), stearic acid, long-chain SFAs $> 18:0$] or *trans*

LS was funded by the Biotechnology and Biological Sciences Research Council (BBSRC) UK Joint Programme Initiative "HDHL Biomarkers: Fatty Acid Metabolism—Interlinking Diet with Cardiometabolic Health (FAME)" (project reference: BB/P028217/1).

Author disclosures: This work was conducted by an expert group of the European branch of the International Life Sciences Institute (ILSI Europe). The research question addressed in this publication and potential contributing experts in the field were identified by the Qualitative Fat Intake (QFI) Task Force. Industry members of this task force are listed on ILSI Europe's website: http://ilsieurope.eu/wp-content/uploads/sites/3/2019/11/Qualitative-Fat-Intake_TFonepager_Sept2019.pdf. Experts are not paid for the time spent on this work;

however, the nonindustry members within the expert group were offered support for travel and accommodation costs from the QFI Task Forces to attend meetings to discuss the manuscript. The expert group carried out the work, i.e., collecting/analyzing data/information and writing the scientific paper separate to other activities of the task forces. The research reported is the result of a scientific evaluation in line with ILSI Europe's framework to provide a precompetitive setting for public-private partnership. ILSI Europe facilitated scientific meetings and coordinated the overall project management and administrative tasks relating to the completion of this work. For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies. JAL is Deputy Chair of the UK Scientific Advisory Committee for Nutrition (SACN) and was an expert on SACN's Saturated Fats working group. MF is an employee of ILSI Europe. SSS-M has received unrestricted grants from the Global Dairy Platform, Dairy Research Institute, and Dairy Australia for a meta-analysis on cheese and blood lipids (2012) and a meta-analysis of dairy and mortality (2015). She received the Wiebe Visser International Dairy Nutrition Prize and has received recent research funding (2019) for epidemiological studies on dairy products and cardiometabolic diseases from the Dutch Dairy Association and the Danish Dairy Research Foundation.

Supplemental Method 1, Supplemental Figures 1–12, and Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Abbreviations used: CMD, cardiometabolic disease; CRP, C-reactive protein; CVD, cardiovascular disease; FA, fatty acid; HKSJ, Hartung-Knapp-Sidik-Jonkman; Lp(a), lipoprotein (a); PAI-1, plasminogen activator inhibitor-1; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; REML, restricted maximum likelihood; SACN, Scientific Advisory Committee on Nutrition; SLR, systematic literature review; TC, total cholesterol; TG, triacylglycerol; UFA, unsaturated fatty acid; WMD, weighted mean difference; %TE, percent total energy.

FAs with another group of SFAs, UFAs, or *trans* FAs. Only dietary interventions exchanging $\geq 1.5\%$ TE of palmitic or stearic acid, or $\geq 1\%$ TE of other FAs were considered eligible for inclusion. Studies were excluded if any of the foregoing criteria was not met, if >1 group of SFAs was exchanged, if the amount of dietary fat exchanged could not be expressed as %TE, if studies reported results from parenteral/enteral nutrition interventions, or if they included critically ill patients (e.g., cancer).

RCTs published before 14 February, 2021 were searched in PubMed, Embase, Scopus, and the Cochrane CENTRAL register for clinical trials using 2 predefined comprehensive query syntaxes (**Supplemental Method 1**). The first search focused on serum lipids and lipoproteins, whereas the second search aimed to identify RCTs presenting all other predefined eligible outcomes. Finally, additional references were identified from previous systematic reviews of RCTs on dietary fat and cardiometabolic health.

Selection and data collection process

Results from literature searches were imported into reference manager software packages [Zotero 5.0 (Corporation for Digital Scholarship) and Endnote X9 (Clarivate)] to remove duplicates. References were then uploaded to the Covidence systematic review software (Veritas Health Innovation) for further identification of duplicates and the screening process. Each title/abstract imported into Covidence was randomly assigned to 2 independent reviewers for screening, and decision conflicts were addressed by a third reviewer where necessary. Full texts of selected titles/abstracts were retrieved and screened following the same process. Finally, full-text articles deemed eligible were allocated to 2 independent reviewers who each used a predefined extraction table template to collect all relevant data items. Pairs of extracted data were then compared and combined into a single final version for each eligible study. Numerical data items from figures were extracted using the WebPlotDigitizer web-based tool version 4.4 (available at: <https://apps.automeris.io/wpd/>).

Data items

Outcome data items to be extracted were classified into 5 categories of biomarkers of CMD risk: circulating lipid profiles, markers of inflammation, markers of glycemic control, markers of hemostasis, or metabolic hormone concentrations (**Supplemental Table 1**). Results from FA profiles in plasma/serum or other blood fractions were not considered in this SLR, because they are mostly reported in dietary fat replacement RCTs to assess compliance to the intervention diets rather than considered as biomarkers of cardiometabolic health. Data from each reported outcome were sought at baseline and at the end of intervention. Because this SLR assessed the effect of chronic dietary fat replacements, only measurements performed on participants in the fasting state were extracted.

In addition, study characteristic details were extracted for each eligible RCT and included country, year of publication,

industrial funding source (yes/no), participant information (i.e., biological sex, age, BMI, body weight, health status, medication, physical activity level, smoking habits, occupation, ethnicity), study design (i.e., crossover or parallel), duration of intervention and any run-in or washout periods (d), level of participant feeding control (i.e., full control of all foods consumed, control of intervention foods only, or dietary advice only without any food provided), and composition of intervention diets (type of food, macronutrient composition, energy provided, detailed FA composition). No assumption was made in case of missing data from 1 of the aforementioned variables, and these data were reported as not specified. However, studies were excluded if detailed FA compositions of the intervention diets were not available or could not be expressed as %TE.

Study risk of bias assessment

Risk of bias of included studies was assessed using the Cochrane Risk of Bias Tool 2.0 for parallel or crossover RCTs where appropriate, with the aim to quantify the effect of adhering to the intervention as specified in the study protocol (i.e., “per-protocol”) (14). Briefly, the tool assessed the risk of bias arising from 5 domains: 1) randomization process, 2) deviations from the intended interventions, 3) missing outcome data, 4) measurement of the outcomes, and 5) selection of the reported results. An additional domain was assessed in crossover RCTs for potential risk of bias arising from period and carryover effects. Each domain was attributed a risk of bias score (i.e., low-risk, some concerns, high-risk), which was used to calculate the overall risk of bias score for each included RCT. The overall risk of bias score was judged as “low-risk” if all domains were also judged as low risk, “some concerns” if 1 domain was judged as concerning but no domain was judged as high risk, and “high-risk” if ≥ 1 domain was judged as high risk or if several domains were scored as concerning in a way that may substantially affect the confidence in the reported results. Risk of bias was first assessed by 1 reviewer and then independently validated by a second reviewer, using full-text articles as the main source of information for the assessments along with secondary publications or the RCT’s registered information (e.g., clinicaltrials.gov) where necessary.

Eligibility and preparation for synthesis

Outcomes were selected for synthesis in this SLR if presented in ≥ 2 of the eligible RCTs. Quantitative meta-analyses were performed separately for every outcome that was reported in ≥ 3 independent RCTs which conducted similar dietary fat replacements, and if the outcome of interest could be reasonably assumed to follow a normal distribution. In quantitative syntheses, outcome data items at the end of intervention were expressed as means $\pm$ SDs in SI units. Missing data items (missing time point, or item not expressed as mean $\pm$ SD) were obtained either by contacting the authors of the original full-text articles, or by converting median values, SEs, or IQRs using the methods proposed by Hozo et al. (15). Because the outcomes of interest

were all continuous and measured on similar scales across studies, intervention effects were measured as a weighted mean difference (WMD) between 2 dietary interventions. To account for within-participant variance in crossover RCTs as opposed to between-participant variance in parallel trials, we calculated effect measures and their SDs in crossover RCTs using correlation coefficients from 1 of the crossover trials included in the meta-analyses (16) (Supplemental Table 2). Forest plots were generated for each suitable outcome to display results from meta-analyses, grouped by type of dietary fat replacement. Findings ineligible for quantitative meta-analyses were described in qualitative syntheses and tabulated to report details on dietary fat replacements, number of participants, and outcome measurements in each dietary intervention arm.

Statistical analyses

Statistical synthesis.

All statistical analyses were conducted in Stata version 16.1 (StataCorp), and P values < 0.05 were considered statistically significant. Studies in sufficient number were pooled using an inverse variance random-effect meta-analysis model to account for potential heterogeneity. The restricted maximum likelihood (REML) method was used to estimate heterogeneity variance. This method is recommended for meta-analyses of continuous outcomes containing a small number of studies (approximately $n \leq 10$) as an improvement of the traditional DerSimonian-Laird approach (17, 18). In addition, we used the Hartung-Knapp-Sidik-Jonkman (HKSJ) correction to estimate the 95% CIs of the summary effects (19, 20). This method provides more conservative 95% CIs than the commonly used Wald-type method when pooling a small number of studies (18, 21, 22). Statistical heterogeneity was quantified using the τ^2 and I^2 values along with Cochran's Q statistic for heterogeneity.

Sensitivity analyses were performed by repeating the meta-analyses without studies for which the confidence in some of the reported results was particularly low, e.g., when reviewers suspected typing errors in values or units reported. This issue was particularly prevalent in articles published between 1980 and 2000 and for which original authors could not be contacted.

Methods to explore heterogeneity and publication bias.

In meta-analyses including $n \geq 10$ studies, substantial heterogeneity was investigated using meta-regression analyses for the impact of the amount of dietary fat exchanged (per 5%TE) on the observed summary effect, expecting that a larger amount of exchanged dietary fat would lead to greater observed effects. Meta-regression analyses were based on the REML-HKSJ approach and were presented as bubble plots if statistically significant. To comply with Cochrane recommendations on meta-analyses including a small number of studies, no further methods were planned or conducted to explore substantial heterogeneity (23). In meta-analyses including $n \geq 10$ studies we investigated potential publication bias using visual inspection of funnel plots and

Egger's statistical test (24). Statistically significant Egger's tests were addressed using the trim-and-fill method based on a linear estimator to correct any funnel plot asymmetry (25).

Results

Study selection and characteristics

Figure 1 summarizes the selection process and the included RCTs. We identified 14,050 records, of which 7155 were screened after removal of duplicates. After the exclusion of 6472 records at the first stage of screening based on titles and abstracts, 683 records were assessed in detail using the full-text articles. A total of 639 records were further excluded for not meeting the predefined inclusion criteria, mainly because they did not report sufficient information about the dietary intervention ($n = 286$); reported ineligible dietary interventions ($n = 225$), outcomes ($n = 7$), or study designs ($n = 55$); or because no English full-text article was available ($n = 66$). Overall, 44 full-text articles met the inclusion criteria and were included in this SLR (16, 26–68). Among those, 35 articles reporting 34 RCTs were included in quantitative meta-analyses, whereas 9 articles reporting 10 RCTs were included solely in the qualitative synthesis.

Table 1 presents characteristics of the included RCTs along with details of the dietary interventions. Among the 44 included RCTs, 36 were conducted in a crossover design and 8 in a parallel design. The most common interventions investigated were the dietary substitution of palmitic acid with a mixture of UFAs ($n = 20$) (26, 27, 29–31, 34, 35, 37, 40, 41, 44–46, 51, 54–58, 67), followed by the replacement of palmitic with oleic acid (18:1n-9) ($n = 10$) (32, 33, 36, 47, 49–53, 62), the substitution of palmitic with stearic acid ($n = 5$) (16, 28, 43, 48, 56), and the substitution of stearic acid with a mixture of UFAs ($n = 4$) (26, 38, 39, 42, 56). The number of participants included in the studies ranged from 6 to 101 (42, 59, 60), and intervention duration varied between 14 and 112 d (26, 42, 64, 67). Most of the RCTs included enrolled both men and women ($n = 21$), apart from 12 RCTs conducted in men only (32, 41, 42, 46, 51, 52, 54, 56, 57, 64, 65, 68) and 5 RCTs conducted in women only (35, 43, 44, 48, 58). Finally, most RCTs included healthy participants but 10 trials included participants with moderately to highly elevated fasting serum or plasma lipids, although some authors did not specify the cutoff used for fasting lipids (Table 1) (29, 35, 37, 40, 41, 45, 46, 57, 59, 60).

Risk of bias assessment

Table 2 presents results from the risk of bias assessment of the included RCTs. Thirteen of the 44 RCTs were judged as “low risk of bias” and 18 presented “some concerns.” Furthermore, 13 crossover RCTs were judged as “high risk of bias,” mostly due to insufficient washout periods between dietary interventions in comparison with the duration of intervention. Indeed, when assessing the risk of carryover effects between interventions, washout periods ≥ 14 d were

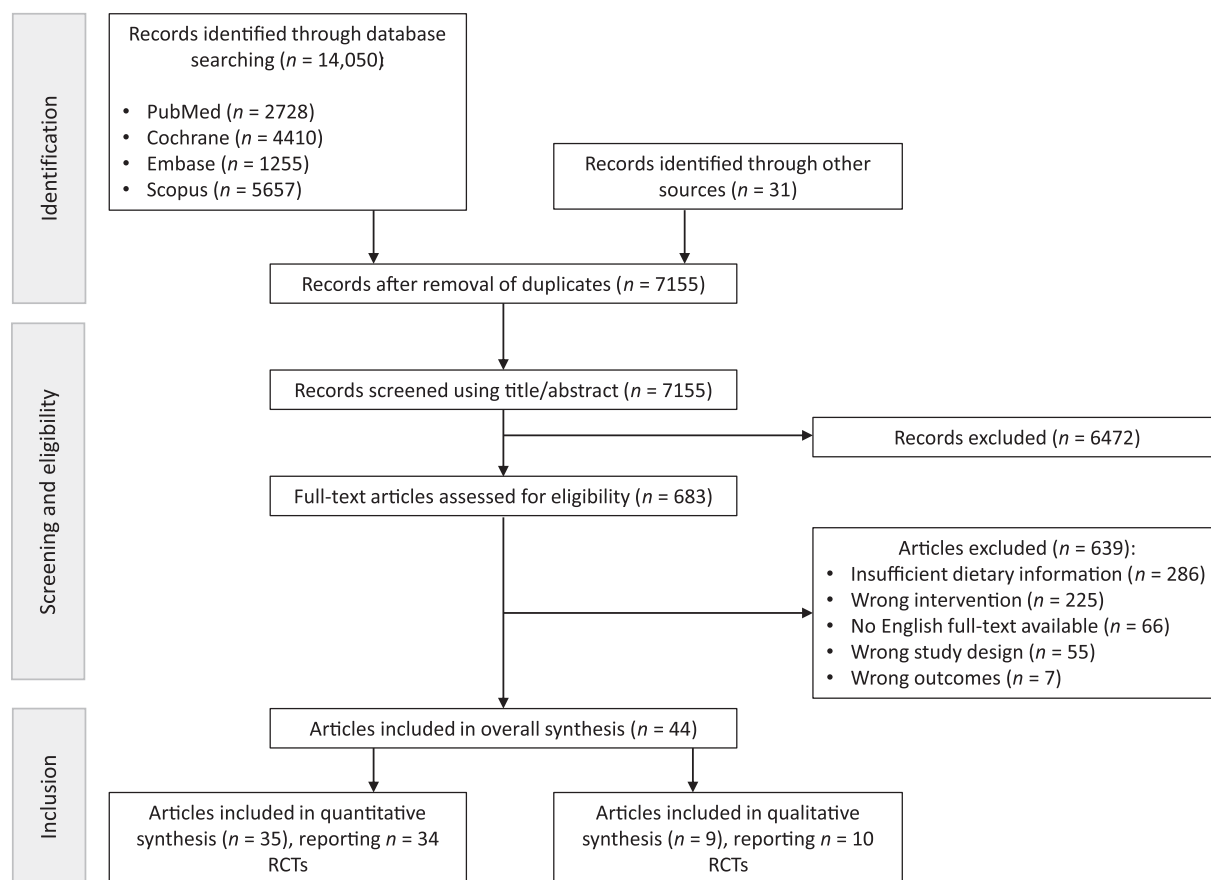


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included RCTs. RCT, randomized controlled trial.

deemed acceptable regardless of the duration of interventions, and shorter washout periods were judged acceptable only when combined with interventions of ≥ 28 d to ensure ≥ 14 d of dietary intervention with minimal risks of carryover effects.

Effect of dietary fat replacement on fasting lipid profiles TC and LDL cholesterol.

As shown in **Figures 2** and **3**, quantitative syntheses revealed no statistically significant effects on TC or LDL cholesterol of the dietary replacements of palmitic with stearic acid (WMD: -0.34 mmol/L; 95% CI: -0.72 , 0.04 mmol/L; $I^2 = 87.2\%$, $n = 5$ RCTs, and WMD: -0.28 mmol/L; 95% CI: -0.71 , 0.15 mmol/L; $I^2 = 94.0\%$, $n = 5$ RCTs, respectively) or stearic acid with a mixture of UFAs (WMD: 0.03 mmol/L; 95% CI: -0.20 , 0.27 mmol/L; $I^2 = 75.0\%$, $n = 4$ RCTs, and WMD: -0.01 mmol/L; 95% CI: -0.34 , 0.31 mmol/L; $I^2 = 85.0\%$, $n = 4$ RCTs, respectively). However, statistically significant decreases in TC and LDL-cholesterol concentrations, albeit with evidence of high heterogeneity, were observed when exchanging dietary palmitic acid with either oleic acid (TC: WMD: -0.21 mmol/L; 95% CI: -0.33 , -0.10 mmol/L; $I^2 = 87.2\%$, $n = 9$ RCTs, and LDL cholesterol: WMD: -0.16 mmol/L; 95% CI: -0.28 , -0.03 mmol/L;

$I^2 = 89.6\%$, $n = 9$ RCTs) or a mixture of UFAs (TC: WMD: -0.41 mmol/L; 95% CI: -0.55 , -0.26 mmol/L; $I^2 = 93.1\%$, $n = 19$ RCTs, and LDL cholesterol: WMD: -0.36 mmol/L; 95% CI: -0.50 , -0.21 mmol/L; $I^2 = 96\%$, $n = 18$ RCTs). The latter effect on TC and LDL cholesterol was dependent on the amount of dietary palmitic acid replaced with UFAs according to meta-regression analyses, with each additional 5%TE of palmitic acid exchanged associated with a 0.12- and 0.17-mmol/L decrease in fasting TC (P value = 0.03) (**Figure 4A**) and LDL-cholesterol (P value = 0.001) (**Figure 4B**) concentrations, respectively. Sensitivity analyses on the effect of replacing dietary palmitic with oleic acid, which excluded 2 RCTs with potential reporting errors in the full-text articles, showed similar effects on TC and LDL-cholesterol concentrations (**Supplemental Figures 1, 2**).

The impact of other dietary fat substitutions on TC and LDL-cholesterol concentrations was investigated in 18 RCTs (34, 35, 40–42, 44, 51–54, 59–61, 63–66, 68) (**Table 3**). In particular, findings from 4 RCTs suggested that the dietary replacement of medium-chain SFAs with UFAs may not have any impact on TC concentrations (59–61, 63). However, decreased TC and LDL-cholesterol concentrations were reported after replacing dietary myristic acid with either

TABLE 1 Characteristics of 44 eligible RCTs on dietary fat exchange and biomarkers of cardiometabolic diseases¹

Authors (country)	Participants who completed the study, n (% men/women)	Mean age, y; mean BMI, kg/m ²	Participant characteristics	Study design, type of dietary intervention, duration of run-in, intervention, and washout (d)	Dietary intervention arms, n	Reported dietary fat replacements and amount exchanged (%TE)	Outcomes measured	Industrial funding (yes/no)
RCTs included in meta-analyses (n = 34) van Rooijen et al. (16) (Netherlands)	34 (59/41)	61.5; 25.4	Healthy	Crossover, semicontrolled, 28-d intervention, ≥ 28-d washout	2	160 (6.1) ↔ 180 (6.5)	apoA-I, apoB, apoBapoA-I ratio, C-peptide, CRP, glucose, HDL-C, HOMA-IR, IL-6, insulin, LDL-C, TCHDL-C ratio, TNF-α, TC, TG	Yes
Stonehouse et al. (26) (Australia)	64 (31/69)	32.6; 22.8	Healthy	Parallel, semicontrolled, 14-d run-in, 112-d intervention	3	160 (7.3) ↔ MUFAs + PUFAs (7.2) 180 (10.6) ↔ MUFAs + PUFAs (8.3)	apoA-I, apoB, apoBapoA-I ratio, glucose, HDL-C, LDL-C, leptin, TC, TCHDL-C ratio, TG	No
Sun et al. (27) (China)	100 (47/53)	40; 22.2	Healthy	Crossover, fully controlled, 35-d intervention, 14-d washout	2	160 (3.2) ↔ MUFAs + PUFAs (3.3)	apoA-I, apoB, glucose, HDL-C, HOMA-IR, insulin, LDL-C, TC, TG	No
Ly et al. (67) (China)	88 (47/53)	21.6; 21.0	Healthy	Parallel, semicontrolled, 7-d run-in, 112-d intervention	3	160 (1.9) ↔ MUFAs + PUFAs (1.2)	apoA-I, apoB, apoE, CRP, glucose, HDL-C, HOMA-IR, insulin, LDL-C, leptin, Lp(a), NEFAs, TC, TG	No
Ng et al. (28) (Malaysia)	85 (25/75)	34.4; 26.1	Healthy	Parallel, fully controlled, 21-d run-in, 56-d intervention	3	160 (6.0) ↔ 180 (7.0) 160 (5.4) ↔ 180 (6.8)	apoA-I, apoB, C-peptide, glucose, HDL-C, HOMA-IR, insulin, LDL-C, leptin, Lp(a), TC, TCHDL-C ratio, TG	No
Karupiah et al. (29) (Malaysia)	34 (47/53)	23.4; 25.1	Healthy, with normal (n = 21) or mildly elevated (n = 13) TC concentrations	Crossover, fully controlled, 28-d intervention, 14-d washout	2	160 (1.8) ↔ MUFAs + PUFAs (1.5)	apoA-I, apoB, CRP, glucose, HDL-C, LDL-C, HDL-C ratio, NEFA, TC, TG, VLDL-C	Yes
Kien et al. (30) (USA)	18 (50/50)	29.5; 23.3	Healthy	Crossover, fully controlled, 21-d intervention, 7-d washout	2	160 (13.7) ↔ MUFAs + PUFAs (13.9)	Adiponectin, apoE, HDL-C, LDL-C, LDL-C: HDL-C ratio, TC, TG	No
Rosqvist et al. (31) (Sweden)	37 (70.3/29.7)	C160 diet: 26.7; 20.8; MUFAs + PUFAs diet: 27.1; 19.9	Healthy	Parallel, semicontrolled, 49-d intervention	2	160 (5.2) ↔ MUFAs + PUFAs (7.5)	Adiponectin, glucose, insulin	No

(Continued)

TABLE 1 (Continued)

Authors (country)	Participants who completed the study, <i>n</i> (% men/women)	Mean age, <i>y</i> ; mean BMI, kg/m ²	Participant characteristics	Study design, type of dietary intervention, duration of run-in, intervention, and washout (d)	Dietary intervention arms, <i>n</i>	Reported dietary fat replacements and amount exchanged (%TE)	Outcomes measured	Industrial funding (yes/no)
Tholstrup et al. (32) (Denmark)	32 (100/0)	29.6; 22.9	Healthy, <i>n</i> = 6 smokers	Crossover, semicontrolled, 21-d intervention, no washout	3	160 (4.6) ↔ 18:1 (4.8)	CRP, glucose, HDL-C, insulin, LDL-C, PAI-1 activity, TC, TC:HDL-C ratio, TG	No
Voon et al. (33) (Malaysia)	45 (20/80)	30.1; 23.1	Healthy	Crossover, fully controlled, 35-d intervention, no washout	3	160 (4.9) ↔ 18:1 (6.8)	apoA-I, apoB, LDL-C, Lp(a), TC, TC:HDL-C ratio, TG	No
Teng et al. (34) (Malaysia)	41 (19.5/80.5)	28.8; 21.9	Healthy	Crossover, semicontrolled, 35-d intervention, 7-d washout	3	160 (5.2) ↔ MUFAs + PUFAs (9.4) 160 (5.8) ↔ 18:1-trans (9.9)	apoA-I, apoB, CRP, HDL-C, IL-6, LDL-C, TC, TC:HDL-C ratio, TG, TNF-α	No
Utarwuthipong et al. (35) (Thailand)	16 (0/100)	Range: 44–67; <25	Hyperlipidemic	Crossover, semicontrolled, 70-d intervention, no washout	4	160 (1.8) ↔ MUFAs + PUFAs (17.3) 160 (5.5) ↔ MUFAs + PUFAs (21.5) 160 (2.7) ↔ MUFAs + PUFAs (18.4) 160 (3.8) ↔ 18:2n-6 (4.6) 160 (2.8) ↔ 18:2n-6 (3.4)	HDL-C, LDL-C, TC, TG	No
Mensink (36) (Netherlands)	44 (25/75)	41; 23.9	Healthy, normolipidemic	Crossover, semicontrolled, 21-d intervention, 7-d washout	2	160 (4.2) ↔ 18:1 (2.9)	CRP, glucose, HDL-C, LDL-C, TC, TC:HDL-C ratio	Yes
Vega-López et al. (37) (USA)	15 (33/66)	63.9; 26	Elevated LDL-C (>3.36 mmol/L)	Crossover, fully controlled, 35-d intervention, no washout	4	160 (7.5) ↔ MUFAs + PUFAs (6.2) 160 (8.3) ↔ MUFAs + PUFAs (9.7)	apoA-I, apoA-II, apoB, glucose, HDL-C, HDL ₂ -C, HDL ₃ -C, HOMA-IR, insulin, LDL-C, Lp(a), TC, TC:HDL-C ratio, TG, VLDL-C	No
Thijssen et al. (38, 39) (Netherlands)	45 (60/40)	51; 24.9	Healthy, normolipidemic	Crossover, semicontrolled, 35-d intervention, 7-d washout	3	180 (19.7) ↔ MUFAs + PUFAs (20.2) 180 (19.6) ↔ MUFAs + PUFAs (20.0)	apoA-I, apoB, fibrinogen, HDL-C, LDL-C, PAI-1 activity, TC, TC:HDL-C ratio, TG	Yes
Gill et al. (40) (United Kingdom)	35 (49/51)	55; 26.3	Mildly hypercholesterolemic	Crossover, semicontrolled, 42-d intervention, 56-d washout	3	160 (3.0) ↔ MUFAs + PUFAs (3.6) 160 (6.1) ↔ MUFAs (6.6) 160 (3.1) ↔ MUFAs (3.0)	apoA-I, apoB, CRP, HDL-C, insulin, LDL-C, Lp(a), NEFAs, TC, TG, VLDL-C	No

(Continued)

TABLE 1 (Continued)

Authors (country)	Participants who completed the study, n (% men/women)	Mean age, y; mean BMI, kg/m ²	Participant characteristics	Study design, type of dietary intervention, duration of run-in, intervention, and washout (d)	Dietary intervention arms, n	Reported dietary fat replacements and amount exchanged (%TE)	Outcomes measured	Industrial funding (yes/no)
Cater and Denke (41) (USA)	7 (100/0)	66; 27	Mildly hypercholesterolemic, n = 3 subjects with history of CAD	Crossover, fully controlled, 21-d intervention, 7-d washout	3	160 (19.3) ↔ MUFAs + PUFAs (21.2) > 180 (17.0) ↔ MUFAs + PUFAs (19.0)	HDL-C, LDL-C, TC, TG, VLDL-C	No
Hunter et al. (42) (United Kingdom)	6 (100/0)	28; 24.7	Healthy	Crossover, fully controlled, 14-d intervention, 35-d washout	3	180 (10.7) ↔ 18:1 (11.1) 180 (10.7) ↔ MUFAs + PUFAs (10.3)	Fibrinogen, HDL-C, LDL-C, PAI-1 activity, TC, TG, tPA activity	No
Snook et al. (43) (USA)	16 (0/100)	28; NS	Healthy	Crossover, fully controlled, 35-d intervention, 49-d washout	3	160 (10.0) ↔ 18:0 (10.8)	apoA-I, apoB, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, TC, TG	No
Müller et al. (44) (Norway)	27 (0/100)	27; 26.5	Healthy	Crossover, fully controlled, 17-d intervention, 7-d washout	3	160 (5.5) ↔ MUFAs + PUFAs (4.5) Total <i>trans</i> (6.8) ↔ MUFAs + PUFAs (5.6)	apoA-I, apoB, HDL-C, LDL-C, LDL-CHDL-C ratio, Lp(a), TC, TG	Yes
Schwab et al. (45) (Finland)	14 (42.9/57.1)	63; 27.2	Elevated LDL-C (> 3.36 mmol/L)	Crossover, fully controlled, 32-d intervention, no washout	5	160 (2.0) ↔ MUFAs + PUFAs (1.6)	HDL-C, LDL-C, TC, TC:HDL-C, VLDL-C	No
Cater et al. (46) (USA)	9 (100/0)	66; 27	Mildly hypercholesterolemic, n = 3 subjects with history of CAD	Crossover, fully controlled, 21-d intervention, 7-d washout	3	160 (19.3) ↔ MUFAs + PUFAs (21.3)	HDL-C, LDL-C, TC, TG, VLDL-C	No
Sundram et al. (47) (Malaysia)	27 (66/33)	29.4; 22.7	Healthy	Crossover, semicontrolled, 28-d intervention, no washout	4	160 (4.1) ↔ 18:1 (2.7)	apoA-I, apoB, apoB:apoA-I ratio, HDL-C, LDL-C, LDL-C:HDL-C ratio, Lp(a), TC, TG, VLDL-C	No
Schwab et al. (48) (USA)	12 (0/100)	23.5; 22.1	Healthy, n = 6 using oral contraceptives	Crossover, semicontrolled, 28-d intervention, 14-d washout	2	160 (3.3) ↔ 18:0 (4.9)	apoA-I, apoB, HDL-C, HDL-TG, LDL-C, LDL-TG, TC, TG, VLDL-C, VLDL-TG	No
Temme et al. (49) (Netherlands)	32 (43.7/56.3)	41; 25	Healthy, n = 9 smokers, n = 2 using oral contraceptives	Crossover, semicontrolled, 42-d intervention, 14- to 21-d washout	3	160 (7.5) ↔ 18:1 (8.4)	apoA-I, apoA-I:apoB ratio, apoB, HDL-C, HDL-C:LDL-C ratio, LDL-C, Lp(a), TC, TG	Yes
Choudhury et al. (50) (Australia)	21 (48/52)	27.8; 24.1	Healthy	Crossover, semicontrolled, 30-d intervention, no washout	2	160 (5.0) ↔ 18:1 (7.3)	HDL-C, LDL-C, TC, TG	No

(Continued)

TABLE 1 (Continued)

Authors (country)	Participants who completed the study, n (% men/women)	Mean age, y; mean BMI, kg/m ²	Participant characteristics	Study design, type of dietary intervention, duration of run-in, intervention, and washout (d)	Dietary intervention arms, n	Reported dietary fat replacements and amount exchanged (%TE)	Outcomes measured	Industrial funding (yes/no)
Sundram et al. (51) (Malaysia)	23 (100/0)	21; 20.1	Healthy	Crossover, fully controlled, 21-d intervention, no washout	3	160 (4.3) ↔ 18:1 (5.1) 160 (3.0) ↔ MUFAs + PUFAs (6.8) 160 (7.3) ↔ MUFAs + PUFAs (6.8)	apoA-I, apoB, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, LDL-C:HDL-C ratio, Lp(a), TC, TG, VLDL-C	NS
Nestel et al. (52) (Australia)	34 (100/0)	49; 25.7	Healthy	Crossover, semicontrolled, 21-d intervention, no washout	3	160 (3.3) ↔ 16:1 (3.8) 160 (3.4) ↔ 18:1 (2.7)	HDL-C, LDL-C, TC, TG	Yes
Zock et al. (53) (Netherlands)	59 (39/61)	Men: 28; 22.3 Women: 29; 22.4	Healthy, n = 8 smokers	Crossover, fully controlled, 21-d intervention, no washout	3	140 (10.2) ↔ 16:0 (10.2) 140 (10.5) ↔ 18:1 (10.0)	apoA-I, apoB, HDL-C, HDL-C:LDL-C ratio, LDL-C, TC, TG	No
Denke and Grundy (54) (USA)	14 (100/0)	63; 25.5	n = 5 subjects with history of CAD, n = 7 smokers	Crossover, fully controlled, 21-d intervention, 7-d washout	3	160 (9.9) ↔ 18:1 (9.3) 120 (17.5) ↔ MUFAs + PUFAs (16.3) 160 (15.5) ↔ MUFAs + PUFAs (16.6)	HDL-C, TC, TG, VLDL-C	No
Ng et al. (55) (Malaysia)	27 (74/26)	23.9; 19.5	Healthy, normolipidemic	Crossover, fully controlled, 35-d intervention, no washout	2	160 (4.9) ↔ MUFAs + PUFAs (4.8)	HDL-C, LDL-C, LDL-C:HDL-C ratio, TC, TG	No
Bonanome and Grundy (56) (USA)	11 (100/0)	64; 24	n = 4 subjects with a history of CAD using antihypertensive medication and nitroglycerine	Crossover, fully controlled, 21-d intervention, no washout	3	160 (14.8) ↔ 18:0 (15.3) 160 (15.8) ↔ MUFAs + PUFAs (17.4) 180 (16.3) ↔ MUFAs + PUFAs (17.7)	HDL-C, LDL-C, LDL-C:HDL-C ratio, TC, TG, VLDL-C	NS
Mattson and Grundy (57) (USA)	20 (100/0)	58.7; NS	Healthy, with normal or elevated TC and TG concentrations	Crossover, fully controlled, 28-d intervention, no washout	3	160 (15.3) ↔ MUFAs + PUFAs (15.2) 160 (14.8) ↔ MUFAs + PUFAs (15.2)	HDL-C, LDL-C, TC, TG, VLDL-C	No
Baudet et al. (58) (France)	24 (0/100)	46; NS	Healthy	Crossover, fully controlled, 35-d intervention, no washout	4	160 (3.1) ↔ MUFAs + PUFAs (2.8) 160 (2.1) ↔ MUFAs + PUFAs (0.7)	TC, TG	Yes
RCTs included in qualitative synthesis only (n = 10)								
Liu et al. (59) (China)	101 (66/34)	53.7; 25.9	Hypertriglyceridemic	Parallel, semicontrolled, 56-d intervention	2	Men: <120 (1.8) ↔ 18:2n-6 (1.7) Women: <120 (1.9) ↔ 18:2n-6 (1.6)	apoA-I, apoB, apoE, glucose, HDL-C, LDL-C, TC, TG	Yes
Xue et al. (60) (China)	101 (66/34)	53.7; 25.9	Hypertriglyceridemic	Parallel, semicontrolled, 56-d intervention	2	<120 (1.8) ↔ MUFAs + PUFAs (1.3)	Adiponectin, apoA-I, apoA-II, apoB, glucose, HDL-C, LDL-C, TC, TG	NS

(Continued)

TABLE 1 (Continued)

Authors (country)	Participants who completed the study, n (% men/women)	Mean age, y; mean BMI, kg/m ²	Participant characteristics	Study design, type of dietary intervention, duration of run-in, intervention, and washout (d)	Dietary intervention arms, n	Reported dietary fat replacements and amount exchanged (%TE)	Outcomes measured	Industrial funding (yes/no)
Nosaka et al. (61) (Japan)	64 (75/25)	37.6; 25	Healthy	Parallel, semicontrolled, 84-d intervention	2	<12.0 (3.0) ↔ 18:1 (1.6)	Glucose, HDL-C, HDL-TG, LDL-C, LDL-TG, TC, TG, VLDL-C, VLDL-TG	NS
Judd et al. (68) (USA)	50 (100/0)	42; 26.2	Healthy, smokers and nonsmokers	Crossover, fully controlled, 35-d intervention, no washout	6	18:0 (8.0) ↔ 18:1 (7.1) 18:0 (4.1) ↔ total <i>trans</i> (4.1) 18:0 (8.1) ↔ total <i>trans</i> (8.0) 18:0 (4.0) ↔ total <i>trans</i> (3.9)	apoA-I, apoB, HDL-C, HDL ₂ -C, HDL ₃ -C, TC, TC:HDL-C ratio, TG	Yes
Temme et al. (62) (Netherlands)	32 (43.8/56.2)	Men: 43; 25 Women: 40; 25	Healthy, normolipidemic, n = 9 smokers	Crossover, semicontrolled, 42-d intervention, 14- to 21-d washout	3	16:0 (6.1) ↔ 18:1 (6.8)	Fibrinogen, PAI-1 activity	Yes
Temme et al. (63) (Netherlands)	60 (38/62)	Men: 43; 25 Women: 40; 24	Healthy, n = 11 smokers, n = 10 using oral contraceptives	Parallel, semicontrolled, 42-d intervention	3	<12.0 (9.9) ↔ 18:1 (10.1) <12.0 (9.9) ↔ 14:0 (9.7) 14:0 (9.6) ↔ 18:1 (10.4)	apoA-I, apoA-I:apoB ratio, apoB, HDL-C, Lp(a), TC, TC:HDL-C ratio, TG	Yes
Ghafoorunnisa et al. (64) (India)	12 (100/0)	35; 21	Healthy	Crossover, fully controlled, 56-d intervention, 42-d washout	2	16:0 (5.0) ↔ 18:2n-6 (3.7)	HDL-C, LDL-C, TC, TG, VLDL-C	No
	24 (50/50)	Men: 43; 23 Women: 38; 24	Healthy	Crossover, semicontrolled, 112-d intervention, no washout	2	16:0 (6.0) ↔ 18:2n-6 (3.7)	HDL-C, LDL-C, TC, TG, VLDL-C	No
Tholstrup et al. (65) (Denmark)	12 (100/0)	23.8; 23.5	Healthy	Crossover, fully controlled, 21-d intervention, 35-d washout	3	14:0 (13.4) ↔ 16:0 (12.8)	apoA-I, apoB, fibrinogen, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, LDL-C:HDL-C ratio, TC, TG, tPA activity, VLDL-C	No
Zock and Katan (66) (Netherlands)	62 (50/50)	24.5; NS	Healthy, normolipidemic, n = 8 smokers	Crossover, fully controlled, 21-d intervention, no washout	3	18:0 (9.0) ↔ 18:2n-6 (8.1) Total <i>trans</i> (7.6) ↔ MUFAs + PUFAs (7.5)	apoA-I, apoA-I:apoB ratio, apoB, HDL-C, HDL-C:LDL-C ratio, LDL-C, TC, TG	NS

[†]Fully controlled intervention: all foods consumed were provided to participants, for either home or on-site consumption (on campus, metabolic ward, etc.). Semicontrolled intervention: experimental foods were provided to participants along with dietary advice for nonexperimental foods. Fatty acids considered: lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), stearic acid (18:0), palmitoleic acid (16:1n-7), oleic acid (18:1n-9), linoleic acid (18:2n-6), α -linolenic acid (18:2n-3). CAD, coronary artery disease; CRP, C-reactive protein; HDL-C, HDL cholesterol; HDL₂-C, HDL₂ cholesterol; HDL₃-C, HDL₃ cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); NEFA, nonesterified fatty acid; NS, not specified; PAI-1, plasminogen activator inhibitor-1; RCT, randomized controlled trial; TC, total cholesterol; TG, triacylglycerol; tPA, tissue plasminogen activator; VLDL-C, VLDL cholesterol; %TE, percent total energy.

TABLE 2 Risk of bias assessment of 44 eligible RCTs on dietary fat exchange and biomarkers of cardiometabolic diseases, from the Cochrane Risk of Bias 2.0 tool for parallel or crossover RCTs (14)

Authors	Year	Journal	Randomization process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
RCTs included in meta-analyses (<i>n</i> = 34)								
van Rooijen et al. (16)	2020	Clin Nutr	Low	Low	Low	Low	Low	Low
Stonehouse et al. (26)	2020	Am J Clin Nutr	Low	Low	Low	Low	Low	Low
Sun et al. (27)	2019	Asia Pac J Clin Nutr	Some concerns	Low	Low	Low	Low	Some concerns
Lv et al. (67)	2018	Food Nutr Res	Some concerns	Low	Low	Low	Low	Some concerns
Ng et al. (28)	2018	Nutrients	Low	Low	Low	Low	Low	Low
Karupaiah et al. (29)	2016	Lipids Health Dis	Low	Low	Low	Low	Low	Low
Kien et al. (30)	2014	Am J Clin Nutr	Low	High	Low	Low	Low	High
Rosqvist et al. (31)	2014	Diabetes	Low	Low	Low	Low	Low	Low
Tholstrup et al. (32)	2011	Am J Clin Nutr	Low	High	Some concerns	Low	Low	High
Voon et al. (33)	2011	Am J Clin Nutr	Some concerns	Low	Low	Low	Low	Some concerns
Teng et al. (34)	2010	Lipids	Low	High	Low	Low	Low	High
Utarwuthipong et al. (35)	2009	Int J Med Sci	Some concerns	Low	Low	Low	Low	Some concerns
Mensink (36)	2008	Eur J Clin Nutr	Some concerns	Low	Low	Low	Low	High
Vega-López et al. (37)	2006	Am J Clin Nutr	Low	Low	Low	Low	Low	Some concerns
Thijssen et al. (38, 39)	2005	Nutr Metab/Am J Clin Nutr	Some concerns	High	Low	Low	Low	High
Gill et al. (40)	2003	Am J Clin Nutr	Some concerns	Low	Low	Low	Low	Some concerns
Cater and Denke (41)	2001	Am J Clin Nutr	Low	High	Low	Low	Low	Low
Hunter et al. (42)	2000	J Nutr Biochem	Some concerns	Low	Low	Low	Low	Some concerns
Snook et al. (43)	1999	Eur J Clin Nutr	Some concerns	Low	Low	Low	Low	Some concerns
Müller et al. (44)	1998	Lipids	Low	High	Low	Low	Low	High
Schwab et al. (45)	1998	Nutr Metab	Some concerns	Some concerns	Low	Low	Low	Some concerns
Cater et al. (46)	1997	Am J Clin Nutr	Low	High	Low	Low	Low	High
Sundram et al. (47)	1997	J Nutr	Low	Low	Low	Low	Low	Low
Schwab et al. (48)	1996	Metab Clin Exp	Low	Low	Low	Low	Low	Low
Temme et al. (49)	1996	Am J Clin Nutr	Some concerns	Some concerns	Low	Low	Low	Some concerns
Choudhury et al. (50)	1995	Am J Clin Nutr	Low	Low	Low	Low	Low	Low
Sundram et al. (51)	1995	J Nutr Biochem	Some concerns	High	Low	Low	Low	High
Nestel et al. (52)	1994	J Lipid Res	Low	High	Low	Low	Low	High
Zock et al. (53)	1994	Arterioscler Thromb	Some concerns	High	Low	Low	Low	High
Denke and Grundy (54)	1992	Am J Clin Nutr	Some concerns	High	Low	Low	Low	High
Ng et al. (55)	1991	Am J Clin Nutr	Some concerns	Low	Low	Low	Low	High
Bonanome and Grundy (56)	1988	N Engl J Med	Some concerns	High	Low	Low	Low	Some concerns
Mattson and Grundy (57)	1985	J Lipid Res	Some concerns	Low	Low	Low	Low	High
Baudet et al. (58)	1984	J Lipid Res	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

(Continued)

TABLE 2 (Continued)

Authors	Year	Journal	Randomization process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
RCTs included in qualitative synthesis only ($n = 10$)								
Liu et al. (59)	2009	Asia Pac J Clin Nutr	Low	Low	Low	Low	Low	Low
Xue et al. (60)	2009	Eur J Clin Nutr	Low	Low	Low	Low	Low	Low
Nosaka et al. (61)	2003	J Atheroscler Thromb	Some concerns	Low	Low	Low	Some concerns	Some concerns
Judd et al. (68)	2002	Lipids	Low	Low	Low	Low	Low	Low
Temme et al. (62)	1999	Thromb Haemost	Some concerns	Some concerns	Low	Low	Low	Some concerns
Temme et al. (63)	1997	J Lipid Res	Some concerns	Low	Low	Low	Low	Some concerns
Ghafoorunnissa et al. (64)	1995	Lipids	Some concerns	Low	Low	Low	Low	Some concerns
Tholstrup et al. (65)	1994	Am J Clin Nutr	Some concerns	Low	Low	Low	Low	Some concerns
Zock and Katan (66)	1992	J Lipid Res	Some concerns	High	Low	Low	Low	High

^aRCT, randomized controlled trial.

palmitic (53, 65) or oleic acid (53, 63). Furthermore, 3 RCTs reported decreased or unchanged TC concentrations in response to a replacement of dietary stearic with oleic or linoleic acid (18:2n-6) (42, 66, 68). Finally, 2 crossover RCTs observed beneficial effects of exchanging 6.8–7.6%TE dietary *trans*-FAs with a mixture of UFAs on TC and LDL-cholesterol concentrations (44, 66).

HDL cholesterol.

Pooled analyses (presented in Figure 5) showed no statistically significant effect on HDL-cholesterol concentrations of the dietary replacements of palmitic with stearic acid (WMD: -0.06 mmol/L; 95% CI: $-0.14, 0.03$ mmol/L; $I^2 = 75.0\%$, $n = 5$ RCTs), stearic acid with a mixture of UFAs (WMD: 0.05 mmol/L; 95% CI: $-0.02, 0.12$ mmol/L; $I^2 = 32.6\%$, $n = 4$ RCTs), or palmitic acid with a mixture of UFAs (WMD: -0.02 mmol/L; 95% CI: $-0.05, 0.01$ mmol/L; $I^2 = 83.9\%$, $n = 18$ RCTs). However, there was a statistically significant albeit small decrease in HDL-cholesterol concentration, with large heterogeneity, when replacing dietary palmitic with oleic acid based on the pooled analysis of 9 RCTs (WMD: -0.05 mmol/L; 95% CI: $-0.10, -0.005$ mmol/L; $I^2 = 78.6\%$). Results remained similar when excluding 2 RCTs with potential reporting errors in the full-text articles (Supplemental Figure 3) (45, 56). Meta-regression analyses revealed no effect of the amount of dietary palmitic acid exchanged for UFAs on the concentrations of HDL cholesterol (P value = 0.48).

The impact of other dietary FA substitutions was further assessed in 14 RCTs conducted between 1992 and 2010 (34, 35, 42, 44, 51, 59–61, 63–66, 68), which are described in Table 3. Overall, increased HDL-cholesterol concentrations were observed when replacing dietary medium-chain SFAs with myristic acid (63), stearic acid with oleic or linoleic acid (66, 68), and *trans*-FAs with a mixture of UFAs (44, 66). In contrast, the replacement of dietary palmitic acid with UFAs (35, 51) or *trans*-elaidic acid (*trans*-18:1n-9) (51), and myristic with palmitic acid (65), decreased concentrations of HDL cholesterol. Finally, the included RCTs did not reveal any significant impact of replacing medium-chain SFAs with UFAs on HDL-cholesterol concentrations (59–61, 63).

TC:HDL cholesterol ratio.

Replacing dietary palmitic acid with oleic acid or a mixture of UFAs led to a trend for a decrease in the TC:HDL cholesterol ratio, but the quantitative syntheses based on 3 and 4 RCTs, respectively, did not reach statistical significance (Supplemental Figure 4).

Other dietary fat replacements were studied in 7 RCTs conducted between 1997 and 2020 (Table 3) (16, 26, 28, 34, 38, 63, 68). No effects on the TC:HDL cholesterol ratio were observed when replacing dietary medium-chain SFAs with myristic or oleic acid (63), or when replacing dietary stearic acid with a mixture of UFAs (26, 38). Furthermore, the dietary replacement of palmitic with stearic acid was found to either increase or not affect the TC:HDL cholesterol ratio in 2 recent RCTs (16, 28).

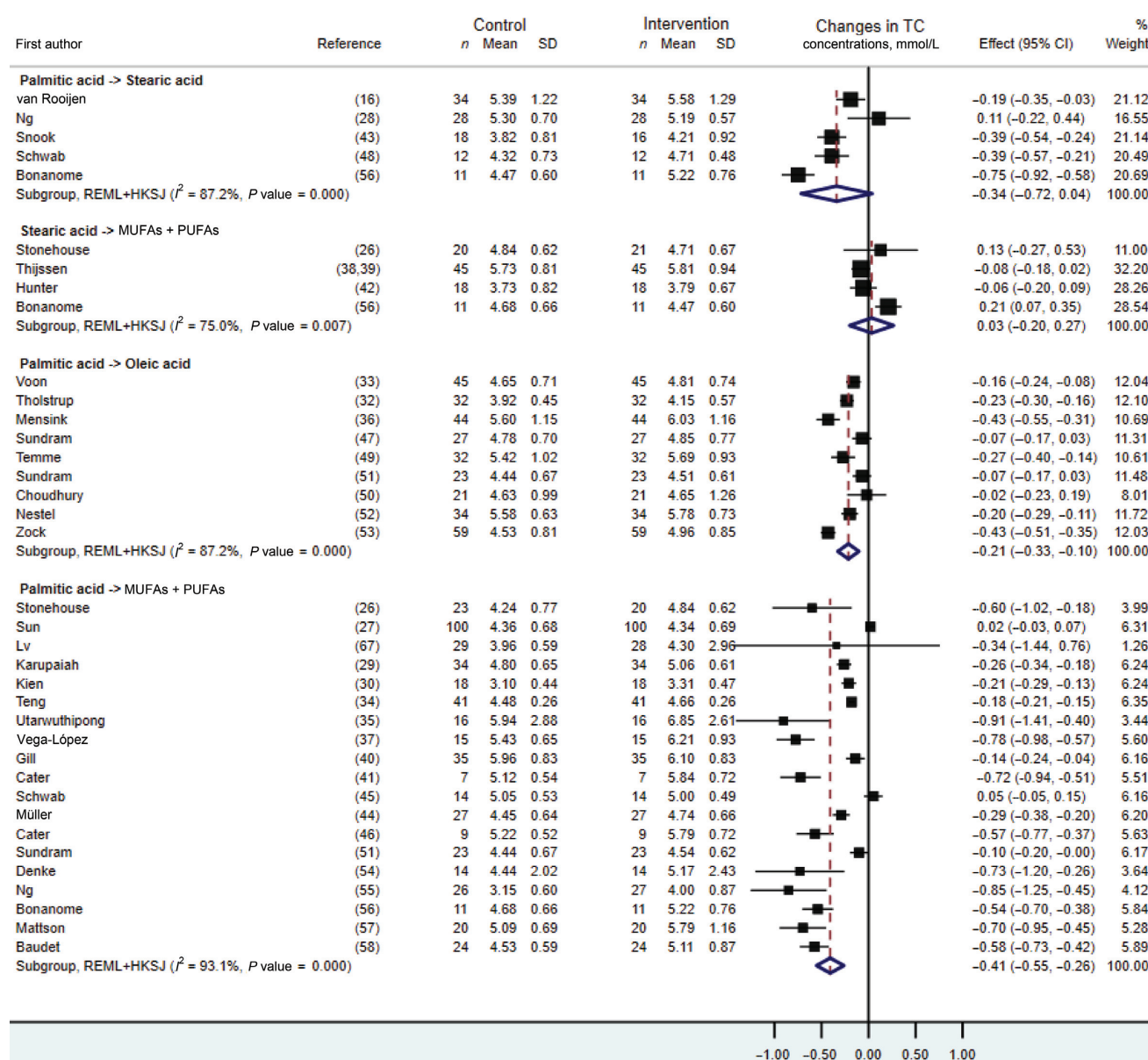


FIGURE 2 Forest plot of the effect of dietary fat substitutions on TC in randomized controlled trials. HKSJ, Hartung-Knapp-Sidik-Jonkman; REML, restricted maximum likelihood; TC, total cholesterol.

LDL cholesterol:HDL cholesterol ratio.

The replacement of dietary palmitic acid with a mixture of UFAs and its impact on the LDL cholesterol:HDL cholesterol ratio was investigated in 6 RCTs and showed a trend for a beneficial effect (i.e., decrease), although the quantitative synthesis did not reach statistical significance (WMD: -0.25 ; 95% CI: $-0.60, 0.09$; $I^2 = 17.6\%$, $n = 6$ RCTs) (Supplemental Figure 5). There was no correlation coefficient value available to correct the effect measures of the LDL cholesterol:HDL cholesterol ratio in crossover trials (Supplemental Table 1).

Other dietary fat replacements and their impact on LDL cholesterol:HDL cholesterol or HDL cholesterol:LDL cholesterol ratios were investigated in 8 RCTs which are

described in Table 3 (44, 47, 49, 51, 53, 56, 65, 66). Overall, findings from 2 RCTs suggested a beneficial effect (i.e., decreased LDL cholesterol:HDL cholesterol ratio) of dietary myristic acid compared with palmitic acid (53, 65), and of UFAs compared with *trans*-FAs (44, 66). However, the included RCTs showed no emerging trend of the impact of replacing dietary palmitic with oleic acid (47, 49, 51, 53) or stearic acid with UFAs (56, 66) on the LDL cholesterol:HDL cholesterol ratio.

VLDL cholesterol.

We observed no effect of the dietary exchange of palmitic acid for a mixture of UFAs on VLDL-cholesterol concentrations, and no evidence of interstudy heterogeneity

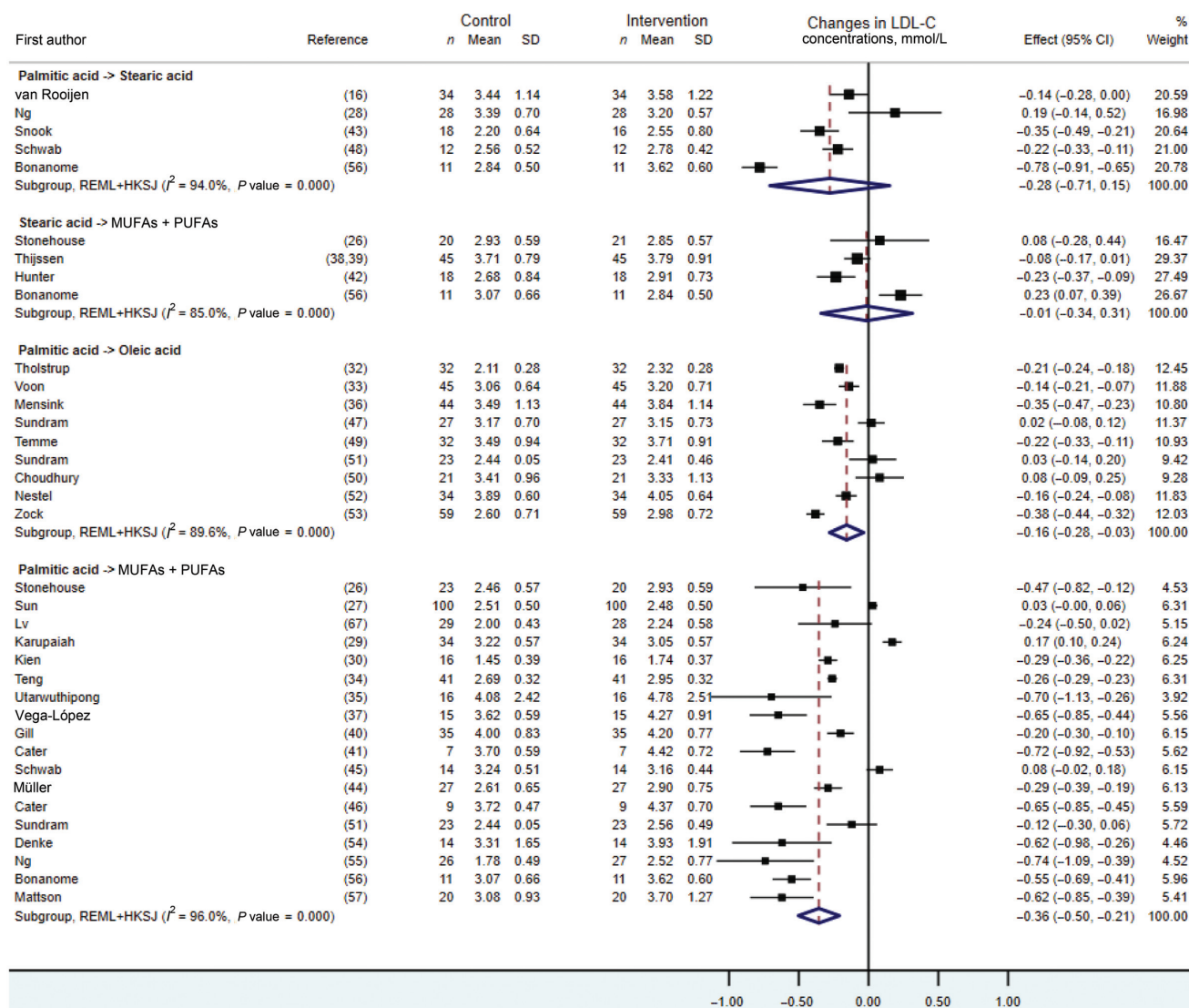


FIGURE 3 Forest plot of the effect of dietary fat substitutions on LDL-C in randomized controlled trials. HKSJ, Hartung-Knapp-Sidik-Jonkman; LDL-C, LDL cholesterol; REML, restricted maximum likelihood.

(WMD: 0.02 mmol/L; 95% CI: -0.09, 0.13 mmol/L; $I^2 = 0\%$, $n = 10$ RCTs) (**Supplemental Figure 6**). There was no correlation coefficient value available to correct the effect measures of VLDL-cholesterol concentrations in crossover trials (Supplemental Table 1).

The impact of other dietary fat replacements on VLDL-cholesterol fasting concentrations was investigated in 11 additional RCTs (40, 41, 47, 48, 51, 54, 56, 61, 64, 65) conducted between 1988 and 2003. As described in Table 3, the included RCTs showed no changes in VLDL-cholesterol concentrations after replacing dietary palmitic with stearic (48, 56) or linoleic acid (64). In particular, 1 crossover RCT conducted in 27 participants over 28 d observed reductions in VLDL-C concentrations when replacing dietary palmitic (4.1%TE) with oleic acid (2.7%TE) (47). In contrast, a 2003 parallel RCT conducted in 64 participants over 84 d found that dietary oleic acid might increase VLDL-cholesterol

concentrations compared with dietary medium-chain SFAs (61).

Triacylglycerol.

There was no statistically significant effect on triacylglycerol (TG) concentrations of the dietary substitution of palmitic with stearic acid, stearic acid with a mixture of UFAs, palmitic with oleic acid, or palmitic acid with a mixture of UFAs (Figure 6). In the latter, we found no effect of the amount of dietary palmitic acid exchanged for UFAs (P value = 0.36). These results remained unchanged when excluding 2 RCTs with potential reporting errors in the full-text articles (Supplemental Figure 7) (32, 51).

Other dietary fat substitutions and their impact on TG concentrations were described in 17 RCTs conducted between 1992 and 2010 (Table 3) (34, 35, 40–42, 44, 53, 54, 59–61, 63–66, 68). Four RCTs focused on

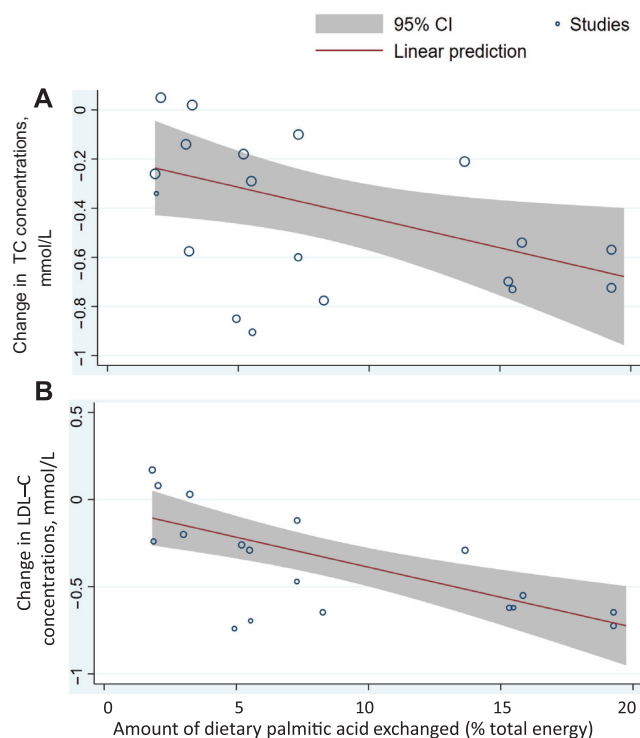


FIGURE 4 Dose-response meta-regression analysis of the change in (A) TC or (B) LDL-C concentration according to the amount of dietary palmitic acid exchanged with unsaturated fat (MUFAs + PUFAs). LDL-C, LDL cholesterol; TC, total cholesterol.

medium-chain SFAs and suggested their potential beneficial effect (i.e., decreased TG concentrations) compared with diets enriched in linoleic acid or a mixture of UFAs (59, 60), but not oleic acid (61, 63). Furthermore, dietary myristic acid does not seem to affect TG concentrations compared with palmitic or oleic acids according to 2 trials (53, 63). However, 1 crossover RCT which included 12 participants over 21 d observed beneficial effects of dietary myristic acid compared with palmitic acid on TG concentrations (65). Finally, there was no evidence of an impact of replacing dietary *trans*-FAs with a mixture of UFAs on TG concentrations, according to 2 trials (44, 66).

apoA-I.

In quantitative syntheses presented in Figure 7, we observed no statistically significant effect on apoA-I concentrations after the dietary replacement of palmitic with stearic acid, oleic acid, or a mixture of UFAs. These results remained unchanged after the exclusion of 2 RCTs containing potential reporting errors in the full-text articles (Supplemental Figure 8) (28, 29). The impact of other dietary fat replacements on apoA-I concentrations was investigated in 12 RCTs conducted between 1992 and 2020 (Table 3) (26, 34, 38, 40, 44, 53, 59, 60, 63, 65, 66, 68). Among those, 3 RCTs reported significant increases in apoA-I when replacing dietary medium-chain SFAs with myristic acid (63), stearic with oleic acid (68), or *trans*-FAs with UFAs

(66) and 1 RCT reported reductions in apoA-I concentrations when replacing dietary myristic with palmitic or oleic acid (53).

apoB.

In pooled meta-analyses, we observed no statistically significant effect on apoB concentrations of the dietary replacement of palmitic with stearic acid (Figure 8). However, small reductions in apoB concentration were observed in response to the dietary replacement of palmitic acid with oleic acid (WMD: -0.05 g/L; 95% CI: -0.07 , -0.04 g/L; $I^2 = 0.0\%$, $n = 5$ RCTs) or a mixture of UFAs (WMD: -0.06 g/L; 95% CI: -0.10 , -0.01 g/L; $I^2 = 98.8\%$, $n = 9$ RCTs), with the latter showing evidence of high statistical heterogeneity.

Other dietary fat replacements and their impact on apoB concentrations were investigated in 12 RCTs and are described in Table 3 (26, 34, 38, 40, 44, 53, 59, 60, 63, 65, 66, 68). The effects of replacing medium-chain SFAs with UFAs was investigated in 3 RCTs, which reported no effect of oleic acid (63), a beneficial effect (decreased apoB concentrations) of linoleic acid (59), and a deleterious effect of a mixture of UFAs (60). Furthermore, there was no evidence for a significant effect of myristic acid compared with palmitic acid (53, 65); however, 1 crossover RCT which included 59 participants over 21 d reported decreased apoB concentrations when myristic acid was replaced with oleic acid (53). Finally, 2 RCTs observed reductions in apoB concentrations when replacing dietary *trans*-FAs with a mixture of UFAs (44, 66).

Other lipid-related outcomes

Three RCTs reported that replacing dietary palmitic acid with a mixture of UFAs did not affect the concentrations of nonesterified fatty acids (NEFAs) (Supplemental Figure 9). Table 3 describes findings on other lipid outcomes, including the apoA-I:apoB ratio, apoA-II, apoE, HDL₂ cholesterol, HDL₃ cholesterol, TG content in lipoproteins, and lipoprotein (a) [Lp(a)]. The following qualitative synthesis section will highlight the main findings on these outcomes reported in eligible RCTs.

Additional lipoprotein concentrations, such as apoA-I:apoB ratio, apoA-II, or apoE, were measured in 11 RCTs (16, 26, 37, 47, 49, 51, 59, 60, 63, 66, 67). In particular, 3 RCTs found beneficial effects (i.e., increase) on the apoA-I:apoB ratio after the dietary replacement of medium-chain SFAs with myristic or oleic acid (63), stearic with linoleic acid (66), or *trans*-FAs with a mixture of UFAs (66). In contrast, 1 recent crossover RCT which included 35 participants over 21 d observed deleterious effects of dietary stearic acid compared with palmitic acid on the apoA-I:apoB ratio (16). Moreover, 1 RCT observed significant increases in apoA-II concentrations with substitution of dietary medium-chain SFAs with a mixture of UFAs (60). One trial further reported increased apoE concentrations, in men only, when replacing dietary medium-chain SFAs with linoleic acid (59). Based on findings from 2 RCTs, apoA-II and apoE concentrations were

TABLE 3 Qualitative synthesis of dietary FA exchanges and measured outcomes from eligible randomized controlled trials which were not eligible for quantitative meta-analyses¹

Authors	Type and amount of dietary FA exchanged (%TE)		Outcomes measured and not pooled	Changes in outcomes in the intervention diet compared with control ²
	Control diet	Intervention diet		
van Rooijen et al. (16)	16:0 (6.1)	18:0 (6.5)	apoB:apoA-I ratio, C-peptide, CRP, glucose, HOMA-IR, IL-6, insulin, TC:HDL-C ratio, TNF- α	↑ apoB:apoA-I ratio, HOMA-IR (women only), IL-6, insulin (women only), TC:HDL-C ratio, TNF- α ; ↓ C-peptide (men only)
Stonehouse et al. (26)	16:0 (7.3) 18:0 (10.6)	MUFAs + PUFAs (7.2) MUFAs + PUFAs (8.3)	apoB:apoA-I ratio, leptin apoA-I, apoB, apoB:apoA-I ratio, glucose, leptin, TC:HDL-C ratio	NSD NSD
Sun et al. (27)	16:0 (3.2)	MUFAs + PUFAs (3.3)	HOMA-IR	NSD
Lv et al. (67)	16:0 (1.9)	MUFAs + PUFAs (1.2)	apoE, HOMA-IR, leptin, Lp(a)	NSD
Ng et al. (28)	16:0 (6.0)	18:0 (7.0)	C-peptide, glucose, leptin, Lp(a), TC:HDL-C ratio, HOMA-IR, insulin	NSD
	16:0 (5.4)	18:0 (6.8)	C-peptide, glucose, leptin, Lp(a), TC:HDL-C ratio, HOMA-IR, insulin	NSD
Karupiah et al. (29)	16:0 (1.8)	MUFAs + PUFAs (1.5)	N/A	NSD
Kien et al. (30)	16:0 (13.7)	MUFAs + PUFAs (13.9)	Adiponectin	NSD
Rosqvist et al. (31)	16:0 (5.2)	MUFAs + PUFAs (7.5)	Adiponectin	NSD
Tholstrup et al. (32)	16:0 (4.6)	18:1 (4.8)	CRP, glucose, insulin, PAI-1 activity	NSD
Voon et al. (33)	16:0 (4.9)	18:1 (6.8)	Lp(a)	NSD
Teng et al. (34)	16:0 (5.2) 16:0 (5.8)	MUFAs + PUFAs (9.4) 18:1- <i>trans</i> (9.9)	IL-6, TNF- α	NSD
Utarwuthipong et al. (35)	16:0 (1.8) 16:0 (5.5) 16:0 (2.7) 16:0 (3.8) 16:0 (2.8) 16:0 (4.2) 16:0 (7.5) 16:0 (8.3)	MUFAs + PUFAs (17.3) MUFAs + PUFAs (21.5) MUFAs + PUFAs (18.4) 18:2n-6 (4.6) 18:2n-6 (3.4) 18:1 (2.9) MUFAs + PUFAs (6.2) MUFAs + PUFAs (9.7)	apoA-I, apoB, CRP, IL-6, TC, TC:HDL-C ratio, TG, TNF- α , LDL-C, HDL-C HDL-C, LDL-C, TC, TG N/A HDL-C, LDL-C, TC, TG HDL-C, LDL-C, TC, TG HDL-C, LDL-C, TC, TG CRP, glucose apoA-II, HDL ₂ -C, HDL ₃ -C, HOMA-IR, Lp(a)	↓ HDL-C NSD ↓ HDL-C ↓ LDL-C, TC ↓ LDL-C, TC ↓ HDL-C, TC ↓ HDL ₃ -C NSD
Mensink (36)	16:0 (4.2)	MUFAs + PUFAs (6.2)		NSD
Vega-López et al. (37)	16:0 (7.5)	MUFAs + PUFAs (9.7)		NSD
Thijssen et al. (38, 39)	18:0 (19.7) 18:0 (19.7)	MUFAs + PUFAs (20.2) MUFAs + PUFAs (20.0)	apoA-I, apoB, fibrinogen, PAI-1 activity, TC:HDL-C ratio	NSD NSD
Gill et al. (40)	16:0 (3.0) 16:0 (6.1)	MUFAs + PUFAs (3.6) MUFAs (6.6)	Lp(a)	NSD
	16:0 (3.1)	MUFAs (3.0)	apoA-I, apoB, CRP, HDL-C, insulin, LDL-C, Lp(a), NEFA, TC, TG, VLDL-C	↑ insulin; ↓ apoB, LDL-C, TC
Cater and Denke (41)	16:0 (19.3) > 18:0 (17.0)	MUFAs + PUFAs (21.2) MUFAs + PUFAs (19.0)	N/A	↑ insulin; ↓ apoB, LDL-C, TC
Hunter et al. (42)	18:0 (10.7) 18:0 (10.7)	18:1 (11.1)	HDL-C, LDL-C, TC, TG, VLDL-C Fibrinogen, HDL-C, LDL-C, PAI-1 activity, TC, tPA activity	↓ LDL-C, TC NSD
Snook et al. (43)	18:0 (10.7) 16:0 (10.0)	MUFAs + PUFAs (10.3) 18:0 (10.8)	Fibrinogen, PAI-1 activity, tPA activity HDL ₂ -C, HDL ₃ -C	NSD NSD

(Continued)

TABLE 3 (Continued)

Authors	Type and amount of dietary FA exchanged (%TE)		Outcomes measured and not pooled	Changes in outcomes in the intervention diet compared with control ²
	Control diet	Intervention diet		
Müller et al. (44)	16:0 (5.5) Total <i>trans</i> (6.8)	MUFAs + PUFAs (4.5) MUFAs + PUFAs (5.6)	Lp(a) apoA-I, apoB, HDL-C, LDL-C, LDL-C:HDL-C ratio, Lp(a), TC, TG	NSD ↑ HDL-C; ↓ apoB, LDL-C, LDL-C:HDL-C ratio, TC
Schwab et al. (45)	16:0 (2.0)	MUFAs + PUFAs (1.6)	N/A	NSD
Cater et al. (46)	16:0 (19.3)	MUFAs + PUFAs (21.3)	N/A	NSD
Sundram et al. (47)	16:0 (4.1)	18:1 (2.7)	apoBapoA-I ratio, LDL-C:HDL-C ratio, Lp(a), VLDL-C	↓ VLDL-C
Schwab et al. (48)	16:0 (3.3)	18:0 (4.9)	HDL-TG, LDL-TG, VLDL-C, VLDL-TG	NSD
Temme et al. (49)	16:0 (7.5)	18:1 (8.4)	apoA-I:apoB ratio, HDL-C:LDL-C ratio, Lp(a)	NSD
Choudhury et al. (50)	16:0 (5.0)	18:1 (7.3)	N/A	NSD
Sundram et al. (51)	16:0 (4.3)	18:1 (5.1)	apoBapoA-I ratio, HDL ₂ -C, HDL ₃ -C, LDL-C:HDL-C ratio, Lp(a), VLDL-C	↑ LDL-C:HDL-C ratio; ↓ HDL-C
	16:0 (3.0)	MUFAs + PUFAs (6.8)	apoA-I, apoB, apoBapoA-I ratio, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, LDL-C:HDL-C ratio, Lp(a), TC, TG, VLDL-C	↓ LDL-C:HDL-C ratio
Nestel et al. (52)	16:0 (7.3) 16:0 (3.3) 16:0 (3.4)	MUFAs + PUFAs (6.8) 16:1 (3.8) 18:1 (2.7)	apoBapoA-I ratio, HDL ₂ -C, HDL ₃ -C, Lp(a) HDL-C, LDL-C, TC, TG	NSD ↓ HDL-C
Zock et al. (53)	14:0 (10.2) 14:0 (10.5) 16:0 (9.9)	16:0 (10.2) 18:1 (10.0) 18:1 (9.3)	apoA-I, apoB, HDL-C, HDL-C:LDL-C ratio, LDL-C, TC, TG	NSD ↓ apoA-I, HDL-C, HDL-C:LDL-C ratio, LDL-C, TC ↑ HDL-C:LDL-C ratio; ↓ apoA-I, apoB, HDL-C, LDL-C, TC ↑ HDL-C:LDL-C ratio ↓ LDL-C, TC
Denke and Grundy (54)	12:0 (17.5) 16:0 (15.5) 16:0 (4.9)	MUFAs + PUFAs (16.3) MUFA + PUFA (16.6) MUFAs + PUFAs (4.8)	HDL-C:LDL-C ratio HDL-C, LDL-C, TC, TG, VLDL-C	NSD NSD
Ng et al. (55)	16:0 (14.8)	18:0 (15.3)	N/A	NSD
Bonanome and Grundy (56)	16:0 (15.8) 18:0 (16.3)	MUFAs + PUFAs (17.4) MUFAs + PUFAs (17.7)	LDL-C:HDL-C ratio, VLDL-C LDL-C:HDL-C ratio, VLDL-C	↓ LDL-C:HDL-C ratio NSD
Mattsson and Grundy (57)	16:0 (15.3) 16:0 (14.8)	MUFAs + PUFAs (15.2) MUFAs + PUFAs (15.2)	N/A	NSD
Baudet et al. (58)	16:0 (3.1) 16:0 (2.1)	MUFAs + PUFAs (2.8) MUFAs + PUFAs (0.7)	N/A	NSD
Liu et al. (59)	Men: <12:0 (1.81) Women: <12:0 (1.87)	Men: 18:2n-6 (1.69) Women: 18:2n-6 (1.59)	apoA-I, apoB, apoE, glucose, HDL-C, LDL-C, TC, TG	NSD Observed in men only: ↑ TG, apoE, ↓ apoB, LDL-C
Xue et al. (60)	<12:0 (1.8)	MUFAs + PUFAs (1.3)	Adiponectin, apoA-I, apoA-II, apoB, apoE, glucose, HDL-C, LDL-C, TC, TG	↑ apoA-II, apoB, LDL-C, TG
Nosaka et al. (61)	<12:0 (3.0)	18:1 (1.6)	glucose, HDL-C, HDL-TG, LDL-TG, TC, TG, VLDL-C, VLDL-TG	↑ VLDL-C
Judd et al. (68)	18:0 (8.0)	18:1 (7.1)	apoA-I, apoB, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, TC, TC:HDL-C ratio, TG	↑ apoA-I, HDL-C, HDL ₃ -C; ↓ LDL-C, TC, TC:HDL-C ratio, TG
	18:0 (4.1)	Total <i>trans</i> (4.1)		NSD

(Continued)

TABLE 3 (Continued)

Authors	Type and amount of dietary FA exchanged (%TE)		Outcomes measured and not pooled	Changes in outcomes in the intervention diet compared with control ²
	Control diet	Intervention diet		
Temme et al. (62)	18:0 (8.1)	Total <i>trans</i> (8.0)	Fibrinogen, PAI-1 activity apoA-I, apoA-IIapoB ratio, apoB, HDL-C, LDL-C, Lp(a), TC, TC:HDL-C ratio, TG	↑ LDL-C, TC, TC:HDL-C ratio; ↓ apoB ↑ apoB, LDL-C, TC ↓ PAI-1 activity ↑ apoA-I:apoB ratio
	18:0 (4.0)	Total <i>trans</i> (3.9)		
	16:0 (6.1)	18:1 (6.8)		
Temme et al. (63)	<12:0 (9.9)	18:1 (10.1)		
Ghafoorunissa et al. (64)	<12:0 (9.9)	14:0 (9.7)	HDL-C, LDL-C, TC, TG, VLDL-C	↑ apoA-I, apoA-II:apoB ratio, HDL-C ↓ LDL-C, TC NSD NSD
	14:0 (9.6)	18:1 (10.4)		
	16:0 (5.0)	18:2n-6 (3.7)		
	16:0 (6.0)	18:2n-6 (3.7)		
Tholstrup et al. (65)	14:0 (13.4)	16:0 (12.8)	apoA-I, apoB, fibrinogen, HDL-C, HDL ₂ -C, HDL ₃ -C, LDL-C, LDL-C:HDL-C ratio, TC, TG, tPA activity, VLDL-C	↑ LDL-C, LDL-C:HDL-C ratio, TG; ↓ HDL-C, TC
Zock and Katan (66)	18:0 (9.0)	18:2n-6 (8.1)	apoA-I, apoA-IIapoB ratio, apoB, HDL-C, HDL-C:LDL-C ratio, LDL-C, TC, TG	↑ apoA-I:apoB ratio, HDL-C, HDL-C:LDL-C ratio; ↓ apoB, LDL-C, TC, TG
	Total <i>trans</i> (7.6)	MUFAs + PUFAs (7.5)		↑ apoA-I, apoA-II:apoB ratio, HDL-C, HDL-C:LDL-C ratio; ↓ apoB, LDL-C, TC

FAs considered: lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), stearic acid (18:0), palmitoleic acid (16:1n-7), oleic acid (18:1n-7), linoleic acid (18:2n-6), α -linolenic acid (18:2n-3), CAD, coronary artery disease; CRP, C-reactive protein; FA, fatty acid; HDL-C, HDL cholesterol; HDL₂-C, HDL₂ cholesterol; HDL₃-C, HDL₃ cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); N/A, not applicable; NEFA, nonesterified fatty acid; NSD, no significant difference; PAI-1, plasminogen activator inhibitor-1; TC, total cholesterol; TG, triacylglycerol; tPA, tissue plasminogen activator; VLDL-C, VLDL cholesterol; ↑, increase; ↓, decrease; %TE, percent total energy.

²Comparisons reported as statistically significant in the original full-text articles.

not affected by the dietary replacement of palmitic acid with a mixture of UFAs (37, 67).

Five RCTs measured the concentrations of HDL₂ cholesterol and HDL₃ cholesterol in plasma or serum in response to dietary replacements of myristic with palmitic acid (65); of palmitic acid with stearic acid (43), oleic acid (51), or a mixture of UFAs (37, 51); and of stearic acid with oleic acid or *trans* FAs (68). Whereas no effects were observed on HDL₂ cholesterol, 1 study reported decreased HDL₃-cholesterol concentrations in response to the replacement of dietary palmitic acid with a mixture of UFAs (37), and another reported a greater HDL₃-cholesterol concentration after replacing dietary stearic with oleic acid (68). Furthermore, 2 RCTs measured the TG content of HDL, LDL, and VLDL fractions, and reported no changes after replacing dietary medium-chain SFAs with oleic acid (61) or palmitic with stearic acid (48).

Finally, 10 RCTs assessed the impact of various dietary fat exchanges on concentrations of Lp(a) (28, 33, 37, 40, 44, 47, 49, 51, 63, 67), including the replacement of palmitic acid with a mixture of UFAs ($n = 5$ RCTs) (37, 40, 44, 51, 67) or oleic acid ($n = 4$ RCTs) (33, 47, 49, 51). None of the included RCTs reported significant changes in Lp(a) concentrations after the dietary interventions.

Effect of dietary fat replacement on markers of glycemic control

Glucose.

Six RCTs investigated the impact of replacing dietary palmitic acid with a mixture of UFAs on fasting glucose concentrations, without showing any statistically significant overall effect (WMD: -0.04 mmol/L; 95% CI: -0.10 , 0.01 mmol/L; $I^2 = 35.5\%$, $n = 6$ RCTs) (Supplemental Figure 10A). In addition, 8 RCTs measured glucose concentrations in response to other dietary fat exchanges (16, 26, 28, 32, 36, 59–61), but none reported statistically significant changes (Table 3).

Insulin.

Similar results were observed in the pooled analysis of 5 RCTs which showed no overall effect of replacing dietary palmitic acid with a mixture of UFAs on fasting insulin concentrations (WMD: -2.60 pmol/L; 95% CI: -9.66 , 4.47 pmol/L; $I^2 = 68.9\%$, $n = 5$ RCTs) (Supplemental Figure 10B). Four RCTs further assessed the effects of replacing dietary palmitic acid with stearic acid (16, 28), oleic acid (32), or MUFAs (40) on insulin concentrations. Results from these trials, as described in Table 3, suggest a tendency for increased fasting insulin concentrations when replacing dietary palmitic acid with stearic acid or MUFAs (16, 40).

Other markers of glycemic control and insulin resistance.

As detailed in Table 3, 2 RCTs investigated the impact of replacing dietary palmitic with stearic acid on HOMA-IR and C-peptide concentrations (16, 28), 1 of which observed

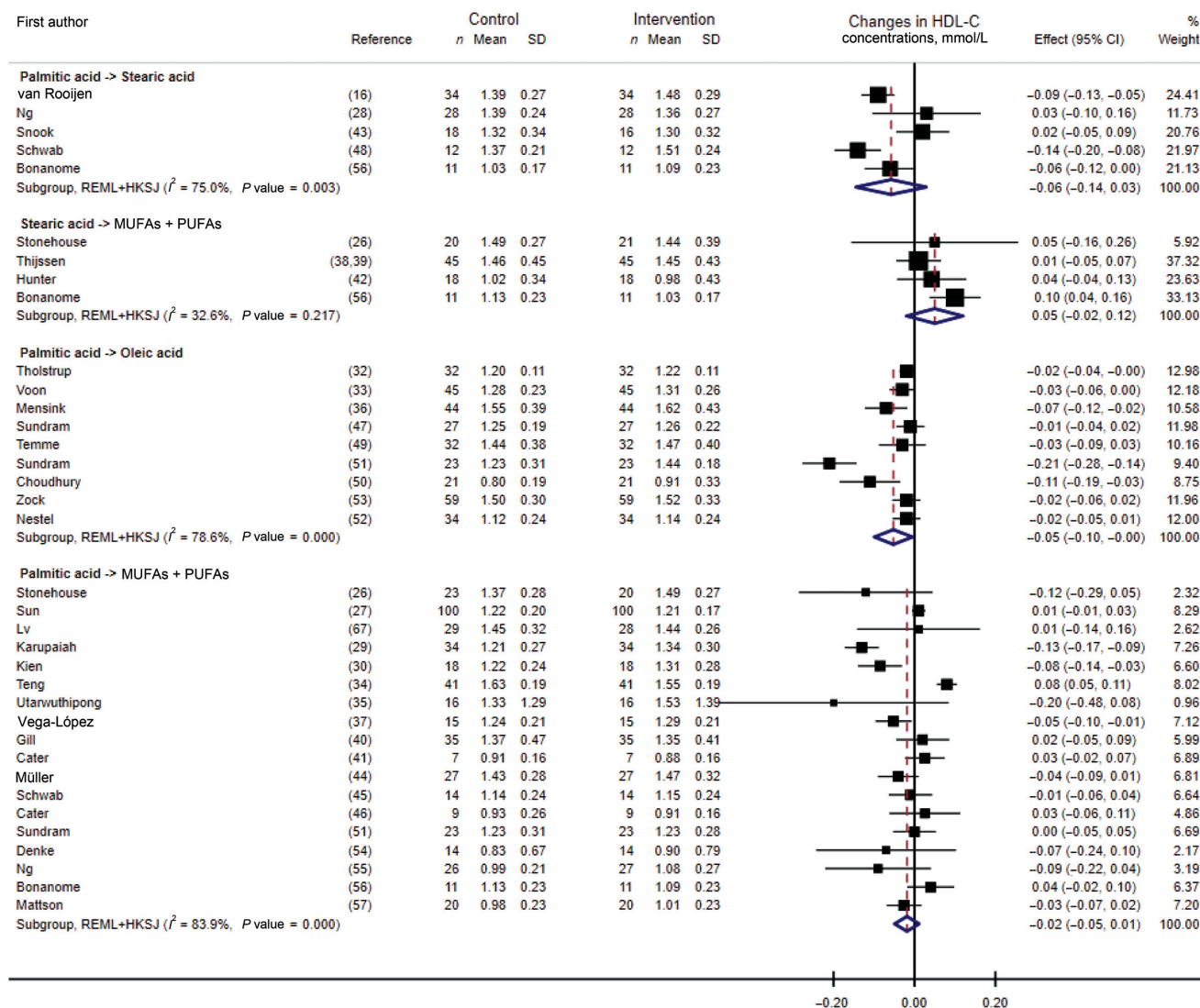


FIGURE 5 Forest plot of the effect of dietary fat substitutions on HDL-C in randomized controlled trials. HDL-C, HDL cholesterol; HKSJ, Hartung-Knapp-Sidik-Jonkman; REML, restricted maximum likelihood.

decreased C-peptide concentrations and increased HOMA-IR after a diet rich in stearic acid compared with a palmitic acid-rich diet (16). Furthermore, 3 trials investigated the effects of replacing dietary palmitic acid with a mixture of UFAs, without showing any significant impact on HOMA-IR (27, 37, 67).

Effect of dietary fat replacement on markers of inflammation

Three RCTs investigated the effects of replacing dietary palmitic acid with a mixture of UFAs on C-reactive protein (CRP) or high-sensitivity CRP concentrations and showed no overall effect (WMD: -0.02 mg/L; 95% CI: -0.04 , 0.01 mg/L; $I^2 = 0.0\%$, $n = 3$ RCTs) (Supplemental Figure 11). In addition, CRP concentrations in response to the dietary replacement of palmitic acid with stearic acid, oleic

acid, *trans*-elaidic acid, or MUFAs were assessed in 5 trials (Table 3) (16, 32, 34, 36, 40). Only 1 crossover study, which included 41 participants over 35 d, observed a detrimental impact on CRP concentrations (i.e., increase) after a diet rich in *trans*-FAs compared with a palmitic acid-rich diet (34). Other markers of inflammation, such as IL-6 and TNF- α , were investigated in 2 RCTs (16, 34), 1 of which showed detrimental changes in these 2 markers (i.e., increased concentrations) after replacing dietary palmitic with stearic acid (16).

Effect of dietary fat replacement on metabolic hormone concentrations and markers of hemostasis

Six RCTs measured concentrations of adiponectin (30, 31, 60) or leptin (26, 28, 67) in response to dietary fat replacements (Table 3). The authors did not report any

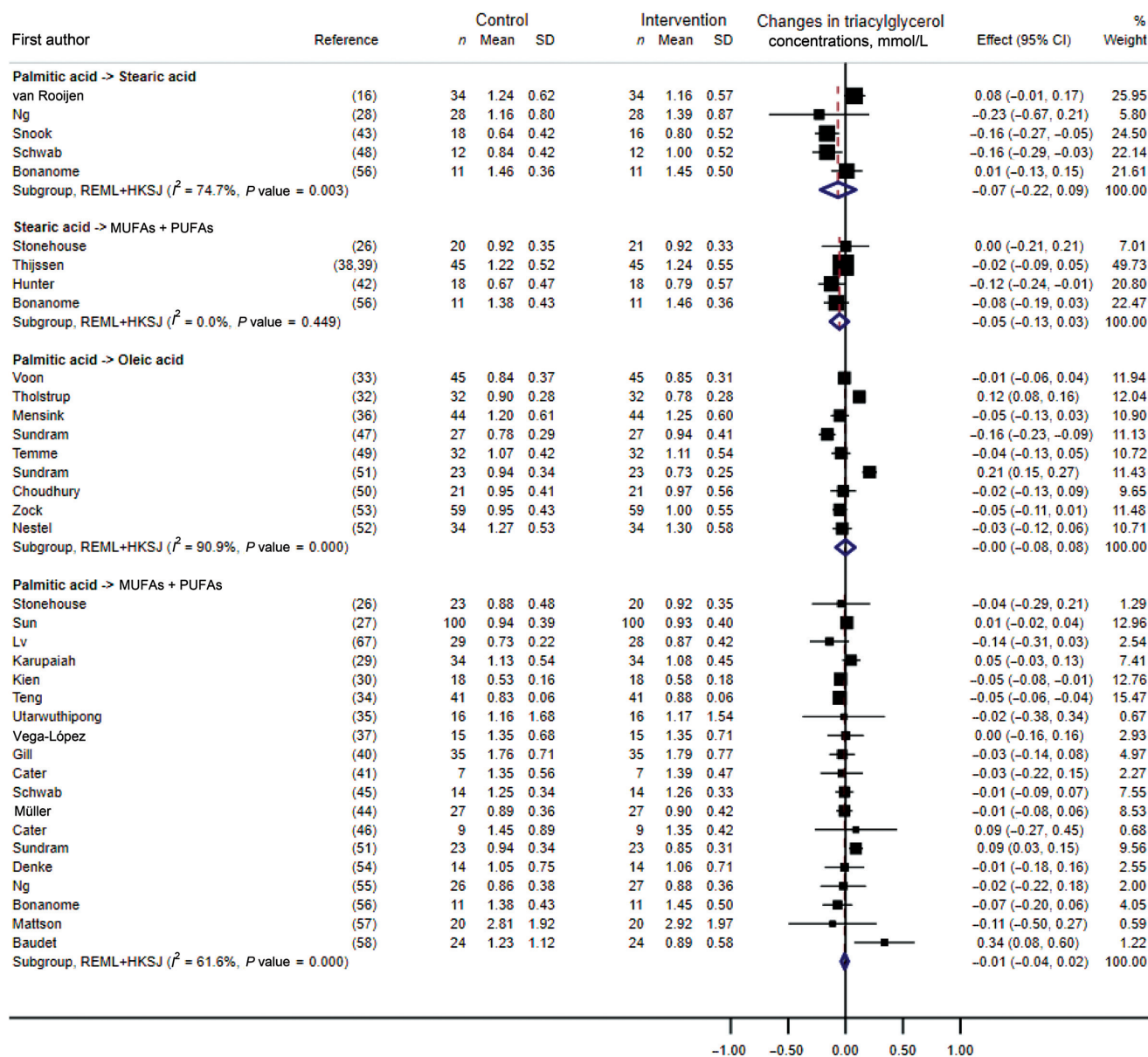


FIGURE 6 Forest plot of the effect of dietary fat substitutions on triacylglycerol concentrations in randomized controlled trials. HKSJ, Hartung-Knapp-Sidik-Jonkman; REML, restricted maximum likelihood.

effects on these 2 hormones of replacing dietary palmitic acid with stearic acid or a mixture of UFAs, medium-chain SFAs with a mixture of UFAs, or stearic acid with a mixture of UFAs.

Similarly, 5 RCTs investigated the response of markers of hemostasis, such as fibrinogen concentration, tissue-type plasminogen activator activity, and plasminogen activator inhibitor-1 (PAI-1) activity, to dietary fat exchanges (Table 3) (32, 39, 42, 62). The dietary interventions assessed in these trials included the replacement of myristic with palmitic acid, of palmitic or stearic acids with oleic acid, and of stearic acid with a mixture of UFAs. Only 1 of these RCTs observed a beneficial effect (i.e., decrease) of replacing palmitic with oleic acid on PAI-1 activity (62).

Reporting biases

As per our predefined protocol, the assessment of reporting bias was conducted for quantitative syntheses that included ≥ 10 RCTs, which applied to those assessing the impact of replacing dietary palmitic acid with a mixture of UFAs on concentrations of TC, LDL cholesterol, HDL cholesterol, and TG. The results from Egger's tests did not indicate any signs of publication bias or small study effects in the quantitative synthesis of HDL cholesterol (P value = 0.12). However, potential publication bias was found in the syntheses of TC (P value = 0.006), LDL cholesterol (P value = 0.04), and TG (P value = 0.04). For these outcomes, contour-enhanced funnel plots and corrections using the trim-and-fill method yielded similar summary effects to the ones observed without

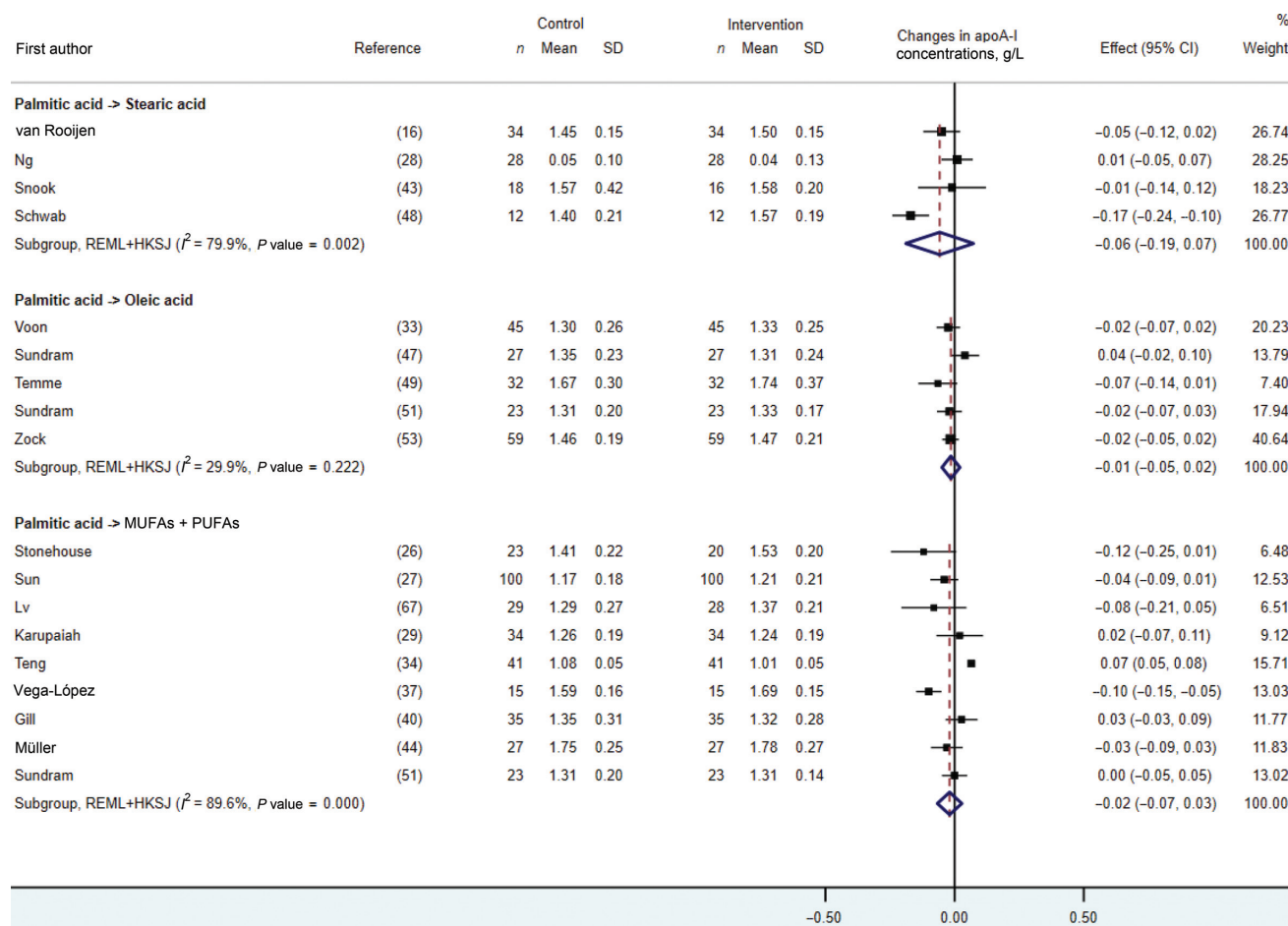


FIGURE 7 Forest plot of the effect of dietary fat substitutions on apoA-I concentrations in randomized controlled trials. HKSJ, Hartung-Knapp-Sidik-Jonkman; REML, restricted maximum likelihood.

corrections (WMD for TC: -0.30 mmol/L; 95% CI: -0.44 , -0.15 mmol/L, **Supplemental Figure 12A**; WMD for LDL cholesterol: -0.34 mmol/L; 95% CI: -0.47 , -0.20 mmol/L, **Supplemental Figure 12B**; and WMD for TG: 0.00 mmol/L; 95% CI: -0.03 , 0.03 mmol/L, **Supplemental Figure 12C**).

Discussion

This systematic review of RCTs is the first, to our knowledge, to investigate the role of replacement of individual dietary SFAs on biomarkers of CMD risk. In our meta-analyses, we found the isoenergetic dietary replacement of $\geq 1.5\%$ TE of palmitic acid with oleic acid or UFAs for a duration of ≥ 14 d had significant beneficial impacts on lipid CMD risk markers, including TC, LDL cholesterol, and apoB concentrations in adults, albeit with high heterogeneity. In particular, there was a significant linear relation between the amount of dietary palmitic acid exchanged with UFAs and the decreases observed in fasting LDL-cholesterol and TC concentrations. There was, however, no significant effect of the latter dietary substitution on other lipid CMD risk markers such as circulating HDL-cholesterol, VLDL-cholesterol, TG, apoA-I, or NEFA concentrations, or the TC:HDL cholesterol or LDL

cholesterol:HDL cholesterol ratios. Our qualitative synthesis highlighted the abundance of RCTs investigating the effects of dietary palmitic acid, and to a lesser extent stearic acid, whereas trials on other SFAs such as myristic or lauric acids were much scarcer. Most of the trials included focused on traditional biomarkers of CMD risk such as fasting lipid profiles, with little evidence on other risk factors such as markers of inflammation, hemostasis, glycemic control, or metabolic hormones.

Our findings are in line with results from the 2019 UK Scientific Advisory Committee on Nutrition (SACN) on SFA and health, which reported adequate evidence from RCTs supporting the hypothesis that a replacement of overall dietary SFAs with MUFAs or PUFAs might lead to lower concentrations of TC and LDL cholesterol (8). In addition, the report did not suggest any effect on HDL-cholesterol concentrations (moderate evidence quality), TG concentrations (adequate evidence quality), or the TC:HDL cholesterol ratio (limited evidence quality) (8). Furthermore, our SLR adds novel evidence regarding the apolipoprotein responses to individual dietary SFAs, which were not investigated in the 2019 SACN report. In quantitative meta-analyses,

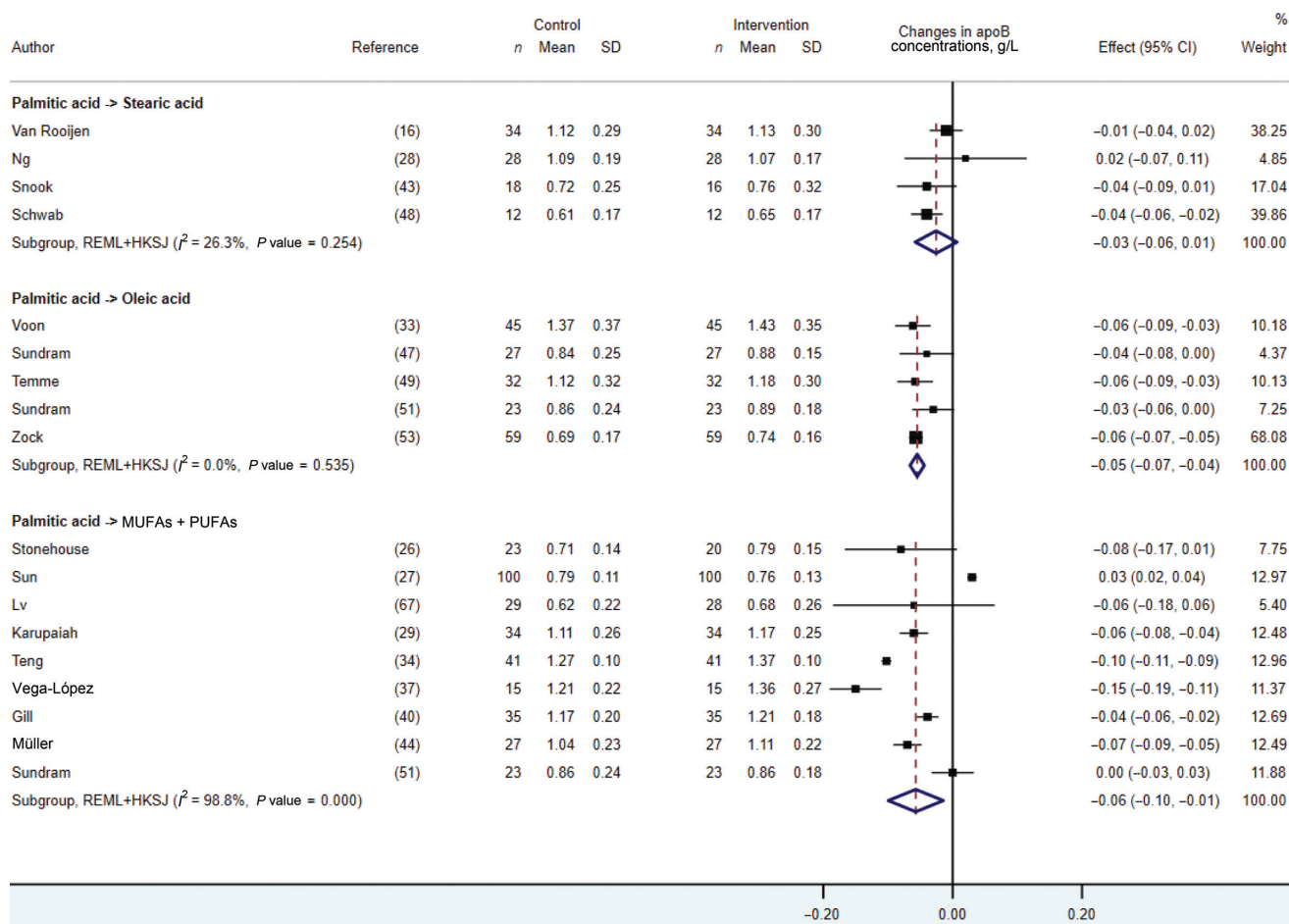


FIGURE 8 Forest plot of the effect of dietary fat substitutions on apoB concentrations in randomized controlled trials. HKSJ, Hartung-Knapp-Sidik-Jonkman; REML, restricted maximum likelihood.

we observed similar effects of the replacements of dietary palmitic acid with UFAs or oleic acid on apoB and LDL-cholesterol, and on apoA-I and HDL-cholesterol concentrations, which reflects the main apoproteins associated with these lipoproteins.

Although there is no previous SLR and meta-analysis of RCTs on the effects of individual dietary SFAs available in the literature to our knowledge, in 2014 Fattore et al. (69) systematically reviewed RCTs on the effects of palm olein-rich diets compared with other dietary fats on fasting lipids. Their meta-analyses included some RCTs also reviewed in our SLR, and authors observed beneficial effects on LDL-cholesterol concentrations of diets rich in stearic acid ($n = 8$) or MUFAs ($n = 20$), but not PUFAs ($n = 14$), in comparison with palm olein-rich diets. They further reported that PUFA-rich diets might decrease concentrations of TC ($n = 16$), HDL cholesterol ($n = 16$), apoA-I ($n = 7$), and apoB ($n = 7$) (69). These results suggested contrasting effects of palm olein on different CVD risk markers and might be confounded by the composition of the palm olein used in the included RCTs, which contained palmitic acid as the main source of SFA but was also a small dietary source of oleic and linoleic acids.

Overall, our findings are supported by experimental evidence suggesting that as opposed to dietary UFAs, SFAs and particularly palmitic acid are associated with downregulation of the expression of LDL receptors on the surface of hepatocytes. This can result in higher circulating concentrations of LDL cholesterol and a potential increased risk of developing and/or exacerbating atherosclerosis (70, 71). In addition, previous RCTs have suggested that dietary SFAs may be associated with higher concentrations of E-selectin (72, 73), a biomarker of atherosclerosis and endothelial activation, although this SLR did not identify RCTs investigating the impact of individual SFAs on this cell adhesion molecule.

The limited number of RCTs may have contributed to the lack of identified statistically significant effects of replacing dietary palmitic acid with UFAs on markers of glycemic control (i.e., fasting glucose and insulin concentrations) or inflammation (i.e., CRP concentrations) in our meta-analyses. However, when looking at overall dietary SFAs, authors from the 2019 SACN report observed beneficial effects of SFA substitution with PUFAs but not MUFAs on fasting glucose concentrations, a potential deleterious effect of dietary MUFAs but not PUFAs on fasting insulin

concentrations, and beneficial effects of both MUFAs and PUFAs on glycated hemoglobin (a long-term biomarker of glycemic control) based on adequate-quality evidence from RCTs (8). There is, to our knowledge, no SLR or meta-analysis looking at the effect of such dietary replacements on CRP concentrations.

Furthermore, replacing dietary palmitic acid with stearic acid may have little to no effect on lipid CMD risk markers, such as LDL cholesterol, TC, and apoB, but the evidence based on 4–5 RCTs with low numbers of participants is very uncertain. Our findings on the dietary substitution of stearic acid with UFAs, which did not affect concentrations of LDL cholesterol, HDL cholesterol, TC, or TG in meta-analyses based on 4 RCTs, contrast with meta-analyses on dietary palmitic acid substituted with UFAs. This supports the hypothesis that dietary stearic acid might be less detrimental than other SFAs such as palmitic acid on lipid CMD risk markers. However, these findings were based on only 4 RCTs, 2 of which were classified as high risk of bias because of insufficient washout periods between the intervention diets. Predictive studies based on linear regression equations previously suggested the potential lack of detrimental effects of dietary stearic acid compared with other SFAs on fasting lipids (11, 74). The underlying mechanisms to support this proposal are not yet elucidated, and some studies suggested stearic acid might be poorly absorbed compared with other SFAs (56, 75) or could be directly converted into oleic acid, although this metabolic pathway seems to be minimal in humans (76).

Finally, this SLR led to the identification of important gaps in the literature regarding individual dietary SFAs. In particular, there is a lack of RCTs investigating the impact of medium-chain SFAs, lauric acid, and myristic acid in comparison with other SFAs and/or UFAs. Overall, our qualitative synthesis suggested dietary myristic acid might have more deleterious effects than palmitic acid, oleic acid, or medium-chain SFAs on fasting lipid profiles, but no other emerging trends were evident from the other included RCTs. The potential atherogenic effect of dietary myristic acid has been previously investigated in predictive regression studies (74, 77), but a consensus on the true effect of myristic acid on cardiometabolic health has not yet been reached (78–80). Moreover, our qualitative synthesis highlighted that very few RCTs assessed the impact of individual SFAs on other biomarkers of cardiometabolic health status, such as metabolic hormone concentrations or markers of hemostasis and inflammation.

Overall, strengths of this SLR and meta-analysis pertain to its broad yet specific focus on individual dietary SFA substitutions. Our findings are the first and the most up-to-date, to our knowledge, to provide an exhaustive overview of the currently known causal effects of single dietary SFAs on a wide range of CMD risk biomarkers. This “single SFA” approach, which was ensured by strict a priori-defined inclusion criteria, allowed the investigation of the causal effect of specific isoenergetic dietary substitutions on cardiometabolic health while minimizing potential

confounding from other dietary FAs or macronutrients. This SLR also benefitted from a strong methodology based on the Cochrane and PRISMA guidelines. Nevertheless, some limitations also need to be acknowledged. Firstly, some of the included crossover trials with insufficient washout periods might present a high risk of bias due to potential carryover effects. This may have led to imprecise estimations of the beneficial effects of UFA-rich diets compared with palmitic acid-rich diets on some of the lipid outcomes reviewed in this SLR. In addition, we observed high statistical heterogeneity in meta-analyses on TC, LDL-cholesterol, HDL-cholesterol, and apolipoprotein concentrations, which might have prevented the detection of statistically significant effect sizes, particularly in meta-analyses with few RCTs reporting effects distributed around the null. However, some of the observed high heterogeneity might be explained by correlation coefficients used to estimate corrected intervention effects which account for the intraparticipant variation specific for this type of study design. Although this approach is recommended by the Cochrane handbook for systematic reviews (23), this may have led to underestimated CIs of the effects from individual RCTs. Furthermore, our analyses focused on individual dietary SFAs and might not account for potential food matrix effects from dietary sources of SFAs, such as red meat (81), dairy foods (82), or coconut, palm, and, to a lesser extent, other plant-based oils (83). For instance, dairy food intakes may be associated with lower CMD risks, despite being important dietary sources of palmitic acid and stearic acid (84, 85). Finally, the small number of studies included in quantitative syntheses precluded the detailed investigation of potential dose–response relations, high interstudy heterogeneity, and publication bias.

To conclude, our findings on the replacement of dietary palmitic acid with oleic acid or UFAs are overall in line with current public health recommendations which suggest reducing dietary SFAs in favor of UFAs to help prevent CMD. This further supports the hypothesis that dietary SFAs should not be considered as a homogeneous nutrient group, and that individual SFAs might have differential impacts on cardiometabolic health. However, our quantitative findings need to be interpreted with caution owing to the presence of high statistical heterogeneity and a low number of RCTs. With most of the available evidence focusing on dietary palmitic, and to a lesser extent stearic acid, and their impact on lipid profiles, further RCTs designed to investigate different SFAs such as lauric and myristic acids and their impact on other clinical biomarkers of CMD risk such as markers of inflammation, endothelial activation, and glycemic control are warranted. Overall, a more complete picture of the impact of dietary SFAs on metabolic health status would greatly contribute to the improvement of public health guidelines for the prevention of CMD.

Acknowledgments

We thank Dr. Odgerel Baasan, Dr. Wendy Blom, Dr. Marjolijn Bragt, Dr. Nils Billecke, Dr. Mathilde Fleith, and

Dr. Agnes Méheust as members of the ILSI Europe expert group who initiated the work and for their early contributions to the literature search. The authors' responsibilities were as follows—LS, MF, SL, JL, and RPM: performed the literature searches; LS, MF, KGJ, PJJ, JL, SL, RPM, and JAL: contributed to the screening of titles, abstracts, and full-text records; LS: performed the statistical analyses, under the supervision of SSS-M and SL, and drafted the manuscript; LS and JL: performed the risk of bias assessments; MF, KGJ, PJJ, JL, SL, RPM, SSS-M, and JAL: contributed to the interpretation of the data and revised each draft of the manuscript for important intellectual content; and all authors: contributed to data extraction from full-text records and read and approved the final manuscript.

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