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Original Research Article

Impact of saturated compared with unsaturated dietary fat on insulin sensitivity, pancreatic β-cell function, and glucose tolerance: a systematic review and meta-analysis of randomized, controlled trials

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A B S T R A C T

Background: The impact of the dietary fat type on type 2 diabetes (T2D) remains unclear.
Objectives: We aimed to evaluate the effects of replacing dietary saturated fatty acids (SFA) with mono or polyunsaturated fatty acids (MUFA and PUFA, respectively) on insulin sensitivity, pancreatic β-cell function, and glucose tolerance, as surrogate endpoints for T2D.
Methods: We conducted a systematic review and meta-analysis of randomized controlled trials that replaced ≥5% of total energy intake provided by SFA with MUFA or PUFA and reported indexes of insulin sensitivity, β-cell function, and/or glucose tolerance. We searched MEDLINE, Scopus, and the Cochrane Library (CENTRAL) up to 9 January, 2023. Eligible interventions had to be isocaloric, with no significant difference in other macronutrients. Data were synthesized using random-effects model meta-analysis.
Results: Of 6355 records identified, 10 parallel and 20 crossover trials with 1586 participants were included. The mean age of the participants was 42 y, 47% were male, mean body mass index (BMI; in kg/m^2) was 26.8, median baseline fasting glucose was 5.13 mmol/L, and the median duration of interventions was 5 wk. Replacing SFA with MUFA or PUFA had no significant effects on insulin sensitivity [standardized mean difference (SMD) SFA compared with MUFA: 0.01, 95% confidence interval (CI): −0.06 to 0.09, I^2 = 0% and SMD SFA compared with PUFA: 0, 95% CI: −0.15 to 0.14, I^2 = 0%]. Replacing SFA with MUFA did not significantly impact the β-cell function, evaluated by the disposition index (mean difference: −12, 95% CI: −158 to 133, I^2=0%). Evidence on glucose tolerance (SFA compared with MUFA or PUFA) and on β-cell function when SFA were replaced with PUFA was scant.
Conclusions: Short-term substitution of saturated with unsaturated fat does not significantly affect insulin sensitivity nor the β-cell function (the latter in the SFA compared with MUFA comparison). Future studies are needed to elucidate longer term effects of dietary fat saturation on glucose homeostasis. This trial was registered at PROSPERO as CRD42020178382.

Keywords: saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, insulin sensitivity, insulin secretion, type 2 diabetes, beta-cell function, dietary fat

Introduction

Maintaining a healthy diet is a cornerstone for preventing morbidity and mortality. In a systematic analysis of the burden of diseases in the United States between 1990 and 2010, dietary composition was the leading risk factor for disability-adjusted life years, a health metric combining years of life lost to premature mortality and years lived with disability [1]. However, determining what constitutes a healthful dietary composition is far from straightforward. Despite decades of research, the role of different fat types in health outcomes remains controversial.

Nutritional guidelines for the general population by the WHO recommend limiting saturated fat intake to <10% of total energy intake and replacing saturated with unsaturated fat [2]. The principal rationale

Abbreviations: clamp-IS, insulin sensitivity calculated by euglycemic hyperinsulinemic clamps; ISI, insulin sensitivity index; IVGTT, intravenous glucose tolerance test; K_g, glucose disappearance constant; M, glucose metabolized; M/I, glucose metabolized per unit of plasma insulin concentration; QUICKI, quantitative insulin sensitivity check index; T2D, type 2 diabetes.

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underlying this recommendation is based on the well-established fact that saturated fat intake raises serum LDL-cholesterol [3]. Because elevated serum LDL-cholesterol is a major risk factor for atherosclerosis, reducing saturated fat intake is expected to protect from cardiovascular disease. In a Cochrane meta-analysis of randomized clinical trials, reducing saturated fat intake for ≥2 y decreased cardiovascular disease [4]. When reducing saturated fatty acid (SFA) intake in the context of a constant caloric intake, it is crucial to consider the replacement nutrient. A Presidential Advisory from the American Heart Association concluded that replacing saturated fat with either polyunsaturated fat or monounsaturated fat reduced cardiovascular events and all-cause mortality, whereas replacing saturated fat with refined carbohydrates was not beneficial [5].

Type 2 diabetes (T2D) is a public health emergency, affecting currently 10% of the world's adult population [6]. A healthy diet is considered a mainstay in preventing T2D, and medical nutrition therapy is an essential component of prediabetes or diabetes management. Current guidelines on medical nutrition therapy suggest no ideal macronutrient composition of diets [7]. Because T2D patients are at an increased risk of cardiovascular disease, replacing saturated fat with unsaturated fats is proposed for its serum LDL-cholesterol-lowering effects, following guidelines for the general population [7]. However, data regarding the effects of different dietary fat types on T2D incidence are equivocal. Four large-scale epidemiological studies with long follow-up periods reported no association between saturated fat intake and T2D incidence after adjustment for other variables, such as body mass index (BMI; in kg/m^2) [8–11]. In a randomized trial in postmenopausal women (the Women's Health Initiative), a 3%–5% decrease in saturated fat intake in the context of a low-fat dietary intervention did not result in decreased self-reported T2D incidence after a follow-up of 8.1 y [12]. In this trial, saturated fat was primarily replaced by carbohydrates [12]. In contrast, there is some evidence from cohort studies suggesting that replacing saturated with polyunsaturated fat may be a more beneficial strategy. The Nurses' Health Study in females found that polyunsaturated fat consumption was inversely associated with T2D risk [10] and the Iowa's Women Health Study in older females reported that substituting polyunsaturated for saturated fat was inversely related to T2D risk [9]. In line with these, an analysis combining subjects from the Nurses' Health Study, Nurses' Health Study II, and the Health Professionals Follow-up Study found that replacing 5% of energy intake from saturated fat with linoleic acid, an ω-6 PUFA, was associated with 14% reduced incidence of T2D [13].

A significant challenge when conducting trials in nutrition is ensuring participants' adherence to the assigned diets. Because adherence proves difficult to maintain beyond a few months, most nutritional trials are short-term and do not allow for the evaluation of hard endpoints, such as T2D incidence. Therefore, trials that aim to examine the effects of dietary fat on T2D have used surrogate endpoints, such as indexes of insulin resistance and pancreatic β-cell function. Reduced insulin sensitivity, as measured by clamps [14], intravenous glucose tolerance tests (IVGTTs) [15], oral glucose tolerance tests (OGTTs) [16], or homeostatic model assessment of insulin resistance (HOMA-IR) [17,18], is an independent predictor of the progression from normal to impaired glucose tolerance and T2D in multiple cohort studies with individuals of diverse ethnic origin.

In subjects with normal glucose tolerance, β cells compensate for a decrease in the insulin sensitivity of peripheral tissues by increasing the insulin secretory response. The product of insulin sensitivity and secretion, termed disposition index, is constant for a given degree of glucose tolerance [19] and can be used as a measure of the β-cell function adjusted for the prevailing insulin sensitivity [20,21]. The disposition index decreases in the progression from normal glucose tolerance to T2D [21,22]. A low disposition index is an independent predictor of future T2D development [21–23] and increases in the disposition index in individuals with prediabetes after lifestyle or pharmacological interventions are inversely associated with T2D incidence [24].

Given the inconclusive data regarding the impact of the dietary fat type on T2D, we set out to perform a systematic review and meta-analysis of randomized, controlled trials (RCTs) that examined the effects of dietary fat type on surrogate endpoints of T2D. Our objectives were to evaluate the impact of replacing saturated with mono or polyunsaturated dietary fat on insulin sensitivity, glucose tolerance, and β-cell function.

Methods

We report our methods and results according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [25]. Methods were specified in advance and documented in a protocol registered on PROSPERO, registration CRD42020178382 (https://www.crd.york.ac.uk/prospero/).

Eligibility criteria

We systematically searched for RCTs that compared ≥1 diets rich in SFA with ≥1 diet(s) rich in monounsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs), with a difference of ≥5% of total energy intake provided by SFA compared with MUFA/PUFA (PUFA in this study refers to total PUFA, unless otherwise stated). This difference could be achieved through dietary advice, provision of key food items, or provision of whole meals. In the case of trials with dietary advice interventions and partial provision of foods, we limited our selection to those that asserted participants' compliance by food questionnaires or measurement of biomarkers of saturated/unsaturated fat intake. To limit confounding factors, we only included trials in which dietary interventions were isocaloric, with no other significant difference besides the dietary fat type. In eligible studies, the proportions of daily energy intake provided as total fat, carbohydrates, and proteins had to be comparable between the different diets. In addition, the fiber content had to be similar between the compared diets, with a maximal difference of 10% deemed acceptable in our systematic review. We searched for such trials with a dietary intervention duration of minimum 1 wk, conducted in adults (age >18 y) at any baseline glucose tolerance status.

We excluded trials in pregnant females, acute clinical settings (intensive care unit, postsurgical patients, enteral solutions, or parenteral solutions), trials with nutritional supplements (capsules and pills), trials examining acute postprandial effects of a single meal, and trials reported in non-English language. Trials assessing the effects of specific dietary patterns (such as the Mediterranean diet, the healthy Nordic diet, and vegan diets) were ineligible, given that these patterns not only affect the dietary fat type but also include several other dietary modifications. Trials evaluating the effects of trans unsaturated fat were outside the scope of this systematic review. Trials with concomitant interventions regarding another macronutrient or lifestyle factors were excluded if the co-intervention differed between the saturated/unsaturated fat dietary groups.

Outcomes of interest

Trials were eligible if they reported postintervention values or baseline values and changes from baseline for any of the following outcomes: insulin sensitivity, glucose tolerance, and pancreatic β-cell

function (see Box 1 for further explanations on methods to evaluate these outcomes) [26,27]. The primary outcomes assessed were the between-group differences in SFA compared with the MUFA/PUFA postintervention values of insulin sensitivity, β-cell function, and glucose tolerance. We searched for the measures of insulin sensitivity both based on fasting values, such as HOMA-IR, the HOMA-S [28,29] and the quantitative insulin sensitivity check index (QUICKI) [30], and measures based on dynamic tests [31]. The latter include the Matsuda index derived from OGTTs [32], other oral insulin sensitivity indexes (ISI) derived from OGTTs [33–37] or mixed meal tests [38], ISIs derived from IVGTTs [39], insulin suppression or tolerance tests [40,41], and indexes derived from euglycemic hyperinsulinemic clamps, such as the quantity of glucose metabolized (M) and of glucose metabolized per unit of plasma insulin concentration (M/I) [42]. Eligible measures of glucose tolerance included the area under the curve of glucose ($AUC_{glucose}$) calculated from OGTT or mixed meal tests [43] and the glucose disappearance constant (K_g) from IVGTTs [44]. For the β-cell function, we sought trials that reported the disposition index [20,45]. We considered disposition indexes calculated by any combination of indexes of insulin secretion and insulin sensitivity [46,47]. We did not consider the index the HOMA-B for this review. Although HOMA-IR is widely accepted as a reliable measure of insulin resistance, HOMA-B is more controversial due to its poor correlation to gold standard, clamp-based indexes [48,49]. HOMA-B may be inappropriate as a measure of the β-cell function when considered in isolation [49].

Study selection and data collection process

Studies were identified through an electronic search of MEDLINE via PubMed, Scopus, and the CENTRAL up to 9 January, 2023. The detailed search strategy used for each database is provided in the **Supplemental Material**. Retrieved records were imported in reference manager EndNote X9, and duplicates removed. Two review authors (ML and CGDSC) independently screened remaining records based on title and abstract and then reviewed potentially eligible studies in full text. For conference proceedings and the abstracts of trials, we manually searched online for subsequent publications of the same trial to complete data. Reference lists of included trials and prior reviews on the topic were also searched for additional relevant studies.

A data extraction form was developed in Excel, including study characteristics, participants' characteristics, parameters of the dietary interventions, and outcome measures (**Supplemental Material**). Data from each included trial were extracted independently by 2 review authors (ML and CGDSC) and cross-checked by 1 (ML). When outcomes were reported in graphs, data were extracted using a web-based semi-automated tool (https://automeris.io/WebPlotDigitizer/): in this case, data were extracted independently by the 2 reviewers, and the mean of the 2 values was retained. In each stage of the study selection and data collection, disagreements were resolved by discussion between the 2 review authors. Missing information about collected data items was requested by e-mail from contact authors. Multiple reports of the same trial were sought based on the following criteria: trial

BOX 1
Methods to evaluate insulin sensitivity and β-cell function

- Clamps

Two types of clamps exist: euglycemic hyperinsulinemic and hyperglycemic [42]. In the first case, insulin is infused intravenously at a constant rate to provoke hyperinsulinemia, simultaneously with glucose administered at a variable rate. The glucose infusion rate is equivalent to glucose uptake by tissues and represents whole-body sensitivity to insulin. In the hyperglycemic clamp, a priming infusion of glucose is given to induce hyperglycemia and thereafter glucose is administered at a variable rate to maintain hyperglycemia. This clamp allows us to assess insulin secretory response; the glucose infusion rate represents glucose metabolism. Clamps provide very useful information but they are costly and time-consuming, and requiring trained personnel.

- Glucose tolerance tests

They consist of IVGTTs [26] or OGTTs [27], during which glucose is administered either intravenously or orally. Plasma glucose and insulin concentrations can then be used to quantify insulin sensitivity, insulin response to glucose, and glucose tolerance. Glucose tolerance tests are less labor-intensive than clamps and allow for the evaluation of insulin sensitivity and β-cell function simultaneously. Like clamps, they are nonphysiological as a meal will provide other macronutrients in addition to glucose. The mixed meal test is a variant where a meal containing proteins, fat, and carbohydrates is given orally.

A number of models and equations have been developed based on these tests.

- From tolerance tests

Insulin sensitivity indexes have been validated against the euglycemic hyperinsulinemic clamp [32–34].

The disposition index represents insulin secretion corrected by whole-body insulin sensitivity and provides an accurate measure of β-cell function. It is calculated by multiplying the values of insulin sensitivity and insulin secretion, after testing that the indices used have a hyperbolic relationship [20].

- From fasting values

HOMA is based on the assumption that fasting glucose and insulin are regulated via a feedback loop. Two equations are available, 1 to calculate insulin resistance (HOMA-IR) and the other β-cell function (HOMA-B). Insulin sensitivity (HOMA-S) can also be calculated as 1/HOMA-IR. HOMA is practical as fasting values are often readily available, but the indices lack precision and HOMA-B does not work as well in healthy as in subjects with diabetes [28,49].

QUICKI is also calculated with fasting insulin and glucose values, but values are log-transformed [30].

As with all endocrine tests, dynamic tests are much more sensitive than baseline (fasting) measures. Assessments of insulin secretion and glucose tolerance that are derived from stimulated tests (oral or intravenous) will provide far richer data than simple fasting measures.

registration number, authors, location/setting, type of intervention, number of participants, and baseline data. These reports were considered as a single study, and data were collated.

Assessment of risk of bias

Risk of bias was evaluated using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [50]. Judgments of risk of bias (low risk, high risk, or some concerns) and all items taken into account in the decision trees were recorded for each of the domains addressed by RoB2: bias arising from the randomization process, bias due to deviations from the intended intervention (effects of adherence), bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. In crossover trials, risk of bias arising from the period and carryover effect was also evaluated [51]. The minimum washout period deemed acceptable with a view to avoid carryover effects was 1 wk. The overall risk of bias was determined as low risk when the trial had been judged at a low risk in all domains; high risk when the trial had been judged at a high risk in $\geq$1 domain, or as having some concerns in $\geq$3 domains; and overall some concerns in all remaining cases.

Evaluations were performed independently by 2 review authors (ML and CGDSC). Discrepancies in judgments were resolved by discussion to reach a consensus between the 2 review authors, with a third senior review author (MC) arbitrating whenever necessary.

Data synthesis and statistical analysis

Data collected were grouped by studies of SFA compared with MUFA and SFA compared with PUFA. For each group, data were further categorized by the indexes used to evaluate the outcomes of interest: ISI from IVGTTs, HOMA-IR, Hyperinsulinemic-euglycemic clamp (clamp-IS), glucose tolerance K_g, glucose tolerance $AUC_{glucose}$, and disposition index.

Data conversion was done to have comparable measures among studies. Mean, standard deviation of the postintervention effect, and the sample size for each study were required to perform the meta-analysis. Outcomes from different subgroups (for example, by sex) reported separately within a study were treated as separate studies. For trials that included >1 diet of the same saturation category (for example, 2 different SFA-rich diets) sharing the same control group, we selected only 1 diet of each saturation category, preferring diets with more common sources of fat. A sensitivity analysis was conducted to check whether the results are sensitive to the diet selection for these studies. All sequences in each of the crossover studies were included to allow the evaluation of the effect difference of replacing dietary SFA with MUFA/PUFA. The possibility of taking into account the within-patient correlation effect in crossover studies was explored by seeking the information of statistics difference between diets. All but 2 [52–54] of the included crossover studies in this meta-analysis did not report any variability of the effect difference or any statistics with paired comparisons to derive the measure. In this case, diets were considered independent of each other. This approach is expected to inflate standard deviations of the difference between treatments and rather underweight crossover studies in the meta-analysis. Possible carryover effects in crossover studies were addressed as an element of risk of bias.

Missing dietary effect values were imputed by simple conversion from the available measures in each study using standard methods based on the Cochrane Handbook for Systematic Reviews of Interventions [55]. Missing means were estimated using reported median, first and third quartiles. Higgins' transformations [56] were used to convert geometric means and standard deviation using the lognormal distribution assumption. The results of conversions were verified for plausibility. Missing standard deviations were estimated from reported CIs or the first and third quartiles (interquartiles). In addition, we explored the possibility of imputing missing baseline and preintervention values to adjust the postintervention effect or incorporating it as an explanatory variable in the meta-regression models.

In the meta-analysis, random-effects models were used. The random-effects model assumes that the effect variability across studies is due to real differences in the diet effect in each study as well as sampling variability. The random-effects model was fitted by estimating the amount of residual/heterogeneity (τ^2) using the restricted maximum-likelihood method. The true effect was estimated using weighted least squares with the weight of study i equal to $w_i = 1/(\upsilon_i + \tau^2)$, where υ_i is the sampling variance of study i and τ^2 is the variability among the true effects that are not accounted for by the model (standard inverse-variance method). The statistical analysis was undertaken in R version 4.1.2, using the package "meta." The total variability due to heterogeneity (I^2) and Q test were used to assess heterogeneity among studies. Funnel plots were used to assess for publication bias and systematic heterogeneity.

The postintervention differences between SFA and MUFA and between SFA and PUFA were estimated by each index/method for each outcome of interest. The mean difference of the effect of different diets was used to estimate the effect difference in the meta-analysis. To obtain larger datasets, data from trials using different methods to assess insulin sensitivity were pooled and HOMA-S data were converted to HOMA-IR data (HOMA-IR = 1/HOMA-S) for 1 study [57]. When the same trial reported >1 index, only 1 index was retained for the pooled analysis (preferentially clamp-IS, then IVGTT-ISI, then HOMA-IR based on the sensitivity of these methods). For pooled insulin sensitivity data, a standardized mean difference (SMD) was used to estimate the effect difference.

To explain heterogeneity among studies, univariate meta-regressions on pooled data were performed to explore the association between the effect of the diets and the following variables: age, sex, BMI, fasting glucose, intervention duration, and percentage difference in SFA between the compared diets.

The robustness of the model was further evaluated by performing sensitivity analyses on the pooled dataset. These were performed by study design (parallel/crossover) and by risk of bias score. Univariate meta-regressions on these variables were used to explore their possible associations with the effect of diets.

Results

The systematic review of the literature retrieved a total of 6355 articles. Of these, 219 were selected for full-text analysis based on title and abstract, with 13 added based on manual research of reference lists of eligible papers and previous reviews. Finally, 30 studies were included in this systematic review. The most common causes for study ineligibility were: a difference in saturated compared with unsaturated fat below the predefined 5% cut-off (n = 58), multiple publications from the same cohort (n = 42) (only the ones relevant to the outcomes of interest were selected), and missing data on dietary fatty acid composition (n = 24). More detailed information on study selection can be found on the PRISMA flowchart (Figure 1).

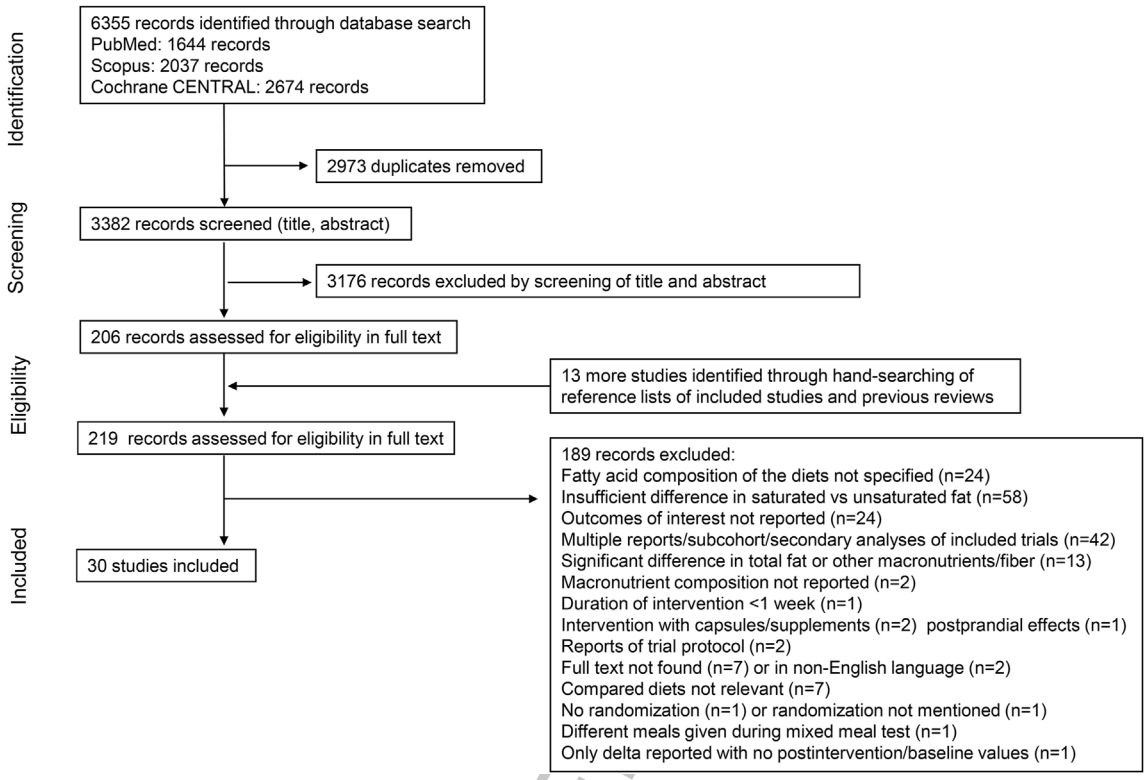

FIGURE 1. Flowchart of the analysis.

Replacement of SFA with MUFA

Characteristics of studies

Twenty-one trials (Table 1) evaluated the effect of replacing SFA with MUFA [52–54,58–81]. The median age of the participants was 38 y (IQR: 22), 38% were male, and mean BMI was 26.4 (SD: 3.6). Mean baseline fasting glucose was 5.1 mmol/L (SD: 0.42). Six [58,61,64,65,67,75,77,78,80] and 15 trials [52–54,59,60,62,63,66,68–71,73,74,75,79,81] were, respectively, of the parallel and crossover design. Eight studies were unblinded for participants [54,58,59,61,65–67,72,73,75,78], 8 studies were single-blind for participants [60,62–64,68,74,77,80,81], and 5 were double-blind [52,53,69–71,76,79]. The median duration of the dietary intervention was 4 wk (IQR: 2, range: 1–24 wk). Median percentage total energy intake provided as SFA in the SFA-rich diet was 18% (range: 11–29), compared with 8% (range: 4–21) in the MUFA-rich diets. Dietary interventions were designed for weight maintenance in all but 2 studies [62,74], in which no weight change objective was specified. The dietary intervention provided whole meals in 12 studies [52,53,58–60,62,63,66,69–71,74,78,79,81], key food items in 8 studies [54,61,64,65,67,68,75–77,80], and dietary advice in 1 [72,73]. Compliance with assigned diets was ascertained by the analysis of blood fatty acid composition in the large majority of trials, alone (8 trials) [52,53,60–62,66,70,71,79,81] or in combination with dietary records (9 trials) [58,64,65,67–69,72,73,75–78,80]. Blood fatty acid composition was analyzed in plasma/serum lipid pools (cholesterol esters, phospholipids, triglycerides) or in nonesterified fatty acids. In the remaining studies, compliance was ascertained by dietary records in 3 studies [54,59,63] and by supervised consumption of most meals in 1 [74].

Additional information on the design of studies, participants' characteristics, dietary interventions, and reported outcomes is provided in Table 1 and Supplemental Table 1.

There were 4 studies with >1 diet of the same saturation category sharing the same control group [59,63,70,74]. For these studies, we have selected dietary olive oil, native palm oil, palm oil, and butter group instead of high-oleic blended cooking oil, cocoa butter, or cheese group. One study that reported geometric mean was not included as the conversion to arithmetic mean was beyond the interpretable range [60].

Five studies were deemed at the low risk of bias [54,58,65,67,75,77,78], 12 having some concerns [52,53,59,61,64,66,68–71,74,76,79–81], and 4 at the high risk of bias [60,62,63,72,73] (Table 1 and Supplemental Table 3). In 3 of the 4 studies judged at the high risk of bias [60,63,72,73], this was due to the absence of a washout period at crossover, with the consequent risk of carryover effects. The main reason for studies having some concerns was the lack of information about the randomization process.

Effects on insulin sensitivity

Of the 21 trials that compared SFA-rich compared with MUFA-rich diets, 20 evaluated insulin sensitivity [52–54,58–75,77–81]. Of these, 13 assessed insulin sensitivity by HOMA-IR (analyzed as 13 comparisons because of different subgroups and the exclusion of 1 study as explained above) [52–54,58–60,62,65,70–75,77–79,81], 8 (analyzed as 11 comparisons) by the ISI from IVGTTs [61,64,65,67–69,72,73,75,80], and 4 by hyperinsulinemic-euglycemic clamps (analyzed as 5 comparisons) [52,53,58,62,66,78].

There were no significant postintervention between-group differences between the SFA and MUFA dietary groups in the pooled analysis [SMD: 0.01, 95% confidence interval (CI): −0.06 to 0.09, $P = 0.97$, $I^2 = 0\%$, 22 comparisons, $n = 1526$], as illustrated in Figure 2. This finding was consistent when data were analyzed separately by the method of assessment of insulin sensitivity (HOMA-IR, ISI-IVGTT, and clamp-IS, Supplemental Figures 1–3).

In prespecified analyses by univariate meta-regression, we assessed the influence of age, sex, BMI, baseline fasting glucose, duration of

TABLE 1
Studies substituting MUFA for SFA

Study [ref] country	*n*	Design	Blinding part/invest	Age (y)	% M	Glycemia (mmol/L)	BMI (kg/m^2)	% SFA/MUFA/PUFA		Main source of fat		Duration	Washout	Outcomes	Bias risk
								SFA	MUFA	SFA	MUFA				
Uusitupa et al. 1994 [76] Finland[1]	10	Crossover	Yes/Yes	23	0	4.5	21.5	20/12/4	9/19/10	Butter	Rapeseed oil margarine	3	2	GT (IVGTT)	Some
Fasching et al. 1996 [62] Austria	8	Crossover	Yes/No	26	100	4.99[2]	22.4	29/15/10	21/20/12	SFA-rich vegetable fat	MUFA-rich lard	1	2	IS (clamp)	High
Louheranta et al. 1998 [68] Finland	14	Crossover	Yes/No	22	0	NR	22.6	19/12/6	13/19/6	Cocoa butter	Olive oil	4	2	IS (IVGTT)	Some
Vessby et al. 2001 [80]/ Giacco 2007 et al. [64] 5 countries[3]	82	Parallel	Yes/Unclear	49	53	5.2	26.5	18/13/5	10/21/5	Various substitutions		12	NA	IS (IVGTT), GT (IVGTT), BCL (IVGTT)	Some
Lovejoy et al. 2002 [69] United States	25	Crossover	Yes/Yes	28	48	4.9	23.5	11/9/6	6/15/6	Fat blends		4	2	IS (IVGTT) BCL (IVGTT)	Some
Vega-Lopez et al. 2006 [79] United States	15	Crossover	Yes/Yes	64	33	5	26	15/11/4	6/15/9	Palm oil	Canola oil	5	2	IS (HOMA-IR)	Some
Paniagua et al. 2007 [72, 73] Spain	11	Crossover	No/No	62	36	5.5	32.6	23/9/6	9/23/6	Butter/meat	Olive oil	4	0	IS (HOMA-IR, IVGTT) GT (MMT)	High
Bos et al. 2010 [58]/Van Dijk 2009 et al. [78] Netherlands	20	Parallel	No/Yes	55	43	4.99	26.8	19/11/5	11/20/7	Butter	Olive oil	8	NA	IS (HOMA-IR, clamp)	Low
Jebb et al. 2010 [67] UK	182	Parallel	No/Unclear	51	42	5.4	28.4	16/12/6	10/16/7	Various substitutions		24	NA	IS (IVGTT)	Low
Iggmann et al. 2011 [66] Sweden	20	Crossover	No/No	51	70	5.8	26.3	19/11/4	8/16/9	Dairy fat	Rapeseed oil	3	3	IS (clamps) GT (IVGTT)	Some
Gulseth et al. 2019 [65]/ Tierney et al. 2011 [75] 8 countries[4]	211	Parallel	No/Yes	55	49	5.9	32.3	18/13/6	10/19/7	Various substitutions		12	NA	IS (IVGTT, HOMA-IR) BCL (IVGTT)	Low
Kien et al. 2013 [53]/ Kien et al. 2015 [52] United States	8	Crossover	Yes/Yes	29	50	4.53	23.4	18/16/5	4/29/7	Palm oil	Hazelnut oil	3	1	IS (HOMA-IR, IVGTT, clamp) BCL (IVGTT)	Some
Filippou et al. 2014 [60] Malaysia	41	Crossover	Yes/No	29	24	4.9	23	11/10/4	4/17/4	Palm oil	High-oleic sunflower oil	6	0	IS (HOMA-IR) GT (MMT)	High
Chiu et al. 2014 [61] United States	68	Parallel	No/Yes	38	55[5] 34[6]	4.8[5] 4.9[6]	33.9	15/10/7[5] 15/20/7[6]	7/18/8[5] 7/29/7[6]	Substitutions of dairy products		4	NA	IS (IVGTT) BCL (IVGTT)	Some
Vafeiadou et al. 2015 [77] UK	129	Parallel	Yes/No	44	44	5	26.7	18/11/4	8/19/6	Various substitutions		16	NA	IS (HOMA-IR)	Low
Tien Lee et al. 2016 [74] Malaysia	32	Crossover	Yes/No	30	41	5.26	25.5	23/4/2	6/18/3[7] 11/12/4[8]	Coconut oil	Olive oil HOBO[8]	6	3	IS (HOMA-IR) GT (MTT)	Some
Chang et al. 2016 [60] Malaysia[1]	47	Crossover	Yes/No	33	26	5.8	28.7	12/13/6	5/21/6	Palm olein	High-oleic sunflower oil	6	0	IS (HOMA-IR) BCL (MMT)	High
Brassard et al. 2017 [59] Canada	77	Crossover	No/Yes	39	47	5.16	30.8	13/13/5 12/12/5	6/20/5	Cheese Butter	Olive oil	4	4	IS (HOMA-IR)	Some
Meng et al. 2019 [71]/Matthan et al. 2019 [70] United States	20	Crossover	Yes/Yes	64	0	5.1	26.4	15/8/4[9] 16/10/4[10]	7/16/6	Palm oil cocoa butter	Safflower oil	5	2	IS (HOMA-IR)	Some

(*continued on next page*)

TABLE 1 (*continued*)

Study [ref] country	*n*	Design	Blinding part/invest	Age (y)	% M	Glycemia (mmol/L)	BMI (kg/m^2)	% SFA/MUFA/PUFA		Main source of fat		Duration	Washout	Outcomes	Bias risk
								SFA	MUFA	SFA	MUFA				
Hosseinabadi et al. 2021 [54] Iran	30	Crossover	No/No	38	27	4.38	25.9	15/10/4	8/16/5	Ghee	Olive oil	4	2	IS (HOMA-IR)	Low
Loganathan et al. 2022 [81] Malaysia	40	Crossover	Yes/No	34	15	4.92	21.7	14/12/3	8/17/5	Cocoa butter	Olive oil	4	2	IS (HOMA-IR)	Some

The table shows the sample size (*n*), whether study design was crossover or parallel and had blinding of participants and/or investigators. Also shown are mean age of participants, sex distribution (expressed as percent male, M), baseline fasting glycemia, and mean BMI of participants. The percentage of energy from SFA/MUFA/PUFA and main source of fat in the SFA compared with MUFA dietary groups, duration of the intervention and washout (in wk), reported outcomes, and overall risk of bias (low, some concerns, or high) are indicated. Studies are listed by publication date order.

Abbreviations: BCL, β-cell function; GT, glucose tolerance; HOBO, high-oleic blended cooking oil; IS, insulin sensitivity; IVGTT, intravenous glucose tolerance test; MMT; NA, not applicable; NR, not reported; ref, reference; UK, United Kingdom.

[1] Not included in the meta-analysis.
[2] Mean of range reported.
[3] Finland, Denmark, Sweden, Italy, and Australia.
[4] Norway, Ireland, UK, France, The Netherlands, Spain, Poland, and Sweden.
[5] High-protein subgroup.
[6] Moderate-protein subgroup.
[7] Olive oil subgroup.
[8] HOBO subgroup.
[9] Palmitic subgroup.
[10] Stearic subgroup.

intervention, and percentage difference in SFA between the compared diets on the effect differences. None of these variables significantly affected the dietary effects on insulin sensitivity. In sensitivity analyses, the results did not vary by study design (parallel compared with crossover) nor by risk of bias score (low risk/some concerns compared with high risk). In studies with >1 diet of the same saturation category [59,63,70,74], results were not sensitive to the diet of each saturation category we selected for our analysis. The funnel plot did not suggest any small study effect or publication bias (Supplemental Figure 4).

Effects on glucose tolerance

We identified 6 trials [63,64,66,72–74,76,80] that evaluated glucose tolerance by dynamic tests ($n = 288$). Of these, 3 trials assessed K_g by IVGTTs [64,66,76,80], and 3 assessed $AUC_{glucose}$ (by mixed meal test [63,72,73] or OGTT [74]). Trials were deemed too few by the method to perform a meta-analysis, but no significant between-group differences in glucose tolerance was detected between SFA and MUFA diets in any of the individual trials.

Effects on β-cell function

Five trials evaluated β-cell function by the disposition index derived from IVGTTs [52,53,61,64,65,69,75,80]. Meta-analysis of these data showed no significant postintervention differences in the β-cell function between SFA and MUFA diets, with very low heterogeneity (mean difference: −12, 95% CI: −158 to 133, $P = 0.68$, $I^2 = 0\%$, 8 comparisons, $n = 543$) (Figure 3). The trial by Chang et al. [60] was not included in the meta-analysis, as the disposition index was based on mixed meal tests, and arithmetic means could not be derived from the reported geometric means. In line with the other trials, this trial reported no significant difference between the SFA and MUFA diets.

In an exploratory analysis, univariate meta-regression did not detect any impact of the examined variables (mentioned above) on the effect of diets on the β-cell function. Results were robust to trial design and risk of bias.

Replacement of SFA with PUFA

Characteristics of studies

Thirteen trials evaluated the effects of replacing SFA with PUFA [57,59,62,77,79,82–89], of which 5 [77,82,86–88] and 8 [57,59,62,79,83–85,89] were of parallel and crossover design, respectively. Six of these trials were unblinded for participants [59,82,84–86,89], 2 were single-blind for participants [62,77], and 5 were double-blind [57,79,83,87,88]. Most studies aimed at weight maintenance, whereas the 2 overfeeding trials by Rosqvist et al. [87,88] aimed at 3% weight gain and 1 trial did not state the parameter [62].

The mean age of the participants was 44 y (SD: 11), 57% were male, and their mean BMI was 27.5 (SD: 3.5). Median baseline fasting glucose was 5.25 mmol/L (IQR: 0.73). The median duration of the dietary intervention was 6 wk (IQR: 4, range: 1–30 wk). Median percentage total energy intake provided as SFA in the SFA-rich diet was 18% (range: 12–39) compared with 10% (range: 6–17) in PUFA-rich diets. The PUFA content of a PUFA-rich diet consisted predominantly of ω-6 PUFAs. Whole meals were provided in 6 trials [59,62,79,83,84,86], key food items in 5 [57,77,82,87,88], dietary advice in 1 [89], and in the remaining study it was unclear [85]. Compliance was assessed by the analysis of blood fatty acid composition in most studies, alone in 5 [62,79,82,84,86] and in conjunction with dietary records in 5 [77,85,87–89], or by dietary records only in the remaining 3 trials [57,59,83].

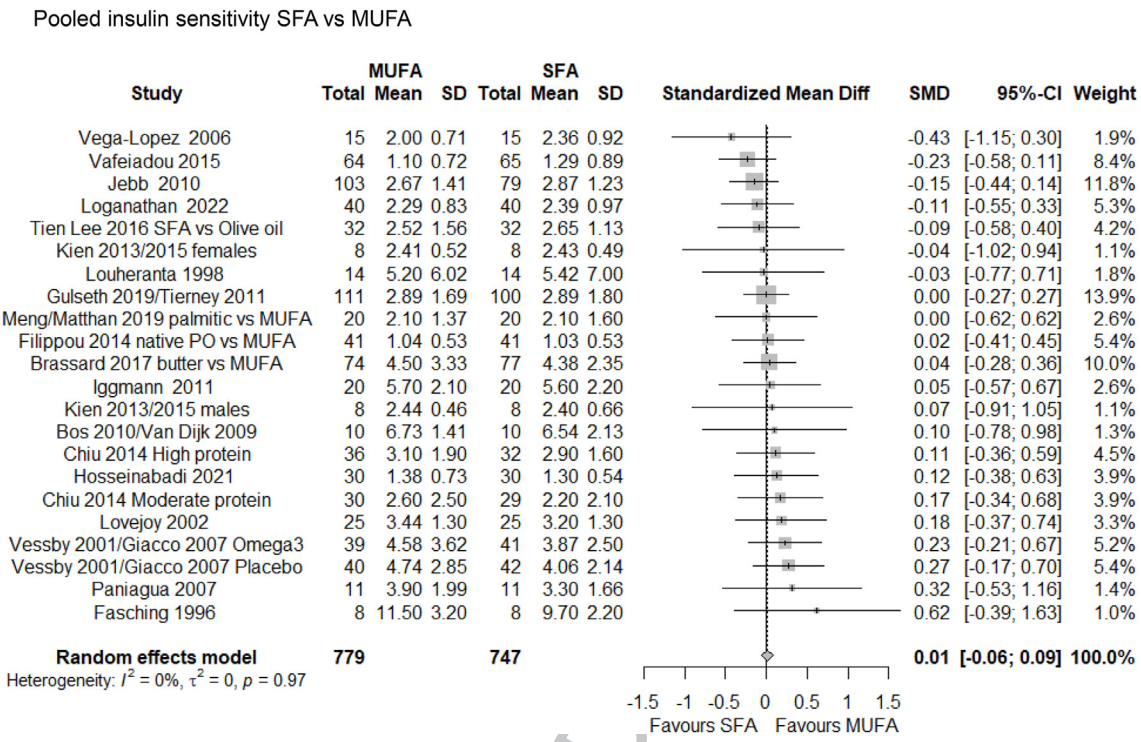

FIGURE 2. Effects of substituting MUFA for SFA on insulin sensitivity. Data from trials that evaluated insulin sensitivity by different methods were pooled (see Methods section) and standardized mean differences (SMDs) were calculated. PO, palm oil.

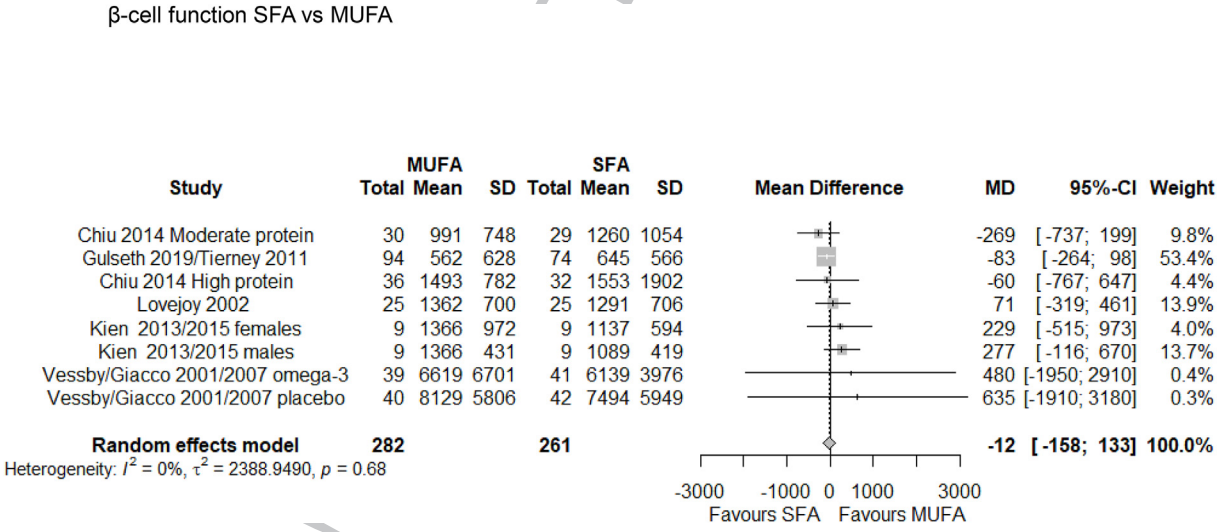

FIGURE 3. Effects of substituting MUFA for SFA on the β-cell function, as assessed by intravenous glucose tolerance tests (IVGTT)-derived disposition index. Mean differences (MDs) between dietary groups were calculated.

Seven trials were judged at low risk of bias [57,77,82,83,86–88], 4 at intermediate risk (some concerns) [59,79,84,85], and 2 at high risk of bias [62,89] (Supplemental Table 3). In the latter, this judgment was due to the absence of washout at crossover [89] and the lack of difference in the measured SFAs between the SFA and PUFA dietary groups [62]. Additional information about the trials can be found in Table 2 and Supplemental Table 2.

Effects on insulin sensitivity

All 13 trials evaluated insulin sensitivity, most of them by HOMA indexes (9 trials by HOMA-IR [59,77,79,82–84,86–88] and 1 trial by HOMA-S [57]). One evaluated ISI by IVGTTs [57], and 4 used hyperinsulinemic-euglycemic clamps [62,85,86,89]. The meta-analysis showed no postintervention between-group difference between PUFA and SFA groups, either in the pooled analysis (Figure 4, SMD: 0.00, 95% CI: −0.15 to 0.14, I^2 = 0%,13 comparisons, n = 688), or in analyses separated by method (HOMA-IR or clamp-IS, Supplemental Figures 5 and 6). The aforementioned variables did not affect effect differences in univariate meta-regression, and the funnel plot was symmetric (Supplemental Figure 7). In a sensitivity analysis, our choice of the SFA diet in a study with 2 SFA diets [59] did not affect results.

TABLE 2
Studies substituting PUFA for SFA

Study [ref] country	*n*	Design	Blinding part/invest	Age(y)	% M	Glycemia (mmol/L)	BMI (kg/m^2)	% SFA/MUFA/PUFA		Main source of fat		Duration	Washout	Outcomes	Bias risk
								SFA	PUFA	SFA	MUFA				
Heine et al. 1989 [85] The Netherlands	14	Crossover	Unclear/ Unclear	52	57	9.5	25.4	(a)	(b)	NR		30	Unclear	IS (clamp) GT (MMT)	Some
Fasching et al. 1996 [62] Austria	8	Crossover	Yes/No	26	100	5[1]	22.4	29/15/10	15/13/25	SFA-rich vegetable fat	PUFA-rich vegetable fat	1	2	IS (clamp)	High
Summers et al. 2002 [89] UK	17	Crossover	No/Yes	54	47	6.4	30	20/12/3	8/10/9	Various substitutions		5	0	IS (clamp)	High
Vega-Lopez et al. 2006 [79] United States	15	Crossover	Yes/Yes	64	33	5	26	15/11/4	7/8/13	Palm oil	Soybean oil	5	2	IS (HOMA-IR)	Some
Forsythe et al. 2010 [84] United States	8	Crossover	No/ Unclear	45	100	6	30	31/21/5	17/25/15	Various substitutions		6	4	IS (HOMA-IR)	Some
Bjermo et al. 2012 [82] Sweden	61	Parallel	No/No	57	34	5.3	30.8	20/NR/4[2]	10/NR/14[2]	Butter	Sunflower oil	10	NA	IS (HOMA-IR) GT (OGTT) BCL (OGTT)	Low
Rosqvist et al. 2014 [87] Sweden	37	Parallel	Yes/Yes	27	70	4.6	20.3	16/13/5	12/12/13	Palm oil	Safflower oil	7	NA	IS (HOMA-IR)	Low
Vafeiadou et al. 2015 [77] UK	131	Parallel	Yes/No	44	44	5	26.7	18/11/4	8/12/11	Various substitutions		16	NA	IS (HOMA-IR)	Low
Brassard et al. 2017 [59] Canada	77	Crossover	No/Yes	39	47	5.2	30.8	13/13/5[3] 12/12/5[4]	6/13/12	Cheese Butter	Corn oil	4	4	IS (HOMA-IR)	Some
Drouin-Chartier et al. 2018 [83] Canada	30	Crossover	Yes/Yes	40	100	5.3	32.7	13/14/5	6/14/12	Lard	Safflower oil	4	4	IS (HOMA-IR)	Low
Maki et al. 2018 [57] United States	22	Crossover	Yes/Yes	45	48	NR	27.7	25/(19)[5]	11/(34)[5]	Coconut oil	Corn oil	4	3	IS (HOMA-S, IVGTT) GT (IVGTT) BCL (IVGTT)	Low
Lundsgaard et al. 2019 [86] Denmark	9	Parallel	No/No	33	100	5.1	26.4	39/21/4	10/19/34	Various substitutions		6	NA	IS (HOMA-IR, clamp)	Low
Rosqvist et al. 2019 [88] Sweden	60	Parallel	Yes/Yes	42	62	5.65	27.9	18/16/5	12/15/12	Palm oil	Sunflower oil	8	NA	IS (HOMA-IR) GT (OGTT)	Low

The table shows the sample size (*n*), whether study design was crossover or parallel and had blinding of participants and/or investigators. Also shown are mean age of participants, sex distribution (expressed as percent male, M), baseline fasting glycemia, and mean BMI of participants. The percentage of energy from SFA/MUFA/PUFA and main source of fat in the SFA compared with PUFA dietary groups, duration of the intervention and washout (in wk), reported outcomes, and overall risk of bias (low, some concerns, or high) are indicated. Studies are listed by publication date order.
Abbreviations: BCL, β-cell function; GT, glucose tolerance; IS, insulin sensitivity; IVGTT, intravenous glucose tolerance test; NA, not applicable; NR, not reported; ref, reference.
[1] Mean of the range reported in the article.
[2] Energy intake from linoleic acid, the total % PUFA energy intake is not reported.
[3] Cheese subgroup.
[4] Butter subgroup.
[5] Percentage of energy intake from SFA/unsaturated fatty acids, the latter including both MUFA and PUFA. On the basis of the description of oils used in the diets, unsaturated fat consists predominantly of PUFA.
(a) SFA/PUFA ratio 0.33, (b) SFA/PUFA ratio 0.91. The exact fatty acid composition of the diets is not provided.

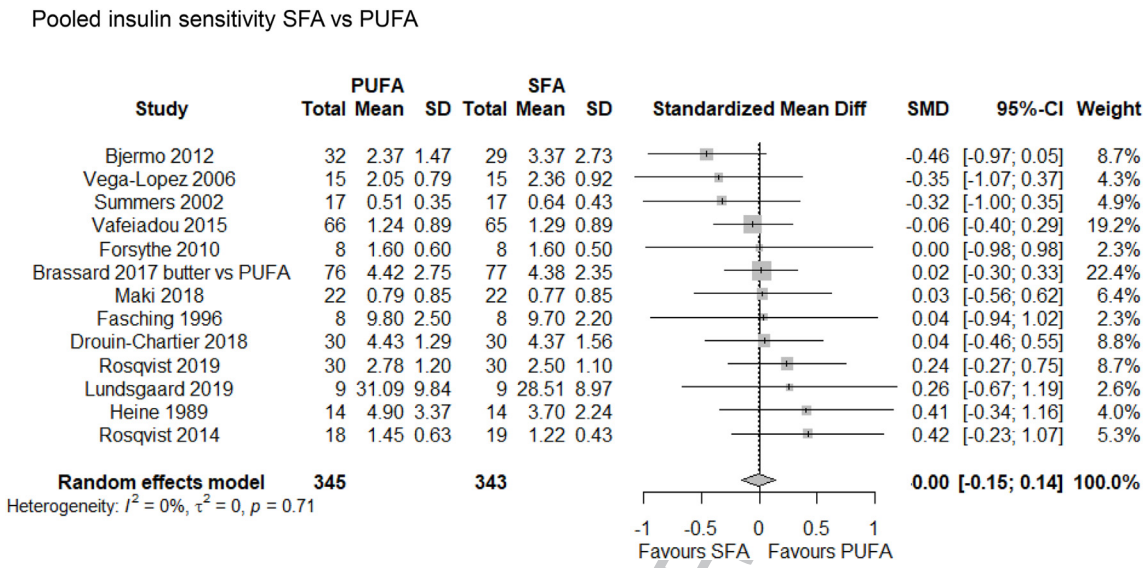

FIGURE 4. Effects of substituting PUFA for SFA on insulin sensitivity. Data from trials that evaluated insulin sensitivity by different methods were pooled, and standardized mean differences (SMDs) were calculated.

Effects on glucose tolerance

Four studies reported glucose tolerance [57,82,85,88]. A crossover trial by Maki et al. [57] evaluated the effects of corn compared with coconut oil and found no difference in the glucose tolerance test assessed by K_g from IVGTTs ($n = 22$) after 4 wk of intervention. Three studies evaluated glucose tolerance by $AUC_{glucose}$ of mixed meal [85] or OGTT [82,87] ($n = 14$, $n = 61$, and $n = 60$, after 30, 10, and 8 wk of intervention, respectively). All 3 studies reported no statistically significant difference between diet interventions.

Effects on β-cell function

Only Maki et al. [57] evaluated the effect of SFA replacement for PUFA on the disposition index (IVGTTs) and found no difference between groups.

Discussion

In this systematic review and meta-analysis of 30 RCTs, we found that the replacement of SFA with either MUFA or PUFA for a median duration of 4 and 6 wk, respectively, did not significantly alter insulin sensitivity. We identified no significant impact of replacing SFA with MUFA on the β-cell function. These results were homogeneous among trials. The evidence on the replacement of SFA with PUFA on the β-cell function was insufficient to draw conclusions. Replacing SFA with MUFA or PUFA did not alter glucose tolerance, but data on this outcome were scant.

An important strength of this review is the comparability of dietary interventions in all macronutrient components, except for the component under investigation, for example, the dietary fat type. To decrease the potential for confounding by other nutritional factors, we opted for stringent eligibility criteria. Another strength of this work is ascertaining compliance with the assigned diets. In most trials, this was done by fatty acid composition analysis in blood lipid pools. In the few trials that did not analyze fatty acid composition, compliance was ascertained by dietary records or supervised meal intake. Other strengths include the comprehensive literature search strategy in multiple databases, rendering the possibility of having missed relevant trials unlikely. To assess the β-cell function, we selected studies reporting disposition index, a variable that adjusts insulin secretion for the prevailing insulin sensitivity; this is essential for the correct interpretation of insulin responses. Finally, limiting the selection of studies to RCTs has the inherent advantage of limiting potential confounding from other dietary and nondietary factors. Saturated fat intake has been associated with adverse health behaviors, such as smoking and sedentary lifestyle [90], introducing residual confounding.

An important limitation of the studies included in this review is the short duration of dietary interventions. In univariate meta-regression, dietary effects on insulin sensitivity and β-cell function did not differ by the duration of intervention. However, the maximum duration of intervention was 6 mo (SFA compared with MUFA) and 7.5 mo (SFA compared with PUFA); thus, even the longest trials were of relatively short-term. Because of this short-term nature of nutritional trials, we only considered those with a difference between SFA and MUFA or PUFA of ≥5% of energy intake substitution. Even with a sizable difference between SFA and MUFA/PUFA interventions (median: 10%), the effects of dietary modifications on glucose homeostasis may be subtle and slow. The HEPFAT (Role of Dietary Fatty Acids in Fatty Liver and Insulin Resistance) [82], LIPOGAIN (Metabolic Consequences of Moderate Weight Gain - Role of Dietary Fat Composition) [87] and LIPOGAIN-2 (Role of Fatty Acids in Skeletal Muscle Hypertrophy and Ectopic Fat Accumulation During Overfeeding) [88] trials, included in our meta-analysis, showed that SFA-rich diets resulted in more liver fat accumulation than isocaloric PUFA-rich diets. Interestingly, this did not translate to significant differences in HOMA-IR, an index reflecting predominantly hepatic insulin resistance [49]. It is conceivable that longer exposures to different dietary fat types might have led to measurable differences in insulin resistance and other glucose homeostasis-related outcomes.

Another limitation is the small number of participants in most trials. Certain trials lacked sample size calculations for the outcomes of interest of our review and may thus be underpowered. This was either because the primary outcome of the trial was different (for example, lipid effects) or because trials lacked sample size calculation, particularly in older publications. Furthermore, few studies reported glucose tolerance and adequate measures of the β-cell function that adjust insulin secretion for insulin sensitivity. In studies using dynamic tests,

such as glucose tolerance tests, these data should have been available but were not analyzed or reported.

In this meta-analysis, the fat component of the diets was categorized depending on the degree of saturation of the predominant fatty acids, as this categorization is extensively used in nutritional guidance and scientific literature. However, there is evidence suggesting that fats within the same saturation class from different food sources may have distinct effects on glucose homeostasis. For example, red meat and dairy fat are common sources of saturated fat. Red meat and particularly processed red meat intake is positively associated with T2D incidence [91,92], whereas neither high-fat nor low-fat dairy intake is associated with T2D, and yogurt intake is inversely associated with T2D [93,94]. This may be due to other factors and dietary components besides fatty acids, such as antioxidants, phenolic compounds, vitamins, other macronutrients, and different processing and cooking methods. Therefore, the food source is an important consideration, as highlighted by nutrition experts who propose shifting from nutrient-based to food-based recommendations [95,96]. Our study compared saturated with mono or polyunsaturated fat from various food sources (Tables 1 and 2), because comparisons of individual food sources would have resulted in too few studies to pool. Even if this may be a limitation of our study, effects of replacement of SFA with MUFA/PUFA were neutral for all different fat sources.

Prospective studies examining the associations of individual plasma phospholipid fatty acids on T2D incidence have shown that fatty acids within the same saturation category are not homogeneous in their effects [97–99]. Among circulating SFA, even-chain palmitic and myristic acid are positively associated with T2D, whereas the odd-chain SFA pentadecanoic and heptadecanoic acid and very-long-chain SFA are inversely associated with T2D [98,99]. Among circulating PUFA, plant-derived n-3 linolenic acid and n-6 linoleic acid are inversely associated, marine-derived n-3 eicosapentaenoic and docosahexaenoic acid are not associated, and γ- and dihomo-γ-linoleic acid are positively associated with T2D [97]. The above evidence supports a more nuanced view regarding the effects of circulating fatty acids, but it cannot be directly translated to dietary fatty acids. Circulating fatty acids only partially reflect dietary intake, because they are also synthesized by hepatic de novo lipogenesis and converted through elongation and desaturation, with the exception of essential fatty acids [100]. In observational studies, circulating palmitic, stearic, and myristic correlated most strongly with alcohol, soft drinks, and potato consumption, and only weakly with the consumption of classic dietary sources of saturated fat, such as meat and dairy [87]. In trials included in our study, the direction of changes in circulating fatty acids was consistent with the dietary intervention. The most sizable differences in trials that measured blood fatty acid composition were observed in circulating palmitic (increased in SFA compared with MUFA/PUFA groups), oleic (increased in MUFA compared with the SFA group), and linoleic acid (increased in PUFA compared with the SFA group).

Despite the overall neutral effects of replacing SFA with MUFA/PUFA in our study, we cannot exclude that this replacement may have different results in specific subgroups of individuals. For example, in the LIPGENE Dietary Intervention Study, the disposition index was significantly improved when SFA was replaced with MUFA in individuals who were normoglycemic at baseline. This was not seen in the overall cohort of participants with metabolic syndrome, and especially in people with T2D who have much lower disposition index and potentially less modifiable β-cell function [65]. In our meta-regression analyses, we evaluated the impact of mean baseline glucose of the entire patient cohorts on effect differences because individual patient data for subgroup analysis was unavailable.

Finally, saturated fat may affect glucose homeostasis through indirect mechanisms. The Nurses' Health Study found that saturated fat intake was associated with weight gain [101]. It is possible that saturated fat may exert negative effects on glucose homeostasis through weight gain. This would not have been captured in the trials included in this meta-analysis because the diets were designed to be isocaloric, and most studies aimed at weight maintenance. In the case of studies aiming at weight gain, calories were adjusted to induce similar weight gain.

Previous meta-analyses of RCTs on the effects of different dietary fat types have also yielded mostly neutral results on insulin sensitivity and glucose-related outcomes, except for the meta-analysis by Imamura et al. [102]. Brown et al. [103] compared high with low PUFA intake, with ≥10% difference between the interventions, and found no overall effect of PUFA on HOMA-IR. Most of the trials included in this meta-analysis assessed the effects of high intake of PUFA attained through n-3 supplements and only a minority of them through dietary supplementation. Similarly, Akinkuolie et al. [104] examined the effect of n-3 supplementation on insulin sensitivity and found no differences. Again, in all but 1 trial with fatty fish supplementation, high PUFA intake was attained through the intake of capsules. Wanders et al. [105] found a slight decrease in HOMA-IR when plant-derived PUFA replaced either SFA or carbohydrates. The decrease in HOMA-IR was NS for a 5% change in PUFA but became significant in trials in the upper tertile of the PUFA dose [105]. In a meta-analysis comparing high-MUFA with low-MUFA diets in patients with abnormal glucose tolerance, no differences were observed in HOMA-IR in 6 trials [106]. However, in this meta-analysis, the low-MUFA comparator diets were heterogeneous (low-fat, high-protein, low GI, control, and 1 high-SFA diet). Sellem identified 3 trials that replaced SFA (palmitic acid) with unsaturated fatty acids and the effect of this replacement on HOMA-IR was NS [107]. Compared with our meta-analysis, Imamura et al. [102] took a different approach: they included trials that did not have to be balanced in terms of other macronutrients, and there was no cut-off of energy replacement. Instead, their model included macronutrients as covariates, and dose–response effects of replacements were calculated using multiple treatment meta-regression. They found that a 5% substitution of SFA with either MUFA or PUFA significantly decreased HOMA-IR but not IVGTT-derived ISI. No difference in 2-h glucose tolerance was found by either replacement. Insulin secretion in IVGTTs was increased by PUFA and not affected by MUFA, but they did not report a disposition index of the β-cell function (that is, corrected for prevailing insulin sensitivity).

In conclusion, currently available data from RCTs indicate that replacing SFA with unsaturated fats does not have significant short-term effects on insulin sensitivity or β-cell function (the latter when SFA are compared with MUFA). Adequate measures of the β-cell function were rarely reported, even if these can be calculated by tests that are easy to perform, such as OGTTs. Future trials with longer follow-up periods, rigorous design, and clear sample calculation are needed to elucidate the longer term effects of dietary fat types on glucose homeostasis.

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Author contributions

The authors' responsibilities were as follows—ML, MC, JK: conceived the project; ML, CGDSC: reviewed the studies and extracted data; ML, PK, MP: analyzed data; ML, CGDSC, PK: wrote the first draft of the manuscript; MC: was the senior reviewer and edited the manuscript; and all authors: reviewed the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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Data availability

Data described in the manuscript will be made freely available upon request by contacting the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.07.018.

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