S3 Text. Eligibility criteria, literature search, data preparation, imputation, and reference list

Eligibility criteria

The protocol is appended in S1 Text. The objective of this review was to quantify effects of isocaloric replacement of major macronutrients intake, focusing on different types of fatty acids, on fasting glucose, fasting insulin and insulin resistance. Eligibility criteria were 1) randomised controlled feeding trials of isocaloric exchange of different types of dietary fat, total carbohydrates and total protein; 2) trials reporting different types of dietary fat intake and examining post-intervention values or changes in the values of fasting glucose, fasting insulin or measures of insulin resistance as effects of dietary modification on glucose homeostasis; and 3) trials recruiting adults aged 18 years or older.

Studies were excluded if trials tested effects of interventions that limited comparability of isocaloric exchange of major macronutrients: trials testing interventions concomitant with macronutrient composition, such as dietary fibre intake, vegan diet, diet with high glycaemic index (GI), and others, and an uneven intervention of weight-loss or other dietary or lifestyle factors; trials testing interventions of dietary advice only, whereas trials partially providing meals or foods were included; interventions of a single meal to test acute effects of foods, such as postprandial effects of the tested meals or breakfast or evening snacks, rather than a habitual diet. We also excluded observational or non-randomized studies, studies recruiting pregnant women or children (aged <18 years), publications of commentaries or reviews or case-reports, and duplicate publications from the same. Duplicate publications identified were compiled as well to extract additional information if available.

Literature strategy

We identified eligible publications systematically using the following electronic databases: PUBMED; EMBASE; OVID (EMBASE, Agris, Amed, HMIC, PsycINFO); WEB OF KNOWLEDGE (BIOSIS, WEB OF SCIENCE, CAB abstracts); CINAHL; The Cochrane Library; Grey literature sources (SIGLE; system for information on grey literature in Europe, British library inside database, and dissertation abstracts online); and Faculty of 1000.

Search was conducted by using three sets of search terms: exposure terms, outcome terms, and study-design terms (see Text S2). At least a term of each of the three sets was specified to be present in search. If search restrictions for a study design and for a search field of a title and abstract were available, such restrictions were applied. Language and years of publications were not restricted. Search by subject headings or key words was included if available.

Electronic search was carried out on 17 December 2010. The search was updated on 18 February 2012 and on 26 November 2015. After confirming that five databases were enough to identify eligible trials, the latter two searches were carried out in five databases (n of additional articles, not included in the subsequent paragraphs): PubMed (n=346), OVID (n=363), EMBASE (n=99), Web of Knowledge (n=1548) and Cochrane Library (n=37). In each search engine, removal of duplicates was applied if available. Search results from the multiple databases were merged and the number of duplicates (Figure 1 of the main manuscript) was calculated.

In addition to the electronic search, we hand-searched eligible publications. For the hand search, we reviewed references of each publication identified and also published review articles [1–20] that were identified in electronic searches.

In PubMed, 605 articles were identified by the following search query: ("Fatty Acids, Omega-6"[MeSH] OR "Fatty Acids, Omega-3"[MeSH] OR "Fatty Acids, Unsaturated"[MeSH] OR "Fatty Acids, Monounsaturated"[MeSH] OR "Trans Fatty Acids"[MeSH] OR "monounsaturated"[tiab] OR "mono-unsaturated"[tiab] OR "unsaturated"[tiab] OR "polyunsaturated"[tiab] OR "saturated"[tiab] OR "trans-unsaturated"[tiab] OR "trans-fatty"[tiab] OR "trans fatty"[tiab] OR "trans unsaturated"[tiab] OR "trans fat"[tiab] OR "omega-6"[tiab] OR "omega-3"[tiab] OR "n-6"[tiab] OR "n-3"[tiab] OR "low-fat"[tiab] OR "high-fat"[tiab] OR "high-carbohydrate"[tiab] OR "low-carbohydrate"[tiab] OR "high-protein"[tiab] OR "low-protein"[tiab] OR "isocaloric"[tiab] OR "palmitic"[tiab] OR "palmitate"[tiab] OR "stearic"[tiab] OR "stearate"[tiab] OR "myristic"[tiab] OR "myristate"[tiab] OR "lauric"[tiab] OR "laurate"[tiab] OR "SFA"[tiab] OR "oleic"[tiab] OR "oleate"[tiab] OR "palmitoleic"[tiab] OR "palmitoleate"[tiab] OR "MUFA"[tiab] OR "linoleic"[tiab] OR "linoleate"[tiab] OR "octadecadienoic acid"[tiab] OR "PUFA"[tiab] OR "vaccenic acid"[tiab] OR "vaccenate"[tiab] OR "conjugated linoleic"[tiab] OR "CLA"[tiab] OR "TFA"[tiab] OR "coconut oil"[tiab] OR "butter"[tiab] OR "lard"[tiab] OR "seed oil"[tiab] OR "safflower oil"[tiab] OR "sunflower oil"[tiab] OR "corn oil"[tiab] OR "sesame oil"[tiab] OR "soybean oil"[tiab] OR "soyabean oil"[tiab] OR "rapeseed oil"[tiab] OR "canola oil"[tiab] OR "olive oil"[tiab] OR "nut oil"[tiab] OR "linseed oil"[tiab] OR "grapeseed oil"[tiab] OR "peanut oil"[tiab] OR "avocado oil"[tiab] OR "palm oil"[tiab] OR "vegetable oil"[tiab] OR "margarine"[tiab] OR "hydrogenated oil"[tiab] OR "fish oil"[tiab]) AND ("Insulin resistance"[MeSH] OR "Glucose clamp technique"[MeSH] OR "glucose tolerance test"[MeSH] OR "Hemoglobin A, Glycosylated"[MeSH] OR "insulin"[tiab] OR "fasting serum glucose"[tiab] OR "fasting plasma glucose"[tiab] OR "fasting glucose"[tiab] OR "glucose tolerance"[tiab] OR "glucose clamp"[tiab] OR "euglycemic"[tiab] OR "hyperglycemic"[tiab] OR "hyperinsulinemic"[tiab] OR "minimal model"[tiab] OR "hemoglobin A1c"[tiab] OR "glycated hemoglobin"[tiab] OR "proinsulin"[tiab] OR "C-peptide"[tiab]) AND ("randomized"[tiab] OR "intervention"[tiab] OR "ward"[tiab] OR "feeding"[tiab] OR "trials"[tiab] OR "trial"[tiab] OR "supplements"[tiab] OR "supplement"[tiab] OR "supplementation"[tiab]) NOT ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "case-control"[tiab] OR "cohort"[tiab] OR "case-report"[tiab] OR "ad libitum"[tiab] OR "adolescents" OR "children" OR "gestational"[tiab] OR "pregnant"[tiab] OR "pregnancy"[tiab]) NOT ("rats"[tiab] OR "monkeys"[tiab] OR "primates"[tiab] OR "rabbits"[tiab] OR "cats"[tiab] OR "dogs"[tiab] OR "mice"[tiab] OR "pigs"[tiab] OR "cows"[tiab]) Limits:Humans, Clinical Trial, Randomized Controlled Trial, All Adult: 19+ years

In EMBASE, 369 articles were identified by the following search query: ((("monounsaturated" or "mono-unsaturated" or "unsaturated" or "polyunsaturated" or "saturated" or "trans fatty" or "trans unsaturated" or "trans fat" or "trans-unsaturated" or "trans-fatty" or "omega-6" or "omega-3" or "n-3" or "n-6" or "low-fat" or "high-fat" or "low-carbohydrate" or "high-carbohydrate" or "low-protein" or "high-protein" or "isocaloric" or "palmitic" or "palmitate" or "stearic" or "stearate" or "myristic" or "myristate" or "lauric" or "laurate" or "SFA" or "oleic" or "oleate" or "palmitoleic" or "palmitoleate" or "MUFA" or "linoleic" or "linoleate" or "octadecadienoic acid" or "PUFA" or "vaccenic acid" or " accinate" or "CLA" or "TFA" or "hydrogenated oil" or "coconut oil" or "butter" or "lard" or "seed oil" or "safflower oil" or "sunflower oil" or "corn oil" or "sesame oil" or "soybean oil" or "soyabean oil" or "rapeseed oil" or "canola oil" or "olive oil" or "nut oil" or "linseed oil" or "grapeseed oil" or "peanut oil" or "avocado oil" or "palm oil" or "vegetable oil" or "margarine" or "fish oil") and ("fasting glucose" or "fasting plasma glucose" or "fasting serum glucose" or "glucose tolerance" or "glucose clamp" or "insulin" or "euglycemic" or "hyperglycemic" or "hyperinsulinemic" or "minimal model" or "hemoglobin A1c" or "glycated hemoglobin" or "proinsulin" or "C-peptide") and ("trials" or "trial" or "randomized" or "feeding" or "ward" or "intervention" or "supplements" or "supplement" or "supplementation")) not ("rats" or "monkeys" or "primates" or "rabbits" or "cats" or "dogs" or "mice" or "pigs" or "cows") not ("case-control" or "cohort" or "case-report" or "ad libitum" or "adolescents" or "children" or "gestational" or "pregnant" or "pregnancy")):ti,ab; Limited to: controlled clinical trial from Evidence Based Medicine; randomized controlled trial from Evidence Based Medicine; article from Publication Types; article in press from Publication Types; conference abstract from Publication Types; conference paper from Publication Types;'adult from Age Groups; aged from Age Groups; humans

In OVID (combined search at OVID, AGRICOLA, AMED, EMBASE, and PsycINFO), 1380 articles were identified after removing duplicates within OVID. ((("monounsaturated" or "mono-unsaturated" or "unsaturated" or "polyunsaturated" or "saturated" or "trans fatty" or "trans unsaturated" or "trans fat" or "trans-unsaturated" or "trans-fatty" or "omega-6" or "omega-3" or "n-3" or "n-6" or "low-fat" or "high-fat" or "low-carbohydrate" or "high-carbohydrate" or "low-protein" or "high-protein" or "palmitic" or "palmitate" or "stearic" or "stearate" or "myristic" or "myristate" or "lauric" or "laurate" or "SFA" or "oleic" or "oleate" or "palmitoleic" or "palmitoleate" or "MUFA" or "linoleic" or "linoleate" or "octadecadienoic acid" or "PUFA" or "vaccenic acid" or "vaccinate" or "CLA" or "TFA" or "hydrogenated oil" or "coconut oil" or "butter" or "lard" or "seed oil" or "safflower oil" or "sunflower oil" or "corn oil" or "sesame oil" or "soybean oil" or "soyabean oil" or "rapeseed oil" or "canola oil" or "olive oil" or "nut oil" or "linseed oil" or "grapeseed oil" or "peanut oil" or "avocado oil" or "palm oil" or "vegetable oil" or "margarine" or "fish oil") and ("fasting glucose" or "fasting plasma glucose" or "fasting serum glucose" or "glucose tolerance" or "glucose clamp" or "insulin" or "euglycemic" or "hyperglycemic" or "hyperinsulinemic" or "minimal model" or "hemoglobin A1c" or "glycated hemoglobin" or "proinsulin" or "C-peptide") and ("trials" or "trial" or "randomized" or "cross-over") and ("diet" or "dietary" or "feeding" or "ward" or "supplements" or "supplement" or

"supplementation")) not ("cross-sectional" or "case-control" or "cohort" or "ecological" or "case-series" or "case-report" or "ad libitum" or "dietary advice" or "dietary monitoring" or "dietary recommendation" or "review" or "meta-analysis" or "statement" or "guideline" or "adolescents" or "children" or "gestational" or "pregnant" or "pregnancy" or "rats" or "monkeys" or "primates" or "rabbits" or "cats" or "dogs" or "mice" or "pigs" or "cows"));
Limits: keywords search in abstracts, human, age (18 or older)

In Web Of Science, the following queries were searched for three different databases: Web of Knowledge, BIOSIS, and CABI abstracts. We compiled 328 articles from Web-of-Knowledge, 240 from BIOSIS, and 183 from CABI.

Search queries and results in Web of Science database

# Query	Terms applied in electronic search	Web-of-Knowledge	BIOSIS	CABI
# 1	TS=("hydrogenated oil" OR "*nut oil" OR "butter" OR "lard" OR "*lower oil" OR "corn oil" OR "*bean oil" OR "*seed oil" OR "canola oil" OR "avocado oil" OR "palm oil" OR "sesame oil" OR "olive oil" OR "margarine" OR "fish oil" OR "n-3" OR "omega-3" OR "n-6" OR "omega-6" OR "*turated fat*" OR "trans fat*" OR "n-6" OR "omega-6" OR "low-fat" OR "high-fat" OR "isocaloric" OR "palmit*" OR "stear*" OR "myrist*" OR "laur*" OR "oleic" OR "SFA" OR "MUFA" OR "linole*" OR "octadecadienoic" OR "PUFA" OR "vaccen*" OR "CLA" OR "TFA")	>100,000	>100,000	>100,000
# 2	TS=("fasting glucose" OR "fasting serum glucose" OR "fasting plasma glucose" OR "glucose tolerance" OR "insulin" OR "glucose clamp" OR "euglycemic " OR "minimal model" OR "hyperglycemic" OR "hyperinsulinemic" OR "proinsulin" OR "C-peptide")	>100,000	>100,000	52741
# 3	TS=("trials" or "trial" or "randomized" or "feeding" or "ward" or "intervention" or "supplements" or "supplement" or "supplementation")	>100,000	>100,000	>100,000
# 4	#1 AND #2 AND #3	603	443	298
# 5	TI=("meta-analysis" or "review" or "case-control" or "cohort" or "case-report" or "ad libitum" or "adolescents" or "children" or "gestational" or "pregnant" or "pregnancy")	>100,000	>100,000	>100,000
# 6	TI=("rat*" or "monkey*" or "rabbit*" or "cat*" or "dog*" or "primate*" or "mouse" or "mice" or "pig*")	>100,000	>100,000	>100,000
# 7	#6 NOT #7 NOT #8 Refined by: [excluding] Document Type=(REVIEW)	330	241	185
# 8	Removing duplicates.	328	240	183

In CINAHL (EBSCOhost), 165 articles were identified by including the following search in title or abstract: ”((("monounsaturated" or "mono-unsaturated" or "unsaturated" or "polyunsaturated" or "saturated" or "trans fatty" or "trans unsaturated" or "trans fat" or "trans-unsaturated" or "trans-fatty" or "omega-6" or "omega-3" or "n-3" or "n-6" or "low-fat" or "high-fat" or "low-carbohydrate" or "high-carbohydrate" or "low-protein" or "high-protein" or "isocaloric" or "palmitic" or "palmitate" or "stearic" or "stearate" or "myristic" or "myristate" or "lauric" or "laurate" or "SFA" or "oleic" or "oleate" or "palmitoleic" or "palmitoleate" or "MUFA" or "linoleic" or "linoleate" or "octadecadienoic acid" or "PUFA" or "vaccenic acid" or " accinate" or "CLA" or "TFA" or "hydrogenated oil" or "coconut oil" or "butter" or "lard" or "seed oil" or "safflower oil" or "sunflower oil" or "corn oil" or "sesame oil" or "soybean oil" or "soyabean oil" or "rapeseed oil" or "canola oil" or "olive oil" or "nut oil" or "linseed oil" or "grapeseed oil" or "peanut oil" or "avocado oil" or "palm oil" or "vegetable oil" or "margarine" or "fish oil") and ("fasting glucose" or "fasting plasma glucose" or "fasting serum glucose" or "glucose tolerance" or "glucose clamp" or "insulin" or "euglycemic" or "hyperglycemic" or "hyperinsulinemic" or "minimal model" or "hemoglobin A1c" or "glycated hemoglobin" or "proinsulin" or "C-peptide") and ("trials" or "trial" or "randomized" or "feeding" or "ward" or "intervention" or "supplements" or "supplement" or "supplementation")) not ("rats" or "monkeys" or "primates" or "rabbits" or "cats" or "dogs" or "mice" or "pigs" or "cows") not ("case-control" or "cohort" or "case-report" or "ad libitum" or "adolescents" or "children" or "gestational" or "pregnant" or "pregnancy")); narrow by SubjectAge: - Aged, 80 and over, Aged: 65+ years, Adult: 19-44 years, Middle Aged: 45-64 years

In Cochrane Library, 760 articles were identified, after removing 10 within the databse for: "monounsaturated" or "mono-unsaturated" or "unsaturated" or "polyunsaturated" or "saturated" or "trans fatty" or "trans unsaturated" or "trans fat" or "trans-unsaturated" or "trans-fatty" or "omega-6" or "omega-3" or "n-3" or "n-6" or "low-fat" or "high-fat" or "low-carbohydrate" or "high-carbohydrate" or "low-protein" or "high-protein" or "isocaloric" or "palmitic" or "palmitate" or "stearic" or "stearate" or "myristic" or "myristate" or "lauric" or "laurate" or "SFA" or "oleic" or "oleate" or "palmitoleic" or "palmitoleate" or "MUFA" or "linoleic" or "linoleate" or "octadecadienoic acid" or "PUFA" or "vaccenic acid" or " accinate" or "CLA" or "TFA" or "hydrogenated oil" or "coconut oil" or "butter" or "lard" or "seed oil" or "safflower oil" or "sunflower oil" or "corn oil" or "sesame oil" or "soybean oil" or "soyabean oil" or "rapeseed oil" or "canola oil" or "olive oil" or "nut oil" or "linseed oil" or "grapeseed oil" or "peanut oil" or "avocado oil" or "palm oil" or "vegetable oil" or "margarine" or "fish oil" in Title, Abstract or Keywords and "fasting glucose" or "fasting plasma glucose" or "fasting serum glucose" or "glucose tolerance" or "glucose clamp" or "insulin" or "euglycemic" or "hyperglycemic" or "hyperinsulinemic" or "minimal model" or "hemoglobin A1c" or "glycated hemoglobin" or "proinsulin" or "C-peptide" in Title, Abstract or Keywords and "trials" or "trial" or "randomized" or "feeding" or "ward" or "intervention" or "supplements" or "supplement" or "supplementation" in Title, Abstract or Keywords not "Case-Control Studies" or "Cohort Studies" or "case-control" or "cohort" or "case-report" or "ad libitum" or "adolescents" or "children" or "gestational" or "pregnant" or "pregnancy" in Title, Abstract or Keywords not "rats" or "monkeys" or "primates" or "rabbits" or "cats" or "dogs" or "mice" or "pigs" or "cows" in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials".

In SIGLE, one article was identified in the search of ("fasting plasma glucose" OR "fasting serum glucose" OR "fasting glucose" OR "insulin" OR "glucose clamp" OR "euglycemic " OR "minimal model" OR "hyperglycemic" OR "hyperinsulinemic" OR "proinsulin" OR "C-peptide" OR "hemoglobin A1c" OR "glycated hemoglobin") AND ("n-3" OR "omega-3" OR "*turated fat*" OR "trans *fat*" OR "n-6" OR "omega-6" OR "low-fat" OR "high-fat" OR "isocaloric" OR "palmit*" OR "stear*" OR "myrist*" OR "laur*" OR "oleic" OR "SFA" OR "MUFA" OR "linole*" OR "octadecadienoic" OR "PUFA" OR "vaccen*" OR "CLA" OR "TFA" OR "hydrogenated oil" OR "*nut oil" OR "butter" OR "lard" OR "*lower oil" OR "corn oil" OR "*bean oil" OR "*seed oil" OR "canola oil" OR "avocado oil" OR "palm oil" OR "margarine" OR "fish oil" OR "*e oil"). In Faculty of 1000, no article was identified.

Data preparation

Demographics and key characteristics of trials are presented in S1 Table and S2 Table. Some trials presented results after stratification by demographics [21–24]. While the number of trials was unchanged, each stratum was analyzed as an independent trial. Some trials with more than 2 arms included non-comparable arms [25–27], for example, comparing four arms of high-fat high-GI diet, low-fat high-GI diet, high-fat low-GI diet, and low-fat low-GI diet. Each of these trials was considered having multiple independent trials: for example, one trial comparing between high-fat high-GI diet and low-fat high-GI; and one comparing between high-fat low-GI and low-fat low-GI.

Information for meta-analysis was not always reported in a publication. Missing information was replaced with information available in other publications from the same trial; obtained from authors after direct contact; imputed from available information (e.g. midpoints of a range if only a range was presented) [28]. Simple imputation included average ages not presented in three papers [29–31]. For Tardy *et al*. and Vidon et al, a midpoint of an age range was used. For Poppitt *et al*., the information was taken from another publication from the same authors [32], of which the identifical sampling frame was confirmed. A prevalence of diabetes was not presented in Sundram et al. [33] and in Noakes *et al*. [34] Mean plus two standard deviations (SD) of fasting glucose was less than 7 mmol/L (126 mg/dL) and thus all adults in the two trials were considered as adulst without diabetes (prevalence=0). Only one trial recruited type 1 diabetes patients [35], considerd to be 100% prevalence of diabetes, as well as many other trials not clarifying patieitns with type 1 or type 2 diabetes. The other imputation with uncertainty is described in the next section in the subsequent subsection.

We obtained addition information by contacting authors [36–52]. In the current meta-regression model, percent energy from major macronutrients, percent energy from trans fat, and fibre were considered as required. For the assessment of heterogeneity, other covariate information was needed. If information on covariates was missing as well as the main exposures (major macronutrients) and outcomes (glycaemic outcomes), we contacted a corresponding author of the publication. If a publication indicated measurements of the selected outcomes but did not present the post-intervention values, we requested them (means and SD) of each trial arm. Other information we requested included confirmation of a study design related to eligibility criteria (e.g. randomisation, provision of meals) or of key demographics of paricipants (mean age, body-mass index). If the eligibility criteria were not confirmed through contact, trials were excluded.

According to eligibility criteria, we excluded trials in which composition of macronutrients was not reported or not informative enough to compute the composition after we reviewed publications and contacted authors. In several publications, a ratio of PUFA to SFA or a similar metrics was available [53–58]. Using such information on dietary fat composition and % energy from total fat, we calculated % energy from SFA, MUFA, and PUFA. For Tardy *et al*., imputation was performed with a minor assumption. The authors reported that 64.5% of energy from fat came from the test fat presented in the publication in details including compositions of each individual fatty acid [30]. The rest, a non-test fat, came from *trans*-free vegetable oil including rapeseed oil. For fat composition of the rapeseed oil was informed from the French food composition table (http://www.afssa.fr/TableCIQUAL/index.htm). Gannon *et al*. did not present macronutrient composition [45], but the information was available in the other publication from the same group [59]. Of the two publications by Bjermo *et al*. and Iggman *et al*., the authors provided % energy of major fatty acids after we contacted the authors [48,51].

The outcome measures were often presented in a figure [22,26,31,33,39,43,44,60–68] that displayed blood concentrations of glucose, insulin, or other molecules, for example, over 120 or 180 minutes after intravenous infusion of glucose or an oral glucose tolerance test. For the graphical information, point estimates and error bars were digitalized to numeric information by two authors independently (FI and MCOO) with a publically available software (Dagra®, Blue Leaf Software Ltd., Hamilton, New Zealand), and two values for a single estimate were averaged.

Acute insulin response (AIR), a gold-standard measure of β-cell function, was used when area-under the curve of AIR to an intravenous glucose dose constant across trials (300 mg/kg) [27,39,66,69–72]. Insulin measurements at 6, 10, or 19 min of AIR after infusion were divided by the minute for standardisation of the outcome per min across trials: this treatment alter estimates numerically, but did not alter interpretation of results. Insulin sensitivity index was assessed with a comparable manner across trials [22,39,53,66,68–72] with glucose infusion rate of 300 mg/kg and a slight difference in frequency in blood sampling up to 3 hours (-5 or -15 min to 180 min).

Imputation

Missing information was imputed systematically. Uncertainty attributable to use of random values was accounted for by undertaking a multiple imputation as described in the last paragraph in this sub-section. We imputed post-intervention values if only p-values were reported so that p-values could be reproduced. For example, post-inetrvention values with p-values >0.05 were imputed to produce p>0.05; otherwise, we considered, publication bias would have been expected by excluding non-significant results, but including signfiicant effects.

If standard deviations (SDs) of post-intervention values were missing, but ones at baseline were available, the balisene SDs were used under assumption that the variability between individuals did not change. If SD still remained missing, SD were imputed by using available SD in different trials and demographic information. The imputation of SD was assumed not to influence our results as demonstrated elsewhere [73,74].

In cross-over trials, within-trial covariance should be accounted for because outcome values are correlated to the degree of within-individual correlations [75]. The information was not reported in any pubilcations, but calculable by using reported information [76]. Thus, we calculated within-individual correlations for outcomes we evaluated [22,34,36,43,46,49–51,54,61,64,69,70,77–96]. For the cross-over trials without the information, *r* were imputed by modelling a multiple-outcome hierarchical regression with covariates of age, sex (% men), diabetes status, sites (US or Canada, Europe, or other areas), and durations of interventions.

Intakes of fibre and trans fat were included as covariates in our analysis. Caloric restriction, body-mass index (BMI), and weight change over time were included in assessment of heterogeneity. The influences of caloric restiction and of weight change were evaluated in sensitivity analysis. Information on these variables was not always available. Trans fat was important as a covariate (see the next paragraph), but available only in nineteen trials. Thus, for trials without information on trans fat, we imputed the values by considering biological plausibility. To impute the information on the other variables, a regression-based approach was taken for fibre intake [24,30,33,43,48,50,97–

101], total caloric intake [24,43,102–104], BMI [31], and weight change [21,25,26,31,43,55,57,61,65,69,72,85,88,92,96,103–109]. These variables to impute were modelled simultaneously in sequential equations that included predictors of age, sex, caloric restriction (yes or no), diabetes status, and sites. The process was undertaken in two steps: first to obtain trial means of the continuous variables; and then to obtain within-trial variability around the means.

Trans fat is one of the energy-contributing nutrient, providing typically <2% of total energy intake in a population. To estimate effects of isocaloric replacement between major macronutrients, meta-analysis of feeding trials need to adjust for trans fat that can vary within a trial, although this was not done in macronutrient meta-analysis [110,111]. Of 100 trials, 16 trials (46 arms) provided the estimates of trans-fat intakes [21,30,31,33,37,40,50,70,71,85,91,96,97,107,109,112–115]. Using the available information, we performed regression-based imputation by using relationships between trans-fat, SFA, MUFA, PUFA, and whether or not a trial aimed to test a trans fat. Before imputation, trans fat was log-transformed, so that regression met the assumption of normal distribution of the imputed variable and that imputed values could not be zero or negative. Additionally, as three alternative imputations, three ratios of trans-fat to MUFA, to MUFA+PUFA, to SFA+MUFA+PUFA in the 19 trials were used to impute trans-fat intakes, for which different considerations for conversions of unsaturated fatty acids to trans fat and to saturated fat. As presented in S4 Table, sensitivity analyses were performed to assess if results differed by these approaches. Results did not vary substantially by the approach, and regression-based imputation tended to give conservative results overall.

We recognised the uncertainty of imputation by using a pseudo-random number function. To account for the uncertainty, we conducted multiple imputation by generating ten datasets based on ten different imputation seeds. Ten independent estimates were pooled to obtain the main estimate which precision was based on both within-imputation and between-imputation variance estimates [116]. This decision was made post hoc as we observed the between-imputation variability appeared to be not always trivial, ranging from 0.1% to 40% of the total variability (between-imputation variability + within-imputation variability). Thus, the estimation procedure was undertaken in the all meta-analyses in this study, including the main analyses, stratified analysis, and sensitivity analysis.

The uncertainty in estimating within-trial correlation r was additionally examined by fixing r to be a single value across all non-parallel trials. We repeated meta-analyses nineteen times: in each repeat, a between-arm correlation of each non-parallel trial was fixed to have a single value from 0.05 to 0.95 with an increment of 0.05. The results are presented in S1 Fig. We found little evidence for the influence of r if we consider the reasonable values around r=0.6. The figure also indicates that, if r=0 had been modelled, powers of crossover trials would have been lost, indicating importance of taking the approach modelling r in analysis.

References of Supplementary Information

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