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Effects of total fat intake on body fatness in adults (Review)

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[Intervention Review]

Effects of total fat intake on body fatness in adults

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ABSTRACT

Background

The ideal proportion of energy from fat in our food and its relation to body weight is not clear. In order to prevent overweight and obesity in the general population, we need to understand the relationship between the proportion of energy from fat and resulting weight and body fatness in the general population.

Objectives

To assess the effects of proportion of energy intake from fat on measures of body fatness (including body weight, waist circumference, percentage body fat and body mass index) in people not aiming to lose weight, using all appropriate randomised controlled trials (RCTs) of at least six months duration.

Search methods

We searched CENTRAL, MEDLINE, Embase, Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) to October 2019. We did not limit the search by language.

Selection criteria

Trials fulfilled the following criteria: 1) randomised intervention trial, 2) included adults aged at least 18 years, 3) randomised to a lower fat versus higher fat diet, without the intention to reduce weight in any participants, 4) not multifactorial and 5) assessed a measure of weight or body fatness after at least six months. We duplicated inclusion decisions and resolved disagreement by discussion or referral to a third party.

Data collection and analysis

We extracted data on the population, intervention, control and outcome measures in duplicate. We extracted measures of body fatness (body weight, BMI, percentage body fat and waist circumference) independently in duplicate at all available time points. We performed random-effects meta-analyses, meta-regression, subgrouping, sensitivity, funnel plot analyses and GRADE assessment.

Main results

We included 37 RCTs (57,079 participants). There is consistent high-quality evidence from RCTs that reducing total fat intake results in small reductions in body fatness; this was seen in almost all included studies and was highly resistant to sensitivity analyses (GRADE high-consistency evidence, not downgraded). The effect of eating less fat (compared with higher fat intake) is a mean body weight reduction of 1.4 kg (95% confidence interval (CI) -1.7 to -1.1 kg, in 53,875 participants from 26 RCTs, I^2 = 75%). The heterogeneity was explained in subgrouping and meta-regression. These suggested that greater weight loss results from greater fat reductions in people with lower fat intake at baseline, and people with higher body mass index (BMI) at baseline. The size of the effect on weight does not alter over time and is mirrored by reductions in BMI (MD -0.5 kg/m^2, 95% CI -0.6 to -0.3, 46,539 participants in 14 trials, I^2 = 21%), waist circumference (MD -0.5

cm, 95% CI -0.7 to -0.2, 16,620 participants in 3 trials; I^2 = 21%), and percentage body fat (MD -0.3% body fat, 95% CI -0.6 to 0.00, P = 0.05, in 2350 participants in 2 trials; I^2 = 0%).

There was no suggestion of harms associated with low fat diets that might mitigate any benefits on body fatness. The reduction in body weight was reflected in small reductions in LDL (-0.13 mmol/L, 95% CI -0.21 to -0.05), and total cholesterol (-0.23 mmol/L, 95% CI -0.32 to -0.14), with little or no effect on HDL cholesterol (-0.02 mmol/L, 95% CI -0.03 to 0.00), triglycerides (0.01 mmol/L, 95% CI -0.05 to 0.07), systolic (-0.75 mmHg, 95% CI -1.42 to -0.07) or diastolic blood pressure(-0.52 mmHg, 95% CI -0.95 to -0.09), all GRADE high-consistency evidence or quality of life (0.04, 95% CI 0.01 to 0.07, on a scale of 0 to 10, GRADE low-consistency evidence).

Authors' conclusions

Trials where participants were randomised to a lower fat intake versus a higher fat intake, but with no intention to reduce weight, showed a consistent, stable but small effect of low fat intake on body fatness: slightly lower weight, BMI, waist circumference and percentage body fat compared with higher fat arms. Greater fat reduction, lower baseline fat intake and higher baseline BMI were all associated with greater reductions in weight. There was no evidence of harm to serum lipids, blood pressure or quality of life, but rather of small benefits or no effect.

PLAIN LANGUAGE SUMMARY

Effect of cutting down the fat we eat on body weight

The ideal proportion of energy from fat in our food and its relation to body fatness is not clear. This review looked at the effect of cutting down the proportion of energy from fat in our food on body fatness in adults who are not aiming to lose weight. Body fatness was measured using body weight, body mass index, waist circumference and percent body fatness. The evidence is current to October 2019. The review found that cutting down on the proportion of fat in our food leads to a small but noticeable decrease in body weight, body mass index, percentage body fat and waist circumference. The effect did not change over time, but reducing fat intake to a greater extent results in greater weight reduction. We assessed potential harms of reducing total fat, but found no evidence of harm on serum lipids, blood pressure or quality of life.

SUMMARY OF FINDINGS

Summary of findings 1. Low dietary fat compared with usual fat for controlling body fatness

Low dietary fat compared with higher dietary fat for body fatness

Patient or population: adults from the general population including those who were healthy, with risk factors and with long-term conditions
Settings: any setting, including the community and institutions, for at least 6 months
Intervention: lower dietary total fat (intended that participants reduce dietary fat intake to ≤ 30% energy (≤ 30%E) from fat, and at least partially replace the energy lost with carbohydrates (simple or complex), protein or fruit and vegetables)
Comparison: higher dietary total fat (intended that participants consume > 30% energy from total fats. The higher fat arm could be 'usual dietary intake', specifying a higher total fat intake, or one aiming to modify the type of fats consumed, such as increasing monounsaturated or polyunsaturated fats)

Methods: randomised controlled trials (RCTs)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual fat	Low dietary fat				
Body fatness (represented by body weight, kg) Follow-up: 6 to 96 months	Median weight change -0.04 kg[1]	The mean body weight in the low fat groups was **1.42 kg lower** (1.73 to 1.10 lower)	—	53,875 (26 RCTs, 33 comparisons)	⊕⊕⊕⊕ **high** [2,3,4,5,6,7]	**Reducing total fat intake causes a small reduction in body fatness** (assessed with body weight and other measures of body fatness). Not downgraded
Body fatness (represented by BMI, kg/m^2) Follow-up: 6 to 96 months	Mean change in BMI 0.14 kg/m^2	The mean BMI in the low fat groups was **0.47 kg/m^2 lower** (0.64 to 0.30 lower)		46,604 (15 RCTs)		
Body fatness (represented by waist circumference, cm) Follow-up: 6 to 96 months	Mean change in waist circumference -0.6 cm	Mean waist circumference in low fat participants was **0.47 cm lower** (0.73 to 0.22 lower)		16,685 (4 RCTs)		
Body fatness (represented by percentage body fat) Follow-up: 6 to 96 months	Mean change in percentage body fat 0.7%	Mean percentage of body fat in low fat participants was **0.28% lower** (0.57 to 0 lower)		2415 (3 RCTs)		

Potential harms - serum lipids, mmol/L	Means at baseline in usual fat groups (in mmol/L): Total cholesterol 5.5; LDL cholesterol 4.0; HDL cholesterol 1.4, TG 1.3	Relative to control groups, **total cholesterol** in the low fat arm was **0.23 mmol/L lower** (95% CI -3.2 to -0.14), **LDL cholesterol was 0.13 mmol/L lower** (95% CI -0.21 to -0.05), **HDL cholesterol was 0.02 mmol/L lower** (95% CI -0.03 to 0.00), and **TG was 0.01 mmol/L higher** (95% CI -0.05 to 0.07).		Total chol: 9812 (22 RCTs) LDL chol: 8137 (19 RCTs) HDL chol: 8268 (20 RCTs) TG: 8672 (18 RCTs)	⊕⊕⊕⊕ **high** [4,8,9,10,11]	**We found no evidence that reducing total fat intake harms serum lipids**. It leads to small reductions in total and LDL cholesterol, with little change in HDL cholesterol or TG.
Potential harms - blood pressure (BP), mmHg	Mean change in usual fat groups (in mmHg): systolic BP -1.2; diastolic BP -0.9	Relative to control groups,**systolic BP** in the low fat arm was **0.75 mmHg lower** (95% CI -1.42 to -0.07) and **diastolic BP was 0.52 mmHg lower** (95% CI -0.95 to -0.09).		Systolic BP: 6078 (10 RCTs) Diastolic BP: 6078 (10 RCTs)	⊕⊕⊕⊕ **high** [4,8,12, 13, 14]	**We found no evidence that reducing total fat intake harms BP**. It leads to small reductions in systolic and diastolic BP.
Potential harms - quality of life (QoL)	Mean change in usual fat group was 0.03	Relative to control groups,**QoL** in the low fat arm was **0.04 higher** (95% CI 0.01 to 0.07) on a scale of 0 to 10, where 0 is worst and 10 best QoL.		40,130 (1 RCT)	⊕⊕◯◯ **low** [15,16, 17,18,19]	**We found no evidence that reducing total fat intake harms QoL**. It may lead to small rises in QoL.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]The median weight change in the control groups over the course of each study was -0.04 kg, ranging from -1.91 kg to 2.13 kg.
[2] **Risk of bias:** While most studies were unblinded for participants and allocation concealment was often unclear (as randomisation was described poorly), RCT results in adults were remarkably consistent in their direction. Sensitivity analyses removing studies not at low summary risk of bias did not lose the statistically significant relative weight reduction in the low fat arm, and neither did running fixed-effect (rather than random-effects) meta-analysis or removing studies with attention bias favouring those in the low fat arm, or those with other interventions alongside the fat reduction. Together this suggests that the risk of bias was low. Not downgraded.
[3] **Inconsistency:** The direction of effects in these RCTs was remarkably consistent - in almost every study, participants eating lower total fat intakes were lower in weight (on average) at the study end than participants eating a higher percentage of total fat. The only inconsistency (where heterogeneity arose) was in the size of this effect. The heterogeneity was partly explained by the degree of reduction of fat intake, by the BMI of participants, and by the level of control group fat intake, which together explained 16% of between-study variance (in meta-regression). The reduction in weight in those taking on lower fat diets was seen in very different populations and from six months to several years. It was also consistent when we excluded studies that gave additional support, time or encouragement to the low fat arms, and where we excluded studies that delivered

additional dietary interventions (on top of the change in dietary fats). The results were consistent in direction, and much of the heterogeneity in the size of the effect was explained by the selected factors. Effects on body weight are supported by similar effects on BMI, waist circumference and percentage of body fat. Not downgraded.

[4] **Indirectness:** All included RCTs directly compared (and randomised participants) to lower versus usual fat intake. Participants were directly relevant as they came from all parts of the world, included men and women, and people who were healthy, with risk factors or with long-term conditions at baseline. The studies all addressed weight directly and did not use proxy measures. Not downgraded.

[5] **Imprecision:** Over 50,000 participants were included in RCTs of at least six months duration, and effect sizes were highly statistically significant in main analyses and subgroups. There was little imprecision. If the true effect on weight was at either end of the 95% CI, we would interpret the effect in the same way. Not downgraded.

[6] **Publication bias:** The funnel plot did not suggest publication bias. The consistent weight loss was despite the fact that none of the studies included intended to alter weight in either arm, so that publication bias for this outcome is unlikely. Not downgraded.

[7] **Dose response:** Subgrouping and meta-regression supported the presence of a dose-response gradient - greater reduction in total fat intake lead to greater weight loss. Not upgraded.

[8] **Risk of bias:** While most studies were unblinded for participants and allocation concealment was often unclear (as randomisation was described poorly), RCT results in adults were remarkably consistent in their direction. Sensitivity analyses removing studies not at low summary risk of bias were not performed, but individual studies at low summary risk of bias generally supported reductions in total and LDL cholesterol and little effect on HDL, TG, systolic and diastolic BP. This suggests low risk of bias. Not downgraded.

[9] **Inconsistency:** While $I^2 > 0.5$ for total and LDL cholesterol, the direction of effects in these RCTs was consistent - in almost every study participants eating lower total fat intakes had lower total and LDL cholesterol (on average) at the study end than participants eating a higher percentage of total fat. The inconsistency (where heterogeneity arose) was in the size of this effect. The results were consistent in direction. Effects on total and LDL cholesterol support each other. Not downgraded.

[10] **Imprecision:** Effect sizes for total and LDL cholesterol were highly statistically significant. There was little imprecision. If the true effect on either total or LDL cholesterol was at either end of the 95% CI, we would interpret the effect in the same way. Not downgraded.

[11] **Publication bias:** The funnel plots were difficult to interpret, but did not suggest publication bias. Not downgraded.

[12] **Inconsistency:** $I^2 < 0.10$ for systolic and diastolic BP. Not downgraded.

[13] **Imprecision:** Effect sizes for systolic and diastolic blood pressure were statistically significant, suggesting small non-clinically relevant reductions in BP. If the true effect on either systolic or diastolic BP was at either end of the 95% CI we would interpret the effect in the same way. Not downgraded.

[14] **Publication bias:** The funnel plots were difficult to interpret, but suggested that studies with smaller reductions, or small rises in BP may be missing. If such studies were added in, then the effect would move closer to zero. Not downgraded.

[15] **Indirectness:** The single very large trial was in women from the USA. Downgraded once.

[16] **Risk of bias:** The single very large trial was at low summary risk of bias. Not downgraded.

[17] **Inconsistency:** Single trial only, no inconsistency but no evidence of consistency. Downgraded once.

[18] **Imprecision:** The effect was statistically significant. Not downgraded.

[19] **Publication bias:** Not possible to assess with a single study. Not downgraded.

BACKGROUND

Description of the condition

Optimal intakes of total fat were debated by the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) expert consultation on fats and fatty acids in human nutrition in 2008. In light of the rising levels of overweight and obesity, particularly in low- and middle-income countries undergoing rapid nutrition transition, this consultation agreed that any effect of total fat intake on body weight was pivotal in making global recommendations on total fat intake. Overweight and obesity are associated with increased risk of many cancers, coronary heart disease and stroke (Manson 1990; Song 2004; WCRF/AICR 2009).

How the intervention might work

A previous systematic review that aimed to assess effects of lower fat intake on body weight did not find any eligible randomised controlled trials (RCTs) (Kelly 2006), but we were aware of RCTs that had randomised participants to lower fat versus higher fat diets, and measured weight or BMI, not as the primary outcome of intervention, but as a process measure or intermediate outcome (Hooper 2012a; Hooper 2015a). Additionally, meta-regression within a systematic review assessing RCTs on the effects of step I and II diets (diets designed by the National Heart, Lung and Blood Institute national cholesterol education programme to reduce the risk of cardiovascular disease in the general population and those at increased cardiovascular risk, respectively), found a strong relationship between total fat intake and body weight (Yu-Poth 1999). This review, however, included studies that were as short as three weeks in duration and studies in which weight loss was a goal of the intervention, which may have overstated any relationship because the advice was to lower both fat and energy intake. It also excluded many trials of reduction in total fat intake that did not fit the step I or II criteria.

More recent reviews that have explored the long-term effects of low fat diets either did not explore weight or body fatness as an outcome (Schwingshackl 2013), or looked at low fat intake as part of a wider health promotion intervention (Ni 2010). Other systematic reviews have explored the relationship between fat intake and body fatness but were either limited to the effect of low fat dairy versus high fat dairy consumption (Benatar 2013), or investigated it as part of overall dietary patterns (Ambrosini 2014), or diet quality (Aljadani 2015).

Why it is important to do this review

The WHO Nutrition Guidance Expert Advisory Group (NUGAG) subgroup on diet and health (www.who.int/nutrition/topics/advisory_group/nugag_dietandhealth_topics/en/) was requested by WHO to assess the relationship between total fat intake and body weight. This was to aid the WHO's understanding of this relationship and enable updating of WHO's guidelines on total fat intake. The expert advisory group aimed to generate a recommendation on the population impact of total fat intake in the development of obesity. The NUGAG group agreed to exclude studies of populations recruited specifically for weight loss and interventions intended to result in weight loss. These studies are potentially confounded by the implicit objective of reducing calorie intake to produce weight loss and might therefore lead to an overemphasis on studies carried out in highly selected obese populations in North America and Europe, which may have limited transferability to non-obese populations or those in developing countries or in countries in transition.

To fulfil the requirements for the new guideline, a systematic review was needed of all available evidence of the longer-term effects of total fat intake on body fatness, in studies not intending to cause weight loss. The WHO therefore commissioned a systematic review and meta-analysis to assess the relationship between total fat intake and indicators of body fatness (including obesity, waist circumference and body mass index) using all appropriate RCTs and cohort studies in adults and children (Hooper 2012b), which was updated in 2015 (Hooper 2015a). This update of the review focusses on RCTs in adults, and a companion review assesses effects in children (Naude 2018).

OBJECTIVES

To assess the effects of proportion of energy intake from fat on measures of weight and body fatness (including body weight, waist circumference, body mass index and percentage of body fat) in adults not aiming to lose weight, using all appropriate RCTs with a duration of at least six months.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include randomised controlled trials (RCTs) in adults aged at least 18 years. They needed to assess effects of reduced fat intake compared with higher fat intake with no intention to reduce weight (in any participants in either or both arms). Trials needed to have a minimum duration of six months, be unconfounded by non-nutritional interventions and assess a measure of body fatness at least six months after the intervention was initiated.

Randomisation of individuals was accepted, or of larger groups where there were at least six of these groups (clusters) randomised. We excluded studies where allocation was not truly randomised (e.g. divisions based on days of the week or first letter of the family name were excluded) or where allocation was not stated as randomised (and no further information was available from the authors). We excluded cross-over studies (as previous weight gain or weight loss is likely to affect future weight trends) unless the first half of the cross-over could be used independently.

We included full-text studies, those published as abstracts only, and unpublished data. We did not include cohort studies in this update.

Types of participants

We accepted studies of adults (≥ 18 years, no upper age limit) at any risk of cardiovascular disease (with or without existing cardiovascular disease). Participants could be of either sex, but we excluded those who were acutely ill (including with immunity problems such as HIV or post-transplant), pregnant or lactating. We excluded intervention studies where participants were chosen for raised weight or body mass index (as most appeared to aim to reduce body weight within interventions, even when this was not explicitly stated in the intervention goals).

Types of interventions

We considered all randomised controlled trials (RCTs) of interventions stating an intention to reduce dietary fat, when compared with a higher (usual or modified fat) intake.

We considered a low fat intake to be one that aimed to reduce fat intake to ≤ 30% energy (≤ 30%E) from fat, and at least partially replace the energy lost with carbohydrates (simple or complex), protein or fruit and vegetables. We considered a higher fat diet to be one that aimed to include > 30% energy from total fats. The higher fat arm could be "usual dietary intake", specifying a higher total fat intake, or one aiming to modify the type of fats consumed (such as increasing mono-unsaturated or poly-unsaturated fats).

As we were interested in the effects of fat intake on body weight and fatness in everyday dietary intake (rather than in people aiming to reduce their body weight in weight-reducing diets), we excluded studies aiming to reduce the weight of some or all participants, as well as those that included only participants who had recently lost weight, or recruited participants according to a raised body weight or BMI. We excluded multifactorial interventions other than diet or supplementation (unless the effects of diet or supplementation could be separated, such as in a 2 x 2 trial where the additional intervention was consistent between the intervention and control groups). We excluded Atkins-type diets aiming to increase protein and fat intake, as well as studies where fat was reduced by means of a fat substitute (like Olestra). We excluded enteral and parenteral feeds, as well as formula weight-reducing diets.

Examples

The following are some examples of the types of studies we would include or exclude based on their intervention and comparison groups. We included studies that reduced fats and encouraged physical activity in one arm and compared this with encouraging physical activity in the control. We excluded studies that reduced fats and encouraged physical activity in one arm and compared this with no intervention in the control. We included studies that reduced fats and encouraged fruit and vegetables in one arm and compared this with no intervention in the control.

We included all trials that intended to reduce dietary fat to ≤ 30%E in one arm compared to higher fat intake (> 30%E from fat) in another arm regardless of the degree of difference between fat intake in the two arms (dose). We explored the effects of the difference in %E from fat between control and intervention groups, as well as the effects of fat intake in the control groups and dietary fat goals in the intervention groups, in subgrouping and meta-regression.

Types of outcome measures

Primary outcomes

The main outcome was body fatness assessed using a variety of measures. These included body weight, body mass index, waist circumference, skinfold thickness and percentage fat. Studies had to assess or report at least one of these measures, or a change in these measures, to be included in the review. Measures of body fatness needed to be assessed at least six months after the intervention was initiated, and data at trial end, or from the latest available time during the trial, were used.

Secondary outcomes

Secondary outcomes included other classic cardiovascular risk factors (systolic or diastolic blood pressure; serum total, low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol, and triglyceride) and quality of life measures (including informal outcomes such as feelings of health and time off work). They were included in the review to assess any possible harms of reducing total fat on quality of life or cardiovascular risk factors.

Tertiary outcomes

Tertiary outcomes were process outcomes and included changes in saturated and total fat intakes, as well as other macronutrients, sugars and alcohol.

This is not a systematic review of the effects of reduced fat on these secondary or tertiary outcomes, but we collated the outcomes from included studies in order to understand whether any effects on weight might be compromised by negative effects on secondary or tertiary outcomes.

Search methods for identification of studies

Electronic searches

The searches for this review were last run in November 2014 as part of a broader review (Hooper 2015a). As the review has now been split and the previous search strategy was unsuitable, a new strategy was run on 18 October 2019, from database inception, in the following databases:

- CENTRAL (Issue 10 of 12, 2019, Cochrane Library)
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to October 17, 2019)
- Embase (Ovid, 1980 to 2019 week 41)

Two clinical trials registers were also searched on 18 October 2019; Clinicaltrials.gov (https://clinicaltrials.gov/) and WHO International Clinical Trials Registry Platform (ICTRP, https://apps.who.int/trialsearch/). The searches are described in Appendix 1. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2011), and for Embase, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

The results were de-duplicated against each other. As we were updating another Cochrane review relating to dietary fat (Hooper 2015b) at the same time, results of the searches for both reviews were combined and de-duplicated before assessment of titles and abstracts.

The search to 2014 is described in Hooper 2015a, and previous searches (to June 2010) in Hooper 2012b.

Searching other resources

We searched for recent and additional publications of all our included studies, using trials registry entries (for outcome data and publication lists), searching on trials registry numbers, and tracking key authors, to ensure the best and most complete information was available for all our included studies. We also checked reference lists of included studies and looked for retraction statements and errata.

Data collection and analysis

Selection of studies

Titles and abstracts identified by searches were loaded into Covidence software, and all authors took part in assessment of titles and abstracts. We only rejected articles on initial screen if the review author could determine from the title and abstract that the article was not a relevant RCT. We rejected articles if they were not reporting a RCT; the trial did not address a low fat intake; the trial was exclusively in children (less than 18 years old), pregnant women or the critically ill; participants were chosen for being overweight or obese; there was an intention to reduce weight in some or all participants; the trial was of less than six months duration; or the intervention was multifactorial.

When a title/abstract could not be rejected with certainty, we obtained the full text of the article for further evaluation.

Data extraction and management

We extracted data concerning participants, interventions and outcomes, and trial quality characteristics onto a form designed for the review. We extracted data on potential effect modifiers (including duration of intervention, control group fat intake, sex, year of first publication, difference in % energy from fat between the intervention and control groups, type of intervention (food or advice provided), the dietary fat goals set for each arm, baseline BMI and health at baseline). Where provided, we collected data on risk factors for cardiovascular disease (secondary and tertiary outcomes).

All trial outcomes were continuous and, where possible, we extracted change data (change in the outcome from baseline to outcome assessment) with relevant data on variance for intervention and control arms (along with numbers of participants at that time point). Where change data were not available, we extracted data at study end (or other relevant time point) along with variance and numbers of participants for each arm. LH, OFJ and AA assessed inclusion of full-text studies independently in duplicate, and discussed disagreements until agreement was reached (including the third member of the team where needed).

Assessment of risk of bias in included studies

We carried out 'Risk of bias' assessment independently in duplicate as part of data extraction. We assessed trial risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011b). For included RCTs, in addition to the tool's domains, we assessed whether:

1. trials were free of differences in diet (between intervention and control arms) other than dietary fat intake;
2. there was any systematic difference in attention or care or time given between the intervention and control groups; and
3. there was evidence that the two arms achieved statistically significant differences in total fat intake (compliance).

These issues were chosen as we felt that these factors may also affect differences in weight between arms. We used the category 'other bias' to note any further issues of methodological concern. Funding was not formally a part of our assessment of bias in RCTs as it is not a core part of the Cochrane 'Risk of bias' tool, but was reported in the Characteristics of included studies.

We assessed each trial for summary risk of bias. Summary risk of bias was considered low in trials with low risk of selection bias (low risk from random sequence generation and allocation concealment) and low risk of detection bias. Summary risk of bias was considered moderate to high in all other included trials.

Measures of treatment effect

The effect measure of choice for continuous outcomes (all review outcomes were continuous outcomes) was the mean difference (MD) with its 95% confidence interval.

Unit of analysis issues

We did not include any cluster-randomised or cross-over trials in this review.

Where there was more than one relevant intervention arm but only one control arm we pooled the relevant intervention arms to create a single pairwise comparison (where the intervention arms were equivalently appropriate for this review) as described in Higgins 2011a. We excluded intervention arms that were not appropriate for this review, or less appropriate than another arm. When two arms were appropriate for different subgroups. then we used the control group once with each intervention arm, but we did not pool the subgroups overall.

When weight or BMI were assessed at more than one time point, we used the data from the latest time point available in general analyses, but we extracted data for all time points for use in subgrouping by study duration.

Dealing with missing data

Where included studies used methods to infer missing data (such as carrying the latest weight data forward), then we used these data in analyses. Where this was not done we used the data as presented.

Assessment of heterogeneity

We examined heterogeneity using the I^2 statistic and considered heterogeneity important where the I^2 was above 50% (Higgins 2003; Higgins 2011a).

Assessment of reporting biases

We drew funnel plots to examine the possibility of publication bias for measures of body fatness with at least 10 included comparisons (Egger 1997). We also compared findings of fixed- and random-effects meta-analysis since the two methods weight small trials differently, and different effect sizes suggest potential small study bias (Page 2019).

Data synthesis

All trial outcomes were continuous and, where possible, we extracted change data (change in the outcome from baseline to outcome assessment) with relevant data on variance for intervention and control arms (along with numbers of participants at that time point). Where change data were not available, we extracted data at study end (or other relevant time point) along with variance and numbers of participants for each arm. We did not use end data where the difference between the intervention and control groups at baseline was greater than the change in that measure between baseline and endpoint in both arms (instead we used change data in forest plots, but without standard deviations

(SDs), so the data did not add to the meta-analyses but provided comparative information).

We combined data by the inverse variance method in random-effects meta-analysis (RevMan 2014) to assess mean differences with 95% confidence intervals between lower and higher fat intake arms.

Summary of findings

We created a 'Summary of findings' table assessing the effects of low dietary fat compared with usual fat for body fatness (combining data on body weight, BMI, waist circumference and percentage body fat, which all assess body fatness) in adults using RCT data, reflecting GRADE assessment of quality of our findings.

Subgroup analysis and investigation of heterogeneity

We classified all dietary interventions as lower fat versus higher fat. Prespecified subgroups for body weight, to explore the stability of findings in different study subgroups, included:

- duration of intervention (6 to < 12 months, 12 to < 24 months, 24 to < 60 months, and 60+ months);
- control group total fat intake (> 35%E from fat, > 30%E to 35%E from fat, > 25%E to 30%E from fat). Control group fat intake is equivalent to baseline fat intake;
- year of first publication of results (1960s, 1970s, 1980s, 1990s, 2000s, 2010s);
- sex (studies of women only, of men only, of men and women mixed);
- difference in %E from fat between control and reduced fat groups (up to 5%E from fat, 5%E to < 10%E from fat, 10%E to < 15%E from fat, 15+%E from fat, or unknown difference);
- type of intervention (dietary advice, advice plus supplements and diet provided);
- total fat goal in the intervention arm (10%E to < 15%E from fat, 15%E to < 20%E from fat, 20%E to < 25%E from fat, 25%E to < 30%E from fat, 30%E from fat, and no specific goal stated);
- achieving fat goals (achieved 30%E from fat or less, did not achieve this);
- mean BMI at baseline (< 25, 25 to < 30, 30+);
- state of health at baseline (not recruited on the basis of risk factors or disease, recruited on the basis of risk factors such as lipids, hormonal levels etc., recruited on the basis of having or having had diseases such as diabetes, myocardial infarction, cancer, polyps);
- assessed energy reduction in the intervention compared with the control group during the intervention period (E intake the same or greater in the low fat group, E intake 1 to 100 kcal/d lower in the low fat group, 101 to 200 kcal/d lower in the low fat group, > 200 Kcal/d lower in the low fat group).

For subgrouping factors that appeared to suggest significant differences in effect size between subgroups, we explored the effects using meta-regression on weight. We performed random-effects meta-regression (Berkley 1995) using the STATA command metareg (Sharp 1998; Sterne 2001; Sterne 2009).

Sensitivity analysis

We carried out sensitivity analyses for primary outcomes, assessing the effect of:

- running fixed-effect meta-analyses (rather than random-effects) (Higgins 2011a);
- excluding studies not at low summary risk of bias
- excluding the largest study (WHI 2006);
- excluding studies that were not free of systematic differences in care (or unclear);
- excluding studies that were not free of dietary differences other than fat (or unclear)

RESULTS

Description of studies

Results of the search

For this update, the electronic searches identified 15,314 possible titles and abstracts (including trials registry entries) for assessment for this review and the sister review being updated (Hooper 2015a). Of these, 14,784 were rejected on title and abstract screening, and 530 were collected in full text for further assessment. Seventy-three full-text publications were included or assessed as pending, and these were grouped into seven new included RCTs (AUSMED 2018; CORDIOPREV 2016; Ma 2016; ODMDC 2017; RISCK 2010; WHT Full-scale; Yadav 2016 including 3584 randomised participants), three ongoing RCTs, six RCTs awaiting further assessment (as existing details were not sufficient to ensure inclusion), and 18 new publications for eight already included RCTs. One previously included trial was excluded (Sondergaard 2003) during reassessment as it was felt on reflection that it was highly unlikely either arm aimed at < 30% E from fat. Combining with the 30 RCTs already included means that this review includes 37 RCTs, three ongoing RCTs and a further six RCTs are awaiting assessment (Figure 1).

Figure 1. Study flow diagram

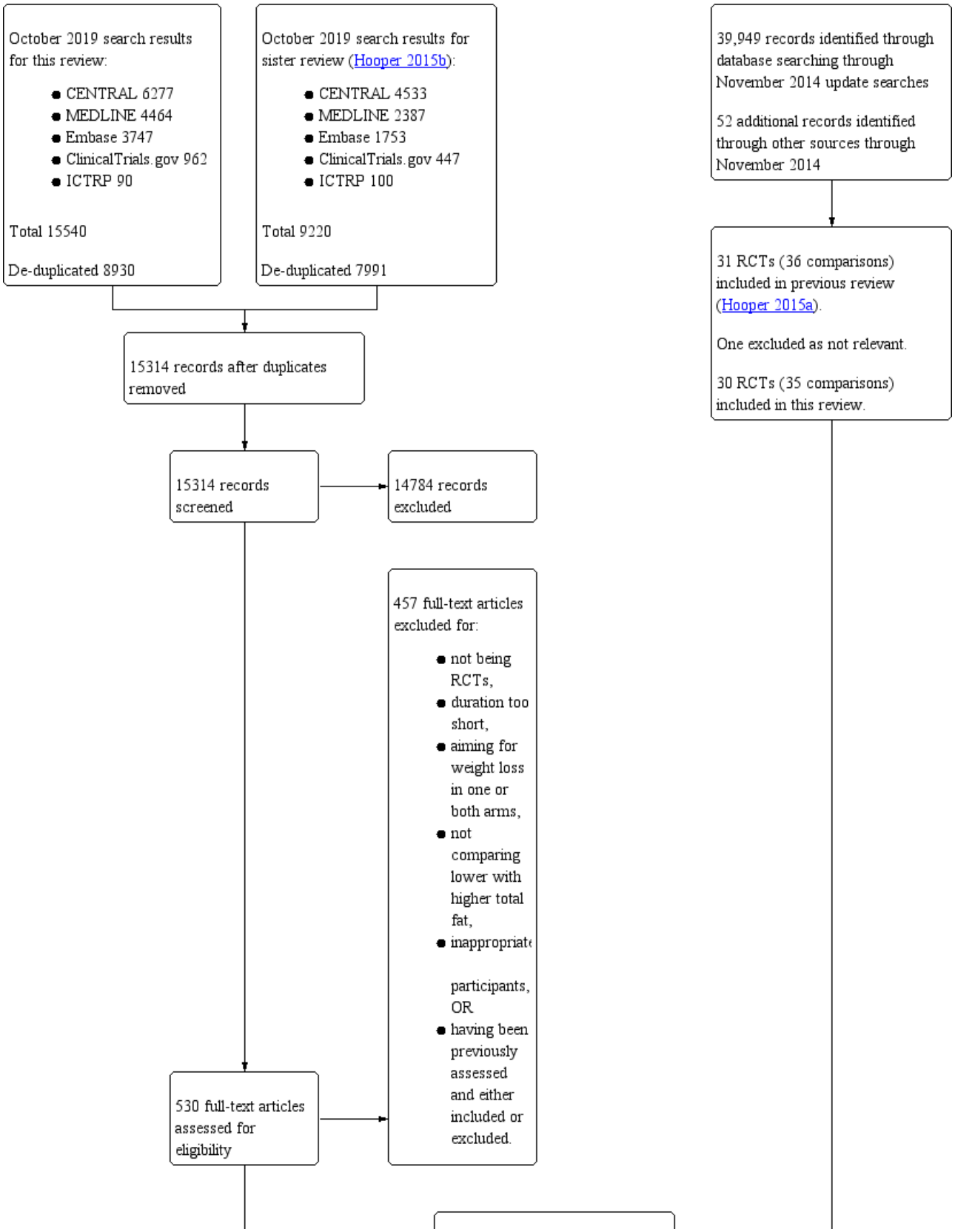
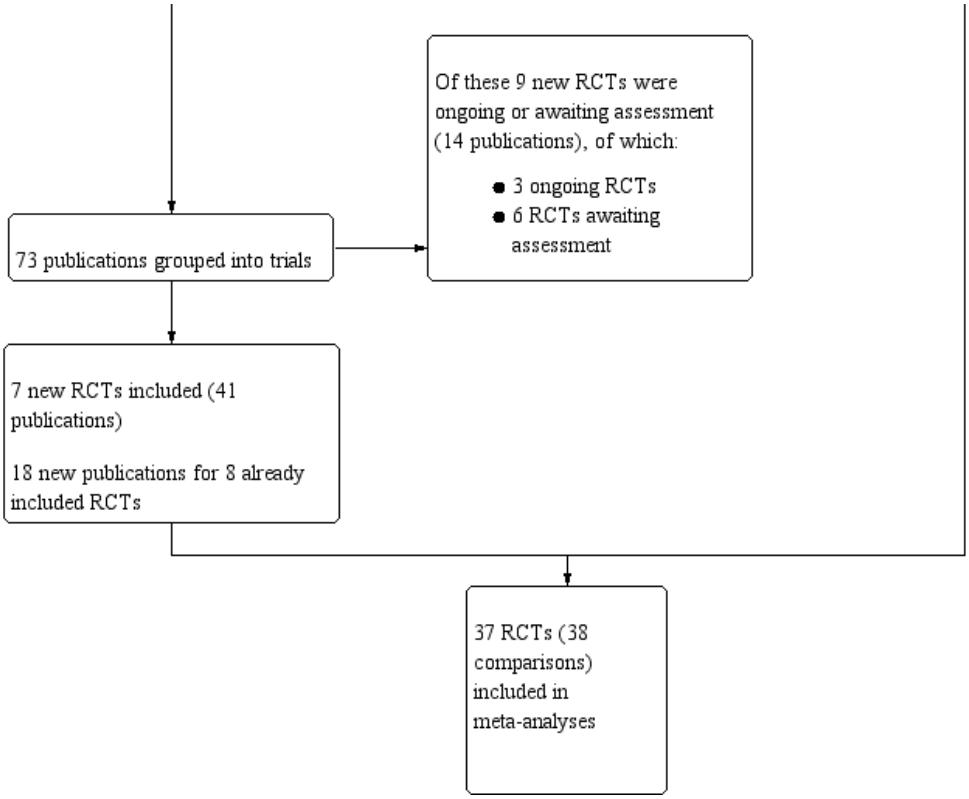


Figure 1. (Continued)



We included all 37 RCTs in forest plots. Twenty-nine RCTs provided full information on at least one body fatness outcome and so were included in meta-analytic pooling. Eight RCTs only provided partial data so are displayed in forest plots (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 2.7) but not included in meta-analysis. They are displayed to allow us to assess whether these results support or detract from meta-analytic findings (AUSMED 2018; beFIT 1997; Black 1994; MeDiet 2006; NDHS Open 1st L&M 1968; NDHS Open 2nd L&M 1968; Rivellese 1994).

Included studies

Of the 37 RCTs (including up to 57,079 participants - exact numbers depending on time point in study and endpoint used), 24 were from North America, 10 from Europe, two from Australia or New Zealand, and one from China. The duration of the trials varied from six months to more than eight years. In four trials, the participants were all men, in 16 all women and in 17 both sexes (one of which reported outcomes by sex). Mean ages and states of health (low, moderate or high risk of cardiovascular disease or breast cancer, where low risk are people without specific risk factors, moderate risk people have risk factors, and those at high risk have experienced CVD or cancer) varied. See Characteristics of included studies for detailed characteristics of the RCTs.

When discussing the 37 RCTs, De Bont 1981 and DEER 1998 are referred to and counted as single studies, although individual arms appear in analyses (data were presented by body weight at baseline for De Bont 1981, and by sex and exercise prescription for DEER 1998). This is because this was how the data were presented in the original papers for these trials and the different arms occasionally appear in different subgroups (making subgrouping more effective). However, Sarkkinen Low & Mod 1993 and Sarkkinen Low Fat 1993 had four distinct dietary arms that worked as two intervention/control pairs, so are presented as separate trials.

As well as the addition of the seven new trials, new publications were located for some already included trials. These allowed updating of three already included trials and addition of new outcome data (WHEL 2007; WHI 2006; WHTFSMP 2003).

Excluded studies

During this update, we added seven new trials to the list of excluded studies (Cocinar para su salud 2016; DIRECT 2009; Drummond 1998; Eckard 2013; HIPERCOL 2018; Nutri-EPA 2017; Troyer 2010). They were excluded for an inappropriate intervention or control (Cocinar para su salud 2016; Drummond 1998; HIPERCOL 2018; Troyer 2010; Nutri-EPA 2017) or because the study aimed to reduce weight in some or all participants (DIRECT 2009; Eckard 2013).

Risk of bias in included studies

To understand the risk of bias in the individual included RCTs in a visual way, see Figure 2. Risk of bias is reported by included arms (so Sarkkinen Low & Mod 1993 and Sarkkinen Low Fat 1993 are reported separately), so are discussed as 38 RCT arms.

Figure 2. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included adult and child RCT comparison.

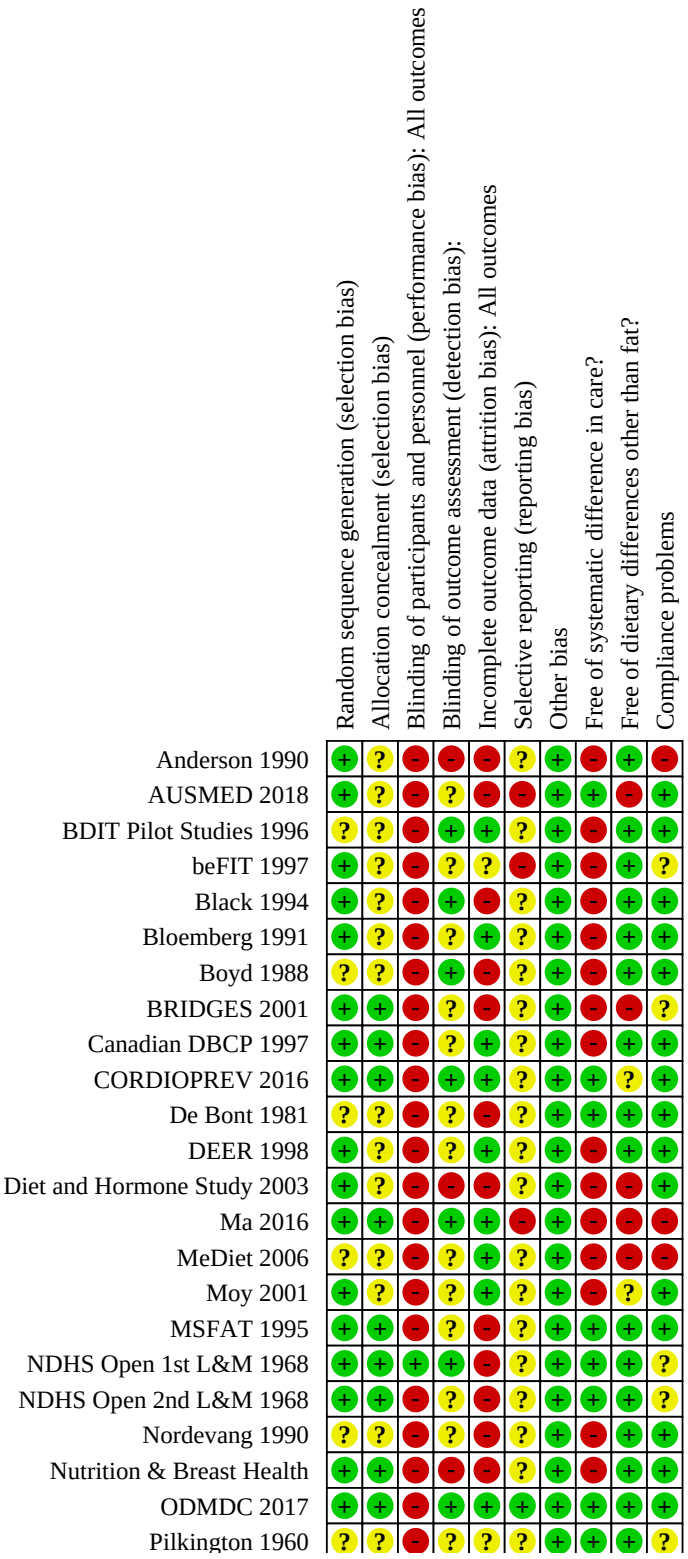
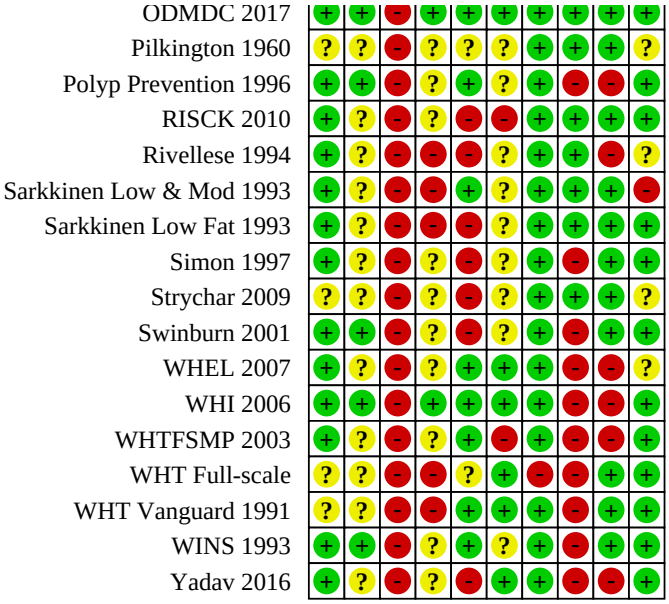


Figure 2. (Continued)



Allocation

Twenty-nine RCT arms had low risk of bias from random sequence generation (as they provided some information on the method of randomisation, suggesting true randomisation was performed in some way); the remainder were at unclear risk. Thirteen RCT arms were at low risk of selection bias (arising from low risk from allocation concealment and randomisation), and the remaining RCTs were at unclear risk.

Blinding

There was a high risk of performance bias due to lack of blinding of participants (which is usual in dietary trials) in 36 included RCTs, and low risk in one of the National Diet and Heart Studies (NDHS Open 1st L&M 1968), which provided trial shops that blinded purchases of usual or low fat products. The risk of detection bias was low in eight trials, high in eight trials, and unclear in the remainder.

Summary risk of bias was low in five included trials (CORDIOPREV 2016; Ma 2016; NDHS Open 1st L&M 1968; ODMDC 2017; WHI 2006) - trials with low risk of selection bias (low risk from random sequence generation and allocation concealment) and low risk of detection bias.

Incomplete outcome data

For RCTs, we assessed those studies that lost more than 10% of participants per year as at high risk of attrition bias; others were at low risk of attrition bias. Sixteen RCT arms were at low risk of attrition bias, 19 were at high risk of attrition bias and three were unclear.

Selective reporting

Most RCTs were at unclear risk of reporting bias (due to the paucity of accessible and prospective trial registrations and protocols, so that we could not assess reporting bias), but six RCT arms were at low risk and five at high risk of bias.

Other potential sources of bias

We considered all RCTs to be at low risk of other types of bias, except for WHT Full-scale which was terminated early, before many participants had outcomes measured, and is poorly reported.

Thirteen RCT arms had low risk of systematic differences in level of care between the intervention and control groups, while 25 had high risk of such differences in care. Differences in attention, training, time from health professionals, number of health checks and/or group support could potentially alter feelings of self efficacy and increase contact with healthcare professionals offering various types of support, and alter participants' ability to look after themselves and maintain a healthy weight.

Some dietary interventions to reduce fat also had specific goals around fruit, vegetables, fibre, alcohol etc., which raises the possibility that any changes in weight may result from these alterations, not from change in fat intake. Eleven RCT arms were at high risk of effects from dietary differences other than fat; two were unclear and the remaining 25 RCTs were at low risk of effects from other dietary advice.

We assessed studies to be at low risk of compliance problems if there was a statistically significant difference in total fat intake during the intervention period (as late as possible during the intervention). We found that 25 trial arms were at low risk, four at high risk and 9 at unclear risk of compliance problems.

Effects of interventions

See: **Summary of findings 1** Low dietary fat compared with usual fat for controlling body fatness

The 'Summary of findings' table assessing the effects of lower dietary fat compared with higher dietary fat intake for body weight, and including the GRADE assessment, is presented (Summary of findings 1).

Effects of reducing dietary fat on weight and body fatness in adults

Body fatness

Body fatness was measured in this review with body weight, BMI, waist circumference and percentage body fatness. Effects on each of these specific measures are reported below. Combining data on all of these measures, we found that eating a lower proportion of energy as fat results in slightly lower body fatness than eating the usual proportion of fat (GRADE assessment: high-quality evidence, not downgraded).

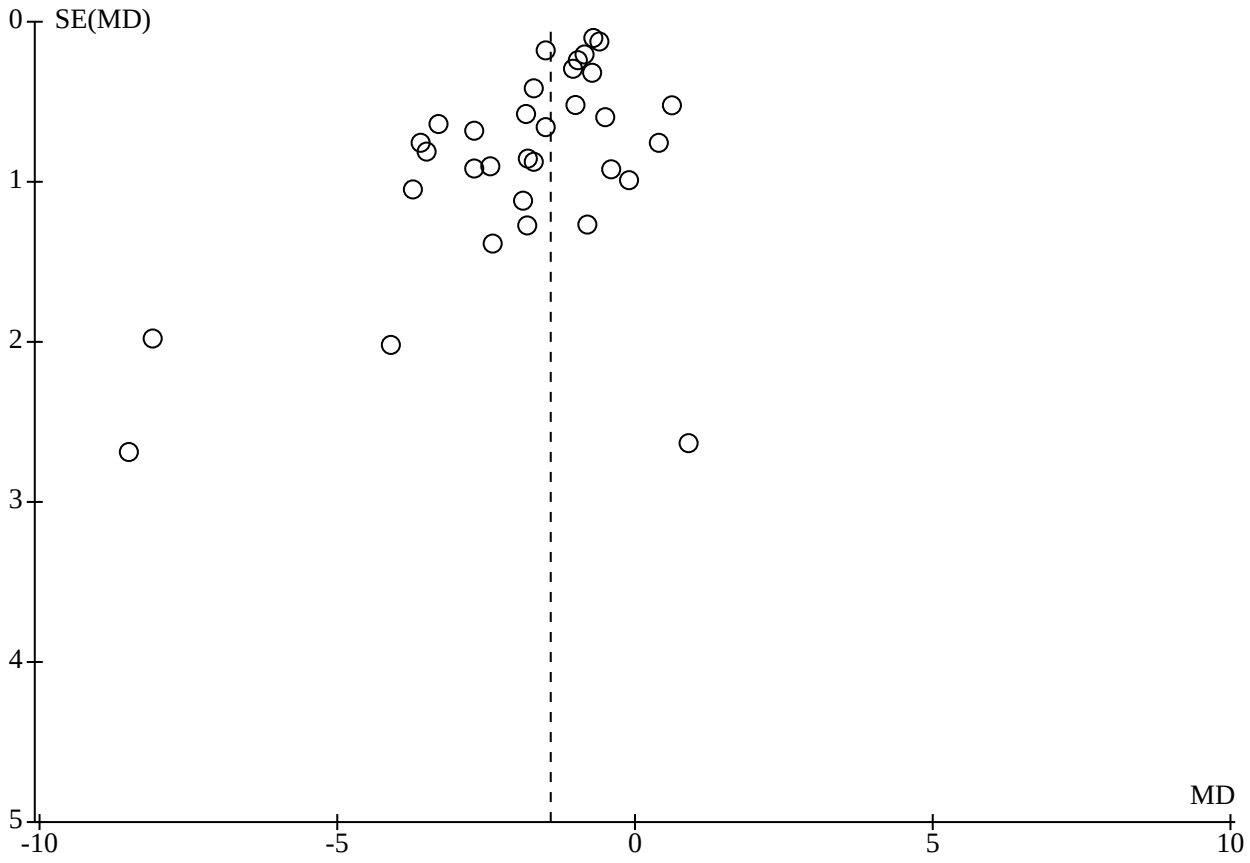
Weight

Eating a lower proportion of energy as fat results in lower body weight (or lower weight gain, or greater weight reduction) than eating the usual proportion of fat (MD -1.4 kg, 95% confidence interval (CI) -1.7 to -1.1, I^2 = 75%, 53,875 participants, 33 estimable comparisons from 26 RCTs, Analysis 1.1, high-quality evidence). The effect was small and consistent; the best estimate of effect was a reduction in weight in the lower fat arm consistently across 30 of the 33 comparisons.

Sensitivity analyses. We ran sensitivity analyses to assess effects of lower fat intake on body weight when analyses were run using different assumptions. Effects using fixed-effect meta-analysis (-0.9 kg, 95% CI -1.1 to -0.8, Analysis 2.1), including only trials at low summary risk of bias (-1.4 kg, 95% CI -1.7 to -1.1, Analysis 2.2), excluding the largest trial, WHI 2006 (-1.5 kg, 95% CI -1.9 to -1.2, Analysis 2.3), excluding trials with more time or attention to the intervention group (-0.9 kg, 95% CI -1.2 to -0.6, Analysis 2.4), excluding trials with dietary differences additional to fat differences (-1.6 kg, 95% CI -2.1 to -1.2, Analysis 2.5) or excluding studies with potential compliance problems (-1.6 kg, -1.9 to -1.2, Analysis 2.6) all suggested lower weight in study populations eating lower fat diets.

Small study bias and missing data. The funnel plot suggested that one or two small studies showing weight gain in the lower fat arm may be missing (Figure 3). The effect of adding any such missing studies back into the meta-analysis would be a small reduction in amount of weight loss in lower fat arms. All of the nine comparisons without an estimable effect size, due to lack of variance data or large baseline differences, were consistent with greater weight reduction in the reduced fat arms (Analysis 2.7). As the effect in fixed-effect analysis, which gives less weight to small studies (-0.9 kg, 95% CI -1.1 to -0.8, Analysis 2.1), is smaller than the effect in random-effects meta-analysis (-1.4 kg, 95% CI -1.7 to -1.1, Analysis 1.1), which gives more weight to smaller studies, there is a suggestion of small study bias in the overall effect size. The weight reduction with reduced fat intake is still present, but may be closer to -0.9 kg (Analysis 2.1) than -1.4 kg.

Figure 3. Funnel plot of comparison: 1 Fat reduction versus usual fat diet, outcome: 1.1 Weight, kg.



Subgrouping. Heterogeneity was high (I^2 = 75%) but only in the degree of weight loss - lower weight in the lower fat arm was remarkably consistent across the included trials. Subgrouping may be able to explain why effects differ in different trials. We used prespecified subgroups to examine the influence of potential effect modifiers of fat intake on body weight. There were significant differences between effects in subgroups of different duration, suggesting that greatest effects on body weight may occur 12 to 24 months from first reducing fat intake, but without any clear progression and with weight reduction in all subgroups (Analysis 3.1). Subgrouping by baseline total fat intake suggested greatest weight reduction in study populations with lower fat intakes at baseline (25 to 30%E from fat), but again, with weight reductions in all subgroups and no clear progression (Analysis 3.2). There were no statistically significant differences between studies first published in different decades, and no suggestion of trend (Analysis 3.3), or between effects in men and women (Analysis 3.4). In trials with a greater difference in fat intake between arms, there appeared to be a greater relative weight reduction in study populations taking the lower fat diet, suggesting a dose effect, with statistically significant differences between subgroups (Analysis 3.5). Similarly, weight reduction was greater when the lower fat arm achieved total fat intake of 30%E or less (Analysis 3.6). Effects differed by intervention type, with greatest weight reduction resulting from dietary advice, less from advice plus supplementary foods, and least (MD -0.61 kg, 95% CI -0.84 to -0.39, Analysis 3.7) when all foods were provided. Effects also differed by subgroup of the fat goal in the lower fat arm, but did not suggest a dose response (Analysis 3.8). There was no statistically significant difference between subgroups with different mean baseline BMI, but there was a suggestion of greater weight loss with higher baseline BMI (Analysis 3.9), but people recruited for having a long-term condition, or risk factors for such a condition appeared to lose more weight than those who were healthy at baseline (Analysis 3.10). In trials where lower fat arm participants were assessed as eating fewer calories, weight loss appeared higher, as expected (Analysis 3.11). Weight loss occurred in all subgroups, but the degree of weight loss appeared higher when study populations reduced their fat intake to a greater extent, to 30%E energy or less, with lower fat intake at baseline, in people who were heavier at baseline, and those with long-term conditions or risk factors for such conditions.

Meta-regression. In light of the subgrouping results, we ran a multiple regression model on dose, BMI, baseline health and control group (baseline) fat intake, all at once. As we included only 33 comparisons (and as a rule of thumb it is appropriate to include an additional factor for every 10 comparisons), we then omitted the factor with the highest P value (health condition, P = 0.44) and re-ran the meta-regression with the final three factors. This suggested statistically significant relationships with all three factors: dose (the fat difference between intervention and control, suggesting that greater fat reduction results in greater weight reduction in the lower fat arm, coefficient -0.20 kg/1% energy from total fat reduction, 95% CI -0.34 to -0.06, P = 0.007); the baseline fat intake (assessed in the control arm, greater weight reduction in people with lower fat intake at baseline, coefficient 0.17 kg/1% energy from fat in the control group, 95% CI 0.04 to 0.29, P = 0.010); and BMI (greater weight reduction in those with higher BMI at baseline, coefficient -0.2 kg for each 1 kg/m^2 rise in BMI, 95% CI -0.39 to -0.004, P = 0.046). Together these factors explained 16% of variance between studies.

GRADE: GRADE assessment suggested that the evidence that reducing total dietary fat results in a small decrease in body weight was of high quality (Summary of findings 1).

Body mass index (BMI), waist circumference and other measures of body fatness

Fewer studies reported BMI than weight, but the effect of a lower proportion of energy from fat on BMI appeared similar to that on weight (MD -0.5 kg/m^2, 95% CI -0.6 to -0.3, I^2 = 60%, 46,539 participants, 15 comparisons, Analysis 1.2). A point estimate suggesting lower BMI in the lower fat arms was consistent across 13 of the 15 comparisons, including one trial that could not be included in meta-analysis due to a lack of data on variance (AUSMED 2018, which reported -0.1 kg/m^2 in the intervention group compared to 0 kg/m^2 in the control, in 65 participants but without any variance data). As BMI reflects very similar information to body weight, and there were fewer studies than for weight, we did not attempt sensitivity analyses and subgrouping for BMI.

Data on waist circumference suggested that waist circumference in those on low fat diets was significantly lower than in those on usual fat diets (MD -0.5 cm, 95% CI -0.7 to -0.2, I^2 = 21%, 16,620 participants in 3 trials, Analysis 1.3), although this was not supported in the trial that did not provide variance data so could not be included in meta-analysis (AUSMED 2018, which reported a mean reduction of 0.4 cm in the lower fat group, and a reduction of 1.1 cm in the control group). Data on percentage of body fat suggested lower percentage of body fat in those eating less dietary fat, but was only marginally significant (MD -0.3% body fat, 95% CI -0.6 to 0, P = 0.05, I^2 = 0%, 2350 participants in 2 trials, Analysis 1.4), though data were more limited on this outcome, from only 3 trials, one of which did not provide variance data (AUSMED 2018, which reported a mean reduction of 0.4% in the lower fat group compared to a reduction of 0.6% in the control).

In summary, other indicators of body fatness support data suggesting lower body weight in those consuming lower fat intakes.

Secondary outcomes - lipids and blood pressure

There was no suggestion of harms associated with low fat diets that might mitigate any benefits on body fatness.

Effects of lower fat compared with higher fat diets suggested that the lower fat diets were associated with lower total cholesterol (MD -0.23 mmol/L, 95% CI -0.32 to -0.14, I^2 = 72%, 9812 participants in 22 trials, Analysis 1.5) and low-density lipoprotein (LDL) cholesterol (MD -0.13 mmol/L, 95% CI -0.21 to -0.05, I^2 = 57%, 8072 participants in 18 trials, Analysis 1.6), without important effects on high-density lipoprotein (HDL, MD -0.02 mmol/L, 95% CI -0.03 to 0.00, I^2 = 23%, 8268 participants in 19 RCTs, Analysis 1.7), triglycerides (MD 0.01 mmol/L, 95% CI -0.05 to 0.07, I^2 = 50%, 8607 participants in 17 trials, Analysis 1.8) or total cholesterol/HDL ratio (MD -0.05, 95% CI -0.14 to 0.04, I^2 = 44%, 3639 participants in 5 trials, Analysis 1.9).

There were small clinically insignificant beneficial effects of a lower fat diet on systolic (-0.75 mmHg, 95% CI -1.42 to -0.07, I^2 = 9%, 6013 participants in nine comparisons, Analysis 1.10) and diastolic (-0.52 mmHg, 95% CI -0.95 to -0.09, I^2 = 7%, 6012 participants in nine comparisons, Analysis 1.11) blood pressure (these were reported in relatively few studies).

Secondary outcomes - effects of reducing fat intake on quality of life measures

Quality of life outcomes were rarely measured or reported. Quality of life was assessed in WHI 2006 and suggested very small improvements in Global Quality of Life in those in the lower fat arm compared to higher fat (MD 0.04, 95% CI 0.01 to 0.07, on a scale of 0 to 10, where 0 is worst and 10 best, in 40,130 participants at trial close, Analysis 1.12). No other relevant data were located.

Tertiary outcomes - effects of reducing fat intake on intakes of energy, protein, carbohydrate, sugars and alcohol

Indications were that, during the studies, energy intake was usually lower in the low fat group than in the control or usual fat groups. Sugar intake was not measured often but, where reported, sugar intake appeared higher in low fat arms (except in MeDiet 2006, see Table 1). Carbohydrate intakes appeared almost universally higher in low fat arms than in usual fat arms, and protein intakes were sometimes higher and sometimes similar. There was no consistent pattern in alcohol intake.

DISCUSSION

Summary of main results

Randomised controlled trials (RCTs) of the effects on body fatness of reducing total fat intake (without any intention to reduce body weight) show a small but highly consistent reduction in weight in the lower fat arm compared with the higher fat arm. There is some heterogeneity between studies in the size of this effect, but not in its presence, and the effect was highly resistant to sensitivity analyses. The heterogeneity was partially explained in subgrouping and meta-regression. The degree of weight loss appeared higher when study populations reduced their fat intake to a greater extent, to 30%E energy or less, in those who were heavier at baseline, and in those with lower fat intake at baseline.

The small reduction in body weight with lower dietary fat intake (MD -1.4 kg, 95% CI -1.7 to -1.1, I^2 = 75%, over 53,875 participants in 33 estimable comparisons from 26 RCTs) was also reflected in a reduction in BMI (MD -0.5 kg/m^2, 95% CI -0.6 to -0.3, I^2 = 60%, 46,604 participants, 15 comparisons), waist circumference (MD -0.5 cm, 95% CI -0.7 to -0.2, I^2 = 21%) and percentage body fat (MD -0.3% body fat, 95% CI -0.6 to 0, I^2 = 0%, P = 0.05, in 2415 participants) in the studies that reported these data. There were no suggestions of harm that might mitigate any benefits on weight, and there was a suggestion of small benefits to serum lipids resulting from lower fat diets.

Overall completeness and applicability of evidence

We have searched very carefully and used a set of comprehensive search strategies to find the full set of RCTs assessing the effect of reducing total fat intake on measures of body fatness. We did this by searching for trials that reduced total fat in one arm and not in the other, regardless of the primary aims or outcomes mentioned in the title or abstracts. Indeed, the included RCTs rarely had weight as a key outcome. There was some evidence of small study bias, with small studies suggesting that smaller weight loss in the low fat arms was missing, so that if such studies were added back the weight reduction in the lower fat arms would be slightly smaller, but still reflect reduced weight in the lower fat arms.

The studies are highly applicable to the question, allowing us to draw conclusions on the effect of altering the percentage of energy from total fat on body fatness.

Quality of the evidence

Summary risk of bias was low in five of the 37 included trials; these were trials with low risk of selection bias (low risk from random sequence generation and allocation concealment) and low risk of detection bias. However, limiting analyses to trials at low summary risk of bias also resulted in lower weight in the lower fat arms. Similarly, excluding trials with more time or attention to the intervention group (attention bias), excluding trials with dietary differences additional to fat differences (in case effects were being driven by other dietary interventions) and excluding studies with potential compliance problems all suggested lower weight in participants eating lower fat diets. This resilience suggests that effects are not simply due to bias; the higher validity trials reflect the main message, that eating a lower proportion of energy from fat results in slightly lower body fatness.

The funnel plot suggests that one or two small studies showing weight gain in the lower fat arm may be missing. Additionally, the effect in fixed-effect analysis, which gives less weight to small studies (-0.9 kg, 95% CI -1.1 to -0.8, Analysis 2.1), is smaller than the effect in random-effects meta-analysis (-1.4 kg, 95% CI -1.7 to -1.1, Analysis 1.1), which gives more weight to smaller studies. Both suggest the presence of small study bias when assessing effects of lower total fat intake on body weight. The effect of adding any such missing studies back into the meta-analysis would be a small reduction in amount of weight loss in lower fat arms. The weight reduction with reduced fat intake is still present, but may be closer to -0.9 kg (Analysis 2.1) than -1.4 kg.

Almost all studies included in this review suffer from performance bias; it is very difficult to blind participants to how much fat they are eating (the exception was one 'shop-based' trial where participants bought potentially fatty foods from a trial shop, and these foods were modified according to intervention group (NDHS Open 1st L&M 1968). Potential problems with participants knowing whether they are in the intervention or control group is that, if they know they are reducing their dietary fat, they may bother less with other healthy lifestyle practices (such as smoking cessation or physical activity), which could in turn impact on body fatness (in opposite ways).

Potential biases in the review process

When compiling the included studies, we tried to locate RCTs that investigated the effects of reducing total dietary fat for at least six months. There was a high degree of heterogeneity among trials from different sources, including the type and number of participants, the duration and nature of interventions, control methods and follow-up. However, our sensitivity analyses and subgrouping to examine the effect of many potential effect modifiers did not affect the statistical significance of the suggested effect; the lower weight in those eating lower fat is remarkably robust to subgroup and sensitivity analyses.

Our review included only published studies (we did not seek unpublished data), which could bias the results due to the lack of publication of negative or inconclusive studies. However, we did include and assess studies that measured body fatness but without

sufficient detail to include in meta-analysis, and almost all these trials also suggested lower weight or body fatness in the lower fat arms.

Our decision to exclude trials that explicitly or implicitly aimed to reduce weight may have led to missing some trials or restricting the number of included studies, especially excluding studies where there was no energy restriction, no explicit aim of weight loss, or encouraging of weight loss for some and not all participants. However, this decision makes the effect we found on weight and other measures of body fatness more reliable in people eating normal diets and avoids the potential confounding effects of dieting and unconscious energy restriction or other diet changes.

The restriction of inclusion to RCTs with a minimum of six months duration led to missing some potentially relevant shorter trials. However, it is essential to draw the line at some point, and longer trials and follow-up ensure that the data are relevant to long-term fatness, which affects long-term health.

A limitation of the review was that we did not assess the causal pathway between restriction of energy from fat and weight and so the mechanism of the effect is not clear. It is likely that restricting energy from fat also reduces energy intake slightly (see Table 1 and Analysis 3.11), which leads to lower body weight. Further evidence that energy intake is important in mediating the effect of lowering fat intake on body weight is suggested by a higher relative weight loss in the low fat arms with greater energy reduction.

Most (23 of 37) included RCTs were published before the year 2000 - this is primarily because most recent studies have focused on weight reduction so were ineligible for this review. However, there was no suggestion when subgrouping by decade of publication that effects have altered over time.

We assessed effects of reducing total fat on quality of life and cardiovascular risk factors (lipids and blood pressure) at the request of WHO to check that, if we found positive effects on body fatness, they were not counteracted by harms to other outcomes. This was not a formal systematic review of effects of total fat on lipids, blood pressure or quality of life (as studies were only included if they assessed at least one measure of body fatness), but our results did not suggest any harms from reducing total fat. However, other potential harms (such as reductions in fat-soluble vitamin status, or gastric symptoms) were not assessed - though we are not aware of any harms such as these reported in our included trials.

Agreements and disagreements with other studies or reviews

The conclusions of this updated review have not altered in overall import from earlier versions of this review (Hooper 2012b; Hooper 2015a). Yu-Poth 1999 found that dietary trials (excluding trials that also assessed exercise interventions) of the National Cholesterol Education Program's Step I and Step II dietary intervention programmes resulted in weight reductions (compared with control groups) of just under 3 kg, and that this was related to the degree of total fat reduction. Their regression suggested that for every 1% decrease in energy as total fat, there was a 0.28 kg decrease in body weight, while our meta-regression found that for every 1% decrease in energy as total fat there was a slightly smaller 0.20 kg decrease in weight (95% CI -0.34 to -0.06, P = 0.007). The slightly smaller effect size in this review may be due to our excluding shorter duration studies and studies that aimed to reduce weight in the intervention arm.

The single trial that set out to assess the effect of reducing total fat intake on body weight, by feeding participants carefully controlled levels of dietary fat and carbohydrate over 6 months (ODMDC 2017), found that body weight in participants eating 20% of energy from fat was 0.6 kg lower than participants eating 30% or 40% of energy from fat. This high-quality trial confirmed our findings of lower weight with lower fat intake, but the effect size was smaller than our suggested effect size. This may have been because the intervention was only for six months; weight effects may have been greater if the feeding had continued over a longer time period.

AUTHORS' CONCLUSIONS

Implications for practice

Attempts should be made to reduce total fat intake in populations where mean total fat intake is 30% or more of energy, in order to support maintenance of healthy weights. For populations where the mean total fat intake is below 30% of energy, then interventions to restrict increases in total fat intake to over 30% of energy may help to avoid obesity.

Implications for research

High-quality trials are needed to investigate the effect on body weight of reducing fat intake in developing or transitional countries with total fat intakes greater than 30% of energy, and of preventing total fat intake rising above 30% of energy in countries with total fat intakes of 25% to 30% of energy. None of the ongoing trials found are being carried out in developing or transitional countries.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anderson 1990

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Moderately hypercholesterolaemic, non-obese Caucasian men and women aged 30 to 50 (USA) CVD risk: moderate Control: randomised 62, analysed 51 Intervention: randomised 56, analysed 47 Mean years in trial: control 0.91, intervention 0.92 % male: control 61, intervention 66 Age: mean control 40.3 (SD 5.4), intervention 40.7 (SD 5.2) (all 30 to 50) Baseline BMI: not reported
Interventions	Reduced fat diet vs usual diet Control aims: no diet intervention Intervention aims: 25%E from fats, 20%E from protein, 55%E from CHO, < 200 mg cholesterol/day (also an intervention arm with similar aims plus increased fibre intake) Control methods: no intervention Intervention methods: seminars and individual eating patterns taught, 10 weeks teaching and 40 weeks maintenance Weight goals: participants were directed to maintain initial body weight throughout the study. Total fat intake (at 1 year): low fat 30 (SD 7.5), control 31 (SD 5.7) %E Saturated fat intake (at 1 year): low fat 9 (SD 2.7), control 10 (SD 2.9) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: diet composition, lipids Available outcomes: weight, total, LDL and HDL cholesterol
Notes	AHA phase II diet (low fat) compared to control group here; a further arm was not used, the low fat plus high fibre arm. This trial was called "Kentucky Low Fat" in previous versions of this review.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Anderson 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	"matched on age, gender & cholesterol level, randomly assigned to intervention group using systematic random procedure"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew allocation.
Blinding of outcome assessment (detection bias)	High risk	Researchers knew allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	20 of 118 (17%) lost over 1 year (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	(The high fibre arm has not been used in the data set). See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	High risk	No significant difference in total fat intake

AUSMED 2018

Study characteristics	
Methods	RCT AUStralian MEDiterranean diet trial for secondary prevention of heart disease (AusMed) Summary risk of bias: moderate to high
Participants	Adults within one year of acute MI (Australia) CVD risk: high Control (Med diet): 37 randomised, 27 analysed at 1 year Intervention (low fat): 36 randomised, 21 analysed Mean years in trial: control 1.0, intervention 1.0 % male: control 79%, intervention 87% Age, years: mean control 61.8 (SD 9.2), intervention 61.8 (SD 9.5) Baseline BMI: mean control 30.8 (SE 0.9), intervention 29.0 (SE 0.9)
Interventions	Low fat vs Med diet Control (Med diet): 35-40%E total fat (of which ≥ 50% MUFA), 15-20%E protein, 40-45%E CHO

AUSMED 2018 *(Continued)*

	Intervention (Low fat diet): < 30%E total fat, < 7%E SFA, 45-65% CHO, 15-25% protein, ≤ 5%E alcohol Control methods: Client-centred counselling and goal-setting with dietitian. Received 2-week model meal plan, MedDiet resource kit, recipe book, shopping list, weekly food intake checklist, label info. Hamper of foods provided at baseline and 3 months including olive oil, nuts, tinned fish and legumes, Greek yogurt. Consultation frequency and data time points were consistent across both arms. Intervention methods: Client-centred counselling and goal-setting with dietitian. Received resources on low fat cooking, label reading, Supermarket vouchers provided at the 3 face-to-face appointments. Weight goals: both diets provided ad libitum with no specific recommendations on energy restriction Total fat intake (at 6 mo): low fat 30.3 (SD 7.2), control 38.7 (SD 7.9) %E Saturated fat intake(at 6 mo): low fat 10.3 (SD 3.5), control 9.5 (SD 2.4) %E Style: diet advice with supplementary foods Setting: community
Outcomes	Stated trial outcomes: primary cardiac endpoints at 12 months, secondary lipids, inflammatory markers, coagulation factors, dietary adherence, body composition and anthropometry, BP, activity, QoL (SF36), adipokine markers, adhesion molecule markers Available outcomes: weight, BMI, waist circumference, percentage body fat, lipids, BP (however weight, BMI, waist circumference, body fat, LDL, TG & BP data were too different at baseline to use these data in meta-analysis).
Notes	Funding: La Trobe University.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a computer-generated stratification (by age and sex)
Allocation concealment (selection bias)	Unclear risk	Unclear, randomisation performed by statistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of their dietary allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear who assessed anthropometry or whether they were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	21 of 36 (58%) in low fat intervention, and 27 of 37 (73%) in Med diet were assessed at 12 months (> 10% dropouts per year)
Selective reporting (reporting bias)	High risk	Trials registry entry in 2016, recruitment started in 2014, recruitment ended in 2018. Some data, such as QoL do not appear to be published yet.
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Consultation frequency and data time points were consistent across both arms.

AUSMED 2018 *(Continued)*

Free of dietary differences other than fat?	High risk	No, variety of other differences, including advice on fruit and vegetables, fish, legumes etc.
Compliance problems	Low risk	Statistically significant difference in fat intake at 6 months

BDIT Pilot Studies 1996

Study characteristics	
Methods	RCT Breast Dysplasia Intervention Trial (BDIT) Summary risk of bias: moderate to high
Participants	Women with mammographic dysplasia (Canada) CVD risk: low Control: 147 randomised, 78 analysed Intervention: 148 randomised, 76 analysed Mean years in trial: control 7.5, intervention 6.8 % male: 0 Age: mean control 45, intervention 44 (all > 30) Baseline BMI: mean intervention 24.3 (SD 3.8), control 24.3 (SD 3.6)
Interventions	Reduced fat intake vs usual diet Control aims: healthy diet advice, no alteration in dietary fat advised, aim to maintain weight Intervention aims: total fat 15%E, replace fat by complex CHO, aim to maintain weight Control methods: seen for advice once every 4 months for 12 months Intervention methods: seen for advice once a month for 12 months Weight goal: low fat group - "isocaloric exchange of complex carbohydrate for fat. We tried to maintain an isocaloric diet to avoid weight loss...". Not discussed for control group Total fat intake (at 9.2 years): low fat 31.7 (SD 7.3) %E, control 35.3 (SD 5.6) %E Saturated fat intake (at 9.2 years): low fat 10.6 (SD 4.6) %E, control 12.3 (SD 4.6) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary fat, serum cholesterol Available outcomes: weight, BMI, total and HDL cholesterol
Notes	Weight data available for 1 year, 2 years and 9 years. Unclear whether participants were still in the trial by 9 years, so 2-year data used in main analysis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"

BDIT Pilot Studies 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Randomisation not described, though randomisation occurred after baseline assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	141 of 295 (48%) lost over 8 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Women in intervention group seen more frequently. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Significant difference in total fat intake

beFIT 1997

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Women and men with mild hypercholesterolaemia (USA) CVD risk: moderate Control: unclear how many randomised, 192 analysed Intervention: unclear how many randomised, 217 analysed Mean years in trial: unclear (max duration 0.5 years) % male: 52 (not divided by intervention group) Age: mean 43.2 (not divided by intervention group) (all > 30) Baseline BMI (not reported by intervention): women with hypercholesterolaemia (n = 84) mean 25.9 (SD 4.9), women with combined hyperlipidaemia (n = 94) mean 29.2 (SD 6.1), men with hypercholesterolaemia (n = 123) mean 26.6 (SD 3.3), men with combined hyperlipidaemia (n = 108) mean 27.5 (SD 3.2)
Interventions	Reduced and modified fat vs usual diet Control aims: asked to delay dietary changes (provided intervention after the randomised trial) Intervention aims: total fat < 30%E, SFA < 7%E, dietary cholesterol < 200 mg/d Control methods: usual intake Intervention methods: 8 weekly classes with nutrition info and behaviour modification with spouses, plus individual appointments at 3 and 6 months

beFIT 1997 *(Continued)*

	Weight goals: intervention group "assigned food group pattern for their calorie needs", no information for control group Total fat intake (at 6 months): intervention 25.2 (SD unclear) %E, control unclear - no significant difference from baseline 34 (SD unclear) %E Saturated fat intake (at 6 months): intervention 7.6% (SD unclear) %E, control unclear - no significant difference from baseline 12 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids Available outcomes: weight, total, LDL and HDL cholesterol, TG (but variance data only provided for the randomised comparison for LDL cholesterol)
Notes	Weight: control 'no change', intervention -2.7 kg at 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified random sampling scheme
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew their allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear what proportion lost over trial as unclear how many recruited
Selective reporting (reporting bias)	High risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Intensive intervention for intervention group, but no intervention during the 6 months of the randomised part of the study for the control group. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Unclear risk	Unclear (as data not provided for control group), though there appears to be a big difference in total fat intake at 6 months

Black 1994

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	People with non-melanoma skin cancer (USA) CVD risk: low Control: randomised 67, analysed 58 Intervention: randomised 66, analysed 38 Mean years in trial: 1.9 % male: control 67%, intervention 54% Age: mean control 52.3 (SD 13.2), intervention 50.6 (SD 9.7) Baseline BMI: data not provided
Interventions	Reduced fat vs usual diet Control aims: no dietary advice Intervention aims: total fat 20%E, protein 15%E, CHO 65%E Control methods: no dietary change, 4 monthly clinic visits Intervention methods: 8 weekly classes, with behavioural techniques, plus 4 monthly clinic visits Weight goals: "to maintain body weight .... patients were instructed to increase their intake of carbohydrate, particularly complex carbohydrate" Total fat intake ("during study" months 4 to 24): low fat 20.7 (SD 5.5), control 37.8 (SD 4.1) %E Saturated fat intake ("during study" months 4 to 24): low fat 6.6 (SD 1.8), control 12.8 (SD 2.0) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: incidence of actinic keratosis and non-melanoma skin cancer Available outcomes: none (weight data provided, but no variance info)
Notes	At 2 years: control -1.5 kg, n = 50?, intervention: -1 kg, n = 51? This trial was named "Veterans Dermatology" in previous versions of this review.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of assignment.
Blinding of outcome assessment (detection bias)	Low risk	Physician blinding: adequate

Black 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	37 of 133 (28%) lost over 2 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	All had 4 monthly clinic visits; the intervention group had 8 behavioural technique classes that the control group did not have.
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Big and statistically significant difference in total fat intake between arms

Bloemberg 1991

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Men with untreated raised total cholesterol (the Netherlands) CVD risk: moderate Control: randomised 41, analysed 40 Intervention: randomised 39, analysed 39 Mean years in trial: control 0.5, randomised 0.5 % male: 100% Age: mean control 47.5 (SD 8.0), intervention 47.2 (SD 8.3) Baseline BMI: mean control 26.3 (SD 2.3), intervention 26.0 (SD 2.6)
Interventions	Reduced and modified fat vs usual diet Control aims: usual diet Intervention aims: 30%E from fat, PUFA/SFA 1.0, dietary cholesterol 20 mg Control methods: no advice provided Intervention methods: individual advice provided face-to-face, followed by 2 phone calls and 5 mailings of information on healthy foods Weight goals: weight and calories not mentioned Total fat intake (change to 6 months): intervention -5.0 (SD 6.5) (33.5 overall), control -1.5 (SD 5.9) (36.8 overall) %E Saturated fat intake (change to 6 months): intervention -4.3 (SD 3.9), control -0.7 (SD 2.9) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids

Bloemberg 1991 *(Continued)*

	Available outcomes: weight, total and HDL cholesterol
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised" and stratified by age and BMI (each dichotomised)
Allocation concealment (selection bias)	Unclear risk	No method stated (as above)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Laboratory staff blinded, but unclear re weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 of 80 (< 1%) lost over 0.5 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Much more time spent on those in the intervention group
Free of dietary differences other than fat?	Low risk	Dietary focus on fats alone
Compliance problems	Low risk	Significant difference in total fat intake, supported by borderline total cholesterol difference

Boyd 1988

Study characteristics

Methods	RCT Summary risk of bias: moderate to high
Participants	Women with severe cyclical mastopathy for at least 5 years (Canada) CVD risk: low Control: randomised 10, analysed 9 Intervention: randomised 11, analysed 10 Mean years in trial: control 0.45, intervention 0.45 % male: 0% Age: mean control 36, intervention 38 (variances unclear)

Boyd 1988 *(Continued)*

	Baseline BMI: no data provided
Interventions	Reduced fat vs usual diet Control aims: given principles of healthy diet, not counselled to alter fat content Intervention aims: total fat 15%E, CHO 65%E Control methods: seen every 2 months to monitor symptoms, nutrition and biochemistry Intervention methods: seen monthly to monitor symptoms, nutrition and biochemistry, teaching materials included food guide, recipes, product information and advice on eating out Weight goals: the intervention goals included the isocaloric replacement of complex carbohydrate for fat (no mention for control group) Total fat intake (at 6 months): low fat 22.8 (SD unclear), control 33.4 (SD unclear) %E Saturated fat intake (at 6 months): low fat 8.8 (SD unclear), control 12.3 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: mastopathy symptoms, plasma hormone and lipids Available outcomes: weight, total cholesterol (but variance data not provided)
Notes	Total cholesterol rose by 0.09 mmol/L in control group (from 4.5 to 4.59) and fell by 0.15 mmol/L in intervention group (4.84 to 4.69). Weight changed in the intervention group (mean fall of 2.1 kg over 6 months, no variance provided), but change, or otherwise, in control group not mentioned. This trial was called "Mastopathy Diet" in previous versions of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Those assessing physical outcomes were blinded; those assessing symptoms were not.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 of 21 (10%) lost over 0.5 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted

Boyd 1988 *(Continued)*

Free of systematic difference in care?	High risk	Minor differences in follow-up frequency. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	While variance not provided there was a very big difference in total fat intake.

BRIDGES 2001

Study characteristics	
Methods	RCT Breast Research Initiative for Determining Effective Strategies for Coping with Breast Cancer (BRIDGES) Summary risk of bias: moderate to high
Participants	Women diagnosed with stage I or II breast cancer over the past 2 years (USA) CVD risk: low Control: randomised unclear (at least 56), analysed 46 Intervention: randomised unclear (at least 50), analysed 48 Mean years in trial: unclear (1 year max follow-up) % male: 0 Age: mean control unclear (71% postmenopausal), intervention unclear (56% postmenopausal) (all 20 to 65) Baseline BMI: not reported
Interventions	Reduced fat vs usual diet Control aims: no formal intervention Intervention diet aims: total fat 20%E, high fibre, plant-based micronutrients Intervention stress: separate parallel arm, stress reduction programme (data not used here) Control methods: no formal intervention Intervention methods: nutrition intervention programme, 15 sessions (42 hours) over 15 weeks, group-based, dietitian-led, 2 individual sessions using social cognitive theory and patient centred counselling to increase self efficacy and confidence Weight goals: "reduction in body mass was not a primary goal of NEP. (NEP was neither designed nor presented to participants as a weight loss or weight control program)." The control group was presented as "individual choice". Total fat intake (at 12 months): low fat 29.9 (SD unclear), control 33.6 (SD unclear) %E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: diet and BMI Available outcomes: weight
Notes	—

BRIDGES 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised", stratified by medical centre, cancer stage and age; randomised number/envelope method by project coordinator
Allocation concealment (selection bias)	Low risk	The project coordinator had contact with those from the University of Massachusetts, but not those from the other 3 centres, and allocation could not be altered later.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear how many recruited, so unclear how many were lost to follow-up (at least 12 of 106 (11%) over 1 year, so > 10%/year
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	High-intensity programme for intervention group, nothing for control group. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Intervention also focused on fibre and plant-based micronutrients. See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Unclear risk	Unclear if difference in total fat intake between arms was statistically significant as no variance provided

Canadian DBCP 1997

Study characteristics

Methods	RCT Canadian Diet and Breast Cancer Prevention (Canadian DBCP) Summary risk of bias: moderate to high
Participants	Women with mammographic densities > 50% breast area (Canada) CVD risk: low Control: randomised 448+, analysed 401 Intervention: randomised 448+, analysed 388 Mean years in trial: control 2.0, randomised 2.0 (note, papers suggested a 10-year follow-up overall) % male: 0% Age: mean control 45.9 (SD unclear), intervention 46.5 (SD unclear)

Canadian DBCP 1997 *(Continued)*

	Baseline BMI: mean control 23.6, intervention 23.4, no variance reported
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: total fat 15%E, protein 20%E, CHO 65%E, isocaloric diet Control methods: encouraged to continue usual diet, interviewed by dietitian every 4 months during first year, then every 3 months in the second year Intervention methods: dietary prescription using food exchange (fat calories replaced by CHO), met with dietitian monthly during first year, then every 3 months. Scales, recipes, shopping guide provided Weight goals: "calories derived from fat were replaced by isocaloric exchange with carbohydrate" Total fat intake (at 2 years): intervention 21.3 (SD 6.2), control 31.8 (SD 6.7) %E Saturated fat intake (at 2 years): intervention 7.1 (SD 2.5), control 11.5 (SD 3.3) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: incidence of breast cancer Available outcomes: weight
Notes	Weight data available for 1 and 2 years, 2-year data used in main analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated by telephone to Dept. of Biostatistics at Ontario Cancer Institute, stratified by centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew what arm they were in.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear who measured or whether blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	At least 107 of at least 896 (12%) lost over 2 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	None reported
Free of systematic difference in care?	High risk	Minor difference in attention for participants in intervention and control in first year

Canadian DBCP 1997 *(Continued)*

Free of dietary differences other than fat?	Low risk	Focus on dietary fat
Compliance problems	Low risk	Significant difference in self-reported total fat intake at 2 years, no reported lipids to confirm

CORDIOPREV 2016

Study characteristics	
Methods	RCT CORonary Diet Intervention with Olive oil and cardiovascular PREVention study (CORDIOPREV study) Summary risk of bias: low
Participants	People with CHD and with high CVD risk (Spain) CVD risk: high Control (Mediterranean diet): 502 randomised, no. analysed varied between publications Intervention: 500 randomised, no. analysed varied between publications Mean years in trial: aim 7.5 years follow-up published for some outcomes % male: control 84%, intervention 83% Age, years: mean control 59.7 (SE 0.4), intervention 59.5 (SE 0.4) Baseline BMI: mean control 31.0 (SE 0.1), intervention 31.2 (SE 0.2)
Interventions	Low fat vs Mediterranean diet Control: Mediterranean diet, 35+%E fat (< 10%E SFA, 22%E MUFA, 6%E PUFA), 15%E protein, up to 50%E CHO, cholesterol < 300mg/d Intervention: Low fat, < 30%E fat (< 10%E SFA, 12-14%E MUFA, 6-8%E PUFA), 15%E protein, up to 55+ %E CHO, cholesterol < 300mg/d Med diet methods: personalised dietetic interviews and support at start and 6-monthly, quarterly group education including talks, meal plans, recipes, shopping lists etc, some baskets of appropriate foods provided occasionally. Olive oil provided free for whole family. Low fat methods: personalised dietetic interviews and support at start and 6-monthly, quarterly group education including talks, meal plans, recipes, shopping lists etc, some baskets of appropriate foods provided occasionally. Weight goals: no energy restriction (in either arm) Total fat intake (at 5 years): low fat 31.7 (SD 6.0), control 41.0 (SD 6.3) %E Saturated fat intake (at 5 years): low fat 7.1 (SD 2.0), control 8.0 (SD 2.1) %E Style: diet advice plus supplementary foods Setting: community
Outcomes	Stated trial outcomes: primary cardiovascular events, secondary intermittent claudication, LDL, lipid ratios, metabolic responses to CHO (glucose and insulin), BP, malignancy, cognition, CVD progression all at 7 years

CORDIOPREV 2016 *(Continued)*

	Available outcomes: weight, BMI, waist circumference, dietary intake, lipids (LDL and some HDL data too different at baseline to use in meta-analysis)
Notes	Note: 7-year completion is due in 2020, current published data are from 2 or 5-year follow-up. Also, caution, total cholesterol data in Gomez-Delgado 2015 is surprising as the change in total cholesterol was not mirrored in changes in LDL, HDL or TGs. **Funding**: CORDIOPREV was supported by Fundacion Patrimonio Comunal Olivarero. Additional funding was received from CITOLIVA, CEAS, Junta de Andalucia (Consejeria de Salud, Consejeria de Agricultura y Pesca, Consejeria de Innovacion, Ciencia y Empresa), Diputaciones de Jaen y Cordoba, Centro de Excelencia en Investigacion sobre Aceite de Oliva y Salud and Ministerio de Medio Ambiente, Medio Rural y Marino, and the Spanish Government.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by sex, age and previous MI.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out by a third party (Andalusian School of Public Health).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of their dietary allocation.
Blinding of outcome assessment (detection bias)	Low risk	Dietitians were the only members of the intervention team who knew dietary assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout levels appeared acceptable, for example, of non-diabetics, 21 of 246 (9%) Med diet and 41 of 216 (19%) Low fat dropped out by 5 years, < 10%/year.
Selective reporting (reporting bias)	Unclear risk	Unclear, trials registry (registered 2009, trial due to complete in 2020) outcomes are all 7-year assessments, and trial has not reached 7 years yet.
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Yes, time and intervention type appear similar between the two groups with the possible exception that olive oil was provided to control group participants.
Free of dietary differences other than fat?	Unclear risk	Unclear, stated they were assessing dietary patterns, but differences other than fat and CHO levels were not clarified
Compliance problems	Low risk	5-year difference in self-reported total fat was statistically significant.

De Bont 1981

Study characteristics

Methods	RCT Summary risk of bias: moderate to high

De Bont 1981 *(Continued)*

Participants	Women with type 2 diabetes (UK) CVD risk: moderate Control: randomised unclear (total in control and intervention 148), analysed 65 (for obese and non-obese) Intervention: randomised unclear, analysed 71 (for obese and non-obese) Mean years in trial: control 0.5, randomised 0.5 % male: 0% Age: mean control 54 (SD 8), intervention 56 (SD 7), (all 35 to 64) (for obese and non-obese) Baseline BMI: non-obese chosen for BMI < 28, obese mean not reported
Interventions	Reduced and modified fat vs usual diet Control aims: usual diet but with CHO ≤ 40%E Intervention aims: 30%E from fat, focus on reducing meat fat, dairy foods and substituting margarines to improve the SFA/PUFA ratio; CHO increased to maintain energy intake Control methods: 3 home visits from a nutritionist over the 6 months of the trial Intervention methods: 3 home visits from a nutritionist over the 6 months of the trial Weight goals: to maintain the required total energy intake, the proportion of carbohydrates in these diets was increased. Total fat intake (change to 6 months): intervention -10.1 (SD 10.8) (overall 31.1), control -1.0 (SD 10.5) (overall 41.8) %E (for obese and non-obese) Saturated fat intake (change to 6 months): intervention -8.1 (SD 5.8), control -1.1 (SD 5.7) %E (for obese and non-obese) Style: diet advice Setting: community
Outcomes	Stated trial outcomes: diet, weight, lipids Available outcomes: weight, total and HDL cholesterol, triglycerides
Notes	Outcome data separated by those obese (BMI ≥ 28) or not obese at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether outcome assessors blinded
Incomplete outcome data (attrition bias)	High risk	12 of 148 (8%) lost over 0.5 years (> 10% per year)

De Bont 1981 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Follow-up similar
Free of dietary differences other than fat?	Low risk	Diet focused on fat
Compliance problems	Low risk	Statistically significant difference in total cholesterol and in fat intake between arms

DEER 1998

Study characteristics	
Methods	RCT Diet and Exercise for Elevated Risk (DEER) Summary risk of bias: moderate to high
Participants	Men and postmenopausal women with raised LDL and low HDL cholesterol (USA) CVD risk: moderate Control: • Men with exercise: randomised 50, analysed 47 • Women with exercise: randomised 44, analysed 43 • Men, no exercise: randomised 47, analysed 46 • Women, no exercise: randomised 47, analysed 46 Intervention: • Men with exercise: randomised 51, analysed 48 • Women with exercise: randomised 43, analysed 43 • Men, no exercise: randomised 49, analysed 49 • Women, no exercise: randomised 46, analysed 45 Mean years in trial: control 1.0, intervention 1.0 % male: 100% in male arms, 0% in female arms Age: mean 47.8 (SD 8.9) for all men (exercise and non-exercise arms) Age: mean 56.9 (SD 5.1) for all women (exercise and non-exercise arms) Baseline BMI: • Men with exercise: intervention 26.6 (SD 2.6), control 26.9 (SD 2.6) • Women with exercise: intervention 26.4 (SD 3.5), control 25.9 (SD 2.4) • Men, no exercise: intervention 26.9 (SD 3.1), control 26.7 (SD 3.2) • Women, no exercise: intervention 26.6 (SD 2.8), control 26.0 (SD 3.9)
Interventions	Reduced fat vs usual diet Control aims: usual diet (and exercise intervention)

DEER 1998 *(Continued)*

	Intervention aims: NCEP step 2 diet: < 30%E from fat, < 7%E from SFA, < 200 mg/d cholesterol (and exercise intervention) Control methods: no advice provided Intervention methods: individual advice provided face-to-face, followed by 8 1-hour group sessions during first 12 weeks, then monthly contact with dietitians by mail, phone, individual or group appointment Weight goals: "weight loss was not emphasised" Total fat intake (change to 12 months): • Men with exercise: intervention -8.2 (SD 5.9) (22.2 overall), control -0.5 (SD 5.7) (29.9 overall) %E • Women with exercise: intervention -8.0 (SD 5.8) (20.4 overall), control 0.3 (SD 6.9) (28.7 overall) %E • Men, no exercise: intervention -8.0 (SD 8.1) (22.4 overall), control -0.7 (SD 5.9) (29.7 overall) %E • Women, no exercise: intervention -5.7 (SD 7.4) (overall 22.7), control -0.2 (SD 6.7) (overall 28.2) %E Saturated fat intake (change to 12 months): • Men with exercise: intervention -3.9 (SD 2.6), control -0.1 (SD 2.6) %E • Women with exercise: intervention -3.0 (SD 2.3), control 0.2 (SD 3.1) %E • Men, no exercise: intervention -3.4 (SD 3.2), control 0.0 (SD 2.4) %E • Women, no exercise: intervention -2.4 (SD 2.8), control 0.2 (SD 2.8) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary intake and lipids Available outcomes: weight, total, LDL and HDL cholesterol, triglycerides, systolic and diastolic BP
Notes	Factorial trial with regards to exercise and reported by sex

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignments by computer, modified Efron procedure, balanced by HDL and LDL
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of randomisation group
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 of 377 (3%) lost over 1 year (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Trials registry entry dated 1999, study completed in 1996

DEER 1998 *(Continued)*

Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Very different levels of attention and review
Free of dietary differences other than fat?	Low risk	Dietary focus on fat
Compliance problems	Low risk	Reported a statistically significant reduction in total fat in low fat compared to control arms, supported by the statistically significant reduction in LDL in low fat compared to control arms

Diet and Hormone Study 2003

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Healthy premenopausal women aged 20 to 40 years (USA) CVD risk: low Control: randomised 107, analysed 96 Intervention: randomised 106, analysed 81 Mean years in trial: control 0.95, intervention 0.88 % male: 0% Age: control mean 33.3, intervention 33.5 (SDs not given) Baseline BMI: mean control 23.8 (SD 3.5), intervention 23.7 (SD 4.2)
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: < 20%E from fat, 25 to 30 g/d fibre, > 8 servings/d fruit and vegetables, CHO 60% to 65%E, protein 15% to 20%E Control methods: received a pamphlet on healthy eating (minimal intervention) Intervention methods: classroom nutrition education (18 group classes) plus 2 individual counselling sessions over 12 months covering knowledge and behavioural skills; appropriate foods served at intervention sessions Weight goals: "not encouraged to reduce total caloric intake and weight was monitored to maintain within 2 kg of baseline weight" Total fat intake (at 12 cycles/months): intervention 22.2 (SD 7.2), control 30.7 (SD 7.5) %E Saturated fat intake (at 12 cycles/months): intervention 14.9 (SD 6.7), control 23.9 (SD 13.2) g/d Style: diet advice Setting: community
Outcomes	Stated trial outcomes: hormonal responses Available outcomes: weight, BMI, dietary intake, hormones, menstrual cycle length

Diet and Hormone Study 2003 *(Continued)*

Notes	No answer to requests for data on deaths or health events. Weight and BMI data provided at 4 and 12 cycles

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned by reference to a random number table"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew allocation.
Blinding of outcome assessment (detection bias)	High risk	Researchers knew allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	36 of 213 (17%) lost over 1 year (> 10% per year). Reasons not stated, greater losses in intervention group
Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Very different levels of attention and review
Free of dietary differences other than fat?	High risk	Intervention group also asked to increase fibre, fruit and vegetables substantially
Compliance problems	Low risk	Statistically significant difference between arms in total fat intake

Ma 2016

Study characteristics

Methods	RCT Summary risk of bias: low
Participants	Adults with uncontrolled persistent asthma (USA) CVD risk: low Control (usual diet): 44 randomised, 44 analysed (ITT analysis, 5 dropouts) Intervention (DASH diet): 46 randomised, 46 analysed (ITT analysis, 3 dropouts) Mean years in trial: control 0.5, intervention 0.5 % male: control 39%, intervention 28% Age, years: mean control 51.4 (SD 12.9), intervention 52.2 (SD 11.9)

Ma 2016 *(Continued)*

	Baseline BMI: mean overall 27.9 (SD 4.8)
Interventions	Low fat (DASH) vs usual diet Control: usual diet Intervention: DASH diet, 27%E from fat, 9-12 servings/d fruit & vegetables, 2-3 servings/d low fat dairy products, reducing SFA, limiting sodium, increase whole grains, nuts, seeds, legumes plus decreased sugar intake, moderate alcohol intake Control methods: standard care Intervention methods: intensive intervention over first 3 months (8 group and 3 individual sessions each 45-60 min), then counselling phone calls monthly for 20-30 min over next 3 months Weight goals: fat intake estimated from caloric needs for weight maintenance Total fat intake (change to 6 months): low fat -5.3 (SE 4.8), control -4.7 (SE 4.7) g/d Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: primary Juniper asthma control questionnaire, secondary lung function, asthma specific QoL, asthma symptom-free days, asthma-related healthcare utilisation, diet adherence, psychosocial predictors of dietary change, comorbidities, generic health-related QoL Available outcomes: weight, BMI, BP, lipids (waist circumference measured but not reported by intervention arm)
Notes	Funding: National Heart Lung and Blood Institute, and Palo Alto Medical Foundation Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based random allocation system
Allocation concealment (selection bias)	Low risk	Randomisation performed by designated personnel without the ability to influence its execution
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew their assignments as they needed to follow the dietary advice.
Blinding of outcome assessment (detection bias)	Low risk	"blinding of outcome assessment and adjudication, data and safety monitoring, and data analysis will be enforced".
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis (although 8 of 90 dropped out over 6 months, > 10% per year, all were analysed)
Selective reporting (reporting bias)	High risk	Trials registration 2012, start date 2013, trial end 2014. Most prespecified outcomes appeared to be reported, though not QoL.
Other bias	Low risk	None noted

Ma 2016 *(Continued)*

Free of systematic difference in care?	High risk	Very different level of support and time with investigators in the two arms
Free of dietary differences other than fat?	High risk	DASH included fruit and vegetable, sodium, alcohol etc. advice as well as fat intake
Compliance problems	High risk	No significant difference in fat intake between arms

MeDiet 2006

Study characteristics	
Methods	RCT MeDiet Project Summary risk of bias: moderate to high
Participants	Healthy postmenopausal women with above median serum testosterone (Italy) CVD risk: low Control: randomised 57, analysed at 6 months 55 Intervention: randomised 58, analysed at 6 months 51 Mean years in trial: control 4.38, intervention 4.28 % male: 0 Age: mean unclear (age range 48 to 69) Baseline BMI: not reported
Interventions	Reduced and modified fat vs usual diet Control aims: advised to increase fruit and vegetable intake Intervention aims: taught Sicilian diet including reduced total, saturated and omega-6 fats, increased blue fish (high in omega 3), increased whole cereals, legumes, seeds, fruit and vegetables Control methods: advice Intervention methods: taught Sicilian diet and cooking by professional chefs, with a weekly cooking course including social dinners Weight goals: not mentioned Total fat intake (at 6 months): low and mod fat 30.9 (SD 11.4), control 34.0 (SD 11.8) %E Saturated fat intake (at 6 months): low and mod fat 8.4 (SD 3.0), control 11.2 (SD 5.0) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: breast cancer, weight, lipids, well-being Available outcomes: weight
Notes	Weight data provided at 6 months (fall of 0.6 kg in control group, fall of 1.3 kg in intervention group), but without variance information
Risk of bias	

MeDiet 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"individually randomised"
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of assignment
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 of 115 (8%) lost over 4 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Intensive cookery course with social element compared with brief advice. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Both groups encouraged to increase fruit and vegetables, but intervention group also encouraged to increase fish, pulses, seeds and whole grains
Compliance problems	High risk	No significant difference in total fat between arms

Moy 2001

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Middle-aged siblings of people with early CHD, with at least one CVD risk factor (USA) CVD risk: moderate Control: randomised 132, analysed 118 Intervention: randomised 135, analysed 117 Mean years in trial: 1.9 % male: control 49%, intervention 55% Age: control mean 45.7 (SD 7), intervention 46.2 (SD 7) Baseline BMI: control mean 29.5 (SD 7), intervention 28.5 (SD 5)
Interventions	Reduced fat intake vs usual diet Control: physician management (physicians informed on risk factor management) Intervention: nurse management, aim total fat 40 g/d or less

Moy 2001 *(Continued)*

	Control methods: physician management with risk factor management at 0, 1 and 2 years Intervention methods: nurse management, appointments 6- to 8-weekly for 2 years Weight goals: not mentioned Total fat intake (at 2 years): low fat 34.1 (SD unclear), control 38.0 (SD unclear) %E Saturated fat intake (at 2 years): low fat 11.5 (SD unclear), control 14.4 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary intake Available outcomes: BMI, HDL and LDL cholesterol, TG
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned via computerised schema after all eligible siblings from a family had been screened
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew their allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Trialists clear about allocation, though unclear whether outcome assessors knew allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 of 267 (12%) lost over 2 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Differences in frequency of follow-up, but unclear what differences in care occurred between the physician and nurse-led care. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Unclear risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Total fat intake not clearly statistically significantly different, though lower in intervention arm, however LDL was statistically significantly lower in intervention.

MSFAT 1995

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Healthy people aged 20 to 55 (Netherlands) CVD risk: low Control: randomised unclear (120?), analysed 103 Intervention: randomised unclear (120?), analysed 117 Mean years in trial: control 0.46, intervention 0.49 % male: control 50%, intervention 50% Age: mean control men 35.6 (SD 10), control women 36.0 (SD 11), intervention men 35.5 (SD 11), intervention women 36.0 (SD 12) (all 19 to 55) Baseline BMI: mean control men 24.9 (SD 2.2), control women 25 (SD 2), intervention men 24.9 (SD 2.3), intervention women 24.7 (SD 2)
Interventions	Reduced fat vs usual diet Control aims: advised to use products from trial shop ad lib. (usual fat products provided) Intervention aims: advised to use products from trial shop ad lib. (low fat products provided) Control methods: participants obtained foods in a study shop at least once a week Intervention methods: participants obtained foods in a study shop at least once a week Weight goals: ad libitum diet Total fat intake (at 6 months): low fat 34.7 (SD unclear), control 42.7 (SD unclear) %E Saturated fat intake (at 6 months): low fat 14.2 (SD unclear), control 18.2 (SD unclear) %E Style: food provided Setting: community
Outcomes	Stated trial outcomes: weight, vitamin and fatty acid intake, anti-oxidative capacity Available outcomes: weight (for subgroup), weight and lipids provided for larger group, but without variance data
Notes	Change from baseline to 6 months for whole group (control 103, intervention 117): Weight, kg: 1.1, 0.4 Total cholesterol, mmol/L: 0.07, -0.09 HDL cholesterol, mmol/L: -0.03, -0.06 LDL cholesterol, mmol/L: 0.15, 0.16 TG, mmol/L: 0.04, -0.04

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"stratified randomisation (according to sex, age, QI index and eating behaviour) by coordinating centre", a statistician at Unilever Research, SAS software, and allocation could not be altered later

MSFAT 1995 *(Continued)*

Allocation concealment (selection bias)	Low risk	"stratified randomisation (according to sex, age, QI index and eating behaviour) by coordinating centre", a statistician at Unilever Research, SAS software, and allocation could not be altered later
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear for weight; staff analysing biochemistry were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	20 of 240 (8%) lost over 0.5 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	Not noted
Free of systematic difference in care?	Low risk	Both groups used study shop. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Big difference between total fat in the two arms, though no variance provided

NDHS Open 1st L&M 1968

Study characteristics	
Methods	RCT National Diet-Heart Study (NDHS) Summary risk of bias: low
Participants	Free-living men (USA) CVD risk: low Control: randomised 382, analysed 348 Intervention B: randomised 385, analysed 332 Intervention X: randomised 54, analysed 46 Mean years in trial: control 1.0, B 0.9, X 0.9 % male: 100 Age: unclear (all 45 to 54) Baseline BMI: not reported
Interventions	Reduced and modified fat diet vs usual diet Control aims: total fat 40%E, SFA 16%E to 18%E, dietary cholesterol 650 to 750 mg/d, P/S 0.4 Intervention B: total fat 30%E, SFA < 9%E, dietary cholesterol 350 to 450 mg/d, PUFA 15%E, P/S 1.5 Intervention X: total fat 30%E, SFA < 9%E, dietary cholesterol 350 to 450 mg/d, PUFA 15%E, P/S 1.5

NDHS Open 1st L&M 1968 *(Continued)*

	Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow-up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention B methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow-up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Intervention X methods: dietary advice but no trial shop Weight goals: weight and calories not mentioned Total fat intake (through study): B 29.7 (SD unclear) %E, X 31.7 (SD unclear), control 34.9 (SD unclear) %E Saturated fat intake (through study): B 7.1 (SD unclear) %E, X 8.9 (SD unclear), control 11.6 (SD unclear) %E Style: B diet provided, X - diet advice Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Available outcomes: total cholesterol (some weight and BP data presented but no variance info)
Notes	At 52 weeks, weight change in the control was not presented, weight change in B was -2.4 kg. Average weight change over the first year (mean of weights at weeks 6, 12, 20, 28, 36 and 44 weeks) was -2.45 kg (-5.4lb) for the low fat group (B) and -1.95 kg (-4.3lb) for the control group (D) At 52 weeks, diastolic BP change from baseline was -2.2 kg in control, -1.9 in B and -5.8 in X

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	Stratified randomisation by the statistical centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intervention B: all reduced saturated fat and purchased blinded foods from a trial shop, double-blind Intervention X: no trial shop, so participants not blinded, though those analysing blood samples etc. were
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded for all outcomes for intervention B, and for lipids etc for intervention X
Incomplete outcome data (attrition bias) All outcomes	High risk	87 of 821 (11%) lost over 1 year (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Yes for intervention B (as both intervention and control received dietary advice and purchased food from trial shop). No for intervention X (as it did not include

NDHS Open 1st L&M 1968 *(Continued)*

		a trial shop as in the control group). See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Unclear risk	Differences in total fat intake, but no variance provided

NDHS Open 2nd L&M 1968

Study characteristics	
Methods	RCT National Diet-Heart Study (NDHS) Summary risk of bias: moderate to high
Participants	Free-living men who had participated in NDHS 1st studies (USA) CVD risk: low Control: randomised 304, analysed 215 Intervention BC (this study had a range of interventions, we were interested in BC for the systematic review): randomised 194, analysed 179 Mean years in trial: control 0.6, intervention BC 0.6 % male: 100 Age: unclear (all 45 to 54) Baseline BMI: not reported
Interventions	Reduced and modified fat vs usual diet Control aims: total fat 40%E, SFA 16%E to 18%E, dietary cholesterol 650 to 750 mg/d, P/S 0.4, X - advice to continue usual diet Intervention aims: BC total fat 30%E to 40%E, SFA reduced, dietary cholesterol 350 to 450 mg/d, increased PUFA, P/S 1.5 to 2.0 Control methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow-up visits with nutritionist), purchase of 'usual fat' items from a trial shop Intervention BC methods: dietary advice to reduce saturated fat and cholesterol (plus 10 follow-up visits with nutritionist), plus purchase of appropriately reduced and modified fat items from a trial shop Weight goals: weight and calories not mentioned Total fat intake (through study): BC 32.5 (SD unclear) %E, control 35.5 (SD unclear) %E Saturated fat intake (through study): BC 7.4 (SD unclear) %E, control 12.0 (SD unclear) %E Style: food provided Setting: community
Outcomes	Stated trial outcomes: lipid levels and dietary assessment Available outcomes: weight
Notes	Weight data provided for the BC intervention group -1.8 kg (-4 lb over 6 months), and -0.9 kg (-2 lb). No info provided for the control group (D)

NDHS Open 2nd L&M 1968 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	Stratified randomisation by the statistical centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Some participants continued with advice to reduce saturated fat and purchased blinded foods from a trial shop, but half of the participants were instructed in their own purchase of appropriate foods from normal shops to compile their own dietary regimen.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	104 of 498 (21%) lost over 0.6 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Trial shop used by both groups, plus dietary advice. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Unclear risk	Unclear as no variance provided for total fat intakes

Nordevang 1990

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Women who had had surgery for breast cancer (Sweden) CVD risk: low Control: randomised 121, analysed 63 Intervention: randomised 119, analysed 106 Mean years in trial: control 1.9, randomised 1.5 % male: 0% Age: mean 58 (not described by randomisation group) Baseline BMI: intervention 6 BMI < 20, 81 BMI 20 to 24.9, 34 BMI ≥ 25; control 9 BMI < 20, 74 BMI 20 to 24.9, 36 BMI ≥ 25
Interventions	Reduced fat vs usual diet

Nordevang 1990 *(Continued)*

	Control aims: usual diet Intervention aims: 20%E to 25%E from fat, increase energy from CHO to replace lost energy Control methods: no advice provided, only seen at baseline and 2 years Intervention methods: 4 to 6 sessions during the first 2 months, group meetings every 6 to 8 weeks, evening classes in low fat cooking, 3 monthly counselling during the first year, then at 18 months Weight goals: "The total energy and/or protein intake was to be held constant". Total fat intake (at 2 years): intervention -12.9 (SD unclear) (24 overall), control -3.1 (SD unclear) (34.1 overall) %E Saturated fat intake (change to 2 years): intervention -6.8 (SD unclear), control -1.9 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary intake Available outcomes: weight, BMI
Notes	No exact variance or P values reported for weight and BMI outcomes, so have estimated variance from P < 0.05 for the difference between the 2 arms for weight. As P > 0.05 for BMI no variance could be estimated This trial was named "Swedish Breast Cancer" in previous versions of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear for those assessing outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome data ignored for those who dropped out (48% of the intervention group), > 10%/year
Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Different levels of time and follow-up in the 2 groups

Nordevang 1990 *(Continued)*

Free of dietary differences other than fat?	Low risk	Focus on fat
Compliance problems	Low risk	Very big difference between groups, though no variance reported

Nutrition & Breast Health

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Premenopausal women at increased risk of breast cancer (USA) CVD risk: low Control: randomised 53, analysed 50 Intervention: randomised 69, analysed 47 Mean years in trial: control 1.0, intervention 0.8 % male: control 0%, intervention 0% Age: mean 38 (SD 7) - not provided by study arm (all 21 to 50) Baseline BMI: not reported
Interventions	Reduced fat vs usual diet Control aims: followed usual diet, given daily food guide pyramid (half of this group randomised to 9 portions/d of fruit and vegetables advice) Intervention aims: total fat 15%E (half of this group randomised to 9 portions/d of fruit and vegetables advice) Control methods: no dietary counselling (offered this at the end of study), but those given fruit and vegetables advice had support as below Intervention methods: met dietitian every 2 weeks until compliant, monthly group meetings, counselling on home diets, restaurants, parties, social support, eating at work, exchange booklets, cookbook Weight goals: "goals were derived such that baseline energy intake would be maintained while meeting study goals". Total fat intake (at 12 months): low fat 15.7 (SD 5.1) %E, control 32.7 (SD 6.1) %E Saturated fat intake (at 12 months): low fat 7.2 (SD unclear) %E, control 11.6 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: body weight, dietary compliance Available outcomes: weight, total, LDL and HDL cholesterol, TG, BMI (but variance data not provided for any but weight)
Notes	Change from baseline to 12 months for the control (n = 23), control plus fruit and vegetables (n = 25), low fat (n = 24), low fat plus fruit and vegetables (n = 23): • Total cholesterol mg/dL: 9, 2, -8, 0 • TG mg/dL: -7, 1, 5, 8 • HDL cholesterol mg/dL: 0, 0, -4, 0

Nutrition & Breast Health *(Continued)*

- LDL cholesterol mg/dL: 11, 2, -6, -2
- BMI kg/m^2: 0, 4, -13, 0

For weight, end data only are provided (no change data) although the intervention group was considerably heavier at baseline (149 lb and 154 lb) than control groups (both 143 lb)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The statistician made envelopes ahead of time; dietitians handed out envelopes at first visit.
Allocation concealment (selection bias)	Low risk	Allocation could not be altered once made.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of allocation.
Blinding of outcome assessment (detection bias)	High risk	Researchers were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	15 of 122 (12%) lost over 1 year (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	High levels of intervention for those on low fat or high fruit and vegetable diets. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	Randomisation to fruit and vegetable intervention was independent of low fat allocation
Compliance problems	Low risk	Significant difference in total fat between arms

ODMDC 2017

Study characteristics

Methods	RCT with 3 arms Optimal Dietary Macronutrient Distribution in China (ODMDC) Summary risk of bias: low
Participants	Healthy young adults (China) CVD risk: low Control:

ODMDC 2017 *(Continued)*

- High fat low CHO: 101 randomised, 101 analysed
- Mod fat mod CHO: 105 randomised, 105 analysed

Intervention:

- low fat high CHO: 101 randomised, 101 analysed

Mean years in trial: control 0.5, intervention 0.5

% male: control high fat: 52%, control mod fat: 48%, intervention low fat 50%
Age, mean (SD), years: control high fat 23.7 (4.3), control mod fat 23.2 (3.9), intervention low fat 23.4 (3.6), range 18-35

Baseline BMI, mean (SD): control high fat 21.9 (25), control mod fat 21.8 (2.6), intervention low fat 21.7 (2.5)

Interventions	Low fat vs moderate fat vs high fat Control: • High fat low CHO: isocaloric diet with 2100 kcal/d for men, 1700 kcal/d for women, 40%E fat, 46%E CHO, 14%E protein, 14 g/d fibre, 300 mg/d cholesterol • Mod fat mod CHO: isocaloric diet with 2100 kcal/d for men, 1700 kcal/d for women, 30%E fat, 56%E CHO, 14%E protein, 14 g/d fibre, 300 mg/d cholesterol Intervention: • Low fat high CHO: isocaloric diet with 2100 kcal/d for men, 1700 kcal/d for women, 20%E fat, 66%E CHO, 14%E protein, 14 g/d fibre, 300 mg/d cholesterol Control & intervention methods: all food provided, encouraged to maintain usual fruit intake and usual levels of physical activity. Diets composed by replacing white rice and wheat flour with soybean oil. Weight goals: "isocaloric" Total fat intake (during intervention): • by menu analysis: high fat 40%E, mod fat 31%E, low fat 20%E • by chemical analysis: high fat 38%E, mod fat 28%E, low fat 18%E Saturated fat intake: unclear Style: all food provided
Outcomes	Stated trial outcomes: primary weight change, secondary waist circumference, blood pressure, lipids, glucose, insulin, glycated protein, adiponectin, leptin Available outcomes: weight change, waist circumference, blood pressure, lipids, glucose, insulin, glycated protein, adiponectin, leptin
Notes	We used both the high fat (40%E) and moderate fat (30%E) arms as higher fat arms, and the low fat (20%E) arm as the lower fat arm. Funding: National Basic Research Program of China (2015CB553604)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list, stratified by centre, age, sex and BMI

ODMDC 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomised by data manager and after run-in period
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not informed of allocations, but would have been aware of these from foods provided
Blinding of outcome assessment (detection bias)	Low risk	Clinical staff and lab personnel who carried out measurements were masked to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the ITT analysis (however 28 of 101 (high fat), 22 of 105 (mod fat), and 16 of 101 (low fat) dropped out during the 6 months of the trial).
Selective reporting (reporting bias)	Low risk	Trials register posted Feb 2015, trial completed in Oct 2015. All primary and secondary outcomes fully reported
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Yes, same process and contact schedule in all arms
Free of dietary differences other than fat?	Low risk	Yes, fat/CHO swaps
Compliance problems	Low risk	All food provided and diet diaries used to assess compliance

Pilkington 1960

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Men with angina or who have had a MI (UK) CVD risk: high Reduced fat: randomised unclear, analysed 12 Modified fat: randomised unclear, analysed 23 Mean years in trial:reduced fat 1.1, modified fat 1.1 % male: reduced fat 100%, modified fat 100% Age: not stated Baseline BMI: not reported
Interventions	Reduced fat vs modified fat diet Reduced fat aims: total fat 20 g/d, advice to avoid dairy fats except skimmed milk plus 1 egg or 21 g cheese/d. Lean meat and fish each allowed once/d, other non-fatty foods allowed in unlimited quantities Modified fat aims: fat aims not stated, dairy produce avoided except skimmed milk, 90 mL/d soya oil provided, lean meat originally prohibited but allowed after 6 months along with 113 g/wk of 'relatively unsaturated margarine'. Fish and vegetables allowed freely Reduced fat methods: unclear; "dietary histories taken before and during treatment"

Pilkington 1960 *(Continued)*

	Modified fat methods: unclear; "dietary histories taken before and during treatment" Weight goals: non-fatty foods not restricted, no weight goals mentioned Total fat intake (during treatment): low fat 15.8 (SD unclear) %E, mod fat 36 (SD unclear) %E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids Available outcomes: weight, total and LDL cholesterol
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear exactly how many were randomised, but paper suggested that all randomised participants were analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry found
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Appeared to be similar levels of assessment and support in both arms
Free of dietary differences other than fat?	Low risk	Dietary focus entirely on fat
Compliance problems	Unclear risk	A large difference in self-reported fat intake per day was reported, which is almost certainly statistically significant, though no measure of variance was reported, however, the lower fat diet resulted in higher total and LDL cholesterol, so unclear

Polyp Prevention 1996

Study characteristics	
Methods	RCT Polyp Prevention Trial Summary risk of bias: moderate to high
Participants	People with at least one adenomatous polyp of the large bowel removed (USA) CVD risk: low Control: 1042 randomised, 943 analysed Intervention: 1037 randomised, 943 analysed Mean years in trial: control 3.05, intervention 3.05 % male: control 64%, intervention 66% Age: mean control 61.5, intervention 61.4 (all at least 35) Baseline BMI: mean control 27.5 (SE 0.12), intervention 27.6 (SE 0.13)
Interventions	Low fat vs usual diet Control: general dietary guidelines Intervention: total fat 20%E, 18 g fibre/1000 kcal, 5 to 8 servings fruit and vegetables daily Control methods: leaflet, no additional information or behaviour modification Intervention methods: > 50 hours of counselling over 4 years, included skill building, behaviour modification, self-monitoring and nutritional materials Weight goals: "weight loss is permitted but not encouraged....counselled to replace fat intake with increased intake of fruit, vegetable and grain products rather than reduce total calorie intake." Total fat intake (at 4 years): low fat 23.8 (SD 6.0), control 33.9 (SD 5.9) %E Saturated fat intake: unclear Style: diet advice Setting: community
Outcomes	Stated trial outcomes: recurrence of polyps, prostate cancer Available outcomes: weight, total cholesterol
Notes	Weight data reported at 1, 2, 3 and 4 years. 3-year data used in main analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned" by computer randomisation centre, stratified according to centre
Allocation concealment (selection bias)	Low risk	Phone call to computer randomisation centre, stratified according to centre
Blinding of participants and personnel (performance bias)	High risk	Participants not blinded

Polyp Prevention 1996 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessors blinded for main trial outcomes, but not clear for body weight
Incomplete outcome data (attrition bias) All outcomes	Low risk	193 of 2079 (9%) lost over 3 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen, clinical trial register set up 10 years after publication of baseline data
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	50 hours behaviour modification in intervention group, not in control. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Fibre, fruit and vegetable goals in intervention group
Compliance problems	Low risk	Significant difference in total fat intake at 4 years; not backed up by different total cholesterol

RISCK 2010

Study characteristics	
Methods	2 × 2 parallel RCT (5 arms) Reading, Imperial, Surrey, Cambridge, and Kings (RISCK) study Summary risk of bias: moderate to high
Participants	People at increased risk of developing metabolic syndrome ≥ 4 (UK) CVD risk: low Control: HM/HGI 145 randomised, 111 analysed; HM/LGI 144 randomised, 116 analysed Intervention: LF/HGI 145 randomised, 116 analysed; LF/LGI 149 randomised, 121 analysed Mean years in trial: control 0.5 (SD x), intervention 0.5 (SD x) % male: 42% overall Age: mean age given overall by gender: Male = 52 ± 10; Female = 51 ± 9 Baseline BMI: overall mean BMI given as male or female: Male = 28.3 ± 3.8; Female = 28.6 ± 5.3
Interventions	Low fat vs usual diet (low fat and high GI, low fat and low GI vs high MUFA and high GI, high MUFA and high GI) - additional arm not used (high sat fatty acid and high GI). Low fat (intervention arm): 28% fat, either 45% or 55% CHO, 12% MUFA, 10% SFA Higher fat (control arm): 38% fat, 45% or 55% CHO, 20% MUFA, 10% SFA Control methods: Provision of key sources of fat (including spreads, cooking oils and margarine) and carbohydrates (including bread, pasta, rice and cereals) in the diet with additional dietary information,

RISCK 2010 *(Continued)*

	tailored to the study group, given in writing and reinforced at individual study visits. Higher fat (38% fat, 20% MUFA, 10% SFA) Intervention methods: Provision of key sources of fat (including spreads, cooking oils and margarine) and carbohydrates (including bread, pasta, rice and cereals) in the diet with additional dietary information, tailored to the study group, given in writing and reinforced at individual study visits. Lower fat (28% fat, 12% MUFA, 10% SFA) Weight goals: Participants were advised that dietary advice was for weight maintenance. Total fat intake (at 6 months); change % of energy; mean (95% CI): • LF/HGI: -10.4 (-12.2, -8.6) vs HM/HGI: -2.3 (-4.1, -0.5) • LF/LGI: -11.8 (-13.5, -10.1) vs HG/LGI: -2.2 (-3.9, -0.4) Saturated fat intake (at 6 months); change % of energy; mean (95%CI): • LF/HGI: -7.3 (-8.3, -6.4) vs HM/HGI: -7.0 (-7.9, -6.0) • LF/LGI: -8.2 (-9.1, -7.3) vs HG/LGI: -6.9 (-7.8, -6.0) Style: dietary advice and supplement Setting: community
Outcomes	Stated trial outcomes: Primary: Change in insulin sensitivity from measures of glucose and insulin during an intravenous glucose tolerance test Secondary: Fasting lipid profile, vascular reactivity and endothelial function, haemostatic factors, markers of the inflammatory response, leptin and adiponectin, urinary microalbumin to creatinine ratio, plasma fatty acid composition, DNA for nutrient-gene interactions. Available outcomes: weight, total cholesterol, triglyceride, LDL and HDL cholesterol, BP, total energy, total fat % energy, SFA % energy, PUFA % energy, MUFA % energy, CHO % energy, sugars % energy, protein g/d
Notes	Funding: UK Food Standards Agency (project NO2031). Foods were supplied by Unilever Food and Health Research Institute (Unilever R&D, Vlaardingen, Netherlands), Cereal Partners UK (Welwyn Garden City, Hertfordshire, United Kingdom), Grampian (Banff, United Kingdom), Weetabix Ltd (Kettering, United Kingdom), and Sainsbury's Supermarkets Ltd (London, United Kingdom).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based minimisation procedure to balance assignment by age, sex, waist, and HDL cholesterol
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and the nutritionist advising on the dietary changes were not blinded to the treatment.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether those who measured adiposity were blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Flow of participants through the study was shown with the CONSORT diagram, 171 out of 720 lost to follow-up over 6 months (reason given - discontinued), > 10%/year

RISCK 2010 *(Continued)*

Selective reporting (reporting bias)	High risk	Study was registered retrospectively in 2005, but weight not mentioned as an outcome, though reported.
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Appeared to be similar levels of assessment and support in both arms
Free of dietary differences other than fat?	Low risk	Focus on fat
Compliance problems	Low risk	Significant difference in total fat intake between arms

Rivellese 1994

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Adults with primary hyperlipoproteinaemia (Italy) CVD risk: moderate Intervention reduced fat: 33 randomised, 27 analysed Intervention modified fat: 30 randomised, 17 analysed Mean years in trial: reduced fat 0.4, modified fat 0.4 % male: reduced fat 82%, modified fat 63% Age, years: reduced fat 47.4 mean (SD 10.3), modified fat 48.6 (SD 8.1) Baseline BMI: reduced fat 24.4 mean (SD 2.9), modified fat 25.2 (SD 2.7)
Interventions	Reduced fat vs modified fat diet Reduced fat aims: total fat 25%E, SFA 8%E, MUFA 15%, PUFA 2%, dietary cholesterol < 300 mg/d, CHO 58%, protein 17%E, soluble fibre 41 g/d Modified fat aims: total fat 38%E, SFA < 10%E, MUFA 20%E, PUFA 10%E, dietary cholesterol < 300 mg/d, CHO 47%E, protein 15%E, soluble fibre 19 g/d Reduced fat methods: seen monthly by dietitian and doctor; feedback based on 7-day food diary each time Modified fat methods: seen monthly by dietitian and doctor; feedback based on 7-day food diary each time Weight goals: neither weight or energy intake goals mentioned for either group Total fat intake (at 5 to 6 months): low fat 27 (SD unclear), mod fat 36 (SD unclear) %E Saturated fat intake (at 5 to 6 months): low fat 6 (SD unclear) %E, mod fat 7 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: metabolic effects Available outcomes: weight, total, LDL and HDL cholesterol, TG

Rivellese 1994 *(Continued)*

Notes	Weight data were presented without variance info. Participants in the low fat arm lost 1.8 kg over the 6 months; the modified fat diet arm lost 1.6 kg.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Following 3 or 6 weeks compliance with control diet run-in, stratified block randomisation with tables of random numbers
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	19 of 63 (30%) lost over 0.4 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Identical follow-up. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Some differences in soluble fibre intake
Compliance problems	Unclear risk	Big difference in total fat intake, but no variance to verify

Sarkkinen Low & Mod 1993

Study characteristics

Methods	RCT (4 arms have been used here as 2 RCTs) Summary risk of bias: moderate to high
Participants	Free-living people aged 30 to 60 with serum total cholesterol levels 6.5 to 8.0 mmol/L (Finland) CVD risk: moderate Control (monoene-enriched): randomised 41, analysed 41 Intervention AHA: randomised 41, analysed 41 Mean years in trial: for all 4 groups 0.5 % male: control 46, AHA 46 Age: mean control 46.4, AHA 47.3 (all 30 to 60) Baseline BMI: mean control 26.6 (SD 3.8), intervention 26.2 (SD 4.0)

Sarkkinen Low & Mod 1993 *(Continued)*

Interventions	Reduced and modified fat vs modified fat diet Control aims mono: total fat 38%E, SFA < 14%E, MUFA 18%E, PUFA < 6%E, rapeseed oil, rapeseed spread and skimmed milk provided Intervention aims AHA: total fat 30%E, SFA < 10%E, MUFA 10%E, PUFA 10%E, sunflower oil, sunflower spread and skimmed milk provided Control and intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Weight goals: dietary written instructions were designed for 5 energy levels (1800, 2000, 2400, 2800 and 3200) based on individual diet and activity assessment Total fat intake (weeks 14 to 28): low and mod fat 34 (SD 4), control 35 (SD 5) %E Saturated fat intake (weeks 14 to 28): low and mod fat 11 (SD 2), control 11 (SD 2) %E Style: dietary advice and supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Available outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	This trial was named "Kuopio Low and Modified fat" in previous versions of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables".
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew allocation.
Blinding of outcome assessment (detection bias)	High risk	Researchers knew allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 of 82 (0%) lost over 0.5 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Similar intensity and duration in both groups. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above

Sarkkinen Low & Mod 1993 *(Continued)*

Compliance problems	High risk	Appeared very little difference in total fat intake between arms

Sarkkinen Low Fat 1993

Study characteristics	
Methods	RCT (4 arms have been used here as 2 RCTs) Summary risk of bias: moderate to high
Participants	Free-living people aged 30 to 60 with serum total cholesterol levels 6.5 to 8.0 mmol/L (Finland) CVD risk: moderate Control (high saturated fat): randomised 37, analysed 12 Intervention low fat: randomised 40, analysed 40 Mean years in trial: for both groups 0.5 % male: control 46, low fat 48 Age: mean control 43.2, low fat 45.8 (all 30 to 60) Baseline BMI: mean control 25.6 (SD 4.2), intervention 26.5 (SD 3.4)
Interventions	Reduced fat vs usual diet (low fat vs control) Control aims: advised total fat 38%E, SFA < 18%E, MUFA 15%E, PUFA < 5%E, rapeseed oil, butter and semi-skimmed milk provided Intervention aims low fat: total fat 28-30%E, SFA < 14%E, MUFA 10%E, PUFA 4%E, butter and rapeseed spread and skimmed milk provided Control and intervention methods: given written dietary instructions and a diet plan with checking and reinforcement for 3 visits, then at 2, 6, 12, 18 and 26 weeks Weight goals: dietary written instructions were designed for 5 energy levels (1800, 2000, 2400, 2800 and 3200) based on individual diet and activity assessment Total fat intake (weeks 14 to 28): low fat 31 (SD 5), control 36 (SD 5) %E Saturated fat intake (weeks 14 to 28): low fat 12 (SD 2), control 15 (SD 2) %E Style: dietary advice and supplement (food) Setting: community
Outcomes	Stated trial outcomes: lipids and blood pressure Available outcomes: BMI, total, LDL and HDL cholesterol, TG, BP
Notes	This trial was named "Kuopio Low Fat" in previous versions of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation stratified for men and women, singles and couples, random number tables".
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described

Sarkkinen Low Fat 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew allocation.
Blinding of outcome assessment (detection bias)	High risk	Researchers knew allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	25 of 77 (32%) lost over 0.5 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Similar intensity and duration in both groups. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Statistically significant difference in total fat intake between arms

Simon 1997

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	Women with a high risk of breast cancer (USA) CVD risk: low Control: randomised 96, analysed 38 Intervention: randomised 98, analysed 34 Mean years in trial: control 1.8, intervention 1.7 % male: 0 Age: mean control 46, intervention 46 Baseline BMI: mean intervention 25.2 (SE 0.8), control 28.1 (SE 0.8)
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: total fat 15%E Control methods: continued usual diet Intervention methods: biweekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including education, goal-setting, evaluation, feedback and self-monitoring Weight goals: weight and calorie goals not discussed Total fat intake (at 12 months): low fat 18.0 (SD 5.6), control 33.8 (SD 7.4) %E

Simon 1997 *(Continued)*

	Saturated fat intake (at 12 months): low fat 6.0 (SD unclear), control 11.3 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: intervention feasibility Available outcomes: weight, total, LDL and HDL cholesterol, TG
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by age and randomised (block size 2)
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants knew their allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether physicians knew allocations
Incomplete outcome data (attrition bias) All outcomes	High risk	122 of 194 (63%) lost over 2 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Very different contact time with dietitian, but medical appointments same in both groups. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Big and statistically significant difference between arms in total fat intake

Strychar 2009

Study characteristics

Methods	RCT Summary risk of bias: moderate to high
Participants	People with well controlled type I diabetes mellitus (Canada)

Strychar 2009 *(Continued)*

	CVD risk: moderate Intervention reduced fat: 18 randomised, 15 analysed Intervention modified fat: 17 randomised, 15 analysed Mean years in trial: reduced fat 0.46, modified fat 0.47 % male: reduced fat unclear, modified fat unclear Age, years: 37.9 (8.1 SD) (not specified by study arm) Baseline BMI: mean reduced fat 24.3 (SD 2.6), modified fat 24.3 (SD 2.7)
Interventions	Reduced fat vs modified fat diet Reduced fat aims: total fat 27%E to 30%E, SFA ≤ 10%E, MUFA 10%, CHO 54% to 57% Modified fat aims: total fat 37%E to 40%E, SFA ≤ 10%E, MUFA 20%E, CHO 43%E to 46%E Reduced fat methods: after initial dietary advice, monitored weekly by phone by a dietitian (24-hour food recall). Glycaemia, insulin doses, CHO at meals, hypoglycaemic attacks all self-monitored daily and reported weekly. Modified fat methods: after initial dietary advice, monitored weekly by phone by a dietitian (24-hour food recall). Glycaemia, insulin doses, CHO at meals, hypoglycaemic attacks all self-monitored daily and reported weekly. Total fat intake (at 6 months): not stated Saturated fat intake (at 6 months): not stated Style: diet advice Setting: community
Outcomes	Stated trial outcomes: triglycerides and other CVD risk factors Available outcomes: weight; BMI; total, LDL and HDL cholesterol; TG; systolic and diastolic blood pressure
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details provided, but participants had to make decisions about what they ate.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	5 of 35 (14%) lost over 0.5 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen

Strychar 2009 *(Continued)*

Other bias	Low risk	None noted
Free of systematic difference in care?	Low risk	Similar intervention in both groups
Free of dietary differences other than fat?	Low risk	Focus on fat and CHO intake
Compliance problems	Unclear risk	Unclear total fat intake

Swinburn 2001

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	People with impaired glucose intolerance or high normal blood glucose (New Zealand) CVD risk: moderate Control: unclear how many randomised (176 between both groups), 51 analysed Intervention: unclear how many randomised (176 between both groups), 48 analysed Mean years in trial: 4.1 over whole trial % male: control 80%, intervention 68% Age: mean control 52.0 (SE 0.8), intervention 52.5 (SE 0.8) Baseline BMI: mean control 29.1 (SE 0.6), intervention 29.3 (SE 0.6)
Interventions	Reduced fat vs usual diet Control aims: usual diet Intervention aims: reduced fat diet (no specific goal stated) Control methods: usual intake Intervention methods: monthly meetings to follow a 1-year structured programme aimed at reducing fat in the diet; included education, personal goal-setting, self-monitoring Weight goals: weight and calories not mentioned; diet was "aimed solely at reducing the total amount of fat in their diet". Total fat intake (at 1 year): low fat 26.1 (SD 7.7), cont 33.6 (SD 7.8) %E Saturated fat intake (at 1 year): low fat 10.0 (SD 4.2), cont 13.4 (SD 4.7) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: lipids, glucose, blood pressure Available outcomes: weight, total, LDL and HDL cholesterol, TG, BP
Notes	This trial was named "Auckland Low Fat" in previous versions of this review.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Swinburn 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	Paper states "individually assigned by simple randomization using an unmarked envelope system"
Allocation concealment (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting; unable to alter allocation later.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	77 of 176 recruited lost to follow-up, 44% over 5 years (> 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Statistically significant difference in total fat intake between arms

WHEL 2007

Study characteristics	
Methods	RCT Women's Healthy Eating and Living (WHEL) study Summary risk of bias: moderate to high
Participants	Women with previously treated early breast cancer (USA) CVD risk: low Control: randomised 1561, analysed 1313 Intervention: randomised 1546, analysed 1308 Mean years in trial: unclear, 11 years max, around 11 years mean? % male: 0 Age: control mean 53.0 (SD 9.0), intervention mean 53.3 (SD 8.9) Baseline BMI: control mean 27.2 (SD 6.1), intervention mean 27.2 (SD 6.1)
Interventions	Reduced fat intake vs usual diet Control: aim 30%E from fat Intervention: aim 15%E to 20%E from fat, 5 vegetables/d, 3 fruit/d, 16 oz vegetable juice and 30 g/d fibre

WHEL 2007 *(Continued)*

	Control methods: given print materials only Intervention methods: telephone counselling programme (31 calls by study end), cooking classes (12 offered in first year, 4 attended on average) and monthly newsletters (48 by study end), all focused on self-efficacy, self-monitoring and barriers, retaining motivation Weight goal: intervention goal was to achieve the change in dietary pattern without weight reduction; weight and calories not mentioned in the control group Total fat intake (at 72 months): low fat 28.9 (SD 9.0), control 32.4 (SD 8.0) %E Saturated fat intake (at 72 months): low fat 7.2 (SD unclear), control 8.9 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: mortality, invasive breast cancer Available outcomes: weight, total, LDL and HDL cholesterol, TG
Notes	Weight measured and reported at 1, 2, 3, 4 and 6 years, and 3-year data used in main analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via computer program
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear whether those assessing weight were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	486 of 3107 (16%) lost over 11 years (< 10% per year)
Selective reporting (reporting bias)	Low risk	NCT entry 2005, study completion date 2007. Breast cancer recurrence and mortality noted as outcomes and published
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	High-intensity intervention compared with leaflets. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Fruit and vegetable intervention in low fat arm, not in control
Compliance problems	Unclear risk	Total fat intake lower in intervention group than control; not statistically significant and not backed by significant differences in total or LDL cholesterol

WHI 2006

Study characteristics	
Methods	RCT Women's Health Initiative (WHI) Summary risk of bias: low
Participants	Postmenopausal women aged 50 to 79 (USA) CVD risk: mixed, mostly low but some participants had CVD at baseline Control: randomised 29,294, analysed 25,056 Intervention: randomised 19,541, analysed 16,297 Mean years in trial: control 8.1, intervention 8.1 % male: 0 Age: mean intervention 62.3 (SD 6.9), control 62.3 (SD 6.9) Baseline BMI: mean intervention 29.1 (SD 5.9), control 29.1 (SD 5.9)
Interventions	Reduced fat vs usual diet Control: diet-related education materials Intervention: low fat diet (20%E from fat) with increased fruit and vegetables Control methods: given copy of 'Dietary Guidelines for Americans' Intervention methods: 18 group sessions with trained and certified nutritionists in the first year, quarterly maintenance sessions thereafter, focusing on diet and behaviour modification Weight goals: "the intervention did not include total energy reduction or weight-loss goals". Total fat intake (at 6 years): intervention 28.8 (SD 8.4) %E, control 37.0 (SD 7.3) %E Saturated fat intake (at 6 years): intervention 9.5 (SD 3.2) %E, control 12.4 (SD 3.1) %E Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: breast cancer, mortality, other cancers, cardiovascular events, diabetes Available outcomes: weight, BMI, waist circumference, body fat %, total, LDL and HDL cholesterol, TG, systolic and diastolic BP, quality of life
Notes	Weight data available at 1 year, 3 years, 6 years and 7.5 years. Latest (7.5 year) data used for main analysis for weight, BMI and waist circumference

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block algorithm stratified by clinical centre and age
Allocation concealment (selection bias)	Low risk	Allocations developed by the WHI Clinical Coordinating Center
Blinding of participants and personnel (performance bias)	High risk	Participants aware of allocation

WHI 2006 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias)	Low risk	Trained clinic staff, who were responsible for anthropometric assessments and administration of FFQs, were blinded to treatment assignments to the extent practical. The dietary intervention staff did not conduct clinical assessments, and clinic staff were not permitted to participate in any intervention activities; participants were instructed not to discuss nutrition activities with clinic staff.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7482 of 48,835 (15%) lost over 8 years (< 10% per year)
Selective reporting (reporting bias)	Low risk	Weight and secondary outcomes reported as in protocol
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Intervention participants received 18 group sessions with behavioural modification plus quarterly maintenance sessions thereafter. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	High risk	Also fruit and vegetable intervention. See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Statistically significant difference in total fat intake

WHT Full-scale

Study characteristics	
Methods	RCT, 2 parallel arms Women's Health Trial (WHT) - full-scale trial Summary risk of bias: moderate to high
Participants	Women at increased risk of breast cancer (USA) CVD risk: low Control: randomised unclear, analysed 318 (1761 recruited overall in the full-scale phase between control & intervention arms, 40% randomised to intervention) Intervention: randomised unclear, analysed 324 Mean years in trial: control 1, randomised 1 % male: 0% Age: mean not stated, but all aged 45 to 69 (27% 45-49, 43% 50-59, 30% 60-69 years) Baseline BMI: Not stated, but weight ~69kg
Interventions	Reduced fat vs usual diet Control aims: maintain usual diet Intervention aims: 20%E from fat Control methods: no advice provided; encouraged to eat usual diet Intervention methods: multiple group intervention sessions over 18 months, emphasising nutrition education and behavioural skills (including fat-counting); participants had to have been offered 8 group sessions at least to be included in outcome assessment over 5-37 months.

WHT Full-scale *(Continued)*

	Weight goals: "there was no emphasis on weight change". Total fat intake (at 1 year): intervention 26.8 (SD unclear), control 38.4 (SD unclear) %E Saturated fat intake: intervention not stated, control not stated %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: breast cancer diagnosis Available outcomes: weight
Notes	Weight data provided at study end (on average 1 year after randomisation) Recruitment was 1986-1988; trial terminated early in 1988.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not blinded; measured by the nurse who went through dietary records.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear due to early termination of study
Selective reporting (reporting bias)	Low risk	Design paper published, weight and serum total cholesterol reported
Other bias	High risk	Data are partial as the trial was terminated early, in 1988. Risk of contamination with data on the WHT Vanguard part of the study
Free of systematic difference in care?	High risk	Different levels of attention and time
Free of dietary differences other than fat?	Low risk	Focus on fat only
Compliance problems	Low risk	Statistically significant difference in total fat intake between arms at 1 year

WHT Vanguard 1991

Study characteristics

WHT Vanguard 1991 *(Continued)*

Methods	RCT Women's Health Trial Vanguard Study (WHT Vanguard) Summary risk of bias: moderate to high
Participants	Women at increased risk of breast cancer (USA) CVD risk: low Control: randomised 184, analysed 159 Intervention: randomised 119, analysed 102 Mean years in trial: control 1.9, randomised 1.9 % male: 0% Age: mean control 55.6 (SD 6.3), intervention 55.6 (SD 6.2) Baseline BMI: mean intervention 26 (SD 4), control 25 (SD 4)
Interventions	Reduced fat vs usual diet Control aims: maintain usual diet Intervention aims: 20%E from fat Control methods: no advice provided, only seen at baseline, then 6, 12 and 24 months for assessment Intervention methods: women were given flexible diet plans and responsible for their own monitoring; they had individual appointments with a nutritionist at 2 and 12 weeks, plus small group meetings (weekly for 8 weeks, then biweekly for 8 weeks, then monthly to 2 years). Weight goals: "there was no emphasis on weight change". Total fat intake (at 2 years): intervention 22.6 (SD 7.1), control 36.8 (SD 8.0) %E Saturated fat intake (at 2 years): intervention 7.2 (SD 2.7), control 12.3 (SD 3.6) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary intake/feasibility Available outcomes: weight, total cholesterol
Notes	Weight data provided at 6, 12 and 24 months. 2-year data used in main analysis Recruitment was in 1985. This trial has several names, but we called it "WHT Feasibility" in previous versions of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.

WHT Vanguard 1991 *(Continued)*

Blinding of outcome assessment (detection bias)	High risk	Not blinded; measured by the nurse who went through dietary records.
Incomplete outcome data (attrition bias) All outcomes	Low risk	42 of 303 (14%) lost over 2 years (< 10% per year)
Selective reporting (reporting bias)	Low risk	Design paper published; weight and serum total cholesterol reported
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Different levels of attention and time
Free of dietary differences other than fat?	Low risk	Focus on fat only
Compliance problems	Low risk	Statistically significant difference in total fat intake between arms at 2 years; there was no lipid data to back this up.

WHTFSMP 2003

Study characteristics	
Methods	RCT Women's Health Trial: Feasibility Study in Minority Populations (WHTFSMP) Summary risk of bias: moderate to high
Participants	Postmenopausal women from diverse ethnic and socioeconomic backgrounds (USA) CVD risk: low Control: randomised 883, analysed 649 at 6 mo, 443 at 12 mo, 194 at 18 mo Intervention: randomised 1325, analysed 1071 at 6 mo, 698 at 12 mo, 285 at 18 mo Mean years in trial: unclear, follow-up from 6 to 18 months % male: 0% Age: mean control 59.8 (SD 6.6), intervention 60.1 (SD 6.6) Baseline BMI: 28.8 (SD 4.7) for all
Interventions	Reduced fat vs usual diet Control aims: maintain usual diet Intervention aims: up to 20%E from fat, reduced saturated fat and dietary cholesterol, increased fruit, vegetables and whole grains Control methods: pamphlet on general dietary guidelines provided, no other follow-up, seen at baseline, then 6, 12 and 18 months for assessment Intervention methods: women allocated to groups of 8 to 15 women with a nutritionist leader, meeting weekly for 6 weeks, bi-weekly for 9 months then quarterly. Women provided with personal fat gram goals Weight goals: weight and calories not mentioned Total fat intake (at 1 year): intervention 25.4 (SD unclear), control 36.0 (SD unclear) %E

WHTFSMP 2003 *(Continued)*

	Saturated fat intake (at 1 year): intervention 8.7 (SD unclear), control 12.1 (SD unclear) %E Style: diet advice Setting: community
Outcomes	Stated trial outcomes: dietary intake/feasibility Available outcomes: weight, BMI, blood pressure (lipids and estradiol appear to have been measured, but data not found)
Notes	Weight and BMI data only found for 6 months of intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using randomly permuted blocks after collection of baseline data
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Weight measured by trained and certified clinical staff, but unclear whether they were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those randomised were analysed for weight.
Selective reporting (reporting bias)	High risk	Unclear; outcome measures not stated in trials register. Study conducted 1991 to 1995; design paper published in 1996. Lipids and estradiol appear to have been measured but no data found.
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Greater time and support provided to intervention group
Free of dietary differences other than fat?	High risk	Suggestion to intervention group to increase fruit, vegetable and whole grain intakes
Compliance problems	Low risk	No reported serum lipids, but saturated fat intake statistically significantly different in intervention and control groups at 6, 12 and 18 months

WINS 1993

Study characteristics

Methods	RCT Women's Intervention Nutrition Study (WINS)

WINS 1993 *(Continued)*

	Summary risk of bias: moderate to high
Participants	Women with localised resected breast cancer (USA) CVD risk: low Control: 1462 randomised, 998 analysed Intervention: 975 randomised, 386 analysed Mean years in trial: overall 5.0 % men: 0 Age: control mean 58.5 (95% CI 43.6 to 73.4), intervention mean 58.6 (95% CI 44.4 to 72.8) (all post-menopausal) Baseline BMI: mean intervention 27.6 (95% CI 27.2 to 28.0), control 27.5 (95% CI 27.2 to 27.8)
Interventions	Reduced fat intake vs usual diet Control aims: minimal nutritional counselling focused on nutritional adequacy Intervention aims: total fat 15%E to 20%E Control methods: 1 baseline dietetic session plus 3-monthly sessions Intervention methods: 8 biweekly individual dietetic sessions, then optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self-monitoring, goal-setting, modelling, social support and relapse prevention and management Weight goals: "fat gram goals were based on energy needed to maintain weight, and no counselling on weight reduction was provided"; not mentioned for control Total fat intake (at 1 year): low fat 20.3 (SD 8.1), control 29.2 (SD 7.4) %E Saturated fat intake (at 1 year): low fat 10.4 (SD 6.7), control 16.6 (SD 9.3) %E Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: dietary fat intake, total cholesterol, weight and waist Available outcomes: weight, BMI
Notes	Weight data reported at 1, 3 and 5 years. 3-year data used in main analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical coordinating centre of WINS
Allocation concealment (selection bias)	Low risk	Statistical coordinating centre as above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear

WINS 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1053 of 2437 (43%) lost over 5 years (< 10% per year)
Selective reporting (reporting bias)	Unclear risk	Protocol not seen
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	Differences in attention - more time for those in intervention group. See 'Control methods' and 'Intervention methods' in the 'Interventions' section above
Free of dietary differences other than fat?	Low risk	See 'Control aims' and 'Intervention aims' in the 'Interventions' section above
Compliance problems	Low risk	Significant difference in total fat intake between arms at 1 year

Yadav 2016

Study characteristics	
Methods	RCT Summary risk of bias: moderate to high
Participants	People with relapsing-remitting multiple sclerosis (MS) (USA) CVD risk: low Control: 29 randomised, 27 analysed Intervention: 32 randomised, 26 analysed Mean years in trial: control 12 mo, intervention 12 mo % male: control 3%, intervention 10% Age: mean control 40.9 (SD 8.5), intervention 40.8 (SD 8.9) Baseline BMI: mean control 28.4 (SD 6.76), intervention 29.3 (SD 7.42)
Interventions	Low fat vs usual diet Control: usual diet Intervention: total fat 10%E, protein 14%E, carbohydrate 76%, focus on starchy plant foods while meat, fish, eggs, dairy foods, vegetable oil are prohibited Control methods: no dietary training; told to follow their usual diet; offered dietary training at end of study period (waiting-list control) Intervention methods: 10 days residential diet training initially, then monthly FFQ and phone contact, plus additional counselling by dietitians in clinic or by phone. Secure online discussion board and personal meetings between participants to discuss diet Weight goals: none mentioned Total fat intake (at 1 year): low fat 14.4 (SD 6.1), control 39 (SD 6) %E Saturated fat intake: unclear Style: diet advice

Yadav 2016 *(Continued)*

	Setting: community
Outcomes	Stated trial outcomes: MS lesion formation (primary), clinical outcomes such as relapse rate, disability progression, fatigue, depression, quality of life, inflammation, safety, tolerability (secondary) Available outcomes: BMI and weight change, lipids (reported)
Notes	Weight and BMI change data reported but without SDs Funding: McDouglal Research and Education Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by medication use with random blocks of 2 and 4, generated using the Excel random number generator function
Allocation concealment (selection bias)	Unclear risk	Unclear; not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants, neurologists, study coordinators and the dietitian knew the group assignments.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear for weight as, although assessing neurologists were blinded, it was not clear whether they took weight measurements.
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% lost over 12 months, though reasons provided for half
Selective reporting (reporting bias)	Low risk	No, all represented
Other bias	Low risk	None noted
Free of systematic difference in care?	High risk	A residential programme, plus lots of support and counselling provided to intervention participants, not to control participants
Free of dietary differences other than fat?	High risk	The focus was on plant-based carbohydrates and participants in intervention group told to omit meat, fish, dairy foods, and vegetable oils so protein and fibre will have been changed.
Compliance problems	Low risk	Dietary fat intake was significantly different between arms.

%E: percentage of total energy intake
AHA: American Heart Association
AusMed: AUStralian MEDiterranean diet trial for secondary prevention of heart disease
BDIT: Breast Dysplasia Intervention Trial
BMI: body mass index
BP: blood pressure
BRIDGES: Breast Research Initiative for Determining Effective Strategies for Coping with Breast Cancer
CHD: coronary heart disease
CHO: carbohydrates
CI: confidence interval
CORDIOPREV: CORonary Diet Intervention with Olive oil and cardiovascular PREVention study

CVD: cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
DBCP: Diet and Breast Cancer Prevention
DEER: Diet and Exercise for Elevated Risk
FFQ: food frequency questionnaire
GI: glycaemic index
HDL: high-density lipoprotein
HGI: High glycaemic index
HM: high monounsaturated fat
IHD: ischaemic heart disease
ITT: intention to treat
LDL: low-density lipoprotein
LF: low fat
LGI: low glycaemic index
MeDiet: Mediterranean Diet
MI: myocardial infarction
MS: multiple sclerosis
MUFA: monounsaturated fatty acid
NCEP: National Cholesterol Education Program
NDHS: National Diet Health Study
NEP: Nutrition Education Program
NDHS: National Diet-Heart Study
ODMDC: Optimal Dietary Macronutrient Distribution in China
P/S: polyunsaturated/saturated fat ratio
PUFA: polyunsaturated fatty acid
QoL: quality of life
RCT: randomised controlled trial
RISCK: Reading, Imperial, Surrey, Cambridge, and Kings Study
SD: standard deviation
SE: standard error
SF36: 36-item Short Form Survey (a quality of life assessment)
SFA: saturated fatty acid
TG: triglycerides
vs: versus
WHEL: Women's Healthy Eating and Living
WHI: Women's Health Initiative
WHT: Women's Health Trial
WHTFSMP: Woment's Health Trial, Feasibility Study in Minority Populations
WINS: Women's Intervention Nutrition Study

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agewall 2001	Multifactorial intervention
Ammerman 2003	No appropriate control group (and not low fat vs modified fat)
Aquilani 2000	No appropriate control group (and not low fat vs modified fat)
Arne 2014	Intervention aimed at weight management
Arntzenius 1985	No appropriate control group (and not low fat vs modified fat)
ASSIST 2001	Intervention was not dietary fat modification or low fat diet
Bakx 1997	Multifactorial intervention
Ball 1965	Those who were overweight were encouraged to reduce their weight

Study	Reason for exclusion
Barnard 2009	Weight reduction encouraged in the conventional diet, but not in the vegan diet arm
Barndt 1977	No appropriate control group (and not low fat vs modified fat)
Baron 1990	Multifactorial intervention
Bazzano 2012	Participants selected on basis of BMI (30 to 45)
Beckmann 1995	Intervention was not dietary fat modification or low fat diet
Bierenbaum 1963	No appropriate control group (and not low fat vs modified fat)
Bloomgarden 1987	Multifactorial intervention
Bonnema 1995	No appropriate control group (and not low fat vs modified fat)
Brehm 2009	Participants recruited on basis of being overweight or obese
Brensike 1982	No appropriate control group (and not low fat vs modified fat)
Broekmans 2003	Intervention was not dietary fat modification or low fat diet
Brown 1984	No appropriate control group (and not low fat vs modified fat)
Bruce 1994	No appropriate control group (and not low fat vs modified fat)
Bruno 1983	Multifactorial intervention
Byers 1995	No appropriate control group (and not low fat vs modified fat)
Caggiula 1996	No appropriate control group (and not low fat vs modified fat)
CARMEN 2000	Participants recruited on basis of BMI (26 to 34)
CCD 2008	Dietary advice to support weight loss provided to all those wanting to lose weight.
Clark 1997	Multifactorial intervention
Cocinar para su salud 2016	Total fat goals unclear, but total fat was < 30%E at baseline and decreased further in both groups
Cohen 1991	Intervention was not dietary fat modification or low fat diet
Coppell 2010	Weight loss recommended
Cox 1996	Multifactorial intervention
Croft 1986	Intervention was not dietary fat modification or low fat diet
Da Qing IGT 1997	Intervention was not dietary fat modification or low fat diet
Dalgard 2001	No appropriate control group (and not low fat vs modified fat)
DAS 1989	No appropriate control group (and not low fat vs modified fat)
Davey Smith 2005	Multifactorial intervention

Study	Reason for exclusion
DeBusk 1994	Multifactorial intervention
Delahanty 2001	No appropriate control group (and not low fat vs modified fat)
Delius 1969	Intervention was not dietary fat modification or low fat diet
Dengel 1995	No appropriate control group (and not low fat vs modified fat)
Diabetes CCT 1995	Intervention was not dietary fat modification or low fat diet
DIET 1998	Multifactorial intervention
DIRECT 2009	Weight reduction aim
DO IT 2006	"Overweight subjects were encouraged to adopt a calorie-restricted diet"
Dobs 1991	No appropriate control group (and not low fat vs modified fat)
Drummond 1998	Both groups taught to reduce fat
Duffield 1982	Multifactorial intervention
Eckard 2013	Energy restricted diet
Elder 2000	No appropriate control group (and not low fat vs modified fat)
Entwistle 2018	Post-transplant patients
Esposito 2003	No appropriate control group (and not low fat vs modified fat)
Esposito 2004	No appropriate control group (both groups aimed at < 30%E from fat)
Esposito 2014	Energy restricted diet
EUROACTION 2008	Multifactorial intervention
FARIS 1997	Multifactorial intervention
Fasting HGS 1997	No appropriate control group (and not low fat vs modified fat)
Ferrara 2000	No appropriate control group (and not low fat vs modified fat)
Finnish Diabetes 2000	Multifactorial intervention
Fleming 2002	No appropriate control group (and not low fat vs modified fat)
Fortmann 1988	Intervention was not dietary fat modification or low fat diet
Foster 2003	Weight reduction in one arm but not the other
Friedman 2012	Weight loss diets
Gaullier 2007	No appropriate control group (and not low fat vs modified fat)
German Fat Reduced	Participants recruited on basis of their BMI (24 to 29)

Study	Reason for exclusion
Glatzel 1966	No appropriate control group (and not low fat vs modified fat)
Goodpaster 1999	No appropriate control group (and not low fat vs modified fat)
Gower 2012	Participants recruited on basis of high BMI
Greenlee 2016	Both groups had < 30% E from fat at baseline
Gregg 2013	Participants recruited on basis of high BMI
Gudlaugsson 2013	Multifactorial intervention
Guelinckx 2010	Participants recruited on basis of high BMI
Guldbrand 2012	Weight loss intended
Hardcastle 2008	Multifactorial intervention
Hartman 1993	No appropriate control group (and not low fat vs modified fat)
Hartwell 1986	No appropriate control group (and not low fat vs modified fat)
Haynes 1984	Intervention was not dietary fat modification or low fat diet
Hellenius 1993	The study aimed for weight loss in one arm and not in the comparison arm
Hildreth 1951	No appropriate control group (and not low fat vs modified fat)
HIPERCOL 2018	No appropriate intervention (classic guidelines plus added educational support vs classic guidelines)
Hutchison 1983	No appropriate control group (and not low fat vs modified fat)
Hyman 1998	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
IMPACT 1995A	Multifactorial intervention
Iso 1991	No appropriate control group (and not low fat vs modified fat)
Ives 1993	Multifactorial intervention
Jalkanen 1991	Multifactorial intervention
Janus 2012	Weight loss intended
Jonasson 2014	Energy restricted diet
Juanola-Falgarona 2014	Energy restricted diet
Jula 1990	Multifactorial intervention
Karvetti 1992	Multifactorial intervention
Kastarinen 2002	Multifactorial intervention

Study	Reason for exclusion
Kattelmann 2010	Weight loss intended
Katzel 1995	Intervention was not dietary fat modification or low fat diet
Kempner 1948	No appropriate control group (and not low fat vs modified fat)
Klemsdal 2010	Participants recruited on basis of high BMI
Korhonen 2003	Multifactorial intervention
Kristal 1997	Multifactorial intervention
Kromhout 1987	No appropriate control group (and not low fat vs modified fat)
Kummel 2008	Intervention was not dietary fat modification or low fat diet
Laitinen 1993	Multifactorial intervention
Laitinen 1994	Multifactorial intervention
Larsen 2011	Energy restricted diet
Leduc 1994	Multifactorial intervention
Leibbrandt 2010	Participants recruited on basis of high BMI
Lewis 1985	Multifactorial intervention
LIILAC 2015	Both arms had > 30% E from fat
Lipid Res Clinic 1984	No appropriate control group (and not low fat vs modified fat)
Luoto 2012	No assessment of total fat intake
Luszczynska 2007	No appropriate control group (and not low fat vs modified fat)
Lyon Diet Heart 1994	Intervention was not dietary fat modification or low fat diet
Mansel 1990	Intervention was not dietary fat modification or low fat diet
MARGARIN	No appropriate control group (and not low fat vs modified fat)
Martin 2011	Participants recruited on basis of high BMI
Maruthur 2014	No relevant outcomes available
Mayneris-Perxachs 2014	No assessment of total fat intake
McCarron 2001	Intervention was not dietary fat modification or low fat diet
McManus 2001	Aimed at weight loss
Medi-RIVAGE 2004	Weight reduction for some low fat diet participants (those with BMI > 25) but not in Mediterranean group

Study	Reason for exclusion
Merrill 2011	Multifactorial intervention
Michalsen 2006	Diet plus stress management vs no intervention
Millar 1973	No appropriate control group (and not low fat vs modified fat)
Milne 1994	No appropriate control group (and not low fat vs modified fat) - the high CHO diet was neither 'usual' or 'low fat' to compare with the modified fat diet
Minnesota HHP 1990	No appropriate control group (and not low fat vs modified fat)
MUFObes low fat 2007	Trial aimed to assess weight maintenance following major weight loss
MUFObes low vs mod 2007	Trial aimed to assess weight maintenance following major weight loss
Mujeres Felices 2003	Diet and breast self examination vs no intervention
Munsters 2010	Weight loss intended
Murillo-Ortiz 2017	Both groups aimed at low fat intake
Naglak 2000	Dietary fat intervention unclear
NCT02353416	Intervention aim > 30% fat, control aim close to 30% fat (as per Italian guidelines)
NCT02368405	Fat goals unclear
NCT02396264	Calories adjusted to maintain weight
Neil 1995	No appropriate control group (and not low fat vs modified fat)
Neverov 1997	Multifactorial intervention
Next Step 1995	Neither mortality nor cardiovascular morbidity data available (only decided after contact with at least one author)
Norway Veg Oil 1968	No appropriate control group (and not low fat vs modified fat)
Novotny 2012	Weight loss intended
Nutri-EPA 2017	Intervention aim > 30% fat, control aim close to 30% fat (as per Italian guidelines)
Nutrition Ed Study 1980	Those who were overweight were provided with a weight reduction booklet
ODES 2006	The study aimed for weight loss in some participants
Oldroyd 2001	Multifactorial intervention
Orazio 2011	Weight loss intended
ORIGIN 2008	Intervention was not dietary fat modification or low fat diet
Ornish 1990	Multifactorial intervention (diet, smoking, stress and exercise) compared to no intervention
Oslo Study 1980	Multifactorial intervention

Study	Reason for exclusion
Otago Weight Loss 2005	Although intake was ad libitum, the aim was for weight loss to occur - participants presumably joined the study on the basis that it was assessing effects on weight loss, so were keen to lose weight
Pascale 1995	Multifactorial intervention
Paz-Tal 2013	No relevant outcomes available
PEP 2001	Multifactorial intervention
PHYLLIS 1993	No appropriate control group (and not low fat vs modified fat)
Portfolio 5	No dietary fat aims in the low-fat arm (aimed for < 7%E SFA and < 200mg/d cholesterol), nor in the portfolio arms (aimed for < 7%E SFA and < 200mg/d cholesterol and also introduced portfolio foods such as sterol margarine, soy, nuts, and viscous fibre)
PREDIMED 2006	Modified fat group was clearly defined, but no fat goals were set for the low fat group. We were unable to verify whether the fat aim was ≤ 30%E
PREMIER 2003	Overweight participants were encouraged to lose weight
Pritchard 2002	The study aimed for weight loss in one arm and not in the comparison arm
Reid 2002	No appropriate control group (and not low fat vs modified fat)
Roderick 1997	Weight reducing advice provided
Roman CHD prev 1986	Multifactorial intervention
Rose 1987	No appropriate control group (and not low fat vs modified fat)
Rusu 2013	Energy restricted diet
Sacks 2009	All arms aimed at a 750 kcal/day deficit to ensure weight loss
Salas-Salvado 2014	No assessment of total fat intake
Schectman 1996	Multifactorial intervention
Schlierf 1995	Multifactorial intervention
Singh 1991	Multifactorial intervention
Singh 1992	No appropriate control group (and not low fat vs modified fat)
Siqueira-Catania 2010	Weight loss intended
SLIM 2008	Multifactorial intervention
Sondergaard 2003	Unlikely that either arm was aiming at less than 30%E from fat (Mediterranean vs usual diet)
Sopotsinskaia 1992	The study aimed for weight loss in one arm and not in the comparison arm
Stanford Weight	The study aimed for weight loss in one arm and not in the comparison arm

Study	Reason for exclusion
Steinbach 1996	Multifactorial intervention
Steptoe 2001	No appropriate control group (and not low fat vs modified fat)
Stevens 2002	Diet plus breast self examination vs no intervention
Stevenson 1988	No appropriate control group (and not low fat vs modified fat)
Sweeney 2004	Intervention was not dietary fat modification or low fat diet
TAIM 1989	Intervention was not dietary fat modification or low fat diet
THIS DIET 2008	Study stated "although this was not a weight loss intervention, participants who were overweight or obese were encouraged to reduce calories to facilitate weight loss".
TOHP I 1992	Multifactorial intervention
TONE 1997	Intervention was not dietary fat modification or low fat diet
Toobert 2003	Multifactorial intervention
Toronto Polyp Prev 1994	No weight or BMI data presented
Tromso Heart 1989	Multifactorial intervention
Troyer 2010	Diet advice the same in both aims for intervention and control
Turku Weight	Both intervention groups aimed to lose weight, while the control group did not
UK PDS 1996	No appropriate control group (and not low fat vs modified fat)
Urbach 1952	No appropriate control group (and not low fat vs modified fat)
Uusitupa 1993	Multifactorial intervention
Wassertheil 1985	Intervention was not dietary fat modification or low fat diet
Weintraub 1992	No appropriate control group (and not low fat vs modified fat)
Westman 2006	Intervention was not dietary fat modification or low fat diet
WHO primary prev 1979	Multifactorial intervention
Williams 1990	Intervention was not dietary fat modification or low fat diet
Williams 1992	Intervention was not dietary fat modification or low fat diet
Williams 1994	Intervention was not dietary fat modification or low fat diet
Wilmot 1952	No appropriate control group (and not low fat vs modified fat)
Wing 1998	No appropriate control group (and not low fat vs modified fat)
Wolever 2008	Weight loss intended in some participants

Study	Reason for exclusion
WOMAN 2007	Lifestyle intervention included exercise and weight as well as diet
Wood 1988	Intervention was not dietary fat modification or low fat diet
Woollard 2003	Multifactorial intervention including smoking, weight, exercise and alcohol components
Working Well 1996	Multifactorial intervention
Young 2010	Weight loss intended

BMI: body mass index
RCT: randomised controlled trial
vs: versus

Characteristics of studies awaiting classification *[ordered by study ID]*

Casas-Agustench 2013

Methods	RCT
Participants	Volunteers aged 25 to 65 years (Spain) CVD risk: moderate (presumed to be at moderate risk for developing CVD based on medical history, physical examination and assessing risk of CVD by interview) Control: NR Intervention: NR Mean years in trial: 1.0 % male: 135 men and 26 women (total 161) Age: between 25 and 65 years Baseline BMI: not reported
Interventions	Skimmed (S; 0.3% fat) vs semi-skimmed (SS; 1.9% fat) milk Control aims: 500 mL semi-skimmed milk/d Intervention aims: 500 mL skimmed milk/d Control methods: 500 mL/d of semi-skimmed (SS) (1.9% fat), [232.5 kcal energy, 9.5 g fat, 6.69 g SFAs, 2.58 g MUFAs, 0.21 PUFAs, 15.5 g protein, 23.5 g carbohydrates] in addition to their usual diet. Intervention methods: 500 mL/d of skimmed (S) milk (0.3% fat), [175 kcal energy, 1.5 g fat, 1.05 g SFAs, 0.40 g MUFAs, 0.03 PUFAs, 16.00 g protein, 24 g carbohydrates] in addition to their usual diet. Weight goals: NR Total fat intake (at 1 year): NR Saturated fat intake (at 1 year): NR Style: NR Setting: community
Outcomes	Stated trial outcomes: CVD risk biomarker Available outcomes: BMI, total, LDL and HDL cholesterol, total cholesterol, triglyceride, SBP, DBP
Date trial is due to complete	Not reported; no trials registry entry located

Casas-Agustench 2013 *(Continued)*

Notes	Awaiting assessment because: the aims in reducing total fat intake (to < 30%E or not) were unclear

DIPI

Methods	RCT
Participants	Adult Danish population with a minimum of one self-reported risk factor for Ischaemic heart disease (IHD) (Denmark), CVD risk: medium Control: NR Intervention: NR Mean years in trial: 1.0 % male: overall 41% male Age: overall median age of 51 years Baseline BMI: 73% were overweight or obese
Interventions	Unclear Targeted substitution dietary guidelines or the Danish official dietary guidelines vs habitual diet Control aims: habitual diet Intervention aims: either targeted substitution dietary guidelines or the Danish official dietary guidelines Control methods: NR Intervention methods: NR Weight goals: NR Total fat intake (at one year): NR Saturated fat intake (at one year): NR Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: dietary intake, blood lipids, glycaemic biomarkers, blood pressure, heart rate, anthropometric measurements Available outcomes: None
Date trial is due to complete	
Notes	Awating assessment as exact fat goals were unclear. Control group advised to follow their habitual diet with one of two intervention groups receiving either targeted substitution dietary guidelines or the Danish official dietary guidelines

ICFAMED

Methods	A Mediterranean diet for preventing heart failure and atrial fibrillation in hypertensive patients (ICFAMED) RCT, 24 months
Participants	People with hypertension aged 55 to 75 years at high cardiovascular risk, but without existing CVD
Interventions	MedDiet: Mediterranean-style diet, dietary advice (individual and group) every three months LFD: Low-fat diet according to American Heart Association guidelines, dietary advice (individual and group) every three months
Outcomes	Primary: heart failure and/or atrial fibrillation Secondary: echocardiographic variables & BP variables Actual outcomes from abstracts: MedDiet: 5 CVD events (atrial fibrillation (AF) 2; ischaemic heart disease (IHD) 2; stroke 1), LFD: 11 CVD events (AF 6, IHD 2, stroke 3). The crude rate for the occurrence of events per 1000 patient-months of follow-up was 197 (95% CI: 06 to 46) for MedDiet, 451 (95% CI: 3 to 8.1) for LFD. The HR for patients with MedDiet compared to LFD was 0.44 (95% CI: 0,15 to 1,26, P > 005).
Date trial is due to complete	Enrollment began in 2012; appeared to have completed in 2017; abstract and poster publications only to date
Notes	Trials registration: ISRCTN27497769 Awaiting assessment because: Unclear whether one arm was higher in saturated fat than the other; awaiting fuller publication to assess

MEDINA

Methods	RCT
Participants	Ninety-four eligible patients who have non-alcoholic fatty liver disease and who are insulin resistant (Australia) Control: 47 to be randomised to control group Intervention: 47 to be randomised to intervention Mean years in trial: 2.0 % male: NR Age: 18 years and older eligible Baseline BMI: between 20 and 39.9 kg/m^2 eligible
Interventions	Mediterranean diet versus a Low Fat Diet (LFD) Control aims: MedDiet Intervention aims: Low fat diet (LFD) Control methods: diet rich in plant based foods including vegetables, whole grains and fruit with the main added fat being extra virgin olive oil. It emphasises increased legumes and raw unsalted nut intake and oily fish. Moderate amounts of fermented dairy and poultry with small amounts of red meat and homemade sweets. Comprised of 44% fat (> 50% monounsaturated), 36% carbohydrate and 17–20% protein and up to 5% alcohol

MEDINA *(Continued)*

	Intervention methods: the Australian Guide to Healthy Eating with an emphasis on portions, low fat options and cooking methods The LFD group will follow the same structure as the MedDiet arm with three face-to-face consultations at baseline, 6 weeks (mid-intervention) and 12 weeks (end of intervention). There will also be the same number of phone call follow-ups at weeks 2, 4 and 9. Participants will be given a supermarket gift voucher to purchase some of the suggested food items. Breakfast is also provided on the day of all face-to-face appointments (Jalna © and Carmen's ©). Weight goals: NR Total fat intake (6 months): NR Saturated fat intake (6 months): NR Style: dietary advice and supermarket gift voucher (for low fat diet group) Setting: community
Outcomes	Stated trial outcomes: Weight, height, waist circumference, hip circumference, neck girth and blood pressure, dietary intake, intrahepatic lipid, plasma fatty acids and urinary metabolites
Date trial is due to complete	Trial started March 2015, final enrolment expected Apr 2017, completion expected Apr 2018
Notes	Awaiting assessment because: Meddiet is 44% fat (> 50 % monounsaturated), 36% carbohydrate and 17–20% protein and up to 5% alcohol; composition of LFD unclear No results publications located

Mottalib 2018

Methods	RCT
Participants	72 participants with uncontrolled T2D (USA) CVD risk: NR Control: NR Intervention: NR Mean years in trial: 0.5 % male: 44% overall Age: mean age overall 59 ± 8 years Baseline BMI: NR
Interventions	Low fat dairy vs full fat dairy or non-fat dairy Control aims: ≥ 3 daily servings of full fat dairy or ≥ 3 daily servings of non-fat dairy Intervention aims: ≥ 3 daily servings of low fat dairy Control methods: dietary advice Intervention methods: dietary advice Weight goals: maintain daily caloric intake and body weight Total fat intake (6 months): NR

Mottalib 2018 *(Continued)*

	Saturated fat intake (6 months): sat fat % calories increased by 3.7 ± 0.8% in full fat group (control) and decreased by 4.4 ± 1.7% in group low fat group (intervention) Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: HbA1c, lipid profile and blood pressure Available outcomes: None yet
Date trial is due to complete	
Notes	Awaiting assessment as: fat goals of the two arms are unclear (full fat and low/non-fat dairy). Characteristics taken from a conference poster

Soul Food Light

Methods	RCT
Participants	African-American adults with Type 2 diabetes, 18 years and above (USA) CVD risk: low Control: 48 randomised, 27 retained Intervention: 49 randomised, 38 retained Mean years in trial: 0.5 % male: control 25%, intervention 22% (total 97) Age: mean control 55.7 (12.1), range 32-86, intervention 58.9 (10.1), range 40-77 Baseline BMI: mean control 34 (8.3), range 18-57; intervention 35.39 (8.1), range 23-55
Interventions	Educational classes (including peer professional groups & supportive family relationships) vs control (diabetes class) Low fat diet vs usual care Control aims: usual care Intervention aims: low fat diet Control methods: referral to a local 8-hour traditional diabetes class Intervention methods: educational classes in low fat dietary strategies, peer professional group discussions, and follow-up by a nurse case manager Weight goals: NR Total fat intake (at 6 months): NR Saturated fat intake (at 6 months): NR Style: diet advice Setting: community
Outcomes	Stated trial outcomes: (HbA1C, lipids, BMI) and dietary behaviours Available outcomes: change in weight, BMI, dietary behaviours, cholesterol and HbA1C

Soul Food Light *(Continued)*

Date trial is due to complete	NR
Notes	Awaiting assessment because: fat goals in both arms are unclear

AF: atrial fibrillation
BMI: body mass index
BP: blood pressure
CVD: cardiovascular disease
DBP: diastolic blood pressure
HbA1c: Haemoglobin A1C
HDL: high density lipoprotein
ICFAMED: A Mediterranean diet for preventing heart failure and atrial fibrillation in hypertensive patients
IHD: ischaemic heart disease
LDL: low density lipoprotein
LFD: low fat diet
MedDiet: Mediterranean-style diet
MUFA: monounsaturated fatty acids
NR: not reported
PUFA: polyunsaturated fatty acid
RCT: randomised controlled trial
S: skimmed
SBP: systolic blood pressure
SFA: saturated fatty acid
SS: semi-skimmed
T2D: type 2 diabetes

Characteristics of ongoing studies *[ordered by study ID]*

NCT02481466 due 2020

Study name	PortfolioEx
Methods	RCT
Participants	200 participants estimated, 21 years and older, BMI less or equal to 40 kg/m^2, measurable arterial thickening (>/= 1.2 mm) at screening, with at least one of (type 2 diabetes, non-diabetic on statin, hypercholesterolaemic and treated with statins or have been prescribed statins but are not taking it because they are either unable (intolerant) or unwilling to take statin drugs, raised blood pressure, > 140/90 (untreated) (Canada) CVD risk: high Control: NR Intervention: NR Mean years in trial: 3.0 % male: NR Age: 21 years and older eligible Baseline BMI: BMI less or equal to 40 kg/m^2
Interventions	Portfolio diet and structured exercise vs DASH-like diet and structured exercise Control aims: DASH-like diet and structured exercise Intervention aims: Portfolio diet and structured exercise

NCT02481466 due 2020 *(Continued)*

	Control methods: advice to follow a DASH-like diet of whole grains, and low fat dairy products with fruits and vegetables and be instructed on the Laval exercise programme—a standardised physical activity/exercise component supervised by trained kinesiologists (exercise physiologists). Intervention methods: participants will receive advice on a therapeutic diet appropriate for hypercholesterolaemia (i.e. < 7% of energy from saturated fat, < 200 mg/d cholesterol) PLUS the combination of viscous fibres, soy protein, plant sterols and nuts, 5% extra monounsaturated fat, and selection of low glycaemic index foods and be instructed on a standardised physical activity/exercise component supervised by kinesiologists Weight goals: NR Total fat intake (1 and 3 years): NR Saturated fat intake (1 and 3 years): NR Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: maximum vessel wall volume of the carotid arteries, coronary atheroma in the large vessels, lipid rich necrotic core, intra-plaque haemorrhage, blood pressure and pulse rate, serum lipids, blood pressure, diet history, quality of life, etc. Available outcomes: none yet
Starting date	Nov 2016, estimated primary completion date Dec 2020, estimated study completion date Dec 2022
Contact information	
Notes	Information based on trial register

NCT02938832 due 2023

Study name	Cardiodiet
Methods	RCT
Participants	Patients treated for ischaemic heart disease who are followed up at the cardiac rehabilitation units (Sweden) CVD risk: high Control: NR Intervention: NR Mean years in trial: 3.0 % male: NR Age: 18 years and older eligible Baseline BMI: NR
Interventions	Traditional low fat diet vs Mediterranean diet Control aims: Mediterranean diet with an energy content (E%) from carbohydrates between 25-30% Intervention aims: traditional low fat diet with 45-60E% from carbohydrates

NCT02938832 due 2023 *(Continued)*

	Control methods: Advice on a Mediterranean dietary regimen with reduced carbohydrates Intervention methods: Advice on traditional low fat diet by dietitian Weight goals: NR Total fat intake (3 years): NR Saturated fat intake (3 years): NR Style: dietary advice Setting: community
Outcomes	Stated trial outcomes: Hba1c > 48 mmol/mol, CVD incidence, blood lipid levels and quality of life Available outcomes: None yet
Starting date	Oct 2016, estimated primary completion date Oct 2021, estimated study completion date Oct 2023
Contact information	
Notes	Information obtained from trial register

NCT03068078 due 2020

Study name	ReDuCtion
Methods	RCT
Participants	Adult Danish population with established type 2 diabetes for more than six months and less than five years and HbA1c in compliance with T2D (above 48 mmol/mol), but without need for adjustment of antidiabetic treatment (Denmark) CVD risk: medium Control: 45 to be randomised to control group Intervention: 90 to be randomised to intervention Mean years in trial: 0.5 % male: NR Age: 18 years and older eligible Baseline BMI: NR
Interventions	Low carbohydrate diet, high in monounsaturated fats (LCD) vs regular diabetes diet (RDD) Control aims: regular diabetes diet (RDD) Intervention aims: Low carbohydrate diet, high in monounsaturated fats (LCD) Control methods: NR Intervention methods: NR Weight goals: NR Total fat intake (6 months): NR Saturated fat intake (6 months): NR

NCT03068078 due 2020 *(Continued)*	
	Style: NR Setting: community
Outcomes	Stated trial outcomes: Measured by HbA1c, serum cholesterol, blood glucose and metabolic markers, NAFLD activity score, quality of life, gut dysbiosis and diet compliance Available outcomes: None yet
Starting date	Nov 2016, due to complete Dec 2019
Contact information	
Notes	Information based on trial register

BMI: body mass index
CVD: cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
HbA1c: Haemoglobin A1C
LCD: Low carbohydrate diet
NAFLD: non-alcoholic fatty liver disease
NR: not reported
RCT: randomised controlled trial
RDD: regular diabetic diet
T2D: type 2 diabetes

DATA AND ANALYSES

Comparison 1. Lower fat vs higher fat diet

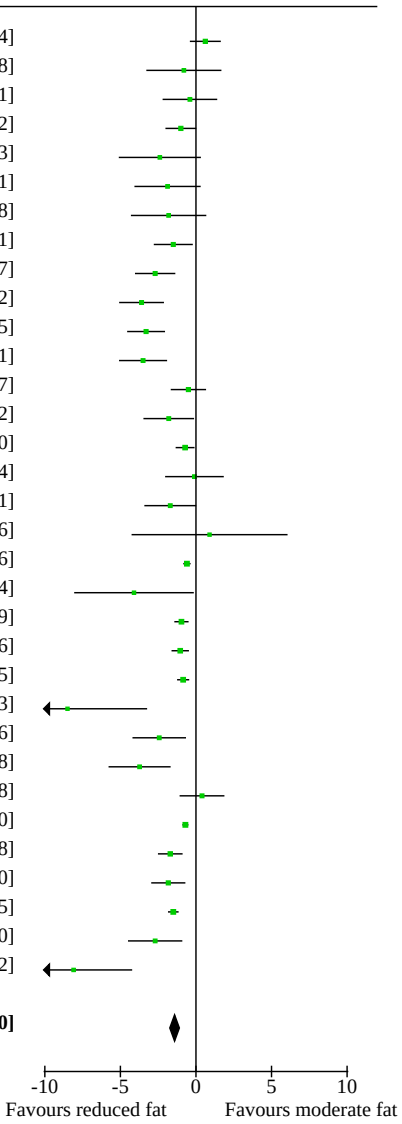
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Weight, kg	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
1.2 BMI, kg/m^2	14	46539	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.64, -0.30]
1.3 Waist circumference, cm	3	16620	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.73, -0.22]
1.4 Body fat, %	2	2350	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.57, 0.00]
1.5 Total cholesterol, mmol/L	22	9812	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.32, -0.14]
1.6 LDL cholesterol, mmol/L	19	8137	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.05]
1.7 HDL cholesterol, mmol/L	20	8268	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.03, 0.00]
1.8 Triglycerides, mmol/L	18	8672	Mean Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.07]
1.9 Total cholesterol/HDL	5	3639	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.14, 0.04]
1.10 Systolic blood pressure, mmHg	10	6078	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.42, -0.07]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.11 Diastolic blood pressure, mmHg	10	6077	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.95, -0.09]
1.12 Quality of life	1	40130	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.07]

Analysis 1.1. Comparison 1: Lower fat vs higher fat diet, Outcome 1: Weight, kg

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (4)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (5)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (6)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (7)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
De Bont 1981 (8)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (9)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (10)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (11)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**

Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%
Test for overall effect: Z = 8.78 (P < 0.00001)
Test for subgroup differences: Not applicable



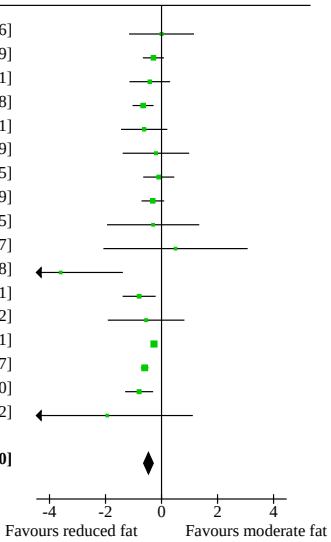
Footnotes

(1) Non-preDM, change to 5 years
(2) preDM by HbA1c, change to 5 years
(3) preDM by IFT/IGT, change to 5 years
(4) Women with exercise
(5) Men with exercise
(6) Men, no exercise
(7) Women, no exercise
(8) non-obese participants (BMI < 28)
(9) obese participants (BMI 28+)
(10) Low GI arms, Calculated from % change based on median baseline
(11) High GI arms; Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 1.2. Comparison 1: Lower fat vs higher fat diet, Outcome 2: BMI, kg/m^2

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BDIT Pilot Studies 1996	24.3	3.8	76	24.3	3.6	81	2.0%	0.00 [-1.16 , 1.16]
CORDIOPREV 2016 (1)	-0.64	1.9	156	-0.35	1.5	166	10.0%	-0.29 [-0.67 , 0.09]
CORDIOPREV 2016 (2)	-0.61	1.74	57	-0.19	2.09	52	4.3%	-0.42 [-1.15 , 0.31]
CORDIOPREV 2016 (3)	-0.51	0.82	47	0.15	1.15	59	10.0%	-0.66 [-1.04 , -0.28]
CORDIOPREV 2016 (4)	-0.33	1.19	55	0.29	2.76	50	3.5%	-0.62 [-1.45 , 0.21]
Diet and Hormone Study 2003	23.5	4.4	81	23.7	3.5	96	1.9%	-0.20 [-1.39 , 0.99]
Ma 2016	-0.5	1.3565	46	-0.4	1.3266	44	6.4%	-0.10 [-0.65 , 0.45]
Moy 2001	-0.1	1	117	0.21	2	118	9.3%	-0.31 [-0.71 , 0.09]
Sarkkinen Low & Mod 1993	26	4	41	26.3	3.6	41	1.0%	-0.30 [-1.95 , 1.35]
Sarkkinen Low Fat 1993	26.2	3.2	40	25.7	4.2	12	0.4%	0.50 [-2.07 , 3.07]
Simon 1997	23.8	4.7	34	27.4	4.9	38	0.6%	-3.60 [-5.82 , -1.38]
Strychar 2009	-0.24	1	15	0.56	0.6	15	5.9%	-0.80 [-1.39 , -0.21]
WHEL 2007 (5)	0.71	1.96	21	1.26	3.02	30	1.5%	-0.55 [-1.92 , 0.82]
WHI 2006 (6)	0.03	3.2	16230	0.3	3.1	24943	18.6%	-0.27 [-0.33 , -0.21]
WHTFSMP 2003	-0.7	1.2	1094	-0.1	1.4	646	17.2%	-0.60 [-0.73 , -0.47]
WINS 1993	26.8	5.608	755	27.6	5.368	1230	7.3%	-0.80 [-1.30 , -0.30]
Yadav 2016	-2.16	6.1	26	-0.22	5.2	27	0.3%	-1.94 [-5.00 , 1.12]
Total (95% CI)			**18891**			**27648**	**100.0%**	**-0.47 [-0.64 , -0.30]**

Heterogeneity: Tau² = 0.04; Chi² = 40.18, df = 16 (P = 0.0007); I² = 60%
Test for overall effect: Z = 5.34 (P < 0.00001)
Test for subgroup differences: Not applicable

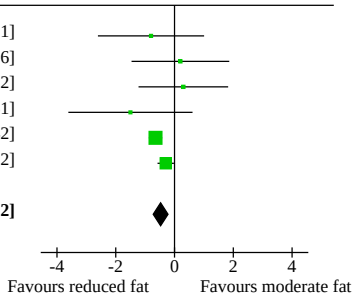


Footnotes
(1) No insulin resistance, change to 2 years (SDs assumed to be SEs)
(2) Liver insulin resistance, change to 2 years (SDs assumed to be SEs)
(3) Muscle insulin resistance, change to 2 years (SDs assumed to be SEs)
(4) Muscle & liver insulin resistance, change to 2 years (SDs assumed to be SEs)
(5) Change in BMI in a subgroup of participants at 4 years
(6) Change from baseline to 7.5 years

Analysis 1.3. Comparison 1: Lower fat vs higher fat diet, Outcome 3: Waist circumference, cm

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CORDIOPREV 2016 (1)	-2.2	8.74	156	-1.4	7.73	166	1.9%	-0.80 [-2.61 , 1.01]
CORDIOPREV 2016 (2)	-1.5	4.11	47	-1.7	4.61	59	2.2%	0.20 [-1.46 , 1.86]
CORDIOPREV 2016 (3)	-1.9	4.15	57	-2.2	3.97	52	2.6%	0.30 [-1.22 , 1.82]
CORDIOPREV 2016 (4)	-0.9	4.82	55	0.6	6.08	50	1.4%	-1.50 [-3.61 , 0.61]
ODMDC 2017	-1.1	1.0131	101	-0.4529	0.8116	206	50.2%	-0.65 [-0.87 , -0.42]
WHI 2006 (5)	1.6	8.6	6154	1.9	8.8	9517	41.6%	-0.30 [-0.58 , -0.02]
Total (95% CI)			**6570**			**10050**	**100.0%**	**-0.47 [-0.73 , -0.22]**

Heterogeneity: Tau² = 0.02; Chi² = 6.31, df = 5 (P = 0.28); I² = 21%
Test for overall effect: Z = 3.69 (P = 0.0002)
Test for subgroup differences: Not applicable

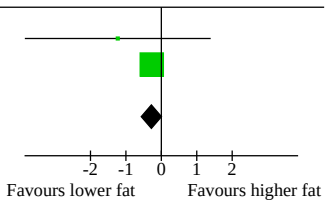


Footnotes
(1) No insulin resistance, change to 2 years (SDs assumed to be SEs)
(2) Muscle insulin resistance, change to 2 years (SDs assumed to be SEs)
(3) Liver insulin resistance, change to 2 years (SDs assumed to be SEs)
(4) Liver & muscle insulin resistance, change to 2 years (SDs assumed to be SEs)
(5) Change from baseline to 7.5 years

Analysis 1.4. Comparison 1: Lower fat vs higher fat diet, Outcome 4: Body fat, %

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
WHEL 2007 (1)	1.04	4.99	21	2.27	4.19	29	1.2%	-1.23 [-3.85 , 1.39]
WHI 2006 (2)	0.4	3.46	905	0.67	3.38	1395	98.8%	-0.27 [-0.56 , 0.02]
Total (95% CI)			**926**			**1424**	**100.0%**	**-0.28 [-0.57 , 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Not applicable

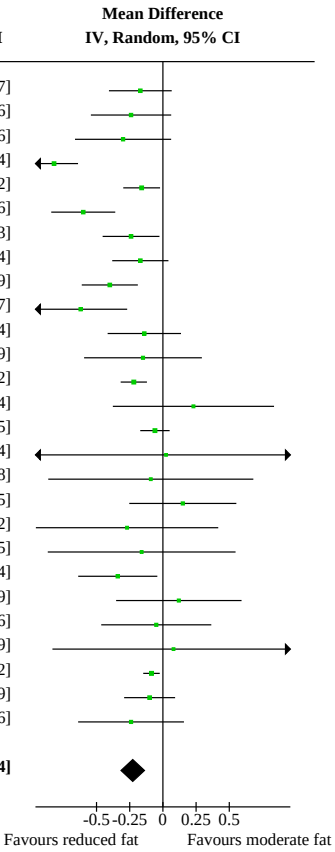


Footnotes
(1) Change in percentage of body fat in a subgroup of 52 participants at 4 years
(2) Change in % body fat from baseline at 6 years, Carty 2011

Analysis 1.5. Comparison 1: Lower fat vs higher fat diet, Outcome 5: Total cholesterol, mmol/L

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 1990	-0.59	0.62	47	-0.42	0.57	51	4.7%	-0.17 [-0.41 , 0.07]
BDIT Pilot Studies 1996	5.14	0.84	54	5.38	0.81	61	3.9%	-0.24 [-0.54 , 0.06]
Bloemberg 1991	-0.32	0.85	39	-0.02	0.79	40	3.2%	-0.30 [-0.66 , 0.06]
CORDIOPREV 2016 (1)	3.34	0.7892	173	4.16	0.8602	151	5.5%	-0.82 [-1.00 , -0.64]
CORDIOPREV 2016 (2)	3.98	0.8367	280	4.14	0.8559	293	6.1%	-0.16 [-0.30 , -0.02]
DEER 1998 (3)	-0.45	0.55	43	0.15	0.59	43	4.7%	-0.60 [-0.84 , -0.36]
DEER 1998 (4)	-0.34	0.5	49	-0.1	0.56	46	5.0%	-0.24 [-0.45 , -0.03]
DEER 1998 (5)	-0.2	0.53	46	-0.03	0.5	45	5.1%	-0.17 [-0.38 , 0.04]
DEER 1998 (6)	-0.53	0.52	48	-0.13	0.53	47	5.1%	-0.40 [-0.61 , -0.19]
De Bont 1981	-0.9	1.09	70	-0.28	0.99	65	3.4%	-0.62 [-0.97 , -0.27]
MSFAT 1995	5.61	1.08	117	5.75	1.01	103	4.2%	-0.14 [-0.42 , 0.14]
Ma 2016	-0.23	1.0852	46	-0.08	1.0613	44	2.5%	-0.15 [-0.59 , 0.29]
ODMDC 2017	-0.2	0.4052	101	0.0192	0.4354	206	6.5%	-0.22 [-0.32 , -0.12]
Pilkington 1960	5.66	0.88	12	5.43	0.85	23	1.6%	0.23 [-0.38 , 0.84]
Polyp Prevention 1996	-0.13	0.77	370	-0.07	0.77	374	6.4%	-0.06 [-0.17 , 0.05]
RISCK 2010 (7)	-0.3685	4.4258	120	-0.392	4.253	111	0.6%	0.02 [-1.10 , 1.14]
RISCK 2010 (8)	-0.3135	2.6704	112	-0.2223	3.1603	109	1.1%	-0.09 [-0.86 , 0.68]
Rivellese 1994	6.78	0.78	27	6.63	0.58	17	2.9%	0.15 [-0.25 , 0.55]
Sarkkinen Low & Mod 1993	6.24	1.06	41	6.51	1.07	12	1.3%	-0.27 [-0.96 , 0.42]
Sarkkinen Low Fat 1993	6.35	1.18	40	6.51	1.07	12	1.3%	-0.16 [-0.87 , 0.55]
Simon 1997	4.87	0.87	34	5.21	0.18	38	3.9%	-0.34 [-0.64 , -0.04]
Strychar 2009	-0.12	0.66	15	-0.24	0.66	15	2.3%	0.12 [-0.35 , 0.59]
Swinburn 2001	-0.2	0.79	51	-0.15	1.3	52	2.8%	-0.05 [-0.46 , 0.36]
WHEL 2007	5.07	11.902	1308	4.99	11.924	1313	0.8%	0.08 [-0.83 , 0.99]
WHI 2006	-0.264	0.828	1133	-0.178	0.825	1699	6.9%	-0.09 [-0.15 , -0.02]
WHT Vanguard 1991	5.53	0.96	202	5.63	1.03	211	5.3%	-0.10 [-0.29 , 0.09]
Yadav 2016 (9)	-0.28	0.74	26	-0.04	0.74	27	2.9%	-0.24 [-0.64 , 0.16]
Total (95% CI)			**4604**			**5208**	**100.0%**	**-0.23 [-0.32 , -0.14]**

Heterogeneity: Tau² = 0.03; Chi² = 93.70, df = 26 (P < 0.00001); I² = 72%
Test for overall effect: Z = 5.05 (P < 0.00001)
Test for subgroup differences: Not applicable

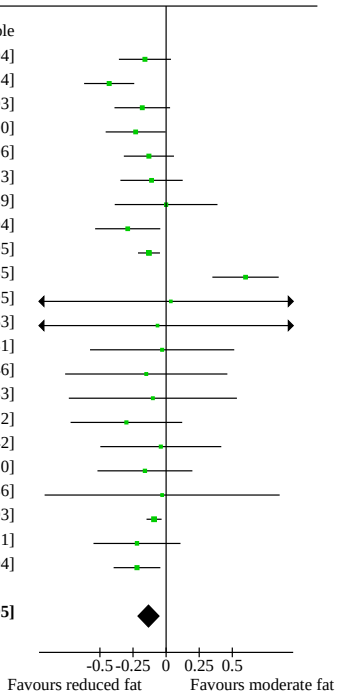


Footnotes
(1) rs4580704 SNP C/C data at 12 months
(2) rs4580704 SNP G/G & C/G data at 12 months
(3) Women with exercise
(4) Men, no exercise
(5) Women, no exercise
(6) Men with exercise
(7) 1. Low GI arms, Calculated from % change based on median baseline
(8) 1. High GI arms; Calculated from % change based on median baseline
(9) Data for all completers, but no SDs provided, so SDs used from compliant only participants

Analysis 1.6. Comparison 1: Lower fat vs higher fat diet, Outcome 6: LDL cholesterol, mmol/L

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018 (1)	0.22	0	31	0.03	0	34		Not estimable
Anderson 1990	-0.56	0.55	47	-0.4	0.43	51	6.8%	-0.16 [-0.36 , 0.04]
DEER 1998 (2)	-0.52	0.45	48	-0.09	0.49	47	7.0%	-0.43 [-0.62 , -0.24]
DEER 1998 (3)	-0.3	0.49	49	-0.12	0.55	46	6.4%	-0.18 [-0.39 , 0.03]
DEER 1998 (4)	-0.37	0.57	43	-0.14	0.5	43	6.0%	-0.23 [-0.46 , -0.00]
DEER 1998 (5)	-0.19	0.49	46	-0.06	0.43	45	7.0%	-0.13 [-0.32 , 0.06]
MSFAT 1995	3.68	0.97	117	3.79	0.81	103	5.8%	-0.11 [-0.35 , 0.13]
Ma 2016	-0.15	0.9495	46	-0.15	0.9287	44	3.1%	0.00 [-0.39 , 0.39]
Moy 2001	-0.69	1.1	117	-0.4	0.8	118	5.5%	-0.29 [-0.54 , -0.04]
ODMDC 2017	-0.17	0.3546	101	-0.0406	0.3354	206	10.4%	-0.13 [-0.21 , -0.05]
Pilkington 1960	1.76	0.39	12	1.16	0.29	23	5.4%	0.60 [0.35 , 0.85]
RISCK 2010 (6)	-0.245	16.5968	120	-0.2808	13.7577	112	0.0%	0.04 [-3.88 , 3.95]
RISCK 2010 (7)	-0.252	13.1595	112	-0.1872	14.7205	108	0.0%	-0.06 [-3.76 , 3.63]
Rivellese 1994	4.82	0.94	27	4.85	0.87	17	1.8%	-0.03 [-0.57 , 0.51]
Sarkkinen Low & Mod 1993	4.21	0.89	41	4.36	0.97	12	1.5%	-0.15 [-0.76 , 0.46]
Sarkkinen Low Fat 1993	4.26	1.03	40	4.36	0.97	12	1.4%	-0.10 [-0.73 , 0.53]
Simon 1997	2.79	0.82	34	3.09	0.99	37	2.7%	-0.30 [-0.72 , 0.12]
Strychar 2009	-0.25	0.7	15	-0.21	0.57	15	2.4%	-0.04 [-0.50 , 0.42]
Swinburn 2001	-0.32	0.64	51	-0.16	1.15	52	3.4%	-0.16 [-0.52 , 0.20]
WHEL 2007	2.92	11.902	1308	2.95	11.277	1313	0.7%	-0.03 [-0.92 , 0.86]
WHI 2006	-0.251	0.758	1133	-0.16	0.753	1699	11.1%	-0.09 [-0.15 , -0.03]
Yadav 2016 (8)	-0.24	0.58	26	-0.02	0.64	27	3.9%	-0.22 [-0.55 , 0.11]
beFIT 1997	4.2	0.94	217	4.42	0.88	192	7.4%	-0.22 [-0.40 , -0.04]
Total (95% CI)			**3781**			**4356**	**100.0%**	**-0.13 [-0.21 , -0.05]**

Heterogeneity: Tau² = 0.01; Chi² = 49.31, df = 21 (P = 0.0005); I² = 57%
Test for overall effect: Z = 3.30 (P = 0.0010)
Test for subgroup differences: Not applicable



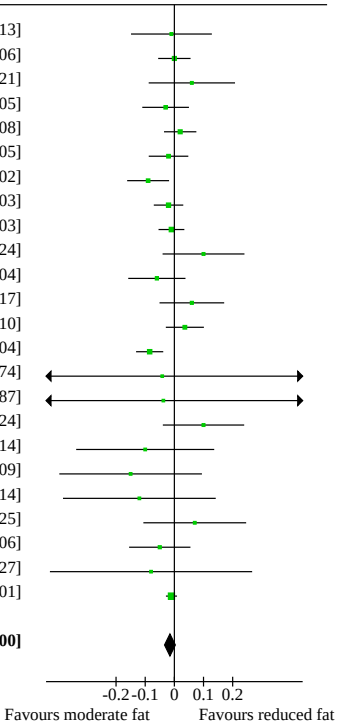
Footnotes

(1) Change data reported as data were too different at baseline to use end data, however no variance for change was presented
(2) Men with exercise
(3) Men, no exercise
(4) Women with exercise
(5) Women, no exercise
(6) 1. Low GI arms, Calculated from % change based on median baseline
(7) 1. High GI arms; Calculated from % change based on median baseline
(8) Data for all completers, but no SDs provided, so SDs used from compliant only participants

Analysis 1.7. Comparison 1: Lower fat vs higher fat diet, Outcome 7: HDL cholesterol, mmol/L

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018	1.24	0.2784	31	1.25	0.2915	34	1.6%	-0.01 [-0.15 , 0.13]
Anderson 1990	0.01	0.14	47	0.01	0.14	51	7.5%	0.00 [-0.06 , 0.06]
BDIT Pilot Studies 1996	1.62	0.41	53	1.56	0.38	57	1.5%	0.06 [-0.09 , 0.21]
Bloemberg 1991	-0.02	0.2	39	0.01	0.16	40	4.3%	-0.03 [-0.11 , 0.05]
CORDIOPREV 2016 (1)	1.13	0.2631	173	1.11	0.2458	151	7.5%	0.02 [-0.04 , 0.08]
DEER 1998 (2)	0.01	0.16	46	0.03	0.17	45	5.6%	-0.02 [-0.09 , 0.05]
DEER 1998 (3)	-0.03	0.17	43	0.06	0.17	43	5.1%	-0.09 [-0.16 , -0.02]
DEER 1998 (4)	0.01	0.14	48	0.03	0.11	47	8.5%	-0.02 [-0.07 , 0.03]
DEER 1998 (5)	-0.02	0.11	49	-0.01	0.11	46	9.9%	-0.01 [-0.05 , 0.03]
De Bont 1981	-0.09	0.4	70	-0.19	0.43	65	1.6%	0.10 [-0.04 , 0.24]
MSFAT 1995	1.34	0.32	117	1.4	0.41	103	3.1%	-0.06 [-0.16 , 0.04]
Ma 2016	0.01	0.2713	46	-0.05	0.2653	44	2.5%	0.06 [-0.05 , 0.17]
Moy 2001	0.044	0.3	117	0.008	0.2	118	5.9%	0.04 [-0.03 , 0.10]
ODMDC 2017	-0.07	0.2026	101	0.0147	0.1803	206	9.4%	-0.08 [-0.13 , -0.04]
RISCK 2010 (6)	-0.0767	10.7573	108	-0.0351	10.0488	107	0.0%	-0.04 [-2.82 , 2.74]
RISCK 2010 (7)	-0.0936	9.0911	104	-0.0559	12.5614	112	0.0%	-0.04 [-2.95 , 2.87]
Rivellese 1994	1.22	0.31	27	1.12	0.16	17	1.6%	0.10 [-0.04 , 0.24]
Sarkkinen Low & Mod 1993	1.43	0.28	41	1.53	0.39	12	0.6%	-0.10 [-0.34 , 0.14]
Sarkkinen Low Fat 1993	1.38	0.34	40	1.53	0.39	12	0.6%	-0.15 [-0.39 , 0.09]
Simon 1997	1.44	0.58	34	1.56	0.55	38	0.5%	-0.12 [-0.38 , 0.14]
Strychar 2009	0.06	0.27	15	-0.01	0.22	15	1.0%	0.07 [-0.11 , 0.25]
Swinburn 2001	0.01	0.14	51	0.06	0.36	52	2.7%	-0.05 [-0.16 , 0.06]
WHEL 2007	1.45	4.705	1308	1.53	4.345	1313	0.3%	-0.08 [-0.43 , 0.27]
WHI 2006	-0.018	0.243	1133	-0.008	0.264	1699	18.7%	-0.01 [-0.03 , 0.01]
Total (95% CI)			**3841**			**4427**	**100.0%**	**-0.02 [-0.03 , 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 29.94, df = 23 (P = 0.15); I² = 23%
Test for overall effect: Z = 1.61 (P = 0.11)
Test for subgroup differences: Not applicable



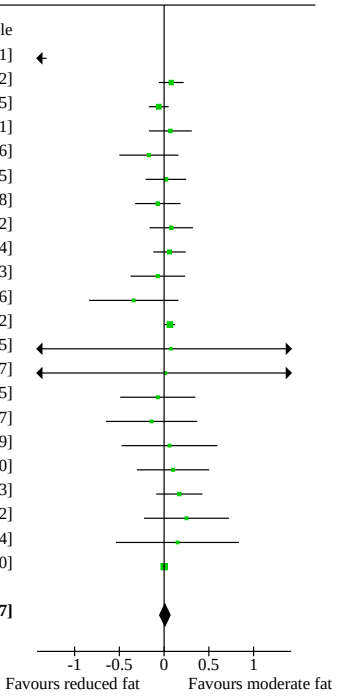
Footnotes

(1) rs4580704 SNP C/C data at 12 months
(2) Women, no exercise
(3) Women with exercise
(4) Men with exercise
(5) Men, no exercise
(6) 1. High GI arms; Calculated from % change based on median baseline
(7) 1. Low GI arms, Calculated from % change based on median baseline

Analysis 1.8. Comparison 1: Lower fat vs higher fat diet, Outcome 8: Triglycerides, mmol/L

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018 (1)	-0.05	0	31	0.03	0	34		Not estimable
Anderson 1990	-1.05	1.99	47	1.06	2.03	51	0.5%	-2.11 [-2.91 , -1.31]
CORDIOPREV 2016 (2)	1.4	0.6576	173	1.32	0.6144	151	9.2%	0.08 [-0.06 , 0.22]
CORDIOPREV 2016 (3)	1.37	0.6693	280	1.43	0.6847	293	11.3%	-0.06 [-0.17 , 0.05]
DEER 1998 (4)	-0.08	0.62	48	-0.15	0.57	47	4.5%	0.07 [-0.17 , 0.31]
DEER 1998 (5)	-0.07	0.67	49	0.1	0.94	46	2.7%	-0.17 [-0.50 , 0.16]
DEER 1998 (6)	-0.12	0.56	43	-0.14	0.51	43	4.9%	0.02 [-0.21 , 0.25]
DEER 1998 (7)	-0.05	0.73	46	0.02	0.48	45	4.2%	-0.07 [-0.32 , 0.18]
De Bont 1981	-0.03	0.83	70	-0.11	0.6	65	4.4%	0.08 [-0.16 , 0.32]
MSFAT 1995	1.3	0.76	117	1.24	0.61	103	6.7%	0.06 [-0.12 , 0.24]
Ma 2016	0.03	0.7461	46	0.1	0.7297	44	3.1%	-0.07 [-0.37 , 0.23]
Moy 2001	-0.4	2	117	-0.06	1.9	118	1.3%	-0.34 [-0.84 , 0.16]
ODMDC 2017	0.13	0.2533	101	0.0651	0.2322	206	16.0%	0.06 [0.01 , 0.12]
RISCK 2010 (8)	0.0042	30.9187	121	-0.072	32.0151	108	0.0%	0.08 [-8.10 , 8.25]
RISCK 2010 (9)	0.0348	32.94	113	0.021	28.3086	110	0.0%	0.01 [-8.04 , 8.07]
Rivellese 1994	1.5	0.68	27	1.57	0.7	17	1.8%	-0.07 [-0.49 , 0.35]
Sarkkinen Low & Mod 1993	1.24	0.6	41	1.38	0.84	12	1.2%	-0.14 [-0.65 , 0.37]
Sarkkinen Low Fat 1993	1.44	0.79	40	1.38	0.84	12	1.1%	0.06 [-0.47 , 0.59]
Simon 1997	1.35	1.05	34	1.25	0.61	37	1.9%	0.10 [-0.30 , 0.50]
Strychar 2009	0.14	0.46	15	-0.03	0.22	15	4.0%	0.17 [-0.09 , 0.43]
Swinburn 2001	0.37	0.71	51	0.12	1.59	52	1.4%	0.25 [-0.22 , 0.72]
WHEL 2007	1.17	7.842	1308	1.02	9.983	1313	0.7%	0.15 [-0.54 , 0.84]
WHI 2006	0.011	0.005	1133	0.011	0.003	1699	19.0%	0.00 [-0.00 , 0.00]
Total (95% CI)			**4051**			**4621**	**100.0%**	**0.01 [-0.05 , 0.07]**

Heterogeneity: Tau² = 0.00; Chi² = 42.17, df = 21 (P = 0.004); I² = 50%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



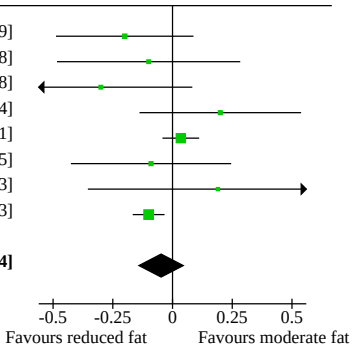
Footnotes

(1) Change data reported as data were too different at baseline to use end data, however no variance for change was presente
(2) rs4580704 SNP C/C data at 12 months
(3) rs4580704 SNP C/G & G/G data at 12 months
(4) Men with exercise
(5) Men, no exercise
(6) Women with exercise
(7) Women, no exercise
(8) 1. High GI arms; Calculated from % change based on median baseline
(9) 1. Low GI arms, Calculated from % change based on median baseline

Analysis 1.9. Comparison 1: Lower fat vs higher fat diet, Outcome 9: Total cholesterol/HDL

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DEER 1998 (1)	-0.2	0.7	46	0	0.7	45	8.3%	-0.20 [-0.49 , 0.09]
DEER 1998 (2)	-0.2	0.9	49	-0.1	1	46	5.1%	-0.10 [-0.48 , 0.28]
DEER 1998 (3)	-0.6	0.9	48	-0.3	1	47	5.1%	-0.30 [-0.68 , 0.08]
DEER 1998 (4)	-0.2	0.8	43	-0.4	0.8	43	6.4%	0.20 [-0.14 , 0.54]
ODMDC 2017	0.04	0.3039	101	0.0053	0.358	206	32.0%	0.03 [-0.04 , 0.11]
Strychar 2009	-0.22	0.55	15	-0.13	0.37	15	6.4%	-0.09 [-0.43 , 0.25]
Swinburn 2001	-0.34	1	51	-0.53	1.73	52	2.7%	0.19 [-0.35 , 0.73]
WHI 2006	-0.2	0.8	1133	-0.1	1	1699	33.9%	-0.10 [-0.17 , -0.03]
Total (95% CI)			**1486**			**2153**	**100.0%**	**-0.05 [-0.14 , 0.04]**

Heterogeneity: Tau² = 0.01; Chi² = 12.46, df = 7 (P = 0.09); I² = 44%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

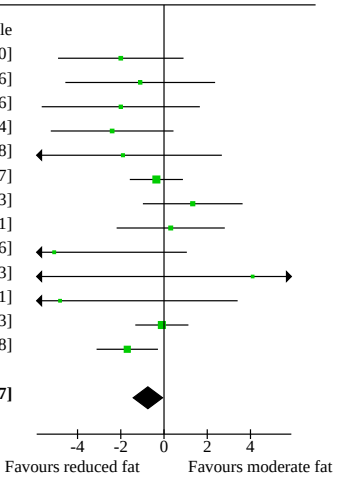


Footnotes
(1) Women, no exercise
(2) Men, no exercise
(3) Men with exercise
(4) Women with exercise

Analysis 1.10. Comparison 1: Lower fat vs higher fat diet, Outcome 10: Systolic blood pressure, mmHg

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018 (1)	-1.1	0	31	-1.4	0	34		Not estimable
DEER 1998 (2)	-1.7	6.4	49	0.3	7.9	46	5.1%	-2.00 [-4.90 , 0.90]
DEER 1998 (3)	-3.5	9.2	46	-2.4	7.6	45	3.7%	-1.10 [-4.56 , 2.36]
DEER 1998 (4)	-3.1	8.4	43	-1.1	8.9	43	3.3%	-2.00 [-5.66 , 1.66]
DEER 1998 (5)	-3	6.8	48	-0.6	7.3	47	5.4%	-2.40 [-5.24 , 0.44]
Ma 2016	-5.5	11.53	46	-3.6	10.6132	44	2.1%	-1.90 [-6.48 , 2.68]
ODMDC 2017	-2.6	5.0655	101	-2.2464	5.3579	207	22.7%	-0.35 [-1.58 , 0.87]
RISCK 2010 (6)	-1.921	7.8812	120	-3.25	9.8956	113	7.9%	1.33 [-0.98 , 3.63]
RISCK 2010 (7)	-2.21	9.9581	113	-2.52	9.0937	110	6.8%	0.31 [-2.19 , 2.81]
Sarkkinen Low & Mod 1993	-2.59	11.19	41	2.49	15.8	37	1.2%	-5.08 [-11.22 , 1.06]
Strychar 2009	3.9	14.4	15	-0.2	21.1	15	0.3%	4.10 [-8.83 , 17.03]
Swinburn 2001	-3.5	17.71	51	1.31	24.37	52	0.7%	-4.81 [-13.03 , 3.41]
WHI 2006	-2.2	16.3	1133	-2.1	16.4	1699	22.7%	-0.10 [-1.33 , 1.13]
WHTFSMP 2003	-3.1	14.5	1101	-1.4	14.7	648	18.2%	-1.70 [-3.12 , -0.28]
Total (95% CI)			**2938**			**3140**	**100.0%**	**-0.75 [-1.42 , -0.07]**

Heterogeneity: Tau² = 0.13; Chi² = 13.13, df = 12 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Not applicable

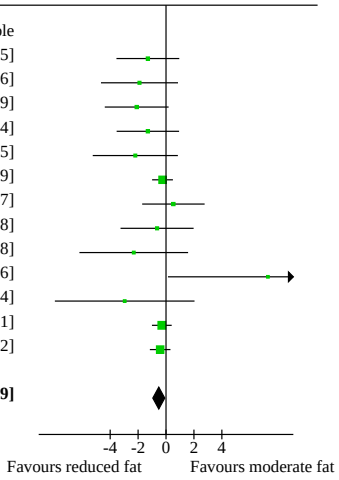


Footnotes
(1) Change data reported as data were too different at baseline to use end data, however no variance for change was presented
(2) Men, no exercise
(3) Women, no exercise
(4) Women with exercise
(5) Men with exercise
(6) 1. High GI arms; Calculated from % change based on median baseline
(7) 1. Low GI arms, Calculated from % change based on median baseline

Analysis 1.11. Comparison 1: Lower fat vs higher fat diet, Outcome 11: Diastolic blood pressure, mmHg

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018 (1)	-0.3	0	31	-0.4	0	34		Not estimable
DEER 1998 (2)	-1.9	5	46	-0.6	5.9	45	3.5%	-1.30 [-3.55 , 0.95]
DEER 1998 (3)	-3	6.6	48	-1.1	7.1	47	2.3%	-1.90 [-4.66 , 0.86]
DEER 1998 (4)	-0.3	5.2	49	1.8	6.1	46	3.4%	-2.10 [-4.39 , 0.19]
DEER 1998 (5)	-2.7	4.6	43	-1.4	5.9	43	3.5%	-1.30 [-3.54 , 0.94]
Ma 2016	-1.5	7.4606	46	0.7	7.2966	44	1.9%	-2.20 [-5.25 , 0.85]
ODMDC 2017	-1.3	3.0393	101	-1.049	3.3021	206	24.9%	-0.25 [-1.00 , 0.49]
RISCK 2010 (6)	-1.215	6.9531	113	-1.744	9.7599	109	3.5%	0.53 [-1.71 , 2.77]
RISCK 2010 (7)	-1.3515	9.9581	120	-0.711	10.4444	114	2.6%	-0.64 [-3.26 , 1.98]
Sarkkinen Low & Mod 1993	-0.93	7.13	41	1.38	10	37	1.2%	-2.31 [-6.20 , 1.58]
Strychar 2009	4.7	11	15	-2.6	8.9	15	0.4%	7.30 [0.14 , 14.46]
Swinburn 2001	-7.16	12	51	-4.2	13.85	52	0.7%	-2.96 [-7.96 , 2.04]
WHI 2006	-2.6	9.4	1133	-2.3	9.4	1699	26.9%	-0.30 [-1.01 , 0.41]
WHTFSMP 2003	-1.06	7.4	1101	-0.64	7.7	648	25.3%	-0.42 [-1.16 , 0.32]
Total (95% CI)			**2938**			**3139**	**100.0%**	**-0.52 [-0.95 , -0.09]**

Heterogeneity: Tau² = 0.05; Chi² = 12.96, df = 12 (P = 0.37); I² = 7%
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Not applicable

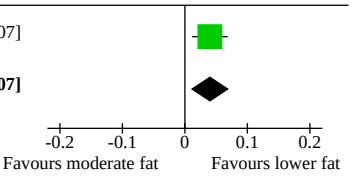


Footnotes
(1) Change data reported as data were too different at baseline to use end data, however no variance for change was presented
(2) Women, no exercise
(3) Men with exercise
(4) Men, no exercise
(5) Women with exercise
(6) 1. High GI arms; Calculated from % change based on median baseline
(7) 1. Low GI arms, Calculated from % change based on median baseline

Analysis 1.12. Comparison 1: Lower fat vs higher fat diet, Outcome 12: Quality of life

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
WHI 2006 (1)	0.07	1.41	15788	0.03	1.44	24342	100.0%	0.04 [0.01 , 0.07]
Total (95% CI)			**15788**			**24342**	**100.0%**	**0.04 [0.01 , 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable



Footnotes
(1) Change in Global Quality of Life to trial close-out (0 worst to 10 best), Assaf 2016

Comparison 2. Lower fat vs higher fat diet on body weight, sensitivity analyses

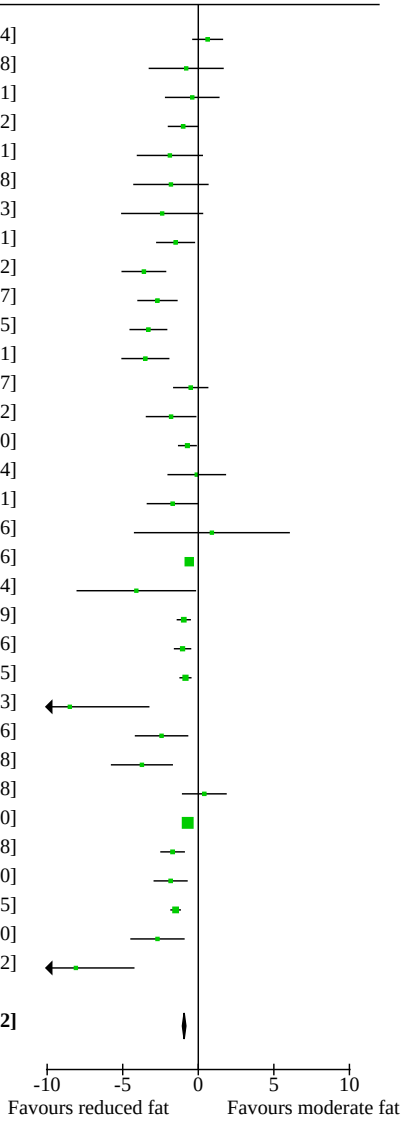
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Weight, kg SA fixed effects	26	53875	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-1.05, -0.82]
2.2 Weight, kg SA including only RCTs at low summary RoB	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
2.2.1 Low summary RoB	4	42212	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.82, -0.52]
2.2.2 Moderate /High RoB	22	11663	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.00, -1.20]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.3 Weight, kg SA excluding the largest trial, WHI	25	12522	Mean Difference (IV, Random, 95% CI)	-1.51 [-1.86, -1.15]
2.4 Weight, kg SA excluding RCTs not free of systematic differences in care	7	1641	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.17, -0.60]
2.5 Weight, kg SA excluding studies not free of dietary differences other than fat	18	5112	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.07, -1.19]
2.6 Weight, kg SA excluding studies with potential compliance problems	20	50907	Mean Difference (IV, Random, 95% CI)	-1.56 [-1.88, -1.23]
2.7 Weight, kg including partial data	35	59013	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]

Analysis 2.1. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 1: Weight, kg SA fixed effects

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Anderson 1990	1.06	2.49	47	0.44	2.68	51	1.2%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	0.2%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	0.4%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	1.2%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-1.27	7.1294	88	0.61	7.8652	92	0.3%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (2)	-1.34	6.3357	98	0.47	11.7962	115	0.2%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	0.2%	-2.39 [-5.11 , 0.33]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	0.8%	-1.50 [-2.79 , -0.21]
DEER 1998 (4)	-4.2	4.2	48	-0.6	3.1	47	0.6%	-3.60 [-5.08 , -2.12]
DEER 1998 (5)	-3.1	3.7	43	-0.4	2.5	43	0.7%	-2.70 [-4.03 , -1.37]
DEER 1998 (6)	-2.8	3.5	49	0.5	2.7	46	0.8%	-3.30 [-4.55 , -2.05]
DEER 1998 (7)	-2.7	3.5	46	0.8	4.2	45	0.5%	-3.50 [-5.09 , -1.91]
De Bont 1981 (8)	-0.4	2.8	36	0.1	2	29	0.9%	-0.50 [-1.67 , 0.67]
De Bont 1981 (9)	-2.7	3.6	34	-0.9	3.5	35	0.5%	-1.80 [-3.48 , -0.12]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	3.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	0.3%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	0.4%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.0%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	21.9%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.1%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (10)	-0.8734	2.6017	117	0.1674	1.8124	115	3.9%	-1.04 [-1.62 , -0.46]
RISCK 2010 (11)	-0.8877	2.1451	111	-0.0402	0.213	110	8.0%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.0%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	0.4%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	0.3%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	0.6%	0.40 [-1.08 , 1.88]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	32.4%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	1.9%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	1.0%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	10.5%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	0.4%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.1%	-8.10 [-11.98 , -4.22]
Total (95% CI)			**22397**			**31478**	**100.0%**	**-0.94 [-1.05 , -0.82]**

Heterogeneity: Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%
Test for overall effect: Z = 16.17 (P < 0.00001)
Test for subgroup differences: Not applicable

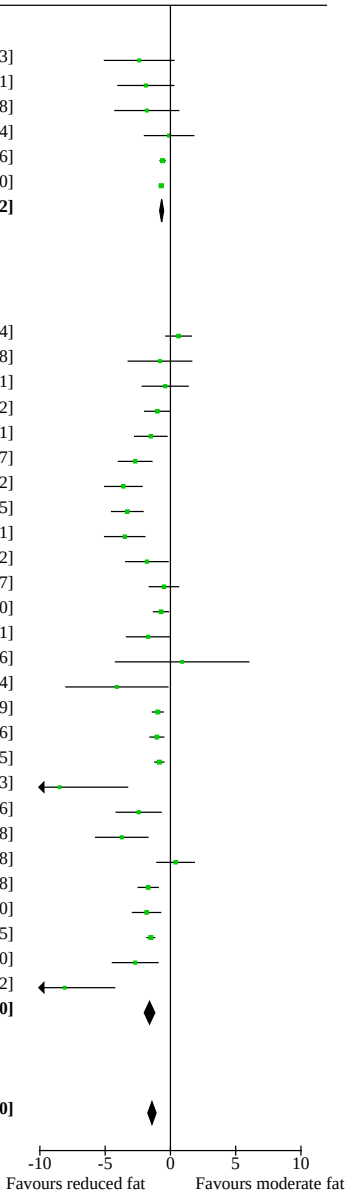


Footnotes

(1) pre-DM by HbA1c, change to 5 years
(2) preDM by IFT/IGT, change to 5 years
(3) Non-preDM, change to 5 years
(4) Men with exercise
(5) Women with exercise
(6) Men, no exercise
(7) Women, no exercise
(8) non-obese participants (BMI < 28)
(9) obese participants (BMI 28+)
(10) Low GI arms, Calculated from % change based on median baseline
(11) High GI arms; Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 2.2. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 2: Weight, kg SA including only RCTs at low summary RoB

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Low summary RoB								
CORDIOPREV 2016 (1)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
WHI 2006 (4)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
Subtotal (95% CI)			**16660**			**25552**	**18.7%**	**-0.67 [-0.82 , -0.52]**
Heterogeneity: Tau² = 0.00; Chi² = 4.27, df = 5 (P = 0.51); I² = 0%								
Test for overall effect: Z = 8.63 (P < 0.00001)								
2.2.2 Moderate /High RoB								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (5)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (6)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (7)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (8)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
De Bont 1981 (9)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (10)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (12)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**5737**			**5926**	**81.3%**	**-1.60 [-2.00 , -1.20]**
Heterogeneity: Tau² = 0.61; Chi² = 97.77, df = 26 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 7.77 (P < 0.00001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 17.80, df = 1 (P < 0.0001), I² = 94.4%								



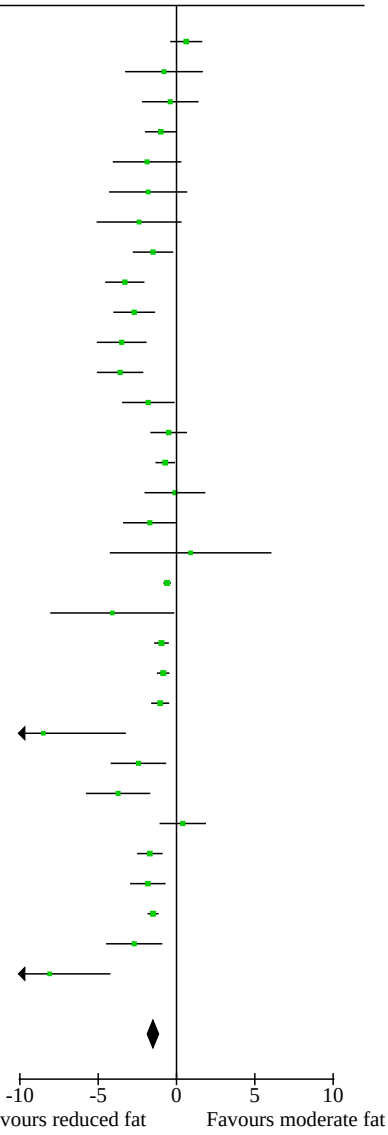
Footnotes

(1) Non-preDM, change to 5 years
(2) pre-DM by HbA1c, change to 5 years
(3) preDM by IFT/IGT, change to 5 years
(4) Change from baseline to 7.5 years
(5) Women with exercise
(6) Men with exercise
(7) Men, no exercise
(8) Women, no exercise
(9) obese participants (BMI 28+)
(10) non-obese participants (BMI < 28)
(11) Low GI arms, Calculated from % change based on median baseline
(12) High GI arms; Calculated from % change based on median baseline
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 2.3. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 3: Weight, kg SA excluding the largest trial, WHI

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 1990	1.06	2.49	47	0.44	2.68	51	4.2%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.6%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.4%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	4.2%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-1.27	7.1294	88	0.61	7.8652	92	1.9%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (2)	-1.34	6.3357	98	0.47	11.7962	115	1.6%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.4%	-2.39 [-5.11 , 0.33]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.5%	-1.50 [-2.79 , -0.21]
DEER 1998 (4)	-2.8	3.5	49	0.5	2.7	46	3.6%	-3.30 [-4.55 , -2.05]
DEER 1998 (5)	-3.1	3.7	43	-0.4	2.5	43	3.4%	-2.70 [-4.03 , -1.37]
DEER 1998 (6)	-2.7	3.5	46	0.8	4.2	45	2.8%	-3.50 [-5.09 , -1.91]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	3.0%	-3.60 [-5.08 , -2.12]
De Bont 1981 (8)	-2.7	3.6	34	-0.9	3.5	35	2.6%	-1.80 [-3.48 , -0.12]
De Bont 1981 (9)	-0.4	2.8	36	0.1	2	29	3.8%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	2.2%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.6%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.2%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.7%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.7%	-0.96 [-1.43 , -0.49]
RISCK 2010 (10)	-0.8877	2.1451	111	-0.0402	0.213	110	5.9%	-0.85 [-1.25 , -0.45]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.4%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.5%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	2.0%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	3.0%	0.40 [-1.08 , 1.88]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.8%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.9%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.0%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.4%	-2.70 [-4.50 , -0.90]
Yadav 2016 (12)	-7.4	7.9	22	0.7	5.4	27	0.7%	-8.10 [-11.98 , -4.22]
Total (95% CI)			**6100**			**6422**	**100.0%**	**-1.51 [-1.86 , -1.15]**

Heterogeneity: Tau² = 0.53; Chi² = 120.06, df = 31 (P < 0.00001); I² = 74%
Test for overall effect: Z = 8.25 (P < 0.00001)
Test for subgroup differences: Not applicable



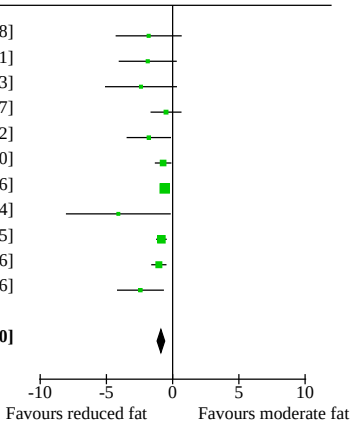
Footnotes

(1) pre-DM by HbA1c, change to 5 years
(2) preDM by IFT/IGT, change to 5 years
(3) Non-preDM, change to 5 years
(4) Men, no exercise
(5) Women with exercise
(6) Women, no exercise
(7) Men with exercise
(8) obese participants (BMI 28+)
(9) non-obese participants (BMI < 28)
(10) High GI arms; Calculated from % change based on median baseline
(11) Low GI arms, Calculated from % change based on median baseline
(12) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 2.4. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 4: Weight, kg SA excluding RCTs not free of systematic differences in care

	Reduced fat			Usual or modified fat				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
CORDIOPREV 2016 (1)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]	
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]	
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]	
De Bont 1981 (4)	-0.4	2.8	36	0.1	2	29	5.2%	-0.50 [-1.67 , 0.67]	
De Bont 1981 (5)	-2.7	3.6	34	-0.9	3.5	35	2.7%	-1.80 [-3.48 , -0.12]	
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	14.0%	-0.72 [-1.34 , -0.10]	
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	32.6%	-0.60 [-0.84 , -0.36]	
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.5%	-4.10 [-8.06 , -0.14]	
RISCK 2010 (6)	-0.8877	2.1451	111	-0.0402	0.213	110	23.1%	-0.85 [-1.25 , -0.45]	
RISCK 2010 (7)	-0.8734	2.6017	117	0.1674	1.8124	115	15.5%	-1.04 [-1.62 , -0.46]	
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.4%	-2.43 [-4.20 , -0.66]	
Total (95% CI)			**759**			**882**	**100.0%**	**-0.89 [-1.17 , -0.60]**	

Heterogeneity: Tau² = 0.05; Chi² = 13.72, df = 10 (P = 0.19); I² = 27%
Test for overall effect: Z = 6.11 (P < 0.00001)
Test for subgroup differences: Not applicable



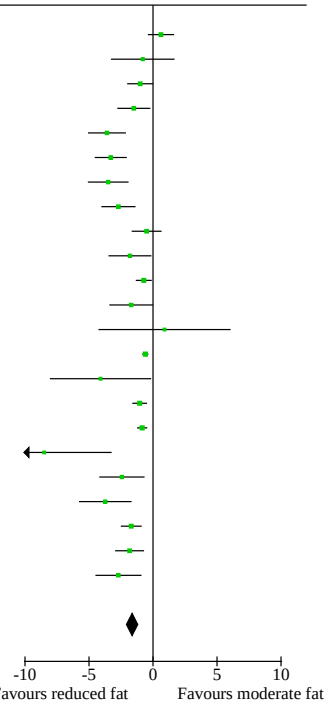
Footnotes

(1) preDM by IFT/IGT, change to 5 years
(2) pre-DM by HbA1c, change to 5 years
(3) Non-preDM, change to 5 years
(4) non-obese participants (BMI < 28)
(5) obese participants (BMI 28+)
(6) High GI arms; Calculated from % change based on median baseline
(7) Low GI arms, Calculated from % change based on median baseline

Analysis 2.5. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 5: Weight, kg SA excluding studies not free of dietary differences other than fat

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 1990	1.06	2.49	47	0.44	2.68	51	5.5%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	2.2%	-0.80 [-3.28 , 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	5.5%	-1.00 [-2.02 , 0.02]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	4.7%	-1.50 [-2.79 , -0.21]
DEER 1998 (1)	-4.2	4.2	48	-0.6	3.1	47	4.2%	-3.60 [-5.08 , -2.12]
DEER 1998 (2)	-2.8	3.5	49	0.5	2.7	46	4.8%	-3.30 [-4.55 , -2.05]
DEER 1998 (3)	-2.7	3.5	46	0.8	4.2	45	3.9%	-3.50 [-5.09 , -1.91]
DEER 1998 (4)	-3.1	3.7	43	-0.4	2.5	43	4.6%	-2.70 [-4.03 , -1.37]
De Bont 1981 (5)	-0.4	2.8	36	0.1	2	29	5.1%	-0.50 [-1.67 , 0.67]
De Bont 1981 (6)	-2.7	3.6	34	-0.9	3.5	35	3.7%	-1.80 [-3.48 , -0.12]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	6.8%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	3.6%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.7%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	7.7%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	1.1%	-4.10 [-8.06 , -0.14]
RISCK 2010 (7)	-0.8734	2.6017	117	0.1674	1.8124	115	6.9%	-1.04 [-1.62 , -0.46]
RISCK 2010 (8)	-0.8877	2.1451	111	-0.0402	0.213	110	7.4%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.6%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	3.5%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	2.9%	-3.73 [-5.78 , -1.68]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	6.2%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	5.2%	-1.83 [-2.96 , -0.70]
WINS 1993	-2.7	15.3	386	0	15.3	998	3.4%	-2.70 [-4.50 , -0.90]
Total (95% CI)			**2192**			**2920**	**100.0%**	**-1.63 [-2.07 , -1.19]**

Heterogeneity: Tau² = 0.64; Chi² = 93.01, df = 22 (P < 0.00001); I² = 76%
Test for overall effect: Z = 7.30 (P < 0.00001)
Test for subgroup differences: Not applicable

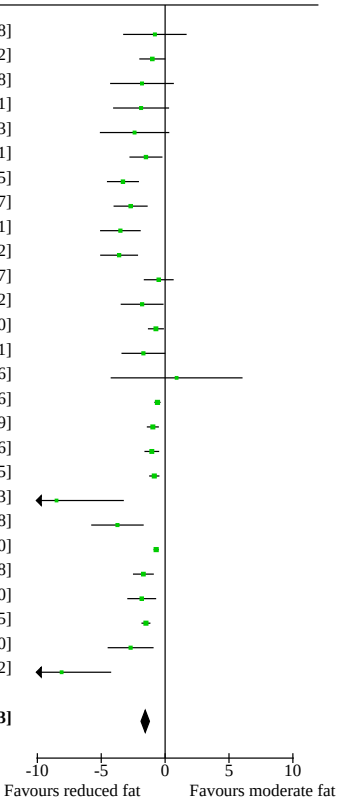


Footnotes
(1) Men with exercise
(2) Men, no exercise
(3) Women, no exercise
(4) Women with exercise
(5) non-obese participants (BMI < 28)
(6) obese participants (BMI 28+)
(7) Low GI arms, Calculated from % change based on median baseline
(8) High GI arms; Calculated from % change based on median baseline

Analysis 2.6. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 6: Weight, kg SA excluding studies with potential compliance problems

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.4%	-0.80 [-3.28 , 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	4.5%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-1.34	6.3357	98	0.47	11.7962	115	1.4%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.8%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.2%	-2.39 [-5.11 , 0.33]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.6%	-1.50 [-2.79 , -0.21]
DEER 1998 (4)	-2.8	3.5	49	0.5	2.7	46	3.7%	-3.30 [-4.55 , -2.05]
DEER 1998 (5)	-3.1	3.7	43	-0.4	2.5	43	3.4%	-2.70 [-4.03 , -1.37]
DEER 1998 (6)	-2.7	3.5	46	0.8	4.2	45	2.8%	-3.50 [-5.09 , -1.91]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	3.0%	-3.60 [-5.08 , -2.12]
De Bont 1981 (8)	-0.4	2.8	36	0.1	2	29	4.0%	-0.50 [-1.67 , 0.67]
De Bont 1981 (9)	-2.7	3.6	34	-0.9	3.5	35	2.6%	-1.80 [-3.48 , -0.12]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	6.2%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.5%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	7.6%	-0.60 [-0.84 , -0.36]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	6.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (10)	-0.8734	2.6017	117	0.1674	1.8124	115	6.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (11)	-0.8877	2.1451	111	-0.0402	0.213	110	7.1%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.4%	-8.50 [-13.77 , -3.23]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.9%	-3.73 [-5.78 , -1.68]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	7.7%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	5.3%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	4.1%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	7.3%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.4%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.7%	-8.10 [-11.98 , -4.22]
Total (95% CI)			**20921**			**29986**	**100.0%**	**-1.56 [-1.88 , -1.23]**

Heterogeneity: Tau² = 0.36; Chi² = 109.65, df = 26 (P < 0.00001); I² = 76%
Test for overall effect: Z = 9.26 (P < 0.00001)
Test for subgroup differences: Not applicable



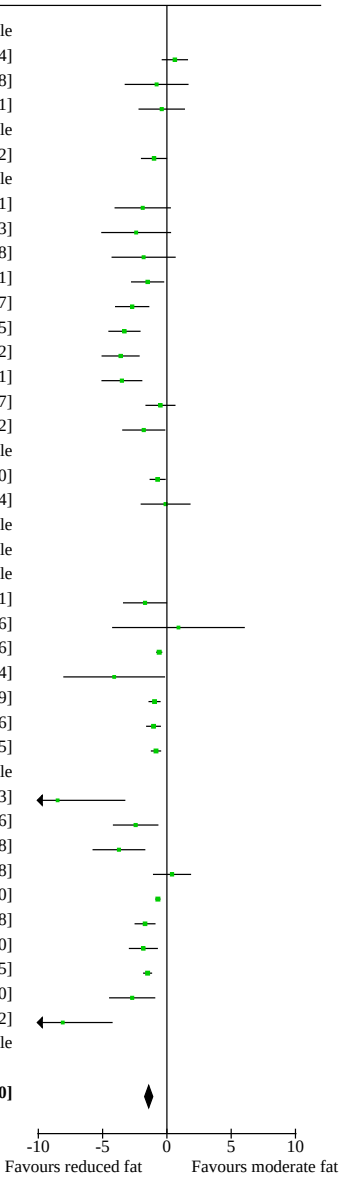
Footnotes

(1) preDM by IFT/IGT, change to 5 years
(2) pre-DM by HbA1c, change to 5 years
(3) Non-preDM, change to 5 years
(4) Men, no exercise
(5) Women with exercise
(6) Women, no exercise
(7) Men with exercise
(8) non-obese participants (BMI < 28)
(9) obese participants (BMI 28+)
(10) Low GI arms, Calculated from % change based on median baseline
(11) High GI arms; Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 2.7. Comparison 2: Lower fat vs higher fat diet on body weight, sensitivity analyses, Outcome 7: Weight, kg including partial data

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AUSMED 2018 (1)	-0.3	0	31	0	0	34		Not estimable
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Black 1994	-2	0	38	0.5	0	58		Not estimable
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Boyd 1988	-2.1	0	1491	0	0	1676		Not estimable
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (4)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (5)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (6)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (8)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
De Bont 1981 (9)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (10)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
Diet and Hormone Study 2003	-0.68	0	81	-0.14	0	96		Not estimable
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
MeDiet 2006	-1.3	0	51	-0.6	0	55		Not estimable
NDHS Open 1st L&M 1968	-2.45	0	332	-1.91	0	348		Not estimable
NDHS Open 2nd L&M 1968	-1.8	0	179	-1.2	0	215		Not estimable
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (12)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Rivellese 1994	-1.8	0	27	-1.6	0	17		Not estimable
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (13)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (14)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
beFIT 1997	-2.7	0	217	0	0	192		Not estimable
Total (95% CI)			**24844**			**34169**	**100.0%**	**-1.42 [-1.73 , -1.10]**

Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%
Test for overall effect: Z = 8.78 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Change data reported as data were too different at baseline to use end data, however no variance for change was presented
(2) pre-DM by HbA1c, change to 5 years
(3) Non-preDM, change to 5 years
(4) preDM by IFT/IGT, change to 5 years
(5) Women with exercise
(6) Men, no exercise
(7) Men with exercise
(8) Women, no exercise
(9) non-obese participants (BMI < 28)
(10) obese participants (BMI 28+)
(11) Low GI arms, Calculated from % change based on median baseline
(12) High GI arms; Calculated from % change based on median baseline
(13) Change from baseline to 7.5 years
(14) Data for 22 of 26 intervention participants who were compliant with diet

Comparison 3. Lower fat vs higher fat diet on body weight, subgrouping

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Weight, kg Subgrouping by trial duration	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 duration 6 to < 12 months	12	4298	Mean Difference (IV, Random, 95% CI)	-1.35 [-1.78, -0.92]
3.1.2 duration 12 to < 24 months	16	51665	Mean Difference (IV, Random, 95% CI)	-2.07 [-2.57, -1.56]
3.1.3 duration 24 to < 60 months	9	49171	Mean Difference (IV, Random, 95% CI)	-1.18 [-1.65, -0.70]
3.1.4 duration 60+ months	5	41300	Mean Difference (IV, Random, 95% CI)	-1.00 [-1.79, -0.21]
3.2 Weight, kg Subgrouping by baseline fat intake	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.2.1 > 35%E from fat	13	45802	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.59, -0.91]
3.2.2 > 30 to 35%E from fat	11	6322	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.40, -0.22]
3.2.3 > 25 to 30%E from fat	2	1751	Mean Difference (IV, Random, 95% CI)	-3.17 [-3.82, -2.52]
3.3 Weight, kg Subgrouping by decade of first publication	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.3.1 1960s	1	35	Mean Difference (IV, Random, 95% CI)	-4.10 [-8.06, -0.14]
3.3.2 1970s	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.3.3 1980s	2	288	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.80, -0.01]
3.3.4 1990s	11	5689	Mean Difference (IV, Random, 95% CI)	-1.86 [-2.49, -1.22]
3.3.5 2000s	7	46502	Mean Difference (IV, Random, 95% CI)	-1.15 [-1.85, -0.46]
3.3.6 2010s	5	1361	Mean Difference (IV, Random, 95% CI)	-1.04 [-1.58, -0.51]
3.4 Weight, kg Subgrouping by sex	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.4.1 Studies of women only	14	49877	Mean Difference (IV, Random, 95% CI)	-1.49 [-1.98, -1.00]
3.4.2 Studies of men only	3	304	Mean Difference (IV, Random, 95% CI)	-2.74 [-4.32, -1.17]
3.4.3 Studies of men & women	10	3694	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.45, -0.59]
3.5 Weight, kg Subgrouping by difference in %E from fat	26	53875	Mean Difference (IV, Random, 95% CI)	-1.36 [-1.67, -1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
between control & reduced fat groups				
3.5.1 Up to 5%E fat difference	6	3136	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.77, 0.47]
3.5.2 5% to < 10% E fat difference	9	44641	Mean Difference (IV, Random, 95% CI)	-1.76 [-2.25, -1.28]
3.5.3 10% to < 15%E fat difference	6	5664	Mean Difference (IV, Random, 95% CI)	-1.23 [-1.72, -0.74]
3.5.4 15+%E fat difference	5	404	Mean Difference (IV, Random, 95% CI)	-3.91 [-7.61, -0.22]
3.5.5 %E fat difference not stated	1	30	Mean Difference (IV, Random, 95% CI)	-2.43 [-4.20, -0.66]
3.6 Weight, kg Subgrouping by achieving < 30%E from fat	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.6.1 Intervention did not achieve < 30%E from fat or less	6	1139	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.32, -0.47]
3.6.2 Intervention achieved < 30%E from fat or less	20	52736	Mean Difference (IV, Random, 95% CI)	-1.55 [-1.93, -1.18]
3.7 Weight, kg Subgrouping by type of intervention	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.7.1 Dietary advice	22	52433	Mean Difference (IV, Random, 95% CI)	-1.65 [-2.09, -1.21]
3.7.2 Dietary advice plus supplements	2	915	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.29, -0.65]
3.7.3 Diet provided	2	527	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.84, -0.39]
3.8 Weight, kg Subgrouping by lower fat arm fat goal	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.8.1 Goal 30%E from fat	2	213	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.66, -0.26]
3.8.2 Goal 25 to < 30%E from fat	5	1470	Mean Difference (IV, Random, 95% CI)	-1.77 [-2.56, -0.99]
3.8.3 Goal 20 to < 25%E from fat	4	2456	Mean Difference (IV, Random, 95% CI)	-0.71 [-0.96, -0.46]
3.8.4 Goal 15 to < 20%E from fat	13	49481	Mean Difference (IV, Random, 95% CI)	-1.73 [-2.35, -1.10]
3.8.5 Goal 10 to < 15%E from fat	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8.6 Goal unclear	2	255	Mean Difference (IV, Random, 95% CI)	-1.82 [-4.93, 1.28]
3.9 Weight, kg Subgrouping by mean BMI at baseline	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.9.1 BMI at baseline < 25	9	1936	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.34, -0.37]
3.9.2 BMI at baseline ≥ 25 to 29.9	15	51113	Mean Difference (IV, Random, 95% CI)	-1.66 [-2.11, -1.21]
3.9.3 BMI at baseline ≥ 30	1	462	Mean Difference (IV, Random, 95% CI)	-1.99 [-3.40, -0.59]
3.9.4 BMI at baseline unclear	1	364	Mean Difference (IV, Random, 95% CI)	-1.70 [-2.52, -0.88]
3.10 Weight, kg Subgrouping by baseline health status	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.10.1 Healthy people, not recruited on the basis of risk factors or illness	4	44088	Mean Difference (IV, Random, 95% CI)	-0.88 [-1.26, -0.49]
3.10.2 People recruited on the basis of risk factors such as lipids, BMI, hormone levels, risk scores	11	2833	Mean Difference (IV, Random, 95% CI)	-1.85 [-2.49, -1.21]
3.10.3 People with disease such as DM, MI, cancer, polypsp	11	6954	Mean Difference (IV, Random, 95% CI)	-1.48 [-2.16, -0.80]
3.11 Weight, kg Subgrouping by assessed energy reduction	26	53875	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.73, -1.10]
3.11.1 E intake the same or greater in low fat group	4	3159	Mean Difference (IV, Random, 95% CI)	-0.59 [-0.85, -0.32]
3.11.2 E intake 1 to 100kcal/d less in low fat group	5	2442	Mean Difference (IV, Random, 95% CI)	-1.04 [-1.68, -0.41]
3.11.3 E intake 101 to 200 kcal/d less in low fat group	5	43221	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.38, -0.10]
3.11.4 E intake > 201 kcal/d less in low fat group	7	4406	Mean Difference (IV, Random, 95% CI)	-2.22 [-2.83, -1.61]
3.11.5 E intake unclear	6	647	Mean Difference (IV, Random, 95% CI)	-2.07 [-3.33, -0.80]

Analysis 3.1. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 1: Weight, kg Subgrouping by trial duration

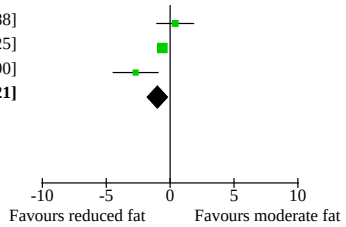
Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 duration 6 to < 12 months								
BDIT Pilot Studies 1996	58	7	100	60	8	106	3.3%	-2.00 [-4.05 , 0.05]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	7.4%	-1.00 [-2.02 , 0.02]
De Bont 1981 (1)	-0.4	2.8	36	0.1	2	29	6.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (2)	-2.7	3.6	34	-0.9	3.5	35	4.3%	-1.80 [-3.48 , -0.12]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	9.9%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	3.5%	-0.10 [-2.04 , 1.84]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	12.1%	-0.60 [-0.84 , -0.36]
RISCK 2010 (3)	-0.8734	2.6017	117	0.1674	1.8124	115	10.3%	-1.04 [-1.62 , -0.46]
RISCK 2010 (4)	-0.8877	2.1451	111	-0.0402	0.213	110	11.3%	-0.85 [-1.25 , -0.45]
Simon 1997	63.82	10.4	67	68.45	12.29	76	1.2%	-4.63 [-8.35 , -0.91]
Strychar 2009	-0.83	3	15	1.6	1.8	15	4.0%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-2.97	4.39	66	-0.08	3.6	70	5.6%	-2.89 [-4.24 , -1.54]
WHT Vanguard 1991	-3.16	3.7	179	-0.22	3	113	8.9%	-2.94 [-3.71 , -2.17]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	11.6%	-1.50 [-1.85 , -1.15]
Subtotal (95% CI)			**2353**			**1945**	**100.0%**	**-1.35 [-1.78 , -0.92]**
Heterogeneity: Tau² = 0.39; Chi² = 60.77, df = 13 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 6.15 (P < 0.00001)								
3.1.2 duration 12 to < 24 months								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	7.4%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59	7	100	60	8	106	3.8%	-1.00 [-3.05 , 1.05]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	4.5%	-0.40 [-2.21 , 1.41]
Canadian DBCP 1997	61.4	8.6	385	62.9	9.2	397	6.4%	-1.50 [-2.75 , -0.25]
DEER 1998 (5)	-2.8	3.5	49	0.5	2.7	46	6.4%	-3.30 [-4.55 , -2.05]
DEER 1998 (6)	-3.1	3.7	43	-0.4	2.5	43	6.1%	-2.70 [-4.03 , -1.37]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	5.5%	-3.60 [-5.08 , -2.12]
DEER 1998 (8)	-2.7	3.5	46	0.8	4.2	45	5.1%	-3.50 [-5.09 , -1.91]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.9%	0.90 [-4.26 , 6.06]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	1.4%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-1.96	4.06	975	0.01	3.46	989	10.1%	-1.97 [-2.30 , -1.64]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.8%	-8.50 [-13.77 , -3.23]
Swinburn 2001	-3.32	5.52	66	0.59	13.47	70	1.8%	-3.91 [-7.33 , -0.49]
WHEL 2007	73	17.21	1463	73.8	18.11	1484	6.3%	-0.80 [-2.08 , 0.48]
WHI 2006	74	16.5	17026	75.9	16.5	24977	10.2%	-1.90 [-2.22 , -1.58]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	8.3%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-2.93	4.8	177	-0.62	3.8	110	7.5%	-2.31 [-3.31 , -1.31]
WINS 1993	-2.3	15.1	854	0	15.1	1310	6.2%	-2.30 [-3.60 , -1.00]
Yadav 2016 (9)	-7.4	7.9	22	0.7	5.4	27	1.4%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**21618**			**30047**	**100.0%**	**-2.07 [-2.57 , -1.56]**
Heterogeneity: Tau² = 0.62; Chi² = 65.89, df = 18 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 8.06 (P < 0.00001)								
3.1.3 duration 24 to < 60 months								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	3.2%	-0.80 [-3.28 , 1.68]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	9.2%	-1.50 [-2.79 , -0.21]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	6.1%	-1.70 [-3.41 , 0.01]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	22.5%	-0.96 [-1.43 , -0.49]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	4.5%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.2	18.77	1355	74.1	18.46	1363	8.2%	0.10 [-1.30 , 1.50]
WHI 2006 (10)	-0.8	10.1	16297	-0.1	10.1	25056	27.5%	-0.70 [-0.90 , -0.50]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	11.0%	-1.83 [-2.96 , -0.70]
WINS 1993	-1.8	15.1	698	0	15.1	1044	7.8%	-1.80 [-3.25 , -0.35]
Subtotal (95% CI)			**20027**			**29144**	**100.0%**	**-1.18 [-1.65 , -0.70]**
Heterogeneity: Tau² = 0.20; Chi² = 18.01, df = 8 (P = 0.02); I² = 56%								
Test for overall effect: Z = 4.86 (P < 0.00001)								
3.1.4 duration 60+ months								
CORDIOPREV 2016 (11)	-1.34	6.3357	98	0.47	11.7962	115	7.9%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (12)	-0.18	5.4225	30	2.21	6.0576	39	6.9%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (13)	-1.27	7.1294	88	0.61	7.8652	92	9.6%	-1.88 [-4.07 , 0.31]
Swinburn 2001	1.06	4.57	51	1.26	4.9	52	12.4%	-0.20 [-2.03 , 1.63]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	16.1%	0.40 [-1.08 , 1.88]
WHI 2006	75.6	16.8	14409	76.2	16.6	22321	34.4%	-0.60 [-0.95 , -0.25]

Analysis 3.1. (Continued)

WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	16.1%	0.40 [-1.08 , 1.88]
WHI 2006	75.6	16.8	14409	76.2	16.6	22321	34.4%	-0.60 [-0.95 , -0.25]
WINS 1993	-2.7	15.3	386	0	15.3	998	12.7%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**16370**			**24930**	**100.0%**	**-1.00 [-1.79 , -0.21]**

Heterogeneity: Tau² = 0.44; Chi² = 10.82, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 2.47 (P = 0.01)

Test for subgroup differences: Chi² = 8.47, df = 3 (P = 0.04), I² = 64.6%

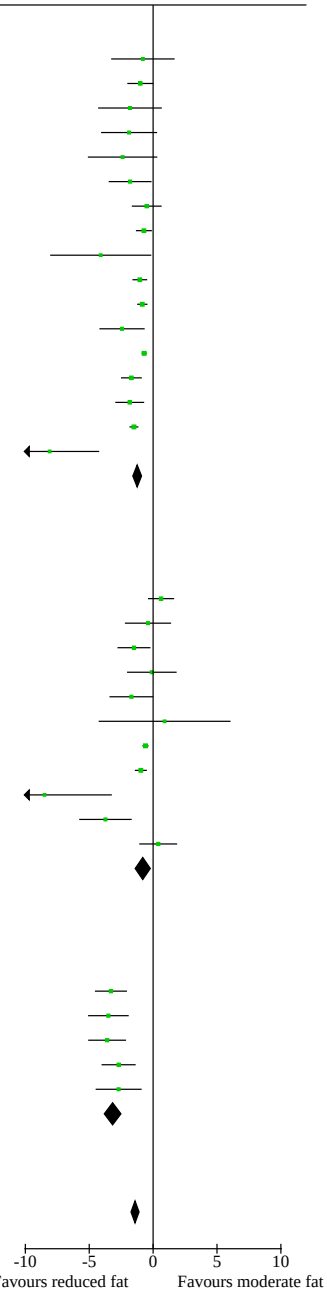


Footnotes

(1) non-obese participants (BMI < 28)
(2) obese participants (BMI 28+)
(3) Low GI arms, Calculated from % change based on median baseline
(4) High GI arms; Calculated from % change based on median baseline
(5) Men, no exercise
(6) Women with exercise
(7) Men with exercise
(8) Women, no exercise
(9) Data for 22 of 26 intervention participants who were compliant with diet
(10) Change from baseline to 7.5 years
(11) preDM by IFT/IGT, change to 5 years
(12) Non-preDM, change to 5 years
(13) pre-DM by HbA1c, change to 5 years

Analysis 3.2. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 2: Weight, kg Subgrouping by baseline fat intake

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 > 35%E from fat								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
De Bont 1981 (4)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (5)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
RISCK 2010 (6)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (7)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
WHI 2006 (8)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
Yadav 2016 (9)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**18752**			**27050**	**55.8%**	**-1.25 [-1.59 , -0.91]**
Heterogeneity: Tau² = 0.20; Chi² = 43.88, df = 16 (P = 0.0002); I² = 64%								
Test for overall effect: Z = 7.15 (P < 0.00001)								
3.2.2 > 30 to 35%E from fat								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
Subtotal (95% CI)			**3073**			**3249**	**30.6%**	**-0.81 [-1.40 , -0.22]**
Heterogeneity: Tau² = 0.44; Chi² = 30.66, df = 10 (P = 0.0007); I² = 67%								
Test for overall effect: Z = 2.68 (P = 0.007)								
3.2.3 > 25 to 30%E from fat								
DEER 1998 (10)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (11)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
DEER 1998 (12)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (13)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**572**			**1179**	**13.6%**	**-3.17 [-3.82 , -2.52]**
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 4 (P = 0.87); I² = 0%								
Test for overall effect: Z = 9.54 (P < 0.00001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 32.53, df = 2 (P < 0.00001), I² = 93.9%								



Footnotes

(1) preDM by IFT/IGT, change to 5 years
(2) pre-DM by HbA1c, change to 5 years
(3) Non-preDM, change to 5 years
(4) obese participants (BMI 28+)
(5) non-obese participants (BMI < 28)
(6) Low GI arms, Calculated from % change based on median baseline
(7) High GI arms; Calculated from % change based on median baseline
(8) Change from baseline to 7.5 years
(9) Data for 22 of 26 intervention participants who were compliant with diet
(10) Men, no exercise

Analysis 3.2. (Continued)

(9) Data for 22 of 26 intervention participants who were compliant with diet
(10) Men, no exercise
(11) Women, no exercise
(12) Men with exercise
(13) Women with exercise

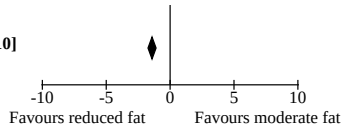
Analysis 3.3. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 3: Weight, kg Subgrouping by decade of first publication

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 1960s								
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Subtotal (95% CI)			**12**			**23**	**0.6%**	**-4.10 [-8.06 , -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.03 (P = 0.04)								
3.3.2 1970s								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.3.3 1980s								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
De Bont 1981 (1)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (2)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
Subtotal (95% CI)			**146**			**142**	**7.1%**	**-0.91 [-1.80 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.99 (P = 0.05)								
3.3.4 1990s								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (3)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (4)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (5)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (6)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**2538**			**3151**	**46.4%**	**-1.86 [-2.49 , -1.22]**
Heterogeneity: Tau² = 1.02; Chi² = 61.18, df = 13 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 5.71 (P < 0.00001)								
3.3.5 2000s								
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (7)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
Subtotal (95% CI)			**19088**			**27414**	**21.6%**	**-1.15 [-1.85 , -0.46]**
Heterogeneity: Tau² = 0.41; Chi² = 28.98, df = 6 (P < 0.0001); I² = 79%								
Test for overall effect: Z = 3.27 (P = 0.001)								
3.3.6 2010s								
CORDIOPREV 2016 (8)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (9)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (10)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (12)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**613**			**748**	**24.3%**	**-1.04 [-1.58 , -0.51]**
Heterogeneity: Tau² = 0.23; Chi² = 20.05, df = 7 (P = 0.005); I² = 65%								
Test for overall effect: Z = 3.84 (P = 0.0001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**

Analysis 3.3. (Continued)

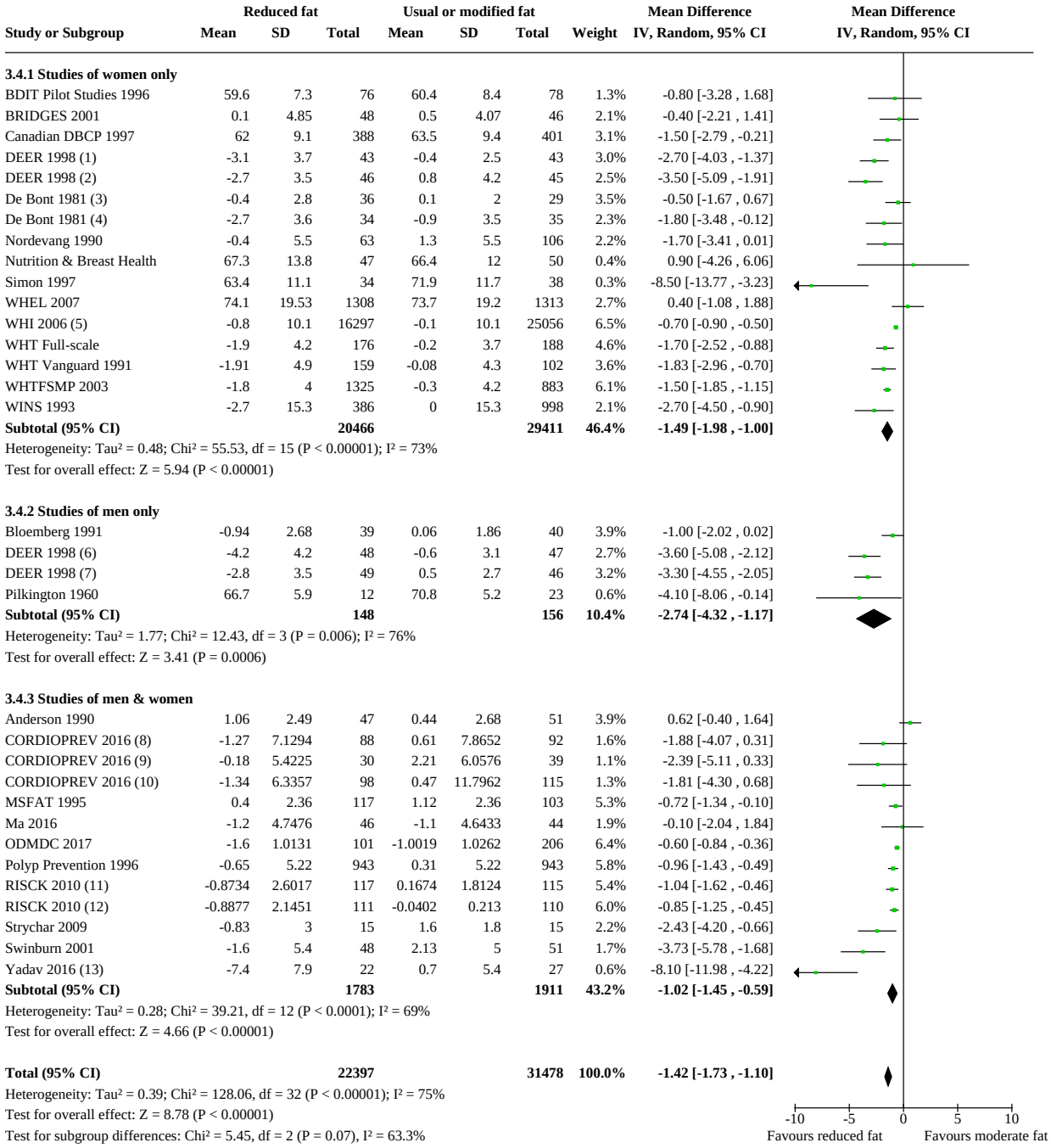
Total (95% CI)	**22397**	**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**

Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%
Test for overall effect: Z = 8.78 (P < 0.00001)
Test for subgroup differences: Chi² = 6.64, df = 4 (P = 0.16), I² = 39.8%



Footnotes
(1) obese participants (BMI 28+)
(2) non-obese participants (BMI < 28)
(3) Men, no exercise
(4) Women with exercise
(5) Men with exercise
(6) Women, no exercise
(7) Change from baseline to 7.5 years
(8) Non-preDM, change to 5 years
(9) pre-DM by HbA1c, change to 5 years
(10) preDM by IFT/IGT, change to 5 years
(11) Low GI arms, Calculated from % change based on median baseline
(12) High GI arms; Calculated from % change based on median baseline
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.4. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 4: Weight, kg Subgrouping by sex



Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 Studies of women only								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (1)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (2)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
De Bont 1981 (3)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (4)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (5)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**20466**			**29411**	**46.4%**	**-1.49 [-1.98 , -1.00]**
Heterogeneity: Tau² = 0.48; Chi² = 55.53, df = 15 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 5.94 (P < 0.00001)								
3.4.2 Studies of men only								
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
DEER 1998 (6)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (7)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Subtotal (95% CI)			**148**			**156**	**10.4%**	**-2.74 [-4.32 , -1.17]**
Heterogeneity: Tau² = 1.77; Chi² = 12.43, df = 3 (P = 0.006); I² = 76%								
Test for overall effect: Z = 3.41 (P = 0.0006)								
3.4.3 Studies of men & women								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
CORDIOPREV 2016 (8)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (9)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (10)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (12)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**1783**			**1911**	**43.2%**	**-1.02 [-1.45 , -0.59]**
Heterogeneity: Tau² = 0.28; Chi² = 39.21, df = 12 (P < 0.0001); I² = 69%								
Test for overall effect: Z = 4.66 (P < 0.00001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.45, df = 2 (P = 0.07), I² = 63.3%								

Footnotes

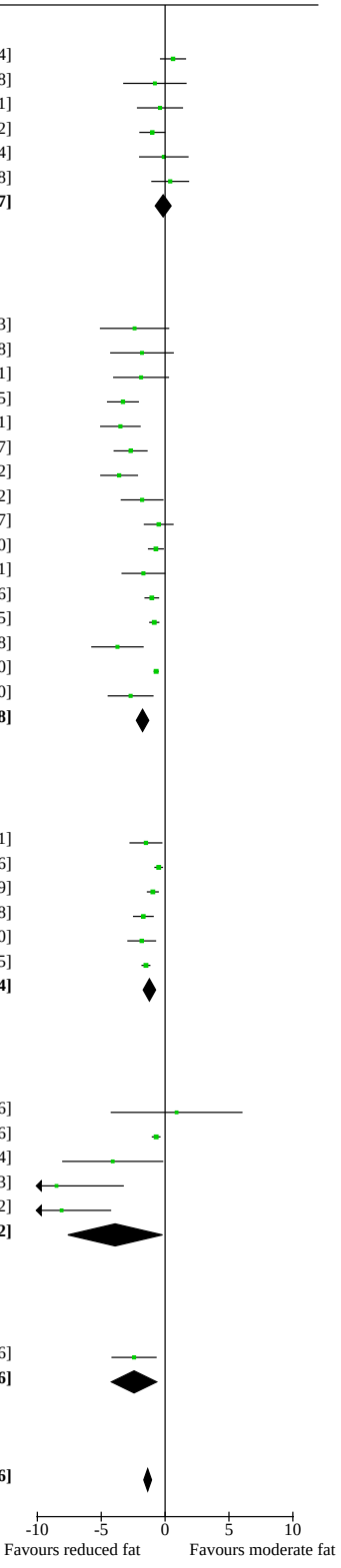
(1) Women with exercise
(2) Women, no exercise
(3) non-obese participants (BMI < 28)
(4) obese participants (BMI 28+)
(5) Change from baseline to 7.5 years
(6) Men with exercise
(7) Men, no exercise
(8) pre-DM by HbA1c, change to 5 years
(9) Non-preDM, change to 5 years
(10) preDM by IFT/IGT, change to 5 years

Analysis 3.4. (Continued)

(9) Non-preDM, change to 5 years
(10) preDM by IFT/IGT, change to 5 years
(11) Low GI arms, Calculated from % change based on median baseline
(12) High GI arms; Calculated from % change based on median baseline
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.5. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 5: Weight, kg Subgrouping by difference in %E from fat between control & reduced fat groups

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.5.1 Up to 5%E fat difference								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.7%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.2%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.0%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.7%	-1.00 [-2.02 , 0.02]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.8%	-0.10 [-2.04 , 1.84]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.5%	0.40 [-1.08 , 1.88]
Subtotal (95% CI)			**1564**			**1572**	**14.8%**	**-0.15 [-0.77 , 0.47]**
Heterogeneity: Tau² = 0.08; Chi² = 5.71, df = 5 (P = 0.34); I² = 12%								
Test for overall effect: Z = 0.47 (P = 0.64)								
3.5.2 5% to < 10% E fat difference								
CORDIOPREV 2016 (1)	-0.18	5.4225	30	2.21	6.0576	39	1.0%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (2)	-1.34	6.3357	98	0.47	11.7962	115	1.2%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (3)	-1.27	7.1294	88	0.61	7.8652	92	1.5%	-1.88 [-4.07 , 0.31]
DEER 1998 (4)	-2.8	3.5	49	0.5	2.7	46	3.1%	-3.30 [-4.55 , -2.05]
DEER 1998 (5)	-2.7	3.5	46	0.8	4.2	45	2.3%	-3.50 [-5.09 , -1.91]
DEER 1998 (6)	-3.1	3.7	43	-0.4	2.5	43	2.9%	-2.70 [-4.03 , -1.37]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	2.5%	-3.60 [-5.08 , -2.12]
De Bont 1981 (8)	-2.7	3.6	34	-0.9	3.5	35	2.2%	-1.80 [-3.48 , -0.12]
De Bont 1981 (9)	-0.4	2.8	36	0.1	2	29	3.3%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.0%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.1%	-1.70 [-3.41 , 0.01]
RISCK 2010 (10)	-0.8734	2.6017	117	0.1674	1.8124	115	5.2%	-1.04 [-1.62 , -0.46]
RISCK 2010 (11)	-0.8877	2.1451	111	-0.0402	0.213	110	5.7%	-0.85 [-1.25 , -0.45]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.6%	-3.73 [-5.78 , -1.68]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	6.2%	-0.70 [-0.90 , -0.50]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.0%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**17611**			**27030**	**47.6%**	**-1.76 [-2.25 , -1.28]**
Heterogeneity: Tau² = 0.52; Chi² = 64.36, df = 15 (P < 0.00001); I² = 77%								
Test for overall effect: Z = 7.14 (P < 0.00001)								
3.5.3 10% to < 15%E fat difference								
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.0%	-1.50 [-2.79 , -0.21]
ODMDC 2017	-1.6	1.0131	51	-1.1	1.0335	105	5.9%	-0.50 [-0.84 , -0.16]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.5%	-0.96 [-1.43 , -0.49]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.4%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.4%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	5.8%	-1.50 [-1.85 , -1.15]
Subtotal (95% CI)			**3042**			**2622**	**27.9%**	**-1.23 [-1.72 , -0.74]**
Heterogeneity: Tau² = 0.24; Chi² = 21.16, df = 5 (P = 0.0008); I² = 76%								
Test for overall effect: Z = 4.95 (P < 0.00001)								
3.5.4 15+%E fat difference								
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.3%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	50	-0.9	1.0131	101	5.9%	-0.70 [-1.04 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.5%	-4.10 [-8.06 , -0.14]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**165**			**239**	**7.6%**	**-3.91 [-7.61 , -0.22]**
Heterogeneity: Tau² = 13.75; Chi² = 25.22, df = 4 (P < 0.0001); I² = 84%								
Test for overall effect: Z = 2.08 (P = 0.04)								
3.5.5 %E fat difference not stated								
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.0%	-2.43 [-4.20 , -0.66]
Subtotal (95% CI)			**15**			**15**	**2.0%**	**-2.43 [-4.20 , -0.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.69 (P = 0.007)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.36 [-1.67 , -1.06]**
Heterogeneity: Tau² = 0.38; Chi² = 128.67, df = 33 (P < 0.00001); I² = 74%								
Test for overall effect: Z = 8.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 19.98, df = 4 (P = 0.0005), I² = 80.0%								



Analysis 3.5. (Continued)

Test for subgroup differences: Chi² = 19.98, df = 4 (P = 0.0005), I² = 80.0%

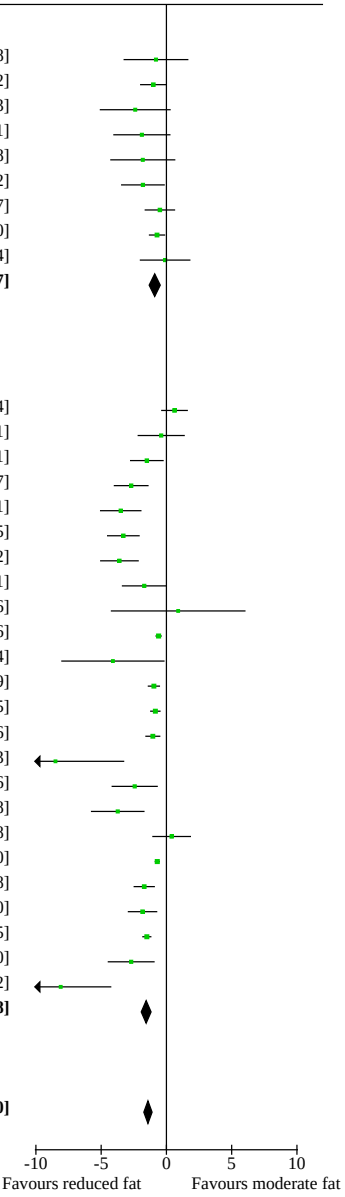
Favours reduced fat Favours moderate fat

Footnotes

(1) Non-preDM, change to 5 years
(2) preDM by IFT/IGT, change to 5 years
(3) pre-DM by HbA1c, change to 5 years
(4) Men, no exercise
(5) Women, no exercise
(6) Women with exercise
(7) Men with exercise
(8) obese participants (BMI 28+)
(9) non-obese participants (BMI < 28)
(10) Low GI arms, Calculated from % change based on median baseline
(11) High GI arms; Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.6. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 6: Weight, kg Subgrouping by achieving < 30%E from fat

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.6.1 Intervention did not achieve < 30%E from fat or less								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
CORDIOPREV 2016 (1)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (2)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (3)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
De Bont 1981 (4)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (5)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Subtotal (95% CI)			**564**			**575**	**22.2%**	**-0.90 [-1.32 , -0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 5.01, df = 8 (P = 0.76); I² = 0%								
Test for overall effect: Z = 4.14 (P < 0.0001)								
3.6.2 Intervention achieved < 30%E from fat or less								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (6)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (7)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
DEER 1998 (8)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (9)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (10)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**21833**			**30903**	**77.8%**	**-1.55 [-1.93 , -1.18]**
Heterogeneity: Tau² = 0.45; Chi² = 123.01, df = 23 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 8.09 (P < 0.00001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.12, df = 1 (P = 0.02), I² = 80.5%								

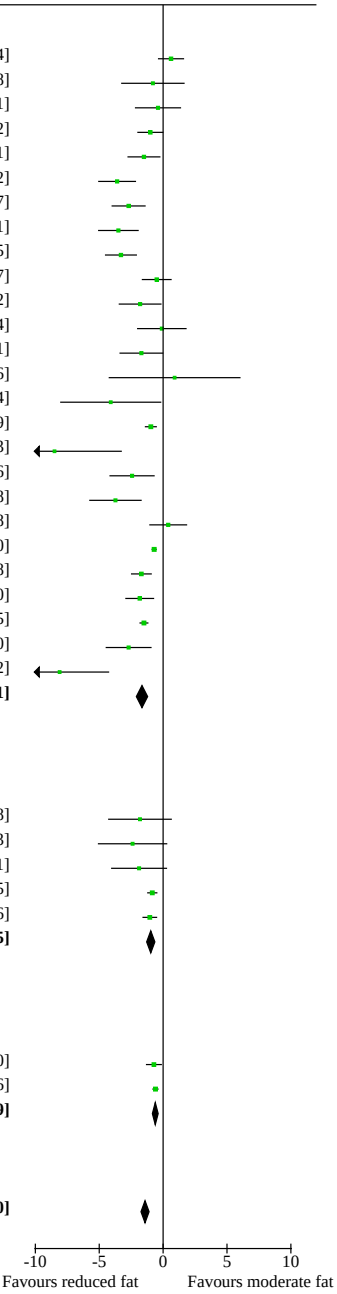


Footnotes

(1) Non-preDM, change to 5 years
(2) pre-DM by HbA1c, change to 5 years
(3) preDM by IFT/IGT, change to 5 years
(4) obese participants (BMI 28+)
(5) non-obese participants (BMI < 28)
(6) Women with exercise
(7) Women, no exercise
(8) Men, no exercise
(9) Men with exercise
(10) High GI arms; Calculated from % change based on median baseline
(11) Low GI arms, Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.7. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 7: Weight, kg Subgrouping by type of intervention

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.7.1 Dietary advice								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (1)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (2)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (3)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
DEER 1998 (4)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
De Bont 1981 (5)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (6)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (7)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (8)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**21735**			**30698**	**72.9%**	**-1.65 [-2.09 , -1.21]**
Heterogeneity: Tau² = 0.70; Chi² = 114.64, df = 25 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 7.35 (P < 0.00001)								
3.7.2 Dietary advice plus supplements								
CORDIOPREV 2016 (9)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (10)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (11)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
RISCK 2010 (12)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
RISCK 2010 (13)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
Subtotal (95% CI)			**444**			**471**	**15.4%**	**-0.97 [-1.29 , -0.65]**
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 4 (P = 0.63); I² = 0%								
Test for overall effect: Z = 5.91 (P < 0.00001)								
3.7.3 Diet provided								
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Subtotal (95% CI)			**218**			**309**	**11.7%**	**-0.61 [-0.84 , -0.39]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 5.33 (P < 0.00001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 17.40, df = 2 (P = 0.0002), I² = 88.5%								



Footnotes

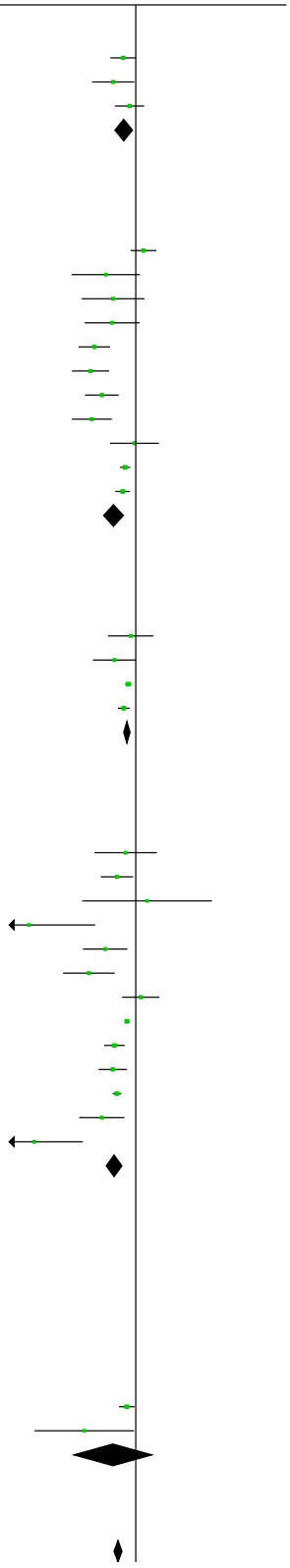
(1) Men with exercise
(2) Women with exercise
(3) Women, no exercise
(4) Men, no exercise
(5) non-obese participants (BMI < 28)
(6) obese participants (BMI 28+)
(7) Change from baseline to 7.5 years
(8) Data for 22 of 26 intervention participants who were compliant with diet
(9) preDM by IFT/IGT, change to 5 years
(10) Non-preDM, change to 5 years

Analysis 3.7. (Continued)

(9) preDM by IFT/IGT, change to 5 years
(10) Non-preDM, change to 5 years
(11) pre-DM by HbA1c, change to 5 years
(12) High GI arms; Calculated from % change based on median baseline
(13) Low GI arms, Calculated from % change based on median baseline

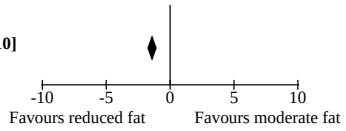
Analysis 3.8. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 8: Weight, kg Subgrouping by lower fat arm fat goal

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.8.1 Goal 30%E from fat								
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
De Bont 1981 (1)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (2)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
Subtotal (95% CI)			**109**			**104**	**9.7%**	**-0.96 [-1.66 , -0.26]**
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 2.69 (P = 0.007)								
3.8.2 Goal 25 to < 30%E from fat								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
CORDIOPREV 2016 (3)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (4)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (5)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
DEER 1998 (6)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (7)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (8)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (9)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
RISCK 2010 (10)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
RISCK 2010 (11)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
Subtotal (95% CI)			**723**			**747**	**32.7%**	**-1.77 [-2.56 , -0.99]**
Heterogeneity: Tau² = 1.18; Chi² = 51.73, df = 10 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 4.41 (P < 0.0001)								
3.8.3 Goal 20 to < 25%E from fat								
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
Subtotal (95% CI)			**1155**			**1301**	**16.5%**	**-0.71 [-0.96 , -0.46]**
Heterogeneity: Tau² = 0.01; Chi² = 3.24, df = 3 (P = 0.36); I² = 8%								
Test for overall effect: Z = 5.53 (P < 0.00001)								
3.8.4 Goal 15 to < 20%E from fat								
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (12)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**20281**			**29200**	**35.2%**	**-1.73 [-2.35 , -1.10]**
Heterogeneity: Tau² = 0.64; Chi² = 59.35, df = 12 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 5.43 (P < 0.00001)								
3.8.5 Goal 10 to < 15%E from fat								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.8.6 Goal unclear								
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Subtotal (95% CI)			**129**			**126**	**5.8%**	**-1.82 [-4.93 , 1.28]**
Heterogeneity: Tau² = 3.62; Chi² = 2.73, df = 1 (P = 0.10); I² = 63%								
Test for overall effect: Z = 1.15 (P = 0.25)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**



Analysis 3.8. (Continued)

Total (95% CI)	**22397**	**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**	
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%					
Test for overall effect: Z = 8.78 (P < 0.00001)					
Test for subgroup differences: Chi² = 14.00, df = 4 (P = 0.007), I² = 71.4%					

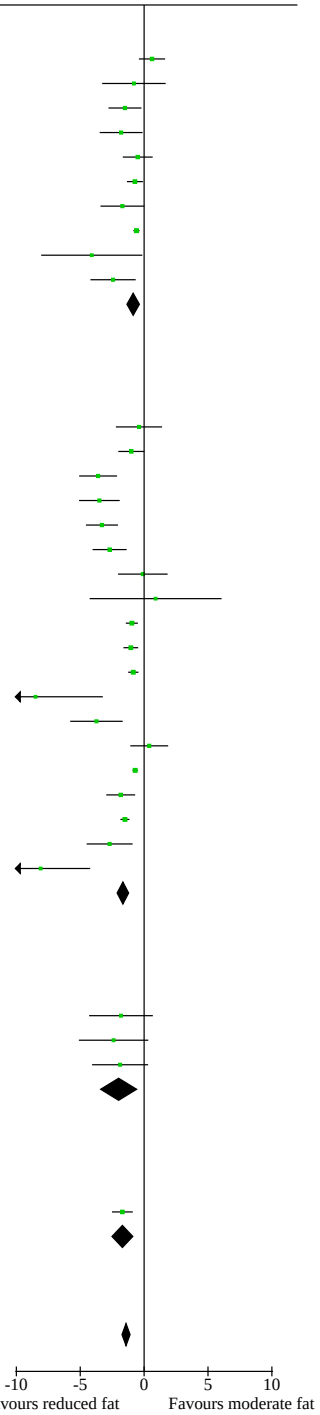


Footnotes

(1) obese participants (BMI 28+)
(2) non-obese participants (BMI < 28)
(3) Non-preDM, change to 5 years
(4) preDM by IFT/IGT, change to 5 years
(5) pre-DM by HbA1c, change to 5 years
(6) Men, no exercise
(7) Men with exercise
(8) Women with exercise
(9) Women, no exercise
(10) High GI arms; Calculated from % change based on median baseline
(11) Low GI arms, Calculated from % change based on median baseline
(12) Change from baseline to 7.5 years
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.9. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 9: Weight, kg Subgrouping by mean BMI at baseline

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.9.1 BMI at baseline < 25								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
De Bont 1981 (1)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (2)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
Subtotal (95% CI)			**889**			**1047**	**30.8%**	**-0.86 [-1.34 , -0.37]**
Heterogeneity: Tau² = 0.23; Chi² = 17.93, df = 9 (P = 0.04); I² = 50%								
Test for overall effect: Z = 3.44 (P = 0.0006)								
3.9.2 BMI at baseline # 25 to 29.9								
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
DEER 1998 (3)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (4)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
DEER 1998 (5)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (6)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (7)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
RISCK 2010 (8)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WHI 2006 (9)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (10)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**21116**			**29997**	**60.6%**	**-1.66 [-2.11 , -1.21]**
Heterogeneity: Tau² = 0.53; Chi² = 95.59, df = 18 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 7.24 (P < 0.00001)								
3.9.3 BMI at baseline # 30								
CORDIOPREV 2016 (11)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (12)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (13)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
Subtotal (95% CI)			**216**			**246**	**4.0%**	**-1.99 [-3.40 , -0.59]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 2.78 (P = 0.005)								
3.9.4 BMI at baseline unclear								
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
Subtotal (95% CI)			**176**			**188**	**4.6%**	**-1.70 [-2.52 , -0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.09 (P < 0.0001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.25, df = 3 (P = 0.06), I² = 58.6%								



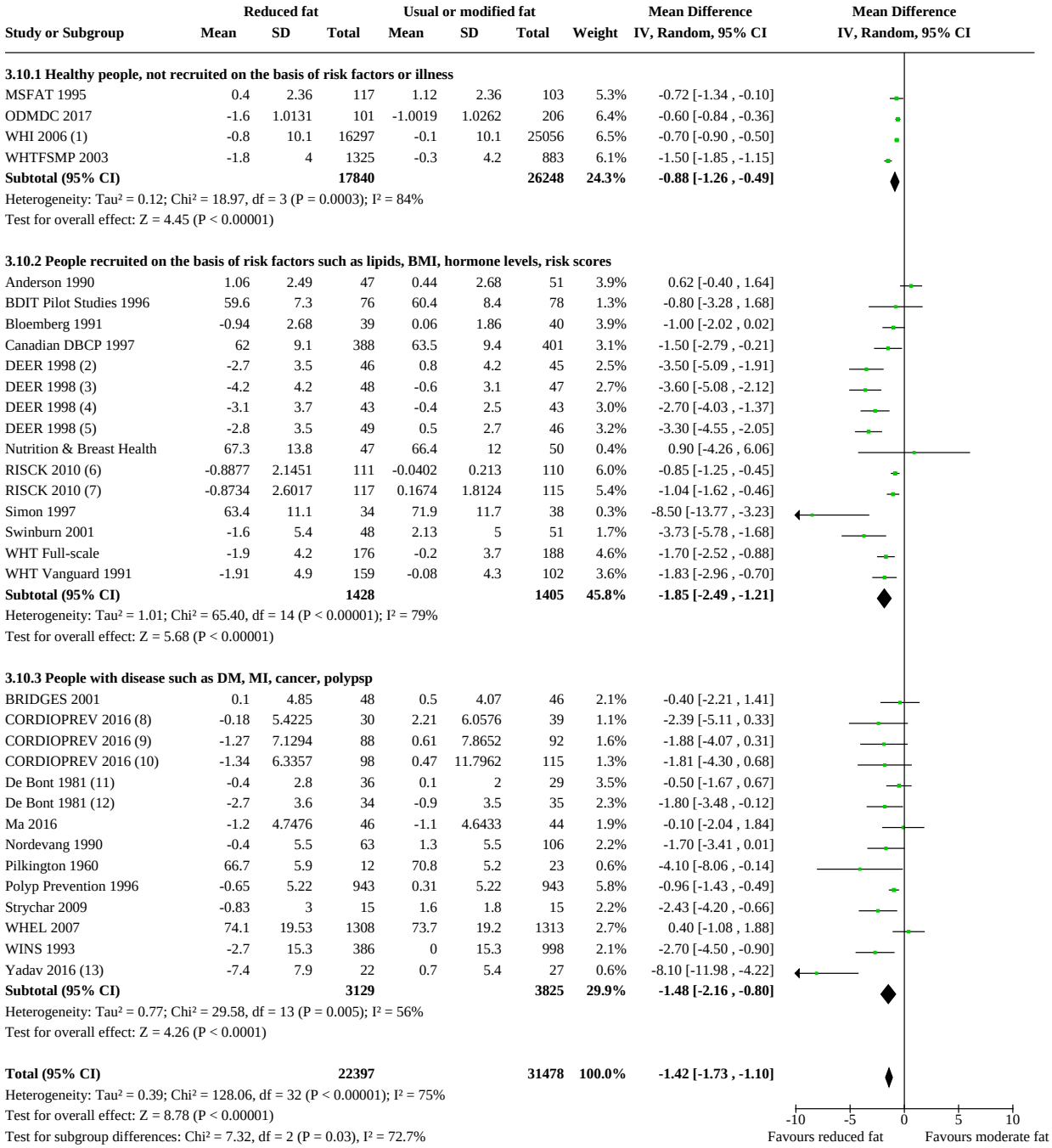
Footnotes

(1) obese participants (BMI 28+)
(2) non-obese participants (BMI < 28)
(3) Men with exercise
(4) Women, no exercise
(5) Men, no exercise

Analysis 3.9. (Continued)

(4) Women, no exercise
(5) Men, no exercise
(6) Women with exercise
(7) Low GI arms, Calculated from % change based on median baseline
(8) High GI arms; Calculated from % change based on median baseline
(9) Change from baseline to 7.5 years
(10) Data for 22 of 26 intervention participants who were compliant with diet
(11) preDM by IFT/IGT, change to 5 years
(12) Non-preDM, change to 5 years
(13) pre-DM by HbA1c, change to 5 years

Analysis 3.10. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 10: Weight, kg Subgrouping by baseline health status



Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.10.1 Healthy people, not recruited on the basis of risk factors or illness								
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
WHI 2006 (1)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
Subtotal (95% CI)			**17840**			**26248**	**24.3%**	**-0.88 [-1.26 , -0.49]**
Heterogeneity: Tau² = 0.12; Chi² = 18.97, df = 3 (P = 0.0003); I² = 84%								
Test for overall effect: Z = 4.45 (P < 0.00001)								
3.10.2 People recruited on the basis of risk factors such as lipids, BMI, hormone levels, risk scores								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (2)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
DEER 1998 (3)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (4)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (5)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
RISCK 2010 (6)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
RISCK 2010 (7)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
Subtotal (95% CI)			**1428**			**1405**	**45.8%**	**-1.85 [-2.49 , -1.21]**
Heterogeneity: Tau² = 1.01; Chi² = 65.40, df = 14 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 5.68 (P < 0.00001)								
3.10.3 People with disease such as DM, MI, cancer, polypsp								
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
CORDIOPREV 2016 (8)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
CORDIOPREV 2016 (9)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (10)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
De Bont 1981 (11)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
De Bont 1981 (12)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**3129**			**3825**	**29.9%**	**-1.48 [-2.16 , -0.80]**
Heterogeneity: Tau² = 0.77; Chi² = 29.58, df = 13 (P = 0.005); I² = 56%								
Test for overall effect: Z = 4.26 (P < 0.0001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.32, df = 2 (P = 0.03), I² = 72.7%								

Footnotes

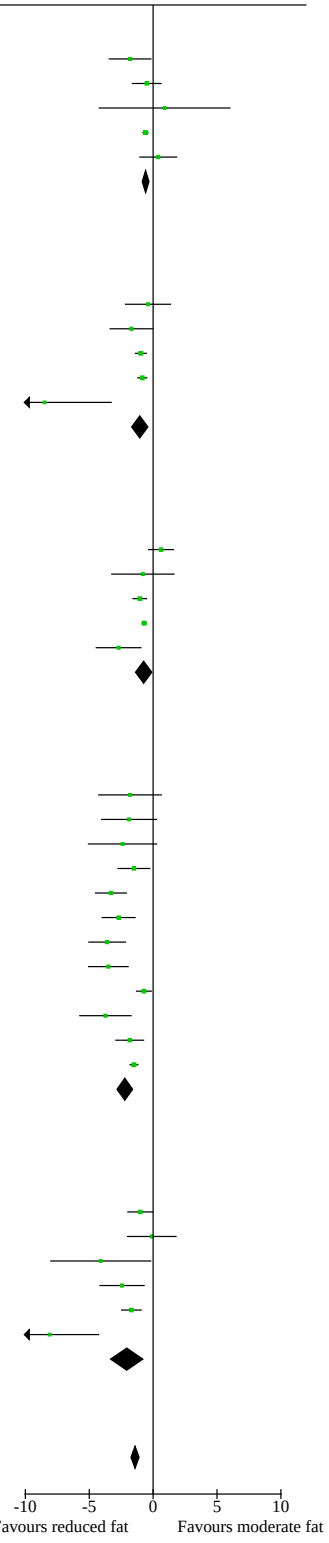
(1) Change from baseline to 7.5 years
(2) Women, no exercise
(3) Men with exercise
(4) Women with exercise
(5) Men, no exercise
(6) High GI arms; Calculated from % change based on median baseline
(7) Low GI arms, Calculated from % change based on median baseline
(8) Non-preDM, change to 5 years
(9) pre-DM by HbA1c, change to 5 years
(10) preDM by IFT/IGT, change to 5 years

Analysis 3.10. (Continued)

(9) pre-DM by HbA1c, change to 5 years
(10) preDM by IFT/IGT, change to 5 years
(11) non-obese participants (BMI < 28)
(12) obese participants (BMI 28+)
(13) Data for 22 of 26 intervention participants who were compliant with diet

Analysis 3.11. Comparison 3: Lower fat vs higher fat diet on body weight, subgrouping, Outcome 11: Weight, kg Subgrouping by assessed energy reduction

Study or Subgroup	Reduced fat Mean	SD	Total	Usual or modified fat Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.11.1 E intake the same or greater in low fat group								
De Bont 1981 (1)	-2.7	3.6	34	-0.9	3.5	35	2.3%	-1.80 [-3.48 , -0.12]
De Bont 1981 (2)	-0.4	2.8	36	0.1	2	29	3.5%	-0.50 [-1.67 , 0.67]
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.4%	0.90 [-4.26 , 6.06]
ODMDC 2017	-1.6	1.0131	101	-1.0019	1.0262	206	6.4%	-0.60 [-0.84 , -0.36]
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	2.7%	0.40 [-1.08 , 1.88]
Subtotal (95% CI)			**1526**			**1633**	**15.2%**	**-0.59 [-0.85 , -0.32]**
Heterogeneity: Tau² = 0.01; Chi² = 4.06, df = 4 (P = 0.40); I² = 2%								
Test for overall effect: Z = 4.33 (P < 0.0001)								
3.11.2 E intake 1 to 100kcal/d less in low fat group								
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	2.1%	-0.40 [-2.21 , 1.41]
Nordevang 1990	-0.4	5.5	63	1.3	5.5	106	2.2%	-1.70 [-3.41 , 0.01]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	5.8%	-0.96 [-1.43 , -0.49]
RISCK 2010 (3)	-0.8877	2.1451	111	-0.0402	0.213	110	6.0%	-0.85 [-1.25 , -0.45]
Simon 1997	63.4	11.1	34	71.9	11.7	38	0.3%	-8.50 [-13.77 , -3.23]
Subtotal (95% CI)			**1199**			**1243**	**16.5%**	**-1.04 [-1.68 , -0.41]**
Heterogeneity: Tau² = 0.22; Chi² = 9.21, df = 4 (P = 0.06); I² = 57%								
Test for overall effect: Z = 3.23 (P = 0.001)								
3.11.3 E intake 101 to 200 kcal/d less in low fat group								
Anderson 1990	1.06	2.49	47	0.44	2.68	51	3.9%	0.62 [-0.40 , 1.64]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	1.3%	-0.80 [-3.28 , 1.68]
RISCK 2010 (4)	-0.8734	2.6017	117	0.1674	1.8124	115	5.4%	-1.04 [-1.62 , -0.46]
WHI 2006 (5)	-0.8	10.1	16297	-0.1	10.1	25056	6.5%	-0.70 [-0.90 , -0.50]
WINS 1993	-2.7	15.3	386	0	15.3	998	2.1%	-2.70 [-4.50 , -0.90]
Subtotal (95% CI)			**16923**			**26298**	**19.2%**	**-0.74 [-1.38 , -0.10]**
Heterogeneity: Tau² = 0.28; Chi² = 12.47, df = 4 (P = 0.01); I² = 68%								
Test for overall effect: Z = 2.27 (P = 0.02)								
3.11.4 E intake > 201 kcal/d less in low fat group								
CORDIOPREV 2016 (6)	-1.34	6.3357	98	0.47	11.7962	115	1.3%	-1.81 [-4.30 , 0.68]
CORDIOPREV 2016 (7)	-1.27	7.1294	88	0.61	7.8652	92	1.6%	-1.88 [-4.07 , 0.31]
CORDIOPREV 2016 (8)	-0.18	5.4225	30	2.21	6.0576	39	1.1%	-2.39 [-5.11 , 0.33]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	3.1%	-1.50 [-2.79 , -0.21]
DEER 1998 (9)	-2.8	3.5	49	0.5	2.7	46	3.2%	-3.30 [-4.55 , -2.05]
DEER 1998 (10)	-3.1	3.7	43	-0.4	2.5	43	3.0%	-2.70 [-4.03 , -1.37]
DEER 1998 (11)	-4.2	4.2	48	-0.6	3.1	47	2.7%	-3.60 [-5.08 , -2.12]
DEER 1998 (12)	-2.7	3.5	46	0.8	4.2	45	2.5%	-3.50 [-5.09 , -1.91]
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	5.3%	-0.72 [-1.34 , -0.10]
Swinburn 2001	-1.6	5.4	48	2.13	5	51	1.7%	-3.73 [-5.78 , -1.68]
WHT Vanguard 1991	-1.91	4.9	159	-0.08	4.3	102	3.6%	-1.83 [-2.96 , -0.70]
WHTFSMP 2003	-1.8	4	1325	-0.3	4.2	883	6.1%	-1.50 [-1.85 , -1.15]
Subtotal (95% CI)			**2439**			**1967**	**35.3%**	**-2.22 [-2.83 , -1.61]**
Heterogeneity: Tau² = 0.62; Chi² = 34.49, df = 11 (P = 0.0003); I² = 68%								
Test for overall effect: Z = 7.14 (P < 0.00001)								
3.11.5 E intake unclear								
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	3.9%	-1.00 [-2.02 , 0.02]
Ma 2016	-1.2	4.7476	46	-1.1	4.6433	44	1.9%	-0.10 [-2.04 , 1.84]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	0.6%	-4.10 [-8.06 , -0.14]
Strychar 2009	-0.83	3	15	1.6	1.8	15	2.2%	-2.43 [-4.20 , -0.66]
WHT Full-scale	-1.9	4.2	176	-0.2	3.7	188	4.6%	-1.70 [-2.52 , -0.88]
Yadav 2016 (13)	-7.4	7.9	22	0.7	5.4	27	0.6%	-8.10 [-11.98 , -4.22]
Subtotal (95% CI)			**310**			**337**	**13.8%**	**-2.07 [-3.33 , -0.80]**
Heterogeneity: Tau² = 1.45; Chi² = 16.85, df = 5 (P = 0.005); I² = 70%								
Test for overall effect: Z = 3.21 (P = 0.001)								
Total (95% CI)			**22397**			**31478**	**100.0%**	**-1.42 [-1.73 , -1.10]**
Heterogeneity: Tau² = 0.39; Chi² = 128.06, df = 32 (P < 0.00001); I² = 75%								
Test for overall effect: Z = 8.78 (P < 0.00001)								
Test for subgroup differences: Chi² = 26.99, df = 4 (P < 0.0001), I² = 85.2%								



Footnotes

Analysis 3.11. (Continued)

Footnotes
(1) obese participants (BMI 28+)
(2) non-obese participants (BMI < 28)
(3) High GI arms; Calculated from % change based on median baseline
(4) Low GI arms, Calculated from % change based on median baseline
(5) Change from baseline to 7.5 years
(6) preDM by IFT/IGT, change to 5 years
(7) pre-DM by HbA1c, change to 5 years
(8) Non-preDM, change to 5 years
(9) Men, no exercise
(10) Women with exercise
(11) Men with exercise
(12) Women, no exercise
(13) Data for 22 of 26 intervention participants who were compliant with diet

ADDITIONAL TABLES

Table 1. Dietary intake of energy, sugars, carbohydrate and protein during trials

Trial	Energy intake (SD), kcal		Sugars intake, %E		CHO intake, %E		Protein intake, %E		Alcohol intake, %E		No. of participants	
	Int.	Cont	Int.	Cont	Int.	Cont	Int.	Cont	Int.	Cont	Int.	Cont
Anderson 1990, 1 yr	1882 (521)	2010 (528)	—	—	53 (8.9)	50 (7.9)	17 (3.4)	18 (4.3)	—	—	47	51
AUSMED 2018, 6 mo	1800 (541)	2014 (461)	5.7 (4.1)	5.4 (4.4)	42.5 (7.1)	34.8 (7.2)	21.8 (5.8)	19.4 (4.2)	1.1 (2.4)	3.0 (4.1)	31	34
BDIT Pilot Studies 1996, 9 yrs	1460 (376)	1578 (365)	—	—	49.6 (7.5)	46.9 (6.2)	15.5 (2.4)	15.3 (2.6)	2.3 (3.3)	1.7 (2.4)	76	81
beFIT 1997	(data not reported in control groups)											
Black 1994, during trial	1995 (564)	2196 (615)	—	—	60.3 (6.3)	44.6 (6.9)	17.7 (2.2)	15.7 (2.4)	3.2 (3.4)	3.2 (3.9)	57?	58?
Bloemberg 1991, Δ to 6 mo	—	—	—	—	4.4 (6.5)	1.2 (6.1)	0.33 (2.9)	0.57 (1.7)	—	—	39	41
Boyd 1988, 6 mo	1491 (NR)	1676 (NR)	—	—	56.3 (NR)	48.1 (NR)	17.9 (NR)	15.8 (NR)	4.8 (NR)	4.2 (NR)	10	9
BRIDGES 2001, Δ to 6 mo	-34 (79)	+ 22 (79)	—	—	—	—	—	—	—	—	48	46
Canadian DBCP 1997, 2 yrs	1540 (317)	1759 (437)	—	—	60.3 (8.3)	48.8 (8.1)	18.0 (3.2)	16.9 (2.8)	—	—	104	100
CORDIOPREV 2016, 5 yrs	1716 (363)	2024 (381)	-	-	45.6 (6.0)	38.5 (6.3)	18.9 (2.0)	17.3 (2.1)	-	-	406	447
De Bont 1981, Δ to 6 mo	-98 (369)	-120 (485)	—	—	7.9 (9.5)	-0.1 (10.9)	2.4 (7.0)	1.7 (5.9)	-0.2 (1.6)	-0.4 (2.6)	71	65
DEER 1998 (diet alone), Δ to 1 yr	Women: -220 (356) Men: -285 (541)	Women: -19 (367) Men: -25 (482)	—	—	Women: +5.5 (8.0) Men: +8.0 (9.3)	Women: -0.2 (7.3) Men: +1.1 (6.6)	—	—	—	—	46, 49	45, 46
DEER 1998 (diet and ex), Δ to 1 yr	Women: -191 (343) Men:	Women: -54 (410)	—	—	Women: +7.8 (6.2)	Women: -0.3 (7.9)	—	—	—	—	43, 48	43, 47

Table 1. Dietary intake of energy, sugars, carbohydrate and protein during trials *(Continued)*

	-167 (516)	Men: +141 (437)			Men: +9.3 (8.3)	Men: +1.4 (6.3)						
Diet and Hormone Study 2003, 1 yr	1921 (386)	2063 (610)	—	—	64.3 (9.0)	54.6 (9.2)	14.5 (2.9)	14.1 (3.8)	est: 1 (2)	est: 1 (2)	81	96
Ma 2016, 6 mo	-	-	-	-	-	-	-	-	-	-	46	44
MeDiet 2006, 6 mo	1676 (639)	1654 (498)	18.7 (6.9)	21.9 (9.2)	27.2 (17.0)	25.8 (11.0)	14.9 (4.7)	16.2 (5.1)	5.6 (11.1)	1.6 (2.2)	51?	55?
Moy 2001, 2 yrs	1825 (NR)	2092 (NR)	—	—	—	—	—	—	—	—	117	118
MSFAT 1995, 6 mo	2460 (NR)	2699 (NR)	—	—	47 (NR)	41 (NR)	16 (NR)	14 (NR)	3 (NR)	3 (NR)	117	103
NDHS Open 1st L&M 1968 6 mo	2154 (432)	2228 (456)	—	—	48.7 (12.3)	44.7 (11.7)	18.6 (3.4)	17.4 (3.1)	3.7 (3.7)	3.8 (4.0)	339	346
NDHS Open 2nd L&M 1968 6 mo	2249 (492)	2196 (427)	—	—	45.7 (12.7)	44.1 (11.1)	17.3 (3.5)	7.3 (3.0)	3.5 (4.2)	4.2 (4.0)	491	214
Nordevang 1990, Δ to 2 yrs	-215 (P < 0.01)	-143 (P < 0.01)	+4.8 (P < 0.01)	+1.4 (P < 0.01)	+11.0 (P < 0.01)	+2.7 (P < 0.01)	+1.7 (P < 0.01)	+0.3 (P > 0.05)	+0.2 (P > 0.05)	+0.4 (P > 0.05)	63	106
Nutrition & Breast Health, 1 yr	1780 and 1960	1571 and 1687	—	—	—	—	—	—	—	—	23 and 25	24 and 23
ODMDC 2017, during trial (by menu analysis)	Male: 2094 (NR) Female: 1697 (NR)	HF male: 2103 (NR) HF female: 1704 (NR)	-	-	66 (NR)	HF 46 (NR) MF 56 (NR)	14 (NR)	HF 14 (NR) MF 14 (NR)	-	-	101	HF 101, MF 105
Pilkington 1960, 1 yr	NR	NR	—	—	—	—	—	—	—	—	12	23
Polyp Prevention 1996, yr 4	1978 (471)	2030 (518)	—	—	58.3 (7.4)	47.1 (7.2)	17.3 (2.5)	16.5 (2.4)	—	—	605	581

Table 1. Dietary intake of energy, sugars, carbohydrate and protein during trials *(Continued)*

RISCK 2010 Δ to 6 mo (LF/HGI vs HM/HGI (95% CI)	-198.4 (-310.7,88.4)	-129.1 (-239, -19.1)	3.8 (2.4, 5.3)	0.5 (-0.9, 1.9)	8.1 (6.3, 9.9)	1.9 (0.1, 3.7)	-0.3 (-5.7, 5.1)	-2.2 (-7.5, 3.1)			95	93
RISCK 2010 Δ to 6 mo (LF/LGI vs HM/LGI (95% CI)	-313.1 (-418.3, 210.3)	-74.1 (-181.6, 35.9)	3.5 (2.1, 4.8)	-0.5 (-1.9, 0.8)	8.5 (6.8,10.2)	1.6 (-0.2, 3.4)	-2.8 (-7.8, 2.2)	-3.4 (-1.9, 8.6)			110	101
Rivellese 1994, 6 mo	NR	NR	14	10	55	48	18	16	—	—	27	17
Sarkkinen Low Fat 1993; Sarkkinen Low & Mod 1993, wks 14 to 28	AHA 1791 (382) Mono 1887 (478) Low fat 1648 (430)	1982 (406)	—	—	AHA 48 (5) Mono 47 (6) Low fat 51 (5)	46 (6)	AHA 17 (2) Mono 17 (20) Low fat 19 (3)	16 (2)	—	—	AHA 41 Mono 41 Low fat 40	37
Simon 1997, 1 yr	1570 (NR)	1594 (NR)	—	—	—	—	—	—	—	—	65	68
Strychar 2009, 6 mo	NR	NR	—	—	—	—	—	—	—	—	15	15
Swinburn 2001, 1 yr	1887 (672)	2269 (750)	—	—	54.2 (10.5)	45.8 (10.9)	18.4 (3.5)	16.6 (3.9)	3.6 (7.0)	5.7 (7.0)	49	61
WHEL 2007, 1 yr	1664 (345)	1635 (384)	—	—	65.3 (8.5)	57.1 (9.3)	—	—	—	—	197	196
WHI 2006, 7.5 yrs	1446 (510)	1564 (595)	—	—	52.7 (9.8)	44.7 (8.5)	—	—	—	—	14246	22083
WHT Full-scale, data only available after trial end	-	-	-	-	-	-	-	-	-	-	448	457
WHT Vanguard 1991, 2 yrs	1356 (358)	1617 (391)	—	—	59.0 (8.8)	46.9 (8.9)	19.2 (3.9)	16.8 (3.8)	—	—	163	101
WHTFSMP 2003, Δ to 18 mo	-488 (NR)	-255 (NR)	—	—	—	—	—	—	—	—	285	194
WINS 1993, 5 yrs	-167 (P < 0.0001 vs cont)	0	—	—	—	—	—	—	—	—	380	648

Table 1. Dietary intake of energy, sugars, carbohydrate and protein during trials *(Continued)*

Yadav 2016	-	-	-	-	-	-	-	-	-	-	26	27	

- Signifies that no data have been presented on this intake in this trial arm
AHA: American Heart Association
CHO: carbohydrate
CI: confidence interval
Cont: control arm
HF: high fat
HGI: high glycaemic index
HM: high monounsaturated fat diet
Int: intervention arm
LF: low fat
LGI: low glycaemic index
MF: moderate fat
Mono: monounsaturates
NR: not reported
SD: standard deviation

APPENDICES

Appendix 1. Searches run October 2019

The searches for this review were last run in November 2014 as part of a broader review (Hooper 2015a). As the review has now been split and the previous search strategy was unsuitable, a new strategy has been run in October 2019, from database inception.

The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter (Lefebvre 2011), and for Embase, terms as recommended in the Cochrane Handbook have been applied (Lefebvre 2011).

CENTRAL

#1 MeSH descriptor: [Weight Gain] explode all trees

#2 MeSH descriptor: [Weight Loss] explode all trees

#3 (obesity):ti,ab,kw

#4 (obese):ti,ab,kw

#5 (adipos*):ti,ab,kw

#6 ("weight gain"):ti,ab,kw

#7 ("weight loss"):ti,ab,kw

#8 (overweight):ti,ab,kw

#9 ("over weight"):ti,ab,kw

#10 (overeat*):ti,ab,kw

#11 (over NEXT eat*):ti,ab,kw

#12 (weight NEXT change*):ti,ab,kw

#13 (((bmi or "body mass index") NEAR/2 (gain or loss or change))):ti,ab,kw

#14 ("body fat"):ti,ab,kw

#15 ("body composition"):ti,ab,kw

#16 ("body constitution"):ti,ab,kw

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH descriptor: [Dietary Fats] explode all trees

#19 MeSH descriptor: [Diet, Fat-Restricted] explode all trees

#20 ((fat* NEAR/2 (total or intake or consum* or ate or eat or reduce* or restrict* or low* or diet*))):ti,ab,kw

#21 #18 or #19 or #20

#22 #17 and #21

MEDLINE OVID

1 exp Weight Gain/

2 exp Weight Loss/

3 obesity.ab,ti.

4 obese.ab,ti.

5 adipos$.ab,ti.

6 weight gain.ab,ti.

7 weight loss.ab,ti.

8 overweight.ab,ti.

9 over weight.ab,ti.

10 overeat$.ab,ti.

11 over eat$.ab,ti.

12 weight change$.ab,ti.

13 ((bmi or body mass index) adj2 (gain or loss or change)).ab,ti.

14 body fat$.ab,ti.

15 body composition.ab,ti.

16 body constitution.ab,ti.

17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 exp Dietary Fats/

19 exp Diet, Fat-Restricted/

20 (fat$ adj2 (total or intake or consum$ or ate or eat or reduce$ or restrict$ or low$ or diet$)).ab,ti.

21 18 or 19 or 20

22 17 and 21

23 randomized controlled trial.pt.

24 controlled clinical trial.pt.

25 randomized.ab.

26 placebo.ab.

27 clinical trials as topic.sh.

28 randomly.ab.

29 trial.ti.

30 23 or 24 or 25 or 26 or 27 or 28 or 29

31 exp animals/ not humans.sh.

32 30 not 31

33 22 and 32

Embase OVID

1 exp body weight gain/

2 exp body weight loss/

3 obesity.ab,ti.

4 obese.ab,ti.

5 adipos$.ab,ti.

6 weight gain.ab,ti.

7 weight loss.ab,ti.

8 overweight.ab,ti.

9 over weight.ab,ti.

10 overeat$.ab,ti.

11 over eat$.ab,ti.

12 weight change$.ab,ti.

13 ((bmi or body mass index) adj2 (gain or loss or change)).ab,ti.

14 body fat$.ab,ti.

15 body composition.ab,ti.

16 body constitution.ab,ti.

17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 exp fat intake/

19 exp low fat diet/

20 (fat$ adj2 (total or intake or consum$ or ate or eat or reduce$ or restrict$ or low$ or diet$)).ab,ti.

21 18 or 19 or 20

22 17 and 21

23 random$.tw.

24 factorial$.tw.

25 crossover$.tw.

26 cross over$.tw.

27 cross-over$.tw.

28 placebo$.tw.

29 (doubl$ adj blind$).tw.

30 (singl$ adj blind$).tw.

31 assign$.tw.

32 allocat$.tw.

33 volunteer$.tw.

34 crossover procedure/

35 double blind procedure/

36 randomized controlled trial/

37 single blind procedure/

38 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39 (animal/ or nonhuman/) not human/

40 38 not 39

41 22 and 40

42 limit 41 to embase

Clinicaltrials.gov

Condition or disease: weight loss OR weight gain OR body weight OR weight change OR obesity OR obese OR overweight

Intervention/treatment: Fat, Dietary OR fat

Study type: Interventional Studies (Clinical Trials)

ICTRP

Condition: weight loss OR weight gain OR body weight OR weight change OR obesity OR obese OR overweight

Intervention: Fat, Dietary OR fat

Appendix 2. Searches run in 2014

MEDLINE search run to collect adult and child RCTs and cohort studies 15 November 2014

Search adapted from that run in 2010, to search for both adult and child RCTs and cohort studies, but omitting dietary exposures other than dietary fat.

Run 15 November 2014.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Weight Gain/ (24259)
2 exp Weight Loss/ (30933)
3 obesity.ab,ti. (152189)
4 obese.ab,ti. (86464)
5 adipos$.ab,ti. (71315)
6 weight gain.ab,ti. (44371)
7 weight loss.ab,ti. (59414)
8 overweight.ab,ti. (42626)
9 over weight.ab,ti. (349)
10 overeat$.ab,ti. (1934)
11 over eat$.ab,ti. (275)
12 weight change$.ab,ti. (8042)
13 ((bmi or body mass index) adj2 (gain or loss or change)).ab,ti. (2786)
14 body fat$.ab,ti. (24784)
15 body composition.ab,ti. (23804)
16 body constitution.ab,ti. (257)
17 exp Dietary Fats/ (73523)
18 exp Diet, Fat-Restricted/ (3040)
19 (fat$ adj2 (total or intake or consum$ or ate or eat or reduce$ or restrict$ or low$ or diet$)).ab,ti. (63037)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (366287)
21 17 or 18 or 19 (114331)
22 20 and 21 (28779)
23 randomized controlled trial.pt. (399992)
24 controlled clinical trial.pt. (90666)
25 Randomized controlled trials/ (99585)
26 random allocation.sh. (84070)
27 double blind method.sh. (132423)
28 single-blind method.sh. (20589)
29 23 or 24 or 25 or 26 or 27 or 28 (658672)
30 (animals not (human and animals)).sh. (5551801)
31 29 not 30 (590901)
32 clinical trial.pt. (501242)
33 exp Clinical trial/ (816129)
34 (clin$ adj25 trial$).ti,ab. (291641)
35 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. (137043)
36 placebos.sh. (34004)

37 placebo$.ti,ab. (169148)
38 random$.ti,ab. (764596)
39 research design.sh. (82260)
40 comparative study.sh. (1730651)
41 exp Evaluation studies/ (206135)
42 follow up studies.sh. (520109)
43 prospective studies.sh. (390949)
44 (control$ or prospectiv$ or volunteer$).ti,ab. (3243146)
45 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (5767873)
46 45 not 30 (4293785)
47 31 or 46 (4323589)
48 exp Cohort Studies/ (1438154)
49 (cohort$ or quintile$ or quartile$ or quantile$ or tertile$).mp. (411555)
50 (follow-up$ or followup$).mp,tw. (970994)
51 longitud$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (208935)
52 ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp. (587538)
53 48 or 49 or 50 or 51 or 52 (2092058)
54 53 not 30 (1996509)
55 47 or 54 (4973664)
56 22 and 55 (9237)
57 limit 56 to (english language and yr="2010 - 2015") (3294)
58 exp Case-Control Studies/ (710182)
59 (case adj3 control$).tw. (93452)
60 (case adj3 series).tw. (42174)
61 case study/ (1736496)
62 letter.pt. (885169)
63 exp Drug Therapy/ (1125358)
64 exp Surgery/ (35422)
65 exp Biochemical Phenomena/ (3179065)
66 exp OBESITY/dt, ec, ra, ri, rt, su, ve [Drug Therapy, Economics, Radiography, Radionuclide Imaging, Radiotherapy, Surgery, Veterinary] (21417)
67 exp HIV/ (89024)
68 exp HIV infections/ (246055)
69 cancer.ti. (653428)
70 (tumour or tumor).ti. (242371)
71 lung.ti. (197074)
72 asthma.ti. (66394)
73 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 (8021499)
74 57 not 73 (1961)

EMBASE search run to collect adult and child RCTs and cohort studies on 14th November 2014

Search adapted from that run in 2010, to search for both adult and child RCTs and cohort studies, but omitting dietary exposures other than dietary fat.

Run 14 November 2014.

Database: EMBASE <1974 to 2014 November 14>
Search Strategy:
---
1 exp Weight Gain/ (67847)
2 exp weight reduction/ (104267)
3 obesity.ab,ti. (197751)
4 obese.ab,ti. (114407)
5 overweight.ab,ti. (55916)
6 over weight.ab,ti. (671)
7 ((weight or bmi or body mass index) adj2 (gain or loss or change or reduc$)).ab,ti. (154396)
8 exp fat intake/ (42075)
9 exp low fat diet/ (6962)
10 (fat$ adj2 (total or intake or consum$ or ate or eat or reduce$ or restrict$ or low$ or diet$)).ab,ti. (76246)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 (440097)
12 8 or 9 or 10 (102724)

13 11 and 12 (27385)
14 controlled study/ (4458191)
15 randomized controlled trial/ (355956)
16 clinical trial/ (839688)
17 major clinical study/ (2275896)
18 (trial$ or control$).tw. (3805000)
19 (blind$ or placebo).tw. (383515)
20 placebo/ (260940)
21 14 or 15 or 16 or 17 or 18 or 19 or 20 (8434269)
22 exp human/ (15270878)
23 nonhuman/ (4404779)
24 23 not 22 (3499956)
25 21 not 24 (6542287)
26 exp Longitudinal Study/ (70712)
27 exp Prospective Study/ (266457)
28 (cohort$ or quintile$ or quartile$ or tertile$ or quantile$).mp. (498531)
29 (follow-up$ or followup$).mp,tw. (1184342)
30 longitud$.mp. (214152)
31 ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp. (615851)
32 26 or 27 or 28 or 29 or 30 or 31 (2100044)
33 32 not 24 (2060027)
34 33 or 25 (7492226)
35 13 and 34 (12448)
36 limit 35 to (english language and yr="2010 - 2015") (6329)
37 exp Case-Control Studies/ (90210)
38 (case adj3 control$).tw. (107292)
39 (case adj3 series).tw. (51300)
40 case study/ (28823)
41 letter.pt. (860483)
42 exp Drug Therapy/ (1859698)
43 exp Surgery/ (3481521)
44 exp Biochemical Phenomena/ (81777)
45 exp obesity/cn, di, dr, dt, rt, su [Congenital Disorder, Diagnosis, Drug Resistance, Drug Therapy, Radiotherapy, Surgery] (33545)
46 exp HIV/ (138030)
47 exp HIV infections/ (303673)
48 cancer.ti. (812504)
49 (tumour or tumor).ti. (277200)
50 lung.ti. (240253)
51 asthma.ti. (82529)
52 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 (6915750)
53 36 not 52 (5003)

CINAHL search run to collect adult and child RCTs and cohort studies on 1st December 2014

Interface EBSCO host research databases, Advanced search, CINAHL Complete

#	Query	Limiters/Expanders	Results
S1	(MH "weight gain+")	Search modes - Boolean/Phrase	62,681
S2	(MH "weight loss+")	Search modes - Boolean/Phrase	14,411
S3	TI obesity OR AB obesity	Search modes - Boolean/Phrase	32,659
S4	TI obese OR AB obese	Search modes - Boolean/Phrase	15,905
S5	TI adipos* OR AB adipos*	Search modes - Boolean/Phrase	6,462

(Continued)

S6	TI weight gain OR AB weight gain	Search modes - Boolean/Phrase	6,645
S7	TI weight loss OR AB weight loss	Search modes - Boolean/Phrase	11,452
S8	TI overweight OR AB overweight	Search modes - Boolean/Phrase	12,405
S9	TI over weight OR AB over weight	Search modes - Boolean/Phrase	1,157
S10	TI overeat* OR AB overeat*	Search modes - Boolean/Phrase	418
S11	TI over eat* OR AB over eat*	Search modes - Boolean/Phrase	321
S12	TI weight change* OR AB weight change*	Search modes - Boolean/Phrase	3,689
S13	(TI ((bmi or body mass index) N2 (gain or loss or change))) OR (AB ((bmi or body mass index) N2 (gain or loss or change)))	Search modes - Boolean/Phrase	862
S14	TI body fat* OR AB body fat*	Search modes - Boolean/Phrase	5,932
S15	TI body composition OR AB body composition	Search modes - Boolean/Phrase	5,353
S16	TI body constitution OR AB body constitution	Search modes - Boolean/Phrase	26
S17	(MH "Dietary Fats+")	Search modes - Boolean/Phrase	17,455
S18	(MM "Diet, Fat-Restricted")	Search modes - Boolean/Phrase	901
S19	(TI (fat* N2 (total or intake or consum* or ate or eat or reduc* or restrict* or low* or diet*))) OR (AB (fat* N2 (total or intake or consum* or ate or eat or reduc* or restrict* or low* or diet*)))	Search modes - Boolean/Phrase	11,074
S20	(S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16)	Search modes - Boolean/Phrase	99,408
S21	(S17 OR S18 OR S19)	Search modes - Boolean/Phrase	25,122
S22	(S20 AND S21)	Search modes - Boolean/Phrase	6,404
S23	PT randomized controlled trial	Search modes - Boolean/Phrase	45,326
S24	TX "controlled clinical trial"	Search modes - Boolean/Phrase	7,628
S25	MM "Randomized Controlled Trials"	Search modes - Boolean/Phrase	668
S26	MM "Random Assignment"	Search modes - Boolean/Phrase	147
S27	MM "Double-Blind Studies"	Search modes - Boolean/Phrase	76
S28	MM "Single-Blind Studies"	Search modes - Boolean/Phrase	26

(Continued)

S29	S23 OR S24 OR S25 OR S26 OR S27 OR S28	Search modes - Boolean/Phrase	52,650
S30	SU (animals not (human and animals))	Search modes - Boolean/Phrase	53,619
S31	S29 NOT S30	Search modes - Boolean/Phrase	52,575
S32	PT clinical trial	Search modes - Boolean/Phrase	77,533
S33	MH "Clinical Trials+"	Search modes - Boolean/Phrase	184,793
S34	TI (clin* N25 trial*) OR AB (clin* N25 trial*)	Search modes - Boolean/Phrase	53,327
S35	TI ((singl* or doubl* or trebl* or tripl* or quad*) N (blind* or mask*)) OR AB ((singl* or doubl* or trebl* or tripl* or quad*) N (blind* or mask*))	Search modes - Boolean/Phrase	300
S36	MM "Placebos"	Search modes - Boolean/Phrase	828
S37	TI placebo* OR AB placebo*	Search modes - Boolean/Phrase	27,852
S38	TI random* OR AB random*	Search modes - Boolean/Phrase	144,733
S39	MM "study design"	Search modes - Boolean/Phrase	5,275
S40	MM "comparative studies"	Search modes - Boolean/Phrase	283
S41	MH "Evaluation Research+"	Search modes - Boolean/Phrase	20,984
S42	MM "prospective studies"	Search modes - Boolean/Phrase	800
S43	TI (control* or prospectiv* or volunteer*) OR AB (control* or prospectiv* or volunteer*)	Search modes - Boolean/Phrase	357,450
S44	S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	Search modes - Boolean/Phrase	542,974
S45	S44 NOT S30	Search modes - Boolean/Phrase	535,502
S46	S31 OR S45	Search modes - Boolean/Phrase	541,731
S47	MH "prospective studies+"	Search modes - Boolean/Phrase	254,176
S48	TX cohort* or quintile* or quartile* or quantile* or tertile*	Search modes - Boolean/Phrase	152,914
S49	TX follow-up* or followup*	Search modes - Boolean/Phrase	249,854
S50	TX longitud*	Search modes - Boolean/Phrase	103,954
S51	TX ((prospectiv* or observation*) N5 (research* or data* or stud*))	Search modes - Boolean/Phrase	382,309

(Continued)

S52	S47 OR S48 OR S49 OR S50 OR S51	Search modes - Boolean/Phrase	613,040
S53	S52 NOT S30	Search modes - Boolean/Phrase	610,840
S54	S46 OR S53	Search modes - Boolean/Phrase	963,714
S55	S22 AND S54	Search modes - Boolean/Phrase	3,017
S56	S22 AND S54	Limiters - Published Date: 20100101-20151231; English Language Search modes - Boolean/Phrase	1,236
S57	MH "Case Control Studies+"	Limiters - Published Date: 20100101-20151231; English Language Search modes - Boolean/Phrase	23,820
S58	TX case N3 control*	Limiters - Published Date: 20100101-20151231; English Language Search modes - Boolean/Phrase	35,592
S59	TX case N3 series	Limiters - Published Date: 20100101-20151231; English Language Search modes - Boolean/Phrase	10,407
S60	MM "Case Studies"	Search modes - Boolean/Phrase	623
S61	PT letter	Search modes - Boolean/Phrase	198,888
S62	MH "Drug Therapy+"	Search modes - Boolean/Phrase	109,541
S63	MH "Surgery, Operative+"	Search modes - Boolean/Phrase	385,583
S64	MH "Biochemical Phenomena+"	Search modes - Boolean/Phrase	29,949
S65	MH "Obesity+/DT/EC/RA/RT/SU"	Search modes - Boolean/Phrase	5,470
S66	MH "Human Immunodeficiency Virus+"	Search modes - Boolean/Phrase	5,947
S67	MH "HIV Infections+"	Search modes - Boolean/Phrase	62,282
S68	TI cancer	Search modes - Boolean/Phrase	137,532
S69	TI tumor OR tumour	Search modes - Boolean/Phrase	21,392
S70	TI lung	Search modes - Boolean/Phrase	24,925
S71	TI asthma	Search modes - Boolean/Phrase	15,732
S72	S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71	Search modes - Boolean/Phrase	913,702
S73	S56 NOT S72	Search modes - Boolean/Phrase	765

CENTRAL search run as part of the update in March 2014

#1 lipid near (low* or reduc* or modifi*)

#2 cholesterol* near (low* or modifi* or reduc*)

#3 (#1 or #2)

#4 MeSH descriptor: [Nutrition Therapy] explode all trees

#5 diet* or food* or nutrition*

#6 (#4 or #5)

#7 (#3 and #6)

#8 fat* near (low* or reduc* or modifi* or animal* or saturat* or unsaturat*)

#9 MeSH descriptor: [Diet, Atherogenic] explode all trees

#10 MeSH descriptor: [Diet Therapy] explode all trees

#11 (#7 or #8 or #9 or #10)

#12 MeSH descriptor: [Cardiovascular Diseases] this term only

#13 MeSH descriptor: [Heart Diseases] explode all trees

#14 MeSH descriptor: [Vascular Diseases] explode all trees

#15 MeSH descriptor: [Cerebrovascular Disorders] this term only

#16 MeSH descriptor: [Brain Ischemia] explode all trees

#17 MeSH descriptor: [Carotid Artery Diseases] explode all trees

#18 MeSH descriptor: [Dementia, Vascular] explode all trees

#19 MeSH descriptor: [Intracranial Arterial Diseases] explode all trees

#20 MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees

#21 MeSH descriptor: [Intracranial Hemorrhages] explode all trees

#22 MeSH descriptor: [Stroke] explode all trees

#23 coronar* near (bypas* or graft* or disease* or event*)

#24 cerebrovasc* or cardiovasc* or mortal* or angina* or stroke or strokes or tia or ischaem* or ischem*

#25 myocardi* near (infarct* or revascular* or ischaem* or ischem*)

#26 morbid* near (heart* or coronar* or ischaem* or ischem* or myocard*)

#27 vascular* near (peripheral* or disease* or complication*)

#28 heart* near (disease* or attack* or bypas*)

#29 (#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)

#30 (#11 and #29)

F E E D B A C K

Tobias 2016, July 2016

Summary

In their systematic review and meta-analysis of 32 randomized controlled trials, representing 54,000 participants, Hooper et al. reported that a lower proportion of energy intake from total fat was associated with a small reduction in body weight (difference = 1.5 kg).[1] The authors' conclusion, however, was contradicted by findings from their parallel meta-analysis of 25 observational cohort studies. The

erroneous conclusion from the review of trials is a consequence of biased study selection criteria, inclusion of short-term follow-up (<12 months), and other methodologic flaws.

First, their criteria explicitly included only trials in which weight loss was not an objective of the intervention. This led to the exclusion of several long-term, rigorously conducted RCTs designed specifically to test the hypothesis that the fat composition of the diet affects weight change. The criteria used by Hooper et al. resulted in a heterogeneous subset of the of low-fat dietary intervention RCTs, which included trials conducted to test the effects of low-fat diets on endpoints such as cancer incidence or lipids in higher risk study populations. In fact, only three trials in their meta-analysis were among healthy participants, not recruited on the basis of risk factors or disease. The authors' contend that including only studies not intending to alter weight would reduce potential publication bias. On the contrary, we believe this would increase the likelihood of publication bias, since investigators of diet trials not explicitly conducted for weight loss would not be motivated to publish null or contrary results. Since the point of this work is to advise generally healthy individuals as to how to maintain or lose weight, it is bizarre to specifically exclude trials designed to answer that question.

Second, the authors' included short-term trials (of as little as 6 months duration). Six months is typically when the effect of dietary interventions on body weight wane and weight regain commences; thus short-term results do not reflect sustained effects at 1 year or longer, which is of primary interest.[2]

Third, most of the studies included by Hooper et al. were seriously confounded by factors other than the fat content of the diet. Some of the trials coupled a low-fat intervention with other advice, such as eating more fruits and vegetables, which obscures the interpretation of the findings. The other key characteristic is the differences in intensity or attention between intervention groups (e.g., fewer or no in-person visits, dietary counseling meetings, etc), because the control group was often simply assigned to maintain their usual diet. Aspects related to the intensity of a dietary intervention, such as behavioral support, are modest predictors of weight loss success;[3] thus, most RCT's designed to assess the effects of diet composition on weight intentionally balanced the intensity of interventions, but these were the studies explicitly excluded by Hooper it al. In our previous meta-analysis of RCTs comparing low-fat vs. higher fat dietary interventions, we conducted stratified analyses by these key trial characteristics.[4] We observed that significant long-term weight loss favoring low-fat interventions was observed only for trials in which the comparator group was "usual diet" or received less attention during the intervention from study investigators. This was true regardless of whether the RCTs had a weight loss focus or not. Comparisons between low-fat and higher fat interventions of similar intensity demonstrated no benefit of low-fat over higher fat diets, regardless of weight loss goal. Indeed, the overall results of these trials favored a small but statistically significant greater weight loss with higher fat diets. Our findings clearly demonstrated the biased impact of differential attention across treatment groups.

Only 4 RCTs in Hooper's meta-analysis (419 total participants) remained after exclusion of trials in which control groups were asked simply to maintain usual diet or received differentially less attention than the low-fat intervention arms. Three were 6 month trials, and the fourth was published in 1960 among men with recent myocardial infarction to examine lipid changes after a 1 year intervention with either a low-fat or a "unsaturated-fat" diet.[5] These 4 RCTs also were judged by Hooper et al. to have relatively high "risk of bias" according to authors' methodological quality criteria.

In summary, the results from the most recent Hooper et al. meta-analysis provide no convincing evidence for recommending a low-fat diet for the prevention of weight gain and obesity in the general population. In fact, their strict exclusion criteria restricting the analysis only to trials in which weight-loss was not intended led to biased results. Although the authors' felt that limiting their analysis to non-weight loss trials would enhance validity, this selectively excluded trials designed to avoid confounding by intensity of intervention and other factors. Analysis of trials that include those specifically testing interventions for weight control, that exclude short-term trials, and account for key trial characteristics yield consistent results that are consonant with observational studies. Would we derive recommendations for statin use in the primary prevention of coronary heart disease solely from trials with a completely different disease endpoint? Promoting low fat diets for weight control can lead to increased consumption of refined carbohydrates, causing increased weight gain,4 an array of adverse metabolic effects,[6] and premature death.[7] The overall body of scientific evidence clearly demonstrates that dietary recommendations should focus not on lowering the total fat content of the diet but rather on specific types of fats and carbohydrates and, more importantly, on specific foods and overall dietary patterns.[8]

References

1. Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. The Cochrane database of systematic reviews. 2015(8):CD011834.
2. Willett WC. Dietary fat plays a major role in obesity: no. Obesity reviews: an official journal of the International Association for the Study of Obesity. May 2002;3(2):59-68.
3. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. Jama. Sep 3 2014;312(9):923-933.
4. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. The lancet. Diabetes & endocrinology. Dec 2015;3(12):968-979.
5. Pilkington TR, Stafford JL, Hankin VS, Simmonds FM, Koerselman HB. Practical Diets for Lowering Serum Lipids. British medical journal. Jan 2 1960;1(5165):23-25.

6. Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. Jama. Nov 16 2005;294(19):2455-2464.
7. Wang DD, Li Y, Chiuve SE, et al. Association of Specific Dietary Fats With Total and Cause-Specific Mortality. JAMA internal medicine. Jul 5 2016.
8. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Reply

Thank you for your interest in our systematic review (1). You are incorrect; we did not state anywhere in the review that "a lower proportion of energy intake from total fat was associated with a small reduction in body weight (difference = 1.5 kg)". We were not interested in associations, we were interested in causality, so we included RCTs that reduced total fat in one randomised arm and not in the other. In the abstract, we stated "There is consistent evidence from RCTs in adults of a small weight-reducing effect of eating a smaller proportion of energy from fat; this was seen in almost all included studies and was highly resistant to sensitivity analyses. The effect of eating less fat (compared with usual diet) is a mean weight reduction of 1.5 kg (95% confidence interval (CI) -2.0 to -1.1 kg), but greater weight loss results from greater fat reductions."

Yes, we only included studies where weight loss was NOT a goal (where fat reduction was assessed for its effect on cardiovascular disease, cancer risk or other health issues). The reason for this was that we were interested not in weight-reducing diets for overweight people, but in usual diets eaten day to day by generally healthy people all over the world. This issue was discussed in great detail by the World Health Organization NUGAG committee before the review was commissioned and the committee was very clear that their instructions were in setting goals for generally healthy populations and not therapeutic diets for those who were already overweight or obese. Therapeutic weight-reducing diets are very different and, whatever their macronutrient or food composition, cannot be disentangled from the overriding and conscious requirement to eat less food (i.e. reduce energy intake). Indeed, and importantly, the participants in the studies we reviewed were not recruited to studies that aimed to promote weight loss in participants, or where participants were aware that one of the aims of the study was to promote a loss in their weight to achieve a healthy weight. This also meant that we did not include studies where low fat diets were compared to other therapeutic diets (such as very low carbohydrate diets).

Our review assesses the effects on weight of encouraging normal populations to reduce their total fat intake over the long term. The studies included durations of 6 months up to over 8 years. The effect in studies of between 6 and 12 months duration was a reduction of 1.74 kg in the low fat group compared to control (95% CI -2.34 to -1.13), similar to that at 12 to 24 months (-2.00 kg, 95% CI -2.51 to -1.48) and at 24 to 60 months (-1.18 kg, 95% CI -1.65 to -0.70). The effect over more than 5 years was smaller (-0.68 kg, 95% CI -1.66 to 0.29) but two of the four large RCTs still showed statistically significantly lower weight in the intervention groups (perhaps reflecting differences in the intensity of the intervention delivery and support this far into the trials), and meta-regression did not suggest a significant effect of duration on the extent of weight reduction in the low fat group compared to control. Dr Tobias' own systematic review also clearly shows, in studies where there was no intention to reduce weight "that low-fat interventions led to greater weight loss" compared to usual diets (abstract of (2)).

Strategies to help obese adults and children to lose weight are also clearly very important – but how to lose weight is a different question from how populations should eat day to day, year to year (there are a set of specific systematic reviews about weight reduction strategies in different populations on the Cochrane Library).

We used sensitivity analysis to assess the effect of "attention bias" (see Analysis 3.1). We removed studies where there appeared to have been more attention and/or time spent on the intervention group than the control group. Five studies provided data for this meta-analysis, finding that there was still a statistically significantly reduced weight in the low fat group (-1.25 kg, 95% CI -2.09 to -0.41). Three further trials did not provide variance data so could not be included in the meta-analysis, but they all clearly showed greater weight reduction in the low fat compared to usual fat arms, on average (though their statistical significance could not be assessed). This is a very consistent effect, is not dependent on short duration, and does not rely on increased attention or behavioural strategies in the low fat arms.

We reiterate, "Trials where participants were randomised to a lower fat intake versus usual or moderate fat intake, but with no intention to reduce weight, showed a consistent, stable but small effect of low fat intake on body fatness: slightly lower weight, BMI and waist circumference compared with controls. Greater fat reduction and lower baseline fat intake were both associated with greater reductions in weight."

References

1. Hooper L, Abdelhamid A, Bunn DK, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. Cochrane Database of Systematic Reviews 2015;8:Art. No.: CD011834.doi: 10.1002/14651858.CD011834.
2. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes & Endocrinology 2015;3:968-79.

Contributors

Julia Lowe, feedback editor for Cochrane Heart

WHAT'S NEW

Date	Event	Description
22 December 2019	New search has been performed	Searches for RCTs updated to October 2019, omitted CINAHL search, included searches of ClinicalTrials.gov and WHO ICTRP trials registries.
22 December 2019	New citation required but conclusions have not changed	Cohort data omitted. Summary risk of bias assessed for all included trials, 'Risk of bias' assessment updated across all included studies. Comparison of fixed- and random-effects meta-analysis used in addition to funnel plots and displaying missing data to understand small study bias. Seven new RCTs included in the review and meta-analyses (plus three ongoing studies and six trials awaiting assessment). Data updated for three of the 30 previously included trials. All analyses and results updated, summary of findings updated. No important changes in the bottom line of the review. We have removed data on children from this review as effects of total fat on body weight in children have now been assessed in a separate review (Naude 2018).

HISTORY

Review first published: Issue 6, 2020

Date	Event	Description
19 August 2016	Feedback has been incorporated	Comment and authors' response added.
2 March 2016	Amended	The description of data included in the main analysis for the WHI study was incorrect, so the entry for the "Characteristics of Included Studies" table now reflects that the weight, BMI and waist circumference data used in the main analyses were 7.5 year follow up data (as is appropriate). The data in the forest plots were already correct. Additionally the main reference for WHI is now indicated as the paper that provides this 7.5 year follow up data. The first paragraph of the text on "Associations between total dietary fat in youth and measures of body fatness in children, young people and adults (as seen in cohorts)" was unclear, so we have tried to clarify these results. Table 2 is helpful to read in understanding this section.
21 July 2015	New search has been performed	The searches were run on 12 November 2014.
11 July 2015	New citation required and conclusions have changed	We split a previously published review (Reduced and modified dietary fat for preventing cardiovascular disease, DOI: 10.1002/14651858.CD002137.pub3) into six smaller review up-

Date	Event	Description
		dates. The conclusions are therefore now focused on the effects of total fat intake on body weight instead of the effects of reducing or modifying fat intake overall on cardiovascular disease risk. At the request of the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) group we extended this review to include cohort studies, and studies in children and young people. This split review update includes 32 randomised controlled trials and also 30 sets of analyses of 25 cohorts.
11 June 2010	New citation required and conclusions have changed	—
9 September 2008	Amended	—
1 February 2000	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

The WHO NUGAG subgroup on diet and health (which included LH and CMS) discussed and developed the question for this review. The protocol was drafted by LH and approved by the NUGAG subgroup on diet and health. Charlene Bridges of the Cochrane Heart Group carried out the searches for this update. LH, AA, OFJ, DB and CSE assessed the eligibility of studies for inclusion for the update, AA, OFJ and LH carried out data extraction and entered data into RevMan. LH carried out the GRADE assessment for this update and wrote the first drafts of this update. All authors contributed to the analysis, and agreed on the final draft of this review. LH is the guarantor.

DECLARATIONS OF INTEREST

AA: the World Health Organization (WHO) provided funding to the University of East Anglia towards the cost of carrying out the update of this systematic review, which partly covered the salary of AA. AA received funding from WHO to cover expenses associated with attendance at meetings of the NUGAG subgroup on diet and health.

OFJ: the World Health Organization (WHO) provided funding to the University of East Anglia towards the cost of carrying out the update of this systematic review, which partly covered the salary of OFJ.

DB: none known.

LH: the World Health Organization (WHO) provided funding to the University of East Anglia towards the cost of carrying out the update of this systematic review, which partly covered the salary of LH. LH is a member of the WHO NUGAG subgroup on diet and health and received funding from WHO to cover expenses associated with attendance at meetings of the NUGAG subgroup on diet and health.

CMS: none known.

SOURCES OF SUPPORT

Internal sources

- University of East Anglia, UK

  For the original version of this systematic review: help with acquiring papers for the review, time for Lee Hooper to work on the review.

External sources

- The World Health Organization (WHO) provided funding to Durham University towards the cost of carrying out the original version of this systematic review, Switzerland

  No funding was received for the searching, analysis, or writing up of the data from randomised controlled trials in adults for the first version of the review. The funders did not have any vested interests in the findings of this research

- WHO provided funding to the University of East Anglia (PI Lee Hooper) for the update of this systematic review and translation into a Cochrane review, Switzerland

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was originally a section of a larger review (Hooper 2012a), which was split off and extended to include RCT and cohort data, and cover evidence of children and adults (Hooper 2015a). Data on children has now been split into a separate review (Naude 2018). This update includes only information on adults and is limited to RCTs only.