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Intermittent fasting for the prevention of cardiovascular disease (Review)

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[Intervention Review]

Intermittent fasting for the prevention of cardiovascular disease

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ABSTRACT

Background

Cardiovascular disease (CVD) is the leading cause of death worldwide. Lifestyle changes are at the forefront of preventing the disease. This includes advice such as increasing physical activity and having a healthy balanced diet to reduce risk factors. Intermittent fasting (IF) is a popular dietary plan involving restricting caloric intake to certain days in the week such as alternate day fasting and periodic fasting, and restricting intake to a number of hours in a given day, otherwise known as time-restricted feeding. IF is being researched for its benefits and many randomised controlled trials have looked at its benefits in preventing CVD.

Objectives

To determine the role of IF in preventing and reducing the risk of CVD in people with or without prior documented CVD.

Search methods

We conducted our search on 12 December 2019; we searched CENTRAL, MEDLINE and Embase. We also searched three trials registers and searched the reference lists of included papers. Systematic reviews were also viewed for additional studies. There was no language restriction applied.

Selection criteria

We included randomised controlled trials comparing IF to ad libitum feeding (eating at any time with no specific caloric restriction) or continuous energy restriction (CER). Participants had to be over the age of 18 and included those with and without cardiometabolic risk factors. Intermittent fasting was categorised into alternate-day fasting, modified alternate-day fasting, periodic fasting and time-restricted feeding.

Data collection and analysis

Five review authors independently selected studies for inclusion and extraction. Primary outcomes included all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and heart failure. Secondary outcomes include the absolute change in body weight, and glucose. Furthermore, side effects such as headaches and changes to the quality of life were also noted. For continuous data, pooled mean differences (MD) (with 95% confidence intervals (CIs)) were calculated. We contacted trial authors to obtain missing data. We used GRADE to assess the certainty of the evidence.

Main results

Our search yielded 39,165 records after the removal of duplicates. From this, 26 studies met our criteria, and 18 were included in the pooled analysis. The 18 studies included 1125 participants and observed outcomes ranging from four weeks to six months. Of quantitatively analysed data, seven studies compared IF with ab libitum feeding, eight studies compared IF with CER, and three studies compared IF with both ad libitum feeding and CER. Outcomes were reported at short term (≤ 3 months) and medium term (> 3 months to 12 months) follow-up.

None of the included studies reported on all-cause mortality, cardiovascular mortality, stroke, myocardial infarction or heart failure.

Body weight was reduced with IF compared to ad libitum feeding in the short term (MD -2.88 kg, 95% CI -3.96 to -1.80; 224 participants; 7 studies; low-certainty evidence). We are uncertain of the effect of IF when compared to CER in the short term (MD -0.88 kg, 95% CI -1.76 to 0.00; 719 participants; 10 studies; very low-certainty evidence) and there may be no effect in the medium term (MD -0.56 kg, 95% CI -1.68 to 0.56; 279 participants; 4 studies; low-certainty evidence).

We are uncertain about the effect of IF on glucose when compared to ad libitum feeding in the short term (MD -0.03 mmol/L, 95% CI -0.26 to 0.19; 95 participants; 3 studies; very-low-certainty of evidence) and when compared to CER in the short term: MD -0.02 mmol/L, 95% CI -0.16 to 0.12; 582 participants; 9 studies; very low-certainty; medium term: MD 0.01, 95% CI -0.10 to 0.11; 279 participants; 4 studies; low-certainty evidence).

The changes in body weight and glucose were not deemed to be clinically significant.

Four studies reported data on side effects, with some participants complaining of mild headaches. One study reported on the quality of life using the RAND SF-36 score. There was a modest increase in the physical component summary score.

Authors' conclusions

We are uncertain about the effects of intermittent fasting on clinical events such as mortality, myocardial infarction and heart failure due to lack of data for these outcomes. The individual meta-analyses show that intermittent fasting may be effective in reducing weight when compared to ad libitum feeding and may be as effective as continuous energy restriction. Despite this, these changes appear to be clinically insignificant at short-term follow-up. The quality of the available evidence is low to very low which means that many areas of uncertainty remain. Further research is needed to understand which patient groups would and would not benefit from intermittent fasting (e.g. patients with diabetes or eating disorders) as well as the effect on longer-term outcomes such as all-cause mortality and myocardial infarction.

PLAIN LANGUAGE SUMMARY

Does limiting the times you eat (intermittent fasting) prevent cardiovascular disease?

What is cardiovascular disease?

Cardiovascular disease (CVD) is the leading cause of death worldwide. Smoking, diabetes and being overweight are risk factors for CVD, which means that they increase your chances of developing CVD. CVD can often be prevented by a healthy lifestyle, such as keeping to a healthy weight or losing weight if you need to.

Following a diet

Some people choose to lose weight by following a diet; for example, by eating less fat, or by reducing the number of calories they eat. Intermittent fasting is a type of diet involving patterns of eating and fasting (not eating foods); it does not limit what foods you eat, but limits when you can eat them. Eating patterns in intermittent fasting include: fasting for one or two days each week; fasting every other day; or eating only during certain hours and fasting for at least 12 hours every day.

Why we did this Cochrane Review

Diets that involve intermittent fasting are becoming popular. We wanted to find out if intermittent fasting could reduce or prevent CVD.

What did we do?

We searched for studies that tested intermittent fasting against 'usual eating' (someone eats whatever foods they want whenever they like), or against 'energy restriction' diets (someone limits the number of calories they eat).

We wanted to find out whether intermittent fasting affected mortality, cardiovascular mortality, risk of stroke, heart attack or heart failure. We also looked at whether intermittent fasting affected body weight and blood sugar levels.

Search date: we included evidence published up to 12 December 2019.

What we found

We found 26 relevant studies; we then used the results from 18 of the studies to compare the different diets. The 18 studies included 1125 adults (aged over 18 years). Some people in the studies had risk factors for CVD and some people had no risk factors. Most studies were funded by universities and research centres; two studies were funded by companies that make diet foods.

The studies compared intermittent fasting against usual eating (in seven studies); energy restriction diets (eight studies); and usual eating and energy restriction diets (three studies). The studies lasted from four weeks to six months. Results were reported after three months (short-term), and between three and 12 months (medium-term).

We didn't find any data on mortality, cardiovascular mortality or risk of stroke, heart attack or heart failure.

We found that people may lose more weight by intermittent fasting than by usual eating over three months (evidence from 7 studies in 224 people); but not when compared against energy restriction diets for three months (10 studies; 719 people) or longer (3 to 12 months; 4 studies; 279 people).

We also found that intermittent fasting did not appear to affect blood sugar levels when compared against usual eating over three months (3 studies; 95 people); energy restriction diets over three months (9 studies; 582 people); or energy restriction diets over 3 to12 months (4 studies; 279 people).

The weight losses and changes in blood sugars reported in the studies were small. These changes were not deemed to be clinically significant.

Only four studies reported unwanted effects of intermittent fasting: some people taking part reported mild headaches. Only one study reported on people's well-being, showing a small increase in scores for physical well-being.

Our confidence in our results

We are not confident in our results. We found limitations in the ways that the studies were designed, conducted and reported; and in some studies, the results varied widely, or were not consistent. Our results are likely to change if more evidence becomes available.

Key messages

We did not find enough good certainty evidence to know whether intermittent fasting could prevent CVD. We found that intermittent fasting may help people to lose more weight than 'eating as usual' (not dieting) but was similar to energy restriction diets. We need further research to test the benefits and potential harms of intermittent fasting, and to test if it might affect how many people die or develop CVD.

Summary of findings 1. IF compared to ad libitum (short term) for the prevention of cardiovascular disease

IF compared to ad libitum (short term) for the prevention of cardiovascular disease

Patient or population: the prevention of cardiovascular disease
Setting: outpatient
Intervention: IF
Comparison: ad libitum (short term) (≤ 3 months)

Outcomes (4 to 12 weeks follow-up)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Risk with ad libitum	Risk with IF				
All-cause mortality						No trials reported data on these outcomes
CV Mortality						
Stroke						
MI						
Heart failure						
Absolute change in body weight (kg) (4 to 12 weeks follow-up)	The mean change from baseline ranged from -1.4 to 1 kg.	MD 2.88 lower (3.96 lower to 1.80 lower)	-	224 (7 studies)	⊕⊕⊖⊖ **low[a,b]**	The difference between groups is not clinically meaningful, as it represents less than a 5% reduction in baseline body weight.
Absolute change in Glucose (mmol/L) (8 to 12 weeks follow-up)	The mean change from baseline ranged from -0.33 to 0.01 mmol/L.	MD 0.03 lower (0.26 lower to 0.19 higher)	-	95 (3 studies)	⊕⊖⊖⊖ **very low[c,d]**	The difference between groups is not clinically meaningful, as it represents less than a 5% reduction in baseline glucose.

*__The risk in the intervention group__ (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; **CV:** cardiovascular **IF:** Intermittent fasting; **MD:** mean difference; **MI:** myocardial infarction; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] We downgraded by one level for inconsistency, due to substantial heterogeneity (I^2 = 85%).
[b] We downgraded by one level for study limitations, due to high risk of performance bias in all studies, an unclear or high risk of selection bias (inadequate allocation concealment), and an unclear risk of detection bias in 6 of the 7 studies.
[c] We downgraded by one level for study limitations, due to high risk of performance bias in all studies, an unclear or high risk of selection bias (inadequate allocation concealment), and a high or unclear risk of attrition bias in 2 of the 3 studies.
[d] We downgraded by two levels for imprecision, due to very low sample size and a wide confidence interval that includes both a possible benefit and a possible harm.

Summary of findings 2. IF compared to CER (short term) for the prevention of cardiovascular disease

IF compared to CER (short term) for the prevention of cardiovascular disease

Patient or population: the prevention of cardiovascular disease
Setting: outpatient
Intervention: IF
Comparison: CER (Short term) (≤ 3 months)

Outcomes (4 to 12 weeks follow-up)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Risk with CER	Risk with IF				
All-cause mortality						No trials reported data on these outcomes
CV Mortality						
Stroke						
MI						
Heart failure						
Absolute change in body weight (kg) (4 to 12 weeks follow-up)	The mean change from baseline ranged from -7.4kg to -1.7kg	MD 0.88 lower (1.76 lower to 0.0 higher)	-	719 (10 studies)	⊕⊖⊖⊖ **very low[a,b,c]**	The difference between groups is not clinically meaningful, as it represents less than a 5% reduction in baseline body weight.
Absolute change in Glucose (mmol/L) (4 to 12 weeks follow-up)	The mean change from baseline	MD 0.02 lower (0.16 lower to 0.12 higher)	-	582 (9 studies)	⊕⊖⊖⊖ **very low[c,d,e]**	The difference between groups is not clinically meaningful, as it represents

	ranged from -0.4 to 1.1 mmol/L.				less than a 5% reduction in baseline glucose.

*__The risk in the intervention group__ (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).

CER: continuous energy restriction; **CI:** confidence interval; **CV:** cardiovascular **IF:** Intermittent fasting; **MD:** mean difference; **MI:** myocardial infarction; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] We downgraded by one level for inconsistency, due to substantial heterogeneity (I^2 = 66%).
[b] We downgraded by one level for study limitations, due to high risk of performance bias in all studies, an unclear or high risk of selection bias (inadequate allocation concealment), and an unclear risk of detection bias in 5 of the 10 studies.
[c] We downgraded by one level for imprecision, due to a wide confidence interval that includes both a possible benefit and a possible harm.
[d] We downgraded by one level for inconsistency, due to substantial heterogeneity (I^2 = 73%).
[e] We downgraded by one level for study limitations, due to an unclear or high risk of selection bias (inadequate allocation concealment), and an unclear risk of detection bias in 5 of the 10 studies.

Summary of findings 3. IF compared to CER (medium term) for the prevention of cardiovascular disease

IF compared to CER (medium term) for the prevention of cardiovascular disease

Patient or population: the prevention of cardiovascular disease
Setting: outpatient
Intervention: IF
Comparison: CER (medium term) (> 3 months to 12 months)

Outcomes (4 months - 6 months follow-up)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Risk with CER	Risk with IF				
All-cause mortality						No trials reported data on these outcomes
CV Mortality						

Stroke						
MI						
Heart failure						
Absolute change in body weight (kg) (4 months - 6 months follow-up)	The mean change from baseline ranged from -9.4kg to -5kg	MD 0.56 lower (1.68 lower to 0.56 higher)	-	279 (4 studies)	⊕⊕⊖⊖ **low[a,b]**	The difference between groups is not clinically meaningful, as it represents less than a 5% reduction in baseline body weight.
Absolute change in glucose (mmol/L) (4 months - 6 months follow-up)	The mean change from baseline ranged from -0.2 to 0.09 mmol/L.	MD 0.01 higher (0.10 lower to 0.11 higher)	-	279 (4 studies)	⊕⊕⊖⊖ **low[a,b]**	The difference between groups is not clinically meaningful, as it represents less than a 5% reduction in baseline glucose.

*__The risk in the intervention group__ (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).

CER: continuous energy restriction; **CI:** confidence interval; **CV:** cardiovascular **IF:** Intermittent fasting; **MD:** mean difference; **MI:** myocardial infarction; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] We downgraded by one level for study limitations, due to high risk of performance bias in all studies, an unclear or high risk of selection bias (inadequate allocation concealment), and an unclear risk of detection bias in 2 of the 4 studies.
[b] We downgraded by one level for imprecision, due to a wide confidence interval that includes both a possible benefit and a possible harm.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the leading cause of death worldwide and is recognised by the United Nations as a major global health burden (Westerman 2017). CVD encompasses a variety of diseases. These include heart failure, hypertension, ischaemic heart disease, such as stable angina and acute coronary syndromes, cerebrovascular disease such as stroke, valvular abnormalities such as aortic stenosis and arrhythmias such as atrial fibrillation (Lopez 2020; Stewart 2017).

CVD is largely due to the pathological process of atherosclerosis. Atherosclerosis is a chronic inflammatory process involving build up of lipids within the inner wall of arteries, stimulating infiltration by immunocytes and the subsequent formation of a fibrous cap by vascular smooth muscle cells (Bergheanu 2017). As the atherosclerotic plaque develops, a central necrotic core is formed containing necrotic cells, cell debris and cholesterol crystals (Hansson 2011). The plaque can lead to blood vessel stenosis and progress to plaque rupture causing a myocardial infarction (MI) (Sakakura 2013).

Multiple factors increase the risk of developing CVD including leading a sedentary lifestyle, smoking, consuming a diet high in salt, fatty acids and sugar, being overweight/obese, having poor lipid control (elevated plasma low-density lipoprotein (LDL) and total cholesterol levels), having a raised blood pressure, as well as suffering from diabetes (ESC 2016).

Obesity is strongly associated with CVD, increasing the risk of developing heart failure, coronary heart disease, hypertension and atrial fibrillation (Carbone 2019). Specifically, recent data suggest that obesity increases the risk of heart failure with preserved ejection fraction (HFpEF) (Pandey 2017). Additionally, obesity causes a chronic state of low-grade inflammation in the body leading to increased macrophage activation and plaque instability, further driving coronary heart disease (De Rosa 2017; Lovren 2015). The prevalence of obesity has also increased drastically over the last few decades and may be a key factor in increasing the prevalence of CVD (Capewell 2008).

Diabetes mellitus (DM) is also strongly associated with CVD (Schmidt 2019). DM leads to 5.2 million deaths globally, increasing the likelihood of developing peripheral arterial disease and heart failure (Glovaci 2019). One of the biggest causes of Type 2 DM is obesity. Obesity leads to end-organ adipose tissue becoming insulin-resistant (Hardy 2012). Multiple trials have been published looking at weight loss for the remission of Type 2 DM, including the DiRECT trial which recorded 46% Type 2 DM remission in the weight loss group as opposed to 4% remission in the control group (Lean 2017).

The World Health Organization (WHO) estimates that 80% of premature heart disease and stroke is preventable (WHO EU 2016). Despite CVD mortality declining in the UK by 68% between 1980 and 2013, hospital admissions have increased (Bhatnagar 2016). CVD is also the leading cause of disability-adjusted life years around the world (Perk 2012), and lead to approximately 31% of global deaths in 2016 (WHO 2016).

Prevention of CVD is a top priority of many public health institutions, promoted by advising patients to maintain a healthy lifestyle. The National Institute for Health and Care Excellence (NICE) guidelines for the prevention of CVD focus on reducing salt intake, saturated fats and increasing physical exercise (NICE 2010). The American Heart Association (AHA) along with the American College of Cardiology (ACC) have published an extensive report on the prevention of CVD (ACC/AHA 2019). The European Society of Cardiology (ESC) has also published 2016 guidelines on CVD prevention in clinical practice (ESC 2016). The World Heart Federation (WHF) is also committed to preventing CVD and has published guidelines on rheumatic heart disease, atherosclerotic disease, metabolic syndrome, as well as general heart disease prevention (WHF 2017). Finally, the WHO also has guidance on the assessment and management of cardiovascular risk (WHO 2007).

Description of the intervention

Intermittent fasting (IF) is a dietary regimen involving energy restriction for specific periods of time (Anton 2018). This may mean consuming all the daily caloric intake in a certain time frame e.g. eight hours, or it may mean eating one day and completely fasting the next day. Intermittent fasting is also referred to as intermittent energy restriction (IER) in the literature. There are a variety of different types of intermittent fasting including alternate-day fasting (ADF), periodic fasting (PF), time-restricted feeding (TRF) and religious fasts (Anton 2018; de Cabo 2019) described below.

- **Periodic fasting:** this is defined as a cyclical feeding pattern that entails fasting (consumption of 25% or less of required calories). This includes, but is not exclusive to fasting for one to two days per week with ad libitum feeding for the remaining days, in a once-weekly or a twice-weekly regimen (Anton 2018;Cioffi 2018).
- **Alternate-day fasting (ADF):** this is defined as a cyclical feeding pattern that entails complete fasting (consumption of no calories) for a period of 24 hours, followed by ad libitum feeding for 24 hours (Harris 2018).
    - Modified alternate-day fasting: this is a subtype of ADF which involves the consumption of 25% or less of maintenance calories for a period of 24 hours, followed by ad libitum feeding for the next 24 hours (Harris 2018).
- **Time-restricted feeding (TRF):** this is defined as complete fasting (consumption of no calories) for at least 12 hours per day with ad libitum feeding for the rest of the day; repeated every day (Cioffi 2018).
- **Common religious fasts:**
    - the Islamic Ramadhan fast: Muslims across the world fast for one month every year from sunrise to sunset. This fast refraining from eating and drinking (Trepanowski 2010). The fast varies in the number of hours depending on where in the world the observers are fasting as it depends on the time of sunrise and sunset. The month of Ramadhan shifts every year depending on the Islamic lunar calendar (Adler-Lazarovits 2019). During the period between sunset and sunrise, Muslims are free to consume food and drink with no caloric restriction (ad libitum feeding) (Trepanowski 2010).
    - Greek Orthodox fasts: observers abstain from dairy products, eggs, and meat for 40 days during the nativity fast, for 48 days

during the Lent fast, and for 15 days during the assumption fast (Trepanowski 2010).

There has been a growing interest in the potential role of intermittent fasting in preventing CVD (Johnstone 2015; Malinowski 2019). In the literature, intermittent fasting is often compared to the following.

- **ontinuous energy restriction (CER):** a reduced daily caloric intake to achieve weight loss with no time restriction (Cioffi 2018). For example, this may involve a deficit of 500 calories daily.
- **Ad libitum feeding:** food intake based on the participants' usual eating habits with no time or calorie restriction (Rynders 2019). For example, a person may consume whatever they wish to eat whenever they want on a daily basis.

A look at the current literature

An AHA investigation into the effect of ADF and PF on preventing CVD found a weight loss reduction of 3% to 8% over three to 24 weeks (AHA 2017). Additionally, they found a reduction in serum cardiovascular markers including a reduction of 6% to 21% in total cholesterol, a reduction of 7% to 32% in LDL cholesterol, and a reduction of 14% to 42% in triglycerides (TG) (AHA 2017). Improvement in blood glucose concentration was only seen in those with elevated blood glucose initially (AHA 2017), indicating that intermittent fasting may benefit patients with diabetes, however, it is difficult to tell as patients with diabetes tend to be excluded from these studies.

Additionally, Trepanowski 2017 published a year-long randomised controlled trial (RCT) comparing ADF to CER and ad libitum feeding. They found an increase in high-density lipoprotein (HDL) levels (6.2 mg/dL, 95% confidence interval (CI) 0.1 mg/dL to 12.4 mg/dL) relative to the CER group at six months as well as an increase in LDL levels (11.5 mg/dL, 95% CI, 1.9 mg/dL to 21.1 mg/dL) relative to CER group at 12 months, indicating that ADF did not outperform CER (Trepanowski 2017). Interestingly, no significant difference was seen between intervention groups for weight loss, fat mass, lean mass, visceral fat mass, and a higher dropout rate was seen in the intermittent fasting group, questioning the sustainability of the diet in the long term (Trepanowski 2017).

A number of recent systematic reviews have investigated how intermittent fasting/IER compares to CER and ad libitum feeding in reducing weight and preventing CVD (Cioffi 2018; Ganesan 2018; Harris 2018; Meng 2020; Welton 2020). Cioffi 2018 focused on IER versus CER. The authors reported no significant benefit of IER over CER on weight loss, glucose, glycated haemoglobin (HbA1c), and lipid profile (Cioffi 2018). Similarly, Harris 2018 found six RCTs that looked at IER compared to CER, but also compared it to ad libitum feeding. Meta-analyses showed that IER was superior to ad libitum feeding for weight loss (-4.14 kg, 95% confidence interval (CI) -6.30 kg to -1.99 kg; P ≤ 0.001), but also showed no difference between IER and CER for weight loss (-1.03 kg, 95% CI -2.46 kg to 0.40 kg; P = 0.156) (Harris 2018).

How the intervention might work

It has been hypothesised that these intermittent fasting regimens influence cardiometabolic outcomes via effects on circadian biology (Patterson 2017). Regimens that exclude or dramatically restrict evening energy intake lead to reduced postprandial insulin and glucose exposure than during the day (Frape 1997; Gibbs 2014). Specifically, it has been hypothesised that time-restricted feeding regimens lead to improved oscillations in circadian clock gene expression and improved body weight regulation by imposing a diurnal rhythm of food intake aligned with the 24-hour light-dark cycle (Hatori 2012). Furthermore, research in shift-workers, who eat most of their calories at night and are at an increased risk for obesity, has demonstrated alterations in appetite-regulating hormones (leptin and ghrelin, for instance) that may increase energy intake (Crispim 2011; Schiavo-Cardozo 2013; Wirth 2014). Therefore, changes in meal timing with respect to the 24-hour light-dark cycle may have an important influence on energy intake, weight control, and glucose metabolism.

It is speculated that intermittent fasting might change the human microbiome. The human microbiome is the collective genomes of micro-organisms in the human gastrointestinal tract and is known to be dynamic and undergo daily cyclical fluctuations in its composition (Zarrinpar 2014). Obesogenic diets affect the composition of the microbiome and diminish the cyclical fluctuations. Intermittent fasting (especially time-restricted feeding) is reported to restore key microbiota, reset the composition of the microbiome and restore the cyclical fluctuations (Zarrinpar 2014).

Non-circadian mechanisms also play a role. Intermittent fasting has been shown to reduce blood pressure in animals as well as humans (Malinowski 2019). A year-long intermittent fasting study of 1422 participants conducted at the Buchinger Wilhelmi clinic in Germany revealed a reduction in both systolic and diastolic blood pressure, which may be explained by an increase in parasympathetic drive due to an increase in brain-derived neurotrophic factor (BDNF), an increase in noradrenaline excretion and increased sensitivity of natriuretic peptides and insulin (Wilhelmi 2019). Intermittent fasting without calorie restriction alleviates inflammation (Hatori 2012), which itself is a pathogenic factor in both obesity (Bolus 2018) and diabetes (Donath 2011).

Ramadan fasting has been shown to improve the lipid profile in the healthy, obese, and dyslipidaemic (Santos 2018). Ramadan fasting may increase serum HDL levels and decrease serum very-low-density lipoproteins (VLDL), LDL, and small and dense LDL (sdLDL) levels by increasing fatty acid oxidation in the liver, increasing production of the HDL precursor apolipoprotein A (apoA), and decreasing the production of the LDL precursor apolipoprotein B (apoB)(Adlouni 1998; Hammouda 2013).

Studies have shown that the benefit of intermittent fasting may also be due to reduced caloric consumption. Fasting for the whole day or consuming ≤ 25% of the normal caloric intake per day was shown to reduce caloric intake by 30% for the next three days (Antoni 2016). Most fasting regimens force observers to eat in a restricted time period. This may be a 16-hour fast, whereby the observer would fast from 8 PM the previous day to mid-day the next day and then ad libitum feed for eight hours. Due to the short nature of the feeding window, less food may be consumed thus reducing caloric intake (Patterson 2017).

Why it is important to do this review

Intermittent fasting is becoming more popular for health and fitness and in October 2016, the search term "diet fasting intermittent alternate day" received 210,000 searches (Patterson

2017). Intermittent fasting was also in the top 10 diet searches on diet on Google trends in the USA in 2018 (Google trends 2018). The popularity of intermittent fasting makes us question whether there is a potential benefit of it as a lifestyle intervention in preventing or reducing the burden of CVD. The majority of existing human studies are cross-sectional and observational studies which focus on the benefits of religious fasting such as Ramadan fasting. The existing trials report inconsistent results on the benefit of intermittent fasting. Moreover, the comparisons between intermittent fasting and calorie restriction diets are not conclusive. Finally, each trial has addressed a limited number of cardiovascular risk factors and therefore a comprehensive review is needed.

This review aims to bring together all the relevant RCTs in a single systematic review, reporting the effects of intermittent fasting in humans and providing a comprehensive report on the impact of intermittent fasting on CVD.

OBJECTIVES

To determine the role of intermittent fasting in preventing and reducing the risk of cardiovascular disease (CVD) in people with or without prior documented CVD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in which the participants undergo intermittent fasting compared to ad libitum feeding (normal diet) or caloric restriction for the primary or secondary prevention of cardiovascular disease (CVD).

Since blinding of participants may not be possible in these types of studies, we included open-label RCTs. We planned to include cluster-RCTs. We included trials reported as full text, those published as abstract only, and unpublished data to minimise publication bias. Furthermore, we included relevant arms of multi-arm trials.

We excluded non-randomised and observational studies, single-arm studies, case reports, letters, study protocols, narrative reviews, and meta-analyses. Furthermore, we excluded cross-over trials as they are unsuitable to investigate the irreversible primary outcomes of this study.

Types of participants

We included adults (aged 18 years or older) with or without CVD or documented cardiometabolic risk factors. If available, we planned to extract relevant data from trials that included only a subset of eligible patients, if the data were reported separately. If the data were not reported separately, we only included studies if ≥ 80% of the study population were eligible for our review (Naude 2019). We planned to assess this decision with a sensitivity analysis.

Where the data were unavailable, we tried to contact the trial authors to obtain the relevant data.

We excluded trials where the participants were children (aged under 18 years). No other exclusion criteria were applied to the study population.

Types of interventions

The following types of intermittent fasting were focused on in this review.

- **Alternate day fasting (ADF):** this was defined as a cyclical feeding pattern that entails complete fasting (consumption of no calories) for a period of 24 hours, followed by ad libitum feeding for the next 24 hours (Harris 2018).
- **Modified alternate day fasting (Modified ADF):** this was defined as a cyclical feeding pattern that entails fasting (consumption of 25% or less of maintenance calories) for a period of 24 hours, followed by ad libitum feeding for 24 hours (Harris 2018). If the % of caloric intake was not stated, then a cut off of ≤ 600 calories was used (roughly 25% of a recommended daily caloric intake for a male/mixed population).
- **Periodic fasting (PF):** this was defined as a cyclical feeding pattern that entails fasting (consumption of 25% or less of required calories). This includes fasting for one to two days per week with ad libitum feeding for the remaining days, in a once-weekly or twice-weekly regimen (Anton 2018; Cioffi 2018). If the % of caloric intake was not stated, then a cut off of ≤ 600 calories was used (roughly 25% of a recommended daily caloric intake for a male/mixed population).
- **Time-restricted feeding (TRF):** this is defined as complete fasting (consumption of no calories) for at least 12 hours per day with ad libitum feeding for the rest of the day; repeated every day (Cioffi 2018).

We included the Islamic fast, provided that the fasting period exceeded 12 hours with ad libitum feeding between sunset and sunrise (Adler-Lazarovits 2019; Trepanowski 2010). Notably, religious fasts were only included if the study was an randomised controlled trial. Ramadan fasting studies tend to be observational due to the obligatory nature of the fast and therefore would be excluded the majority of the time.

We excluded RCTs in which the participant fast does not meet the criterion for a minimum of 12 hours of caloric restriction to 25% or less of the maintenance caloric requirement. In addition, we excluded religious fasts that did not meet this criterion; this includes but is not limited to the following.

1. Christian Lent fasts
2. Daniel Fasts
3. Buddhist fasts
4. Jewish fasts

With regards to the comparator, we included RCTs in which intermittent fasting was compared to either ad libitum feeding (normal diet or no intervention) or continuous energy restriction (CER), defined as a minimum of 25% reduction in caloric intake, which does not meet our aforementioned criterion of intermittent fasting. We excluded studies in which intermittent fasting was compared to exercise therapies, surgical techniques, or pharmacological medications.

Types of outcome measures

Primary outcomes

1. All-cause mortality
2. Cardiovascular (CV) mortality

3. Stroke
4. Myocardial infarction (MI)
5. Heart failure

We assessed all the above-mentioned outcomes at short-term follow-up (≤ 3 months), medium-term follow-up (> 3 months to 12 months) and long-term follow-up (> 12 months).

Stroke, MI, and heart failure were measured by the number of participants with at least one event during follow-up.

Secondary outcomes

1. Absolute change in body weight
2. Absolute change in body mass index (BMI)
3. Absolute change in waist circumference
4. Absolute change in total cholesterol levels (TC)
5. Absolute change in low-density lipoprotein cholesterol levels (LDL)
6. Absolute change in high-density lipoprotein cholesterol levels (HDL)
7. Absolute change in total triglyceride levels (TG)
8. Absolute change in systolic blood pressure (SBP)
9. Absolute change in diastolic blood pressure (DBP)
10. Absolute change in C-reactive protein (CRP)
11. Absolute change in fasting plasma glucose
12. Absolute change in glycated haemoglobin (HbA1C)
13. Incidence of headaches (side effect)
14. Incidence of dizziness (side effect)
15. Incidence of weakness (side effect)
16. Quality of life

We assessed outcomes 1-12 at short-term follow-up (≤ 3 months), medium-term follow-up (> 3 months to 12 months) and long-term follow-up (>12 months). The absolute change was the mean change from the baseline provided for each group. Where data for the absolute change from baseline were not available, we contacted the trial authors to obtain the absolute changes or the raw values to calculate the standard deviations (SDs). Where we could not contact the trial authors, we were able to impute the SD values using another study in the systematic review given it had a similar intervention and follow-up. If that was also not the case, then we narratively discussed the study instead.

We assessed outcomes 13-15 (side effects) at any point during follow-up and reported them narratively.

We assessed outcome 16 (quality of life) narratively at any point during follow-up. We intended to use validated quality of life scales such as the World Health Organization Quality Of Life Assessment Instrument (WHOQOL), Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), Nottingham Health Profile (NHP), Euro-Quality of Life Questionnaire (EuroQoL, EQ-5D), as well as cardiovascular specific scales such as the Seattle Angina Questionnaire (SAQ), the Minnesota Living with Heart Failure (MLHF) questionnaire and the Atrial Fibrillation Severity Scale (AFSS). The papers included quality of life as an outcome reported on it generally and did not specify specific time points.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 12 December 2019.

1. Cochrane Central Register of Controlled Trials (CENTRAL) Issue 12 of 12, December 2019 (Cochrane Library)
2. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to December 10, 2019)
3. Embase (Ovid, 1980 to 2019, week 49)

Search strategies for each database are available in Appendix 1. The Cochrane sensitivity-precision maximising RCT filter Lefebvre 2011, was applied to MEDLINE (Ovid) and an adaptation of it to Embase. We searched all databases from their inception to the present, and we imposed no restriction on publication language or status.

Searching other resources

In addition, we carried out the following searches.

1. We searched reference lists of all relevant reviews retrieved by electronic searching to identify other potentially eligible trials or ancillary publications.
2. We searched the following conference proceedings on 11 January 2020 via their websites, from their inception to present: ESC Congress 365 (congress365.escardio.org) (2013 onwards), ACC Annual Scientific Sessions (http://www.onlinejacc.org/content/ meeting-abstract-supplements) (1983 onwards), AHA Annual Scientific Sessions (circ.ahajournals.org)(1983 onwards), American Society for Nutrition meeting (https://meeting.nutrition.org)(2006 onwards), British Nutrition Foundation conference (https://www.nutrition.org.uk/bnfevents.html)(2006 onwards).
3. We contacted corresponding authors of included studies for any additional published or unpublished data.
4. We contacted the authors of trials when information in the study report was lacking or unclear.

We also examined any relevant retraction statements and errata for included studies.

We searched the following clinical trial registers for ongoing or unpublished trials on 11 January 2020. The search terms used are in Appendix 1.

1. ClinicalTrials.gov (clinicaltrials.gov).
2. European (EU) Clinical Trials Register (clinicaltrialsregister.eu).
3. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Data collection and analysis

Selection of studies

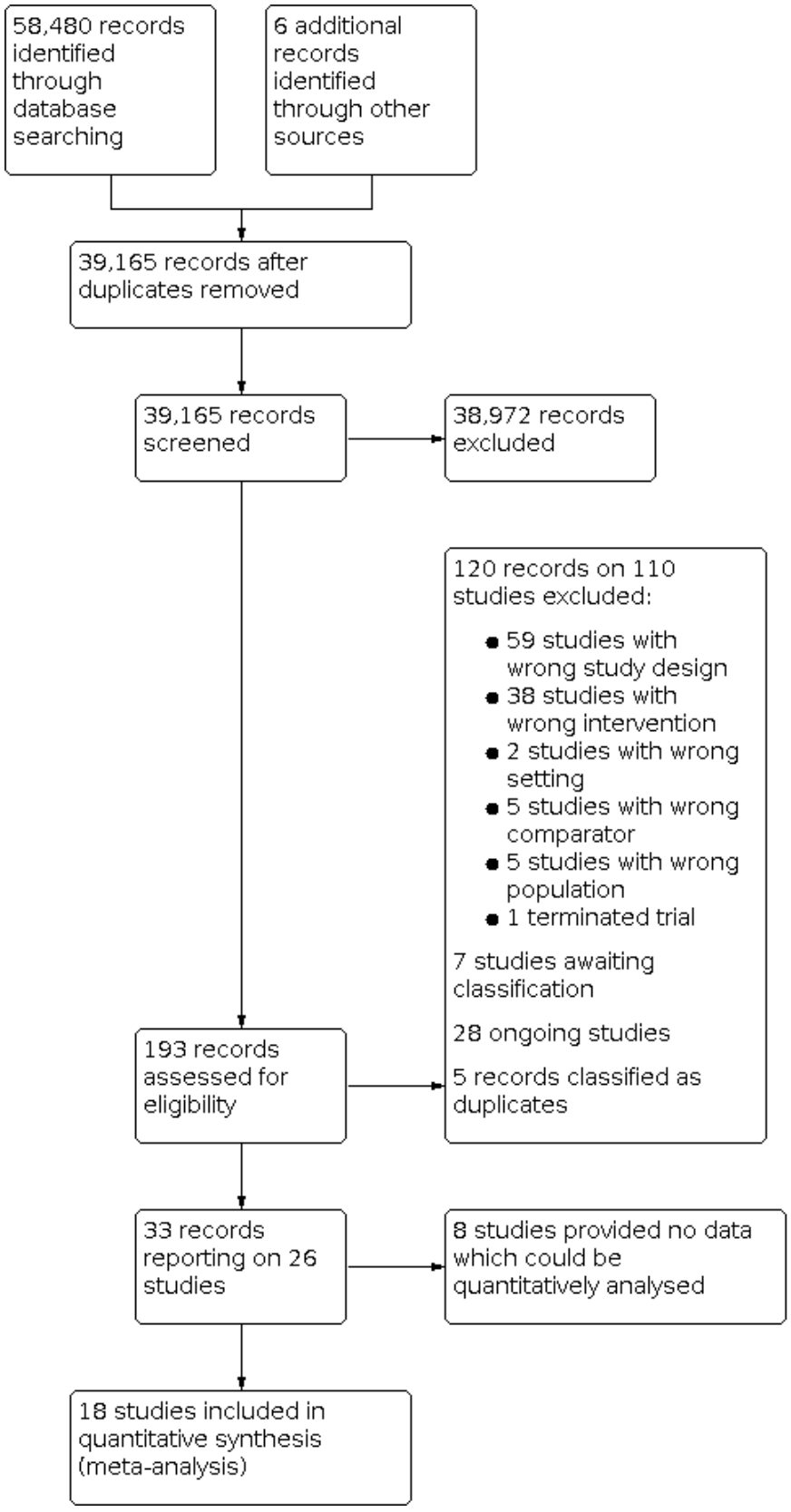
Five review authors (MA, HE, OM, SZ, and MFKF) independently screened titles and abstracts of studies retrieved using the aforementioned search strategies and then coded these as 'retrieve' (if eligible or potentially eligible/unclear) or 'do not retrieve'. The studies were screened by a minimum of two review authors. Any discrepancies were resolved through consensus amongst all review authors. Full texts of potentially eligible studies

were retrieved. Two review authors (MA and SZ) independently screened these full texts and identified studies that met inclusion criteria.

MA and SZ recorded any articles excluded after full-text assessment and their reasons for exclusion in the 'Characteristics of excluded studies' table. We also identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report is the unit of interest in the review.

We also included a PRISMA flowchart to depict the study selection process (see Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form for study characteristics and outcome data that we piloted on at least one study included in the review. Two review authors (HE and OM) extracted study characteristics from included studies. We extracted the following study characteristics.

1. Reference and design: author, publication year, country of publication, study design, number of centres, and sources of funding.
2. Interventions: intervention groups in the study.
3. Participants: the indication for enrolment in the study, the total number of randomised participants and number of participants in each group, the attrition rate, and the inclusion and exclusion criteria for enrolment into the study.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported and the length of follow-up.
5. Baseline characteristics of participants including: age, number of males, smoking status, hypertension, dyslipidaemia, diabetes mellitus, history of cardiovascular disease (CVD), body mass index (BMI), C-reactive protein (CRP), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), : triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, fasting plasma glucose, fasting insulin, leptin, glycated haemoglobin (HbA1C), and homeostatic model assessment of insulin resistance.
6. Comments: general comments regarding the trial design and conduct or specific methodological comments that we believe may influence the data or outcomes.

Two review authors (HE and OM) independently extracted outcome data from included studies. They spot-checked study characteristics for accuracy against the trial report. They resolved disagreements by consensus. One review author (MFKF) transferred data into the Review Manager 5 file (RevMan 2014). Two review authors (HE and OM) double-checked if the data were entered correctly by comparing the data presented in the systematic review with the study reports.

Certain studies reported outcomes in units different to the ones used in this paper. In that case, the following conversions were used.

1. mg/dL to mmol/L (total cholesterol, HDL, LDL). The value was divided by 38.67 (Rugge B 2011).
2. mg/dL to mmol/L (triglycerides). The value was divided by 88.57 (Rugge B 2011).
3. mg/dL to mmol/L (glucose). The value was divided by 18 (Riemsma R 2016).
4. Standard error (SE) to standard deviation (SD). The value was multiplied by the square root of the sample size (Altman 2005).

Assessment of risk of bias in included studies

Two review authors (HE and MA) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by consulting a third review author (AD). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear, using Cochrane 'Risk of bias' criteria, and we provided a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on the risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table.
When considering treatment effects, we took the risk of bias for the studies that contribute to that outcome into account.

For cluster-RCTs, two review authors (HE and MA) assessed the risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by consulting a third review author (AD). We assessed the risk of bias according to the following domains.

1. Recruitment bias.
2. Baseline imbalance.
3. Loss of clusters.
4. Incorrect analysis.
5. Comparability with individually-randomised trials.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and we if required, we planned to report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We planned to analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We analysed continuous data as mean difference (MD) with 95% CIs as outcomes were measured using the same method. We entered data presented as a scale with a consistent direction of effect.

Defining clinically significant changes in continuous outcomes can be difficult as there is a mixture of opinions in the literature and each change may be specific to a particular patient group with particular baseline characteristics. In this review, we defined clinically meaningful differences as the following.

- **Body weight:** a minimum of 5% reduction in body weight from baseline level (Pi-Sunyer 2015; Topol 2010; Swift 2016; Williamson 2015).
- **BMI:** a minimum of 5% reduction in BMI from the baseline level. For example, if the average mean baseline BMI was 30 kg/m^2, a difference between treatment group and comparator of 1.5 kg/m^2 would be considered clinically significant.
- **Waist circumference:** a minimum of 5% reduction in waist circumference from the baseline level. For example, if the average mean baseline waist circumference was 100 cm, a

difference between treatment group and comparator of 5 cm would be considered clinically significant.

- **Lipid profile:** a minimum 10% change from baseline (Bradley 2009).
- **Blood pressure:** 5 mm Hg reduction in either systolic or diastolic blood pressure (Bradley 2009).
- **CRP:** 5% reduction
- **Glucose:** 5% reduction
- **HbA1c:** a minimum reduction of 0.5%. (Bradley 2009).

Due to high levels of attrition in the included studies, we used per-protocol analysis. Intention-to-treat analysis was not possible due to missing data. The majority of our included studies reported their outcomes using per-protocol analysis. We imputed data for Pinto 2019.

Unit of analysis issues

We included individual-RCTs. No cluster-RCTs were found.

For any studies with more than two interventions of interest and a single comparator arm, we divided the comparator between the intervention arms to avoid double counting the participants. This only applied to one study (Hutchison 2019). The control group (ad libitum) had a total of 11 participants so could not be divided equally. Therefore six participants were allocated to the Intermittent fasting (IF)70 comparison and five to the IF100 comparison throughout the analysis tables. Alternating the allocated values (in other words five to the IF70 comparator and six to the IF100 comparator) did not change our results. The comparator group for CER had a total of 24 participants which were divided equally (12 and 12) between IF100 and IF70 analyses.

Trials with multiple follow-up times were used where available. Data given at ≤ 3 months were analysed as short-term follow-up and > 3 months to 12 months as medium-term follow-up. Where there were multiple follow-up times within the same time period (e.g. four months and six months in medium-term follow-up), the latter value were included. This is with exception of Sundfor 2018 ,which provided data at six and 12 months. The values at six months were used as more of the outcomes in that study were reported at six months compared to 12 months and is coincidently more consistent with the other studies at medium term.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. Nevertheless, we did not believe any of the data introduced bias to our results; a sensitivity analysis was therefore not performed. We dealt with data that we considered were not missing at random by imputing missing data based on predicted values, using regression analysis.

The following study authors were contacted to gather more data to calculate or have access to absolute changes for our given outcomes: Harvie 2011; Harvie 2013; Pinto 2019; Schubel 2018; Tinsley 2017; Tinsley 2019; Trepanowski 2017.

Standard deviation (SD) values were imputed for Pinto 2019 using correlation coefficients as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Correlation coefficients were generated by looking at Catenacci 2016, which reported the baseline, follow-up and change from baseline values separately. These coefficients were then used to impute the missing SD values for Pinto 2019. Furthermore, we made sure that Catenacci 2016 had a similar intervention, time of follow-up and outcomes to Pinto 2019.

Assessment of heterogeneity

We used the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis and we used an I^2 statistic value of 50% or higher as a measure of substantial heterogeneity. Where we identified substantial heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis if this was possible. We were unable to do this for Analysis 1.1 due to insufficient data.
We also inspected forest plots visually for signs of heterogeneity.

Assessment of reporting biases

We planned to create a funnel plot to explore possible reporting bias for the primary outcomes where 10 or more trials met the inclusion criteria (Sterne 2011). Unfortunately, this was not possible as no data was available on the primary outcomes.

Data synthesis

We undertook meta-analyses only where this was considered meaningful. For example, this includes situations where the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

We performed the following analyses.

1. **Intermittent fasting versus ad libitum feeding**
2. **Intermittent fasting versus continuous energy restriction (CER)**

Where there was such evidence for homogenous effects across studies, we planned to analyse the data using RR and summarise all data using the fixed-effect model (Riley 2011; Wood 2008). We used the random-effects model where we found high levels of heterogeneity, for example as indicated by a high I^2 statistic value (50% or higher). We used both models in that case but only reported the most conservative. We performed statistical analyses according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where the studies include a mixture of change-from-baseline and final value scores in some of the outcomes, we pooled the analysis of mean differences as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Due to high levels of attrition in the included studies, we used per-protocol analysis. Intention-to-treat analysis was not possible due to missing data. The majority of our included studies reported their outcomes using per-protocol analysis. We only imputed data for one study (Pinto 2019). We considered imputing missing data for more studies, however, we were uncertain of whether missing data would be indeed imputable. This is because we cannot ascertain

if patients lost to follow-up would show similar outcomes as those who adhered to the dietary intervention.

Subgroup analysis and investigation of heterogeneity

We analysed the following subgroups.

1. Male and female patients
2. Overweight and obese (BMI ≥ 25) and non-overweight patients (BMI < 25).
3. Patients with and without diabetes.
4. Intermittent fasting type: alternate-day fasting, modified alternate-day fasting, periodic fasting and time-restricted feeding.

We used the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We undertook the following sensitivity analysis.

1. To include only published trials where data were available from full-text publications and excluded trials only available as abstracts, or from trialists.

We had planned to undertake the following but this was not possible.

1. To include only those trials at low risk of bias, as specified in the Assessment of risk of bias in included studies section. The blinding of participants was not possible for the interventions comparing (Intermittent fasting versus ad libitum eating or calorie restriction), leaving us with six total domains for potential biases. We did not include 'other bias' in the definition of overall low risk of bias, so defined low risk of bias as those determined to have a low risk of bias in at least four of the domain that must include low risk of selection and reporting biases, which are the most important domains of bias in this review.
2. To only include studies if ≥ 80% of the study population were eligible for our review (Naude 2019), and planned to assess this decision in a sensitivity analysis.
3. We had planned to conduct a sensitivity analysis to assess the impact of missing data in cases where we thought it introduced serious bias. However, we did not believe any of the missing data introduced bias to our results, so did not perform a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

Two review authors (SZ and MFKF) used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes. We constructed the 'Summary of findings' tables using GRADEpro software (GRADEpro 2015). We justified all decisions to downgrade the certainty of the evidence using footnotes and we made comments to aid the reader's understanding of the review where necessary.

We included the following outcomes in the 'Summary of findings' tables.

1. All-cause mortality
2. Cardiovascular (CV) mortality
3. Stroke
4. Myocardial infarction (MI)
5. Heart failure
6. Absolute change in body weight
7. Absolute change in fasting plasma glucose

There are three 'Summary of findings' tables.

- IF versus ad libitum feeding at short-term follow-up (≤ 3 months)
- IF vs CER at short-term follow-up (≤ 3 months)
- IF vs CER at medium-term follow-up (> 3 months to 12 months)

Two review authors (SZ and MFKF) independently assessed the quality of the evidence and resolved any disagreements through consensus. We justified, documented, and incorporated our judgements into the reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

For the review, 39,165 records were identified after removal of duplicates. From reading titles and abstracts 38,972 records were eliminated as not being relevant to the review. Papers were obtained for 193 records. From these 193 records, 120 records on 110 studies were excluded (see Characteristics of excluded studies). Reasons for exclusion include wrong study design, wrong intervention, wrong setting and wrong population. Seven studies were placed in the awaiting classification section and 28 articles were categorised as ongoing trials. Nine9 further articles were found to be duplicates and added to the relevant study as an additional reference. A total of 26 studies were included (see Characteristics of included studies) and 18 were included in the quantitative synthesis.

Included studies

The trials dated from 2011 to 2019 and were conducted worldwide (Australia, the USA, South Korea, the UK, Iran, Germany and Norway). The studies included in the quantitative analysis included: Bhutani 2013; Carter 2018; Catenacci 2016; Cho 2019; Chow 2019; Griffiths 2016; Harvie 2011; Harvie 2013; Hutchison 2019; Parvaresh 2019; Pinto 2019; Schubel 2018; Stekovic 2019; Sundfor 2018; Tinsley 2017; Tinsley 2019; Varady 2011; Varady 2013.

Eight other studies were included Amodio 2016; Conley 2018; Corley 2019; Ferraris 2019; Kroeger 2015; Moro 2016; Trepanowski 2017; Varady 2016a. These studies met the inclusion criteria but were not included in the quantitative analysis. This was due to several reasons which included no available data, no relevant outcomes, data presented in a form other than absolute change. An attempt was made at contacting all authors with some having no contact details, some not replying to emails, and others declining to share data with us.

In total, the quantitatively analysed studies recruited 1125 participants and observed outcomes ranging from four weeks to six months. No studies included data on all-cause mortality, cardiovascular mortality, stroke, myocardial infarction and heart failure at any point during follow-up. The majority of the studies actively excluded participants who have a prior history of cardiovascular disease (CVD) and none of them purely focused on patients with current CVD. The most common inclusion criterion was the inclusion of overweight and obese participants.

Out of the studies included in the quantitative analysis; seven studies compared intermittent fasting (IF) to ab libitum feeding, eight studies compared IF with continuous energy restriction (CER) and three studies compared IF with both ad libitum feeding and CER.

Twelve studies recruited participants who were overweight or obese. Three studies only recruited participants who had diabetes mellitus. Two studies focused on alternate day fasting (ADF), six studies focused on modified ADF, seven studies focused on periodic fasting, and three studies focused on time-restricted feeding (TRF). Seventeen studies reported body weight as an outcome, 14 reported on body mass index (BMI), nine reported on waist circumference, 13 reported on lipid profile, 11 on blood pressure, four on C-reactive protein (CRP), 11 on glucose and four on glycated haemoglobin (HbA1c).

The attrition rate for recorded, analysed data was 15.2%. Based on quantitatively analysed studies with post-attrition recorded data for age and sex, the mean age of the participants was 37.3 years. Of these 45.4% of participants were male.

Funding of the included studies was provided by a variety of institutions including: University of Illnois, University of South Australia, Yonsei University College of Medicine, MTI Biotech Inc. and Texas Tech University, University of Minnesota Healthy Foods Healthy Lives, LighterLife (UK) Ltd and Elmholtz Association of German Research Center.

The details of each included study are shown in Characteristics of included studies.

Excluded studies

Of studies excluded, 59 were due to study design, 38 due to wrong intervention, five due to patient population, two due to the wrong setting, one was terminated and five due to the wrong comparator.

Risk of bias in included studies

We display 'Risk of bias' assessments in Figure 2; Figure 3.

Figure 2. 'Risk of bia's summary: review authors' judgements about each risk of bias item for each included study.

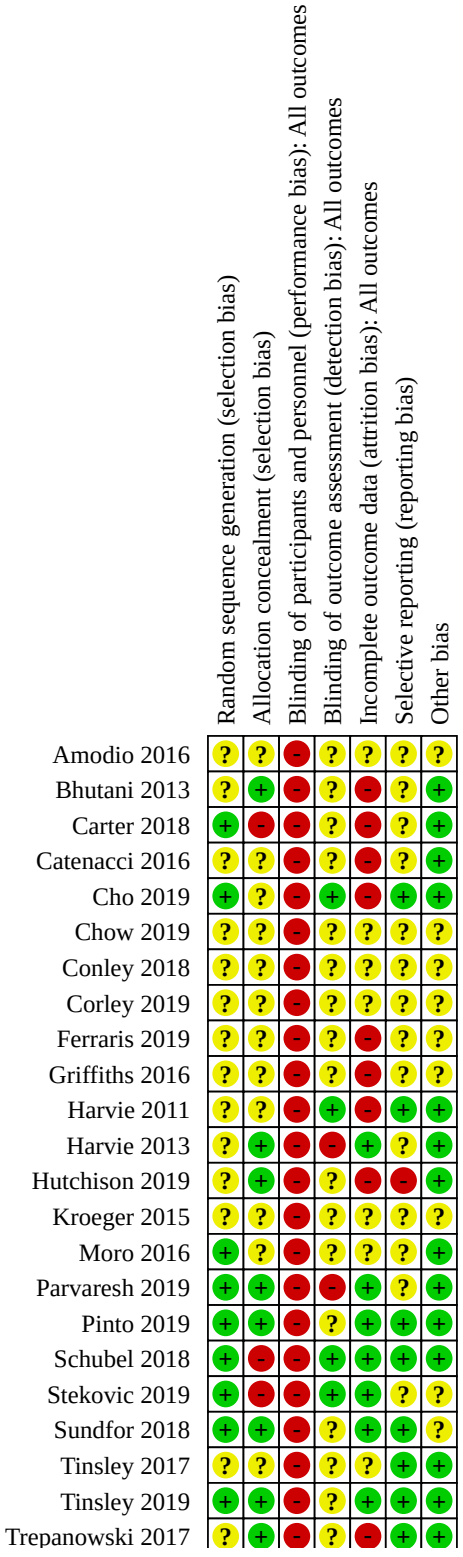


Figure 2. (Continued)

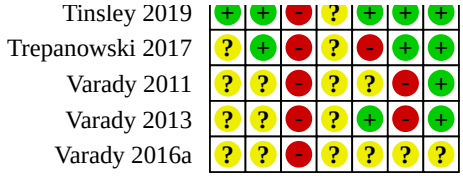
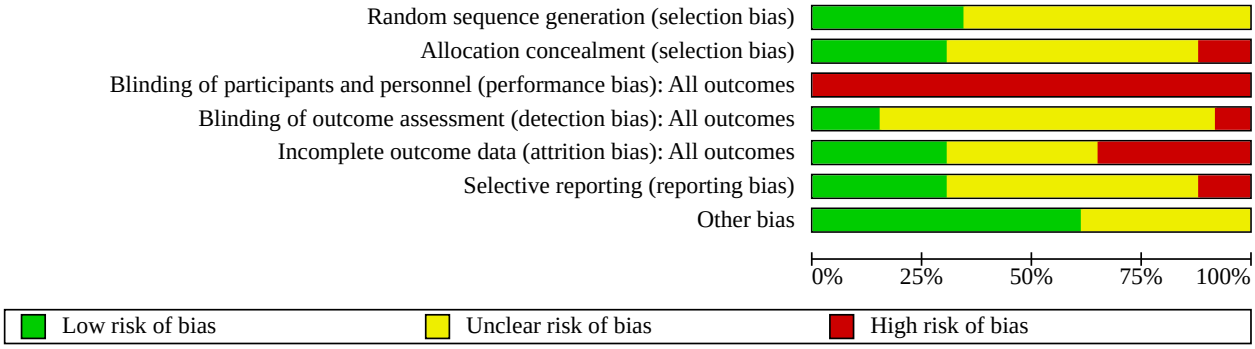


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

All the included trials were randomised controlled trials, however, detail of the randomisation process was not provided in 17 studies (Amodio 2016; Bhutani 2013; Catenacci 2016; Chow 2019; Conley 2018; Corley 2019; Ferraris 2019; Griffiths 2016; Harvie 2011; Harvie 2013; Hutchison 2019; Kroeger 2015; Tinsley 2017; Trepanowski 2017; Varady 2011; Varady 2013; Varady 2016a). The nine remaining studies which provided some detail of the randomisation process (Carter 2018; Cho 2019; Moro 2016; Parvaresh 2019; Pinto 2019; Schubel 2018; Stekovic 2019; Sundfor 2018; Tinsley 2019) were considered at low risk of bias.

Allocation concealment

With regards to allocation concealment, 15 studies were rated as unclear risk (Amodio 2016; Catenacci 2016; Cho 2019; Chow 2019; Conley 2018; Corley 2019; Ferraris 2019; Griffiths 2016; Harvie 2011; Kroeger 2015; Moro 2016; Tinsley 2017; Varady 2011; Varady 2013; Varady 2016a). Eight studies were rated as low risk (Bhutani 2013; Harvie 2013; Hutchison 2019; Parvaresh 2019; Pinto 2019; Sundfor 2018; Tinsley 2019; Trepanowski 2017) and three studies as high risk (Carter 2018; Schubel 2018; Stekovic 2019).

Blinding

Performance bias

Blinding of participants is not easy in dietary studies, as the participants usually have to follow instructions to attain the specific dietary goals. This is especially the case in intermittent fasting studies, in which specific meal timings are imposed on participants. Where participants are not blinded, it is difficult to ensure that study staff, healthcare providers and outcome assessors are blinded. We therefore judged blinding of participants and personnel to be inadequate in all studies.

Detection bias

Blinding of outcome assessment was deemed unclear in 20 studies (Amodio 2016; Bhutani 2013; Carter 2018; Catenacci 2016; Chow 2019; Conley 2018; Corley 2019; Ferraris 2019; Griffiths 2016; Hutchison 2019; Kroeger 2015; Moro 2016; Pinto 2019; Sundfor 2018; Tinsley 2017; Tinsley 2019; Trepanowski 2017; Varady 2011; Varady 2013; Varady 2016a). Four studies were deemed low risk (Cho 2019; Harvie 2011; Schubel 2018; Stekovic 2019), and two studies were deemed high risk (Harvie 2013; Parvaresh 2019).

Incomplete outcome data

As the primary outcomes for this review (all-cause mortality and cardiovascular events) were not reported in any of the original studies, owing to their short length of follow-up, assessment of whether incomplete outcome data had been addressed was based on the extent of dropout and whether dropouts had been considered in the analysis. In five studies, the risk of attrition bias was deemed to be low due to relatively low dropout rates of <7.5% (Parvaresh 2019; Pinto 2019; Stekovic 2019; Sundfor 2018; Varady 2013). In three studies, the risk of attrition bias was deemed to be low because all participants were included in the intention-to-treat analysis (Harvie 2013; Schubel 2018; Tinsley 2019). For six studies, as only the abstracts were available, the risk of attrition bias was rated as unclear (Amodio 2016; Chow 2019; Conley 2018; Corley 2019; Kroeger 2015; Varady 2016a). Three further studies were rated as unclear due to lack of information (Moro 2016; Tinsley 2017; Varady 2011). Other studies had high dropout rates which were unaccounted for in the analysis and these studies were therefore deemed to be at high risk of attrition bias.

Selective reporting

Most of the included studies have either reported that the participants did not experience any of our primary outcomes, have published their outcome data, or have provided the data they did possess. For this reason, we have graded almost all the included full-text studies as at low risk of selective reporting (Cho 2019; Harvie 2011; Pinto 2019; Schubel 2018; Sundfor 2018; Tinsley 2017; Tinsley 2019; Trepanowski 2017). For eight studies that were only available as abstracts, the risk of reporting bias was deemed to be unclear (Amodio 2016; Chow 2019; Conley 2018; Corley 2019; Ferraris 2019; Griffiths 2016; Kroeger 2015; Varady 2016a). With regards to Varady 2011 the results were reported as percentage changes. We tried to contact these authors to provide absolute changes, but it is possible that they did not reply as they felt that their data did not reflect the expected or hoped-for pattern of events. This study was rated as high risk of reporting bias. Two other studies were rated at high risk (Hutchison 2019; Varady 2013). The remaining seven studies were assessed as unclear risk of bias (Bhutani 2013; Carter 2018; Catenacci 2016; Harvie 2013; Moro 2016; Parvaresh 2019; Stekovic 2019).

Other potential sources of bias

No other potential sources of bias could be identified.

Effects of interventions

See: **Summary of findings 1** IF compared to ad libitum (short term) for the prevention of cardiovascular disease; **Summary of findings 2** IF compared to CER (short term) for the prevention of cardiovascular disease; **Summary of findings 3** IF compared to CER (medium term) for the prevention of cardiovascular disease

Primary outcomes

No studies identified in our review included any data on all-cause mortality, cardiovascular mortality, stroke, myocardial infarction and heart failure at any point during follow-up.

Physical body parameters

Body weight (kg)

Seven trials of 224 patients compared intermittent fasting (IF) versus ad libitum. Body weight was reduced in the intermittent fasting (IF) group (mean difference (MD) -2.88, 95% confidence interval (CI) -3.96 to -1.80; I^2 = 85%) (Analysis 1.1).

Ten trials of 719 patients compared IF to continuous energy restriction (CER) at short-term follow-up. Body weight was reduced in the intermittent fasting group (MD -0.88, 95% CI -1.76 to 0.00; I^2 = 66%) (Analysis 2.1).

Additionally, four trials with a total of 279 patients compared IF with CER at medium-term follow-up. Intermittent fasting had no effect on body weight (MD -0.56, 95% CI -1.68 to 0.56; I^2 = 0%) (Analysis 3.1).

Although changes to body weight were seen in Analysis 1.1 and Analysis 2.1, they did not meet our criteria for clinical significance. We attribute the high heterogeneity in Analysis 1.1; Analysis 2.1 primarily to the heterogeneous designs of the included trials. Notably, the investigation of different subtypes of IF in the trials may have added significantly to the heterogeneity. Furthermore, the different inclusion criteria of the included trials may have compounded this; notable variables include gender, baseline weight and diabetic status are notable inclusion and exclusion criteria employed by trialists that may explain the heterogeneity.We explored this using subgroup analysis, as further outlined below.

The GRADE ratings for this outcome when IF was compared with ad libitum feeding (short term) and CER (medium term) (Summary of findings 1; Summary of findings 3) were low. This is because of high risk of bias in allocation concealment, detection bias, attrition bias and high heterogeneity. When IF was compared to CER at short-term follow-up (Summary of findings 2), a GRADE rating of very low was given due to substantial heterogeneity, high risk of performance bias, unclear or high risk of selection and detection bias and a wide confidence interval that includes a possible benefit and possible harm.

Subgroup analyses of body weight (kg)

Only Analysis 2.1 (IF versus CER at short-term follow-up) met our criteria of a minimum of 10 studies in order to perform subgroup analysis.

1. **Subtypes of intermittent fasting (IF):** Analysis 2.2 focused on the different subgroups of IF (alternate day fasting (ADF), PF and modified ADF). No studies focused on time-restricted feeding. The test for subgroup difference did not identify any difference in effect by type of IF (P = 0.1).
2. **Females only versus non-females only:** Analysis 2.3 focused on studies conducted on only females versus male studies. Female-only studies showed effect (MD -0.56, 95% CI -1.96 to 0.84; participants = 226; studies = 3; I^2 = 73%). There was no male-only studies.
3. **Overweight and obese only versus non-overweight only:** Analysis 2.4 focused on overweight versus non-overweight participants. The test for subgroup differences did not indicate that the effect of IF was different depending on body weight at baseline (P = 0.18).
4. **Diabetes only versus non-diabetes only:** Analysis 2.5 focused on participants with and without diabetes. The test for subgroup differences did not indicate that the effect of IF was different depending on whether or not participants had diabetes (P = 0.16).

Body mass index (BMI) (kg/m^2)

Four trials of 115 patients compared IF to ad libitum with an MD of -0.92 kg/m^2 (95% CI -1.36 to -0.48) favouring IF but without clinical significance. There was marked heterogeneity of effects (I^2 = 61%) (Analysis 1.2).

Nine trials of 651 patients compared IF to CER at short-term follow-up (MD -0.43 kg/m^2, 95% CI -0.76, to -0.10) favouring IF but without clinical significance. There was some heterogeneity of effect (I^2 = 34%)(Analysis 2.6).

Additionally, four trials with a total of 279 patients compared IF to CER at medium-term follow-up. There was no effect on BMI (MD -0.15 kg/m^2, 95% CI -0.58 to 0.29). There was no heterogeneity (I^2 = 0%) (Analysis 3.2).

We attribute the high heterogeneity in Analysis 1.2 primarily to the heterogeneous designs of the included trials. As mentioned

previously, there were insufficient trials to formally assess the effects of baseline variability on the outcomes.

Waist circumference (cm)

Two trials of 87 patients compared IF versus ad libitum feeding. Intermittent fasting was shown to be superior to ad libitum feeding in reducing waist circumference (MD -4.19 cm, 95% CI -6.38 to -2.01; I^2 = 0%)(Analysis 1.3). However, this is not clinically significant.

Eight trials of 557 patients compared IF to CER at short-term follow-up. Intermittent fasting showed no effect compared to CER (MD -0.83 cm, 95% CI -2.11 to 0.44; I^2 = 60%) (Analysis 2.7). Additionally, 3 trials of 258 patients compared IF to CER at medium-term follow-up. We found no effect on waist circumference (MD -0.66 cm, 95% CI -2.55 to 1.23) and there was marked heterogeneity of effects (I^2 = 58%) (Analysis 3.3).

We attribute the high heterogeneity in Analysis 2.7; Analysis 3.3 primarily to the heterogeneous designs of the included trials. Notably, the investigation of different subtypes of IF in the trials may have added significantly to the heterogeneity. Furthermore, the different inclusion criteria of the included trials may have compounded this; notable variables include gender, baseline weight and diabetic status are notable inclusion and exclusion criteria employed by trialists that may explain the heterogeneity. Unfortunately, there were insufficient trials to formally assess this using subgroup analysis.

Lipid profile

Absolute change in total cholesterol levels (TC) (mmol/L)

Four trials of 125 patients compared IF versus ad libitum. A reduction in total cholesterol was observed favouringIF (MD -0.31 mmol/L, 95% CI -0.51 to -0.12; I^2 = 0%) (Analysis 1.4).

Eight trials of 539 patients compared IF versus CER at short-term follow-up. There was difference in total cholesterol between both groups (MD -0.07 mmol/L, 95% CI -0.18 to 0.03; I^2 = 0%) (Analysis 2.8).

Additionally, three trials of 258 patients compared IF versus CER at medium-term follow-up. There was no difference in total cholesterol between both groups (-0.04 mmol/L, 95% CI -0.17 to 0.10) and there was no heterogeneity (Analysis 3.4).

Absolute change in low-density lipoprotein cholesterol levels (LDL) (mmol/L)

Four trials of 125 patients compared IF with ad libitum. No change was observed in LDL levels (MD -0.22 mmol/L, 95% CI -0.40 to 0.05; I^2 = 0%) (Analysis 1.5).

Nine trials of 569 patients compared IF with CER at short-term follow-up. No change was seen (MD -0.07 mmol/L, 95% CI -0.16 to 0.01; I^2 = 0%) (Analysis 2.9).

Additionally, three trials of 258 patients compared IF with CER at medium-term follow-up. There was no difference in LDL between both groups (MD -0.06 mmol/L. 95% CI -0.18 to 0.05) and there was no heterogeneity (Analysis 3.5).

Absolute change in high-density lipoprotein cholesterol levels (HDL) (mmol/L)

Four trials of 125 patients compared IF with ad libitum. No change was seen (MD -0.10 mmol/L, 95% CI -0.25 to 0.05; I^2 = 65%) (Analysis 1.6).

Nine trials of 569 patients compared IF with CER at short-term follow-up. No change was seen (MD -0.01 mmol/L, 95% CI -0.06 to 0.04; I^2 = 59%) (Analysis 2.10).

Additionally, three trials of 258 patients compared IF with CER at medium-term follow-up. There was no difference in HDL between both groups (-0.00 mmol/L, 95% CI -0.07 to 0.07) and there was marked heterogeneity (I^2 = 52%) (Analysis 3.6).

Absolute change in total triglyceride levels (TG) (mmol/L)

Four trials of 125 patients compared IF to ad libitum. No change was seen (MD -0.06 mmol/L, 95% CI -0.25 to 0.14; I^2 = 50%) (Analysis 1.7).

Eight trials of 539 patients compared IF to CER at short-term follow-up. There was no difference in change in TG between both groups (MD -0.07 mmol/L, 95% CI -0.19 to 0.06; I^2 = 43%) (Analysis 2.11).

Additionally, four trials of 279 patients compared IF to CER at medium-term follow-up. There was no difference in TG between both groups (MD -0.02 mmol/L, 95% CI -0.16 to 0.12) and there was no heterogeneity (Analysis 3.7).

We attribute the high heterogeneity in Analysis 1.7; Analysis 3.6 primarily to the heterogeneous designs of the included trials. Notably, the investigation of different subtypes of IF in the trials may have added significantly to the heterogeneity. Furthermore, the different inclusion criteria of the included trials may have compounded this; notable variables include gender, baseline weight and diabetic status are notable inclusion and exclusion criteria employed by trialists that may explain the heterogeneity. Unfortunately, there were insufficient trials to formally assess this using subgroup analysis.

Blood pressure

Absolute change in systolic blood pressure (SBP) (mmHg)

Five trials of 201 patients compared IF versus ad libitum. A reduction in blood pressure was seen favouring IF (MD -4.47 mmHg, 95% CI -6.94 to -2.01; I^2 = 0%) (Analysis 1.8).

Seven trials of 548 patients compared IF with CER at short-term follow-up. There was no difference in change in SBP between both groups (MD -1.75 mmHg, 95% CI -4.61 to 1.11; I^2 = 24%) (Analysis 2.12).

Additionally, three trials of 258 patients compared IF with CER at medium-term follow-up. There was no change in SBP between both groups (MD 1.37 mmHg, 95% CI -4.98 to 7.72) and there was marked heterogeneity (I^2 = 52%) (Analysis 3.8).

Absolute change in diastolic blood pressure (DBP) (mmHg)

Five trials of 201 patients compared IF to ad libitum with no difference in change in DBP between both groups (MD -1.07 mmHg, 95% CI -3.33 to 1.18; I^2 = 0%) (Analysis 1.9).

Seven trials of 548 patients compared IF with CER at short-term follow-up. There was no difference in change in DBP between both groups (MD -0.97 mmHg, 95% CI -2.35 to 0.42; I^2 = 0%) (Analysis 2.13).

Additionally, three trials of 258 patients compared IF with CER at medium-term follow-up. There was no change in DBP between both groups (MD -1.00 mmHg, 95% CI -4.67 to 2.67 and there was some heterogeneity (I^2 = 37%) (Analysis 3.9).

C-reactive protein (CRP) (mg/L)

Two trials of 43 patients compared IF with ad libitum with no difference in change in CRP between both groups (MD -1.19 mg/L, 95% CI -2.54 to 0.16) and there was no heterogeneity (Analysis 1.10).

Two trials of 190 patients compared IF with CER at short-term follow-up. There was no difference in change in CRP between both groups (MD 0.31 mg/L, 95% CI -0.56 to 1.17) and there was no heterogeneity (Analysis 2.14).

Additionally, one trial of 89 patients compared IF with CER at medium-term follow-up. There was no change in CRP between both groups (MD 0.46 mg/L, 95% CI -0.87 to 1.79) (Analysis 3.10).

Glucose and glycated haemoglobin (HbA1c)

Absolute change in fasting plasma glucose (mmol/L)

Three trials of 95 patients compared IF with ad libitum with no difference in change in glucose between both groups (MD -0.03 mmol/L, 95% CI -0.26 to 0.19; I^2 = 15%) (Analysis 1.11).

Nine trials of 582 patients compared IF with CER at short-term follow-up. There was no difference in change in glucose between both groups (MD -0.02 mmol/L, 95% CI -0.16 to 0.12; I^2 = 73%) (Analysis 2.15).

Additionally, four trials of 279 patients compared IF with CER at medium-term follow-up. There was no difference in change in glucose between both groups (MD 0.01 mmol/L, 95% CI -0.10 to 0.11) and there was no heterogeneity (Analysis 3.11).

We attribute the high heterogeneity in Analysis 2.15 primarily to the heterogeneous designs of the included trials. Notably, the investigation of different subtypes of IF in the trials may have added significantly to the heterogeneity. Furthermore, the different inclusion criteria of the included trials may have compounded this; notable variables include gender, baseline weight and diabetic status are notable inclusion and exclusion criteria employed by trialists that may explain the heterogeneity. Unfortunately, there were insufficient trials to formally assess this using subgroup analysis.

The GRADE rating for this outcome when IF is compared to ad libitum feeding was very low (we are uncertain about our findings). This was because of high risk of performance bias, unclear or high risk of selection and attrition bias, a very low sample size and a wide confidence interval that includes a possible benefit and harm. The same rating was given when IF was compared to CER at short-term follow-up. Again, this is due to substantial heterogeneity, unclear or high risk of selection and detection bias and a wide confidence interval that includes a possible benefit and harm. When IF is compared to CER at medium-term follow-up, a low rating was given due to risk of bias and a wide confidence interval as above.

Absolute change in glycated haemoglobin (HbA1C) (mmol/L)

Four trials of 310 patients compared IF to CER at short-term follow-up. There was no difference in change in HbA1c between both groups (MD 0.01 mmol/L, 95% CI -0.07 to 0.08) and there was no heterogeneity (Analysis 2.16).

Side effects and quality of life

A total of four trials (Carter 2018; Harvie 2013; Schubel 2018; Varady 2013) reported on headaches and no studies reported any data on dizziness and weakness. Pooling all the data, 13 out of 187 participants in the intermittent fasting groups had at least a mild headache (7.0%), where two participants withdrew from the study due to the intensity of it (Carter 2018). Only one trial (Harvie 2011) reported on the quality of life using the RAND SF-36 score. There was a modest increase in the physical component summary score.

Sensitivity analyses

Summary

No major differences were noted between this sensitivity analysis of published trials and the original analyses.

Body weight (kg)

Six trials of 203 patients compared IF to ad libitum (MD -3.04 kg, 95% CI -4.45 to -1.62; I^2 = 86%) (Analysis 4.1). Sensitivity analysis did not change our original findings.

Nine trials of 710 patients compared IF to CER at short-term follow-up (MD -0.77 kg, 95% CI -1.66 to 0.12; I^2 = 67%) (Analysis 5.1). Sensitivity analysis did not change our original findings.

Additionally, four trials with a total of 279 patients compared IF to CER at medium-term follow-up (MD -0.56 kg, 95% CI -1.68 to 0.56; I^2 = 0%) (Analysis 6.1). Sensitivity analysis did not change our original findings.

BMI (kg/m^2)

Four trials of 115 patients compared IF to ad libitum (MD -0.92, 95% CI -1.36 to -0.48; I^2 = 61%) (Analysis 4.2). Sensitivity analysis did not change our original findings.

Eight trials of 642 patients compared IF with CER at short-term follow-up (MD -0.40, 95% CI -0.74 to -0.06; I^2 = 38%) (Analysis 5.6). Sensitivity analysis did not change our original findings.

Additionally, four trials with a total of 279 patients compared IF with CER at medium-term follow-up (MD -0.15, 95% CI -0.58 to 0.29; I^2 = 0%) (Analysis 6.2). Sensitivity analysis did not change our original findings.

Waist circumference (cm)

Two trials of 87 patients compared IF with ad libitum (MD -4.19 cm, 95% CI -6.38 to -2.01; I^2 = 0%) (Analysis 4.3). Sensitivity analysis did not change our original findings.

Seven trials of 548 patients compared IF with CER at short-term follow-up (MD -0.74 cm, 95% CI -2.08 to 0.59; I^2 = 64%) (Analysis 5.7). Sensitivity analysis did not change our original findings.

Absolute change in total cholesterol levels (TC) (mmol/L)

Four trials of 125 patients compared IF with ad libitum (MD -0.31 mmol/L, 95% CI -0.51 to -0.12; I^2 = 0%) (Analysis 4.4). Sensitivity analysis did not change our original findings.

Eight trials of 573 patients compared IF with CER at short-term follow-up (MD -0.09 mmol/L, 95% CI -0.20 to 0.02; I^2 = 0%) (Analysis 5.8). Sensitivity analysis did not change our original findings.

Absolute change in low-density lipoprotein cholesterol levels (LDL) (mmol/L)

Four trials of 125 patients compared IF with ad libitum (MD -0.22 mmol/L, 95% CI -0.40 to -0.05; I^2 = 0%) (Analysis 4.5). Sensitivity analysis did not change our original findings.

Eight trials of 560 patients compared IF with CER at short-term follow-up (MD -0.08 mmol/L, 95% CI -0.17 to 0.02; participants = 560; studies = 9; I^2 = 0%) (Analysis 5.9). Sensitivity analysis did not change our original findings.

Absolute change in high-density lipoprotein cholesterol levels (HDL) (mmol/L)

Four trials of 125 patients compared IF with ad libitum (MD -0.10 mmol/L, 95% CI -0.25 to 0.05; I^2 = 65%) (Analysis 4.6). Sensitivity analysis did not change our original findings.

Eight trials of 560 patients compared IF with CER at short-term follow-up (MD -0.00 mmol/L, 95% CI -0.05 to 0.04; I^2 = 37%) (Analysis 5.10). Sensitivity analysis did not change our original findings.

Absolute change in total triglyceride levels (TG) (mmol/L)

Four trials of 125 patients compared IF with ad libitum (MD -0.06 mmol/L, 95% CI -0.25 to 0.14; I^2 = 50%) (Analysis 4.7). Sensitivity analysis did not change our original findings.

Seven trials of 530 patients compared IF with CER at short-term follow-up (MD -0.09 mmol/L, 95% CI -0.18 to 0.00; I^2 = 1%) (Analysis 5.11). Sensitivity analysis did not change our original findings.

Additionally, four trials of 279 patients compared IF with CER at medium-term follow-up (MD -0.02 mmol/L, 95% CI -0.16 to 0.12; I^2 = 0%) (Analysis 6.7). Sensitivity analysis did not change our original findings.

Absolute change in systolic blood pressure (SBP) (mmHg)

Five trials of 201 patients compared IF with ad libitum (MD -4.47 mmHg, 95% CI -6.94 to -2.01; I^2 = 0%) (Analysis 4.8). Sensitivity analysis did not change our original findings.

Seven trials of 548 patients compared IF with CER at short-term follow-up (MD -1.75 mmHg, 95% CI -4.61 to 1.11; I^2 = 24%) (Analysis 5.12). Sensitivity analysis did not change our original findings.

Absolute change in diastolic blood pressure (DBP) (mmHg)

Five trials of 201 patients compared IF with ad libitum (MD -1.07 mmHg, 95% CI -3.33 to 1.18; I^2 = 0%) (Analysis 4.9). Sensitivity analysis did not change our original findings.

Seven trials of 548 patients compared IF to CER at short-term follow-up (MD -0.97 mmHg, 95% CI -2.35 to 0.42; participants = 548; studies = 8; I^2 = 0%) (Analysis 5.13). Sensitivity analysis did not change our original findings.

CRP (mg/L)

Two trials of 43 patients compared IF to ad libitum with no difference in change in CRP between both groups (-1.19 mg/L, 95% CI -2.54 to 0.16) and there was no heterogeneity (Analysis 4.10). Sensitivity analysis did not change our original findings.

Absolute change in fasting plasma glucose (mmol/L)

Three trials of 95 patients compared IF to ad libitum (MD -0.03 mmol/L, 95% CI -0.26 to 0.19; I^2 = 15%) (Analysis 4.11). Sensitivity analysis did not change our original findings.

Eight trials of 573 patients compared IF to CER at short-term follow-up (MD -0.01 mmol/L, 95% CI -0.15 to 0.12; I^2 = 73%) (Analysis 5.15). Sensitivity analysis did not change our original findings.

Additionally, three trials of 279 patients compared IF to CER at medium-term follow-up (MD 0.01 mmol/L, 95% CI -0.10 to 0.11; I^2 = 0%) (Analysis 6.10). Sensitivity analysis did not change our original findings.

Absolute change in glycated haemoglobin (HbA1C) (mmol/L)

Three trials of 301 patients compared IF to CER at short-term follow-up. There was no difference in change in HbA1c between both groups (MD 0.01, 95% CI -0.07 to 0.09) and there was no heterogeneity (Analysis 5.16). Sensitivity analysis did not change our original findings.

DISCUSSION

Summary of main results

In total, 26 randomised controlled trials (RCTs) were included in this review, 18 of which (1125 participants) provided data for the quantitative synthesis. Of these studies, seven studies recruited participants who were overweight or obese; three recruited patients who were obese; and two studies excluded obese participants. Two studies only recruited participants with type 2 diabetes mellitus. Notably, none of the included RCTs were at low summary risk of bias (randomisation, allocation concealment, selection and detection bias all at low risk for supplementation trials; randomisation, allocation concealment and detection bias all at low risk for dietary advice trials).

Randomised controlled trials of the effects of intermittent fasting (IF) compared to ad libitum feeding, showed a reduction in value of some outcomes in favour of IF. However the results reported did not seem to be clinically significant. We attribute this to the primarily short-term follow-up periods for these parameters; the cardiometabolic effects of dietary interventions often need sufficient time to present, which would not be expected in studies reporting short-term outcomes only. None of the trials found in the literature investigated the long-term effects of IF on cardiometabolic risk factors. There was insufficient evidence to assess the effects of IF compared to ad libitum feeding on glycated haemoglobin (HbA1C) as it was reported in only one study (Schubel 2018). This was probably designed due to the short follow-up periods of these studies.

Whilst a statistical difference was found to favour IF compared to ad libitum feeding in reducing patient weight, body mass index (BMI), waist circumference, reduction in total cholesterol (TC), and reduction in systolic blood pressure (SBP), the clinical significance of these findings may not be entirely evident. We decided to use a cut-off of a difference of 5% or larger from baseline value as a cut-off for clinically significant difference between both diets in accordance with previous literature (Pi-Sunyer 2015; Topol 2010). None of the differences in parameters met our criteria for clinical significance, although this may be due to a short follow-up period.

Compared to continuous energy restriction (CER), IF caused a reduction in some of the outcomes, but this was most obvious in body weight and BMI after short-term follow-up. However, none of the differences were large enough to meet our criteria for clinical significance. Furthermore, both diets were equally effective in terms of their effects on changes in TC, low-density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), plasma glucose, HbA1C,or C-reactive protein (CRP).

None of the studies identified in our review included any data on our intended primary outcomes of all-cause mortality, cardiovascular mortality, stroke, myocardial infarction and heart failure at any point during follow-up. As such, we cannot currently comment on the effect of IF compared to ad libitum feeding or CER on these outcomes.

Overall completeness and applicability of evidence

We conducted a careful search and used a set of comprehensive search strategies in attempt to find the full set of available RCTs in published literature that assess the effects of IF compared with CER and ad libitum feeding in our specified outcomes. This resulted in 18 trials that randomised a total of 1125 participants to IF, CER and ad libitum feeding. To reduce selection bias, we contacted authors of trials that appeared to have randomised appropriate participants to appropriate intervention and comparator but may not have published relevant outcomes at the time of conducting our search. If trial authors had assessed any of our outcomes, we requested data and included the trial. This enabled us to include several additional trials. Whilst we have made every possible effort to include all available data published on this topic, we acknowledge that there is a small possibility that some data may have been inadvertently missed.

None of the studies identified in our review included any data on our intended primary outcomes of all-cause mortality, cardiovascular mortality, stroke, myocardial infarction and heart failure at any point during follow-up. As such, we were unable to comment on the effect of IF compared to ad libitum feeding or CER on these outcomes. This reflects the paucity of available data on the effects of IF on these major adverse cardiovascular events. This illustrates a significant limitation in the clinical utility of the results of this review; whilst they demonstrate promising findings regarding the effects of IF on the well-documented risk factors of cardiovascular disease, we are unable to comment as to whether this is sufficient to translate into reduced incidence of all-cause mortality, stroke, myocardial infarction or heart failure.

Quality of the evidence

Figure 2; Figure 3 display the risk of bias of included trials. None of the 18 RCTs that provided data was at low summary risk of bias (at low risk of selection bias, performance bias and detection bias, plus the low risk of performance bias in supplemental trials). Predominantly, this was due to the fact that none of the studies were deemed at low risk of performance bias. This is a significant limitation in investigating lifestyle interventions such as dieting and intermittent fasting as blinding of participants is not easy in dietary studies. This is because the participants usually have to follow instructions to attain specific dietary goals. This is especially the case in intermittent fasting studies, in which specific meal timings are imposed on participants. Where participants are not blinded, it is difficult to ensure that study staff, healthcare providers and outcome assessors are blinded. We, therefore, judged blinding to be inadequate in all studies. However, it is noteworthy that aside from this fact, none of the RCTs in this study were deemed to be at low risk of bias in the remaining domains.

We had planned to assess the validity of evidence in meta-analyses by running sensitivity analyses that removed trials not at low summary risk of bias. As none of the studies were deemed to be at low risk of bias, this was not possible.

Furthermore, a noteworthy limitation of our study is the exclusion of non-randomised studies. This allowed for the inclusion of high-quality studies as it eliminates selection bias as an important confounder of the results. Nevertheless, the use of non-randomised trials would have increased the clinical generalisability of our results as such studies often reflect clinical practice more accurately than randomised trials.

Potential biases in the review process

Potential adverse effects include psychological, neurological and physical problems; whilst we have collated all available data regarding these adverse effects, there was an overall paucity of data regarding this aspect. However, we did not specifically contact the authors of included and excluded trials for additional data on these outcomes. Unfortunately, the data on adverse effects were insufficient to conduct a quantitative synthesis. We had predicted this in the study protocol and thus planned to conduct a qualitative analysis on this outcome.

Furthermore, one problem with cardiovascular disease outcomes is that they are all interconnected. For example, loss of weight is attributed to improvement in dyslipidaemia. Contrarily, there has been evidence to suggest that weight loss is associated with transient hypertriglyceridaemia (Phinney 1991). As such, it is indiscernible whether the results obtained in this study and its constituent RCTs were directly due to intermittent fasting or whether they arise due to these complex interactions. Moreover, most trials included in this meta-analysis were short-to-medium term, with little data from long-term trials. As such, we are unable to decipher whether these findings are a transient physiological reaction to a stressor or whether they are indeed secondary to the dietary interventions; thus posing an important confounder.

Similarly, a problem with dietary interventions is that they are strong psychosocial interventions aimed at improving patients' cardiovascular risks. This is often (but not always) accompanied by an increase in the patient's resolve to follow a "healthier" lifestyle.

Prominently, studies have shown a significant increase the amount of physical exercise performed in patients who commence dietary interventions (Phinney 2004). This is yet another confounding variable that we did not account for in the analysis. The trials included in this study did not record whether a change in baseline physical activity was noted in the enrolled patients, neither did they report physical activity in patients of different groups. In addition, we did not specifically request such data from the trial authors. As such, this remains a confounding variable which was not accounted for in our analysis.

While we tried hard to locate all available trials and collect additional outcome data where possible, there was evidence of some small-study bias. Some smaller trials showing increased weight with IF may be missing. If these trials were replaced they would tend to increase risk ratios. This suggests that there is some underlying small-study bias within our review.

Furthermore, we had planned to conduct several sensitivity analyses. For example, we had planned to conduct a sensitivity analysis where we include only published trials where data are available from full-text publications and exclude trials only available as abstracts. We had also planned to conduct a sensitivity analysis where we only included studies if ≥ 80% of the study population were eligible for our review; in all trials included, all the patients in the study were eligible for our review and thus this analysis was not possible. Finally, as previously discussed, we had planned to assess the validity of evidence in meta-analyses by running sensitivity analyses that removed trials, not at low summary risk of bias. As none of the studies were deemed to be at low risk of bias, this was not possible.

Due to high levels of attrition in the included studies, we used per-protocol analysis. Intention-to-treat analysis was not possible due to missing data. The majority of our included studies reported their outcomes using per-protocol analysis. We only imputed data for one study (Pinto 2019). We considered imputing missing data for more studies, however, we were uncertain of whether missing data would be indeed imputable. This is because we cannot ascertain if patients lost to follow-up would show similar outcomes as those who adhered to the dietary intervention. We recognise the limitations of this approach, namely introducing bias. Notably, intermittent fasting requires strict adherence; this limits the generalisability of our data as results from per-protocol analysis only apply to the cohort of patients who have indeed adhered to the intervention. Previous studies have suggested that intermittent fasting may not be sustainable in the long-term due to high attrition amongst participants in clinical trials (Trepanowski 2017). This is reflected in our findings where a high risk of attrition bias was noted amongst our included studies.

Agreements and disagreements with other studies or reviews

This is the first Cochrane Review investigating the effects of intermittent fasting on cardiovascular disease. One recent review (Welton 2020) included randomised and observational trials of intermittent fasting and its effects on cardiovascular risk factors; most notably, weight loss. This study concluded that studies comparing intermittent fasting to calorie restriction found equivalent results. This conflicts with our findings that intermittent fasting seems to cause a reduction in BMI when compared to CER. There are several reasons for this discrepancy. First, numerous types of intermittent fasting exist, and the inclusion of different types of intermittent fasting may explain this. For example, their review does not provide specific definitions for intermittent fasting. In our review, we have defined intermittent fasting by the different subtypes commonly discussed in the literature. The majority of the time, modified alternate-day fasting (ADF) is defined as a period of caloric restriction for one day which includes 25% or less of maintenance caloric requirement. However, in certain studies, the percentage caloric intake was not given and instead a numerical caloric intake was provided. For this, we included studies which had a consumption of ≤ 600 calories. With regards to time-restricted feeding (TRF), the majority of studies highlighted a minimum of around 12 hours of fasting. This was used as a cut-off in this review.

The discordance in the definition may result in a discrepancy in the inclusion or exclusion of trials, thus leading to different results. Another explanation for the discrepancy may be due to their inclusion of non-randomised studies. Whilst these studies are invaluable for providing epidemiological data, the observational nature of these trials yields a high risk of bias and introduces several confounding variables. For this reason, we chose to exclude these studies from our analysis, as is the protocol for most reviews conducted under the Cochrane Heart group. Despite these differences, the (Welton 2020) review documented improved glycaemic control with IF, findings comparable to our own.

In addition, another systematic review (Harris 2018) showed similar effects of IF compared to ad libitum feeding for weight loss (−4.14 kg; 95% CI −6.30 to −1.99; P ≤ 0.001), but no significant difference between IF and CER for weight loss (−1.03 kg; 95% CI −2.46 to 0.40; P = 0.156). In addition to the aforementioned reasons, we attribute the discrepancy between their findings and ours to the relatively fewer studies in their review compared to this review.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence regarding the role of intermittent fasting in the primary and secondary prevention of cardiovascular disease. The individual meta-analyses show that intermittent fasting may be effective in reducing weight when compared to ad libitum feeding and may be as effective as continuous energy restriction. Despite this, these changes appear to be clinically insignificant at short-term follow-up. The quality of the available evidence is low to very low which mean sthat many areas of uncertainty remain. Further research is needed to understand which patient groups would and would not benefit from intermittent fasting. This includes patients with diabetes and patients with eating disorders. Currently, there is a scarcity of safety data and future randomised controlled trials (RCTs) need to address the safety of intermittent fasting along with the efficacy and provide a valid risk-benefit analysis for such patient groups (e.g. patients with diabetes or eating disorders).

Implications for research

As mentioned above, it would be useful to study intermittent fasting in specific patient groups and to determine where it can and cannot be indicated. RCTs in the future should explicitly integrate the safety of intermittent fasting into each study. Furthermore, this review reported no data on primary outcomes such as all-cause mortality, cardiovascular mortality, stroke, myocardial

infarction and heart failure. It would be useful to see whether intermittent fasting may be beneficial in these outcomes but may require longer-term studies with regular follow-up. We suggest a prospectively randomised open blinded end-point (PROBE) study which compares long-term outcomes between intermittent fasting, calorie restriction and ad libitum feeding. We especially suggest a follow-up of five years or greater in order to assess major adverse cardiovascular events. Ideally, separate trials should include patients with and without established cardiovascular disease as well as cardiovascular risk factors. We hope this would ascertain the benefit of intermittent fasting in the primary and secondary prevention of cardiovascular disease.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amodio 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	Menopausal women with metabolic syndrome **Inclusion criteria:** none provided **Exclusion criteria:** none provided
Interventions	**2-arm trial** **Intervention (n = 12):** moderately hypocaloric diet (1600 Kcal/day) during 8 hours (7 AM-3 PM; **Comparator (n = 11):** moderately hypocaloric diet (1600 Kcal/day) for 45 days ad libitum
Outcomes	Weight loss, fasting plasma glucose, triglycerides
Notes	**Type of paper:** abstract only. **Funding:** no data on sources of funding were provided.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Abstract only and allocation concealment not indicated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only and loss to follow-up not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Bhutani 2013

Study characteristics	
Methods	Randomised, controlled, parallel-arm feeding trial
Participants	83 participants based in the USA aged between 25-65 years. BMI between 30 and 39.9 kg/m2. **Inclusion criteria:** age 25-65 years; BMI between 30 and 39.9 kg/m^2; weight stable for 3 months prior to the beginning of the study (i.e. less than 5 kg weight loss or weight gain); nondiabetic; no history of cardiovascular disease; lightly active (i.e. <3 hours/week of light intensity exercise at 2.5-4.0 metabolic equivalents [METs] for 3 months prior to the study); nonsmoker; no history of bariatric surgery; and not taking weight loss, lipid, or glucose lowering medications. **Exclusion criteria:** peri-menopausal women were excluded from the study, and post-menopausal women (absence of menses for more than 2 years) were required to maintain their current hormone replacement therapy regimen for the duration of the study.
Interventions	**4-arm trial** **Intervention (n = 16):** modified Alternate Day fasting (ADF) (25% of normal) **Comparator (n = 16):**a d libitum feeding **Other arms not included:** combination (ADF+ exercise) and exercise-alone arm
Outcomes	Body weight, waist circumference, blood pressure
Notes	**Type of paper: full-text publication** **Funding:** • American Heart Association. Grant Number: 12PRE8350000 • University of Illinois, Chicago, Departmental funding **ADF-** alternate day fasting

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed for each stratum by selecting an intervention at random from an opaque envelope."
Allocation concealment (selection bias)	Low risk	Quote:"Randomization was performed for each stratum by selecting an intervention at random from an opaque envelope."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Additional participants were randomised to groups that had high dropout rates (i.e. the ADF and exercise group) to ensure that the total number of participants would be the same in each group at the end of the study.

Bhutani 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not stated.
Other bias	Low risk	Nothing to note.

Carter 2018

Study characteristics	
Methods	Parallel-arm randomised clinical trial
Participants	137 participants based in Australia aged ≥ 18 years with type 2 diabetes who were overweight or obese (BMI ≥ 27). **Inclusion criteria:** adults (≥18 years of age) with type 2 diabetes who were overweight or obese (BMI ≥ 27 [calculated as weight in kilograms divided by height in meters squared]) **Exclusion criteria:** pregnant or breastfeeding.
Interventions	**2-arm trial** **Intervention (n = 70):** intermittent energy restriction group followed a diet of 500 to 600 kcal/day for 2 days of the week and followed their usual diet for the other 5 days. **Comparator (n = 67):** continuous energy restriction
Outcomes	Body weight, BMI, HbA1c
Notes	**Type of paper:** abstract **Funding:** Ms Carter was supported by a University of South Australia postgraduate award. Dr Clifton was supported by a National Health and Medical Research Council principal research fellowship.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:"Randomization was completed using an online generated random number allocation sequence and was not blinded; participants were allocated to groups by the study dietitian according to the randomization schedule."
Allocation concealment (selection bias)	High risk	There was lack of blinding when assigning the interventions to the participants; quote:"participants were allocated to groups by the study dietitian."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	High rates of dropout; quote: "97 participants (70.8%) completed the study, and the dropout rates were similar in both groups (21 participants [31.3%] in

Carter 2018 *(Continued)*

All outcomes		the continuous energy restriction group and 19 participants [27.1%] in the intermittent energy restriction group; P = .71)."
Selective reporting (reporting bias)	Unclear risk	Not stated.
Other bias	Low risk	Nothing to note.

Catenacci 2016

Study characteristics	
Methods	Parallel randomised clinical trial
Participants	29 participants based in the USA aged between 18 and 55 years with a BMI > 30. **Inclusion criteria:** (18-55 years, BMI ≥30 kg/m^2, non-smoker, ≤4.5 kg weight change over past 6 months) were invited to a screening visit. **Exclusion criteria:** volunteers were excluded if they had diabetes, CVD, uncontrolled hypertension, severe dyslipidaemia (or were on lipid-lowering therapy), cancer, thyroid disease, seizures, migraines, significant renal, hepatic or gastrointestinal disorders, binge eating disorder, current depression, history of bariatric surgery, or were taking medications known to affect appetite or energy metabolism. Women who were currently pregnant, planning pregnancy, or lactating were also excluded.
Interventions	**2-arm trial** **Intervention (n = 13):** zero-calorie alternate day fasting **Comparator (n = 12):** continuous calorie restriction
Outcomes	Body weight, BMI, lipid profile, glucose
Notes	**Type of paper:** full-text publication **Funding:** NIH R21 AT002617-02, NIH UL1 TR001082, NIH DK 048520, the Colorado Obesity Research Institute (CORI), and the Intramural Research Program of the National Institute on Aging. Dr. Melanson is supported with resources and the use of facilities at the Denver VA Medical Center.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	There was no mention of a method for allocation sequence concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Catenacci 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of dropout; Of the 45 people who consented at screening, 16 participants (35.6%) either dropped out or were withdrawn prior to randomisation. Then, 1 of the 15 participants (6.67%) in the ADF group dropped out from the 8-week intervention, and 2 out of 14 participants (14.3%) withdrawn from the CR group in this period. By the 24-week follow-up, the dropout rate was 21.4% (3 out of 14 participants) in the ADF group and 16.7% (2 out of 12 participants) in the CR group.
Selective reporting (reporting bias)	Unclear risk	Not stated.
Other bias	Low risk	Nothing to note.

Cho 2019

Study characteristics	
Methods	Multiple-arm randomised controlled clinical trial
Participants	112 participants based in South Korea aged between 20 and 65 with a BMI > 23. **Inclusion criteria and exclusion criteria:** Eligibility requirements were: age 20–65 years; BMI >23.0 kg/m^2 (overweight or obese for Asian populations, according to the World Health Organization [17]); stable weight for 3 months prior to the study (i.e. weight loss or weight gain <5 kg); no history of bariatric surgery; no secondary obesity, such as hypothyroidism; non-diabetic; aspartate amino-transferase (ASP) or alanine amino-transferase (ALT) levels < 200 mg/dL; serum creatinine level < 2.0 mg/dL, no pancreatitis or related disorders; no acute infectious diseases (i.e. pneumonia, acute enteritis, or urinary infection); no chronic inflammatory diseases (i.e. rheumatoid arthritis, or lupus); no history of cardiovascular diseases; no history of cancer; not taking anti-obesity, anti-diabetic, diuretic, central-nervous system, antidepressant, antipsychotic, or steroid medications; no pregnant or lactating women; no overeating behaviour; no >30 g of daily alcohol intake; not a night-time or shift-work worker; no chronic malabsorption syndrome or cholestasis; no other medical conditions that would preclude subjects from participating in exercise and physical test.
Interventions	**2-arm trial** **Intervention (n = 8):** modified alternate day fasting (25% of normal) **Comparator (n = 5):** ad libitum feeding
Outcomes	Body weight, BMI, lipid profile, CRP, glucose
Notes	**Type of paper:** full-text publication **Funding:** This study was supported by a 2013 Faculty Research Grant from the Yonsei University College of Medicine (6-2013-0021) and the Bio & Medical Technology Development Program, through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2013M3A9B6046413, NRF-2018R1D1A1B07049223).
Risk of bias	

Cho 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"Block randomization was performed with a computer-generated random number sequence. An independent statistician generated the allocation sequence."
Allocation concealment (selection bias)	Unclear risk	Quote:"An independent statistician generated the allocation sequence, and the study coordinator assigned the participants to interventions in chronological order as the participants enrolled. Only outcome assessors were blinded to group allocation" It is unclear what was meant by assignment in chronological order, and this statement suggests that the allocation sequence was not concealed from the study coordinators, in contradiction to the later statement that "only outcome assessors were blinded to group allocation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only outcome assessors were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of dropout; Dropout of 7 out of 26 participants (26.9%) in ADF group. Dropout of 6 out of 22 participants (27.3%) in control group
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the Methods section were reported in the Results section. An assessment based on ClinicalTrials.gov (NCT03652532) cannot be made because the trial was registered post-hoc.
Other bias	Low risk	Nothing to note.

Chow 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	21 overweight participants: 18F/3M, mean (SE), age: 44.7 years (2.7), BMI:34.6 kg/m2(1.7) **Inclusion and exclusion criteria:** nothing noted
Interventions	**2 arm trial** **Intervention (n=11):** time restricted feeding **Comparator (n=10):** ad libitum feeding
Outcomes	Weight, lean mass, triglycerides, visceral fat, glucose
Notes	**Type of paper:** abstract only **Funded by:** University of Minnesota Healthy Foods Healthy Lives (17SFR-2YR50LC)
Risk of bias	

Chow 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Abstract only and allocation concealment not indicated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only and loss to follow-up not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Conley 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	24 Participants **Inclusion and exclusion criteria:** nothing noted
Interventions	**2-arm trial** **Intervention:** twice-weekly diet **Comparator:** standard energy-restricted diet (SERD) (2050 KJ (500 calorie) reduction per day) for 6 months.
Outcomes	Weight, waist circumference (WC), fasting blood glucose, blood lipids, blood pressure and dietary intake were measured at baseline
Notes	**Type of paper:** abstract only **Funding:** no data provided Abstract did not provide detail on how many people were in each arm of the trial and no contact details were provided, therefore the few data provided in the abstract cannot be included in the meta-analysis at this stage.
Risk of bias	

Conley 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Abstract only and allocation concealment not indicated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment is only indicated by quote: "... [outcomes were] measured at baseline, 3 and 6 months by a blinded investigator"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only and loss to follow-up not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Corley 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	Obese and overweight men **Inclusion and exclusion criteria:** no data provided
Interventions	**2-arm trial** **Intervention:** intermittent fast consisting of two days of 25% restriction and 5 days of isocaloric intake per week over six weeks **Comparator:** 79% daily restriction
Outcomes	Primary outcomes: body composition, resting energy expenditure. Secondary outcomes were change in HbA1c, blood pressure, fasting lipids, leptin,ghrelin, adiponectin and thyroid function tests
Notes	**Type of paper:** abstract only **Funding:** no data There were no contact details provided to contact the authors to include any data, therefore this study has not been quantitatively analysed.

Risk of bias

Bias	Authors' judgement	Support for judgement

Corley 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Abstract only and allocation concealment not indicated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only and loss to follow-up not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Ferraris 2019

Study characteristics	
Methods	Randomised controlled clinical trial
Participants	18 professional cyclists **Inclusion and exclusion criteria:** none provided
Interventions	**2-arm trial** **Intervention:** 30 days of isocaloric time-restricted feeding performed with the 16/8 method (16 hours fasting and 8 hour window for feeding) **Comparator:** ad libitum feeding
Outcomes	Body fat percentage, leucocyte number, IGF1
Notes	**Type of paper:** abstract only **Funding:** no data provided

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Abstract only and allocation concealment not indicated.

Ferraris 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reported that 1 participant out of 9 (11.1%) left the TRF group and 1 participant out of 9 (11.1%) left the control group. These represent high attrition rates due to the small sample size.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Griffiths 2016

Study characteristics	
Methods	Randomised clinical trial
Participants	9 participants in Australia **Inclusion and exclusion criteria:** no data provided
Interventions	**2-arm trial** **Intervention (n = 4):** periodic fasting. 3 very low energy diet (VLED) shakes a day (~2,500 kJ/day) on any 2 days a week and to eat to appetite on other days. **Comparator (n = 5):** participants randomised to continuous energy restriction were instructed to reduce their energy intake by 30% everyday in accordance with the Australian Guide to Healthy Eating
Outcomes	Body weight, BMI, waist circumference, lipid profile, glucose, HbA1c
Notes	**Type of paper:** abstract only **Funding:** no data provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment

Griffiths 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 out of the 5 participants (20%) dropped out in IF arm.
Selective reporting (reporting bias)	Unclear risk	Unclear from abstract.
Other bias	Unclear risk	Not stated.

Harvie 2011

Study characteristics	
Methods	Parallel-arm randomised clinical trial
Participants	107 premenopausal women based in the UK aged between 30 and 45 with a BMI between 24 and 40 kg/m2 **Inclusion criteria and exclusion criteria:** participants were non-smokers, not currently dieting or losing weight, with regular menstrual cycles and no evidence of hyperandrogenism or polycystic ovary syndrome, and no oral contraceptive use during the previous 6 months. They did not have high intakes of alcohol (>28 units/week) or phytoestrogens, and were not suffering from diagnosed diabetes, CVD, major psychiatric morbidity or cancer.
Interventions	**2-arm trial** **Intermittent fasting (n = 45):** periodic fasting 2 consecutive days per week consuming 25% of normal caloric intake. **Comparator (n = 47):** continuous energy restriction
Outcomes	Weight change, insulin sensitivity, total cholesterol and serum LDL levels, serum HDL levels, triglycerides, andSBP and D BP.
Notes	**Type of paper:** full-text publication **Funding:** Breast Cancer Campaign, World Cancer Research Fund, Genesis Appeal Manchester UK, Intramural Research Program of the National Institute on Aging of the NIH, The Danish Research Council for Health and Disease, Tanita Europe BV Middlesex UK for provision of Tanita TBF-300. Author was contacted for raw data to calculate absolute changes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	There was no mention of a method for allocation sequence concealment.

Harvie 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory personnel were blinded to the sample identity.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Eighteen women withdrew from the study before 6 months (IER=11, CER=7) representing 21% IER and 13% CER subjects ($\chi 2$ =1.16, P=0.28). The main reasons for drop out were comparable between the groups: stress (IER=3, CER=2), pregnancy (IER=2, CER=1), change in employment (IER=2, CER=1), problems adhering to the diet (IER=3, CER=3) and personal illness (infected pacemaker, IER=1)."
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the Methods section were reported in the Results section.
Other bias	Low risk	Nothing to note.

Harvie 2013

Study characteristics	
Methods	Multiple-arm randomised clinical trial
Participants	115 overweight women based in the UK aged between 20 and 69 with a BMI between 24–45 kg/m2 **Inclusion criteria:** women were eligible for the study if their BMI was 24–45 kg/m^2 and/or body fat was >30% of total weight, and their reported adult weight gain since the age of 20 years exceeded 7 kg. There was no age restriction but participants entered were between 20 and 69 years of age. **Exclusion criteria:** women were excluded if they were currently dieting or losing weight, or suffering from diabetes, major CVD, respiratory, psychiatric or musculoskeletal morbidity.
Interventions	**3 arms** **Intervention (n = 33):** periodic fasting 2 consecutive days per week consuming 25% of normal caloric intake. **Comparator (n = 33):** continuous energy restriction. This group was prescribed a daily energy-restricted Mediterranean-type diet that was relatively high in protein (25% energy) with moderate carbohydrate (45% energy from low-glycaemic-index carbohydrates) and moderate fat (30% fat; 15% MUFA, 8% PUFA and 7% SFA) intakes. A third trial arm included periodic fasting with ad libitum protein and fat and thus was not included in this analysis.
Outcomes	Lipid profile, HbA1c, glucose, body weight, waist circumference
Notes	Author was contacted for raw data to calculate absolute changes **Type of paper:** full-text publication

Harvie 2013 *(Continued)*

Funding:tThe present study was supported by the Genesis Breast Cancer Prevention (Registered Charity no. 1109839) and, in part, by the Intramural Research Program of the National Institute on Aging, Baltimore, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Low risk	Group allocation was established by opaque, sealed envelopes that contained the assignment for each participant.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Anthropometric measures were performed by research dietitians who were not blinded to the treatment groups. Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Personnel performing laboratory measurements, and inputting and analysing trial data were blinded to group allocations. Anthropometric measures were performed by research dietitians who were not blinded to the treatment groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although data on all randomised participants were analysed (Intention-to-treat analysis), the dropout rate was high; 10 out of 38 participants (26.3%) in the intermittent energy and carbohydrate restriction (ad libitum protein and fat) group, 4 our of 37 participants (10.8%) in the intermittent energy and carbohydrate restriction group, and 13 out of 40 participants (32.5%) in the control group.
Selective reporting (reporting bias)	Unclear risk	Outcomes unspecified.
Other bias	Low risk	Nothing to note.

Hutchison 2019

Study characteristics

Methods	Multiple-arm randomised controlled clinical trial
Participants	88 female participants based in Australia aged between 35 and 70 years with a BMI between 25-42 kg/m2 **Inclusion and exclusion criteria:** patients were aged 35 to 70 years; BMI 25 to 42 kg/m^2; weight stable (±5% of their screening weight) for > 6 months prior to study entry; nondiabetic; nonsmoker; sedentary or lightly active (i.e., < 2 moderate- to high-intensity exercise sessions/week); consumed < 140 g alcohol per week; no history of CVD, eating disorders, or psychiatric disorders (including those taking antidepressants); not pregnant or breastfeeding; and not taking medication that may affect study outcomes (e.g. phentermine, orlistat, metformin, excluding antihypertensive/lipid-lowering medication).
Interventions	**4-arm trial:** IF100, IF70, DR70, Control (ad libitum feeding) **Interventions (n = 22, n = 22):** IF100, IF70 (Both were used in this analysis) **Comparator (n = 24, n = 11):** DR70, Control

Hutchison 2019 *(Continued)*

Outcomes	Body weight, waist circumference, lipid profile, blood pressure, glucose
Notes	**Type of paper:** full-text publication **Funding:** the research was funded by a National Health and Medical Research Council (NHMRC) Project Grant APP1023401. LKH was supported by an Australian Research Council Future Fellowship FT120100027. BL was supported by an Australian Government Research Training Program Scholarship. **Control (C)**: continuous energy intake at 100 % of baseline energy requirements; **IF100**: intermittent fasting diet at 100 % of baseline energy requirements; **IF70**: intermittent fasting diet at 70 % of baseline energy requirements; **DR70**: continuous energy restriction at 70 % of baseline energy requirements.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Low risk	Although block randomisation was performed, the block sizes varied between 4 and 8 participants, which reduces the risk of determining allocations.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates varied substantially between two of the groups that had different interventions (12% for the IF70 and IF100 groups but 4% for the DF70 group), and different reasons were provided for dropout although it was not stated what reasons corresponded to which group.
Selective reporting (reporting bias)	High risk	Outcomes of interest that were pre-specified in the clinical trial registry (ClinicalTrials.gov: NCT01769976) were not reported in the published study, including energy expenditure, hunger, mood and cognitive function.
Other bias	Low risk	Nothing to note.

Kroeger 2015

Study characteristics

Methods	Randomised controlled trial
Participants	48 obese participants **Inclusion and exclusion criteria:** none provided
Interventions	**2-arm trial**

Kroeger 2015 *(Continued)*

	Intervention: ADF (75% restriction fast day alternated with ad libitum feed day), **Comparator:** CR (25% restriction everyday), for a 6-month weight loss period followed by a 6-month weight maintenance period.
Outcomes	Body weight, fat mass, visceral fat mass, fat free mass, plasma glucose, insulin levels and insulin resistance.
Notes	**Type of paper:** abstract only **Funding:** none provided **Other:** absolute changes were provided in the abstract but the number of people in each of the arms was not stated. No contact details were provided to contact the authors to provide extra data. **ADF-** Alternate day fasting **CR-** calorie restriction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only and method of randomisation not stated in abstract.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only and loss to follow-up not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

Moro 2016

Study characteristics

Methods	Randomised controlled trial
Participants	34 participants based in the USA who have performed resistance training continuously for the last 5 years. **Inclusion and exclusion criteria:** the criteria for entering the study were that participants must have performed resistance training continuously for at least 5 years (training 3–5 days/week with at least 3

Moro 2016 *(Continued)*

	years experience in split training routines), be presently engaged in regular resistance training at the time of recruitment, be life-long steroid free, and have no clinical problems that could be aggravated by the study procedures.
Interventions	**2-arm trial** **Intervention (n = 17):** time restricted feeding (16 hours fasting, 8 hours feeding) **Comparator (n = 17):** ad libitum feeding/normal diet
Outcomes	Lipid profile
Notes	**Other:** data presented as percentage changes. Authors contacted for absolute changes but no response was given. Therefore, data unfortunately not included in quantitative analysis. **Funding:** this research was conducted with authors' institutional founds **Type of paper:** full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to a time-restricted feeding group (TRF; n = 17) or standard diet group (ND; n = 17) through computer-generated software.
Allocation concealment (selection bias)	Unclear risk	Although it was stated quote: "the research staff conducting outcome assessments was unaware of the assignment of the subjects (i.e. a single blind design)", it was not indicated how the assignment sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The research staff conducting outcome assessments was unaware of the assignment of the subjects (i.e. a single blind design)."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was no information provided regarding dropout or the number of completers.
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Low risk	Nothing to note.

Parvaresh 2019

Study characteristics	
Methods	Parallel-arm randomised clinical trial
Participants	70 participants based in Iran aged between 25 and 60 with a 25 ≤ BMI ≤ 40 kg/m2

Parvaresh 2019 *(Continued)*

	Inclusion and exclusion criteria: the patients were eligible to enter the study if they were aged 25–60 and overweight (25 ≤ BMI ≤ 40 kg/m^2). Individuals with weight changes ≥5% for 3 months preceding the study, history of liver cardiovascular, renal, and metabolic disease, smoking or taking any medication or following a special diet in the last 6 months, which is known to impact on body weight, serum lipids, or glucose metabolism, breast feeding, post-menopausal and pregnant women were excluded.
Interventions	**2-arm trial** **Intervention (n = 35):** ADF (alternate day fasting) **Comparator (n = 34):** continuous energy restriction
Outcomes	Body weight, BMI, Waist circumference, lipid profile, blood pressure, glucose
Notes	**Funding:** this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. **Type of paper:** full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by using by computer-generated random numbers and was concealed from the researchers as well as participants."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by using by computer-generated random numbers and was concealed from the researchers as well as participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	The compliance to the prescribed diet was recorded using self-reporting, which might have resulted in misstatements.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout out of 35 participants (2.9%) in CER group and no dropout in ADF group.
Selective reporting (reporting bias)	Unclear risk	All outcomes pre-specified in the Methods section were reported in the Results section.
Other bias	Low risk	Nothing to note.

Pinto 2019

Study characteristics

Methods	Parallel-arm randomised clinical trial
Participants	45 participants based in the UK aged between 35 and 37

Pinto 2019 *(Continued)*

	Inclusion and exclusion criteria: the main inclusion criteria were non-smoking men and women aged 35–75 years with a waist circumference exceeding the cut-off determined by the World Health Organization to confer a high risk of cardiometabolic disease [32]: >102 cm and >88 cm for men and women, respectively (> 90 cm and > 80 cm, for men and women respectively, with South Asian or East Asian ethnic background [33]). There were no inclusion/exclusion criteria based on BMI since this index does not provide information on body fat distribution. The exclusion criteria included kidney or cardiovascular disease, cancer, diabetes, chronic liver disease; previous bariatric surgery or other major surgery (e.g. organ transplantation); significant psychiatric disorder or uncontrolled depression; eating disorders; participation in a weight management drug trial in the previous 3 months; uncontrolled epilepsy; taking medication likely to affect metabolic rate and/or weight (e.g. beta blockers, corticosteroids, diuretics); lactose intolerant; alcohol or substance abuse. Women who were currently pregnant, lactating or planning pregnancy were also excluded.
Interventions	**2-arm trial** **Intervention (n = 21):** periodic fasting on two consecutive days **Comparison (n=22):** continuous energy restriction
Outcomes	Body weight, BMI, lipid profile, glucose
Notes	**Other:** missing change from baseline standard deviation values were imputed by generating correlation co-efficients for each outcome from a similar paper (Catenacci 2016) and then imputing the missing standard deviation values. **Funding:** this work was supported by LighterLife (UK) Ltd, who funded the running costs of the trial and provided the food packs used for the IER fasting days. **Type of paper:** full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment was randomly allocated by the lead researcher using a computer online MinimPy 0.3 (Copyright (c) 2011 Mahmoud Saghaei, http://minimpy.sourceforge.net) by minimization for sex, BMI, ethnicity and waist circumference."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by using by computer-generated random numbers and was concealed from the researchers as well as participants"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rates; no dropout in the control group and a dropout rate of 2 out of 23 participants (8.7%) in the intermittent fasting group.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes (clinicaltrials.gov NCT02679989) were reported.
Other bias	Low risk	Nothing to note.

Schubel 2018

Study characteristics	
Methods	Multiple-arm randomised controlled trial
Participants	150 participants based in Germany aged between 35 and 65 with a BMI ≥25 and <40 **Inclusion criteria:** • women and men • BMI≥ 25kg/m^2 and < 40kg/m^2 • age 35 to 65 years **Exclusion criteria** • diagnosed diabetes mellitus • HbA1c levels ≥6.5% and/or fasting plasma glucose levels >126 mg/dl • known hepatic or renal dysfunction, or severely increased gamma-glutamyl transpeptidase, glutamate oxaloacetate transaminase, glutamic-pyruvic transaminase, creatinine, urea and/or uric acid levels • history of cancer within the past10 years, known eating disorders (e.g. bulimia nervosa, anorexia nervosa, binge-eating) • increased or decreased thyroid-stimulating hormone levels • severe bleeding tendency • medication for immunosuppression or modulation of fat metabolism • participation in an intervention study within the past three months • current pregnancy or were pregnant or breastfeeding during the past 12 months
Interventions	**3-arm trial** **Intervention (n = 49):** ICR group were advised to restrict their energy intake on 2 self-selected nonconsecutive days per week to 25% of the individual energy requirement. The remaining 5 days of the week were based on a eucaloric balanced diet **Comparators (n=49, n = 52):** continuous energy restriction arm and control/ad libitum feeding arm
Outcomes	Lipid profile, glucose, CRP
Notes	All arms were included in analysis. **Funding:** the HELENA Trial was funded by the Helmholtz Association of German Research Centers (Cross Program Topic: Metabolic Dysfunction). MRI examinations were performed in and financed by the Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg. The financing of the MRI was also supported by the Stiftung zur Förderung der Erforschung der Zivilisationserkrankungen, Baden-Baden, Germany. CMU was funded by the Huntsman Cancer Foundation, Salt Lake City, UT and by NIH grant U01 CA 206110. **Type of paper:** full-text publication **ICR-** Intermittent calorie restriction

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The web-based software RANDI2 was used to generate the random allocation sequence."

Schubel 2018 *(Continued)*

Allocation concealment (selection bias)	High risk	Participants were assigned by stratified block randomisation with a fixed block size. This means that the executors can predict the next assignment, and this is clearly incompatible with allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Because the HELENA Trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The technical staff was blinded for downstream laboratory work and data management.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in intention-to-treat analysis; dropout rates were also low at 4 out of 49 participants (8.2%) in the intermittent calorie restriction group and 2 out of 52 participants (3.8%) in the control group.
Selective reporting (reporting bias)	Low risk	The vast majority of pre-specified outcomes (ClinicalTrials.gov: NCT02449148) were reported in the Results section, with the exception of some secondary outcomes such as effect on quality of life.
Other bias	Low risk	Nothing to note.

Stekovic 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	60 participants based in Australia aged between 35 and 65 with a BMI between 22.0 and 30.0 kg/m2 **Inclusion criteria:** age between 35 and 65 years, both inclusive • BMI between 22.0 and 30.0 kg/m^2, both inclusive • stable weight (change <±10% current body weight) for 3 months prior to the study • fasting blood glucose < 110mg/dL without glucose-lowering medication • LDL-cholesterol < 180mg/dL without lipid-lowering medication • blood pressure < 140/90 mmHg without blood pressure-lowering medication • stable weight (change < ± 10%) for 3 months immediately prior to the study **Exclusion criteria:** • history of metabolic disorder • history of cardiovascular disease • acute or chronic inflammatory disorder • known malignancy • use of tobacco products within 5 years (smokers not eligible for the study) • abuse of recreational drugs within 5 years • alcohol abuse (more than 15 drinks/week) • dietary restrictions (e.g. vegetarianism and veganism) • women and men on hormonal supplementation • women or men on hormone-based contraceptive agents within the past 2 months • therapy with antidepressants within the past 6 months

Stekovic 2019 *(Continued)*

- regular therapy with acetylsalicylic acid or current medication to regulate blood sugar, blood pressure or lipids
- women who are pregnant, breast-feeding or aiming to become pregnant during the course of the trial

Interventions	**2-arm trial** **Intervention (n = 29):** ADF 25% of caloric intake **Comparator (n = 28):** control/ad libitum feeding
Outcomes	Body weight change, BMI, blood pressure
Notes	**Funding and acknowledgements:** F.M. is grateful to the Austrian Science Fund FWF (SFB LIPOTOX F3007& F3012, W1226, P29203, P29262, P27893, P 31727), the Austrian Federal Ministry of Education, Science and Research, and the University of Graz for grants “Unkonventionelle Forschung-InterFast” and “ fly-sleep” (BMWFW-80.109/0001-WF/V/3b/2015), as well as the field of excellence program BioHealth. We acknowledge support from NAWI Graz and the BioTechMed-Graz flagship project “EPIAge.” G.K. is supported by the Ligue Contre le Cancer Comité de Charente-Maritime (équipe labelisée); Agence National de la Recherche (ANR)–Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la Recherche sur le Cancer (ARC); Cancéropôle Île-de-France;Institut National du Cancer (INCa); Institut Universitaire de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the Leducq Foundation; the Labex Immuno-Oncology; the Recherche Hospitalo-Universitaire Torino Lumière, the Site de Recherche Intégrée sur le Cancer (SIRIC) Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM); and the Paris Alliance of Cancer Research Institutes (PACRI). T.E. is supported by the FFG COIN-project 855987 . J.D. is supported by the Canton of Fribourg and the Swiss National Science Foundation. M.A.A. and R.d.C. are funded by the IRP of the NIA, NIH. H.S. is grateful to support from the K1 Comet Center CBmed (Center for Biomarker Research in Medicine) funded by the Austrian Research Promotion Agency (FFG) and the Styrian Research Agency (SFG). **Type of paper:** full-text publication **ADF**- alternate day fasting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was conducted using an online tool "Randomizer for Clinical Trials’’ (https://www.randomizer.at/) and stratifying participants by sex."

Stekovic 2019 *(Continued)*

Allocation concealment (selection bias)	High risk	Quote: "While we were not able to blind participants regarding their intervention, allocation, clinical, and scientific staff were blinded during the process of collection, archiving, and analyses of collected samples and measurements."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"clinical, and scientific staff were blinded during the process of collection, archiving, and analyses of collected samples and measurements."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The dropout rates were relatively low for both groups; during these 4 weeks of intervention, 1 participant out of 30 (3.3%) dropped out of the ADF group and 2 participants out of 30 (6.7%) dropped out of the control group 3 participants.
Selective reporting (reporting bias)	Unclear risk	Outcomes not pre-specified.
Other bias	Unclear risk	Not clear.

Sundfor 2018

Study characteristics	
Methods	Randomised clinical trial
Participants	112 participants based in Norway aged between 21 and 70 with a BMI of 30 to 45.0 kg/m2 **Inclusion criteria:** waist circumference ≥94/80 cm (men/women) and ≥1 additional metabolic syndrome component: circulating levels of TG ≥ 1.7 mmol/L, HDL cholesterol ≤1.0/1.3 (men/women), blood pressure ≥130/85 mmHg or use of antihypertensive drugs or fasting glucose ≥5.6 mmol/L, and weight stability within ±3 kg during the last three months. **Exclusion criteria:** diabetes if treated with insulin or incretin analogues, bariatric surgery, use of anti-obesity drugs or other drugs affecting body weight, eating disorder, or psychiatric illness, or alcohol or drug abuse that could contribute to difficulties with study procedures.
Interventions	**2-arm trial** **Intervention (n = 54):** twice-weekly diet. Participants in the intermittent energy restriction group were advised to consume 400/600 (female/male) on each of two nonconsecutive days a week and to consume food as usual the remaining five days a week. **Comparator (n = 58):** continuous energy restriction
Outcomes	Body weight, BMI, Waist circumference, lipid profile, blood pressure, glucose, CRP
Notes	**Funding:** not stated **Type of paper:** full-text publication
Risk of bias	

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

Sundfor 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "A statistician prepared a computer-generated random number list"
Allocation concealment (selection bias)	Low risk	The project leader (TS) opened numbered and sealed envelopes consecutively with no exception.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:"Measurements were not blinded, but data entry was done by assistants who were blinded to study group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rates in both groups and intention-to-treat analysis was performed; at 12 months, 4 out of 54 (7.4%) dropout rate in the IER group dropouts and 3 out of 58 (5.2%) dropout rate in the CER group.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes (www.clinicaltrials.gov NCT02480504) were reported.
Other bias	Unclear risk	Study visits were not scheduled according to fasting days among participants in the intermittent energy restriction group, to limit lack of compliance, as participants were allowed to vary the day of the week on which they fasted.

Tinsley 2017

Study characteristics	
Methods	Randomised controlled trial
Participants	18 participants based in the USA. **Inclusion and exclusion criteria:** generally healthy, recreationally active men who had not followed a consistent resistance training programme over the previous three months were eligible for participation in the study.
Interventions	**3-arm trial** **Intervention (n = 10):** time restricted feeding **Comparator (n = 8):** control/ad libitum feeding
Outcomes	Body weight
Notes	**Funding:** not stated **Type of paper:** full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.

Tinsley 2017 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The dropout rates per group were not clarified. It was stated: quote: "6 participants dropped out of the study prior to the 4-week visit (1 from RT-TRF and 5 from RT-ND), 3 participants from the RT-TRF group were excluded from the analysis due to low compliance to the fasting programme (compliance <80%), and one participant from the RT-ND group was excluded from the analysis due to self-report of a major lifestyle change that led to substantial unexpected weight loss. The most common reasons for dropout were illness, injury unrelated to the study, and reported lack of time to complete the programme."
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the Methods section were reported in the Results section.
Other bias	Low risk	Nothing to note.

Tinsley 2019

Study characteristics	
Methods	Randomised control trial
Participants	27 participants aged between 18 and 30 **Inclusion criteria:** participants were required to have prior RT experience, defined as reporting ≥1 year of RT at a frequency of 2 to 4 sessions per week and with weekly training of major upper- and lower-body muscle groups. Additionally, participants were screened for BF% using multi frequency bioelectrical impedance analysis (MFBIA; mBCA 514/515, Seca). The original target BF% range for participants was 15% to 29%; however, due to data from our lab indicating overestimations of body fat via MFBIA compared with a 4-component (4C) model in resistance-trained females (19), individuals with ≤33% body fat at screening were considered eligible. **Exclusion criteria:** individuals were excluded if they did not meet the aforementioned criteria or were pregnant, trying to become pregnant, currently breastfeeding, cigarette smokers, allergic to dairy protein, or had a pacemaker or other electrical implant.
Interventions	**3-arm trial** **Intervention (n = 13):** TRF participants were instructed to consume all calories between 12:00 hours and 20:00 hours each day **Comparator (n = 14):** control diet/ad libitum feeding Third arm was TRF+ β-hydroxy β-methylbutyrate (HMB) supplementation and was not included in this analysis
Outcomes	Body weight

Tinsley 2019 *(Continued)*

Notes	**Funding:** supported by MTI Biotech Inc. and Texas Tech University. In-kind donations were received from MTI Biotech Inc. (HMB and placebo capsule supplements) and Dymatize Enterprises (whey protein supplements). **Type of paper:** full-text publication **TRF-** time restricted feeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed quote: "using sequences produced from a random sequence generator (http://www.random.org)"
Allocation concealment (selection bias)	Low risk	Given that the allocation sequence within each stratum was randomly generated, it is likely to have been adequately concealed; quote: "Eligible participants were... randomly assigned to 1 of the 3 study groups [CD plus placebo (CD), TRF plus placebo (TRF), or TRF plus HMB (TRF_{HMB})] using sequences produced from a random sequence generator (http://www.random.org). Each participant within a given stratum was allocated in a sequential manner to the first available group assignment at the time of baseline [i.e., week 0 (W0)] testing using the random integer sequence for that stratum."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trainers supervising the RT program were asked not to discuss group assignment with participants in order to maintain blinding with respect to the assigned dietary program. However, since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clarified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in intention-to-treat analysis. There were high dropout rates in all groups; dropout rate of 5 out of 14 participants (35.7%) in the control group, and 5 out of 13 participants (38.5%) in the TRF group.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes (ClinicalTrials.gov: NCT03404271) were reported in the Results section.
Other bias	Low risk	Nothing to note.

Trepanowski 2017

Study characteristics

Methods	Randomised controlled trial
Participants	Men and women (n =100) aged 18–65 years with a BMI of 25 to 39.9kg/m2 were recruited from the University of Illinois at Chicago campus. **Inclusion criteria:** as above

Trepanowski 2017 *(Continued)*

	Exclusion criteria: if they had a history of cardiovascular disease, diabetes mellitus, were taking weight loss medications, were not weight stable for 3 months prior to study initiation, were peri-menopausal, pregnant, or smokers.
Interventions	Participants were randomised by a stratified random sample (based on age, sex, and BMI) to 1 of 3 groups for 6-months **Intervention (n = 34):** ADF **Comparator 1 (n = 35):** CR **Comparator 2 (n = 31):** control The 6-month trial was divided into a 3-month quote: “controlled feeding period”, followed by a 3-month “self-selected feeding period”
Outcomes	Body weight, body composition.
Notes	There were no relevant data available to analyse. **Funding:** National Institutes of Health: NHLBI (R01HL106228, T32HL007034), NIDDK (F32DK107157). **Type of paper:** full-text publication **ADF-** alternate day fasting **CR-** Calorie restriction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Low risk	Although block randomisation was performed, the block sizes varied between 1 and 11 participants, which reduces the risk of determining allocations.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of dropout;quote: "A total of n=100 subjects were randomized to the three intervention groups (ADF n=34, CR n=35, control n=31). After 6 months, n=9 (26.5%) dropped out of the ADF group, n=6 (17.1%) dropped out of the CR group, and n=6 (19.4%) dropped out of the control group. Reasons for subject withdrawals included: dissatisfaction with study diets, scheduling conflicts, and personal reasons."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes (ClinicalTrials.gov: NCT00960505) were reported.
Other bias	Low risk	Nothing of note.

Varady 2011

Study characteristics	
Methods	Multiple-arm randomised clinical trial
Participants	60 participants based in the USA aged between 35 and 65 with a BMI between 25 and 39.9 kg/m2 **Key inclusion criteria:** BMI between 25 and 39.9 kg/m^2; age 35 to 65 years; non-diabetic; no history of cardiovascular disease; non-smoker; weight stable (< 6 kg weight loss or gain for 3 months prior to the study); sedentary or lightly active (<3 hours/week of light intensity exercise for 3 months prior to the study); and not taking weight loss, lipid-, or glucose-lowering medications.
Interventions	**4-arm trial** **Intervention (n = 15):** ADF (75% energy restriction for 24 hours alternated with ad libitum feeding for 24 hours) **Comparator 1 (n =15):** CR (25% energy restriction every day), 3) exercise (moderate intensity training 3 x/week) **Comparator 2 (n = 15):** control A fourth arm which focused on exercise (moderate intensity training 3 x/week) was not included in the analysis
Outcomes	Body weight, lipid profile
Notes	Majority of outcomes presented as percentage change. Author was contacted to calculate absolute changes but no response. **Funding:** Departmental grant, Kinesiology and Nutrition, University of Illinois, Chicago **Type of paper:** full-text publication **ADF-** alternate day fasting **CR-** calorie restriction

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates per group not provided. It was stated: quote: "60 subjects commenced the study, with 49 completing the 12-week trial"

Varady 2011 *(Continued)*

Selective reporting (reporting bias)	High risk	Majority of outcomes presented as percentage change. Author was contacted to calculate absolute changes but no response.
Other bias	Low risk	Nothing to note.

Varady 2013

Study characteristics	
Methods	Randomised clinical trial
Participants	32 participants based in the USA aged between 35 and 65 with a BMI between 20 and 29.9 kg/m2 **Inclusion criteria:** BMI between 20 and 29.9 kg/m^2; age between 35 and 65 years; pre-menopausal or post-menopausal (absence of menses for more than 2 years); lightly active (< 3 hours/week of light intensity exercise at 2.5 to 4.0 metabolic equivalents (METs) for 3 months prior to the study); weight stable for 3 months prior to the beginning of the study (< 4 kg weight loss or weight gain); non-diabetic; no history of cardiovascular disease; non-smoker; and not taking weigh- loss, lipid- or glucose-lowering medications.
Interventions	**2-arm trial** **Intervention (n = 15):** ADF 25% of baseline energy needs on fast day and then ad libitum on each alternating feed day. **Comparator (n = 15):** control
Outcomes	Body weight, lipid profile, blood pressure, CRP
Notes	**Funding:** Departmental grant from Kinesiology and Nutrition at the University of Illinois, Chicago. **Type of paper:** full-text publication **ADF-** alternate day fasting

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	Low rates of dropout; rate of 1 out of 16 participants (6.3%) in the ADF group and 1 out of 16 participants (6.3%) in the control group.

Varady 2013 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Quote: "This pilot study was originally designed to compare the effects of ADF in normal weight versus overweight individuals on body weight and CHD risk." Due to a low recruitment rate, we were only able to recruit n = 8 subjects into the normal weight group and n = 8 subjects into the overweight group. In view of this, we decided to combine the normal weight and overweight groups into one group to increase sample size."
Other bias	Low risk	Nothing to note.

Varady 2016a

Study characteristics	
Methods	This study examined the impact of ADF on markers of bone turnover in a 6-month randomised controlled trial.
Participants	Obese participants **Inclusion and exclusion criteria:** none provided
Interventions	**3-arm trial** **Intervention:** alternate day fasting (25% energy intake fast day, alternated with 125% intake feast day) **Comparator 1:** calorie restriction (75% intake every day) **Comparator 2:** control (ad libitum intake every day)
Outcomes	Body weight, fat mass, and lean mass
Notes	**Type of paper:** abstract only There were no available data from the abstract to analyse and it was no possible to reach the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since this trial was a dietary intervention study, it was not feasible for participants or all study personnel to be blinded to the group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract only and blinding of outcome assessment not indicated.
Incomplete outcome data (attrition bias)	Unclear risk	Abstract-only and loss to follow-up not indicated.

Varady 2016a *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Abstract only.
Other bias	Unclear risk	Abstract only.

ADF: alternate day fasting; **BMI:** body mass index; **BP:** blood pressure; CER: Continuous energy restriction; **CRP:** **C**-reactive protein; **CVD:** cardiovascular disease; **DBP:** diastolic blood pressure; **HbA1c:** glycated haemoglobin; **HDL:** high density lipoprotein**; ICR:** Intermittent calorie restriction; **IER:** intermittent energy restriction**; IGF-1:** insulin-like growth factor-1; **LDL:** low-density lipoprotein; **SBP:** systolic blood pressure; **SD:** standard deviation; **SE:** standard error; **TC**: total cholesterol; **TG:** triglycerides; **TRF:** time-restricted feeding.

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

Study	Reason for exclusion
Actrn 2013	Wrong study design
Aghasadeghi 2008	Wrong intervention
Aksungar 2005	Wrong study design
Aksungar 2007	Wrong study design
Al-Barha 2019	Wrong study design
Alhamdan 2016	Wrong study design
Almeneessier 2017	Wrong study design
Almeneessier 2018	Wrong study design
Andrews 1984	Wrong setting
Antoni 2018	Wrong study design
Arguin 2012	wrong intervention
Arnason 2017	Wrong study design
Bachman 2016	Wrong study design
Bahammam 2016	Wrong study design
Bahmani 2013	Wrong study design
Basolo 2019	Wrong study design
Bergendahl 2000	Wrong study design
Bergman 2007	Wrong comparator
Bhutani 2010	Wrong study design
Boden 1996	Wrong study design

Study	Reason for exclusion
Bowen 2018	Wrong intervention
Chan 2007	Wrong study design
Cherif 2017	wrong study design
Chirinos 2016	Wrong intervention
Chowdhury 2016	Wrong study design
Cignarella 2017	Wrong patient population
Cignarella 2018	Wrong patient population
Clayton 2016	Wrong intervention
Clayton 2018	Wrong intervention
Clegg 2014	Wrong intervention
Contaldo 1980	Wrong setting
Corley 2018	Wrong comparator
Corvilain 1995	Wrong study design
Coutinho 2018	Wrong intervention - 550 kcal /day to 660 kcal /day
Ctri 2018	Wrong intervention
Dallongeville 1998	Wrong intervention
Dong 2004	Paediatric population
Edinburgh 2019	Wrong intervention
Fitzgerald 2017	Wrong intervention
Gjedsted 2007	Wrong intervention
Grajower 2019	Wrong study design
Harder-Lauridsen 2017	Wrong intervention
He 2016	Wrong study design
Headland 2018	Wrong intervention
Hirsh 2019	Wrong intervention
Hoddy 2014	Wrong comparator
Hussin 2013	Wrong intervention
Irct201702269856N 2017	Wrong study design

Study	Reason for exclusion
Irct2017070434897N 2017	Wrong study design
ISRCTN16400313	Wrong study design
ISRCTN65605485	Wrong intervention
ISRCTN89657927	Wrong study design
Jafari 2003	Wrong intervention
Jakubowicz 2015	Wrong study design
Jamshed 2019	Wrong study design
Jensen 1988	Wrong study design
Jimenez 2019	Wrong intervention
Johari 2019	Wrong intervention
Johnson 2010	Wrong study design
Kaikkonen 2019	Wrong intervention
Kalam 2019	Wrong study design
Kalam 2019a	Wrong study design
Kamble 2018	Wrong study design
Karimi 2016	Wrong intervention
Kearney 2011	Wrong intervention
Keogh 2014	Wrong intervention
Kessler 2018	Wrong study design
Klempel 2012	Wrong comparator
Kobayashi 2014	Wrong study design
Kohn 2016	Wrong study design
Kolb 1983	Wrong intervention
Kroeger 2012	Wrong comparator
Larijani 2003	Wrong study design
Larson-Meyer 2008	Wrong intervention
Maly 1996	wrong study design
NCT00183027	Wrong intervention

Study	Reason for exclusion
NCT01754350	Wrong intervention
NCT01895179	Wrong study design
NCT01964118	Cross-over trial - wrong study design
NCT02287103	Cross-over trial - wrong study design
NCT02525419	Wrong study design
NCT02633722	Cross-over trial - wrong study design
NCT02970188	Cross-over trial - wrong study design
NCT03459703	cross-over trial - wrong study design
NCT03569852	Cross-over trial- wrong study design
NCT03574103	wrong intervention
NCT04009239	Cross-over trial - wrong study design
NCT 2017	Terminated trial
Ng 2019	Wrong patient population
Ongsara 2017	Wrong study design
Overland 2017	Wrong study design
Parr 2019	Wrong study design
Pavic 2019	Wrong intervention
Pramanik 2012	Wrong intervention
Ravussin 2019	Wrong study design
Ruiz 2013	Wrong study design
Rynders 2019	Wrong study design
Salas-Salvado 2019	Wrong intervention
Santos 2018	Wrong study design
Soeters 2009	Wrong study design
Solianik 2018	Wrong intervention
Sutton 2018	Wrong study design
Takahashi 2011	Wrong patient population
Tang 1995	Wrong intervention

Study	Reason for exclusion
Teng 2013	Wrong intervention
Varady 2016	Review paper - wrong study design
Verboeket-van 1993	Wrong intervention
Washburn 2019	Wrong study design
Webber 1994	Wrong study design
Williams 1998	Wrong intervention

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

Liu 2017

Methods	Randomised controlled trial
Participants	75 overweight and obese women
Interventions	Participants were randomised to 1 of 3 groups for 8 weeks, and provided with foods at 70% (IF70 and CR70), or 100% (IF100) of energy requirements.
Outcomes	Insulin sensitivity
Notes	Does not provide a trial registration number, and may be an early abstract of the published paper Hutchison 2019.

NCT00467220

Methods	Randomised controlled trial
Participants	24 Participants Ages eligible for study: 35 years to 65 years (adult, older adult) Sexes eligible for study: both Accepts healthy volunteers: yes Criteria **Inclusion criteria:** Male and female; Body mass index (BMI) between 20-30 kg/m2; Age between 35-65 years; sedentary (light exercise less than 1 hour per week) or moderately active (1 to 2 hours per week); Weight stable for >3 months prior to the beginning of the study; Able to give written informed consent; Female participants must be post-menopausal for at least 2 years and can not be on hormone replacement therapy (HRT).
Interventions	Arm Intervention/treatment No Intervention: control Participants will follow all study tasks but will not be required to follow a calorie-restricted meal plan.

NCT00467220 *(Continued)*

	Alternate Day Fasting Arm Participants in this arm will be asked to alternate between one day of eating as they wish versus one day on a calorie-restricted meal plan. Participants will follow this alternating meal plan for 3 months. Behavioural: calorie restriction Participants in the "calorie restriction" arm and the "alternate day fasting" arm will be asked to follow a menu plan, for three months, that includes some level of calorie restriction. Calorie restriction Participants in this arm will be asked to follow a calorie-restricted meal plan, daily, for three months. Behavioural: calorie restriction Participants in the "calorie restriction" arm and the "alternate day fasting" arm will be asked to follow a menu plan, for three months, that includes some level of calorie restriction.
Outcomes	**Primary outcome measures:** Adipose tissue dynamics [Time Frame: 12 weeks] Parameters measured will include adipose tissue dynamics (triglyceride turnover, lipolysis, de novo lipogenesis, adipose cell proliferation), adipose tissue morphology (cell size and number), adipose tissue hormone levels (adiponectin, leptin), skin turnover (keratin dynamics), T-lymphocyte proliferation, as well as plasma lipid and lipoprotein, homocysteine, and C-reactive protein levels.
Notes	NCT00467220. It is unclear whether the information above meets our defined intervention. More information is needed.

NCT02148458

Methods	Randomised controlled trial
Participants	53 participants Ages eligible for study: 30 years to 65 years (adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: yes Criteria **Inclusion criteria:** - The participants in this study will be 50 men and women in the 30 to 65 year age range, who have a BMI in the high-normal to moderately overweight range (i.e. 22 to 28 kg/m2), - Participants who are eating usual US diets and are sedentary to moderately active (i.e. not exercise trained). - Participants have at least one of these metabolic abnormalities: pre-hypertension or hypertension (i.e. systolic blood pressure > 120 mmHg or diastolic blood pressure > 80 mmHg or specific treatment of previously diagnosed hypertension)10, sub-optimal lipid levels (i.e. LDL-cholesterol > 100 mg/dL or HDL-cholesterol < 59 mg/dL or specific treatment for this lipid abnormality)11, impaired fasting glucose or glucose intolerance (i.e. fasting glucose > 100 mg/dL or 2hour-glucose during OGTT with a glucose load of 75 g > 140 mg/dL or specific treatment for previously diagnosed type 2 diabetes)12, or high-risk waist circumference (≥ 94 cm in men and ≥ 80 cm in women)13.
Interventions	Arm Intervention/treatment Control group Western diet for 8 weeks, followed by 8 weeks of Western diet with intermittent fasting. Other: control group control group eating their usual Western diet for 8 weeks, followed by 8 weeks of usual diet with intermittent fasting (i.e. 2 non-consecutive days of fasting per week). Experimental: Mediterranean diet Mediterranean diet for 8 weeks, followed by 8 weeks of Mediterranean diet with intermittent fasting. Other: Mediterranean diet

NCT02148458 *(Continued)*

	Mediterranean diet for 8 weeks, followed by 8 weeks of Mediterranean diet with intermittent fasting (i.e. 2 non-consecutive days of fasting per week)
Outcomes	**Primary outcome measures:** Decrease in high sensitivity C-reactive protein (hsCRP) [Time Frame: 16 weeks-- Baseline, 8 weeks, 16 weeks] hsCRP is in mg/L
Notes	It is unclear from the information above that the intervention meets our predefined criteria.

NCT02606669

Methods	Randomised controlled trial
Participants	Ages eligible for study: 21 years to 70 years (adult, older adult) Sexes Eligible for Study: All Accepts healthy volunteers: yes Criteria **Inclusion criteria:** Ability to provide informed consent. Chinese. (both parents must be Chinese) Age above 21 years old. This study will focus only on adult participants, and 21 years old is chosen as the age cut off, as it is the recognised legal age of independent consent. BMI ≥ 25 kg/m2
Interventions	Experimental: intermittent fasting The intervention of interest here is the Intermittent Energy Restriction (IER) or the Intermittent Fasting approach, specifically, the "twice-weekly" diet, where adherence to this dietary intervention consists of fasting for two consecutive days and consuming enough to meet energy requirements for the remaining five days. In this study, fasting will be achieved by using a meal replacement product (Optifast®) supplemented by two scoops of protein powder (Propass®) and a multivitamin, making a total of 540kcal (54g protein, 60g carbohydrates) for each fasting day. Dietary supplement: meal replacement Using a meal-replacement product, supplemented by protein powder and multivitamin No Intervention: control Diet and physical activity advice only. no treatment plan.
Outcomes	**Primary outcome measures:** Change in total body weight (in kg) at 3 months compared to baseline [Time Frame: Baseline to 3 months] **Secondary outcome measures:** Change in quality of life (as determined by RAND Short Form-36 health survey) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in insulin sensitivity % (as determined by the Homeostasis Model Assessment (HOMA)) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in total cholesterol levels (in mmol/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in low-density lipoprotein (LDL)- cholesterol levels (in mmol/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in high-density lipoprotein (HDL)-cholesterol levels (in mmol/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in triglyceride levels (in mmol/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in waist circumference (in cm) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in body fat % (as determined by bio-electrical impedance analysis) at 3 months compared to baseline [Time Frame: Baseline to 3 months]

NCT02606669 *(Continued)*

	Change in hip circumference (in cm) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in alanine transaminase (ALT) levels (in U/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in aspartate aminotransferase (AST) levels (in U/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months] Change in gamma-glutamyl transpeptidase (GGT) levels (in U/L) at 3 months compared to baseline [Time Frame: Baseline to 3 months]
Notes	NCT02606669 - It is unclear from the information above that the intervention meets our predefined criteria.

NCT02948517

Methods	Randomised controlled trial
Participants	31 participants Ages eligible for study: 25 years to 65 years (adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: yes Criteria I**nclusion Criteria:** Male or female Body mass index (BMI) between 30.0 and 40 kg/m2 Age between 25 and 65 years Sedentary (light exercise less than 1 hour per week) or moderately active (moderate exercise 1 to 2 hours per week) Weight stable for >3 months prior to the beginning of the study (gain or loss <4 kg) Able to give written informed consent
Interventions	Arm Intervention/treatment Experimental: Time restricted feeding Time restricted feeding Other: Time restricted feeding Time restricted feeding No Intervention: Control No intervention
Outcomes	**Primary outcome measures:** Body weight [Time Frame: 12 weeks] **Secondary outcome measures:** Plasma lipids [Time Frame: 12 weeks] Blood pressure [Time Frame: 12 weeks] Insulin resistance measured by Homeostatic model assessment (HOMA) [Time Frame: 12 weeks] Inflammatory markers: tumour necrosis factor-alpha (TNF) and Interleukin-6 (IL-6) [Time Frame: 12 weeks]
Notes	NCT02948517- It is unclear from the information above that the intervention meets our predefined criteria.

Ntr 2009

Methods	Randomised controlled trial

Ntr 2009 *(Continued)*

Participants	**Inclusion criteria:** 1. Lean healthy male volunteers; 2. Age 18 - 35 years; 3. BMI 20-25 kg/m2; 4. Stable weight three months prior to study inclusion; 5. Normal oral glucose tolerance test (OGTT) using the ADA-criteria.
Interventions	1. Two weeks standard diet; 2. Two weeks of intermittent fasting. After these two weeks, a study day as previously described will follow where after volunteers change diet (standard vs IF, or IF vs standard).
Outcomes	Primary outcome: insulin sensitivity of glucose metabolism. Secondaryoutcome: insulin sensitivity of lipid and protein metabolism.
Notes	It is unclear from the information above that the intervention meets our predefined criteria.

Spelta 2017

Methods	Randomised controlled trial
Participants	40 overweight/slightly obese HF outpatients (NYHA I-II)
Interventions	Participants assigned to IF or control group for six months. IF scheme is a 'twice-weekly-diet' (ad libitum food for 5 days during the week and fasting -i.e. a maximum of 500 Kcal intake- for two non-consecutive days).
Outcomes	
Notes	More information needed to determine whether paper meets our eligibility criteria. Only abstract was found.

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

ACTRN12619000246189

Study name	Mediterranean diet with or without intermittent fasting in type 2 diabetic patients: a randomized clinical trial
Methods	Randomised controlled trial
Participants	Diagnostic criteria: type 2 diabetes (previously diagnosed with HbA1c >7.0% [53 mmol/mol] and/or taking anti-glycaemic medication) Age minimum: 20 years Age maximum: 75 years Gender: both males and females
Interventions	Arm 1

ACTRN12619000246189 *(Continued)*

	Intensive personalised dietary counselling based on a Mediterranean diet (low in saturated fat [<7% of total energy intake (TEI)] and high in fibre (> 40 g/day), consumed ad libitum and delivered by a nutritionist with minimum 5 years' experience. Arm 2 Intensive personalised dietary counselling based on a Mediterranean diet (low in saturated fat ([<7% of TEI and high in fibre (> 40 g/day]), consumed ad libitum accompanied by time restricted feeding (12 hours fasting every day).
Outcomes	Changes in HbA1c assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, 3 months (primary time point) and 6 months after intervention commencement] Changes in CRP assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in fasting plasma glucose assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in HDL cholesterol assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in LDL cholesterol assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in plasma insulin concentrations assessed by using serum essay analysis performed in a qualified laboratory.[Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in systolic and diastolic blood pressure assessed using automated sphygmomanometry. [Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in total cholesterol assessed by using serum essay analysis performed in a qualified laboratory. [Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Changes in triglycerides assessed by using serum essay analysis performed in a qualified laboratory. [Timepoint: Baseline, and at 3 and 6 months after intervention commencement] Medication changes assessed using a medication record at each visit, asking specifically if there were any changes to the medications or the dose taken. [Timepoint: Baseline, and at 3 and 6 months after intervention commencement]
Starting date	01/04/2019
Contact information	C.Itsiopoulos@latrobe.edu.au
Notes	

ACTRN12619000757112

Study name	The effect of intermittent fasting on muscle mass in overweight, middle-aged men
Methods	Randomised controlled trial
Participants	**Inclusion criteria** 1.Male 2.Age: 35-55 years 3.BMI: 25-35 kg/m2 **Exclusion criteria**

ACTRN12619000757112 *(Continued)*	1. Current diagnosis of type 2 diabetes (HbA1C > 6.5% or 48 mmol/mol) 2. Unable to attend the laboratory for visits and adhere to the 3-day lead-in diet and 10-day intervention diet 3. Currently meeting physical activity guidelines (i.e. doing more than 150 minutes of physical activity per week or >10,000 steps per day) 4. Major or chronic illness that impairs mobility or eating/digestion 5. Previous bariatric surgery 6. Shift workers; 7. Smoker (cigarette, e-cigarette or marijuana) 8. Individuals with strict dietary intake regimens (i.e. vegan, avoidance of principal study foods) 9. Individuals who are currently restricting their dietary intake (i.e. actively trying to diet and lose weight) or participating in regular fasting (defined as fasting >16 hours/day or having completed 12 24-hour fasts within the past year) 10. Participating in shift work (i.e. >3 hours between 22:00 hours and 05:00 hours for 1 day per week (> 50 days per year)) 11. Not weight stable (>5 kg body weight change over last 3 months) 12. Individuals who do not consume breakfast on at least 5 of 7 days per week (i.e. not eating regular meals) 13. On prescribed medications required to be taken with food in the early morning or late evening or taking other prescribed medications for <3 months 14. On prescribed anti coagulation medications (interfering with muscle biopsy procedures)
Interventions	The study design consists of a randomised, parallel-group intervention study in 40 overweight, middle-aged males. The study will involve a 3-day lead-in control diet for all intervention groups, after which subjects will be randomised to 10 consecutive days of either the following. 1. Alternate day fasting (ADF: 25 Energy percentage (En%) food ingestion on day 1, 3, 5, 7 and 100 En% food ingestion on day 2, 4, 6, 8 and 10) 2. Continuous energy restriction (CER: daily intake of 62.5 En% of total energy intake) 3. Time restricted eating (TRE: daily intake of 100 En% of total energy intake in an 8-hour time window) 4. An energy-balanced control diet (CON: daily intake of 100 En% of total energy intake in a 12-hour time window, according to current Australian Healthy Eating guidelines comprising a macronutrient intake of 50% En, CHO, 30% En fat and 20% En protein.).
Outcomes	The primary outcome measurement will be muscle protein synthesis rates (%/day) measured using the rate of labelled water (D2O) uptake from the muscle biopsy samples and alanine enrichments in saliva. [Day 0 and Day 11] Body composition assessed by a DEXA scan: fat-free mass (in % and kg) [Days 0, 4, 8 and 11] Body composition assessed by a DEXA scan: fat mass (in % and kg) [Day s0, 4, 8 and 11] Body composition assessed by a DEXA scan: total body mass (in % and kg) [Dasy 0, 4, 8 and 11] Body water 2H2O enrichment by GC-MS analyses [muscle biopsies at Day 0 and Day 11; plasma samples at days 0,4,8 and 11; and daily saliva samples from day 0-11] Free L-[2,3,3,3-2H4]-alanine muscle enrichments by GC-MS analyses [muscle biopsies at Day 0 and Day 11] Free L-[2,3,3,3-2H4]-alanine plasma enrichments by GC-MS analyses [plasma samples at day 0,4,8 and 11] Glyacemic control (Freestlye Libre continuous glucose monitoring)[Day 0 to Day 11 (15 minutes time intervals throughout the 10-day intervention period)] Plasma amino acid concentrations (total amino acid profile measured by LC-MS)[Day 0, 4, 8 and 11] Plasma gastrointestinal hormone concentrations (PYY, CCK, GLP, GIP and ghrelin)[Days 0, 4, 8 and 11] Plasma glucose concentrations in blood samples analysed by YSI 2900[Days 0, 4, 8 and 11] Plasma insulin concentrations (ELISA) [Days 0, 4, 8 and 11]
Starting date	01/06/2019
Contact information	imre.kouw@acu.edu.au

ACTRN12619000757112 *(Continued)*

Notes	

ChiCTR1800016271

Study name	The effect of intermittent fasting in patients with overweight
Methods	Randomised controlled trial
Participants	**Inclusion criteria** 1. aged 25 to 65 years,male and female 2. BMI = 24 kg/m^2; 3. light physical activity (i.e. < 3 hours/week of light intensity exercise at 2.5 to 4.0 metabolic equivalents (METs) for 3 months prior to the study), weight stable for 3 months prior to the start of this study (i.e. less than 4 kg weight loss or weight gain in recent three months) 4. participants are required to sign informed consent **Exclusion criteria** 1. women who are either in pre-menopause or 2 years post menopause 2. patients with diabetes (FPG = 7.0mmol/L and / or OGTT 2-hour PG = 11.1mmol/L) 3. attended in another study or take weight-loss drugs at the same time or 3 months prior to the beginning of the study 4. obvious renal insufficiency (creatinine = 1.5 mg/dL or > 133umol/L) 5. obvious abnormal liver function (ALT more than 2 times of the normal upper limit) 6. ever suffered from history of stroke or myocardial infarction; be done or are preparing to do coronary angioplasty or coronary artery bypass grafting 7. other serious diseases such as malignant tumour 8. be preparing for pregnancy; other situations that researchers believe that is not suitable for the selected object
Interventions	1:Intermittent fasting 2:Continuous Energy restriction
Outcomes	BMI; waist circumference;total cholesterol;
Starting date	2018-06-01
Contact information	fan_yibing@163.com
Notes	

ChiCTR1800017557

Study name	Effect of time-restricted feeding and continuous feeding in gut microbiome of critically ill patients
Methods	Randomised controlled trial
Participants	Key inclusion & exclusion criteria **Inclusion criteria** ICU patients needing for enteral nutrition by gastric tube **Exclusion criteria** gastrectomy, enterectomy, gastrointestinal haemorrhage, diabetes, intestinal obstruction

ChiCTR1800017557 *(Continued)*

Interventions	Group 1:time-restricted feeding;Group 2:continuous feeding;
Outcomes	bacterial diversity; Albumin
Starting date	2018-08-28
Contact information	icuyaobo@126.com
Notes	

ChiCTR1900020871

Study name	Randomized controlled trial for intermittent fasting therapy for nonalcoholic fatty liver disease
Methods	Randomised controlled trial
Participants	I**nclusion criteria** (1) patients with nonalcoholic fatty liver disease (2) age 18-70 years old (3)Light physical labourers (4) participants are required to sign informed consent **Exclusion criteria** (1) other liver diseases and drug-induced liver damage (2) diabetic patients (FPG = 7.0mmol/L and/or OGTT 2-hour PG=11.1mmol/L) (3) hypertensive patients (systolic blood pressure =140 mmHg and / or diastolic blood pressure = 90 mmHg or taking antihypertensive drugs) (4) those who participated in the study three months before, or participated in other research trials at the same time (5) those who were enrolled in the study three months ago, or at the same time (6) obvious renal insufficiency (creatinine = 1.5 mg/dL or > 133umol/L) (7) those who have had a history of stroke or myocardial infarction (8) have done or are preparing for coronary balloon dilatation or coronary artery bypass surgery (9) suffering from other serious diseases such as malignant tumours (10) pregnant or lactating women (11)participant considered by the investigator not suitable for inclusion
Interventions	1:Health education, sports guidance,Intermittent fasting for 1 day per week;2:Health education, sports guidance,Intermittent fasting for 2 days per week;3:Health education, sports guidance;
Outcomes	BMI; waist circumference; hip circumference; waist-to-hip ratio; liver function;
Starting date	2019-07-01
Contact information	fan_yibing@163.com
Notes	

Irct20150909023957N8

Study name	Effect of low-calorie diets on anthropometric indices, glycemic markers and cardiovascular risk factors in metabolic syndrome

Irct20150909023957N8 *(Continued)*

Methods	Randomised controlled trial
Participants	I**nclusion criteria** Patients with Metabolic Syndrome Age 25-60 years 25 =BMI = 40 kg/m2 Body weight more than 5 kg has not changed during the last 3 months No fasting for 3 months prior to the beginning of the study Ppeople who are willing to cooperate and answer questions and conduct their tests after explaining the work **Exclusion criteria** Smoker History of cardiovascular, pulmonary, renal, thyroid disorders, digestive and liver problems such as hepatitis and ...follow a special diet Severe physical activity People who have been using drugs that have an effect on weight loss, lipid or glucose metabolism over the past 6 months
Interventions	Intervention 1: During 8-week ADF period, participants consumed very low calorie diet (75% energy restriction) during the 3 fast days (Saturday, Monday, Wednesday) and then ate diet that providing 100% of their energy needs on each feed day (3 days a week). In Friday participants consume ad libitum without limitation. ADF participants were provided with meals on each fast day (ranging from 400- 600 kcal), and consumed ad libitum at home on feed day. The feed and fast days began at midnight each day, and all fast day meals were consumed between 12.00 pm and 2.00 pm to ensure that each participant was undergoing the same duration of fasting. all food prepared in the home. Participants were permitted to consume calorie-free foods (such as water, green tea, coffee without sugar (< 400 mg caffeine per day), non-starchy vegetable (such as lettuce, cucumber, green leaf, tomato) and sugar-free gums on the fast day and were encouraged to drink plenty of water. Intervention 2: Control group: in Calorie-restriction group, participants consumed 75% energy needs in each day for 8 weeks and includes 3 main meals and 2 snacks. All participants in two groups were required to prepare all of their meals at home. The baseline energy requirements for the subjects were assessed by Mifflin equation. Daily dietary carbohydrate, fat and protein accounted for 52, 30 and 18% of ingested energy, respectively.
Outcomes	Primary Outcomes BMI. Timepoint: two times, before and after dietary intervention. Method of measurement: BMI was calculated as the weight in kg divided by the square of the height in meters (kg/m2). Body weight and body composition analysis. Timepoint: two times, before and after dietary intervention. Method of measurement: In light clothing, standing without shoes and hose on metal footplates while holding the handles of the bio-impedance analyser (BIA; BC-418, Tanita Europe, Amsterdam, NL). Fasting blood sugar. Timepoint: two times, before and after dietary intervention. Method of measurement: fasting plasma glucose concentrations were measured using auto-analyser (glucose oxidase/peroxidase). HDL cholesterol. Timepoint: two times, before and after dietary intervention. Method of measurement: Plasma HDL-C was measured using detergent oxidase/peroxidase methods. HOMA-IR. Timepoint: Two times, before and after dietary intervention. Method of measurement: fasting glucose (mmol/L) * fasting insulin (µU/L)/ 22.5. LDL cholesterol. Timepoint: two times, before and after dietary intervention. Method of measurement: LDL-C concentration was calculated using the Friedwald equation (LDL= total cholesterol – TAG/ 2.18 – HDL). Plasma insulin. Timepoint: two times, before and after dietary intervention. Method of measurement: plasma insulin levels were measured by Elisa method. Total cholesterol. Timepoint: two times, before and after dietary intervention. Method of measurement: plasma total cholesterol was measured in duplicate using cholesterol oxidase/peroxidase. Triglyceride (TG). Timepoint: two times, before and after dietary intervention. Method of measurement: plasma TG concentration was measured glycerol phosphate oxidase/peroxidase method.

Irct20150909023957N8 *(Continued)*

	Waist circumference. Timepoint: two times, before and after dietary intervention. Method of measurement: waist circumference was measured by a flexible tape to the nearest 0.1 cm, in standing participant at the midway between the lower costal margin of the last palpable rib and the top of the iliac crest during a period of expiration.
Starting date	2019-01-23
Contact information	
Notes	

ISRCTN13374800

Study name	Alternate day fasting as an intervention to improve body composition and blood biochemical markers in overweight patients
Methods	Randomised controlled trial
Participants	Key inclusion & exclusion criteria I**nclusion criteria** 1. 20-55 years of age 2. BMI > 25 kg/m2 3. Previous sedentary lifestyle 4. Absence of diabetes, hypertension and cardiovascular diseases 5. No smoking **Exclusion criteria** 1. Previously undergone bariatric surgery
Interventions	Alternate day fasting (ADF) group: participants in this group have their calorie intake limited to 25% of the baseline energy needs on the fasting days and this is to be ingested within a 12-hour period and divided into six small meals. On the feeding days, ad libitum food intake was permitted over a 12-hour period. On both days, ingestion of food is not permitted in the remaining hours during which the participants are awake. On the feeding days, there is no restriction on calorie intake, but the participants are required to record the specific consumed foods in a food diary. Carloric restriction (CR) group: participants in this group have a hypocaloric diet that is restricted to 75% of the estimated calorie expenditure per day throughout the intervention period.
Outcomes	1. Mean body weight loss is measured using the BodPod and InBody770 at baseline and 4 weeks 2. Fat loss is measured using the BodPod and InBody770 at baseline and 4 weeks 3. Lean mass loss is measured using the BodPod and InBody770 at baseline and 4 weeks 4. Carbohydrate burning is measured using indirect calorimetry at baseline and 4 weeks 5. BMR (Basal Metabolic Rate) is measured using Indirect calorimetry (Spirostik-REE) at baseline and 4 weeks 1. Body water is measured using InBody770 at baseline and 4 weeks 2. Food patterns is measured using a Food Reminder Form that was delivered for all subjects at baseline and 4 weeks
Starting date	08/08/2017
Contact information	
Notes	

ISRCTN32122407

Study name	The effects of early versus late time-restricted feeding on metabolic disease risk factors in adults at increased risk of developing type 2 diabetes: Is there an optimal time to eat?
Methods	Randomised controlled trial
Participants	**Inclusion criteria** Participants must: 1. Be aged 18 – 65 years old 2. Have a BMI = 25 kg/m2 3. Have maintained a stable body weight for the 6 months preceding the study (± 2 kg) 4. Be at increased/moderate/high risk of developing type 2 diabetes, as per the Diabetes UK Diabetes Risk Score (scoring = 7) 5. be able and willing to give informed oral and informed written consent 6. Complete and meet the defined criteria of pre-study questionnaires 7.bBe able and willing to complete daily sleep and food diaries during the study 8. Have an eating period of = 12 hours a day 9. Agree to eat their meals within certain time periods during the day whilst participating in the study 10. Be willing and able to undertake laboratory tests on agreed dates during the study
Interventions	After an initial 1-week baseline period, participants will be randomly assigned to one of three experimental groups for an intervention period of approximately 10 weeks. The first (control) group will be asked to maintain their habitual sleep-wake and feed-fast routines throughout the intervention period. The second, 'early-TRF', group will be asked to maintain their habitual sleep-wake routine, but restrict the duration of their eating times during the day to between 7am and 3pm (± 1 hour). The third, 'late-TRF', group will also be asked to maintain their habitual sleep-wake routine, but restrict the duration of their eating times during the day to between 12pm and 8pm (± 1 hour).
Outcomes	1. Low-density lipoprotein (LDL) cholesterol measured using fasted blood tests at baseline, weeks 3, 5, 8 and 10 2. Insulin resistance measured using the homeostatic model assessment (HOMA) which utilises fasted glucose and insulin levels, at baseline, week 5 and week 10
Starting date	1. Weight measured using scales at baseline, weeks 3, 5, 8 and 10 2. Adiposity measured using the gold standard dual-energy x-ray absorptiometry (DEXA) at baseline and week 10 3. Dietary intake assessed through the use of food diaries at baseline, weeks 2, 4, 7 and 9, as well as 24-hour dietary recalls at baseline, weeks 3, 5, 8 and 10 4. Food preferences assessed using questionnaires at baseline, weeks 3, 5 8 and 10, as well as eye tracking tests at baseline, week 5 and week 10
Contact information	s.lynch@surrey.ac.uk
Notes	

NCT03342742

Study name	Daily caloric restriction and intermittent fasting in overweight and obese adults with autosomal dominant polycystic kidney disease
Methods	Randomised controlled trial
Participants	28 Participants

NCT03342742 *(Continued)*

	Ages eligible for study: 18 years to 65 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** aged 18-65 years ADPKD diagnosis based on the modified Pei-Ravine criteria BMI 25-45 kg/m2 Normal to mildly declined renal function with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 by the CKD-EPI equation Access to the internet with video chat capabilities no plans for extended travel (>2 weeks) during the 3-month intensive period Not currently participating in another interventional study or weight loss program Ability to provide informed consent
Interventions	Arm Intervention/treatment Experimental: Daily Caloric Restriction The daily caloric restriction group will be instructed to reduce energy intake by a 34% daily energy deficit from baseline individual weight maintenance energy requirements. Behavioural: weight loss Weight loss behavioural intervention via one of two strategies. Experimental: intermittent fasting Participants in the intermittent fasting group will be instructed to reduce energy intake to ~20% of estimated energy requirement (delivered as a single meal) three non-consecutive days per week, resulting in a weekly energy deficit of ~34% (similar to the daily caloric restriction group). Behavioural: weight loss Weight loss behavioural intervention via one of two strategies.
Outcomes	Primary outcome measures: Feasibility to enrol and retain participants [Time Frame: Through study completion, an expected duration of 18 months] Numbers of individuals pre-screened Feasibility to enrol participants [Time Frame: Through study completion, an expected duration of 18 months] Numbers of individuals screened Feasibility to retain participants [Time Frame: Through study completion, an expected duration of 18 months] Numbers of individuals enrolled Feasibility to retain participants [Time Frame: Through study completion, an expected duration of 18 months] Numbers of individuals retained Change in Weight Loss [Time Frame: Baseline, 12 weeks, and 1 year] Measurement of body weight pre to post intervention in each group Secondary Outcome Measures: Safety and tolerability, measured as adverse events [Time Frame: 12 weeks and 1 year] Number of participants with treatment-related adverse events in each group as evaluated by the Safety Officer Safety and tolerability, measured as treatment-related adverse events [Time Frame: 12 weeks and 1 year] Number of participants with treatment-related adverse events in each group as evaluated by the Safety Officer Changes in quality of life [Time Frame: Baseline, 12 weeks and 1 year] Quality of life (QOL) will be assessed with the RAND 36 Item Health Survey (RAND-36) physical and mental health component summary score. Changes in mood [Time Frame: Baseline, 12 weeks and 1 year] Mood state will be assessed with the Profile of Mood States 2 (POMS-2) Change in energy intake [Time Frame: Baseline, 12 weeks and 1 year] Self-reported energy intake Change in macronutrient intake [Time Frame: Baseline, 12 weeks and 1 year] Self-reported macronutrient intake

NCT03342742 *(Continued)*

	Change in serum insulin-like growth factor-1 levels [Time Frame: Baseline, 12 weeks and 1 year] Serum insulin-like growth factor-1 (IGF-1) levels will be evaluated in each group Change in insulin-like growth factor binding protein-1 levels [Time Frame: Baseline, 12 weeks and 1 year] Insulin-like growth factor binding protein-1 (IGFBP-1) levels will be evaluated in each group Change in PBMC AMPK expression [Time Frame: Baseline, 12 weeks and 1 year] Peripheral blood mononuclear cell protein expression of AMP-activated kinase (AMPK) in each group Change in PBMC S6K expression [Time Frame: Baseline, 12 weeks and 1 year] Peripheral blood mononuclear cell protein expression of S6 kinase (S6K) in each group Change in β-hydroxybutyrate levels [Time Frame: Baseline, 12 weeks and 1 year] Serum β-hydroxybutyrate levels in each group Change in total kidney volume by magnetic resonance imaging (MRI) [Time Frame: Baseline, 12 weeks and 1 year] Change in total kidney volume by MRI in each group
Starting date	June 4, 2018
Contact information	Kristen Nowak, Ph.D., MPHUniversity of Colorado - Anschutz Medical Campus
Notes	NCT03342742

NCT03411356

Study name	Intermittent fasting versus daily caloric restriction for weight loss
Methods	Randomised controlled trial
Participants	150 participants Ages Eligible for Study: 18 years to 55 years (adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes **Inclusion Criteria** **Female or Male** Age 18-55 years Body Mass Index 27-46 kg/m2 Sedentary: defined as <150 minutes per week of voluntary exercise at moderate intensity or greater and < 60 minutes per day of total habitual physical activity (i.e. work-related, transportation-related) at moderate intensity or greater, over the past 3 months. No self-report of acute or chronic disease (CVD, diabetes, gastrointestinal disorders and orthopedic problems in particular) No plans to relocate within the next 12 months No plans for extended travel (> 2 weeks) within the next 12 months No nicotine use Live or work within 30 minutes of the Anschutz Health and Wellness Center (AHWC) (exceptions may be made at the discretion of the Study PI on a case by case basis for highly-motivated people). Capable and willing to give informed consent, understand exclusion criteria, and accept the randomised group assignment. Have a primary care physician (or are willing to establish care with a primary care physician prior to study enrolment) to address medical issues which may arise during screening or study procedures/interventions. **For Females** Not currently pregnant or lactating Not pregnant within the past 6 months Not planning to become pregnant in the next 12 months

NCT03411356 *(Continued)*

	Sexually active women of childbearing potential may be enrolled if they have had a tubal ligation or use a reliable means of contraception
Interventions	Arm Intervention/treatment Active Comparator: Daily Caloric Restriction (DCR) Participants in this group will focus on daily calorie restriction as their dietary weight loss strategy. Behavioural: Daily Caloric Restriction (DCR) Participants in this group will be given a calorie goal designed to produce a 34.3% energy deficit from estimated baseline weight maintenance energy requirements. Participants in this group will also receive a 12-month comprehensive group-based behavioural weight loss program and will be instructed in specific strategies to support DCR. Randomized groups will meet separately. Participants in this group will also be asked to increase moderate intensity physical activity to a target of 300 minutes per week. Experimental: Intermittent Fasting (IMF) Participants in this group will focus on modified intermittent fasting as their dietary weight loss strategy. Behavioural: Intermittent Fasting (IMF) Participants in this group will be instructed to limit energy intake to 20% of estimated baseline energy requirements on three non-consecutive days per week, and to eat ad libitum the other 4 days per week. Participants in this group will also receive a 12-month comprehensive group based behavioural weight loss program and will be instructed in specific strategies to support IMF. Randomised groups will meet separately. Participants in this group will also be asked to increase moderate intensity physical activity to a target of 300 minutes per week.
Outcomes	Primary outcome measures: Change in Body Weight [Time Frame: Baseline and weeks 4, 13, 26, 39, and 52.] Body weight will be measured via clinic scale. Secondary Outcome Measures: Changes in Body Composition [Time Frame: Baseline and weeks 26, and 52.] Body composition will be assessed with dual-energy x-ray absorptiometry (DXA). Changes in Blood Pressure [Time Frame: Baseline and weeks 13, 26, and 52.] Blood pressure will be measured with a sphygmomanometer. Changes in Fasting Lipids [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of lipid profile. Changes in Insulin Sensitivity [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of insulin and glucose. Insulin sensitivity (homeostasis model assessment of insulin resistance [HOMA-IR]) will be calculated as ([insulin] x [fasting glucose x 0.055]/22.5). Changes in Objectively Measured Energy Intake (EI) [Time Frame: Baseline, weeks 26 and 52] EI will be measured using the doubly-labelled water (DLW) intake-balance method. Changes in Self-Reported Energy Intake (EI) [Time Frame: Baseline and weeks 13, 26, and 52.] Dietary energy intake (kcals/day) will be measured with diet diaries. Changes in Self-reported Diet Composition [Time Frame: Baseline and weeks 13, 26, and 52.] Dietary macronutrient intake will be measured with diet diaries. Changes in Self-Reported Dietary Adherence [Time Frame: Weeks 4, 8, 13, 18, 22, 26, 30, 34, 39, 44, 48, 52] Adherence to prescribed diet will be assessed with a monthly questionnaire. Changes in Resting Energy Expenditure (REE) [Time Frame: Baseline and weeks 26, and 52.] REE will be measured using indirect calorimetry. Changes in Total Daily Energy Expenditure (TDEE) [Time Frame: Baseline and weeks 26, and 52.] TDEE will be measured using the doubly-labelled water (DLW) method. Changes in Physical Activity [Time Frame: Baseline and weeks 13, 26, and 52.] Physical activity will be measured with activity monitors. Changes in Sedentary Behaviour [Time Frame: Baseline and weeks 13, 26, and 52] Sedentary behaviour will be measured with activity monitors. Other Outcome Measures: Changes in Waist Circumference [Time Frame: Baseline and weeks 13, 26, and 52] Waist circumference will be measured with a tape measure just over the iliac crest Changes in Highly Sensitive C Reactive Protein (hs CRP) [Time Frame: Baseline and weeks 26 and 52]

NCT03411356 *(Continued)*

	12 hour fasting blood sample fro measurement of hs CRP Changes in Leptin [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of Leptin Changes in Ghrelin [Time Frame: Baseline and weeks 26, and 52] 12 hour fasting blood sample for measurement of Ghrelin Changes in Brain-Derived Neurotrophic Factor (BDNF) [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of BDNF Predictors of Weight Loss [Time Frame: Baseline and weeks 13, 26, 52, and 78] Predictors of weight loss will be assessed in both groups with questionnaires periodically over the 52 week intervention Difficulty of Test Fast [Time Frame: Baseline] Participants will be asked to perform a test fast i.e. to limit intake to 25% of estimated baseline energy requirements for 1 day at baseline (prior to randomisation and beginning the interventions). Difficulty of the test fast will be assessed using a 1-10 Likert scale with 1 representing no difficulty and 10 representing extreme difficulty. Intervention Preference [Time Frame: Baseline] Intervention preference will be assessed by asking participants which intervention group (IMF or DCR) they would prefer at baseline (prior to randomisation) 6 Month Post-Intervention Follow-Up Body Weight [Time Frame: 26 weeks after completion of the 52-week intervention (i.e. at week 78)] Body weight will be measured via clinic scale. 6 Month Post-Intervention Follow-Up Body Composition [Time Frame: 26 weeks after completion of the 52-week intervention (i.e. at week 78)] Body composition will be assessed with dual-energy x-ray absorptiometry (DXA). Evaluation of Genotype as Predictor of Weight Loss [Time Frame: Baseline] DNA will be isolated from a whole blood sample. DNA genotyping will be performed using a commercial array which covers > 2 million single nucleotide polymorphisms across the human genome. Changes in DNA Methylation [Time Frame: Baseline and weeks 13, 26 and 52] DNA will be isolated from whole blood samples. DNA genotyping will be performed using a commercial array which covers > 2 million single nucleotide polymorphisms across the human genome. DNA methylation will be assessed using commercial arrays which covers >850,000 methylation sites across the human genome. Changes in Stool Microbiome [Time Frame: Baseline and weeks 13, 26, and 52] Stool samples will be collected to evaluate types and relative quantities of bacteria in fecal specimens Changes in Reproductive Hormones [Time Frame: Over one menstrual cycle at baseline, over the first 3 menstrual cycles after starting the 52 week intervention and over one menstrual cycle after completing the 52 week intervention.] Daily urine collection over a menstrual cycle in subset of pre-menopausal women Changes in Peptide YY [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of Peptide YY Changes in Hemoglobin A1C [Time Frame: Baseline and weeks 26 and 52] 12 hour fasting blood sample for measurement of Hemoglobin A1C
Starting date	December 22, 2017
Contact information	Victoria Catenacci, MD
Notes	NCT03411356

NCT03439618

Study name	Comparison of time-restricted feeding and continuous feeding in critically ill patients
Methods	Randomised controlled trial

NCT03439618 *(Continued)*

Participants	380 participants
Interventions	Arm Intervention/treatment continuous feeding The total amount of every days' Enteral Nutritional Suspension was fed at constant speed for 24 hours Other: continuous feeding At the beginning, all enrolled patients were fed by continuous feeding. When the amount calorie of feeding enteral nutritional suspension increased to 80% target calorie (target calorie: 25kilocalorie/kg/day), the patients was randomly into continuous feeding and time-restricted feeding group.In the continuous feeding, the total amount of every days' Enteral Nutritional Suspension was fed at constant speed for 24 hours. Time-restricted feeding The total amount of every days' Enteral Nutritional Suspension was fed at constant speed for 6h (7:00-9:00,11:00-13:00,17:00-19:00). Other: time-restricted feeding At the beginning, all enrolled patients were fed by continuous feeding. When the amount calorie of feeding enteral nutritional suspension increased to 80% target calorie (target calorie: 25kilocalorie/kg/day), the patients was randomly into continuous feeding and time-restricted feeding group. In continuous feeding group, the enteral nutritional suspension was fed at constant speed for 24h.In the time restricted feeding, feeding time should be at 7:00-9:00, 11:00-13:00 and 17:00-19:00 at constant feeding speed.
Outcomes	Primary outcome measures: nitrogen balance [Time Frame: at the time point of 10th feeding day] it equal to Nitrogen intake minus Nitrogen output.Source of nitrogen intake is the enteral nutritional suspension, and the amount of nitrogen can be calculated according to the proportion of nitrogen in enteral nutritional suspension. Main nitrogen losses include urine and faeces. The amount of nitrogen in urine and faeces can be measured by clinical laboratory. Secondary Outcome Measures: delirium [Time Frame: up to 10 days] it is disorders of the mental state and medical condition. It can be evaluated by The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Gastric residual volume [Time Frame: up to 10 days] This index was to evaluate the feeding complications. Nurse can evaluate the volume by pumping the stomach tube with syringe to measure the gastric content amount. diarrhoea [Time Frame: up to 10 days] This index was to evaluate the feeding complications. It is the condition of having at least three loose or liquid bowel movements each day. Incidence of ventilator-associated pneumonia [Time Frame: up to 10 days] This index was to evaluate the feeding complications. Ventilator-associated pneumonia (VAP) is a type of lung infection that occurs in people who are on mechanical ventilation breathing machines for at least 48 hours. The diagnosis of VAP varies among hospitals and providers but usually requires a new infiltrate on chest x-ray plus two or more other factors. These factors include temperature of >38 or <36 °C, a white blood cell count of >12 × 10^9/ml, purulent secretions from the airways in the lung, and/or reduction in gas exchange. glucose fluctuation [Time Frame: up to 10 days] This index was to evaluate the feeding complications. The glucose is measured at the 11:00, 15:00, 21:00, 1:00 and 5:00 five time points. The glucose fluctuation is the maximum glucose amount plus minimum glucose amount. Albumin [Time Frame: up to 10 days] Serum albumin is the main protein of human blood plasma. It can be measured by clinical laboratory.
Starting date	May 9, 2018
Contact information	icuyaobo@126.com
Notes	NCT03439618

NCT03504683

Study name	Effect of time-restricted feeding on 24-hour glycemic control, blood pressure, and cardiovascular disease risk factors
Methods	Randomised controlled trial
Participants	144 participants Ages Eligible for Study: 30 years to 65 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Aged 30-65 years old Prediabetic as determined by HbA1c between 5.7-6.4% or fasting glucose between 100-125 mg/dL BMI between 27-43 kg/m^2 Wake up at a regular time between 5 am- to 8 am
Interventions	Arm Intervention/treatment Experimental: Early Time-Restricted FeedingBehavioural: Early Time-Restricted Feeding Eat between 8 am - 3 pm (or 7 am - 2 pm, if an early riser) Other names: eTRF Early TRF Experimental: Mid-day Time-Restricted FeedingBehavioural: Mid-day Time-Restricted Feeding Eat between 1 pm - 8 pm (or 12 pm - 7 pm, if an early riser) Other names: mTRF Mid-day TRF Placebo Comparator: Control ScheduleBehavioural: Control Schedule Eat between 8 am - 8 pm (or 7 am - 7 pm, if an early riser)
Outcomes	Primary outcome measures: Mean 24-hour glucose levels [Time Frame: 10 weeks] Mean 24-hour glucose levels (mg/dl) Mean 24-hour insulin levels [Time Frame: 10 weeks] Mean 24-hour insulin levels (mU/L) Mean 24-hour C-peptide levels [Time Frame: 10 weeks] Mean 24-hour C-peptide levels (pmol/L). This is also a proxy for total 24-hour insulin secretion. Insulin sensitivity [Time Frame: 10 weeks] Mean value of insulin sensitivity (dl/kg/min/μU/mL) across the three identical meal tolerance tests, as measured by the Oral Minimal Model Beta-cell responsivity index (a measure of beta-cell function) [Time Frame: 10 weeks] Mean value of beta-cell responsivity across the three identical meal tolerance tests, as measured by the Oral Minimal Model Glucose AUCs [Time Frame: 10 weeks] Glucose area-under-the-curve (mg/dl x hr) during each of three identical meal tolerance tests within a 24-hour period Insulin AUC [Time Frame: 10 weeks] Insulin area-under-the-curve (mU/L x hour) during each of three identical meal tolerance tests within a 24-hour period C-peptide AUC [Time Frame: 10 weeks] C-peptide area-under-the-curve (pmol/L x hour) during each of three identical meal tolerance tests within a 24-hour period Peak glucose and mean amplitude of glycaemic excursions (MAGE) glucose values [Time Frame: 10 weeks] mg/dl Secondary Outcome Measures: Mean 24-hour systolic and diastolic blood pressure [Time Frame: 10 weeks]

NCT03504683 *(Continued)*

	mmHg Daily maximum value, minimum value, and amplitude of systolic and diastolic blood pressure [Time Frame: 10 weeks] mmHg Percentage of individuals with non-dipping blood pressure phenotypes [Time Frame: 10 weeks] Heart Rate [Time Frame: 10 weeks] beats per minute Lipids [Time Frame: 10 weeks] Total cholesterol (mg/dl), LDL cholesterol (mg/dl), HDL cholesterol (mg/dl), and triglycerides (mg/dl) High Sensitivity C-Reactive Protein (hs-CRP) [Time Frame: 10 weeks] mg/L Cortisol [Time Frame: 10 weeks] µg/dL 8-isoprostane [Time Frame: 10 weeks] pg/ml Inflammatory biomarkers [Time Frame: 10 weeks] TNF-alpha, IL-1beta, IL-4, IL-6, IL-10 (in pg/ml) Other Outcome Measures: Fat mass and lean mass [Time Frame: 10 weeks] Changes in fat mass and lean mass as measured by dual-energy X-ray absorptiometry (DXA) Body weight [Time Frame: 10 weeks] Change in body weight (kg) as measured by scale weight Bone mineral density [Time Frame: 10 weeks] Changes in bone mineral density (g/cm^2) as measured by dual-energy X-ray absorptiometry (DXA) Chronotype [Time Frame: 10 weeks] Chronotype (i.e., mid-point of sleep in clock time) as measured by the Munich Chronotype Questionnaire Sleep Quality [Time Frame: 10 weeks] Sleep quality as assessed by the Pittsburgh Sleep Quality Index (PQSI) (This study will use the Global PQSI score, which ranges from 0-21, where higher values correspond to worse sleep quality.)
Starting date	April 2020
Contact information	cpeterso@uab.edu
Notes	NCT03504683

NCT03527368

Study name	The Time-Restricted Intake of Meals study (TRIM)
Methods	Randomised controlled trial
Participants	41 participants Ages Eligible for Study: 21 years to 69 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes **Inclusion Criteria** Prediabetes defined by HbA1c 5.7-6.4%, or type 2 diabetes with HbA1c 6.5-6.9% Class I-III obesity (BMI 30-39.9 kg/m2) If on medications for hypertension, stable regimen for at least past 6 months Willingness to adjust timing of feeding Willingness and ability to eat study diet and nothing else during run-in and intervention Willingness to complete measurement procedures

NCT03527368 *(Continued)*

Interventions	Arm Intervention/treatment Experimental: Time-restricted feeding Behavioural: Time-restricted feeding Participants consume food earlier in the day Usual feeding pattern Comparison Behavioural: usual feeding pattern Participants consume food later in the day
Outcomes	Primary outcome measures: Weight Change [Time Frame: 12 weeks] Weight change will be measured in kg Secondary Outcome Measures: Oral glucose tolerance test (OGTT) [Time Frame: 12 weeks] Change in 2-hour glucose on OGTT Blood pressure [Time Frame: 12 weeks] 24-hour ambulatory systolic blood pressure Blood pressure [Time Frame: 12 weeks] 24-hour ambulatory diastolic blood pressure
Starting date	September 24, 2018
Contact information	Nisa Maruthur, MDJohns Hopkins University
Notes	NCT03527368

NCT03539094

Study name	Intermittent Fasting in Multiple Sclerosis (IFMS)
Methods	Randomised controlled trial
Participants	60 participants Ages Eligible for Study: 18 years and older (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Diagnosis of RRMS (2010 Mc Donald criteria) EDSS <6.0 and disease duration ≤ 15 years On an injectable therapy for MS, glatiramer acetate (GA) or beta-interferon (beta-IFN) for at least 3 months prior to the study and with no anticipated changes of the medication for the 12-week study duration Age ≥18 years BMI > 22 and < 35 kg/m2 with stable weight in the 3 months prior to screening
Interventions	Arm Intervention/treatment Experimental: Intermittent fasting The participants randomised to this group will do IF by restricting their diet and consuming few calories two days per week. During the days of fasting, participants will be allowed to drink water, calorie-free beverages, and eat fresh, steamed or roasted non-starchy vegetables. Other: intermittent fasting the participants randomised to this group will do IF by restricting their diet and consuming few calories two days per week. During the days of fasting, subjects will be allowed to drink water, calorie-free beverages, and eat fresh, steamed or roasted non-starchy vegetables. No Intervention: Western diet

NCT03539094 *(Continued)*	
	The participants randomised to this group will eat a standard Western style diet.
Outcomes	Primary Outcome Measures Leptin [Time Frame: 12 weeks] Leptin at week 12 measured in the peripheral blood Secondary Outcome Measures Peripheral metabolic and inflammatory profiling [Time Frame: 12 weeks] Adipokine and inflammatory markers at week 12 measured in the peripheral blood Anthropometric measure [Time Frame: 12 weeks] Weight and height will be combined to report BMI in kg/mg^2 Anthropometric measure [Time Frame: 12 weeks] Waist circumference in cm Gut microbiota [Time Frame: 12 weeks] Gut microbiota richness and composition
Starting date	January 1, 2018
Contact information	picciol@neuro.wustl.edu
Notes	NCT03539094

NCT03689608	
Study name	Daily vs Intermittent Restriction of Energy: Controlled Trial to reduce diabetes risk (DIRECT)
Methods	Randomised controlled trial
Participants	252 participants Ages Eligible for Study: 35 years to 75 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes Criteria **Inclusion Criteria** Weight-stable (< 5 % fluctuation in their body weight for past 6-months at study entry) Score 12 or greater on the AUSDRISK calculator HbA1c <48 mmol/L (measured at screening)
Interventions	Arm Intervention/treatment Experimental: Intermittent Fasting (IF) 3 days fasting per week Other: Intermittent Fasting (IF) Participants will fast 3 days per week. In fasting days, meal replacements at 30% of daily energy requirements will be provided for the first 6 months. Participants will have fortnightly nutrition assessment. Experimental: Daily Restriction (DR) daily energy restriction Other: Daily Restriction (DR) Participants are instructed to restrict energy intake by 30% of daily energy requirements. Meal replacements will be provided for the first 6 months. Participants will have fortnightly nutrition assessment. standard care (SC) usual care Other: standard care (SC) Participants will receive current practice guidelines in a static information format, will not take part in any counselling or receive meal replacements.

NCT03689608 *(Continued)*

Outcomes	Primary Outcome Measures : Glycaemia [Time Frame: 6 months] Change in postprandial glucose HbA1c [Time Frame: 6 months] Change in HbA1c Secondary Outcome Measures: Body weight [Time Frame: 2 months, 6 months, 18 months] changes in body weight in kilograms Body composition [Time Frame: 6 months, 18 months] changes in body fat mass in kilograms waist and hip circumference [Time Frame: 2 months, 6 months, 18 months] changes in waist and hip circumference blood lipids [Time Frame: 2 months, 6 months, 18 months] changes in blood lipid profile (total cholesterol, HDL-, LDL-cholesterol and triglycerides) adherence to intervention [Time Frame: 2 months, 6 months, 18 months] assessed by diet records HbA1c [Time Frame: 2 months, 18 months] Change in HbA1c blood pressure [Time Frame: 2 months, 6 months, 18 months] Changes in systolic blood pressure and diastolic blood pressure Postprandial glucose [Time Frame: 18 months] Change in postprandial glucose
Starting date	September 26, 2018
Contact information	
Notes	NCT03689608

NCT03745612

Study name	Time restricted feeding on weight loss and cardio-protection (TREATY Trial)
Methods	Randomised controlled trial
Participants	120 participants Ages Eligible for Study: 18 years to 75 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes **Inclusion Criteria** Male of female aged between 18 and 75 years old; Body mass index (BMI)of 28.0 to 45.0 kg/m2;
Interventions	Arm Intervention/treatment Experimental: TRF Behavioural: Time restricted feeding Participants will receive a diet of 1500-1800kcal/d for men and 1200-1500 kcal/d for women during a window of 8 hours/day (8 am to 4 pm). Active Comparator: CER continuous energy restriction Behavioural: Continuous Energy Restriction Participants will follow receive a diet of 1500-1800kcal/d for men and 1200-1500kcal/d for women, without a restriction of feeding time.
Outcomes	Primary Outcome Measures :

NCT03745612 *(Continued)*

	Change in body weight over 6 months and 12 months [Time Frame: Baseline to 12 months] Secondary Outcome Measures: Change in body composition [Time Frame: Baseline to 12 months] Change in waist circumference [Time Frame: Baseline to 12 months] Change in liver fat [Time Frame: Baseline to 12 months] Change in visceral fat [Time Frame: Baseline to 12 months] Change in HbA1c [Time Frame: Baseline to 12 months] Change in Blood pressure [Time Frame: Baseline to 12 months] Change in blood lipids [Time Frame: Baseline to 12 months] Change in insulin sensitivity [Time Frame: Baseline to 12 months] Change in β cell function [Time Frame: Baseline to 12 months] Change in pulse wave velocity (PWV) [Time Frame: Baseline to 12 months] Depression measured by the Patient Health Questionnaire-9 (PHQ-9) [Time Frame: Baseline to 12 months] Quality of sleep measured by the Pittsburgh sleep quality index (PSQI) [Time Frame: Baseline to 12 months] Quality of life measured by the 12-item Short-Form Health Survey Questionnaire (SF-12) [Time Frame: Baseline to 12 months]
Starting date	November 30, 2018
Contact information	Huijiezhang2005@126.com
Notes	NCT03745612

NCT03789409

Study name	Intermittent fasting following acute ischemic stroke
Methods	Randomised controlled trial
Participants	68 participants Ages Eligible for Study: 20 years and older (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Patients who was diagnosed first ischaemic stroke within preceding 1 year through brain MRI/CT
Interventions	Arm Intervention/treatment Experimental: Intermittent Fasting Over rehabilitation treatment during and admission (at least 1 week), intermittent fasting (IF) for more than 12 hours (water can be allowed). For subgroup assignment, participants can choose IF1 (eat early in the evening and late in the morning) or Post-IF2 (eat the remaining two meals without breakfast), depending on their own their favour. Dietary Supplement: Intermittent Fasting The aforementioned intermittent fasting in arm/group descriptions. No Intervention: ad libitum Participants will be allowed to have hospital meals and all the desired intake without time limit.
Outcomes	Primary Outcome Measures : Change of Surface electromyography [Time Frame: 1 day before the initiation of intervention, and 6 months after the stroke onset] root mean square and root peak square of compound motor action potential Secondary Outcome Measures:

NCT03789409 *(Continued)*

Change of Korean-modified Barthel index [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Korean version-Modified Barthel Index (minimum of 0 and maximum scores of 100); higher values and a better outcome.
Other Outcome Measures:
Change of Mini mental status exam [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Mini mental status exam(minimum of 0 and maximum scores of 30); higher values and a better outcome.
Change of Beck depression inventory [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Beck depression inventory(minimum of 0 and maximum scores of 63); higher values and a worse outcome.
Change of Wecsler aphasia battery [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Wecsler aphasia battery(minimum of 0 and maximum scores of 100); higher values and a better outcome.
Change of Berg balance scale [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Berg balance scale(minimum of 0 and maximum scores of 56); higher values and a better outcome.
Change of Functional Ambulation Category [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Functional Ambulation Category(minimum of 0 and maximum scores of 5); higher values and a better outcome.
Change of Motricity Index [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Motricity Index(minimum of 0 and maximum scores of 99); higher values and a better outcome.
Change of 10m walking test [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
10m walking test
Change of Grasping force (kg) [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Grasping force (kg)
Change of 9-hole pegboard [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
9-hole pegboard
Change of Jebsen Taylor test [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Jebsen-Taylor Hand Function Test
Change of Nottingham sensory scale [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Nottingham sensory scale(minimum of 0 and maximum scores of 20); higher values and a better outcome.
Change of Arm motor Fugl-Mayer scale [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Arm motor Fugl-Mayer scale; wrist & hand/proximal arm(minimum of 0 and maximum scores of 24 and of 34, respectively); higher values and a better outcome.
Change of Stroke impact scale [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Hand motor, Stroke Impact Scale (minimum of 12 and maximum scores of 60); higher values and a better outcome.
Change of Ashworth scale [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
Ashworth scale; elbow, wrist, knee & ankle(minimum of 0 and maximum scores of 4); higher values and a worse outcome.
Change of Knee joint kinaesthaesia [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset]
The smallest iso-kinetic angle from which the participants could detect any passive flexion or extension movement of their own knee, using Biodex; (minimum of 0 and maximum scores of 360 degree); higher values and a worse outcome.

NCT03789409 *(Continued)*

	Change of Behavioural intention test [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset] Behavioural intention test(minimum of 0 and maximum scores of 146); higher values and a better outcome. Change of Apraxia screen of Tulia [Time Frame: 1 day before the initiation of intervention and 3rd week after start of intervention, 3 months and 6 months after the stroke onset] Apraxia screen of (minimum of 0 and maximum scores of 12); higher values and a better outcome. Change of motor evoked potential [Time Frame: 1 day before the initiation of intervention, and 6 months after the stroke onset] Amplitude (uV) of motor evoked potential was recorded on abductor pollicis brevis and extentor digitorum brevis following trans-cranial magnetic stimulation for cortico-spinal excitability. Change of Weight [Time Frame: 1 day before the start of intervention and 1 weeks and 2 weeks after the start of intervention] Weight (Kg) Change of Temperature [Time Frame: 1 day before the start of intervention and 1 weeks and 2 weeks after the start of intervention] temperature (Celsius) Change of Serum glucose level [Time Frame: 1 day before the start of intervention and 1 weeks and 2 weeks after the start of intervention] Serum glucose level (mg/ml) Change of Hypoglycemia-related severity [Time Frame: every day following the start of intervention until 2 weeks of intervention] Assessment of hypoglycaemic symptoms using Likert scale (minimum of 0 and maximum scores of 10); higher values and a worse outcome.
Starting date	March 4, 2019
Contact information	chhwang1220ciba@gmail.com
Notes	NCT03789409

NCT03791203

Study name	Effectiveness and adherence of Modified Alternate-day Calorie Restriction (MACR) in non-alcoholic fatty liver disease
Methods	Randomised controlled trial
Participants	Ages Eligible for Study: 18 years to 70 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: Yes Criteria Inclusion Criteria: Have elevated ALT or AST level (ALT >41 or AST>34 IU/L) No evidence of other forms of liver diseases For those with diabetes mellitus and dyslipidaemia, they must be on a stable therapy for at least 6 months prior to study enrolment
Interventions	Experimental: Calorie restriction (MACR) Participants restricted 70% of their energy needs over 24 hours on a calorie restriction day alternate with a feeding day for the next 24 hours, where they were allowed eating (ad libitum). The calorie restriction and feeding days begun at 9 am each day, and on the calorie restriction day, meals were consumed between 2 pm and 8 pm to ensure that they underwent the same duration of calorie restriction. On each calorie restriction day, they were allowed energy-free beverages and sugar-free gum and encouraged to drink plenty of water. Diet plans were self-selected using detailed individualised food portion lists, meal plans, and recipes. Participants received phone calls

NCT03791203 *(Continued)*

	from the investigator and four 2-weekly appointments with a dietitian. Adverse experiences were assessed every 2 weeks. No Intervention: control group Participants in the control group continued their usual habitual diet for 8 weeks. No specific dietary advice or educations were provided throughout the entire trial.
Outcomes	Primary Outcome Measures Change from baseline shear wave elastography (SWE) at 8 weeks [Time Frame: Change from baseline at 8 weeks] Through the intercostal approach, SWE measurements were performed in the right liver lobe, at the supine position with the right arm in maximal abduction. The sonographer, assisted by an ultrasonic time-motion image, located a liver portion of at least 6 cm thick, free of large vascular structures. Once the measurement area had been located, the sonographer pressed the probe button to start an acquisition. Patients were asked to hold their breath for about five seconds, while the stiffness of the region of interest was measured and 10 measurements were made for each patient and the median average value of those measurements was recorded in kilopascals (kPa: metric). Change from baseline liver steatosis at 8 weeks [Time Frame: Change from baseline at 8 weeks] Ultra-sonographic measurements including liver steatosis and shear wave elastography (SWE) were performed with the SuperSonic Imagine's Aixplorer® Ultrasound machine (Super Sonic Image, Aix-en Provence, France). All measurements were performed by a single sonographer where the inter-observer agreement level with another experienced sonographer was 85%. Concentration of high-density lipoprotein (HDL) [Time Frame: Change from baseline at 8-weeks] Blood samples (8-10 hours of fasting blood samples) were collected from participants at 8 am to 10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in mmol/L. Concentration of low-density lipoprotein (LDL) [Time Frame: Change from baseline at 8 week] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to 10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in mmol/L. Concentration of triglycerides (TG) [Time Frame: Change from baseline at 8weeks] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in mmol/L. Concentration of total cholesterol (TC) [Time Frame: Change from baseline at 8 weeks] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to 10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in mmol/L. Concentration of fasting blood sugar (FBS) [Time Frame: Change from baseline at 8 weeks] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in mmol/L. Concentration of alanine aminotransferase (ALT) [Time Frame: Change from baseline at 8 weeks] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to 10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in U/L. Concentration of aspartate aminotransferase (AST) [Time Frame: Change from baseline at 8 weeks] Blood samples (8-10 hours of fasting blood samples) were collected at 8 am to 10 am at baseline and 8 weeks post intervention for biochemical analysis. It was measured in U/L. Secondary Outcome Measures: Dietary plan adherence [Time Frame: At 8 weeks] Adherence data were assessed each week as percentage of adherence
Starting date	August 1, 2015
Contact information	Muhammad Izzad Bin Johari, Principal Investigator, University of Science Malaysia
Notes	NCT03791203

NCT03792282

Study name	Time-Restricted Feeding(TRF) on overweight/obese women with Polycystic Ovarian Syndrome (PCOS) (TRF-PCOS)
Methods	Randomised controlled trial
Participants	18 years to 50 years, fFemales **Inclusion Criteria** 1. Age ≥ 18 years 2. BMI≥ 24 kg/m2 3. PCOS has been diagnosed **Exclusion Criteria** 1. Taking medications affecting weight or energy intake/energy expenditure in the last 6 months, including weight loss medications, antipsychotic drugs or other medications as determined by the study physician 2. The body weight fluctuated more than 5% in recent 3 months 3. Liver and kidney dysfunction: renal impairment, creatinine clearance rate < 30 mL/min/1.73 m2, transaminase increased, more than three times higher than the normal limit 4. History of serious cardiovascular or cerebrovascular disease (angina, myocardial infarction or stroke) in the past 6 months 5. History of thyroid diseases 6. Having been in pregnancy 7. Researchers believe that there are any factors that affect assessing subjects' participation in trial 8. History of malignant tumours 9. History of Cushing's syndrome, hypothyroidism, acromegaly, hypothalamic obesity 10. Currently participating in weight loss programs or weight change in the past 3 months (> 5% current body weight) 11. Patients who cannot be followed for 16 months (due to a health situation or migration) 12. Patients who are unwilling or unable to give informed consent
Interventions	Experimental: TRF Participants in this group will focus on time-restricted feeding (TRF) in addition to daily calorie restriction. Active Comparator: RCD Participants in this group will focus on daily reduced calorie diet (RCD).
Outcomes	Primary Outcome Measures :Changes in body weight (Kilograms) [Time Frame: Baseline and 16 weeks]Changes in body weight (kg) Change in insulin resistance [Time Frame: Baseline and 16 weeks]Insulin resistance will be assessed by HOMA-IR Secondary Outcome Measures:Changes in waist circumference (cm) [Time Frame: Baseline and 16 weeks] Changes in abdominal circumference (cm) [Time Frame: Baseline and 16 weeks] Changes in systolic pressure (SBP) [Time Frame: Baseline and 16 weeks] Changes in diastolic pressure (DBP) [Time Frame: Baseline and 16 weeks] Change in β cell function [Time Frame: Baseline and 16 weeks]β cell function will be assessed by HOMA-β Change in LDL-c level [Time Frame: Baseline and 16 weeks] Change in TG level [Time Frame: Baseline and 16 weeks] Change in CHO level [Time Frame: Baseline and 16 weeks]

NCT03792282 *(Continued)*

	Change in liver fibre [Time Frame: Baseline and 16 weeks]liver fibre will be assessed by Controlled attenuation parameter (CAP) evaluated with transient elastography (FibroScan®) Fibroscan Changes in systemic Inflammatory biomarkers [Time Frame: Baseline and 16 weeks]Inflammatory biomarkers (TNFa,CRP and Interleukin-6) are measured by ELISA (enzyme-linked immunosorbent assay). Changes in Oxidative stress markers [Time Frame: Baseline and 16 weeks]Oxidative stress markers include the circulating levels of Catalase,Glutathione Peroxidase, and Malondialdehyde. Change in depressive symptoms as assessed by Patient Health Questionnaire-9 [Time Frame: Baseline and 16 weeks] Change in quality of life measured by the 12-item Short-Form Health Survey Quality of life measured by the 12-item Short-Form Health Survey Questionnaire (SF-12) [Time Frame: Baseline and 16 weeks] Changes in time to return to normal menstrual cycle [Time Frame: Baseline and 16 weeks]Changes in time to return to normal menstrual cycle
Starting date	03/01/2019
Contact information	liuchangqin@xmu.edu.cn
Notes	

NCT03802253

Study name	Time Restricted Feeding on Impaired Glucose Regulation(TRIG Trial)
Methods	Randomised controlled trial
Participants	140 participants Ages Eligible for Study: 18 years to 70 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Aged ≥ 18 years Diagnosis of impaired glucose regulation (i.e. FG between 5.7-6.9mmol/L) +/- impaired glucose tolerance (i.e. 2-hour postprandial PG between 7.8-11.1mmol/L) confirmed by latest OGTT results within 3 months prior to recruitment Body mass index (BMI)of 23.0 to 45.0 kg/m2;
Interventions	Arm Intervention/treatment Experimental: TRF Participants in this group will focus on time restricted feeding (TRF) in addition to daily calorie restriction. Behavioural: Time Restricted Feeding(TRF) Participants will receive a diet of 1200-1500 kcal/day and be instructed to eat only during a window of 8 hours (Finishing the last meal before 4pm) in the first 6 months. 6 months later,Participants will receive a diet of 1200-1500 kcal/day without a restriction of feeding time. Active comparator: RCD Participants in this group will focus on standard care with daily reduced calorie diet (RCD) Behavioural: Reduced Calorie Diet (RCD) Participants will receive a diet of 1200-1500kcal/d and keep their usual eating pattern.
Outcomes	Primary Outcome Measures Changes in fasting blood glucose levels (mmol/L) [Time Frame: 6 months and 12 months] Change in insulin sensitivity [Time Frame: 6 months and 12 months] Insulin sensitivity will be assessed by HOMA-IR

NCT03802253 *(Continued)*

	Incidence of regression to normoglycaemia among the studied population [Time Frame: 6 months and 12 months] Secondary Outcome Measures Changes in body weight (Kilograms) [Time Frame: 6 months and 12 months] Changes in HbA1c levels (%) [Time Frame: 6 months and 12 months] Change in β cell function [Time Frame: 6 months and 12 months] β cell function will be assessed by HOMA-β Changes in serum triglycerides levels (mmol/L) [Time Frame: 6 months and 12 months] Changes in serum low-density lipoprotein levels (mmol/L) [Time Frame: 6 months and 12 months] Changes in serum total cholesterol levels(mmol/L) [Time Frame: 6 months and 12 months] Changes in waist circumference (cm) [Time Frame: 6 months and 12 months] Changes in abdominal circumference (cm) [Time Frame: 6 months and 12 months] Changes in diastolic pressure (DBP) [Time Frame: 6 months and 12 months] Changes in systolic pressure(SBP) [Time Frame: 6 months and 12 months] Incidence of DM [Time Frame: 6 months and 12 months] the incidence of DM among Chinese primary care patients with impaired fasting glucose (including isolated IFG or combined IFG / IGT)
Starting date	June 18, 2019
Contact information	liuchangqin@xmu.edu.cn
Notes	NCT03802253

NCT03805776

Study name	Intermittent fasting in dyslipidemia
Methods	Randomised controlled trial
Participants	60 participants. Ages Eligible for Study: 18 years to 80 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes **Inclusion Criteria** General population with serum HDL less than 40 mg/dL for men and women Adult ages 18- 80 years will be included in the study.
Interventions	Experimental: interventional Will observe intermittent fasting Other: fasting (diet restriction for specific period) 12-14 hours fasting No Intervention: control
Outcomes	Primary Outcome Measures : Lipid profile [Time Frame: 6 weeks] Change in HDL more than 3mg/dL Change in LDL more than 3mg/dl Cholesterol and TG weight loss [Time Frame: 6 weeks] Change in body weight (kg), as measured by scale weight Blood pressure [Time Frame: 6 weeks] Reduction in systolic and diastolic Secondary Outcome Measures: Fasting Glucose [Time Frame: 6 weeks] Fasting glucose mg/dl Fasting Insulin [Time Frame: 6 weeks] Fasting insulin (IU/L) Waist circumference Waist circumference (cm) [Time Frame: 6 weeks] WC in cm

NCT03805776 *(Continued)*

	Lipid profile HbA1c (%) Lipids [Time Frame: 6 weeks] Total cholesterol (mg/dl), LDL cholesterol (mg/dl), HDL cholesterol (mg/dl), and triglycerides (mg/dl) Waist circumference [Time Frame: 6 weeks] Waist circumference (cm)
Starting date	February 20, 2019
Contact information	javeria.farooq@aku.edu
Notes	NCT03805776

NCT04004403

Study name	AlternatedDay fasting combined and NAFLD for the treatment of Non-alcoholic Fatty Liver Disease (NAFLD)
Methods	Randomised controlled trial
Participants	**Inclusion Criteria** - Age between 18 to 65 years old - BMI between 30.0 and 49.9 kg/m2 - NAFLD (hepatic steatosis = 5%) - Prediabetic - Sedentary (<20 min, 2x/week of light activity for 3 mo prior to study) **Exclusion Criteria** - Have chronic liver disease other than NAFLD (hepatitis B or C, primary biliary cirrhosis, sclerosing cholangitis, autoimmune hepatitis, haemochromatosis, Wilson's disease, a1-antitrypsin deficiency) - Consume excessive amounts of alcohol (Michigan Alcohol Screening Test score > 4) - Have a history of known cardiovascular, pulmonary or renal disease - Diagnosed T1DM or T2DM (fasting glucose: >126 mg/dl, 2-h glucose OGTT = 200 mg/dL, HbA1c: >6.5%)) - Have contraindications for participation in an exercise program based on ACSM recommendations - Are not weight stable for 3 months prior to the beginning of study (weight gain or loss > 4 kg) - Are claustrophobic or have implanted metallic/electrical devices (e.g. cardiac pacemaker, neuro-stimulator) - Are not able to keep a food diary or activity log for 7 consecutive days during screening - Are taking drugs that induce steatosis (e.g. corticosteroids, oestrogens, methotrexate, Ca channel blockers) - Are taking drugs that benefit NAFLD (e.g. betaine, pioglitazone, rosiglitazone, metformin, or gemifibrozil) - Are taking drugs that influence study outcomes (weight loss, lipid-lowering, glucose-lowering medications) - Are perimenopausal or have an irregular menstrual cycle (menses that does not appear every 27-32 days) - Are pregnant, or trying to become pregnant - Are smokers
Interventions	Other: Alternate day fasting Other: Exercise
Outcomes	Change in body weight [Time Frame: Change from week 1 to week 24] Change in hepatic steatosis [Time Frame: Change from week 1 to week 24]

NCT04004403 *(Continued)*

	Change in HbA1c [Time Frame: Change from week 1 to week 24] Change in hepatic insulin sensitivity [Time Frame: Change from week 1 to week 24] Change in triglyceride levels [Time Frame: Change from week 1 to week 24]
Starting date	28/06/2019
Contact information	https://clinicaltrials.gov/show/NCT04004403
Notes	NCT04004403

NCT04057339

Study name	The Influence of time-restricted eating in patients with Metabolic Syndrome (TIMET)
Methods	Randomised controlled trial
Participants	144 participants
Interventions	Arm Intervention/treatment Placebo comparator: SOC (Standard of Care) Everyone in this arm will receive standard of care nutritional behavioural counselling and will be required to log their caloric intake through the use of a smartphone app. Behavioural: SOC Participants in this arm will receive nutritional counselling from the study dietician, but will not be required to adopt a 10-hOUr eating window. Experimental: TRE + SOC Everyone in this arm will receive SOC nutritional behavioural counselling and will implement a daily 10-hour window within which they must consume their calories. They will also be required to log their caloric intake through the use of a smartphone app. Behavioural: TRF + SOC Participants in this arm will adhere to a daily, consistent 10-hour eating window for the course of the study as well as receive nutritional counselling from the study dietitian. Other name: Time Restricted Eating
Outcomes	Primary Outcome Measures : Change in fasting glucose [Time Frame: Baseline and 14 weeks] Fasting glucose (mg/dl) Change in fasting glucose levels [Time Frame: Baseline and 14 weeks] Glucose levels as measured by continuous glucose monitor (mg/dl) for 14 days at baseline and end of intervention Secondary Outcome Measures: Change in LDL particle number [Time Frame: Baseline and 14 weeks] LDL particle number (nmol/L) via NMR lipoprofile Change in LDL cholesterol [Time Frame: Baseline and 14 weeks] LDL cholesterol (mg/dl) Change in HDL cholesterol [Time Frame: Baseline and 14 weeks] HDL cholesterol (mg/dl) Change in Triglycerides [Time Frame: Baseline and 14 weeks] Triglycerides (mg/dl) Change in % fat mass [Time Frame: Baseline and 14 weeks] Fat mass as measured by dual-energy X-ray absorptiometry (DXA) Change in hs-CRP [Time Frame: Baseline and 14 weeks] high sensitivity C-reactive protein (mg/L) Change in HbA1c [Time Frame: Baseline and 14 weeks] HbA1c (%)
Starting date	April 8, 2019

NCT04057339 *(Continued)*

Contact information	Ages Eligible for Study: 18 years to 75 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Age 18-75 years BMI > 25 and Metabolic syndrome, as defined as presence of 3 or more of the following criteria. Elevated fasting plasma glucose ≥ 100 mg/dL Elevated waist circumference: In Asians: ≥ 90 cm in men, ≥ 80 cm in women, all other races: ≥ 102 cm in men, ≥ 88 cm in women. Fasting plasma triglycerides ≥ 150 mg/dL, or on drug treatment for elevated triglycerides Reduced High-density lipoprotein (HDL)-cholesterol < 40 mg/dL in males or < 50 mg/dL in females, or drug treatment for reduced HDL-cholesterol, elevated blood pressure, systolic blood pressure ≥ 135 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or drug treatment for hypertension. Own a smartphone (Apple iOS or Android OS) Baseline eating period > 14 hours/day If patients are on cardiovascular medications (HMG CoA reductase inhibitors (statins), other lipid modifying drugs (including over the counter drugs such as red yeast rice and fish oil), anti-hypertensive, anti-diabetes drugs), no dose adjustments will be allowed during the study period.
Notes	NCT04057339

NCT04062773

Study name	Time-restricted feeding on glucose homeostasis and quality of life
Methods	12 wk Randomised controlled trial
Participants	50 participants. Ages Eligible for Study: 21 years to 65 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Must agree to follow time restricted feeding protocol if randomised to the TRF arm. Age 21-65 years T2DM with any diabetes medication BMI of 25-45 kg/m2 Wake up at a regular time between 5 am to 8 am Able to provide informed consent.
Interventions	Arm Intervention/treatment Experimental: TRF Eating restricted to between midday and 6 pm. Behavioural: TRF Time restricted feeding group Placebo comparator: normal timing of food intake. Eating between 8 am and 11 pm. Behavioural: Normal timing of food intake No time restricted feeding
Outcomes	Primary Outcome Measures : HbA1c [Time Frame: 12 weeks] Change in HbA1c between the intervention and control arms. Secondary Outcome Measures: Body weight [Time Frame: 12 weeks] Change in body weight between the intervention and control arms. Insulin sensitivity [Time Frame: 12 weeks]

NCT04062773 *(Continued)*

	Change insulin sensitivity assessed by OGTT between the intervention and control arms. Diabetes medications [Time Frame: 12 weeks] Change in diabetes medications between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in TNF-alpha in pg/mL between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in IL-10 in pg/mL between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in IL-6 in pg/mL between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in IL-18 in pg/mL between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in CRP in mg/L between the intervention and control arms. Inflammatory markers [Time Frame: 12 weeks] Change in adiponectin in µg/mL the intervention and control arms.
Starting date	July 10, 2019
Contact information	Nicola.Guess@dasmaninstitute.org
Notes	NCT04062773

NCT04138160

Study name	Effects of two weeks of twice-weekly intermittent energy restriction on basal and postprandial metabolism
Methods	Randomised controlled trial
Participants	Ages Eligible for Study: 20 years to 35 years (adult) Sexes Eligible for Study: all Accepts Healthy volunteers: yes **Inclusion Criteria** Ages between 20 - 35 years Healthy with a BMI between 20 and 27 kg·m-2 Waist circumference < 94 cm for males and < 80 cm for females Ability to give informed consent
Interventions	Experimental: twice-weekly intermittent energy restriction The twice-weekly intermittent energy restriction (IER) of 70% restriction (~600 kcal) delivered for two non-consecutive days/week and no restriction (so sufficient energy to meet the requirement of participants) on the other 5 days/week. Other: twice-weekly Intermittent energy restriction Substantial (70%) energy restriction for 2 non-consecutive days/week interspersed with normal energy intake (isoenergetic) on the remaining 5 days of the week. Other name: twice-weekly IER Continuous energy restriction The continuous energy restriction (CER) of 20% restriction below the estimated requirement of participants (~1600 kcal) 7 days/week. Other: Continuous energy restriction 20% energy restriction each day relative to the energy requirement. Other name: CER
Outcomes	Primary Outcome Measures: Incremental area under the curve for insulin [Time Frame: Over three hours from baseline]

NCT04138160 *(Continued)*

	Incremental area under the curve for serum insulin will be calculated using samples at 20 minute intervals between baseline and three hours. Secondary Outcome Measures: Incremental area under the curve for arterialised whole blood glucose [Time Frame: Over four hours post baseline] Incremental area under the curve for arterialised whole blood glucose will be calculated using samples collected at 10 minute intervals between baseline and four hours. Incremental area under the curve for composite appetite score [Time Frame: Over four hour from baseline] Composite appetite score will be calculated using 100mm visual analogue score ratings of satiety, fullness, hunger and prospective food consumption collected very 20 minutes between baseline and four hours. Weight of consumption of a pasta meal three hours after baseline [Time Frame: Three hours post baseline] Weight of pasta consumed from a bowl refilled prior to being empty until participants feel comfortably full. Incremental area under the curve for free fatty acid [Time Frame: Over three hours from baseline] Incremental area under the curve for FFA will be calculated using samples at 20 minute intervals between baseline and three hours. Incremental area under the curve for TAG [Time Frame: Over three hours from baseline] Incremental area under the curve for TAG will be calculated using samples at 20 minute Continuous glucose monitoring [Time Frame: Over last 6 days of intervention] Average glucose of 6 days
Starting date	October 18, 2018
Contact information	Ian Macdonald, PhD University of Nottingham
Notes	NCT04138160

NCT04143971

Study name	Intermittent fasting in hypertriglyceridaemic overweight or obese subjects
Methods	Randomised controlled trial
Participants	90 Participants
Interventions	Arm Intervention/treatment Placebo comparator: continuous low calorie diets Low calorie diet with daily calorie restriction Other: low calorie diet continuous low calorie diet Active Comparator: Intermittent Fasting Intermittent fasting every other day, in which daily calorie intake will be up to 30% of required calorie. Other: intermittent fasting diet intermittent fasting diet
Outcomes	Primary Outcome Measures : Weight loss [Time Frame: at 8 weeks] Mean weight change of participants (kg) after 8 weeks of diets Secondary Outcome Measures: Plasma Triglycerides [Time Frame: at 8 weeks] Mean change in plasma triglycerides of participants after 8 weeks of diets
Starting date	December 2, 2019

NCT04143971 *(Continued)*

Contact information	mahwoon3424@gmail.com
Notes	NCT04143971

NCT04155619

Study name	Using early time restricted feeding and timed light therapy to improve glycemic control in adults with type 2 diabetes
Methods	Randomised controlled trial
Participants	Ages Eligible for Study: 30 years to 80 years (adult, older adult) Sexes Eligible for Study: all Accepts Healthy volunteers: no **Inclusion Criteria** Aged 30-80 years old HbA1c between 7.0 % to 10.0% On a stable dose of metformin, sulphonylureas, DPP-IV inhibitors, and/or GLP-1 receptor agonists for at least 6 months, or taking no diabetes medications Stable values of HbA1c for the past 6 months (within 0.7%) Wake up at a regular time between 5 am to 9 am
Interventions	Active Comparator: no change in eating or light exposure habits Behavioural: no change in meal timing Participants will eat within an ≥11-hour daily period (no change in meal timing habits). Behavioural: no change in light exposure Participants will not change their light exposure habits. Experimental: early Time-Restricted Feeding Behavioural: no change in light exposure Participants will not change their light exposure habits. Behavioural: early Time-Restricted Feeding Participants will eat within an 8-hour daily period early in the day, starting within 2 hours of waking up. Other name: eTRF, early TRF Experimental: Timed Light TherapyBehavioural: No change in meal timing Participants will eat within an ≥11-hour daily period (no change in meal timing habits). Behavioural: Timed Light Therapy Participants will use bright light therapy for 60 minutes between 6 am to 3 pm, blue light-blocking glasses for one hour before bedtime, and blackout curtains at night. Other name: Bright Light Therapy Experimental: Early Time-Restricted Feeding and Timed Light TherapyBehavioural: Early Time-Restricted Feeding Participants will eat within an 8-hour daily period early in the day, starting within 2 hours of waking up. Other name: eTRF, early TRF Behavioural: Timed Light Therapy Participants will use bright light therapy for 60 minutes between 6 am to 3 pm, blue light-blocking glasses for one hour before bedtime, and blackout curtains at night. Other name: Bright Light Therapy
Outcomes	Primary Outcome Measures : 24-hour glucose levels [Time Frame: 16 weeks] Time-weighted mean, fasting, peak, standard deviation, and excursion (maximum - minimum) values (mg/dl)

NCT04155619 *(Continued)*

	24-hour insulin levels [Time Frame: 16 weeks] Time-weighted mean, fasting, peak, standard deviation, and excursion values (mU/L) 24-hour C-peptide levels [Time Frame: 16 weeks] Time-weighted mean, fasting, peak, standard deviation, and excursion values (pmol/L). This is also a proxy for total 24-hour insulin secretion. Hemoglobin A1C [Time Frame: 16 weeks] Insulin sensitivity [Time Frame: 16 weeks] Insulin sensitivity (dl/kg/min/μU/mL) during three identical meal tolerance tests, as measured by the Oral Minimal Model. The individual, mean, and excursion values, and time of the peak value will also be calculated. Beta-cell responsivity index (a measure of beta-cell function) [Time Frame: 16 weeks] Beta-cell responsivity during three identical meal tolerance tests, as measured by the Oral Minimal Model. The individual, mean, and excursion values, and time of the peak value will also be calculated. Insulin secretion [Time Frame: 16 weeks] Insulin secretion (mU) across three identical meal tolerance tests, as measured by the Oral Minimal Model. The individual, mean, and excursion values, and time of the peak value will also be calculated. Secondary Outcome Measures: Melatonin Amplitude [Time Frame: 16 weeks] Peak value (pg/mL) Cortisol Amplitude [Time Frame: 16 weeks] Amplitude (μg/dL) Melatonin Phase [Time Frame: 16 weeks] Clock time of dim light melatonin onset (DLMO) Cortisol Phase [Time Frame: 16 weeks] Clock time of cortisol phase Glycemic ("Peripheral") Rhythm Amplitude [Time Frame: 16 weeks] Amplitude or diurnal variation in glucose levels (mg/dl) during a constant glucose infusion procedure Glycemic ("Peripheral") Rhythm Phase [Time Frame: 16 weeks] Time of day that glucose levels experience a nadir during a constant glucose infusion procedure
Starting date	March 2020
Contact information	cpeterso@uab.edu
Notes	NCT04155619

SLCTR/2018/001

Study name	Effectiveness of time restricted diet versus a diet taken throughout the day on weight reduction and metabolic parameters in obese individuals.
Methods	Randomised controlled trial
Participants	**Inclusion criteria** 1.Men and women aged 18-50 years with a BMI of 25 kg/m2 to 35 kg/m2. **Exclusion criteria** 1. Patients with identified secondary cause for obesity 2. Inability to adhere to the suggested meal plan and exercise regimen. 3. Any underlying medical condition which can interfere with the proposed dietary plan and exercise regimen (i.e. diabetes mellitus, Cushing's disease, rheumatoid arthritis and osteoarthritis of knees.) 4. Patients who are on drugs which can interfere with the proposed diet (i.e. prednisolone) 5. Women who are pregnant or breast feeding

SLCTR/2018/001 *(Continued)*	
	6. Patients with diagnosed psychiatric disorder.
Interventions	One group (Group 1) will be given the choice to take the restricted calorie intake at any time during the day. Group 2 will be advised to take the calorie restricted diet during a twelve hour period (e.g. from 6 am to 6 pm).
Outcomes	Weight [At baseline and at the end of 3 months] Fasting blood sugar level [At baseline and at the end of 3 months] HbA1C level [At baseline and at the end of 3 months] Lipid Profile [At baseline and at the end of 3 months] Alanine transaminase level [At baseline and at the end of 3 months]
Starting date	2018-01-02
Contact information	noelsomasundaram@gmail.com
Notes	

ADF: alternate day fasting; **BMI:** body mass indexCER: continuous energy restriction; **CRP: C**-reactive protein; **CVD:** cardiovascular disease; **DBP:** diastolic blood pressure; **HbA1c:** glycated haemoglobin; **HDL:** high density lipoprotein**; IER:** intermittent energy restriction**; IF:** intermittent fasting; **LDL:** low-density lipoprotein; **OCTT:** oral glucose tolerance test; **SBP:** systolic blood pressure; **TC**: total cholesterol; **TG:** triglycerides; **TRF:** time-restricted feeding.

DATA AND ANALYSES

Comparison 1. IF vs Ad libitum (Short term)

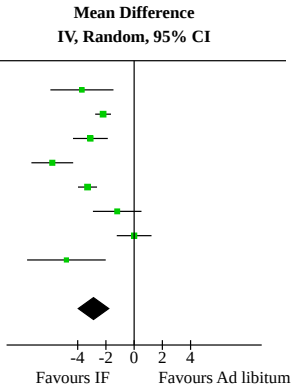
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Absolute change in body weight (kg)	7	224	Mean Difference (IV, Random, 95% CI)	-2.88 [-3.96, -1.80]
1.2 Absolute change in BMI (kg/m^2).	4	115	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.36, -0.48]
1.3 Absolute change in waist circumference (cm)	2	87	Mean Difference (IV, Random, 95% CI)	-4.19 [-6.38, -2.01]
1.4 Absolute change in total cholesterol levels (TC) (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.12]
1.5 Absolute change in LDL (mmol/L	4	125	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.40, -0.05]
1.6 Absolute change in HDL (mmol/L	4	125	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.25, 0.05]
1.7 Absolute change in TG (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.25, 0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Absolute change in SBP (mmHg)	5	201	Mean Difference (IV, Random, 95% CI)	-4.47 [-6.94, -2.01]
1.9 Absolute change in DBP (mmHg)	5	201	Mean Difference (IV, Random, 95% CI)	-1.07 [-3.33, 1.18]
1.10 Absolute change in CRP (mg/L)	2	43	Mean Difference (IV, Random, 95% CI)	-1.19 [-2.54, 0.16]
1.11 Absolute change in Glucose (mmol/L)	3	95	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.26, 0.19]

Analysis 1.1. Comparison 1: IF vs Ad libitum (Short term), Outcome 1: Absolute change in body weight (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-3.9	1.979898987	8	-0.2	2.01246118	5	9.6%	-3.70 [-5.93 , -1.47]
Chow 2019	-3.6	0.6	11	-1.4	0.7	10	15.8%	-2.20 [-2.76 , -1.64]
Hutchison 2019 (1)	-2.7	0.5	22	0.4	1.38564065	5	13.5%	-3.10 [-4.33 , -1.87]
Hutchison 2019 (2)	-5.4	2.5	25	0.4	1.38564065	6	12.6%	-5.80 [-7.28 , -4.32]
Stekovic 2019	-3.5	1.475	29	-0.196	1.101	28	15.5%	-3.30 [-3.98 , -2.63]
Tinsley 2017	-1.1	2.35	10	0.1	1.32	8	11.6%	-1.20 [-2.92 , 0.52]
Tinsley 2019	1	1.84	13	1	1.37	14	13.6%	0.00 [-1.23 , 1.23]
Varady 2013	-5.2	3.485685012	15	-0.4	4.260281681	15	7.8%	-4.80 [-7.59 , -2.01]
Total (95% CI)			**133**			**91**	**100.0%**	**-2.88 [-3.96 , -1.80]**

Heterogeneity: Tau² = 1.84; Chi² = 47.68, df = 7 (P < 0.00001); I² = 85%
Test for overall effect: Z = 5.23 (P < 0.00001)
Test for subgroup differences: Not applicable

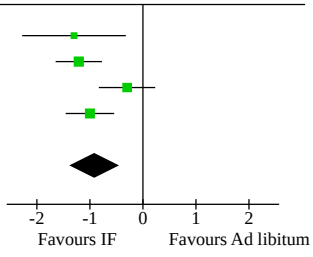


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 1.2. Comparison 1: IF vs Ad libitum (Short term), Outcome 2: Absolute change in BMI (kg/m²).

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-1.4	0.85	8	-0.1	0.89	5	13.8%	-1.30 [-2.28 , -0.32]
Stekovic 2019	-1.23	0.88	29	-0.02	0.8	28	30.3%	-1.21 [-1.65 , -0.77]
Tinsley 2017	-0.3	0.71	10	0	0.43	8	26.5%	-0.30 [-0.83 , 0.23]
Tinsley 2019	0	0.69	13	1	0.5	14	29.4%	-1.00 [-1.46 , -0.54]
Total (95% CI)			**60**			**55**	**100.0%**	**-0.92 [-1.36 , -0.48]**

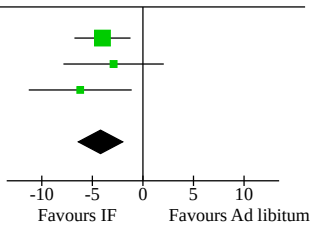
Heterogeneity: Tau² = 0.12; Chi² = 7.62, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: IF vs Ad libitum (Short term), Outcome 3: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-5	4	16	-1	4	16	62.2%	-4.00 [-6.77 , -1.23]
Hutchison 2019 (1)	-4.3	1	22	-1.4	5.64	5	19.4%	-2.90 [-7.86 , 2.06]
Hutchison 2019 (2)	-7.6	5.63	22	-1.4	5.64	6	18.4%	-6.20 [-11.29 , -1.11]
Total (95% CI)			**60**			**27**	**100.0%**	**-4.19 [-6.38 , -2.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.76 (P = 0.0002)
Test for subgroup differences: Not applicable

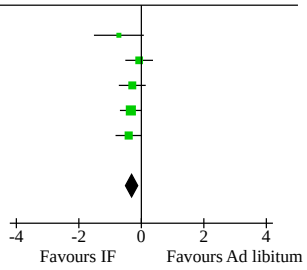


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 1.4. Comparison 1: IF vs Ad libitum (Short term), Outcome 4: Absolute change in total cholesterol levels (TC) (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.1396	0.709369523	8	0.8585	0.7171	5	6.1%	-0.72 [-1.52 , 0.08]
Hutchison 2019 (1)	-0.37	0.15	22	-0.3	0.5	5	19.7%	-0.07 [-0.51 , 0.37]
Hutchison 2019 (2)	-0.59	0.38	22	-0.3	0.5	6	20.8%	-0.29 [-0.72 , 0.14]
Tinsley 2019	-0.181	0.513	13	0.1551	0.40133	14	31.6%	-0.34 [-0.69 , 0.01]
Varady 2013	-0.6724	0.6	15	-0.2673	0.5751	15	21.8%	-0.41 [-0.83 , 0.02]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.31 [-0.51 , -0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 2.36, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)
Test for subgroup differences: Not applicable

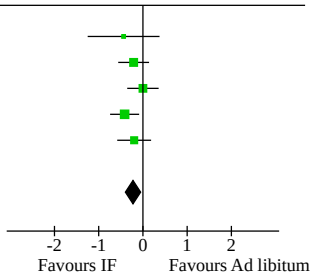


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 1.5. Comparison 1: IF vs Ad libitum (Short term), Outcome 5: Absolute change in LDL (mmol/L

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0	0.724	8	0.437	0.7285	5	4.5%	-0.44 [-1.25 , 0.38]
Hutchison 2019 (1)	-0.37	0.33	22	-0.16	0.4	6	24.4%	-0.21 [-0.56 , 0.14]
Hutchison 2019 (2)	-0.16	0.13	22	-0.16	0.4	5	23.5%	0.00 [-0.35 , 0.35]
Tinsley 2019	-0.2069	0.4735	13	0.2069	0.389	14	27.5%	-0.41 [-0.74 , -0.09]
Varady 2013	-0.4655	0.6007	15	-0.2674	0.4601	15	20.2%	-0.20 [-0.58 , 0.18]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.22 [-0.40 , -0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable

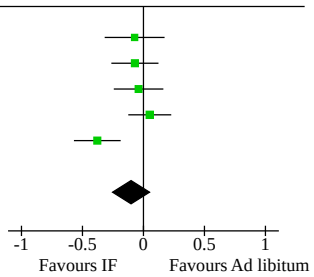


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 1.6. Comparison 1: IF vs Ad libitum (Short term), Outcome 6: Absolute change in HDL (mmol/L

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.075	0.2195	8	0.1474	0.2198	5	17.1%	-0.07 [-0.32 , 0.17]
Hutchison 2019 (1)	-0.1	0.14	22	-0.03	0.23	6	20.6%	-0.07 [-0.26 , 0.12]
Hutchison 2019 (2)	-0.07	0.06	22	-0.03	0.23	5	19.9%	-0.04 [-0.24 , 0.16]
Tinsley 2019	0.0259	0.2494	13	-0.02586	0.2145	14	21.8%	0.05 [-0.12 , 0.23]
Varady 2013	-0.0517	0.3005	15	0.3267	0.23	15	20.7%	-0.38 [-0.57 , -0.19]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.10 [-0.25 , 0.05]**

Heterogeneity: Tau² = 0.02; Chi² = 11.45, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

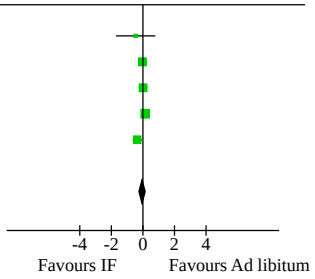


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 1.7. Comparison 1: IF vs Ad libitum (Short term), Outcome 7: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.1423	1.1081	8	0.6007	1.118	5	2.4%	-0.46 [-1.70 , 0.79]
Hutchison 2019 (1)	-0.28	0.12	22	-0.25	0.3	5	24.0%	-0.03 [-0.30 , 0.24]
Hutchison 2019 (2)	-0.24	0.32	22	-0.25	0.3	6	23.5%	0.01 [-0.26 , 0.28]
Tinsley 2019	0.0564	0.3207	13	-0.0903	0.2657	14	27.8%	0.15 [-0.08 , 0.37]
Varady 2013	-0.2484	0.481	15	0.1129	0.306	15	22.4%	-0.36 [-0.65 , -0.07]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.06 [-0.25 , 0.14]**

Heterogeneity: Tau² = 0.02; Chi² = 8.01, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

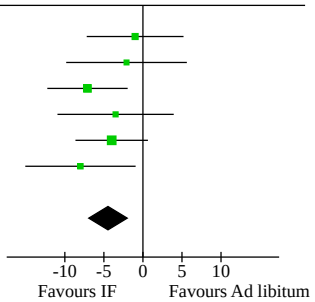


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 1.8. Comparison 1: IF vs Ad libitum (Short term), Outcome 8: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-3	4	16	-2	12	16	15.8%	-1.00 [-7.20 , 5.20]
Hutchison 2019 (1)	-0.6	15	22	1.5	5.64	6	10.2%	-2.10 [-9.82 , 5.62]
Hutchison 2019 (2)	-5.6	3.4	22	1.5	5.64	5	22.9%	-7.10 [-12.24 , -1.96]
Stekovic 2019	-4.5	9.96	29	-1	17.55	28	10.9%	-3.50 [-10.94 , 3.94]
Tinsley 2019	-2	4.96	13	2	7.21	14	28.1%	-4.00 [-8.64 , 0.64]
Varady 2013	-7	7.75	15	1	11.61	15	12.1%	-8.00 [-15.06 , -0.94]
Total (95% CI)			**117**			**84**	**100.0%**	**-4.47 [-6.94 , -2.01]**

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)
Test for subgroup differences: Not applicable

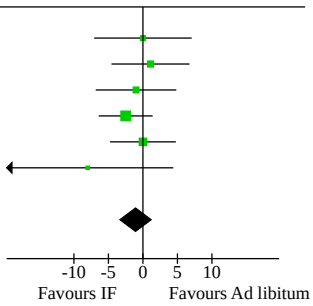


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 1.9. Comparison 1: IF vs Ad libitum (Short term), Outcome 9: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-2	8	16	-2	12	16	10.2%	0.00 [-7.07 , 7.07]
Hutchison 2019 (1)	-0.4	4.69	22	-1.5	6.63	6	15.9%	1.10 [-4.56 , 6.76]
Hutchison 2019 (2)	-2.5	1.4	22	-1.5	6.63	5	14.9%	-1.00 [-6.84 , 4.84]
Stekovic 2019	-2.5	6.87	29	0	8.1	28	33.3%	-2.50 [-6.41 , 1.41]
Tinsley 2019	-1	4	13	-1	8.1	14	22.4%	0.00 [-4.77 , 4.77]
Varady 2013	-6	7.75	15	2	23.24	15	3.3%	-8.00 [-20.40 , 4.40]
Total (95% CI)			**117**			**84**	**100.0%**	**-1.07 [-3.33 , 1.18]**

Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

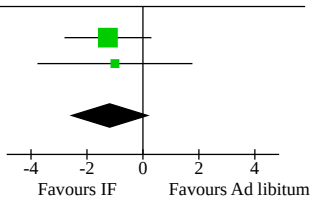


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 1.10. Comparison 1: IF vs Ad libitum (Short term), Outcome 10: Absolute change in CRP (mg/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-0.35	1.39	8	0.9	1.39	5	76.1%	-1.25 [-2.80 , 0.30]
Varady 2013	-1	3.87	15	0	3.87	15	23.9%	-1.00 [-3.77 , 1.77]
Total (95% CI)			**23**			**20**	**100.0%**	**-1.19 [-2.54 , 0.16]**

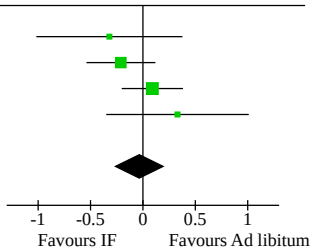
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: IF vs Ad libitum (Short term), Outcome 11: Absolute change in Glucose (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-0.54	0.63	8	-0.22	0.62	5	9.9%	-0.32 [-1.02 , 0.38]
Hutchison 2019 (1)	-0.2	0.47	22	0.01	0.33	6	36.3%	-0.21 [-0.54 , 0.12]
Hutchison 2019 (2)	0.1	0.1	22	0.01	0.33	5	43.3%	0.09 [-0.20 , 0.38]
Tinsley 2019	0	0.26	13	-0.33	1.27	14	10.4%	0.33 [-0.35 , 1.01]
Total (95% CI)			**65**			**30**	**100.0%**	**-0.03 [-0.26 , 0.19]**

Heterogeneity: Tau² = 0.01; Chi² = 3.54, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Comparison 2. IF vs CER (Short term)

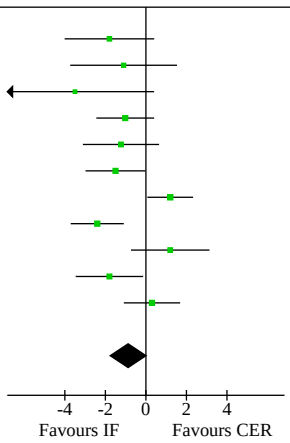
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Absolute change in Body Weight (Total) (kg)	10	719	Mean Difference (IV, Random, 95% CI)	-0.88 [-1.76, 0.00]
2.2 Absolute change in Body Weight (Fasting subgroups) (kg)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 ADF	2	93	Mean Difference (IV, Random, 95% CI)	-0.35 [-2.34, 1.65]
2.2.2 MADF	1	69	Mean Difference (IV, Random, 95% CI)	-2.40 [-3.71, -1.09]
2.2.3 PF	7	557	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.77, 0.11]
2.3 Absolute change in Body Weight (Female subgroup) (Kg)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 Female	3	226	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.96, 0.84]
2.3.2 Male	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
2.4 Absolute change in Body Weight (Overweight subgroups) (kg)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Overweight and obese	9	710	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.66, 0.12]
2.4.2 Non-overweight	1	9	Mean Difference (IV, Random, 95% CI)	-3.50 [-7.41, 0.41]
2.5 Absolute change in Body Weight (Diabetes subgroups) (kg)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 Diabetics	2	146	Mean Difference (IV, Random, 95% CI)	-2.21 [-4.14, -0.29]
2.5.2 Non-diabetics	8	573	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.63, 0.26]
2.6 Absolute change in BMI (kg/m^2).	9	651	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.76, -0.10]
2.7 Absolute change in waist circumference (cm)	8	557	Mean Difference (IV, Random, 95% CI)	-0.83 [-2.11, 0.44]
2.8 Absolute change in total cholesterol (mmol/l)	8	539	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.18, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.9 Absolute change in LDL (mmol/L)	9	569	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.16, 0.01]
2.10 Absolute change in HDL (mmol/L)	9	569	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.06, 0.04]
2.11 Absolute change in TG (mmol/L)	8	539	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.19, 0.06]
2.12 Absolute change in SBP (mmHg)	7	548	Mean Difference (IV, Random, 95% CI)	-1.75 [-4.61, 1.11]
2.13 Absolute change in DBP (mmHg)	7	548	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.35, 0.42]
2.14 Absolute change in CRP (mg/L)	2	190	Mean Difference (IV, Random, 95% CI)	0.31 [-0.56, 1.17]
2.15 Absolute change in Glucose (mmol/L	9	582	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.16, 0.12]
2.16 Absolute change in HbA1c (mmol/L)	4	310	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.08]

Analysis 2.1. Comparison 2: IF vs CER (Short term), Outcome 1: Absolute change in Body Weight (Total) (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-6.8	6.7	70	-5	6.5	67	7.7%	-1.80 [-4.01 , 0.41]
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	6.4%	-1.10 [-3.73 , 1.53]
Griffiths 2016	-5.5	3.1	4	-2	2.8	5	3.8%	-3.50 [-7.41 , 0.41]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	10.7%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	8.8%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-5.4	2.35	22	-3.9	1.96	12	10.4%	-1.50 [-2.98 , -0.02]
Hutchison 2019 (2)	-2.7	0.5	22	-3.9	1.96	12	11.9%	1.20 [0.07 , 2.33]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	11.2%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	8.6%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	9.7%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	10.8%	0.30 [-1.09 , 1.69]
Total (95% CI)			**368**			**351**	**100.0%**	**-0.88 [-1.76 , 0.00]**

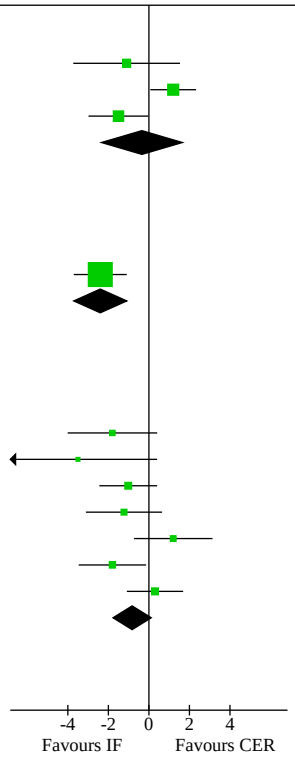
Heterogeneity: Tau² = 1.37; Chi² = 29.37, df = 10 (P = 0.001); I² = 66%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable



Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.2. Comparison 2: IF vs CER (Short term), Outcome 2: Absolute change in Body Weight (Fasting subgroups) (kg)

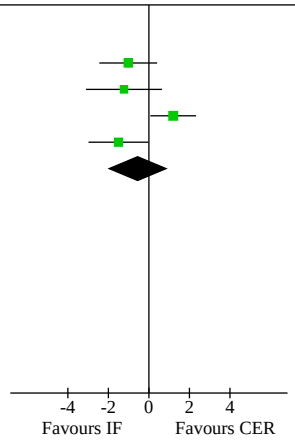
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 ADF								
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	25.1%	-1.10 [-3.73 , 1.53]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	39.1%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	35.8%	-1.50 [-2.98 , -0.02]
Subtotal (95% CI)			**57**			**36**	**100.0%**	**-0.35 [-2.34 , 1.65]**
Heterogeneity: Tau² = 2.33; Chi² = 8.93, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 0.34 (P = 0.73)								
2.2.2 MADF								
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	100.0%	-2.40 [-3.71 , -1.09]
Subtotal (95% CI)			**35**			**34**	**100.0%**	**-2.40 [-3.71 , -1.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.59 (P = 0.0003)								
2.2.3 PF								
Carter 2018	-6.8	6.7	70	-5	6.5	67	11.8%	-1.80 [-4.01 , 0.41]
Griffiths 2016	-5.5	3.1	4	-2	2.8	5	5.0%	-3.50 [-7.41 , 0.41]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	19.0%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	14.4%	-1.23 [-3.11 , 0.65]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	13.9%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	16.4%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	19.4%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**276**			**281**	**100.0%**	**-0.83 [-1.77 , 0.11]**
Heterogeneity: Tau² = 0.69; Chi² = 10.78, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 1.72 (P = 0.09)								
Test for subgroup differences: Chi² = 4.52, df = 2 (P = 0.10), I² = 55.8%								



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 2.3. Comparison 2: IF vs CER (Short term), Outcome 3: Absolute change in Body Weight (Female subgroup) (Kg)

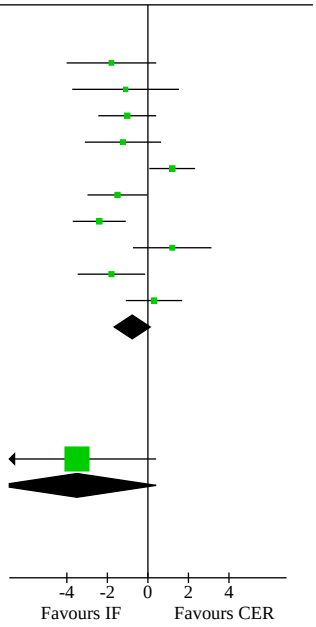
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Female								
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	25.5%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	21.3%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	28.3%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	25.0%	-1.50 [-2.98 , -0.02]
Subtotal (95% CI)			**122**			**104**	**100.0%**	**-0.56 [-1.96 , 0.84]**
Heterogeneity: Tau² = 1.48; Chi² = 11.23, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 0.78 (P = 0.44)								
2.3.2 Male								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 2.4. Comparison 2: IF vs CER (Short term), Outcome 4: Absolute change in Body Weight (Overweight subgroups) (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Overweight and obese								
Carter 2018	-6.8	6.7	70	-5	6.5	67	7.9%	-1.80 [-4.01 , 0.41]
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	6.6%	-1.10 [-3.73 , 1.53]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	11.1%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	9.2%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	12.4%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	10.9%	-1.50 [-2.98 , -0.02]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	11.6%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	9.0%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	10.1%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	11.3%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**364**			**346**	**100.0%**	**-0.77 [-1.66 , 0.12]**
Heterogeneity: Tau² = 1.33; Chi² = 27.37, df = 9 (P = 0.001); I² = 67%								
Test for overall effect: Z = 1.70 (P = 0.09)								
2.4.2 Non-overweight								
Griffiths 2016	-5.5	3.1	4	-2	2.8	5	100.0%	-3.50 [-7.41 , 0.41]
Subtotal (95% CI)			**4**			**5**	**100.0%**	**-3.50 [-7.41 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.76 (P = 0.08)								
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² = 43.8%								



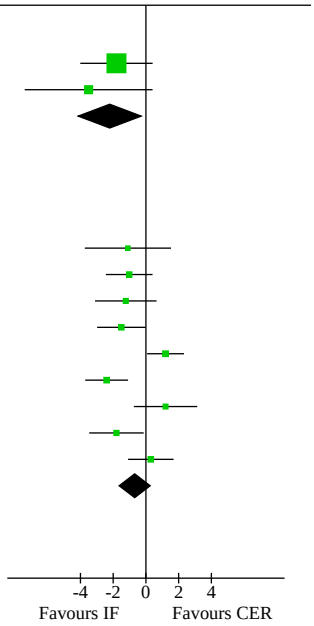
Footnotes

(1) Hutchison 2019 IF100 arm

(2) Hutchison 2019 IF70 arm

Analysis 2.5. Comparison 2: IF vs CER (Short term), Outcome 5: Absolute change in Body Weight (Diabetes subgroups) (kg)

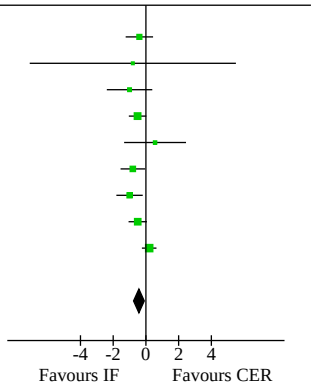
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 Diabetics								
Carter 2018	-6.8	6.7	70	-5	6.5	67	75.7%	-1.80 [-4.01 , 0.41]
Griffiths 2016	-5.5	3.1	4	-2	2.8	5	24.3%	-3.50 [-7.41 , 0.41]
Subtotal (95% CI)			**74**			**72**	**100.0%**	**-2.21 [-4.14 , -0.29]**
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%								
Test for overall effect: Z = 2.25 (P = 0.02)								
2.5.2 Non-diabetics								
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	7.3%	-1.10 [-3.73 , 1.53]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	12.0%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	10.0%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-5.4	2.35	22	-3.9	1.96	12	11.8%	-1.50 [-2.98 , -0.02]
Hutchison 2019 (2)	-2.7	0.5	22	-3.9	1.96	12	13.4%	1.20 [0.07 , 2.33]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	12.6%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	9.8%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	11.0%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	12.2%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**294**			**279**	**100.0%**	**-0.69 [-1.63 , 0.26]**
Heterogeneity: Tau² = 1.41; Chi² = 26.29, df = 8 (P = 0.0009); I² = 70%								
Test for overall effect: Z = 1.42 (P = 0.16)								
Test for subgroup differences: Chi² = 1.95, df = 1 (P = 0.16), I² = 48.6%								



Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.6. Comparison 2: IF vs CER (Short term), Outcome 6: Absolute change in BMI (kg/m²).

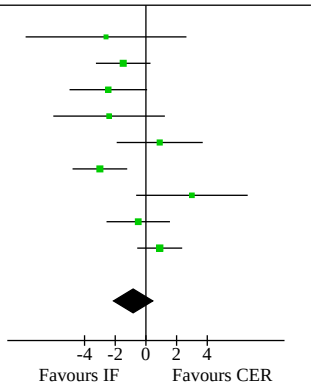
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-2.3	2.5	70	-1.9	2.5	67	10.7%	-0.40 [-1.24 , 0.44]
Catenacci 2016	-3.2	11.54	13	-2.4	1.04	12	0.3%	-0.80 [-7.10 , 5.50]
Griffiths 2016	-1.7	1.1	4	-0.7	1	5	4.8%	-1.00 [-2.39 , 0.39]
Harvie 2011	-2.26	1.41	45	-1.75	1.19	47	18.4%	-0.51 [-1.04 , 0.02]
Harvie 2013	-2.14	1.41	33	-2.7	5.36	33	2.8%	0.56 [-1.33 , 2.45]
Parvaresh 2019	-1.6	2.07	35	-0.8	0.9	34	12.5%	-0.80 [-1.55 , -0.05]
Pinto 2019	-1.4	1.81	21	-0.4	0.53	22	11.3%	-1.00 [-1.81 , -0.19]
Schubel 2018	-2.1	1.6	49	-1.6	1.2	49	17.6%	-0.50 [-1.06 , 0.06]
Sundfor 2018	-2.3	1.1	54	-2.5	1.3	58	21.7%	0.20 [-0.24 , 0.64]
Total (95% CI)			**324**			**327**	**100.0%**	**-0.43 [-0.76 , -0.10]**
Heterogeneity: Tau² = 0.08; Chi² = 12.13, df = 8 (P = 0.15); I² = 34%								
Test for overall effect: Z = 2.57 (P = 0.01)								
Test for subgroup differences: Not applicable								



Analysis 2.7. Comparison 2: IF vs CER (Short term), Outcome 7: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Griffiths 2016	-6.6	4.4	4	-4	3.4	5	4.6%	-2.60 [-7.84 , 2.64]
Harvie 2011	-5.79	4.33	45	-4.31	4.37	47	14.6%	-1.48 [-3.26 , 0.30]
Harvie 2013	-6.16	5.87	33	-3.71	4.52	33	11.3%	-2.45 [-4.98 , 0.08]
Hutchison 2019 (1)	-7.6	5.63	22	-5.2	4.9	12	7.7%	-2.40 [-6.04 , 1.24]
Hutchison 2019 (2)	-4.3	1	22	-5.2	4.9	12	10.3%	0.90 [-1.90 , 3.70]
Parvaresh 2019	-4	4.09	35	-1	3.44	34	14.6%	-3.00 [-4.78 , -1.22]
Pinto 2019	-3	3.45	21	-6	7.95	22	7.7%	3.00 [-0.63 , 6.63]
Schubel 2018	-5.3	6	49	-4.8	4.3	49	13.3%	-0.50 [-2.57 , 1.57]
Sundfor 2018	-6.9	3.6	54	-7.8	4.3	58	16.0%	0.90 [-0.57 , 2.37]
Total (95% CI)			**285**			**272**	**100.0%**	**-0.83 [-2.11 , 0.44]**

Heterogeneity: Tau² = 2.09; Chi² = 20.12, df = 8 (P = 0.010); I² = 60%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable

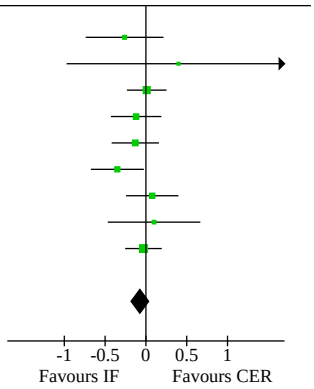


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.8. Comparison 2: IF vs CER (Short term), Outcome 8: Absolute change in total cholesterol (mmol/l)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-0.8223	0.6057	13	-0.5612	0.609	12	5.1%	-0.26 [-0.74 , 0.22]
Griffiths 2016	0	0.4	4	-0.4	1.5	5	0.6%	0.40 [-0.97 , 1.77]
Harvie 2011	-0.41	0.71	45	-0.42	0.44	47	19.6%	0.01 [-0.23 , 0.25]
Harvie 2013	-0.26	0.55	33	-0.14	0.72	33	12.1%	-0.12 [-0.43 , 0.19]
Hutchison 2019 (1)	-0.37	0.15	22	-0.24	0.5	12	13.8%	-0.13 [-0.42 , 0.16]
Hutchison 2019 (1)	-0.59	0.38	22	-0.24	0.5	12	11.0%	-0.35 [-0.67 , -0.03]
Parvaresh 2019	-0.1293	0.5239	35	-0.2069	0.804	34	11.2%	0.08 [-0.24 , 0.40]
Schubel 2018	-1.1	1.7	49	-1.2	1.1	49	3.6%	0.10 [-0.47 , 0.67]
Sundfor 2018	-0.21	0.5	54	-0.18	0.7	58	23.0%	-0.03 [-0.25 , 0.19]
Total (95% CI)			**277**			**262**	**100.0%**	**-0.07 [-0.18 , 0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 5.89, df = 8 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.18)
Test for subgroup differences: Not applicable

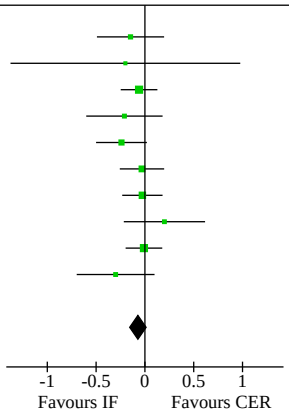


Footnotes
(1) Hutchison 2019 IF70 arm

Analysis 2.9. Comparison 2: IF vs CER (Short term), Outcome 9: Absolute change in LDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-0.5844	0.438	13	-0.437	0.439	12	5.9%	-0.15 [-0.49 , 0.20]
Griffiths 2016	0.1	0.3	4	0.3	1.3	5	0.5%	-0.20 [-1.38 , 0.98]
Harvie 2011	-0.26	0.55	45	-0.2	0.34	47	20.0%	-0.06 [-0.25 , 0.13]
Harvie 2013	-0.14	0.56	33	0.07	1	33	4.6%	-0.21 [-0.60 , 0.18]
Hutchison 2019 (1)	-0.37	0.33	22	-0.13	0.39	12	10.4%	-0.24 [-0.50 , 0.02]
Hutchison 2019 (2)	-0.16	0.13	22	-0.13	0.39	12	13.6%	-0.03 [-0.26 , 0.20]
Parvaresh 2019	-0.0259	0.271	35	0	0.5534	34	16.5%	-0.03 [-0.23 , 0.18]
Schubel 2018	-0.4	1.1	49	-0.6	1	49	4.1%	0.20 [-0.22 , 0.62]
Sundfor 2018	-0.19	0.4	54	-0.18	0.6	58	20.0%	-0.01 [-0.20 , 0.18]
Varady 2011	-0.5834	0.565	15	-0.2834	0.5488	15	4.4%	-0.30 [-0.70 , 0.10]
Total (95% CI)			**292**			**277**	**100.0%**	**-0.07 [-0.16 , 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 5.96, df = 9 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable

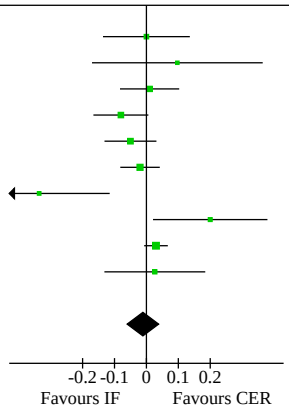


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.10. Comparison 2: IF vs CER (Short term), Outcome 10: Absolute change in HDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-0.1086	0.177	13	-0.1086	0.17	12	8.1%	0.00 [-0.14 , 0.14]
Griffiths 2016	-0.003	0.05	4	-0.1	0.3	5	2.9%	0.10 [-0.17 , 0.36]
Harvie 2011	-0.1	0.25	45	-0.11	0.2	47	12.0%	0.01 [-0.08 , 0.10]
Harvie 2013	-0.02	0.21	33	0.06	0.14	33	12.8%	-0.08 [-0.17 , 0.01]
Hutchison 2019 (1)	-0.1	0.14	22	-0.05	0.1	12	13.4%	-0.05 [-0.13 , 0.03]
Hutchison 2019 (2)	-0.07	0.06	22	-0.05	0.1	12	15.8%	-0.02 [-0.08 , 0.04]
Parvaresh 2019	-0.3362	0.6206	35	0	0.2418	34	4.0%	-0.34 [-0.56 , -0.12]
Schubel 2018	-0.2	0.5	49	-0.4	0.4	49	5.6%	0.20 [0.02 , 0.38]
Sundfor 2018	0.02	0.1	54	-0.01	0.1	58	18.8%	0.03 [-0.01 , 0.07]
Varady 2011	0.026377	0.255	15	0	0.1803	15	6.6%	0.03 [-0.13 , 0.18]
Total (95% CI)			**292**			**277**	**100.0%**	**-0.01 [-0.06 , 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 22.00, df = 9 (P = 0.009); I² = 59%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable

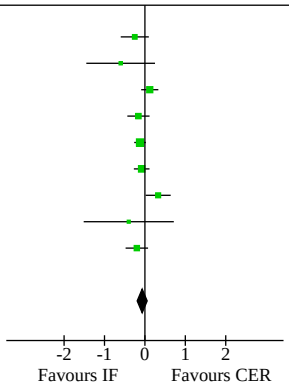


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.11. Comparison 2: IF vs CER (Short term), Outcome 11: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-0.2823	0.4438	13	-0.0316	0.442	12	8.8%	-0.25 [-0.60 , 0.10]
Griffiths 2016	-0.2	0.6	4	0.4	0.7	5	2.0%	-0.60 [-1.45 , 0.25]
Harvie 2011	-0.12	0.57	45	-0.24	0.46	47	15.8%	0.12 [-0.09 , 0.33]
Harvie 2013	-0.2	0.43	33	-0.04	0.68	33	12.0%	-0.16 [-0.43 , 0.11]
Hutchison 2019 (1)	-0.28	0.12	22	-0.16	0.24	12	21.0%	-0.12 [-0.26 , 0.02]
Hutchison 2019 (2)	-0.24	0.33	22	-0.16	0.24	12	17.1%	-0.08 [-0.27 , 0.11]
Parvaresh 2019	-0.1242	0.2776	35	-0.4516	0.8809	34	10.3%	0.33 [0.02 , 0.64]
Schubel 2018	-1.7	3.5	49	-1.3	1.9	49	1.2%	-0.40 [-1.52 , 0.72]
Sundfor 2018	-0.39	0.7	54	-0.19	0.8	58	11.8%	-0.20 [-0.48 , 0.08]
Total (95% CI)			**277**			**262**	**100.0%**	**-0.07 [-0.19 , 0.06]**

Heterogeneity: Tau² = 0.01; Chi² = 13.98, df = 8 (P = 0.08); I² = 43%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable

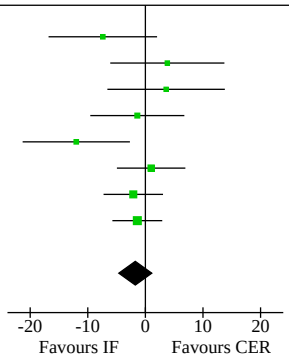


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 2.12. Comparison 2: IF vs CER (Short term), Outcome 12: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-6.27	11.76	45	1.12	30.68	47	7.9%	-7.39 [-16.81 , 2.03]
Harvie 2013	-4.91	24.66	33	-8.72	15.34	33	7.2%	3.81 [-6.10 , 13.72]
Hutchison 2019 (1)	-0.6	15.01	22	-4.2	14.21	12	6.9%	3.60 [-6.60 , 13.80]
Hutchison 2019 (2)	-5.6	3.4	22	-4.2	14.21	12	10.0%	-1.40 [-9.56 , 6.76]
Parvaresh 2019	-13	24	35	-1	14.42	34	8.0%	-12.00 [-21.31 , -2.69]
Pinto 2019	-2	7.46	21	-3	12	22	16.2%	1.00 [-4.94 , 6.94]
Schubel 2018	-6.8	16.2	49	-4.7	8.8	49	19.6%	-2.10 [-7.26 , 3.06]
Sundfor 2018	-6.4	12.6	54	-5	10.6	58	24.2%	-1.40 [-5.73 , 2.93]
Total (95% CI)			**281**			**267**	**100.0%**	**-1.75 [-4.61 , 1.11]**

Heterogeneity: Tau² = 3.91; Chi² = 9.17, df = 7 (P = 0.24); I² = 24%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable

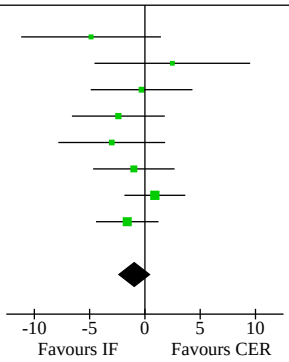


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.13. Comparison 2: IF vs CER (Short term), Outcome 13: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-4.64	8.61	45	0.23	20.27	47	4.8%	-4.87 [-11.19 , 1.45]
Harvie 2013	0.59	17.87	33	-1.89	10.31	33	3.9%	2.48 [-4.56 , 9.52]
Hutchison 2019 (1)	-0.4	4.7	22	-0.1	7.35	12	9.0%	-0.30 [-4.90 , 4.30]
Hutchison 2019 (2)	-2.5	1.4	22	-0.1	7.35	12	10.8%	-2.40 [-6.60 , 1.80]
Parvaresh 2019	-8	7.72	35	-5	12.18	34	8.2%	-3.00 [-7.83 , 1.83]
Pinto 2019	-4	6.31	21	-3	6	22	14.1%	-1.00 [-4.68 , 2.68]
Schubel 2018	-2.6	7.7	49	-3.5	6.1	49	25.3%	0.90 [-1.85 , 3.65]
Sundfor 2018	-6.4	8	54	-4.8	7.2	58	23.9%	-1.60 [-4.43 , 1.23]
Total (95% CI)			**281**			**267**	**100.0%**	**-0.97 [-2.35 , 0.42]**

Heterogeneity: Tau² = 0.00; Chi² = 5.56, df = 7 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

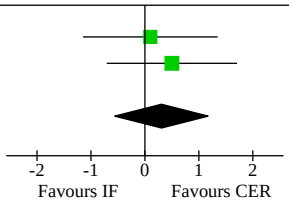


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.14. Comparison 2: IF vs CER (Short term), Outcome 14: Absolute change in CRP (mg/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-1	2.5	45	-1.1	3.54	47	48.4%	0.10 [-1.15 , 1.35]
Schubel 2018	-0.1	3.1	49	-0.6	3	49	51.6%	0.50 [-0.71 , 1.71]
Total (95% CI)			**94**			**96**	**100.0%**	**0.31 [-0.56 , 1.17]**

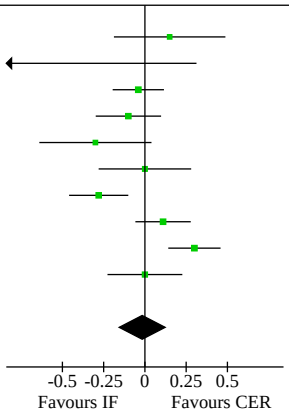
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 2.15. Comparison 2: IF vs CER (Short term), Outcome 15: Absolute change in Glucose (mmol/L

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.33	0.42	13	0.18	0.44	12	8.1%	0.15 [-0.19 , 0.49]
Griffiths 2016	-1.6	1.5	4	1.1	3	5	0.2%	-2.70 [-5.71 , 0.31]
Harvie 2011	-0.1	0.36	45	-0.06	0.4	47	13.1%	-0.04 [-0.20 , 0.12]
Harvie 2013	-0.08	0.39	33	0.02	0.43	33	11.9%	-0.10 [-0.30 , 0.10]
Hutchison 2019 (1)	-0.2	0.47	22	0.1	0.49	12	8.1%	-0.30 [-0.64 , 0.04]
Hutchison 2019 (2)	0.1	0.1	22	0.1	0.49	12	9.5%	0.00 [-0.28 , 0.28]
Parvaresh 2019	-0.28	0.38	35	0	0.38	34	12.4%	-0.28 [-0.46 , -0.10]
Pinto 2019	-0.04	0.34	21	-0.15	0.2	22	12.7%	0.11 [-0.06 , 0.28]
Schubel 2018	-0.1	0.4	49	-0.4	0.4	49	13.0%	0.30 [0.14 , 0.46]
Sundfor 2018	-0.3	0.7	54	-0.3	0.5	58	11.0%	0.00 [-0.23 , 0.23]
Total (95% CI)			**298**			**284**	**100.0%**	**-0.02 [-0.16 , 0.12]**

Heterogeneity: Tau² = 0.03; Chi² = 32.84, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

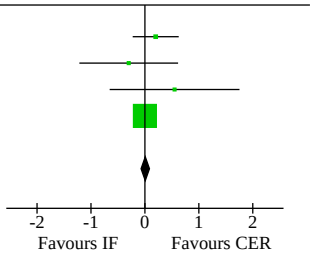


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 2.16. Comparison 2: IF vs CER (Short term), Outcome 16: Absolute change in HbA1c (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-0.3	0.8	70	-0.5	1.6	67	3.3%	0.20 [-0.23 , 0.63]
Griffiths 2016	-1	0.6	4	-0.7	0.8	5	0.7%	-0.30 [-1.22 , 0.62]
Harvie 2013	0.34	2.63	33	-0.21	2.35	33	0.4%	0.55 [-0.65 , 1.75]
Schubel 2018	0	0.2	49	0	0.2	49	95.6%	0.00 [-0.08 , 0.08]
Total (95% CI)			**156**			**154**	**100.0%**	**0.01 [-0.07 , 0.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.03, df = 3 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



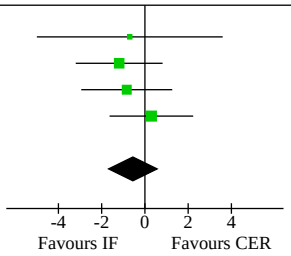
Comparison 3. IF vs CER (Medium term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Absolute change in Body weight (kg)	4	279	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.68, 0.56]
3.2 Absolute change in BMI (kg/m^2)	4	279	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.58, 0.29]
3.3 Absolute change in waist circumference (cm)	3	258	Mean Difference (IV, Random, 95% CI)	-0.66 [-2.55, 1.23]
3.4 Absolute change in total cholesterol (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.17, 0.10]
3.5 Absolute change in LDL (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.05]
3.6 Absolute change in HDL (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.07, 0.07]
3.7 Absolute change in TG (mmol/L)	4	279	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.16, 0.12]
3.8 Absolute change in SBP (mmHg)	3	258	Mean Difference (IV, Random, 95% CI)	1.37 [-4.98, 7.72]
3.9 Absolute change in DBP (mmHg)	3	258	Mean Difference (IV, Random, 95% CI)	-1.00 [-4.67, 2.67]
3.10 Absolute change in CRP (mg/L)	1	89	Mean Difference (IV, Random, 95% CI)	0.46 [-0.87, 1.79]
3.11 Absolute change in glucose (mmol/L)	4	279	Mean Difference (IV, Random, 95% CI)	0.01 [-0.10, 0.11]

Analysis 3.1. Comparison 3: IF vs CER (Medium term), Outcome 1: Absolute change in Body weight (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-5.7	4.97	11	-5	5.06	10	6.8%	-0.70 [-5.00 , 3.60]
Harvie 2011	-7.58	5.19	42	-6.39	4.38	47	31.2%	-1.19 [-3.20 , 0.82]
Harvie 2013	-6.06	4.72	33	-5.22	3.59	27	28.4%	-0.84 [-2.94 , 1.26]
Sundfor 2018	-9.1	5	53	-9.4	5.3	56	33.6%	0.30 [-1.63 , 2.23]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.56 [-1.68 , 0.56]**

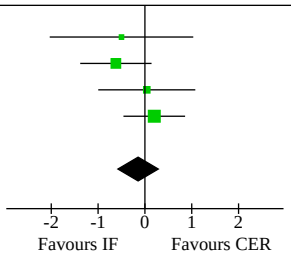
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: IF vs CER (Medium term), Outcome 2: Absolute change in BMI (kg/m^2)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-2.2	1.66	11	-1.7	1.9	10	7.9%	-0.50 [-2.03 , 1.03]
Harvie 2011	-2.92	2.02	42	-2.3	1.59	47	32.0%	-0.62 [-1.38 , 0.14]
Harvie 2013	-1.95	2.62	33	-1.99	1.39	27	17.3%	0.04 [-1.00 , 1.08]
Sundfor 2018	-3	1.6	53	-3.2	1.9	56	42.8%	0.20 [-0.46 , 0.86]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.15 [-0.58 , 0.29]**

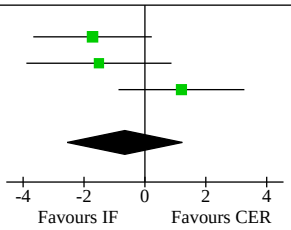
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: IF vs CER (Medium term), Outcome 3: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-7.39	5.4	42	-5.67	3.7	47	35.8%	-1.72 [-3.67 , 0.23]
Harvie 2013	-6.64	5	33	-5.13	4.41	27	30.1%	-1.51 [-3.89 , 0.87]
Sundfor 2018	-8	5.6	53	-9.2	5.4	56	34.1%	1.20 [-0.87 , 3.27]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.66 [-2.55 , 1.23]**

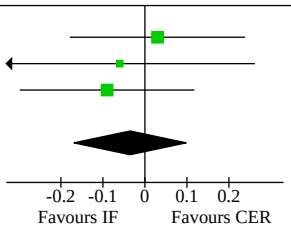
Heterogeneity: Tau² = 1.61; Chi² = 4.74, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: IF vs CER (Medium term), Outcome 4: Absolute change in total cholesterol (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-0.41	0.55	42	-0.44	0.44	47	41.2%	0.03 [-0.18 , 0.24]
Harvie 2013	-0.21	0.57	33	-0.15	0.68	27	17.3%	-0.06 [-0.38 , 0.26]
Sundfor 2018	-0.16	0.6	53	-0.07	0.5	56	41.5%	-0.09 [-0.30 , 0.12]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.04 [-0.17 , 0.10]**

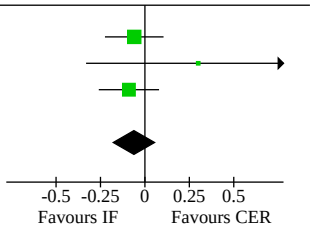
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: IF vs CER (Medium term), Outcome 5: Absolute change in LDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-0.3	0.44	42	-0.24	0.34	47	49.7%	-0.06 [-0.22 , 0.10]
Harvie 2013	-0.1	0.54	33	-0.4	1.6	27	3.4%	0.30 [-0.33 , 0.93]
Sundfor 2018	-0.16	0.4	53	-0.07	0.5	56	46.9%	-0.09 [-0.26 , 0.08]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.06 [-0.18 , 0.05]**

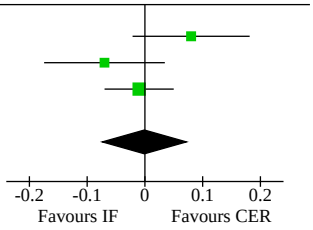
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: IF vs CER (Medium term), Outcome 6: Absolute change in HDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	0	0.27	42	-0.08	0.21	47	28.4%	0.08 [-0.02 , 0.18]
Harvie 2013	-0.04	0.25	33	0.03	0.16	27	27.4%	-0.07 [-0.17 , 0.03]
Sundfor 2018	0.05	0.2	53	0.06	0.1	56	44.2%	-0.01 [-0.07 , 0.05]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.00 [-0.07 , 0.07]**

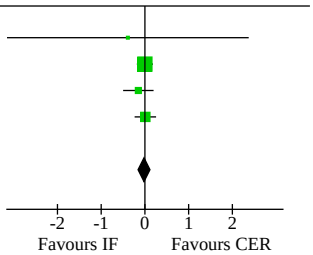
Heterogeneity: Tau² = 0.00; Chi² = 4.21, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: IF vs CER (Medium term), Outcome 7: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.28	3.46	11	0.67	3	10	0.2%	-0.39 [-3.15 , 2.37]
Harvie 2011	-0.25	0.42	42	-0.25	0.47	47	53.9%	0.00 [-0.18 , 0.18]
Harvie 2013	-0.14	0.34	33	0.01	0.87	27	15.2%	-0.15 [-0.50 , 0.20]
Sundfor 2018	-0.35	0.7	53	-0.36	0.6	56	30.6%	0.01 [-0.24 , 0.26]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.02 [-0.16 , 0.12]**

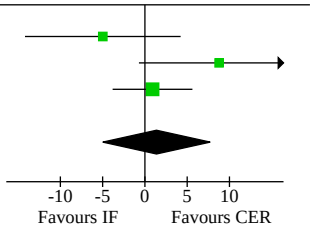
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: IF vs CER (Medium term), Outcome 8: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-5.38	13.69	42	-0.4	28.75	47	27.1%	-4.98 [-14.18 , 4.22]
Harvie 2013	-2.51	23.16	33	-11.28	13.87	27	26.2%	8.77 [-0.71 , 18.25]
Sundfor 2018	-4.9	14.1	53	-5.8	10.7	56	46.7%	0.90 [-3.82 , 5.62]
Total (95% CI)			**128**			**130**	**100.0%**	**1.37 [-4.98 , 7.72]**

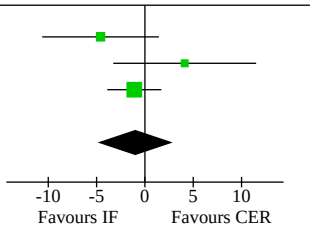
Heterogeneity: Tau² = 16.71; Chi² = 4.20, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: IF vs CER (Medium term), Outcome 9: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-4.95	8.6	42	-0.36	19.06	47	25.5%	-4.59 [-10.63 , 1.45]
Harvie 2013	0.65	18.83	33	-3.47	9.69	27	19.0%	4.12 [-3.27 , 11.51]
Sundfor 2018	-5.8	7.5	53	-4.7	7.4	56	55.6%	-1.10 [-3.90 , 1.70]
Total (95% CI)			**128**			**130**	**100.0%**	**-1.00 [-4.67 , 2.67]**

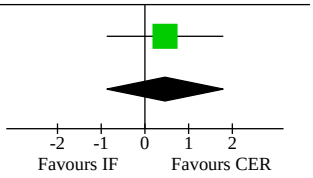
Heterogeneity: Tau² = 4.27; Chi² = 3.20, df = 2 (P = 0.20); I² = 37%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: IF vs CER (Medium term), Outcome 10: Absolute change in CRP (mg/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-0.57	2.73	42	-1.03	3.66	47	100.0%	0.46 [-0.87 , 1.79]
Total (95% CI)			**42**			**47**	**100.0%**	**0.46 [-0.87 , 1.79]**

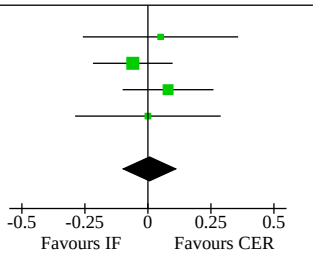
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: IF vs CER (Medium term), Outcome 11: Absolute change in glucose (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.14	0.39	11	0.09	0.33	10	11.3%	0.05 [-0.26 , 0.36]
Harvie 2011	-0.11	0.29	42	-0.05	0.46	47	42.9%	-0.06 [-0.22 , 0.10]
Harvie 2013	-0.05	0.32	33	-0.13	0.38	27	33.0%	0.08 [-0.10 , 0.26]
Sundfor 2018	-0.2	0.9	53	-0.2	0.6	56	12.8%	0.00 [-0.29 , 0.29]
Total (95% CI)			**139**			**140**	**100.0%**	**0.01 [-0.10 , 0.11]**

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



Comparison 4. Sensitivity analysis; published data: IF vs Ad libitum (Short term)

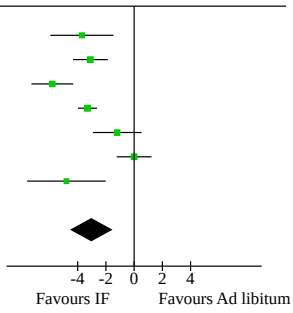
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Absolute change in body weight (kg)	6	203	Mean Difference (IV, Random, 95% CI)	-3.04 [-4.45, -1.62]
4.2 Absolute change in BMI (kg/m^2)	4	115	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.36, -0.48]
4.3 Absolute change in waist circumference (cm)	2	87	Mean Difference (IV, Random, 95% CI)	-4.19 [-6.38, -2.01]
4.4 Absolute change in total cholesterol levels (TC) (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5 Absolute change in LDL (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.40, -0.05]
4.6 Absolute change in HDL (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.25, 0.05]
4.7 Absolute change in TG (mmol/L)	4	125	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.25, 0.14]
4.8 Absolute change in SBP (mmHg)	5	201	Mean Difference (IV, Random, 95% CI)	-4.47 [-6.94, -2.01]
4.9 Absolute change in DBP (mmHg)	5	201	Mean Difference (IV, Random, 95% CI)	-1.07 [-3.33, 1.18]
4.10 Absolute change in CRP (mg/L)	2	43	Mean Difference (IV, Random, 95% CI)	-1.19 [-2.54, 0.16]
4.11 Absolute change in Glucose (mmol/L)	3	95	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.26, 0.19]

Analysis 4.1. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 1: Absolute change in body weight (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-3.9	1.979898987	8	-0.2	2.01246118	5	12.3%	-3.70 [-5.93 , -1.47]
Hutchison 2019 (1)	-2.7	0.5	22	0.4	1.38564065	5	15.6%	-3.10 [-4.33 , -1.87]
Hutchison 2019 (2)	-5.4	2.5	25	0.4	1.38564065	6	14.8%	-5.80 [-7.28 , -4.32]
Stekovic 2019	-3.5	1.475	29	-0.196	1.101	28	17.0%	-3.30 [-3.98 , -2.63]
Tinsley 2017	-1.1	2.35	10	0.1	1.32	8	14.0%	-1.20 [-2.92 , 0.52]
Tinsley 2019	1	1.84	13	1	1.37	14	15.6%	0.00 [-1.23 , 1.23]
Varady 2013	-5.2	3.485685012	15	-0.4	4.260281681	15	10.5%	-4.80 [-7.59 , -2.01]
Total (95% CI)			**122**			**81**	**100.0%**	**-3.04 [-4.45 , -1.62]**

Heterogeneity: Tau² = 2.93; Chi² = 43.53, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.21 (P < 0.0001)
Test for subgroup differences: Not applicable

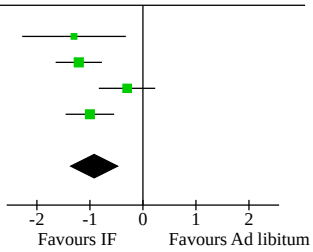


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.2. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 2: Absolute change in BMI (kg/m^2)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-1.4	0.85	8	-0.1	0.89	5	13.8%	-1.30 [-2.28 , -0.32]
Stekovic 2019	-1.23	0.88	29	-0.02	0.8	28	30.3%	-1.21 [-1.65 , -0.77]
Tinsley 2017	-0.3	0.71	10	0	0.43	8	26.5%	-0.30 [-0.83 , 0.23]
Tinsley 2019	0	0.69	13	1	0.5	14	29.4%	-1.00 [-1.46 , -0.54]
Total (95% CI)			**60**			**55**	**100.0%**	**-0.92 [-1.36 , -0.48]**

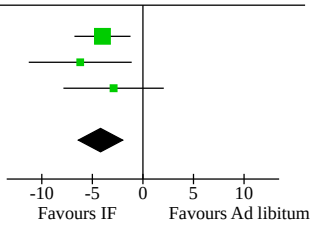
Heterogeneity: Tau² = 0.12; Chi² = 7.62, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 3: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-5	4	16	-1	4	16	62.2%	-4.00 [-6.77 , -1.23]
Hutchison 2019 (1)	-7.6	5.63	22	-1.4	5.64	6	18.4%	-6.20 [-11.29 , -1.11]
Hutchison 2019 (2)	-4.3	1	22	-1.4	5.64	5	19.4%	-2.90 [-7.86 , 2.06]
Total (95% CI)			**60**			**27**	**100.0%**	**-4.19 [-6.38 , -2.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.76 (P = 0.0002)
Test for subgroup differences: Not applicable

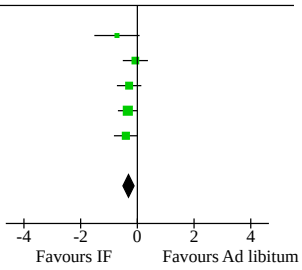


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 4.4. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 4: Absolute change in total cholesterol levels (TC) (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.1396	0.709369523	8	0.8585	0.7171	5	6.1%	-0.72 [-1.52 , 0.08]
Hutchison 2019 (1)	-0.37	0.15	22	-0.3	0.5	5	19.7%	-0.07 [-0.51 , 0.37]
Hutchison 2019 (2)	-0.59	0.38	22	-0.3	0.5	6	20.8%	-0.29 [-0.72 , 0.14]
Tinsley 2019	-0.181	0.513	13	0.1551	0.40133	14	31.6%	-0.34 [-0.69 , 0.01]
Varady 2013	-0.6724	0.6	15	-0.2673	0.5751	15	21.8%	-0.41 [-0.83 , 0.02]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.31 [-0.51 , -0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 2.36, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)
Test for subgroup differences: Not applicable

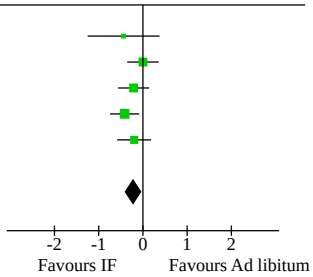


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.5. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 5: Absolute change in LDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0	0.724	8	0.437	0.7285	5	4.5%	-0.44 [-1.25 , 0.38]
Hutchison 2019 (1)	-0.16	0.13	22	-0.16	0.4	5	23.5%	0.00 [-0.35 , 0.35]
Hutchison 2019 (2)	-0.37	0.33	22	-0.16	0.4	6	24.4%	-0.21 [-0.56 , 0.14]
Tinsley 2019	-0.2069	0.4735	13	0.2069	0.389	14	27.5%	-0.41 [-0.74 , -0.09]
Varady 2013	-0.4655	0.6007	15	-0.2674	0.4601	15	20.2%	-0.20 [-0.58 , 0.18]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.22 [-0.40 , -0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable

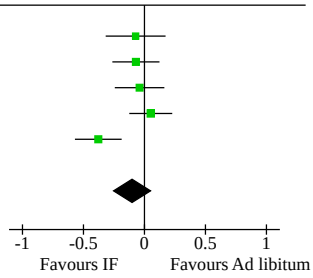


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.6. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 6: Absolute change in HDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.075	0.2195	8	0.1474	0.2198	5	17.1%	-0.07 [-0.32 , 0.17]
Hutchison 2019 (1)	-0.1	0.14	22	-0.03	0.23	6	20.6%	-0.07 [-0.26 , 0.12]
Hutchison 2019 (2)	-0.07	0.06	22	-0.03	0.23	5	19.9%	-0.04 [-0.24 , 0.16]
Tinsley 2019	0.0259	0.2494	13	-0.02586	0.2145	14	21.8%	0.05 [-0.12 , 0.23]
Varady 2013	-0.0517	0.3005	15	0.3267	0.23	15	20.7%	-0.38 [-0.57 , -0.19]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.10 [-0.25 , 0.05]**

Heterogeneity: Tau² = 0.02; Chi² = 11.45, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

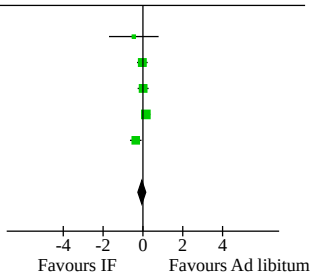


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 4.7. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 7: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	0.1423	1.1081	8	0.6007	1.118	5	2.4%	-0.46 [-1.70 , 0.79]
Hutchison 2019 (1)	-0.28	0.12	22	-0.25	0.3	5	24.0%	-0.03 [-0.30 , 0.24]
Hutchison 2019 (2)	-0.24	0.32	22	-0.25	0.3	6	23.5%	0.01 [-0.26 , 0.28]
Tinsley 2019	0.0564	0.3207	13	-0.0903	0.2657	14	27.8%	0.15 [-0.08 , 0.37]
Varady 2013	-0.2484	0.481	15	0.1129	0.306	15	22.4%	-0.36 [-0.65 , -0.07]
Total (95% CI)			**80**			**45**	**100.0%**	**-0.06 [-0.25 , 0.14]**

Heterogeneity: Tau² = 0.02; Chi² = 8.01, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

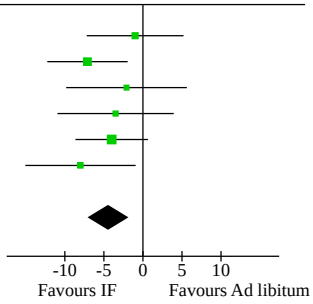


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.8. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 8: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-3	4	16	-2	12	16	15.8%	-1.00 [-7.20 , 5.20]
Hutchison 2019 (1)	-5.6	3.4	22	1.5	5.64	5	22.9%	-7.10 [-12.24 , -1.96]
Hutchison 2019 (2)	-0.6	15	22	1.5	5.64	6	10.2%	-2.10 [-9.82 , 5.62]
Stekovic 2019	-4.5	9.96	29	-1	17.55	28	10.9%	-3.50 [-10.94 , 3.94]
Tinsley 2019	-2	4.96	13	2	7.21	14	28.1%	-4.00 [-8.64 , 0.64]
Varady 2013	-7	7.75	15	1	11.61	15	12.1%	-8.00 [-15.06 , -0.94]
Total (95% CI)			**117**			**84**	**100.0%**	**-4.47 [-6.94 , -2.01]**

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)
Test for subgroup differences: Not applicable

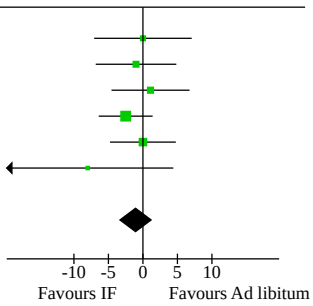


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.9. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 9: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Bhutani 2013	-2	8	16	-2	12	16	10.2%	0.00 [-7.07 , 7.07]
Hutchison 2019 (1)	-2.5	1.4	22	-1.5	6.63	5	14.9%	-1.00 [-6.84 , 4.84]
Hutchison 2019 (2)	-0.4	4.69	22	-1.5	6.63	6	15.9%	1.10 [-4.56 , 6.76]
Stekovic 2019	-2.5	6.87	29	0	8.1	28	33.3%	-2.50 [-6.41 , 1.41]
Tinsley 2019	-1	4	13	-1	8.1	14	22.4%	0.00 [-4.77 , 4.77]
Varady 2013	-6	7.75	15	2	23.24	15	3.3%	-8.00 [-20.40 , 4.40]
Total (95% CI)			**117**			**84**	**100.0%**	**-1.07 [-3.33 , 1.18]**

Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

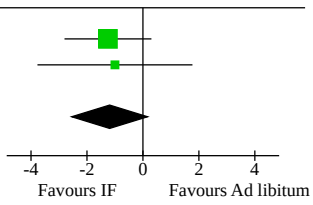


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 4.10. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 10: Absolute change in CRP (mg/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-0.35	1.39	8	0.9	1.39	5	76.1%	-1.25 [-2.80 , 0.30]
Varady 2013	-1	3.87	15	0	3.87	15	23.9%	-1.00 [-3.77 , 1.77]
Total (95% CI)			**23**			**20**	**100.0%**	**-1.19 [-2.54 , 0.16]**

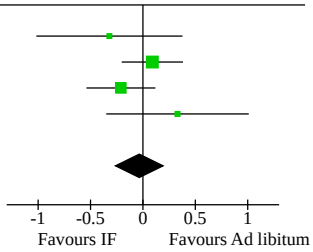
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 4.11. Comparison 4: Sensitivity analysis; published data: IF vs Ad libitum (Short term), Outcome 11: Absolute change in Glucose (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
Cho 2019	-0.54	0.63	8	-0.22	0.62	5	9.9%	-0.32 [-1.02 , 0.38]
Hutchison 2019 (1)	0.1	0.1	22	0.01	0.33	5	43.3%	0.09 [-0.20 , 0.38]
Hutchison 2019 (2)	-0.2	0.47	22	0.01	0.33	6	36.3%	-0.21 [-0.54 , 0.12]
Tinsley 2019	0	0.26	13	-0.33	1.27	14	10.4%	0.33 [-0.35 , 1.01]
Total (95% CI)			**65**			**30**	**100.0%**	**-0.03 [-0.26 , 0.19]**

Heterogeneity: Tau² = 0.01; Chi² = 3.54, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Comparison 5. Sensitivity analysis; published data: IF vs CER (Short term)

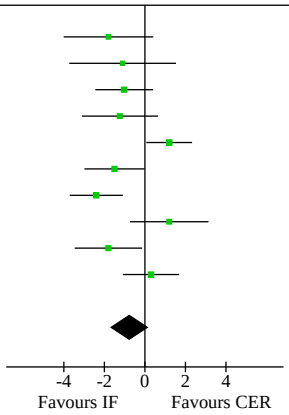
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 kbsolute change in Body Weight (Total) (kg)	9	710	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.66, 0.12]
5.2 Absolute change in Body Weight (Fasting subgroups) (kg)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 ADF	2	93	Mean Difference (IV, Random, 95% CI)	-0.35 [-2.34, 1.65]
5.2.2 MADF	1	69	Mean Difference (IV, Random, 95% CI)	-2.40 [-3.71, -1.09]
5.2.3 PF	6	548	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.61, 0.24]
5.3 Absolute change in Body Weight (Female subgroups) (kg)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.3.1 Female only	1	68	Mean Difference (IV, Random, 95% CI)	-0.11 [-2.75, 2.54]
5.3.2 Male only	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
5.4 Absolute change in Body Weight (Overweight subgroups) (kg)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.4.1 Overweight and obese	9	710	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.66, 0.12]
5.4.2 Non-overweight only	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Absolute change in Body Weight (Diabetes subgroups) (Kg)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.5.1 Diabetics	1	137	Mean Difference (IV, Random, 95% CI)	-1.80 [-4.01, 0.41]
5.5.2 Non-diabetics	8	573	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.63, 0.26]
5.6 Absolute change in BMI (kg/m^2)	8	642	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.74, -0.06]
5.7 Absolute change in waist circumference (cm)	7	548	Mean Difference (IV, Random, 95% CI)	-0.74 [-2.08, 0.59]
5.8 Absolute change in total cholesterol (mmol/L)	8	573	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.20, 0.02]
5.9 Absolute change in LDL (mmol/L)	8	560	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.02]
5.10 Absolute change in HDL (mmol/L)	8	560	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.05, 0.04]
5.11 Absolute change in TG (mmol/L)	7	530	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.18, 0.00]
5.12 Absolute change in SBP (mmHg)	7	548	Mean Difference (IV, Random, 95% CI)	-1.75 [-4.61, 1.11]
5.13 Absolute change in DBP (mmHg)	7	548	Mean Difference (IV, Random, 95% CI)	-0.97 [-2.35, 0.42]
5.14 Absolute change in CRP (mg/L)	2	190	Mean Difference (IV, Random, 95% CI)	0.31 [-0.56, 1.17]
5.15 Absolute change in Glucose (mmol/L)	8	573	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.15, 0.12]
5.16 Absolute change in HbA1c (mmol/L)	3	301	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.09]

Analysis 5.1. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 1: kbsolute change in Body Weight (Total) (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-6.8	6.7	70	-5	6.5	67	7.9%	-1.80 [-4.01 , 0.41]
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	6.6%	-1.10 [-3.73 , 1.53]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	11.1%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	9.2%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	12.4%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	10.9%	-1.50 [-2.98 , -0.02]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	11.6%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	9.0%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	10.1%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	11.3%	0.30 [-1.09 , 1.69]
Total (95% CI)			**364**			**346**	**100.0%**	**-0.77 [-1.66 , 0.12]**

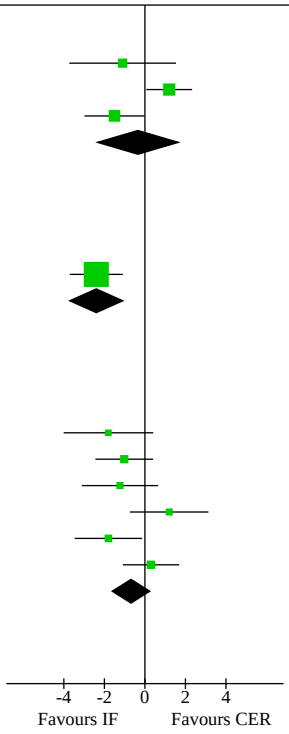
Heterogeneity: Tau² = 1.33; Chi² = 27.37, df = 9 (P = 0.001); I² = 67%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.2. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 2: Absolute change in Body Weight (Fasting subgroups) (kg)

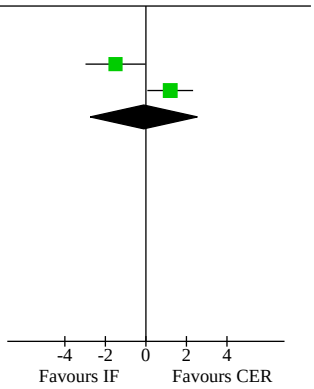
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
5.2.1 ADF								
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	25.1%	-1.10 [-3.73 , 1.53]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	39.1%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	35.8%	-1.50 [-2.98 , -0.02]
Subtotal (95% CI)			**57**			**36**	**100.0%**	**-0.35 [-2.34 , 1.65]**
Heterogeneity: Tau² = 2.33; Chi² = 8.93, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 0.34 (P = 0.73)								
5.2.2 MADF								
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	100.0%	-2.40 [-3.71 , -1.09]
Subtotal (95% CI)			**35**			**34**	**100.0%**	**-2.40 [-3.71 , -1.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.59 (P = 0.0003)								
5.2.3 PF								
Carter 2018	-6.8	6.7	70	-5	6.5	67	12.1%	-1.80 [-4.01 , 0.41]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	20.3%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	15.0%	-1.23 [-3.11 , 0.65]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	14.4%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	17.3%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	20.8%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**272**			**276**	**100.0%**	**-0.69 [-1.61 , 0.24]**
Heterogeneity: Tau² = 0.57; Chi² = 8.80, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 1.45 (P = 0.15)								
Test for subgroup differences: Chi² = 5.09, df = 2 (P = 0.08), I² = 60.7%								



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.3. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 3: Absolute change in Body Weight (Female subgroups) (kg)

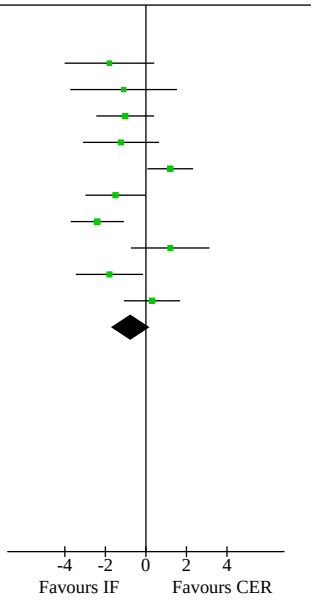
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
5.3.1 Female only								
Hutchison 2019 (1)	-5.4	2.35	22	-3.9	1.96	12	48.4%	-1.50 [-2.98 , -0.02]
Hutchison 2019 (2)	-2.7	0.5	22	-3.9	1.96	12	51.6%	1.20 [0.07 , 2.33]
Subtotal (95% CI)			**44**			**24**	**100.0%**	**-0.11 [-2.75 , 2.54]**
Heterogeneity: Tau² = 3.19; Chi² = 8.08, df = 1 (P = 0.004); I² = 88%								
Test for overall effect: Z = 0.08 (P = 0.94)								
5.3.2 Male only								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 5.4. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 4: Absolute change in Body Weight (Overweight subgroups) (kg)

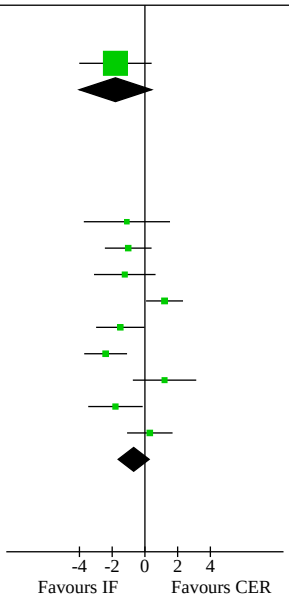
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
5.4.1 Overweight and obese								
Carter 2018	-6.8	6.7	70	-5	6.5	67	7.9%	-1.80 [-4.01 , 0.41]
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	6.6%	-1.10 [-3.73 , 1.53]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	11.1%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	9.2%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	12.4%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	10.9%	-1.50 [-2.98 , -0.02]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	11.6%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	9.0%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	10.1%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	11.3%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**364**			**346**	**100.0%**	**-0.77 [-1.66 , 0.12]**
Heterogeneity: Tau² = 1.33; Chi² = 27.37, df = 9 (P = 0.001); I² = 67%								
Test for overall effect: Z = 1.70 (P = 0.09)								
5.4.2 Non-overweight only								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.5. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 5: Absolute change in Body Weight (Diabetes subgroups) (Kg)

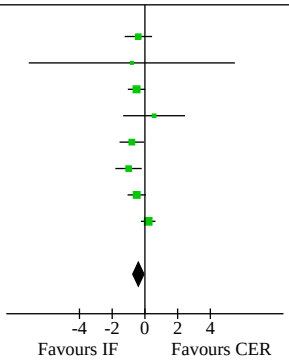
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
5.5.1 Diabetics								
Carter 2018	-6.8	6.7	70	-5	6.5	67	100.0%	-1.80 [-4.01 , 0.41]
Subtotal (95% CI)			**70**			**67**	**100.0%**	**-1.80 [-4.01 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.60 (P = 0.11)								
5.5.2 Non-diabetics								
Catenacci 2016	-8.2	3.24	13	-7.1	3.46	12	7.3%	-1.10 [-3.73 , 1.53]
Harvie 2011	-5.89	3.67	45	-4.87	3.29	47	12.0%	-1.02 [-2.45 , 0.41]
Harvie 2013	-5.79	3.93	33	-4.56	3.86	33	10.0%	-1.23 [-3.11 , 0.65]
Hutchison 2019 (1)	-2.7	0.5	22	-3.9	1.96	12	13.4%	1.20 [0.07 , 2.33]
Hutchison 2019 (2)	-5.4	2.35	22	-3.9	1.96	12	11.8%	-1.50 [-2.98 , -0.02]
Parvaresh 2019	-4.1	3.65	35	-1.7	1.49	34	12.6%	-2.40 [-3.71 , -1.09]
Pinto 2019	-1.8	2.32	21	-3	3.98	22	9.8%	1.20 [-0.74 , 3.14]
Schubel 2018	-6.5	4.8	49	-4.7	3.5	49	11.0%	-1.80 [-3.46 , -0.14]
Sundfor 2018	-7.1	3.7	54	-7.4	3.8	58	12.2%	0.30 [-1.09 , 1.69]
Subtotal (95% CI)			**294**			**279**	**100.0%**	**-0.69 [-1.63 , 0.26]**
Heterogeneity: Tau² = 1.41; Chi² = 26.29, df = 8 (P = 0.0009); I² = 70%								
Test for overall effect: Z = 1.42 (P = 0.16)								
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.36), I² = 0%								



Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.6. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 6: Absolute change in BMI (kg/m²)

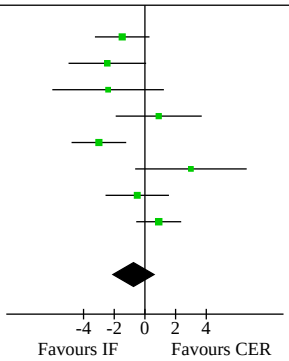
Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-2.3	2.5	70	-1.9	2.5	67	11.4%	-0.40 [-1.24 , 0.44]
Catenacci 2016	-3.2	11.54	13	-2.4	1.04	12	0.3%	-0.80 [-7.10 , 5.50]
Harvie 2011	-2.26	1.41	45	-1.75	1.19	47	19.2%	-0.51 [-1.04 , 0.02]
Harvie 2013	-2.14	1.41	33	-2.7	5.36	33	3.0%	0.56 [-1.33 , 2.45]
Parvaresh 2019	-1.6	2.07	35	-0.8	0.9	34	13.2%	-0.80 [-1.55 , -0.05]
Pinto 2019	-1.4	1.81	21	-0.4	0.53	22	12.0%	-1.00 [-1.81 , -0.19]
Schubel 2018	-2.1	1.6	49	-1.6	1.2	49	18.4%	-0.50 [-1.06 , 0.06]
Sundfor 2018	-2.3	1.1	54	-2.5	1.3	58	22.5%	0.20 [-0.24 , 0.64]
Total (95% CI)			**320**			**322**	**100.0%**	**-0.40 [-0.74 , -0.06]**
Heterogeneity: Tau² = 0.08; Chi² = 11.30, df = 7 (P = 0.13); I² = 38%								
Test for overall effect: Z = 2.31 (P = 0.02)								
Test for subgroup differences: Not applicable								



Analysis 5.7. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 7: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-5.79	4.33	45	-4.31	4.37	47	15.2%	-1.48 [-3.26 , 0.30]
Harvie 2013	-6.16	5.87	33	-3.71	4.52	33	11.9%	-2.45 [-4.98 , 0.08]
Hutchison 2019 (1)	-7.6	5.63	22	-5.2	4.9	12	8.2%	-2.40 [-6.04 , 1.24]
Hutchison 2019 (2)	-4.3	1	22	-5.2	4.9	12	10.9%	0.90 [-1.90 , 3.70]
Parvaresh 2019	-4	4.09	35	-1	3.44	34	15.2%	-3.00 [-4.78 , -1.22]
Pinto 2019	-3	3.45	21	-6	7.95	22	8.2%	3.00 [-0.63 , 6.63]
Schubel 2018	-5.3	6	49	-4.8	4.3	49	13.9%	-0.50 [-2.57 , 1.57]
Sundfor 2018	-6.9	3.6	54	-7.8	4.3	58	16.6%	0.90 [-0.57 , 2.37]
Total (95% CI)			**281**			**267**	**100.0%**	**-0.74 [-2.08 , 0.59]**

Heterogeneity: Tau² = 2.24; Chi² = 19.65, df = 7 (P = 0.006); I² = 64%
Test for overall effect: Z = 1.09 (P = 0.27)
Test for subgroup differences: Not applicable

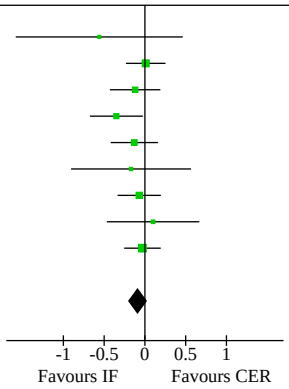


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 5.8. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 8: Absolute change in total cholesterol (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-1.76	1.3	13	-1.2	1.31	12	1.1%	-0.56 [-1.58 , 0.46]
Harvie 2011	-0.41	0.71	45	-0.42	0.44	47	19.1%	0.01 [-0.23 , 0.25]
Harvie 2013	-0.26	0.55	33	-0.14	0.72	33	11.8%	-0.12 [-0.43 , 0.19]
Hutchison 2019 (1)	-0.59	0.38	22	-0.24	0.5	12	10.7%	-0.35 [-0.67 , -0.03]
Hutchison 2019 (1)	-0.37	0.15	22	-0.24	0.5	12	13.4%	-0.13 [-0.42 , 0.16]
Parvaresh 2019	-0.61	1.36	35	-0.44	1.73	34	2.1%	-0.17 [-0.91 , 0.57]
Pinto 2019	-0.15	0.6	21	-0.08	0.16	22	16.0%	-0.07 [-0.34 , 0.20]
Schubel 2018	-1.1	1.7	49	-1.2	1.1	49	3.5%	0.10 [-0.47 , 0.67]
Sundfor 2018	-0.21	0.5	54	-0.18	0.7	58	22.4%	-0.03 [-0.25 , 0.19]
Total (95% CI)			**294**			**279**	**100.0%**	**-0.09 [-0.20 , 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 4.81, df = 8 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable

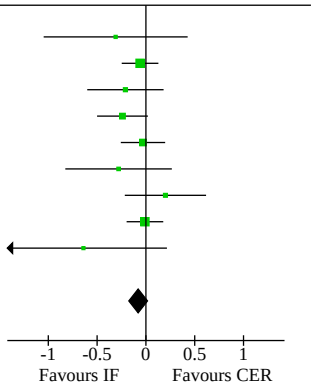


Footnotes
(1) Hutchison 2019 IF70 arm

Analysis 5.9. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 9: Absolute change in LDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-1.25	0.94	13	-0.94	0.94	12	1.7%	-0.31 [-1.05 , 0.43]
Harvie 2011	-0.26	0.55	45	-0.2	0.34	47	25.8%	-0.06 [-0.25 , 0.13]
Harvie 2013	-0.14	0.56	33	0.07	1	33	6.0%	-0.21 [-0.60 , 0.18]
Hutchison 2019 (1)	-0.37	0.33	22	-0.13	0.39	12	13.5%	-0.24 [-0.50 , 0.02]
Hutchison 2019 (2)	-0.16	0.13	22	-0.13	0.39	12	17.6%	-0.03 [-0.26 , 0.20]
Parvaresh 2019	-0.28	1.12	35	0	1.19	34	3.1%	-0.28 [-0.83 , 0.27]
Schubel 2018	-0.4	1.1	49	-0.6	1	49	5.3%	0.20 [-0.22 , 0.62]
Sundfor 2018	-0.19	0.4	54	-0.18	0.6	58	25.9%	-0.01 [-0.20 , 0.18]
Varady 2011	-1.25	1.21	15	-0.61	1.18	15	1.2%	-0.64 [-1.50 , 0.22]
Total (95% CI)			**288**			**272**	**100.0%**	**-0.08 [-0.17 , 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 8 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable

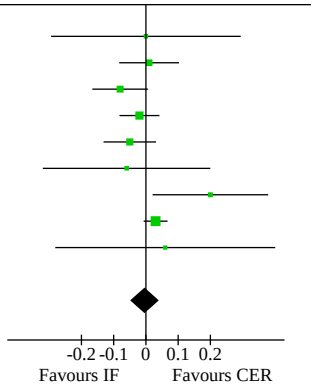


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 5.10. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 10: Absolute change in HDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-0.23	0.38	13	-0.23	0.37	12	1.9%	0.00 [-0.29 , 0.29]
Harvie 2011	-0.1	0.25	45	-0.11	0.2	47	12.8%	0.01 [-0.08 , 0.10]
Harvie 2013	-0.02	0.21	33	0.06	0.14	33	14.0%	-0.08 [-0.17 , 0.01]
Hutchison 2019 (1)	-0.07	0.06	22	-0.05	0.1	12	19.9%	-0.02 [-0.08 , 0.04]
Hutchison 2019 (2)	-0.1	0.14	22	-0.05	0.1	12	15.0%	-0.05 [-0.13 , 0.03]
Parvaresh 2019	-0.06	0.58	35	0	0.52	34	2.4%	-0.06 [-0.32 , 0.20]
Schubel 2018	-0.2	0.5	49	-0.4	0.4	49	4.6%	0.20 [0.02 , 0.38]
Sundfor 2018	0.02	0.1	54	-0.01	0.1	58	28.0%	0.03 [-0.01 , 0.07]
Varady 2011	0.06	0.55	15	0	0.39	15	1.4%	0.06 [-0.28 , 0.40]
Total (95% CI)			**288**			**272**	**100.0%**	**-0.00 [-0.05 , 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 12.76, df = 8 (P = 0.12); I² = 37%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable

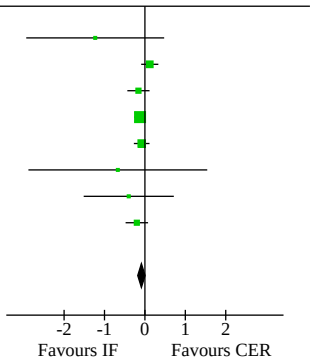


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.11. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 11: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-1.39	2.18	13	-0.16	2.17	12	0.3%	-1.23 [-2.94 , 0.48]
Harvie 2011	-0.12	0.57	45	-0.24	0.46	47	18.0%	0.12 [-0.09 , 0.33]
Harvie 2013	-0.2	0.43	33	-0.04	0.68	33	10.8%	-0.16 [-0.43 , 0.11]
Hutchison 2019 (1)	-0.28	0.12	22	-0.16	0.24	12	38.0%	-0.12 [-0.26 , 0.02]
Hutchison 2019 (2)	-0.24	0.33	22	-0.16	0.24	12	21.6%	-0.08 [-0.27 , 0.11]
Parvaresh 2019	-2.89	5.03	35	-2.22	4.33	34	0.2%	-0.67 [-2.88 , 1.54]
Schubel 2018	-1.7	3.5	49	-1.3	1.9	49	0.7%	-0.40 [-1.52 , 0.72]
Sundfor 2018	-0.39	0.7	54	-0.19	0.8	58	10.5%	-0.20 [-0.48 , 0.08]
Total (95% CI)			**273**			**257**	**100.0%**	**-0.09 [-0.18 , 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 7 (P = 0.42); I² = 1%
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Not applicable

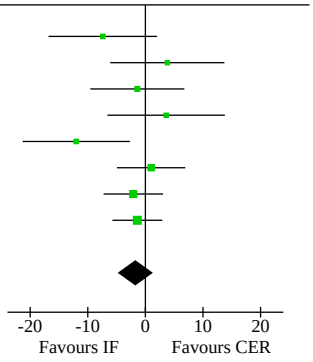


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.12. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 12: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-6.27	11.76	45	1.12	30.68	47	7.9%	-7.39 [-16.81 , 2.03]
Harvie 2013	-4.91	24.66	33	-8.72	15.34	33	7.2%	3.81 [-6.10 , 13.72]
Hutchison 2019 (1)	-5.6	3.4	22	-4.2	14.21	12	10.0%	-1.40 [-9.56 , 6.76]
Hutchison 2019 (2)	-0.6	15.01	22	-4.2	14.21	12	6.9%	3.60 [-6.60 , 13.80]
Parvaresh 2019	-13	24	35	-1	14.42	34	8.0%	-12.00 [-21.31 , -2.69]
Pinto 2019	-2	7.46	21	-3	12	22	16.2%	1.00 [-4.94 , 6.94]
Schubel 2018	-6.8	16.2	49	-4.7	8.8	49	19.6%	-2.10 [-7.26 , 3.06]
Sundfor 2018	-6.4	12.6	54	-5	10.6	58	24.2%	-1.40 [-5.73 , 2.93]
Total (95% CI)			**281**			**267**	**100.0%**	**-1.75 [-4.61 , 1.11]**

Heterogeneity: Tau² = 3.91; Chi² = 9.17, df = 7 (P = 0.24); I² = 24%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable

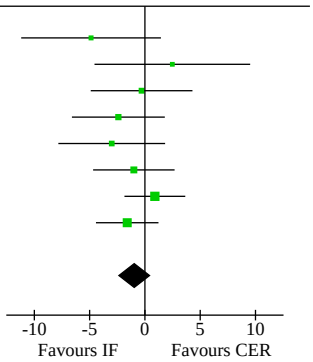


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.13. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 13: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-4.64	8.61	45	0.23	20.27	47	4.8%	-4.87 [-11.19 , 1.45]
Harvie 2013	0.59	17.87	33	-1.89	10.31	33	3.9%	2.48 [-4.56 , 9.52]
Hutchison 2019 (1)	-0.4	4.7	22	-0.1	7.35	12	9.0%	-0.30 [-4.90 , 4.30]
Hutchison 2019 (2)	-2.5	1.4	22	-0.1	7.35	12	10.8%	-2.40 [-6.60 , 1.80]
Parvaresh 2019	-8	7.72	35	-5	12.18	34	8.2%	-3.00 [-7.83 , 1.83]
Pinto 2019	-4	6.31	21	-3	6	22	14.1%	-1.00 [-4.68 , 2.68]
Schubel 2018	-2.6	7.7	49	-3.5	6.1	49	25.3%	0.90 [-1.85 , 3.65]
Sundfor 2018	-6.4	8	54	-4.8	7.2	58	23.9%	-1.60 [-4.43 , 1.23]
Total (95% CI)			**281**			**267**	**100.0%**	**-0.97 [-2.35 , 0.42]**

Heterogeneity: Tau² = 0.00; Chi² = 5.56, df = 7 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

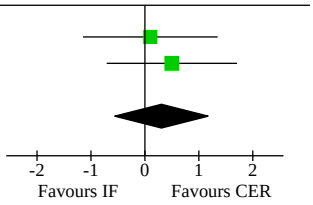


Footnotes
(1) Hutchison 2019 IF70 arm
(2) Hutchison 2019 IF100 arm

Analysis 5.14. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 14: Absolute change in CRP (mg/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-1	2.5	45	-1.1	3.54	47	48.4%	0.10 [-1.15 , 1.35]
Schubel 2018	-0.1	3.1	49	-0.6	3	49	51.6%	0.50 [-0.71 , 1.71]
Total (95% CI)			**94**			**96**	**100.0%**	**0.31 [-0.56 , 1.17]**

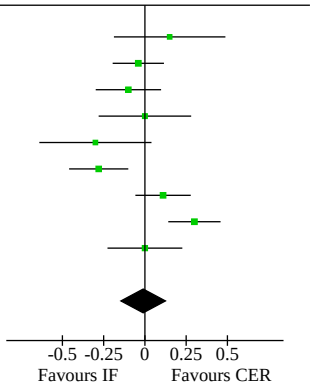
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 5.15. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 15: Absolute change in Glucose (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.33	0.42	13	0.18	0.44	12	8.0%	0.15 [-0.19 , 0.49]
Harvie 2011	-0.1	0.36	45	-0.06	0.4	47	13.2%	-0.04 [-0.20 , 0.12]
Harvie 2013	-0.08	0.39	33	0.02	0.43	33	11.9%	-0.10 [-0.30 , 0.10]
Hutchison 2019 (1)	0.1	0.1	22	0.1	0.49	12	9.5%	0.00 [-0.28 , 0.28]
Hutchison 2019 (2)	-0.2	0.47	22	0.1	0.49	12	7.9%	-0.30 [-0.64 , 0.04]
Parvaresh 2019	-0.28	0.38	35	0	0.38	34	12.5%	-0.28 [-0.46 , -0.10]
Pinto 2019	-0.04	0.34	21	-0.15	0.2	22	12.8%	0.11 [-0.06 , 0.28]
Schubel 2018	-0.1	0.4	49	-0.4	0.4	49	13.1%	0.30 [0.14 , 0.46]
Sundfor 2018	-0.3	0.7	54	-0.3	0.5	58	11.0%	0.00 [-0.23 , 0.23]
Total (95% CI)			**294**			**279**	**100.0%**	**-0.01 [-0.15 , 0.12]**

Heterogeneity: Tau² = 0.03; Chi² = 29.74, df = 8 (P = 0.0002); I² = 73%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable

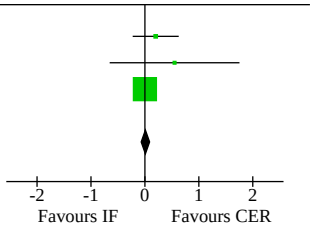


Footnotes
(1) Hutchison 2019 IF100 arm
(2) Hutchison 2019 IF70 arm

Analysis 5.16. Comparison 5: Sensitivity analysis; published data: IF vs CER (Short term), Outcome 16: Absolute change in HbA1c (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Carter 2018	-0.3	0.8	70	-0.5	1.6	67	3.3%	0.20 [-0.23 , 0.63]
Harvie 2013	0.34	2.63	33	-0.21	2.35	33	0.4%	0.55 [-0.65 , 1.75]
Schubel 2018	0	0.2	49	0	0.2	49	96.3%	0.00 [-0.08 , 0.08]
Total (95% CI)			**152**			**149**	**100.0%**	**0.01 [-0.07 , 0.09]**

Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Comparison 6. Sensitivity analysis: published data: IF vs CER (Medium term)

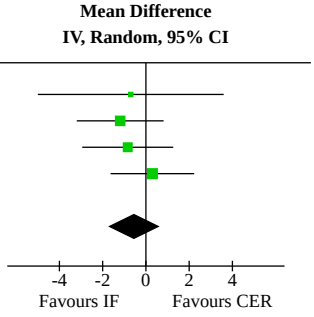
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Absolute change in Body weight (kg)	4	279	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.68, 0.56]
6.2 Absolute change in BMI (kg/m^2)	4	279	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.58, 0.29]
6.3 Absolute change in waist circumference (cm)	3	258	Mean Difference (IV, Random, 95% CI)	-0.66 [-2.55, 1.23]
6.4 Absolute change in total cholesterol (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.17, 0.10]
6.5 Absolute change in LDL (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6 Absolute change in HDL (mmol/L)	3	258	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.07, 0.07]
6.7 Absolute change in TG (mmol/L)	4	279	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.16, 0.12]
6.8 Absolute change in SBP (mmHg)	3	258	Mean Difference (IV, Random, 95% CI)	1.37 [-4.98, 7.72]
6.9 Absolute change in DBP (mmHg)	3	258	Mean Difference (IV, Random, 95% CI)	-1.00 [-4.67, 2.67]
6.10 Absolute change in glucose (mmol/L)	4	279	Mean Difference (IV, Random, 95% CI)	0.01 [-0.10, 0.11]

Analysis 6.1. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 1: Absolute change in Body weight (kg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-5.7	4.97	11	-5	5.06	10	6.8%	-0.70 [-5.00 , 3.60]
Harvie 2011	-7.58	5.19	42	-6.39	4.38	47	31.2%	-1.19 [-3.20 , 0.82]
Harvie 2013	-6.06	4.72	33	-5.22	3.59	27	28.4%	-0.84 [-2.94 , 1.26]
Sundfor 2018	-9.1	5	53	-9.4	5.3	56	33.6%	0.30 [-1.63 , 2.23]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.56 [-1.68 , 0.56]**

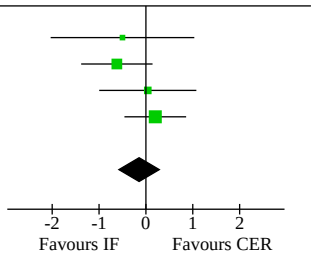
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 2: Absolute change in BMI (kg/m²)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	-2.2	1.66	11	-1.7	1.9	10	7.9%	-0.50 [-2.03 , 1.03]
Harvie 2011	-2.92	2.02	42	-2.3	1.59	47	32.0%	-0.62 [-1.38 , 0.14]
Harvie 2013	-1.95	2.62	33	-1.99	1.39	27	17.3%	0.04 [-1.00 , 1.08]
Sundfor 2018	-3	1.6	53	-3.2	1.9	56	42.8%	0.20 [-0.46 , 0.86]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.15 [-0.58 , 0.29]**

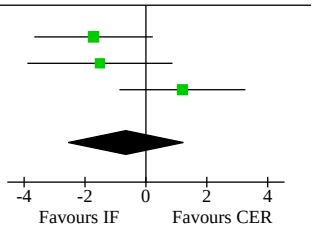
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 3: Absolute change in waist circumference (cm)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-7.39	5.4	42	-5.67	3.7	47	35.8%	-1.72 [-3.67 , 0.23]
Harvie 2013	-6.64	5	33	-5.13	4.41	27	30.1%	-1.51 [-3.89 , 0.87]
Sundfor 2018	-8	5.6	53	-9.2	5.4	56	34.1%	1.20 [-0.87 , 3.27]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.66 [-2.55 , 1.23]**

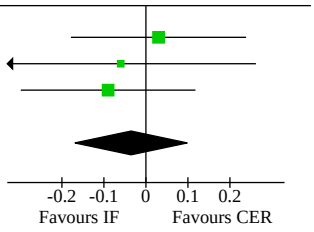
Heterogeneity: Tau² = 1.61; Chi² = 4.74, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 4: Absolute change in total cholesterol (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-0.41	0.55	42	-0.44	0.44	47	41.2%	0.03 [-0.18 , 0.24]
Harvie 2013	-0.21	0.57	33	-0.15	0.68	27	17.3%	-0.06 [-0.38 , 0.26]
Sundfor 2018	-0.16	0.6	53	-0.07	0.5	56	41.5%	-0.09 [-0.30 , 0.12]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.04 [-0.17 , 0.10]**

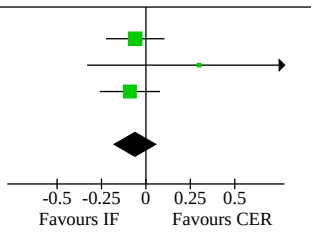
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 5: Absolute change in LDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-0.3	0.44	42	-0.24	0.34	47	49.7%	-0.06 [-0.22 , 0.10]
Harvie 2013	-0.1	0.54	33	-0.4	1.6	27	3.4%	0.30 [-0.33 , 0.93]
Sundfor 2018	-0.16	0.4	53	-0.07	0.5	56	46.9%	-0.09 [-0.26 , 0.08]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.06 [-0.18 , 0.05]**

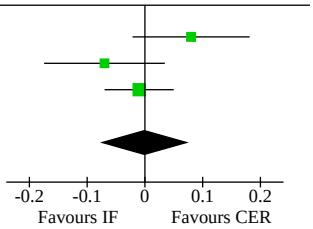
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 6: Absolute change in HDL (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	0	0.27	42	-0.08	0.21	47	28.4%	0.08 [-0.02 , 0.18]
Harvie 2013	-0.04	0.25	33	0.03	0.16	27	27.4%	-0.07 [-0.17 , 0.03]
Sundfor 2018	0.05	0.2	53	0.06	0.1	56	44.2%	-0.01 [-0.07 , 0.05]
Total (95% CI)			**128**			**130**	**100.0%**	**-0.00 [-0.07 , 0.07]**

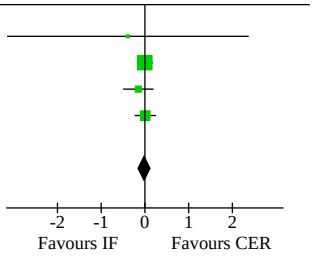
Heterogeneity: Tau² = 0.00; Chi² = 4.21, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 6.7. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 7: Absolute change in TG (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.28	3.46	11	0.67	3	10	0.2%	-0.39 [-3.15 , 2.37]
Harvie 2011	-0.25	0.42	42	-0.25	0.47	47	53.9%	0.00 [-0.18 , 0.18]
Harvie 2013	-0.14	0.34	33	0.01	0.87	27	15.2%	-0.15 [-0.50 , 0.20]
Sundfor 2018	-0.35	0.7	53	-0.36	0.6	56	30.6%	0.01 [-0.24 , 0.26]
Total (95% CI)			**139**			**140**	**100.0%**	**-0.02 [-0.16 , 0.12]**

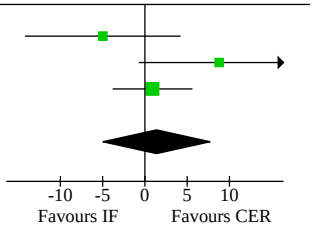
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 6.8. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 8: Absolute change in SBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-5.38	13.69	42	-0.4	28.75	47	27.1%	-4.98 [-14.18 , 4.22]
Harvie 2013	-2.51	23.16	33	-11.28	13.87	27	26.2%	8.77 [-0.71 , 18.25]
Sundfor 2018	-4.9	14.1	53	-5.8	10.7	56	46.7%	0.90 [-3.82 , 5.62]
Total (95% CI)			**128**			**130**	**100.0%**	**1.37 [-4.98 , 7.72]**

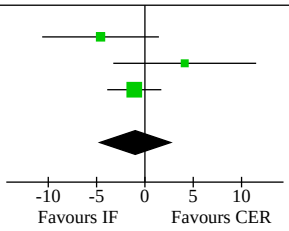
Heterogeneity: Tau² = 16.71; Chi² = 4.20, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 6.9. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 9: Absolute change in DBP (mmHg)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Harvie 2011	-4.95	8.6	42	-0.36	19.06	47	25.5%	-4.59 [-10.63 , 1.45]
Harvie 2013	0.65	18.83	33	-3.47	9.69	27	19.0%	4.12 [-3.27 , 11.51]
Sundfor 2018	-5.8	7.5	53	-4.7	7.4	56	55.6%	-1.10 [-3.90 , 1.70]
Total (95% CI)			**128**			**130**	**100.0%**	**-1.00 [-4.67 , 2.67]**

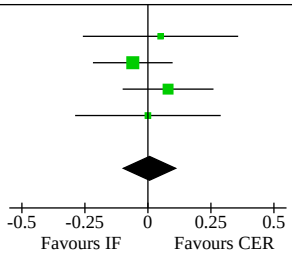
Heterogeneity: Tau² = 4.27; Chi² = 3.20, df = 2 (P = 0.20); I² = 37%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 6.10. Comparison 6: Sensitivity analysis: published data: IF vs CER (Medium term), Outcome 10: Absolute change in glucose (mmol/L)

Study or Subgroup	IF Mean	IF SD	IF Total	CER Mean	CER SD	CER Total	Weight	Mean Difference IV, Random, 95% CI
Catenacci 2016	0.14	0.39	11	0.09	0.33	10	11.3%	0.05 [-0.26 , 0.36]
Harvie 2011	-0.11	0.29	42	-0.05	0.46	47	42.9%	-0.06 [-0.22 , 0.10]
Harvie 2013	-0.05	0.32	33	-0.13	0.38	27	33.0%	0.08 [-0.10 , 0.26]
Sundfor 2018	-0.2	0.9	53	-0.2	0.6	56	12.8%	0.00 [-0.29 , 0.29]
Total (95% CI)			**139**			**140**	**100.0%**	**0.01 [-0.10 , 0.11]**

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

CENTRAL

#1MeSH descriptor: [Fasting] this term only
#2(intermittent* near/3 fast*):ti,ab
#3(fast* near/3 diet*).ti,ab
#4(alternat* near/3 fast*):ti,ab
#5(modified near/2 fast*):ti,ab
#6(food next (abstinence or fast*)):ti,ab
#7((diet* or food) near/2 restricti*):ti,ab
#8time restricted feed*:ti,ab
#9time restricted fast*:ti,ab
#10whole day fast*:ti,ab
#11food tim*:ti,ab
#12(Ramadan or Ramadhan):ti,ab
#13#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

MEDLINE (Ovid)

1 Fasting/ (34093)
2 Fasting.tw. (103717)
3 (intermittent* adj3 fast*).tw. (520)
4 (fast* adj3 diet*).tw. (1888)
5 (alternat* adj3 fast*).tw. (1362)
6 (modified adj2 fast*).tw. (588)
7 (food adj (abstinence or fast*)).tw. (85)

8 ((diet* or food) adj2 restricti*).tw. (12809)
9 time restricted feed*.tw. (118)
10 time restricted fast*.tw. (1)
11 whole day fast*.tw. (1)
12 food tim*.tw. (81)
13 (Ramadan or Ramadhan).tw. (1189)
14 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 (130713)
15 randomized controlled trial.pt. (488336)
16 controlled clinical trial.pt. (93253)
17 randomized.ab. (453148)
18 placebo.ab. (200411)
19 clinical trials as topic.sh. (188167)
20 randomly.ab. (317270)
21 trial.ti. (203972)
22 15 or 16 or 17 or 18 or 19 or 20 or 21 (1235613)
23 exp animals/ not humans.sh. (4613577)
24 22 not 23 (1136377)
25 14 and 24 (19281)

Embase (Ovid)

1 fasting/
2 Fasting.tw.
3 (intermittent* adj3 fast*).tw.
4 (fast* adj3 diet*).tw.
5 (alternat* adj3 fast*).tw.
6 (modified adj2 fast*).tw.
7 (food adj (abstinence or fast*)).tw.
8 ((diet* or food) adj2 restricti*).tw.
9 time restricted feed*.tw.
10 time restricted fast*.tw.
11 whole day fast*.tw.
12 food tim*.tw.
13 (Ramadan or Ramadhan).tw.
14 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
15 random$.tw.
16 factorial$.tw.
17 crossover$.tw.
18 cross over$.tw.
19 cross-over$.tw.
20 placebo$.tw.
21 (doubl$ adj blind$).tw.
22 (singl$ adj blind$).tw.
23 assign$.tw.
24 allocat$.tw.
25 volunteer$.tw.
26 crossover procedure/
27 double blind procedure/
28 randomized controlled trial/
29 single blind procedure/
30 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 or 29
31 (animal/ or nonhuman/) not human/
32 30 not 31
33 14 and 32
34 limit 33 to embase

Clinical trials registers

"intermittent fasting" OR "time restricted feed" OR "alternate day fast"

WHAT'S NEW

Date	Event	Description
25 February 2021	Amended	The conclusion in the abstract section has been reworded to better reflect the results of this review.

HISTORY

Protocol first published: Issue 11, 2019
Review first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

MA, HE, OM, SZ, MF, AD, AS and KS all contributed to the search, data analysis, writing and drafting of this review.

DECLARATIONS OF INTEREST

MA, HE, OM, SZ, MF, AD, AS and KS all state that there is no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Blood Glucose [metabolism]; Body Weight; Caloric Restriction [methods]; Cardiovascular Diseases [*prevention & control]; *Fasting [adverse effects]; Feeding Behavior; Quality of Life; Randomized Controlled Trials as Topic [statistics & numerical data]; Time Factors

MeSH check words

Adult; Humans