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Interventions for weight reduction in obesity to improve survival in women with endometrial cancer (Review)

Agnew H, Kitson S, Crosbie EJ

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[Intervention Review]

Interventions for weight reduction in obesity to improve survival in women with endometrial cancer

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ABSTRACT

Background

This is an updated version of the original Cochrane Review published in Issue 2, 2018.

Diagnoses of endometrial cancer are increasing secondary to the rising prevalence of obesity. Obesity plays an important role in promoting the development of endometrial cancer, by inducing a state of unopposed oestrogen excess, insulin resistance and inflammation. It also affects treatment, increasing the risk of surgical complications and the complexity of radiotherapy planning, and may additionally impact on subsequent survival. Weight-loss interventions have been associated with improvements in breast and colorectal cancer-specific survival, as well as a reduction in the risk of cardiovascular disease, which is a frequent cause of death in endometrial cancer survivors.

Objectives

To evaluate the benefits and harm of weight-loss interventions, in addition to standard management, on overall survival and the frequency of adverse events in women with endometrial cancer who are overweight or obese compared with any other intervention, usual care, or placebo.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was from January 2018 to June 2022 (original review searched from inception to January 2018).

Selection criteria

We included randomised controlled trials (RCTs) of interventions to facilitate weight loss in women with endometrial cancer who are overweight or obese undergoing treatment for, or previously treated for, endometrial cancer compared with any other intervention, usual care, or placebo.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. overall survival and 2. frequency of adverse events. Our secondary outcomes were 3. recurrence-free survival, 4. cancer-specific survival, 5. weight loss, 6. cardiovascular and metabolic event frequency and 7. quality of Life. We used GRADE to assess certainty of evidence. We contacted study authors to obtain missing data, including details of any adverse events.

Main results

We identified nine new RCTs and combined these with the three RCTs identified in the original review. Seven studies are ongoing.

The 12 RCTs randomised 610 women with endometrial cancer who were overweight or obese. All studies compared combined behavioural and lifestyle interventions designed to facilitate weight loss through dietary modification and increased physical activity with usual care. Included RCTs were of low or very low quality, due to high risk of bias by failing to blind participants, personnel and outcome assessors, and significant loss to follow-up (withdrawal rate up to 28% and missing data up to 65%, largely due to the effects of the COVID-19 pandemic). Importantly, the short duration of follow-up limits the directness of the evidence in evaluating the impact of these interventions on any of the survival and other longer-term outcomes.

Combined behaviour and lifestyle interventions were not associated with improved overall survival compared with usual care at 24 months (risk ratio (RR) mortality, 0.23, 95% confidence interval (CI) 0.01 to 4.55, P = 0.34; 1 RCT, 37 participants; very low-certainty evidence). There was no evidence that such interventions were associated with improvements in cancer-specific survival or cardiovascular event frequency as the studies reported no cancer-related deaths, myocardial infarctions or strokes, and there was only one episode of congestive heart failure at six months (RR 3.47, 95% CI 0.15 to 82.21; P = 0.44, 5 RCTs, 211 participants; low-certainty evidence). Only one RCT reported recurrence-free survival; however, there were no events. Combined behaviour and lifestyle interventions were not associated with significant weight loss at either six or 12 months compared with usual care (at six months: mean difference (MD) −1.39 kg, 95% CI −4.04 to 1.26; P = 0.30, I^2 = 32%; 5 RCTs, 209 participants; low-certainty evidence). Combined behaviour and lifestyle interventions were not associated with increased quality of life, when measured using 12-item Short Form (SF-12) Physical Health questionnaire, SF-12 Mental Health questionnaire, Cancer-Related Body Image Scale, Patient Health Questionnaire 9-Item Version or Functional Assessment of Cancer Therapy – General (FACT-G) at 12 months when compared with usual care (FACT-G: MD 2.77, 95% CI −0.65 to 6.20; P = 0.11, I^2 = 0%; 2 RCTs, 89 participants; very low-certainty evidence). The trials reported no serious adverse events related to weight loss interventions, for example hospitalisation or deaths. It is uncertain whether lifestyle and behavioural interventions were associated with a higher or lower risk of musculoskeletal symptoms (RR 19.03, 95% CI 1.17 to 310.52; P = 0.04; 8 RCTs, 315 participants; very low-certainty evidence; note: 7 studies reported musculoskeletal symptoms but recorded 0 events in both groups. Thus, the RR and CIs were calculated from 1 study rather than 8).

Authors' conclusions

The inclusion of new relevant studies has not changed the conclusions of this review.

There is currently insufficient high-quality evidence to determine the effect of combined lifestyle and behavioural interventions on survival, quality of life or significant weight loss in women with a history of endometrial cancer who are overweight or obese compared to those receiving usual care. The limited evidence suggests that there is little or no serious or life-threatening adverse effects due to these interventions, and it is uncertain if musculoskeletal problems were increased, as only one out of eight studies reporting this outcome had any events. Our conclusion is based on low- and very low-certainty evidence from a small number of trials and few women. Therefore, we have very little confidence in the evidence: the true effect of weight-loss interventions in women with endometrial cancer and obesity is currently unknown.

Further methodologically rigorous, adequately powered RCTs are required with follow-up of five to 10 years of duration. These should focus on the effects of varying dietary modification regimens, and pharmacological treatments associated with weight loss and bariatric surgery on survival, quality of life, weight loss and adverse events.

PLAIN LANGUAGE SUMMARY

Weight-loss interventions in endometrial cancer survivors

Background

Endometrial or womb cancer is a common cancer in women and the number of cases is rising. This is due, in part, to increasing levels of obesity, which is a major risk factor for the disease. Whilst survival following endometrial cancer is generally excellent if diagnosed early, affected women are more likely to die early due to an increased risk of heart attack and stroke, and to have poorer quality of life.

What did we want to find out?

We wanted to assess the evidence for weight-loss interventions in endometrial cancer survivors who are overweight or obese to determine whether they were of benefit compared with usual care.

What did we do?

We searched medical databases for well-designed clinical trials (called randomised controlled trials) of interventions (treatments) to facilitate weight loss in women with endometrial cancer who were overweight or obese undergoing treatment for, or previously treated for, endometrial cancer compared with any other intervention, usual care, or placebo (dummy treatment).

What did we find?

We found 12 randomised controlled trials where women were allocated at random to receive one of several interventions. They included 610 women with endometrial cancer who were overweight or obese. The trials were conducted in the US, Australia and New Zealand. All compared lifestyle advice (diet and exercise) plus self-help techniques (to encourage adherence to the advice) with usual care.

Key results

Within the limitations of the included studies, we found no benefit for endometrial cancer survivors who were overweight or obese from receiving lifestyle advice in terms of survival, cardiovascular events (for example, heart attacks or strokes) or quality of life, though such interventions were not associated with significant or serious harms to participants. It is unclear if these interventions increase musculoskeletal symptoms (for example, knee and leg pain and muscle weakness), as only one out of eight studies looking at these symptoms reported any events. Whilst some women lost weight with these interventions, others did not, meaning that overall there was little or no benefit.

What are the limitations of the evidence?

The quality of included studies was low or very low and all were small in terms of the number of participants with very short follow-up times, and not designed to specifically look at the effect of their intervention on survival or other longer-term outcomes. Additional high-quality studies, with appropriate durations of follow-up, are required in this field. There are seven ongoing trials that may add to our knowledge.

How up to date is this evidence?

The evidence is current to June 2022.

Summary of findings 1. Summary of findings table - Lifestyle intervention versus usual care compared to placebo for weight reduction in obesity to improve survival in women with endometrial cancer

Lifestyle intervention versus usual care compared to placebo for weight reduction in obesity to improve survival in women with endometrial cancer

Patient or population: weight reduction in obesity to improve survival in women with endometrial cancer
Setting: hospitals in the USA, Australia and New Zealand
Intervention: lifestyle intervention versus usual care
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with lifestyle intervention versus usual care				
Overall survival (12 months)	Not pooled	Not pooled	Not pooled	(2 RCTs)	⊕⊕⊖⊖ Low[a,b,c]	Unable to calculate RR for mortality as 0 deaths reported in either arm of the studies.
Overall survival (24 months)	100 per 1000	**23 per 1000** (1 to 455)	**RR 0.23** (0.01 to 4.55)	37 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]	RR for mortality calculated.
Adverse events – musculoskeletal	0 per 1000	**0 per 1000** (0 to 0)	**RR 19.03** (1.17 to 310.52)	315 (8 RCTs)	⊕⊖⊖⊖ Very low[a,c,e,f]	Unable to calculate assumed and corresponding risk as 0 events in control groups.
Cancer-specific survival (6 months)	Not pooled	Not pooled	Not pooled	(5 RCTs)	⊕⊕⊖⊖ Low[a,c,g]	Unable to calculate RR for mortality as 0 cancer-related deaths reported in either arm of the studies.
Weight loss (6 months)	The mean weight loss (6 months) was **-1.27** kg[h]	MD **1.39 kg lower** (4.04 lower to 1.26 higher)	-	209 (5 RCTs)	⊕⊕⊖⊖ Low[a,f,g,i]	
Cardiovascular and metabolic event frequency (6 months)	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.47** (0.15 to 82.21)	211 (5 RCTs)	⊕⊕⊖⊖ Low[a,c,f,g]	Unable to calculate assumed and corresponding risk as 0 events in control groups.
Quality of life: FACT-G (12 months)	The mean quality of life: FACT-G (12	MD **2.77 units higher** (0.65 lower to 6.2 higher)	-	89 (2 RCTs)	⊕⊖⊖⊖ Very low[b,k]	FACT-G: Functional Assessment of Cancer Therapy – General

					months) ranged from **0 to +2** units[j]

*__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; **MD:** mean difference; **RR:** risk ratio

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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_435806052766907056.

[a] Although participants, personnel and outcome assessors were not blinded to treatment group allocation this is unlikely to affect this specific outcome measure.
[b] Downgraded one level as included study at high risk of attrition bias due to incomplete outcome reporting.
[c] Downgraded one level due to imprecision as low/no event number and wide confidence intervals.
[d] Downgraded one level due to indirect results (included study contained two participants who, in addition to receiving the intervention, underwent gastric bypass during follow-up and were included in the final analysis).
[e] Downgraded two levels as one study was at high risk of selection bias with randomisation being unblinded, six studies were at high risk of attrition bias due to incomplete outcome reporting and one study was forced to change the intervention three months into randomisation which required retraining of staff and may have introduced confounding.
[f] One study did not report quality-of-life data. This was not considered to impact on this outcome and, therefore, the study was not downgraded.
[g] Downgraded one level as one study was at high risk of selection bias with randomisation being unblinded and three studies were at high risk of attrition bias due to incomplete outcome reporting.
[h] The assumed (control) risk is the median weight change from baseline among the control groups in the studies.
[i] Downgraded one level due to imprecision as wide confidence intervals in two studies, and the confidence intervals in four studies crossed the line of unity.
[j] The assumed (control) risk is the range of scores for change in quality of life from baseline at 12 months in the control groups from the included studies, presented in preference to the median change score due to significant variation.
[k] Downgraded one level due to high risk of performance and detection bias in all studies. Participants, personnel and outcome assessors were unblinded to treatment group allocation, which may have affected the subjective results.

BACKGROUND

This review is an update of a Cochrane Review previously published in Issue 2, 2018 (see Other published versions of this review).

Description of the condition

Endometrial cancer is a cancer of the lining of the uterus and is the fourth most common cancer in women in high-income countries (Cancer Research UK 2018a). Each year, 9700 new cases of endometrial cancer are diagnosed in the UK, and 65,000 in the USA (Cancer Research UK 2018a; NCI 2022). The incidence of the disease has doubled since the early 2000s, and this trajectory is expected to continue. Endometrial cancer has a generally good prognosis if diagnosed early, with eight out of 10 women still alive five years after diagnosis (Cancer Research UK 2018b; NCI 2022). With more women than ever surviving initial treatment for endometrial cancer, interventions aimed at reducing the risk of disease recurrence and optimising general health in the long term (at least five to 10 years following diagnosis) are required.

Endometrial cancer has a strong link with obesity, and it is this relationship that is thought to underpin the rising number of cases (Renehan 2008). As the percentage of the female population who have obesity has increased, so has the number of diagnoses of endometrial cancer. Three biological mechanisms, or themes, have been proposed to explain this association: unopposed oestrogen, insulin resistance and the presence of an inflammatory milieu (tumour environment).

First, oestrogen is a potent stimulator of endometrial cell proliferation or turnover, an effect that is normally counteracted by progesterone during the menstrual cycle. Unopposed oestrogen occurs in two different scenarios; if progesterone levels are low because of absent ovulation (anovulation), such as in polycystic ovary syndrome, or if oestrogen levels exceed progesterone levels. This occurs in postmenopausal women with obesity, when the ovaries no longer produce progesterone, but testosterone, secreted by the ovaries and adrenal glands, is converted into oestrogen by excess fat (adipose) tissue. Unopposed oestrogen is associated with an increased risk of endometrial cancer. It increases the rate of turnover of endometrial cells and thus the chance of acquiring alterations (mutations) within key genes associated with cancer development. Epidemiological studies have confirmed an increased risk of endometrial cancer in women with high oestrogen levels (Dossus 2013).

Second, insulin is also able to stimulate endometrial cell proliferation, activating many of the pathways shown to be critical to endometrial cancer development. Women with obesity have higher insulin levels than their normal-weight counterparts; excess fat tissue reduces the responsiveness of the body to the effects of insulin, so levels increase to compensate. Women with endometrial cancer have elevated serum insulin levels compared with those without the disease (Dossus 2013).

Third, fat tissue produces inflammatory and carcinogenic (cancer promoting) proteins, hence women with obesity have elevated levels compared with women with normal weight. Any, or all of these proteins, may be responsible for the increase in endometrial cancer rates seen in this population (Dossus 2013).

Obesity plays an important role in promoting the development of endometrial cancer, and potentially affects treatment and subsequent survival. The mainstay of treatment for endometrial cancer is surgery to remove the uterus, cervix, fallopian tubes and ovaries. This may be followed by radiotherapy, chemotherapy or both in some women. Women with obesity often have other health problems, including diabetes and sleep apnoea, which can adversely affect their medical fitness to undergo an operation, and increase the risk of complications associated with surgery and radiotherapy. This may lead to compromises in treatment (Papadia 2006). There is debate in the literature whether being overweight or obese has a negative impact on survival. Results from two large cohort studies, in which groups of women with endometrial cancer were followed up, have suggested that women with obesity, with a body mass index (BMI) of 30 kg/m^2 or more, are twice as likely to die during their survivorship as women of a healthy weight. This increases to a six-fold elevation in risk if their BMI is over 40 kg/m^2 (Calle 2003; Reeves 2007). However, these studies did not take into account differences in the cancer grade (how abnormal the cells appeared), stage (how far the disease had spread) or the type of treatment received.

When women with endometrial cancer received standardised treatment in the context of a randomised controlled trial (RCT), researchers were able to demonstrate that BMI had no impact on the risk of recurrence or overall survival. This was despite a high proportion of women with obesity having poorer general health (Crosbie 2012). The extra deaths observed in women with endometrial cancer and obesity may well be unrelated to their cancer. Women with early-stage disease are twice as likely to die from cardiovascular disease, for example myocardial infarctions and strokes, as they are to die from their endometrial cancer (Ward 2012). Excessive weight gain following diagnosis, and indeed, significant weight loss, may be more important than body mass per se. Data from observational studies demonstrate that large weight gains have a detrimental effect on survival, even after adjustment for other factors that influence prognosis, such as cancer grade and stage (El-Safadi 2012; Matsuo 2016). Therefore, measures taken to reduce bodyweight following treatment for endometrial cancer may be beneficial in improving survival, either by reducing the risk of death from endometrial cancer, or by lowering the chance of dying from other causes, in particular cardiovascular disease.

Description of the intervention

This review focused on interventions designed to promote weight loss for women with endometrial cancer who are overweight or obese as their primary goal, and includes non-pharmacological, pharmacological and surgical interventions. These may be used alone, or in combination. Non-pharmacological or 'lifestyle' interventions are those aimed at reducing nutrient intake and increasing physical activity, through diet and exercise, and may be used alongside psychological interventions such as stress management, stimulus control and problem-solving (addressing barriers to adhering to diet and exercise regimens) to induce permanent changes in behaviour. Pharmacological interventions include drugs that act to either reduce fat absorption, the most widely used of which is orlistat, or suppress appetite. Bariatric surgery encompasses procedures designed to limit food intake (e.g. gastric banding), cause malabsorption (e.g. intestinal bypass), or both (e.g. gastric bypass) (Colquitt 2014).

How the intervention might work

Weight-loss interventions may improve survival by influencing any, or all, of the pathways described above that link obesity and endometrial cancer, and have already been shown to be beneficial for survivors of other obesity-related cancers, including breast and colorectal cancer (Morey 2009; Rock 2015; Stolley 2009). Like endometrial cancer, breast cancer appears to be hormonally driven, and weight-loss interventions that have been associated with a loss of 5% or more of bodyweight have been shown to reduce total and free oestradiol (a type of oestrogen) levels in women following treatment for this cancer type, which may reduce the risk of disease recurrence (Rock 2013). Similarly, weight-loss interventions have been shown to lower levels of both insulin and adiponectin (a marker of insulin resistance), and improve insulin sensitivity in women following treatment for breast cancer (Rock 2013; Swisher 2015). They have also been associated with a reduction in the expression of inflammatory and cancer-promoting proteins, and this may explain why they reduce the risk of disease recurrence (Irwin 2015).

In addition to potential improvements in cancer-specific outcomes, weight-loss interventions may also improve overall survival by reducing the risk of cardiovascular disease. This shares many of the same risk factors with endometrial cancer, including obesity and hypertension, both of which were improved when individuals with breast and colorectal cancer underwent intentional weight loss following treatment (Rock 2015). One previous Cochrane Review concluded that physical activity may have a positive effect on quality of life in multiple different cancers, with reductions in anxiety, fatigue and sleep disturbance, and improved emotional well-being. These results should be interpreted cautiously, as included studies were at risk of considerable bias (Mishra 2012). In particular, there was a high risk of performance bias (significant differences between groups beyond simply which intervention they received), as due to the nature of the intervention (i.e. exercise), it was not possible to conceal the treatment allocation from the participants and researcher. A proportion of the included studies was at high risk of selectively reporting only some of the outcomes (reporting bias), failing to be transparent in their allocation of participants to treatment groups (allocation bias) and not managing incomplete outcome data appropriately (attrition bias). The differences in exercise regimens tested meant it was difficult to combine the results to give an overall conclusion.

Why it is important to do this review

The impact of obesity on women's health has been highlighted in several high-profile publications, including the UK Chief Medical Officer's report in December 2015 (Department of Health 2015), and the publication of the British Journal of Obstetrics and Gynaecology's themed issue, *Obesity and Reproductive Health*, in January 2016 (Crosbie 2016). The impact of lifestyle changes, including weight loss, on outcomes following treatment for endometrial cancer was also identified as one of the top 10 research priorities in endometrial cancer in the James Lind and Womb Cancer Alliance Priority Setting Partnership (Wan 2016). Therefore, this updated review is timely in its aim to establish the availability of evidence about the effects of weight-loss interventions on survival and quality of life following treatment for endometrial cancer. This is the first update of this Cochrane Review and will continue to set the scene for high-quality research to assess the feasibility, effectiveness and cost-effectiveness of such interventions.

OBJECTIVES

To evaluate the benefits and harm of weight-loss interventions, in addition to standard management, on overall survival and the frequency of adverse events in women with endometrial cancer who are overweight or obese compared with any other intervention, usual care or placebo.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, which are considered the highest level of evidence, to maximise the quality of included studies. We included studies reported as full text, those published as abstract only and unpublished data to ensure we incorporated all relevant trials.

Types of participants

We included trials that enroled women of all ages, who were either overweight (BMI 25 kg/m^2 or greater) or obese (BMI 30 kg/m^2 or greater), and who were currently undergoing treatment, or had been previously treated, for endometrial cancer, of any grade, stage or histological subtype. Trials were included regardless of primary treatment modality (i.e. surgery, radiotherapy, hormonal treatment or a combination). When studies of participants with mixed BMI were identified, but subgroup data were not provided, we contacted the study authors to request the subgroup data for participants who were overweight or obese only. If authors were unable or unwilling to provide these data, the study was excluded from the meta-analysis.

Types of interventions

We included studies reporting on interventions designed to promote weight loss as one of their primary stated goals, in any healthcare setting, including community-based studies. These could include:

- lifestyle interventions, including dietary and physical activity regimens;
- behavioural strategies to improve adherence to treatment, which may have included self-monitoring of eating habits and physical activity, stress management or stimulus control (eliminating environmental cues associated with undesired eating);
- pharmacological interventions (such as, but not limited to, appetite suppressants, drugs that cause fat malabsorption or serotonin receptor antagonists (drugs that affect appetite) of any dose, route of delivery or duration);
- surgical interventions (including gastric band, sleeve (surgical removal of part of the stomach), or bypass procedure).

Any of these interventions were compared with any other intervention, usual care, or placebo.

Types of outcome measures

Primary and secondary outcome measures were described in terms of the effect of the weight-loss intervention on survival, weight loss, cardiovascular events or quality of life, which are important measures that help determine whether these interventions should be included in routine clinical practice. Inclusion of these outcomes

in the study design were not determinants of the eligibility of the trial for this review.

Primary outcomes

- Overall survival; determined as the time from randomisation until death from any cause.
- Frequency of adverse events, of any nature. This was subdivided into mild–moderate adverse events (e.g. musculoskeletal or abdominal pain), and life-threatening events (e.g. electrolyte imbalance requiring hospitalisation).

Secondary outcomes

- Recurrence-free survival; length of time from randomisation to recurrence of the disease or death.
- Cancer-specific survival; length of time from randomisation to death from endometrial cancer.
- Weight loss; amount of weight lost, in kilograms (kg), between randomisation and end of study.
- Cardiovascular and metabolic event frequency; specifically the number of strokes, myocardial infarctions and hospitalisations for heart failure.
- Quality of life as measured on any validated scale (e.g. Functional Assessment of Cancer Therapy – General (FACT-G) or 12-Item Short Form Survey (SF-12)).

Search methods for identification of studies

We imposed no language restrictions on our searches. Where necessary, we translated the reports.

Electronic searches

For the original review, we ran the search from inception to January 2018, and for the updated review from January 2018 to June 2022 for the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 6; Appendix 1), in the Cochrane Library;
- MEDLINE via OvidSP (January week 2 2018 to 27 June 2022; Appendix 2);
- Embase via OvidSP (2018 week 4 to 2022 week 25; Appendix 3).

Searching other resources

We handsearched the citation lists of included studies and previous systematic reviews and contacted experts in the field to identify further reports of trials. Where additional information was required, we contacted the principal investigator of the trial.

Unpublished and grey literature

We searched the following for ongoing clinical trials.

- International Standard Randomised Controlled Trial Number (ISRCTN) metaRegister of Controlled Trials (www.isrctn.com/)
- Physicians Data Query (www.cancer.gov/publications/pdqwww.nci.nih.gov)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- PsycINFO

Handsearching

We handsearched the reports of conferences in the following sources.

- *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncologist)
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecologic Cancer Society)
- *British Journal of Cancer*
- NCRI Cancer Conference
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)

We searched for other conference abstracts and proceedings using ZETOC and WorldCat Dissertations.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (EndNote) and removed duplicates. Two review authors (HA and SK) independently examined the remaining references. We excluded studies that clearly did not meet the inclusion criteria, and obtained full-text copies of potentially relevant references. Two review authors (HA and SK) independently assessed the eligibility of the retrieved reports and publications. We resolved any disagreement through discussion, or if required, we consulted a third review author (EC). We identified and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and Characteristics of included studies table (Liberati 2009).

Figure 1. Study flow diagram.

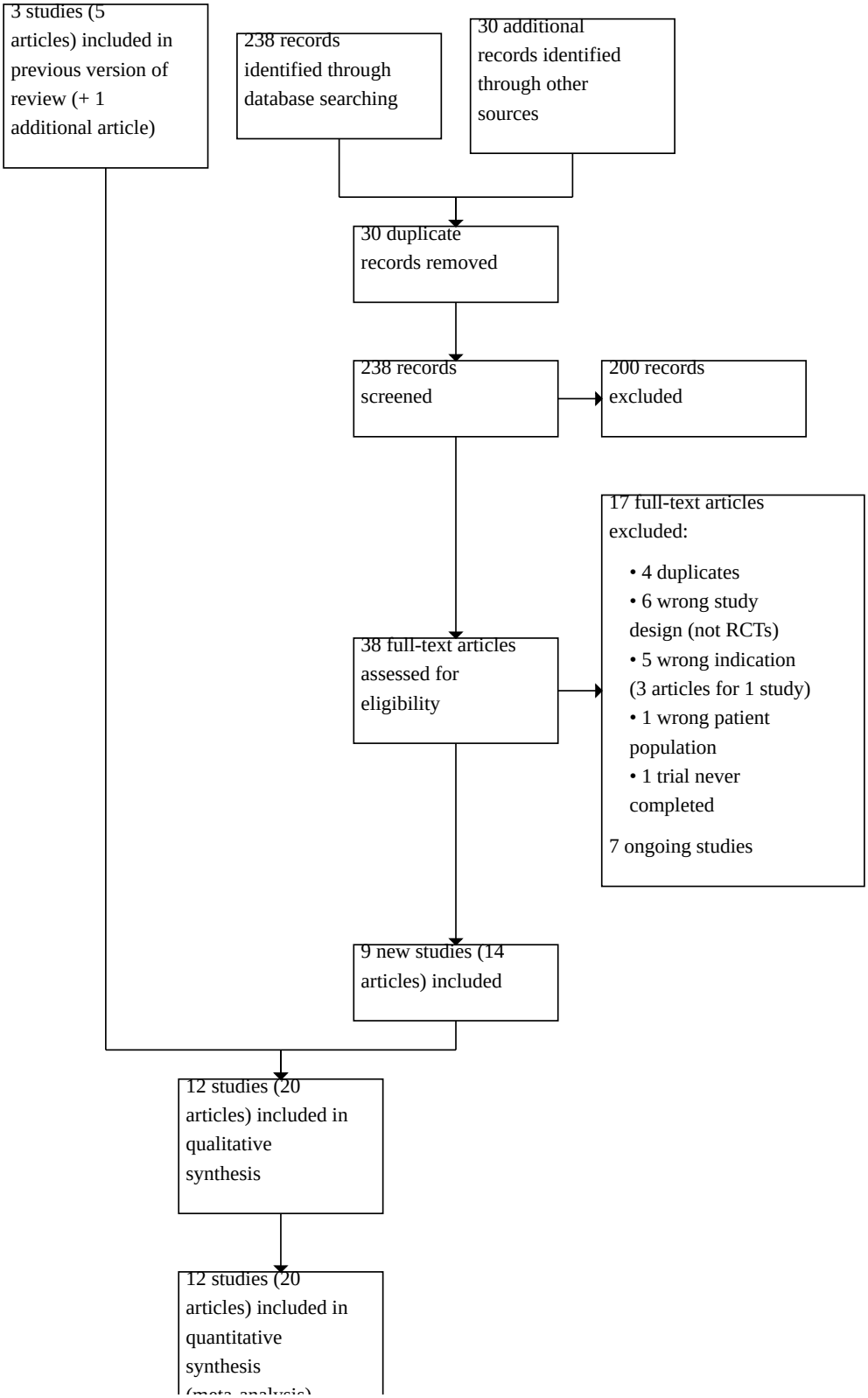
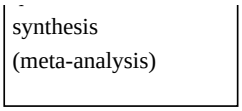


Figure 1. (Continued)



Data extraction and management

Two review authors (HA and SK) independently extracted study characteristics and outcome data from included studies onto a prepiloted data collection form. We noted in the Characteristics of included studies table if outcome data were not reported in a usable format. We resolved disagreements by consensus or by involving a third review author (EC). One review author (HA) transferred data into Review Manager Web (RevMan Web 2020). A second review author (SK) double-checked that data were entered correctly by comparing the data in the Review Manager Web with the study reports. In the case where an included study had more than one report, we collated the available data to ensure maximal information yield and gave priority to the publication with the longest follow-up associated with our review's primary and secondary outcomes.

We extracted the following data.

- Author, year of publication, and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population (total number enroled; baseline patient characteristics: age, comorbidities (e.g. diabetes, cardiovascular disease); European Cooperative Oncology Group (ECOG) Performance Status (PS); BMI; type of endometrial cancer; grade and stage of disease; timing of intervention in relation to treatment of endometrial cancer (i.e. before or after definitive treatment, nature of primary endometrial cancer treatment (e.g. surgery, radiotherapy, hormonal)))
- Intervention details (type of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
- Comparison (nature of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
- Risk of bias in study (see Assessment of risk of bias in included studies)
- Duration of follow-up
- Outcomes: for each outcome, we extracted the outcome definition and unit of measurement (if relevant). For adjusted estimates, we recorded variables adjusted for in the analyses.
- Results: number of participants allocated to each intervention group, total number analysed for each outcome and missing participants
- Notes: funding for trial, and notable conflicts of interest of trial authors

We extracted the results as follows.

- For time-to-event data (survival and disease progression), we extracted the log of the hazard ratio [log (HR)] and its standard error from trial reports. If these were not reported, we attempted to estimate the log (HR) and its standard error using the methods of Parmar 1998. If this were not possible for survival data, we treat them as dichotomous outcomes and estimated the risk ratio (RR) with 95% confidence interval (CI).
- For dichotomous outcomes (e.g. adverse events, cardiovascular events or deaths), if it was not possible to calculate an HR, we estimated an RR with 95% CI; we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint.
- For continuous outcomes (e.g. quality of life measures, weight loss), we extracted the mean and standard deviation (SD) of the outcome of interest and the number of participants assessed in each treatment arm at specific time points and used this to estimate the mean difference (MD) and its SD.

If reported, we extracted both unadjusted and adjusted statistics.

Where possible, we extracted data relevant to an intention-to-treat analysis, in which case participants were analysed in the groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of included studies in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2022), which recommends the explicit reporting of the following individual elements for RCTs.

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (patients and treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes

Two review authors (HA and SK) independently applied the risk of bias criteria using the RoB 1 tool (Higgins 2011); we resolved differences by discussion, or by appealing to a third review author (EC). We checked clinical trial registries for a priori primary and secondary outcome measures to assess the risk of selective reporting. We judged each item as being at high, low, or unclear risk of bias, as set out in the criteria provided by Higgins 2011 and Higgins 2022. We provided a quote from the study report and a statement to justify the judgement for each criterion. We summarised results in both a graph and a narrative summary. When

interpreting treatment effects and meta-analyses, we considered the risk of bias for the studies that contributed to that outcome. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

Measures of treatment effect

We used the following measures of the effect of treatment.

- For time-to-event data, we used the HR, if possible. Where this was not the case, we treated the data as dichotomous and estimated the RR using the Mantel-Haenszel method.
- For dichotomous outcomes, we analysed data based on the number of events and the number of people assessed in the intervention and comparison groups. We used these to calculate the RR and 95% CI using the Mantel-Haenszel method.
- For continuous outcomes, we analysed data based on the mean, SD, and number of people assessed for both the intervention and comparison groups, to calculate MD between treatment arms with a 95% CI. If the MD was reported without individual group data, we used this to report the study results. If studies measured the same outcome using different tools, we planned to calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in RevMan Web 2020.

We undertook meta-analyses only where this was meaningful (i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to be appropriate). We described skewed data reported as medians and interquartile ranges.

Unit of analysis issues

The unit of analysis was the participant. If any trials had multiple treatment groups, we only included the relevant arms or combined similar intervention arms and control arms together in order to create single pair-wise comparisons, and avoid 'double-counting.'

Dealing with missing data

We attempted to contact study authors to obtain missing data (participant, outcome or summary data). Where possible, we conducted analysis of participant data on an intention-to-treat basis; otherwise, we analysed data as reported. We reported on the levels of loss to follow-up, and assessed this as a source of potential bias.

We did not impute missing outcome data.

Assessment of heterogeneity

Where we considered studies similar enough (based on participants, intervention, comparison, settings and outcome measures) to pool the data using meta-analysis, we assessed the degree of heterogeneity by visually inspecting forest plots, by estimating the percentage of heterogeneity (I^2 statistic) between trials that could not be ascribed to sampling variation (Higgins 2003), by formally testing the significance of the heterogeneity (Chi^2 statistic; Deeks 2001), and if possible, by conducting subgroup analyses. We used these I^2 statistic values as an approximate guide to assess heterogeneity as:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We evaluated the value of the I^2 statistic alongside the magnitude and direction of effects, and the P value for the Chi^2 test (Higgins 2011).

If there was evidence of substantial clinical, methodological or statistical heterogeneity across included studies, we did not report pooled results from the meta-analysis, but instead used a narrative approach to data synthesis. In this event, we investigated and reported the possible clinical or methodological reasons for this.

Assessment of reporting biases

We aimed to minimise reporting bias by systematically searching for all eligible studies, including unpublished data and ongoing clinical trials, with no language restrictions. Updates of this review will deal with any time lag bias.

Had we included 10 or more studies that investigated a particular outcome, we planned to examine funnel plots that correspond to the meta-analysis of the outcome to assess the potential for small-study effects, such as publication bias. We planned to visually assess funnel plot asymmetry; if asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

If sufficient, clinically similar studies (in terms of participants, intervention, comparison, settings and outcome measures) were available to ensure meaningful conclusions, we pooled their results in meta-analyses using the random-effects model in Review Manager Web (RevMan Web 2020). Given the number of possible interventions that could have been included in the incorporated studies, we only planned to perform the following meaningful comparisons.

- Lifestyle interventions in addition to usual care versus usual care
- Behavioural interventions in addition to usual care versus usual care
- Pharmacological interventions in addition to usual care versus usual care
- Surgical interventions in addition to usual care versus usual care
- Lifestyle interventions versus behavioural interventions
- Lifestyle interventions versus pharmacological interventions
- Lifestyle interventions versus surgical interventions
- Behavioural interventions versus pharmacological interventions
- Behavioural interventions versus surgical interventions
- Pharmacological intervention versus surgical interventions

The specific method for pooling data depended upon the nature of the outcome measure. If we were unable to pool the data statistically using meta-analysis, we conducted a narrative synthesis of results. We presented the major outcomes and results, organised by intervention categories, according to the major types or aims of the identified interventions.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for the following factors, where possible.

- BMI
- Histological type, stage and grade of endometrial cancer

Sensitivity analysis

If adequate data were available, we planned to perform a sensitivity analysis comparing studies with high and unclear risk of bias and low risk of bias for attrition and outcome reporting, and allocation concealment (the latter is relevant only to pharmacological interventions).

Summary of findings and assessment of the certainty of the evidence

We assessed and reported the certainty of the evidence for each outcome, using the GRADE approach and the following domains: study limitations (suggesting a high likelihood of bias), inconsistency (unexplained heterogeneity), imprecision (wide CIs), indirectness of evidence and publication bias. We created a summary of findings table using GRADEpro GDT software (GRADEpro GDT), and two review authors (HA and SK) independently assessed the certainty of the evidence, using Chapter 14 of the *Cochrane Handbook of Systematic Reviews of Interventions* as a guide (Schünemann 2022). We used a checklist to maximise consistent GRADE decisions, and the GRADE Working Group certainty of evidence definitions (Meader 2014). We downgraded the evidence from high certainty by one level for serious limitations (or by two for very serious limitations) for each outcome, and outlined our rationale in the footnotes.

- **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.

We included the following outcomes in the summary of findings table.

- Overall survival
- Adverse events
- Cancer-specific survival
- Weight loss
- Cardiovascular and metabolic event frequency
- Quality of life

If meta-analyses had not been possible, we planned to present results in a narrative summary of findings table format.

RESULTS

Description of studies

Results of the search

The electronic search retrieved 268 records. Thirty-eight references were potentially eligible and were retrieved as full-text articles. Nine studies (14 references) met the inclusion criteria and seven studies were ongoing. These nine new studies were added to the three studies included in the previous review, in addition to a further reference for Allison 2016, giving a total of 12 studies with 20 references.

See Characteristics of included studies; Characteristics of excluded studies and Characteristics of ongoing studies tables, and the PRISMA flow chart (Figure 1).

Included studies

Study design and setting

Eight RCTs were conducted in a single centre (Clark 2021; Cohen 2018; Edbrooke 2022; McCarroll 2014; Mohammad 2019; von Gruenigen 2008; Yeh 2021; Zamorano 2021), and four were multicentre trials (Allison 2016; Janda 2021; Maxwell-Smith 2019; Nock 2013). Nine RCTs were conducted in the USA (Allison 2016; Clark 2021; Cohen 2018; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008; Yeh 2021; Zamorano 2021), two in Australia (Edbrooke 2022; Maxwell-Smith 2019), and one in both Australia and New Zealand (Janda 2021).

Participants

RCTs randomised 610 women who were overweight or obese and previously treated for endometrial cancer. The mean age of participants ranged from 53 years (Janda 2021) to 66 years (Maxwell-Smith 2019). Five RCTs included data on ethnicity, with most participants identifying as white or Caucasian (ranging from 60% to 100% of participants) (Allison 2016; Janda 2021; Maxwell-Smith 2019; von Gruenigen 2008; Zamorano 2021). Five RCTs included participants with good performance status (ECOG 0 to 2, a way of quantifying the general well-being and physical activity levels of people with cancer) (Allison 2016; Edbrooke 2022; McCarroll 2014; von Gruenigen 2008; Zamorano 2021), while Janda 2021 included one participant with a performance status of 3, despite this being an exclusion criterion. The remaining six RCTs did not report this participant characteristic (Clark 2021; Cohen 2018; Maxwell-Smith 2019; Mohammad 2019; Nock 2013; Yeh 2021). Five RCTs included only participants with stage I or II disease (Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Nock 2013; von Gruenigen 2008). Four RCTs included participants with advanced disease (up to stage III or IV) (Cohen 2018; Edbrooke 2022; Yeh 2021; Zamorano 2021). Three RCTs did not provide details of the stage of disease of participants (Allison 2016; Clark 2021; Mohammad 2019). Only one RCT was conducted concurrently with primary hormonal endometrial cancer treatment (Janda 2021); the remainder had completed primary treatment (majority surgical, but not always reported) (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008; Yeh 2021; Zamorano 2021). Two RCTs had an exclusion criterion of any form of adjuvant treatment (Allison 2016; Janda 2021), and Nock 2013 excluded women who had received adjuvant chemotherapy. One RCT only included participants who had completed or were due to start adjuvant therapy (Edbrooke 2022). The remaining eight RCTs provided varying details regarding the adjuvant treatment received (Clark 2021; Cohen 2018; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; von Gruenigen 2008; Yeh 2021; Zamorano 2021).

Interventions

All studies compared combined behavioural and lifestyle interventions to facilitate weight loss through dietary modification and increased physical activity with usual care. Nine RCTs utilised a two-arm design, comparing one intervention with usual care (Clark 2021; Cohen 2018; Edbrooke 2022; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008; Zamorano 2021). Three RCTs had a three-arm design (Allison 2016; Janda 2021; Yeh 2021), with one RCT comparing two types of lifestyle interventions with usual care (Allison 2016). Both Janda 2021 and Yeh 2021 had metformin arms, which are not relevant to this review question, and therefore can be considered as two-arm studies comparing one intervention with usual care. Counselling was provided either on an individual basis by telephone, text or email (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; Nock 2013; Yeh 2021; Zamorano 2021), a combination of face-to-face group and individual sessions (Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; von Gruenigen 2008), or both.

Primary outcome

Overall survival

- Ten RCTs reported overall survival, defined as the number of deaths occurring during follow-up (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021; Zamorano 2021).

Adverse events

- Nine RCTs reported adverse events, defined as any undesirable symptom or sign occurring after the study had commenced, even if not thought to be directly related to the intervention (Allison 2016; Clark 2021; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021; Zamorano 2021). These were reported as two separate categories; mild–moderate adverse reactions and life-threatening adverse reactions.

Secondary outcome

Recurrence-free survival

- One RCT reported recurrence-free survival, defined as the number of recurrences of the disease occurring during follow-up (Yeh 2021).

Cancer-specific survival

- Nine RCTs reported cancer-specific survival, defined as the number of deaths secondary to endometrial cancer occurring during follow-up (Allison 2016; Clark 2021; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021; Zamorano 2021).

Weight loss

- Nine RCTs reported change in weight from baseline, measured in kilograms (Allison 2016; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021; Zamorano 2021).

Cardiovascular and metabolic event frequency

- Six RCTs reported cardiovascular events, defined as the number of myocardial infarctions, strokes and hospitalisations for heart failure occurring during follow-up (Allison 2016; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021).

Quality of life

- Six RCTs reported change in quality-of-life score from baseline (Allison 2016; Cohen 2018; Edbrooke 2022; McCarroll 2014; von Gruenigen 2008; Zamorano 2021).

Studies used five different instruments to measure quality of life.

- Three RCTs used SF-12 Physical Health questionnaire (Allison 2016; Cohen 2018; Zamorano 2021).
- Two RCTs used SF-12 Mental Health questionnaire (Cohen 2018; Zamorano 2021)
- Three RCTs used FACT-G (Edbrooke 2022; McCarroll 2014; von Gruenigen 2008).
- One RCT used Patient Health Questionnaire 9-Item Version (PHQ-9) (Zamorano 2021)
- One RCT used Cancer-Related Body Image Scale (CRBI) (Zamorano 2021)

We contacted the principal investigator of each RCTs to request unpublished data where it was considered important to the results of the review. Full and detailed responses were obtained from the study authors (Table 1).

Excluded studies

We excluded 13 full-text articles from the review during this update, for the following reasons.

- Six full-text articles were not RCTs (Bantum 2015; Bell 2021; Haggerty 2016; Jernigan 2016; NCT02575872; Rahimy 2021)
- One RCT included a different patient population, with no participants with endometrial cancer being enroled (Groarke 2021)
- Five articles were for the wrong indication. One study (three references) assessed feasibility, safety and acceptability of home-based strength training and specifically not weight loss (Gorzelitz 2022); the primary aim of another was to assess the effect of a ketogenic diet on blood lipid profile compared to a lower-fat diet (Cohen 2019), and another explored the effectiveness of a theory-based behavioural lifestyle intervention on health behaviours and quality of life (Koutoukidis 2019)
- One RCT was never completed due to lack of funding (Basen-Engquist 2016).

Ongoing studies

Seven studies are ongoing (ACTRN12621000050853; NCT03095664; NCT03285152; NCT04000880; NCT04008563; NCT04783467; NCT05233059).

Risk of bias in included studies

See Characteristics of included studies table; Figure 2; and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

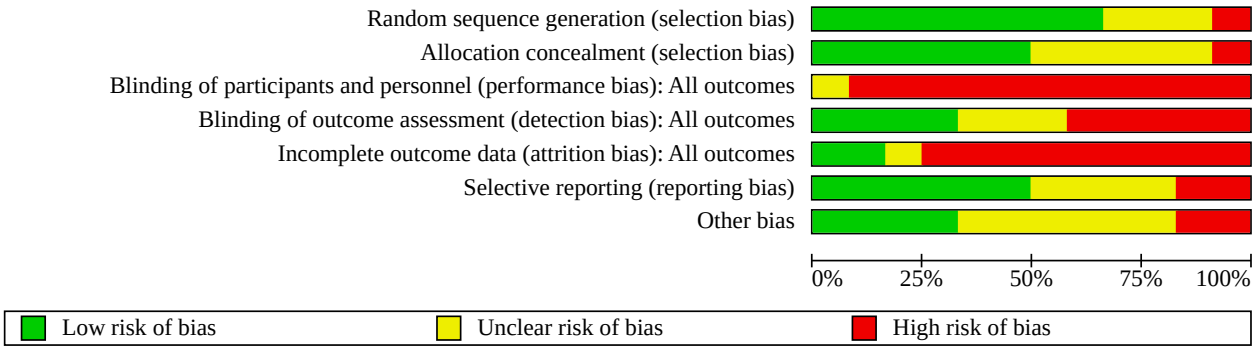
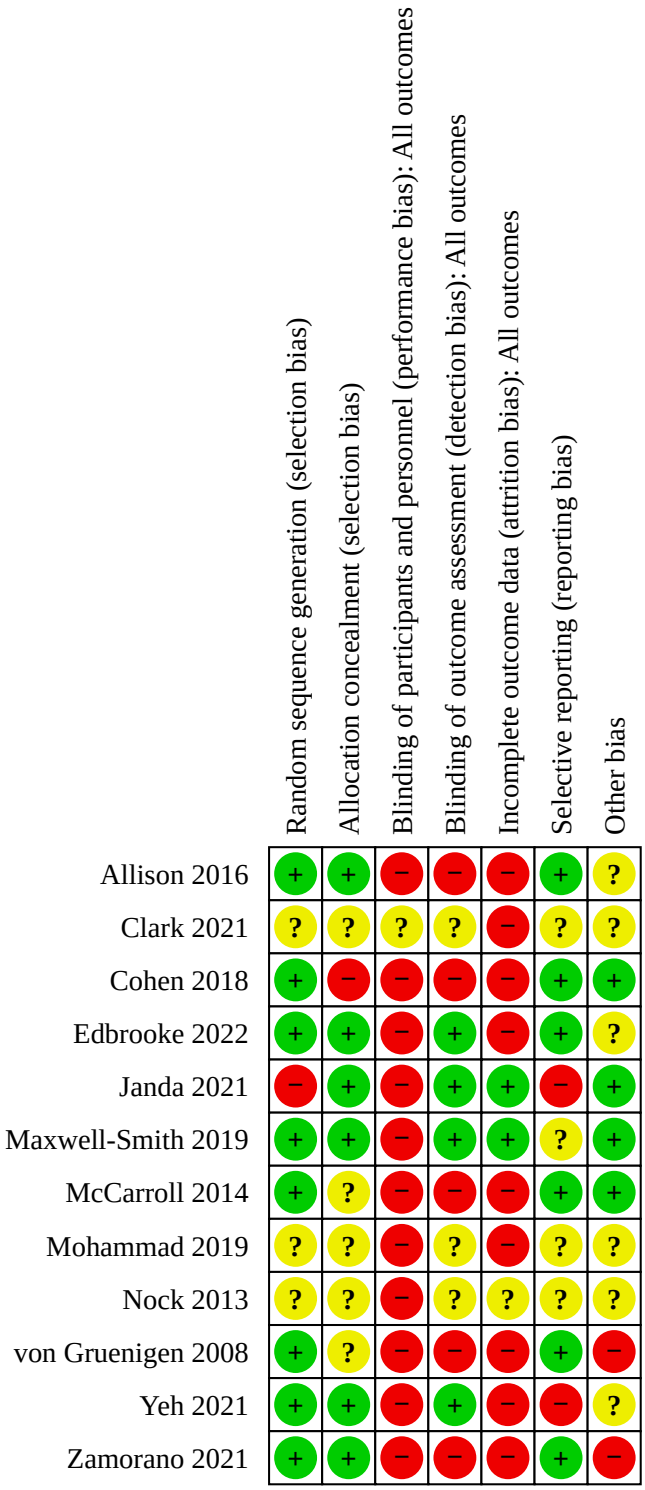


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Eight RCTs were at low risk of selection bias related to random sequence generation (Allison 2016; Cohen 2018; Edbrooke 2022; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008; Yeh 2021; Zamorano 2021). Six RCTs used computer-generated randomisation (Allison 2016; Cohen 2018; Edbrooke 2022; Maxwell-Smith 2019; Yeh 2021; Zamorano 2021). The other two RCTs used block randomisation methods, stratifying participants according to baseline BMI (McCarroll 2014; von Gruenigen 2008). One RCT was at high risk of selection bias related to random sequence generation as randomisation was stratified by diagnosis (cancer versus hyperplasia), BMI, menopausal status and treatment site. Participants could also avoid being randomised to a group based on their involvement in weight loss programmes or if already taking metformin (Janda 2021). Three RCTs were at unclear risk of selection bias related to random sequence generation as they did not describe methods used (Clark 2021; Mohammad 2019; Nock 2013).

Six RCTs were at low risk of selection bias related to allocation concealment as they used appropriate methods of sequentially numbered envelopes (Allison 2016), a randomisation table formulated by an independent statistician (Edbrooke 2022) or computer-generated allocation (Janda 2021; Maxwell-Smith 2019; Yeh 2021; Zamorano 2021). Five RCTs were at unclear risk of bias for allocation concealment as they did not describe the methods used (Clark 2021; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008). One RCT was at high risk of bias related to allocation concealment as participants were enroled and assigned by the project co-ordinator (Cohen 2018).

Blinding

Eleven RCTs were at high risk of performance bias related to blinding of participants and personnel (Allison 2016; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008; Yeh 2021; Zamorano 2021). Due to the nature of the intervention (either group or individual counselling sessions regarding weight loss and physical activity or usual care involving no additional counselling or generic health advice only), it was not possible to blind participants and the research team to group allocation. One RCT had an unclear risk of bias for blinding of personnel and participants as they did not describe their methods used (Clark 2021).

However, it would be possible to blind outcome assessors for all primary and secondary outcomes, thereby reducing the risk of detection bias. Four RCTs did this (Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; Yeh 2021). Five RCTs were at high risk of detection bias as they used unblinded members of the research team to measure all outcomes (Allison 2016; Cohen 2018; McCarroll 2014; von Gruenigen 2008; Zamorano 2021). Three RCTS were at unclear risk of bias related to blinding of outcome assessors as they did not describe their methods used (Clark 2021; Mohammad 2019; Nock 2013).

We considered that blinding was unlikely to affect the findings for the primary outcomes of overall survival and adverse events, or the secondary outcomes of recurrence-free and cancer-specific survival, weight loss and cardiovascular event frequency, but that it may affect quality of life assessments.

Incomplete outcome data

Two RCTs were at low risk for attrition bias; one had no withdrawals from the study and no missing data (Maxwell-Smith 2019) and one had a withdrawal and missing data rate of less than 10%, with 4/71 (5.6%) participants withdrawing (Janda 2021).

One RCT was at unclear risk of attrition bias as these data were not provided (Nock 2013).

The other nine RCTs were at high risk for attrition bias as they had a participant withdrawal or missing data rate (or both) more than 10% (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; McCarroll 2014; Mohammad 2019; von Gruenigen 2008; Yeh 2021; Zamorano 2021). Both Clark 2021 and Edbrooke 2022 had withdrawal rates less than 10%, with rates of 3/39 (7.7%) for Clark 2021 and 0% for Edbrooke 2022. However, Clark 2021 had missing step data for 33% of the intervention group and 22% of the control groups, and Edbrooke 2022 had missing weight loss data for 11/17 (64.7%) of participants and missing quality-of-life data for 3/17 (17.6%) participants – this was largely attributed to effect of the COVID-19 pandemic. Allison 2016 had a withdrawal rate of 9/41 (22.0%) and Cohen 2018 had a withdrawal rate of 5/18 (27.8%), and missing QoL data for a further 5/18 (27.8%) participants. McCarroll 2014 had a withdrawal rate of 16/75 (21.3%) and von Gruenigen 2008 had a withdrawal rate of 7/45 (15.6%) and missing data for an additional 2/22 (9.1%) of participants in the control arm. Mohammad 2019 had a withdrawal rate of 13/106 (12.2%) at 12 months; however, the trial endpoint was 24 months and there were no data supplied for this. Yeh 2021 had a withdrawal rate of 1/7 (14%) and Zamorano 2021 had a withdrawal rate of 19/80 (23.8%).

Selective reporting

Six RCTs were at low risk of reporting bias (Allison 2016; Cohen 2018; Edbrooke 2022; McCarroll 2014; von Gruenigen 2008; Zamorano 2021). Eleven RCTs were registered prior to commencement of recruitment on ClinicalTrials.gov or anzctr.org.au, which gave them an unclear risk of reporting bias as they did not provide these data (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Nock 2013; von Gruenigen 2008; Yeh 2021; Zamorano 2021). Two RCTs also published their protocols prospectively (Janda 2021; Maxwell-Smith 2019). Two RCTs were at high risk of reporting bias as they deviated from a prespecified outcome by not reporting any quality-of-life data, or give a reason for not reporting (Janda 2021; Yeh 2021). Maxwell-Smith 2019 was at unclear risk of bias as they did not report their quality-of-life data due to concerns regarding the licencing of SF-12 to an organisation external to RAND Corporation, which permits non-commercial use. Three RCTs were at unclear risk of bias for selective reporting as they did not supply these data (Clark 2021; Mohammad 2019; Nock 2013).

Other potential sources of bias

No studies reported significant differences in baseline characteristics between their intervention and control groups. Two RCTs did not supply any information regarding funding, ethical approval or conflicts of interest to be able to judge additional sources of bias in these studies (Clark 2021; Mohammad 2019). One study declared a potential conflict of interest that could have impacted on the trial regarding the weight loss intervention website (Yeh 2021). There were additional sources of bias in two

studies. Zamorano 2021 had to change the intervention system from ScaleDown to iOTA (Interactive Obesity Treatment Approach) three months into participant randomisation. This led to a change in method of communication with the programme, participants were lost to follow-up and retraining of staff may have introduced confounding. In von Gruenigen 2008, two participants in the intervention arm underwent gastric bypass during follow-up and continued to be included in the final analysis. Only 30/41 (73.2%) participants in one RCT had completed their outcome assessments at the time of correspondence with the study authors for the previous version of this review (Allison 2016). We contacted the study authors, but no further data were supplied for this review update.

There were insufficient studies investigating each outcome to construct a funnel plot to assess for publication bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Lifestyle intervention versus usual care compared to placebo for weight reduction in obesity to improve survival in women with endometrial cancer

See: Summary of findings 1.

1. Lifestyle interventions in addition to usual care versus usual care

All 12 RCTs compared combined lifestyle and behavioural interventions with usual care (Allison 2016; Clark 2021; Cohen 2018; Edbrooke 2022; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Mohammad 2019; Nock 2013; von Gruenigen 2008; Yeh 2021; Zamorano 2021).

Primary outcomes

1.1 Overall survival (three, six, 12 and 24 months)

There were insufficient data to calculate the effect of combined lifestyle and behavioural interventions on overall survival using the HR. Instead, we treated mortality as a dichotomous outcome and determined the RR.

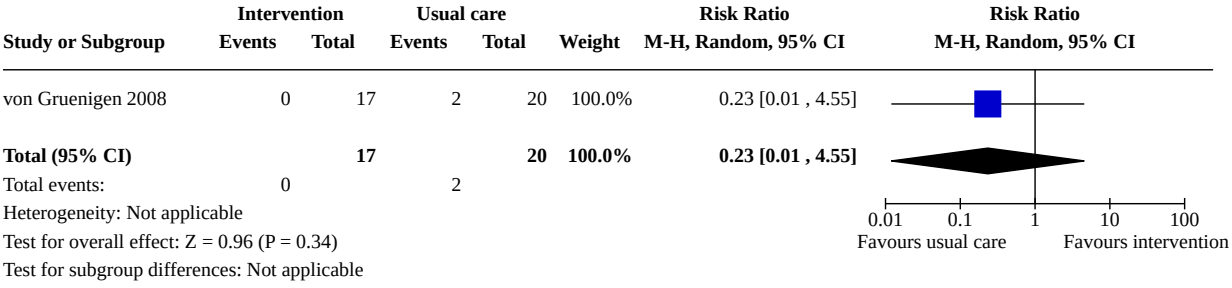
There was no evidence that a combined lifestyle and behavioural intervention, incorporating dietary and physical activity advice with self-monitoring and stimulus control techniques, was associated with an improvement in overall survival at three months as there were no deaths in the intervention or usual care groups of the two studies that reported this outcome (Analysis 1.1) (Clark 2021; Edbrooke 2022). An RR could not, therefore, be calculated and a meta-analysis could not be performed. Neither sensitivity nor subgroup analyses were possible.

There was no evidence that lifestyle and behavioural interventions were associated with an improvement in overall survival at six months as no deaths were observed in the intervention or usual care groups of the five studies that reported this outcome (Analysis 1.2) (Allison 2016; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Yeh 2021). An RR could not, therefore, be calculated and a meta-analysis could not be performed. Neither sensitivity nor subgroup analyses were possible.

There was no evidence that lifestyle and behavioural interventions were associated with an improvement in overall survival at 12 months as there were no deaths in either the intervention or usual care groups of the two studies that reported this outcome (Analysis 1.3) (McCarroll 2014; Zamorano 2021). An RR could not, therefore, be calculated. Sensitivity and subgroup analyses were not possible.

Lifestyle and behavioural interventions were not associated with an improvement in overall survival at 24 months (RR (mortality) 0.23, 95% CI 0.01 to 4.55; P = 0.34; 1 RCT, 37 participants; very low-certainty evidence; Analysis 1.4; Figure 4) (von Gruenigen 2008). Two deaths occurred in the control arm. Sensitivity and subgroup analyses were not possible.

Figure 4. Forest plot of comparison: 1 Lifestyle intervention versus usual care, outcome: 1.3 Overall survival (24 months).



1.2 Adverse events

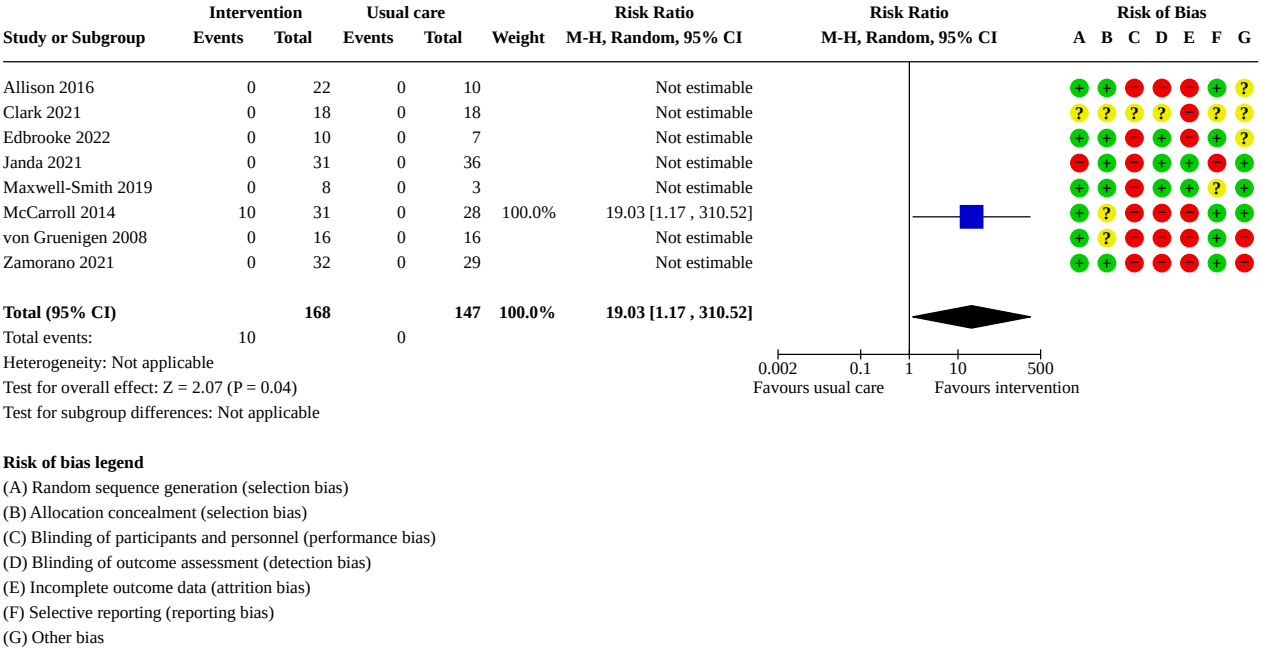
Mild-to-moderate adverse events

Six RCTs reported no mild-to-moderate adverse events related to the study intervention (Allison 2016; Clark 2021; Edbrooke 2022; Maxwell-Smith 2019; von Gruenigen 2008; Yeh 2021).

One RCT reported 13 musculoskeletal events in 10 participants in the intervention group, including knee and leg pain and muscle weakness, which were considered to be possibly related to the study intervention (McCarroll 2014). Participants receiving combined lifestyle and behavioural interventions had a higher risk of musculoskeletal events than those receiving usual care (RR 19.03, 95% CI 1.17 to 310.52; P = 0.04; 8 RCTs, 315 participants; very low-certainty evidence; note: 7 studies reported musculoskeletal

symptoms but recorded 0 events in both groups. Thus, the RR and CIs were calculated from 1 study rather than 8; Analysis 1.5; Figure 5) (McCarroll 2014).

Figure 5. Forest plot of comparison: 1 Lifestyle intervention versus usual care, outcome: 1.4 Adverse events – musculoskeletal.



Two participants in McCarroll 2014 also reported episodes of diarrhoea, which were considered to be possibly related to the study intervention. Lifestyle and behavioural interventions were not associated with an increased risk of diarrhoea (RR 4.53, 95% CI 0.23 to 90.51; P = 0.32; 8 RCTs, 315 participants; very low-certainty evidence; Analysis 1.6) (McCarroll 2014).

One RCT reported one participant in the intervention arm experiencing abdominal pain which was considered to be possibly related to the intervention (Janda 2021). Lifestyle and behavioural interventions were not associated with an increased risk of abdominal pain (RR 3.47, 95% CI 0.15 to 82.21; P = 0.44; 8 RCTs, 315 participants; very low-certainty evidence; Analysis 1.10). This same RCT also reported several adverse events which were considered to be unrelated to the study intervention including exacerbation of asthma (one participant in the intervention arm and one participant in the control arm; Analysis 1.7), primary lung adenocarcinoma (one participant in intervention arm; Analysis 1.8), and ovarian hyperstimulation syndrome (one participant in intervention arm; Analysis 1.9).

One participant in Zamorano 2021 reported feeling overwhelmed because her health conditions prohibited her from achieving the goals set by the invention, and she subsequently did not complete the six-month survey or measurements. Lifestyle and behavioural interventions were not associated with an increased risk of feeling overwhelmed (RR 2.73, 95% CI 0.12 to 64.42; P = 0.53; 8 RCTs, 315 participants; very low-certainty evidence; Analysis 1.14).

Life-threatening adverse events

No life-threatening adverse events related to the study intervention were reported in any of the RCTs.

Secondary outcomes

1.3 Recurrence-free survival (six months)

There was no evidence that combined lifestyle and behavioural interventions were associated with an improvement in recurrence-free survival at six months as there were no deaths reported in either the intervention or usual care groups for the one study that reported this outcome (Analysis 1.15) (Yeh 2021). An RR could not, therefore, be calculated and a meta-analysis could not be performed. No sensitivity or subgroup analyses were possible.

1.4 Cancer-specific survival (three, six, 12 and 24 months)

There was no evidence that combined lifestyle and behavioural interventions were associated with an improvement in cancer-specific survival at three months as there were no deaths reported in either the intervention or usual care groups for the two studies that reported this outcome (Analysis 1.16) (Clark 2021; Edbrooke 2022). An RR could not, therefore, be calculated and a meta-analysis could not be performed. No sensitivity or subgroup analyses were possible.

There was no evidence that combined lifestyle and behavioural interventions were associated with an improvement in cancer-specific survival at six months as there were no deaths reported in either the intervention or usual care groups for the five studies that reported this outcome (Analysis 1.17) (Allison 2016; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; Yeh 2021). An RR could

not, therefore, be calculated and a meta-analysis could not be performed. No sensitivity or subgroup analyses were possible.

There was no evidence that combined lifestyle and behavioural interventions were associated with an improvement in cancer-specific survival at 12 months as there were no deaths reported in either group in the two studies reporting this outcome (Analysis 1.18) (McCarroll 2014; Zamorano 2021). An RR could not, therefore, be calculated. No sensitivity or subgroup analyses were possible.

There was no evidence that combined lifestyle and behavioural interventions were associated with an improvement in cancer-specific survival at 24 months as there were no cancer-specific deaths reported (Analysis 1.19) (von Gruenigen 2008). An RR could not, therefore, be calculated. No sensitivity or subgroup analyses were possible.

1.5 Weight loss (nine weeks; three, six, 12 and 24 months)

Combined lifestyle and behavioural intervention was not associated with weight loss at nine weeks compared to usual care (MD 6.29 kg, 95% CI −0.18 to 12.76; P = 0.06; 1 RCT, 7 participants; low-certainty evidence; Analysis 1.20) (Edbrooke 2022). Subgroup analysis according to baseline BMI did not affect the result (Analysis 1.21). There were insufficient data to perform a subgroup analyses according to histological type, stage and grade of endometrial cancer. No sensitivity analyses were possible.

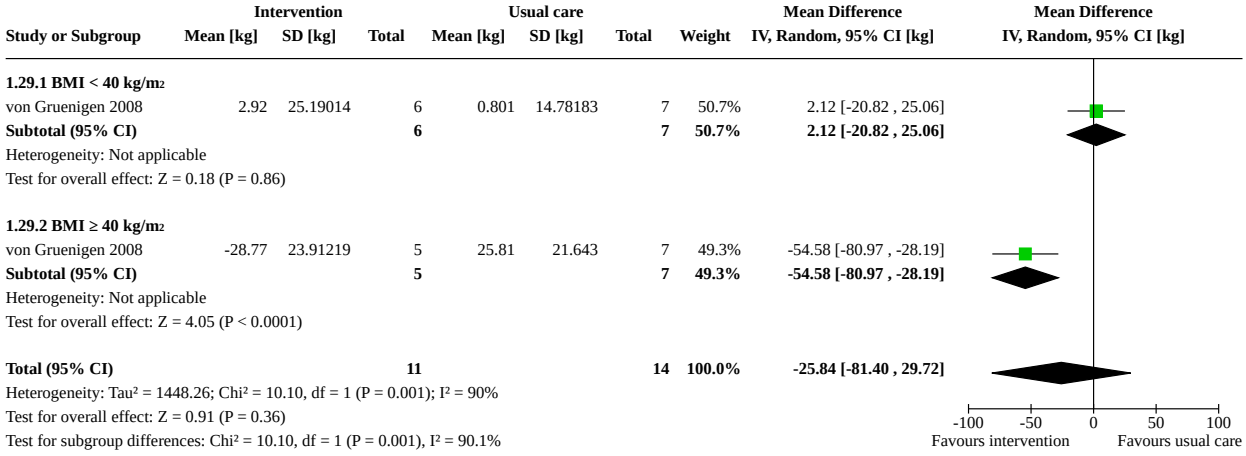
Combined lifestyle and behavioural intervention was not associated with weight loss at three months compared to usual care (MD 5.03 kg, 95% CI −2.67 to 12.73; P = 0.20; 1 RCTs, 6 participants; low-certainty evidence; Analysis 1.22) (Edbrooke 2022). Subgroup analysis according to baseline BMI did not affect the result (Analysis 1.23) (Edbrooke 2022). There were insufficient data available to perform a subgroup analyses according to histological type, stage and grade of endometrial cancer. No sensitivity analyses were possible.

Combined lifestyle and behavioural intervention was not associated with weight loss at six months compared to usual care (MD −1.39 kg, 95% CI −4.04 to 1.26; P = 0.30; 5 RCTs, 209 participants; I^2 = 32%; low-certainty evidence; Analysis 1.24) (Allison 2016; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008). Subgroup analysis according to baseline BMI did not affect the result (Analysis 1.25) (Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008). Insufficient data were available to perform a subgroup analyses according to histological type, stage and grade of endometrial cancer. No sensitivity analyses were possible.

Lifestyle and behavioural intervention was not associated with weight loss at 12 months compared to usual care (MD −1.57 kg, 95% CI −5.46 to 2.31; P = 0.43; 3 RCTs, 152 participants; I^2 = 9%; very low-certainty evidence; Analysis 1.26) (McCarroll 2014; von Gruenigen 2008; Zamorano 2021). Although some individuals lost a considerable amount of weight, most participants lost none or very little, which is why this result was not statistically significant. Subgroup analysis demonstrated no effect of baseline BMI on weight loss following the intervention (Analysis 1.27) (McCarroll 2014; von Gruenigen 2008). No sensitivity analysis was possible.

Overall, a lifestyle and behavioural intervention was not associated with weight loss at 24 months compared with usual care (MD −18.26 kg, 95% CI −38.73 to 2.21; P = 0.08; 1 RCT, 25 participants; very low-certainty evidence; Analysis 1.28) (von Gruenigen 2008). Subgroup analysis demonstrated differences in the amount of weight lost according to baseline BMI (Chi^2 = 10.10, degree of freedom (df) 1, P = 0.001; Analysis 1.29). Participants with a BMI less than 40 kg/m^2 did not achieve greater weight loss following the intervention compared with those receiving usual care at 24 months (MD 2.12 kg, 95% CI −20.82 to 25.06; P = 0.86; 1 RCT, 13 participants; very low-certainty evidence) (von Gruenigen 2008). However, participants with a BMI of 40 kg/m^2 of greater who received the intervention achieved greater weight loss at 24 months than those receiving usual care (MD −54.58 kg, 95% CI −80.97 to −28.19; P < 0.0001; 1 RCT, 12 participants; very low-certainty evidence; Analysis 1.29; Figure 6). These results were influenced by the inclusion of two participants with a BMI over 40 kg/m^2 who underwent bariatric surgery during follow-up and lost a large amount of weight as a consequence. No sensitivity analysis was possible.

Figure 6. Forest plot of comparison: 1 Lifestyle intervention versus usual care, outcome: 1.13 Weight loss stratified by body mass index (BMI) (24 months) (kg).



1.6 Cardiovascular and metabolic event frequency (six and 12 months)

One RCT reported one cardiovascular event (congestive heart failure) in one participant in the intervention group at six months (Janda 2021). Lifestyle and behavioural interventions were not associated with an increased risk of cardiovascular or metabolic events at six months (RR 3.47, 95% CI 0.15 to 2.31; P = 0.43; 5 RCTs, 211 participants; low-certainty evidence; Analysis 1.30; note, 4 studies reported cardiovascular events but recorded 0 events in both groups. Thus, the RR and CIs were calculated from 1 study rather than 5; Allison 2016; Janda 2021; Maxwell-Smith 2019; McCarroll 2014; von Gruenigen 2008).

There were no cardiovascular or metabolic events reported at 12 months (Analysis 1.31) (McCarroll 2014; von Gruenigen 2008).

1.7 Quality of life (nine weeks; three, six and 12 months)

Nine weeks – Functional Assessment of Cancer Therapy – General scale

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at nine weeks compared with usual care when measured using the FACT-G questionnaire (MD 3.51, 95% CI 10.96 to 17.98; P = 0.63; 1 RCT, 16 participants; low-certainty evidence; Analysis 1.32) (Edbrooke 2022). Baseline BMI did not impact on quality-of-life response to the intervention in a subgroup analysis (Analysis 1.33). A sensitivity analysis was not possible.

Three months – Functional Assessment of Cancer Therapy – General scale

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at three months compared with usual care when measured using the FACT-G questionnaire (MD 5.75, 95% CI −11.26 to 22.76; P = 0.53; 1 RCT, 14 participants; low-certainty evidence; Analysis 1.34) (Edbrooke 2022). Baseline BMI did not impact on quality-of-life response to the intervention in a subgroup analysis (Analysis 1.35). A sensitivity analysis was not possible.

Three months – 12-item Short Form Physical Health questionnaire

One RCT with eight participants reported only the mean without the SD in both the intervention and control group using the SF-12 Physical Health questionnaire at three months (Cohen 2018). Therefore, the MD could not be calculated.

Three months – 12-item Short Form Mental Health questionnaire

One RCT with eight participants reported only the mean without the SD in both the intervention and control group using the SF-12 Mental Health questionnaire at three months (Cohen 2018). Therefore, the MD could not be calculated.

Six months – Functional Assessment of Cancer Therapy – General scale

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at six months compared with usual care when measured using the FACT-G questionnaire (MD 2.51, 95% CI −5.61 to 10.64; P = 0.54; 2 RCTs, 95 participants; I^2 = 83%; very low-certainty evidence; Analysis 1.36) (McCarroll 2014; von Gruenigen 2008). Baseline BMI did not impact on quality-of-life response to the intervention in a subgroup analysis (Analysis 1.37). A sensitivity analysis was not possible.

Six months – 12-item Short Form Physical Health questionnaire

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at six months compared with usual care when measured using the SF-12 Physical Health questionnaire (MD −2.29, 95% CI −7.34 to 2.76; P = 0.37; 1 RCT, 30 participants; moderate-certainty evidence; Analysis 1.40) (Allison 2016).

Twelve months – Functional Assessment of Cancer Therapy – General scale

Lifestyle and behavioural intervention was not associated with improvement in quality of life at 12 months when measured using the FACT-G questionnaire (MD 2.77, 95% CI −0.65 to 6.20; P = 0.11, I^2 = 0%; 2 RCTs, 89 participants; very low-certainty evidence; Analysis 1.38) (McCarroll 2014; von Gruenigen 2008). The quality-of-life response to the intervention did not differ according to baseline BMI in a subgroup analysis (Analysis 1.39). A sensitivity analysis was not possible.

Twelve months – 12-item Short Form Physical Health questionnaire

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at 12 months compared with usual care when measured using the SF-12 Physical Health questionnaire (MD −3.50, 95% CI −8.85 to 1.85; P = 0.20; 1 RCT, 61 participants; very low-certainty evidence; Analysis 1.41) (Zamorano 2021). A sensitivity analysis was not possible.

Twelve months – 12-item Short Form Mental Health questionnaire

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at 12 months compared with usual care when measured using the SF-12 Mental Health questionnaire (MD 3.00, 95% CI −2.49 to 8.49; P = 0.28; 1 RCT, 61 participants; very low-certainty evidence; Analysis 1.42) (Zamorano 2021). A sensitivity analysis was not possible.

Twelve months – Cancer-Related Body Image scale

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at 12 months compared with usual care when measured using the CRBI scale (MD −1.10, 95% CI −5.02 to 2.82; P = 0.58; 1 RCT, 61 participants; very low-certainty evidence; Analysis 1.43) (Zamorano 2021). A sensitivity analysis was not possible.

Twelve months – 9-item Patient Health Questionnaire

Combined lifestyle and behavioural intervention was not associated with improvement in quality of life at 12 months compared with usual care when measured using the PHQ-9 questionnaire (MD 0.90, 95% CI −1.79 to 3.59; P = 0.51; 1 RCT, 61 participants; very low-certainty evidence; Analysis 1.44) (Zamorano 2021). A sensitivity analysis was not possible.

2. Other comparisons

We found no studies of other comparisons.

DISCUSSION

Summary of main results

The limited evidence suggests that combined lifestyle and behavioural interventions had no effect on overall survival in women with endometrial cancer who were overweight or obese.

However, studies with longer follow-up would be required to truly estimate the effect and the studies are therefore limited in their directness.

There was no evidence that combined lifestyle and behavioural interventions affected cancer-specific or recurrence-free survival or reduced the number of cardiovascular and metabolic events in women who had survived endometrial cancer at six months, as only one hospitalisation occurred for heart failure during that time, and otherwise the outcome was not reported. Extending to a 12-month follow-up period did not change this conclusion, as either there were no events recorded in the studies or the outcome was not reported.

Dietary and physical activity advice, in combination with behavioural strategies to improve compliance, are not associated with significant weight loss or improvement in quality of life for women with a history of endometrial cancer over a similar follow-up period, when compared with those receiving usual care. BMI at baseline did not affect these results. However, these results should be viewed with caution, as only 12 RCTs met the eligibility criteria for inclusion in this review, all of which were small and meant that no events were recorded for many of these outcomes. At 24 months, participants with class-III obesity (BMI 40 kg/m^2 or greater) in one RCT lost significantly more weight than those receiving usual care (von Gruenigen 2008). However, there were biases in the design of this study, namely the inclusion of participants who had undergone gastric bypass surgery during follow-up. Despite a lack of benefit with regard to the outcomes included in this review, lifestyle and behavioural interventions to induce weight loss in women who had survived endometrial cancer may be associated with a significant risk of musculoskeletal adverse effects, though the low event numbers make relative risk estimates unreliable and none of the adverse events recorded were considered serious or life-threatening.

Summary of findings 1 summarises the main outcomes.

Overall completeness and applicability of evidence

The evidence for each of the outcomes was limited as only 12 studies met the inclusion criteria and each had enroled small numbers of participants. Two studies were undertaken by the same study authors recruiting from the same hospital and pool of women who had survived endometrial cancer and were carried out as a pilot study (von Gruenigen 2008), followed by a definitive RCT using similar methodology (McCarroll 2014). This is likely to impact on the applicability of their findings to other populations. Three RCTs presented limited data as conference abstract, poster or the information provided on Clinical.Trials.gov, which restricts the evaluation of these trials and their contribution to the findings of this review (Clark 2021; Mohammad 2019; Nock 2013).

All studies that could be evaluated (i.e. all except Clark 2021, which could not be evaluated) were at high risk for performance bias due to the nature of the interventions, as they could not blind participants and personnel to treatment group allocation. Five RCTs were also at high risk for detection bias due to the use of unblinded outcome assessors (Allison 2016; Cohen 2018; McCarroll 2014; von Gruenigen 2008; Zamorano 2021). Whilst this is unlikely to have affected objective outcomes, such as weight loss and survival, it may have impacted on more subjective outcomes, such as quality of life. The use of independent, blind outcome assessors, such as in Edbrooke 2022, Janda 2021, Maxwell-Smith 2019, and Yeh 2021, would remove this potential source of bias. Most RCTs were at high risk of attrition bias. Only two studies had a less than 10% loss to follow-up or missing data (or both) (Janda 2021; Maxwell-Smith 2019).

The 12 RCTs used five different questionnaires to measure quality of life. The results presented in the Summary of findings 1 are based on use of the FACT-G questionnaire as two studies used this and we pooled the individual results from the greatest number of participants. These findings were considered of very low-certainty evidence due to the risk of bias in the included studies. The study using the SF-12 Physical Health Component questionnaire, whilst providing evidence of greater certainty at six months, was based on a small number of participants and considered different aspects of quality of life, preventing pooling in the meta-analysis. The overall findings of the studies were similar, with no significant improvement in quality of life found at six or 12 months following weight-loss interventions. In order to improve the certainty of evidence and to allow future meta-analyses of the effect of weight-loss interventions on quality of life to be conducted, it would be advisable for all studies going forward to use a common quality of life assessment tool.

While the study authors were able to provide additional data on the outcome measures included in this review, overall and cancer-specific survival and cardiovascular and metabolic event frequency were not specific outcomes of these studies. This explains the paucity of data available, which were insufficient to allow the calculation of HRs for these outcomes. The short duration of the intervention (six months) and limited follow-up time of the included RCTs, which was between three and 24 months, explains why there were so few deaths and cardiovascular and metabolic events observed. Any conclusions with regards the effect of lifestyle and behavioural interventions on survival should, therefore, be made with caution due to the indirectness of the results within this short follow-up period. For weight-loss interventions to be shown to impact on survival, other longer-term outcomes, and quality of life for women with a history of endometrial cancer, the duration of both the intervention and follow-up period will need to be considerably longer (five to 10 years).

The only studies that met the inclusion criteria for this review had focused solely on lifestyle and behavioural strategies. There were no studies of pharmacological or surgical interventions, which are likely to be more effective than diet and physical activity advice in achieving significant sustained weight loss and hence impact on the outcomes measured in this review (Bray 2016). RCTs comparing these interventions with placebo/usual care are required.

The mean age range of participants in the included studies of between 53 and 66 years is younger than the general endometrial cancer population, with peak incidence occurring between 75 and 79 years (Cancer Research UK 2018a). In future studies with longer follow-up, this could impact on outcomes including overall and cancer-specific survival, and cardiovascular and metabolic event frequency as these are also independently impacted by age. The limited ethnicity data showed that most participants identified as white or Caucasian, which restricts the applicability of the evidence to more ethnically diverse populations. There were limited data available about the other baseline characteristics of participants in the included studies, in particular in regard to their baseline BMI and histological type, stage and grade of

endometrial cancer, which restricted the number of subgroup analyses that could be conducted. This information is vital to investigate whether all women who survive endometrial cancer derive a similar benefit from weight-loss interventions or whether efforts should be targeted at specific subpopulations, such as those with the greatest BMI. Adequately powered studies including participants with both early- and late-stage endometrioid and non-endometrioid endometrial cancer are required to explore these issues further.

Quality of the evidence

There were only 12 RCTs that met the inclusion criteria for the review, meaning that a meta-analysis could rarely be performed. The small number of studies also meant that assessment of the heterogeneity between studies is unlikely to be reliable, particularly with regard to dichotomous outcomes. Ideally, the calculation of the I^2 statistic and sensitivity analyses would have been performed, but often neither were possible in Review Manager Web (RevMan Web 2020).

Using the GRADE method of assessment, the certainty of the evidence for all outcomes was either low or very low, meaning that our confidence in the effect estimate was limited or very limited and that the true effect may, or is likely to, be substantially different from the estimate of effect. The reasons for downgrading certainty of the evidence included serious and very serious risk of bias in the primary studies (e.g. unblinded participants, study personnel and outcome assessors; significant, unexplained, loss of participants to follow-up; forced change in intervention three months into randomisation (Zamorano 2021)); imprecision due to small-study sizes and the risk of introducing an indirect comparison. The latter applied particularly to the study with the longest follow-up period of 24 months (von Gruenigen 2008), which was the only one to show an effect of lifestyle and behavioural interventions on weight loss. The fact that this was only observed at 24 months and not at six or 12 months, despite the intervention being limited to six months' duration, is noteworthy, especially as the study was not originally planned to follow participants beyond 12 months and that, by this point, of the 25 participants remaining, two had undergone gastric bypass and continued to be included in the final analysis.

Potential biases in the review process

The Cochrane Gynaecological, Neuro-oncology and Orphan Cancer group oversaw the search strategy to reduce the risk of introducing bias into the review process. There were no limitations in regard to language or date of publication, and we deliberately searched for ongoing clinical trials. We obtained additional unpublished data through correspondence with study authors and included them in the review. Two review authors independently made decisions regarding the eligibility of studies for inclusion, risk of bias assessment, data collection and grading of evidence, with disagreements settled by a third review author. The main bias related to the small number of included studies, all of which had limited participant numbers, short follow-up times, and were of low or very low methodological quality, which meant that it was frequently not possible to conduct a meta-analysis and prevented the drawing of firm conclusions regarding the clinical effectiveness of the intervention. It also meant that it was not possible to assess for publication bias. There were no conflicts of interest identified for any of the study authors.

Agreements and disagreements with other studies or reviews

Despite increasing awareness of the need to improve survival and quality of life in women with a history of endometrial cancer, there is little published literature evaluating weight-loss interventions in this regard. Of the four systematic reviews previously conducted, three have included at least some of the data from three of the studies incorporated in our review (Allison 2016; McCarroll 2014; von Gruenigen 2008), though they did not appear to have had the same access to unpublished data as this review's authors. Chlebowski 2016 described the results of the SUCCEED trial (*S*urvivors of *U*terine *C*ancer *E*mpowered by *E*xercise and Healthy *D*iet; McCarroll 2014) and preliminary findings from Allison 2016 on weight loss and quality of life, but did not attempt a meta-analysis. Where a meta-analysis was performed, the results were similar to those reported here. Lin 2016 focused on the effect of interventions to increase physical activity, but noted that only one study used an exercise intervention alone without combining it with some form of lifestyle/dietary modification. They found no benefit of these interventions on health-related quality of life (SMD 0.05, 95% CI −0.28 to 0.37; P = 0.78), though there were significant improvements in BMI compared with those receiving usual care. The authors included studies conducted in survivors of all gynaecological malignancies and did not attempt to evaluate the effects of physical activity in specific cancer subtypes. There was also substantial methodological heterogeneity between RCTs, which had widely differing physical activity regimens, ranging from residential rehabilitation courses comprising physical activity education to pelvic floor exercises, which was not investigated further in their analysis. When the eligibility criteria for included studies was extended to non-randomised trials, the results were again similar, with no improvement in quality of life at three and six months (Smits 2015). A fourth systematic review included only epidemiological studies, two single-arm intervention studies and five cross-sectional studies of physical activity, and concluded that increased exercise could contribute to better quality of life in survivors of endometrial cancer (Babatunde 2016). However, they did not conduct a meta-analysis and had undertaken only a limited search of the literature.

No other individual RCT or review to date has evaluated the role of weight-loss interventions in improving survival for women with endometrial cancer. The only evidence available showed a trend towards increased mortality with greater levels of television viewing, as a surrogate marker of inactivity, in women recruited into the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study and who had developed endometrial cancer during long-term follow-up, though this result was not significant (Arem 2016). There was no association between self-reported activity levels following diagnosis and overall survival and unfortunately the study was underpowered to specifically analyse cardiovascular and cancer-related deaths. An adequately powered RCT, of appropriate duration, incorporating survival outcomes is, therefore, required to address this question.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review none of the new included studies have provided additional information to change the conclusions.

There is limited evidence available regarding the efficacy of weight-loss interventions in improving survival and reducing cardiovascular and metabolic event frequency in survivors of endometrial cancer. There is very low-certainty evidence that combined lifestyle and behaviour interventions are not associated with significant weight loss at 12 months and that there is no improvement in quality of life compared to those receiving usual care. The small number and size of the included randomised controlled trials (RCTs) in this review means that any effect size estimates should be viewed with caution. Whilst demonstration of a significant benefit from receiving diet and physical activity education has not been possible, the low-certainty evidence available suggests that it may not be associated with significant or serious adverse events, apart from an increase in musculoskeletal symptoms, and could easily be incorporated into routine follow-up reviews at low cost.

Implications for research

Further trials are required to specifically address the effects of weight-loss interventions on overall, cancer-specific and recurrence-free survival and to compare different dietary modification regimens, including intermittent fasting versus continuous low-calorie diets; pharmacological treatments associated with weight loss, such as orlistat; and bariatric surgery, all of which may be more effective in achieving and sustaining significant weight loss and hence impacting upon these outcomes. Bariatric surgery, in particular, has already been shown to result in greater weight loss than non-surgical weight management, which is maintained in the longer term, and leads to the resolution of diabetes, reducing overall and cardiovascular-caused mortality as well as improving some aspects of quality of life in people without cancer (Arterburn 2015; Colquitt 2014). It would be anticipated that women treated for endometrial cancer would derive similar benefits from undergoing weight-loss surgery, though whether they would also notice improvements in cancer-caused mortality is currently unknown. Any future trials in this area should be of high methodological quality, adequately powered and with at least five years of follow-up to allow time for the impact of these interventions on survival to be determined. Larger trials would also allow the relative benefit of weight-loss interventions on specific subgroups of survivors of endometrial cancer, such as those with body mass index of 40 kg/m^2 or greater and those diagnosed with early- and late-stage disease, to be evaluated.

Of the seven ongoing RCTs that could not be included in this version of the review, four will not address any of these issues as they involve randomisation to different lifestyle or behavioural interventions (or both) or usual care and do not include survival in their outcome measures (ACTRN12621000050853; NCT03285152; NCT04000880; NCT05233059). NCT03095664 is also investigating a behavioural/lifestyle intervention, but the primary outcome of the trial is overall survival which will be measured at five years. Unfortunately, the COVID-19 pandemic caused suspension of enrolment to the trial and will likely affect the results of this study. They are aiming to finish follow-up by the end of 2023. One RCT is investigating bariatric surgery as fertility-sparing treatment of complex atypical endometrial hyperplasia and grade 1 endometrioid endometrial cancer (NCT04008563). However, this is primarily a feasibility trial with follow-up of only 15 months which will limit the contribution of this study to survival outcomes. NCT04783467 is investigating the effect of time-restricted eating (intermittent fasting) on survivors of endometrial cancer with overweight or obesity, this is again primarily a feasibility study, but the long-term goal is the efficacy of this dietary schedule on endometrial cancer prognosis by improving cardiometabolic conditions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Allison 2016

Study characteristics	
Methods	Design: comment: parallel design, 3-arm, open-label randomised controlled trial Setting: multicentre study in the US Follow-up: 6 months

Allison 2016 *(Continued)*

Participants	Number of participants enroled 41 women randomised; 13 into arm A, 13 into arm B and 15 into arm C. 6-month follow-up data were only available for 30 women at the time of undertaking the previous version of this review, and no further data was supplied for this update (11 arm A, 10 arm B, 9 arm C) Inclusion criteria Women aged ≥ 18 years Biopsy-confirmed endometrial cancer of any histological type BMI ≥ 30 kg/m^2 ECOG PS 0-1 No concurrent or planned chemoradiation Access to wireless internet or smartphone, or both Life expectancy > 1 year Exclusion criteria Significant medical condition that would affect compliance with protocol or ability to participate, e.g. uncontrolled hypertension, symptomatic cardiac disease Current participation in another weight-loss programme or taking weight-loss medication Another invasive malignancy in last 5 years (excluding non-melanoma skin cancer) Autoimmune or immunosuppressive condition Currently taking immunosuppressant medication Currently pregnant Baseline participant characteristics Mean age 62.2 years (SD 8.7 years), mean BMI 39.1 kg/m^2 (range 30–67 kg/m^2). 78% of participants were white, 20% black, 2% Latina and 2% other/decline to answer. Study authors did not detail comorbid conditions. Participants had both type I and type II endometrial cancer, though the grade and stage of their malignancy was not provided. All had ECOG PS 0–1 and had undergone surgical treatment of their endometrial cancer. Baseline characteristics of participants according to group allocation were not provided.
Interventions	Arm A Telemedicine arm. Telephone-based weight-loss counselling undertaken by trained interventionists with guided digital measurements of weight, lean mass and fat mass. Counselling and weight-loss measurements occurred at least weekly for the 6 months' duration of the intervention. Quote: "The telemedicine arm included a Wifi scale that recorded at least weekly weights of participants. The scale automatically graphs the weights on a password-protected website which permitted counsellors to have immediate feedback during weekly 15–20 minute counselling sessions teach standard weight-loss skills, including self-monitoring, problem-solving, enlisting social support, and overcoming negative thoughts according to a standard curriculum." Arm B Text4Diet arm. Participants received 3–5 SMS text messages each day for the six-month intervention period. The text message provided tips and reminders to encourage healthy eating and weight loss. Participants also received a digital scale to track and report weight and were prompted to do so once a week by text message.

Allison 2016 *(Continued)*

Quote: "The texting arm receives personalized text messages daily, following different monthly themes, e.g. Do not go to a party hungry. Eat a healthy snack before or bring a healthy dish with you to share. You will be more likely to stick to your goals! Since you have been meal planning do you find that you eat out less often? Y or N-remember the restaurant website is a great way to help you plan a healthy meal to order. Different styles included encouraging statements, yes/no questions or multiple choice questions."

All participants in Arms A and B recorded dietary intake and restricted calories to 1200–1500 kcal/day. They were given an exercise goal of 50–175 minutes/week of moderate, aerobic physical activity, e.g. brisk walking.

Arm C

Enhanced usual care group. Participants provided with handouts based on ACS guidelines on healthy eating and exercise and did not receive any additional input from the research team.

Quote: "… printed information from American Cancer Society guidelines on healthy eating and exercise … encourage weight loss through dietary monitoring and a walking program … these efforts were not reinforced or monitored by study staff …"

Outcomes	Primary outcomes Overall survival: no deaths reported in any arm during study. Adverse events: no adverse events reported in any arm during study. Second outcomes Recurrence-free survival: not reported Cancer-specific survival: no cancer-specific deaths reported in any arm during study. Weight loss: change in weight from baseline at 6 months reported. Cardiovascular and metabolic event frequency: no events reported in any arm. QoL: change in QoL from baseline at 6 months reported using SF-12 Physical Health Component change score. Quote: "Change in quality of life from baseline … SF-12 Physical Health component change score." Power No power calculation performed. Aim of study was to provide estimates of the effect size of the intervention in order to power a full-scale trial. Quote: "The purpose will be to provide estimates for the size of an intervention effect achievable by the experimental intervention in order to power and justify a grant application for a full-scale trial of a weight loss program in women with endometrial cancer. With a sample size of 30 participants per group, the true difference in mean weight loss between the groups can be estimated with a 95% confidence interval size of ±0.50σ, where σ is the population standard deviation of weight loss, assumed in this calculation to be the same in each of the two intervention groups and the control group. We will assess the comparability of variance across the groups and do exploratory analyses of possibly variance-stabilizing transformations. Because this is a pilot study to derive parameters to design an appropriately-powered study, hypothesis testing is not a primary goal of the statistical analysis of the data, although P-values will be calculated."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Allison 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Comment: computer-generated algorithm used at co-ordinating centre to produce randomisation envelopes for each site. Quote: "The coordinating center used a computer generated algorithm to produce the randomization envelopes for each clinical site, with the general parameters of randomizing 1:1:1 across the three conditions."
Allocation concealment (selection bias)	Low risk	Comment: next envelope chosen for each enroled participant. Quote: "The envelopes are then chosen sequentially as each participant was enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded. Quote: "There was no blinding."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessments performed by unblinded study co-ordinators. Quote: "The outcome assessments were conducted by study coordinators and trained medical personnel (for blood draws, DEXA [dual-energy X-ray absorptiometry]). The coordinators knew which condition the participants were in, but other medical personnel were not informed."
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered the study: 13 into arm A, 13 into arm B and 15 into arm C Withdrew from study: 2 in arm A, 2 in arm B, 4 in arm C. 1 unknown Completed the study: 11 in arm A, 11 in arm B, 10 in arm C Intention-to-treat analysis Comment: not performed. Quote: "Given we only had pre–post assessment data and our main analyses used paired t-tests and correlations, we were unable to do intention-to treat analyses."
Selective reporting (reporting bias)	Low risk	Comment: protocol not published, but trial registered prospectively on ClinicalTrials.gov and all prespecified outcomes reported.
Other bias	Unclear risk	Source of funding: (quote): "Cross-TREC study funded by NCI U54-CA155850 – University of Pennsylvania; U54 CA155626 – Harvard University; U54 CA155496CC – Washington University; U01 CA116850 – Fred Hutchinson Cancer Research Center." Ethical approval: obtained Conflicts of interest: no conflicts of interest reported Other details: the study failed to enrol 30 participants into each group within their allotted time. The reasons for this were not provided. 4 centres open to recruitment although only the Universities of Washington and Pennsylvania enroled patients into the study. Only 30 participants had completed 6 months of follow-up at the time of correspondence with the study's chief investigator when writing the original review. We requested further data for this update but received none from the study author.

Clark 2021

Study characteristics	
Methods	Design: parallel, 2-arm, single-blind, randomised controlled trial Prospective trial of survivors of endometrial cancer from September 2018 to December 2019. Survivors randomised 1:1 Setting: single-centre in North Carolina Cancer Hospital, USA Follow-up: 12 weeks
Participants	Number of participants enroled: 39 participants randomised; 19 into intervention arm and 20 into control arm Inclusion criteria Aged ≥ 18 years Confirmed diagnosis of endometrial cancer and had completed therapy (surgery, chemotherapy or radiation) within past 6 months No current evidence of endometrial cancer BMI ≥ 25 kg/m^2 Had approval from their treating physician to engage in moderate-intensity physical activity Had a smartphone with Bluetooth capabilities turned on Had access to email Exclusion criteria Currently undergoing treatment for their cancer Unable to read a sample message aloud Pregnancy History of angina or palpitations with exertion History of uncontrolled pulmonary disease (COPD or asthma) Have ≥ 1 significant medical conditions that in the physician's judgement precluded participation in the walking intervention. Baseline participant characteristics Mean age 55.7 years (range 36–76 years); intervention arm: mean age 55.3 years (range 36–76 years); control arm 56.4 years (range 43–68 years). Baseline BMI (not reported if mean or median) 36.7 kg/m^2 in intervention arm and 35.9 kg/m^2 in the control arm. Comorbid conditions, ECOG PS and ethnicity of participants not reported. Histological type, grade or stage of endometrial cancer not reported. Primary treatment not reported.
Interventions	Intervention arm Received a fitness tracker and weekly tailored fitness messages Quote: "Participants randomized to the message arm will begin receiving encouragement and reminder UNC CHART messages to increase physical activity weekly. Participants on the feedback arm will receive 1 message per week during the 3-month study period."

Clark 2021 *(Continued)*

	Control arm Received a fitness tracker without any fitness messages. Quote: "No feedback messages"
Outcomes	Primary outcomes Overall survival: no deaths reported in either arm during study. Adverse events: no adverse event in either arm during study. Secondary outcomes Recurrence-free survival: not reported. Cancer-specific survival: no cancer-specific deaths reported in either arm during study. Weight loss: change in BMI from baseline at 3 months reported. Cardiovascular and metabolic event frequency: not reported. QoL: not reported. Power Power calculation performed, but there was insufficient detail to allow it to be replicated. Quote: "Powered to detect a clinically significant change in daily step count of 2,000 steps. Wilcoxon Two-sample test and student's T-test was used for comparisons."
Notes	Study authors contacted and poster sent, no further responses to data requests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: randomised 1:1 but no information given regarding randomisation process. Quote: "Survivors were randomized 1:1 to receipt or non-receipt of weekly tailored feedback messages."
Allocation concealment (selection bias)	Unclear risk	Comment: no information given regarding any allocation concealment used.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: due to nature of intervention, participants were unblinded. Unclear how personnel were blinded. Quote: "Masking: single (investigator)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided regarding who performed the outcome assessments and if they were blinded. Quote: "Masking: single (investigator)."
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered into study: 19 in intervention arm, 20 in control arm. Completed study: 18 in intervention arm, 18 in control arm. Reason not completed documented as physician decision.

Clark 2021 *(Continued)*

		Missing data: step data missing in both intervention and control arm. Quote: "Overall, 33% of intervention survivors versus 22% of control survivors had decline in fitness tracker use resulting in missing step data (p=0.46)." Intention-to-treat analysis Comment: no information provided on how missing data was dealt with.
Selective reporting (reporting bias)	Unclear risk	Comment: trial was registered prospectively on ClinicalTrials.gov but without publication/further information from study authors it was unclear if all pre-specified outcomes were reported.
Other bias	Unclear risk	Source of funding: no information provided by study authors. Ethical approval: no information provided by study authors. Conflicts of interest: no information provided by study authors. Other sources: no information provided by study authors.

Cohen 2018

Study characteristics	
Methods	Design: parallel design, 2-arm, open-label randomised controlled trial Setting: single-centre study at the University of Alabama at Birmingham, USA. Women with ovarian or endometrial cancer, recruited between October 2015 and April 2017, from the University of Alabama Gynecologic Oncology clinic and from other treatment centres via physician referral, flyers, local television advertisements and news articles. Follow-up: 12 weeks Fasting serum concentrations of glucose, insulin, C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and β-hydroxybutyrate, and body composition obtained at baseline and 12 weeks.
Participants	Number of participants enroled 73 women randomised; 57 of whom went onto their randomised diet and only 45 of these completed trial. 18/57 who completed baseline testing had endometrial cancer and BMI ≥ 25. 13 kg/m^2 of these participants completed the trial, with 9 randomised into the ketogenic diet intervention arm, and 4 into ACS diet control arm. Inclusion criteria Women aged ≥ 19 years History of endometrial or ovarian cancer Measurable disease or elevated CA-125 BMI > 18.5 kg/m^2 English speaking or reading Able to sign consent and willing to be randomised and adhere to the assigned protocol Exclusion criteria

Cohen 2018 *(Continued)*

	Pre-existing medical conditions: uncontrolled hypertension, unstable angina or myocardial infarction or cerebrovascular accident in 6 months prior to study, congestive heart failure, serious infectious diseases, chronic hepatitis, cirrhosis, chronic malabsorption syndrome, chronic pancreatitis, chronic lung disease, major depressive or psychiatric disorder. Current or medical condition that affects bodyweight such as uncontrolled hypo- or hyperthyroidism. Taking any of the following medications: antipsychotic agents, monoamine oxidase inhibitors, antibiotics for HIV or tuberculosis, weight loss medications or have taken weight loss medications in last 6 months. Currently dieting Baseline participant characteristics These characteristic refer solely to the 13 participants with endometrial cancer and BMI ≥ 25 kg/m^2 who completed the trial. Mean age 59.9 (SD 11.1) years, mean BMI 37.4 (SD 9.9) kg/m^2. Ethnic background of this specific group of study participants was not provided. Comorbidities included hypertension (46.2%), hyperlipidaemia (38.5%), hyperglycaemia (7.7%), hypothyroidism (30.8%) and sleep apnoea (15.4%). Histological type of endometrial cancer was not provided, stage of cancer was: Ia (61.5%), Ib (23.1%), II (7.7%) and IIIb (7.7%). The ECOG PS was not provided, all had undergone primary treatment (details not provided) and 2 were receiving adjuvant treatment during trial (details not provided).
Interventions	Ketogenic diet intervention arm Ketogenic diet (low-carbohydrate and high-fat) with advice provided by dietitian, weekly counselling via telephone or email, sample meal plans and recipes were provided. Urinary ketones measured daily for 2 weeks and weekly thereafter. Quote: "The KD [ketogenic diet]had a macronutrient distribution of ~5% of energy from carbohydrate (≤20 g/d), 25% energy from protein (≤100 g/d), and 70% energy from fat (≥125 g/d). Carbohydrate foods were limited to nonstarchy vegetables such as salad greens, broccoli, and summer squash. Permitted protein foods included meat, poultry, eggs, and fish, provided that they were neither breaded nor battered. Fat-containing foods included olive and coconut oils, avocados, butter, olives, cheese, cream, and small amounts of nuts. KD participants were instructed to avoid all grains and grain products, starchy vegetables, and fruit. Total energy intake was not restricted for either the ACS or KD. A registered dietitian provided diet-specific nutrition education to each participant immediately after baseline testing. Additional counseling was provided via phone and e-mail on a weekly basis, and included distribution of sample meal plans and recipes. When necessary, based on feedback from the participant, diet recommendations were further individualized to enhance adherence, assessed via weekly food record reviews. In addition, KD participants were also asked to measure urinary ketones with Ketostix (Bayer AG, Leverkusen, Germany). They submitted smartphone photographs of their strips via e-mail daily for the first 2 wk, and thereafter on a weekly basis." ACS control arm Low-fat diet with advice provided by dietitian, weekly counselling via telephone or email, sample meal plans and recipes were provided. Quote: "The ACS diet consisted of general guidelines to encourage intake of antioxidants and fiber, while reducing consumption of saturated fat and added sugars … Total energy intake was not restricted for either the ACS or KD. A registered dietitian provided diet-specific nutrition education to each participant immediately after baseline testing. Additional counseling was provided via phone and e-mail on a weekly basis, and included distribution of sample meal plans and recipes. When necessary, based on feedback from the participant, diet recommendations were further individualized to enhance adherence, assessed via weekly food record reviews."
Outcomes	Primary outcomes

Cohen 2018 *(Continued)*

Overall survival: 1 of the 18 participants with endometrial cancer with BMI ≥ 25 kg/m^2 died during the study period (given as reason for withdrawal). It was not reported which group the participant was allocated to, or whether the death was related to cancer or not.

Adverse events: not reported.

Secondary outcomes

Recurrence-free survival: not reported.

Cancer-specific survival: not reported.

Weight loss: change in weight from baseline to 12 weeks reported.

Cardiovascular and metabolic event frequency: not reported.

QoL: change in QoL from baseline to 12 weeks reported using SF-12 Physical Health Component change score and Mental Health Component change score (responses from 5/9 participants in ketogenic diet group and 3/4 participants in ACS group).

Power

Comment: power calculation performed, and there were sufficient details to allow it to be replicated.

Quote: "Statistical power analysis indicated that 25 individuals per group were required to have 80% power to detect a 2.7 ± 4.6 µU/mL difference in fasting insulin, through the use of a 2-sided paired *t* test and a significance alpha level of 0.05."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated blocked randomisation scheme created prior to study opening. Quote: "Participants were randomly assigned, through the use of a computer-generated blocked randomization scheme."
Allocation concealment (selection bias)	High risk	Comment: group allocation performed by the project co-ordinator. Quote: "The project co-ordinator enrolled and assigned participants to their intervention."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded. Quote: "Because this was a diet intervention study, it was not possible for participants or study personnel to be blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessments performed by a mix of blinded and unblinded personnel. Quote: "Research team members were provided only with subject IDs and demographics as needed to complete measurements/analyses." Quote: "Study coordinator, physician, and dietitian were aware of assignment, but DXA [dual-energy X-ray absorptiometry] technicians, nursing staff, and laboratory staff were blinded."
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up

Cohen 2018 *(Continued)*

		Entered into the study: 73 participants; 36 in ACS control arm and 37 in ketogenic diet intervention arm (unknown number of these were women with endometrial cancer with BMI ≥ 25 kg/m^2). 57 participants completed baseline testing; 18 women with endometrial cancer with BMI ≥ 25 kg/m^2. Withdrew from the study: 5 (no information given for which arm) Completed the study: 4 in ACS control arm, 9 in ketogenic diet intervention arm. Missing data: for QoL, analysis performed for 3 participants in ACS control arm and 5 participants in ketogenic diet intervention arm. Intention-to-treat analysis Comment: not performed.
Selective reporting (reporting bias)	Low risk	Comment: protocol not published, but trial registered prospectively on ClinicalTrials.gov and all prespecified outcomes reported.
Other bias	Low risk	Source of funding: (quote) "Supported by American Institute for Cancer Research, UAB Comprehensive Cancer Center, Nutrition Obesity Research Center grant P30DK56336, and Diabetes Research Center grant P60DK079626." Ethical approval: (quote) "UAB's Institutional Review Board approved the study" Conflicts of interest: no conflicts of interest reported.

Edbrooke 2022

Study characteristics	
Methods	Design: parallel design, 2-arm, pilot randomised controlled trial Randomised (2:1) with concealed allocation and assessor blinding Setting: single-centre in Australia (Peter MacCallum Cancer Centre) Follow-up: 3 months. Measures assessed at baseline, 9 weeks and 3 months
Participants	Number of participants enroled 22 participants randomised; 14 into intervention arm and 8 into control arm Of these, 17 had a BMI ≥ 25 kg/m^2; 10 were randomised into intervention arm and 7 into control arm Inclusion criteria Histologically confirmed diagnosis of endometrial cancer managed surgically Scheduled to receive or recently commenced (≤ 2 weeks prior) adjuvant therapy (brachytherapy, radiotherapy, chemotherapy, or any combination of radiotherapy and chemotherapy) Age ≥ 18 years Able to read and write English Able to participate in unsupervised exercise programme

Edbrooke 2022 *(Continued)*

	ECOG PS 0!!2 Life expectancy > 3 months Able to access telehealth (telephone or video conference) for intervention Exclusion criteria Concurrent, actively treated other malignancy or history of other malignancy treated within the past year Unstable psychiatric, cognitive or substance abuse disorders Comorbidities preventing participation in an unsupervised physical activity programme Stage 4 or recurrent disease Met aerobic physical activity guidelines for the past month (150 minutes of moderate-intensity exercise weekly) Baseline participant characteristics Mean age of participants with BMI ≥ 25 kg/m^2 63.9 (SD 6.6) years, with mean BMI 34.6 (SD) 4.9 kg/m^2. Ethnicity data not provided. Comorbid conditions given as a median Colinet comorbidity score of 6, with an interquartile range 1–8. All participants had undergone surgical treatment and were scheduled to receive or recently commenced adjuvant therapy. 82.4% had endometrioid adenocarcinoma, with 5.9% being mixed serous and grade 2 endometrioid adenocarcinoma, 5.9% high-grade serous carcinoma and 5.9% papillary serous adenocarcinoma of the endometrium. Stage of cancer: I (5.9%), Ia (29.4%), Ib (41.2%), II (11.8%), IIIa (5.9%) and IIIc1 (5.9%). All participants had ECOG PS 0–2. Baseline characteristics of participants according to group allocation not provided.
Interventions	Intervention arm 8-week telehealth intervention with diet and physical activity education plus behaviour change and social support. Usual care control arm Usual care
Outcomes	Primary outcomes Overall survival: no deaths reported in either arm during study. Adverse events: no adverse events reported in either arm during study. Secondary outcomes Recurrence-free survival: not reported. Cancer-specific survival: no cancer-specific deaths reported in either arm during study. Weight loss: change in weight from baseline to 3 months. Cardiovascular and metabolic event frequency: not reported. QoL: change in QoL from baseline to 3 months reported using FACT-G score. Power No power calculation performed. Trial assessing the feasibility and safety of the intervention. Quotes: "this was a pilot RCT with a pragmatic sample size" "Additional recruitment sites are required for a larger RCT."

Edbrooke 2022 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: REDCap database module used for randomisation. Quote: "Randomisation was performed using the randomisation module within the REDCap database and managed by an independent data manager."
Allocation concealment (selection bias)	Low risk	Comment: randomisation table created by independent statistician. Quote: "An independent statistician created the randomisation table and this was uploaded into the trial REDCap database." Quote: "The next treatment to be assigned will not be known by any person prior to eligibility criteria being established and the intention to randomise the patient following baseline assessment being declared."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded, this was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: used assessor blinding. Quote: "Blinded (masking used). Who is / are masked / blinded? The people assessing the outcomes. The people analysing the results/data."
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered the study: 10 into intervention arm and 7 into control arm. Withdrew from the study: 0 in intervention arm, 0 in control arm. Quote: "Retention was 100 (95%CI:85%,100%) at 9 weeks, but completion of objective nutrition measures was impacted by COVID-19 restrictions." Completed the study: 10 in intervention arm, 7 in control arm. Missing data: weight loss data were available for 7 participants at 9 weeks (5 in intervention arm and 2 in control arm) and for 6 participants at 3 months (4 in intervention arm and 2 in control arm). QoL data using FACT-G score was available for 16 participants at 9 weeks (9 in intervention arm and 7 in control arm) and for 14 participants at 3 months (8 in intervention arm and 6 in control arm). Quote: "assessment of weight (measured in kg) was impacted by restrictions on face-to-face appointments during the COVID-19 pandemic and participants declining to attend hospital follow-up appointments. Some weights were measured and some were patient-reported." Intention-to-treat analysis Comment: not performed. No information on how missing data were dealt with.
Selective reporting (reporting bias)	Low risk	Comment: protocol not published but trial registered prospectively on anzctr.org.au and all prespecified outcomes reported.
Other bias	Unclear risk	Source of funding: Peter MacCallum Cancer Foundation.

Edbrooke 2022 *(Continued)*

	Ethical approval: obtained. Conflicts of interest: no conflicts of interest reported. Other: recruitment targets not obtained and recruitment ceased early. Quote: "Recruitment has been ceased from 24.3.20 due to restrictions on face-to-face contact and continuation of recruitment to research projects during the COVID-19 pandemic. Recruitment was planned to cease by 30.3.20 and the target sample size was not reached due to participant recruitment difficulties."

Janda 2021

Study characteristics	
Methods	Design: parallel, open-label, 3-arm, randomised trial with participants randomised in a 3:3:5 ratio to the arms. feMMe trial was phase II trial Setting: multicentre study in gynaecological centres in Australia (12 sites) and New Zealand (4 sites) Follow-up: 6 months
Participants	Number of participants enroled 165 women randomised. In the original 3-arm study, 24 into observation arm, 26 into weight loss arm and 41 into metformin arm (total 91). There were 2 additional 2-arm studies. First, those with a contraindication to metformin (16 participants) or already on metformin (47 participants); 31 into observation arm and 32 into weight loss arm. Second, those with a contraindication to weight loss; 5 into observation arm and 6 into metformin arm. Those with a contraindication to weight loss or metformin were pooled with the original 3 arms giving a total of 35 in observation, 36 in weight loss and 47 in metformin arms (118 total). The M+ (those already on metformin) were not included in primary analysis; 25 in observation arm and 22 in weight loss arm (47 total). For this review 2 pooled groups were considered (metformin is not an intervention for weight reduction and therefore not considered in this review). Control group: observation eligible for 3-arm study plus observation not eligible for metformin arm (participants with endometrial cancer only). Intervention group: weight loss eligible for 3-arm study plus weight loss not eligible for metformin arm (participants with endometrial cancer only). Of these, 71 participants were randomised; 38 into control arm and 33 into intervention arm. Inclusion criteria Women aged ≥ 18 years BMI > 30 kg/m^2 Wishing to retain fertility or who were at high risk of surgical complications due to comorbidities or obesity Histologically confirmed complex endometrial hyperplasia with atypia or grade 1 endometrioid endometrial adenocarcinoma on a curette or endometrial biopsy Computer tomography or magnetic resonance imaging scan of pelvis, abdomen and chest (or chest X-ray) suggesting the absence of extrauterine disease Myometrial invasion on magnetic resonance imaging of ≤ 50%

Janda 2021 *(Continued)*

No lymph vascular invasion on curetting or pipelle, if able to be assessed on sample

Serum CA-125 ≤ 30 U/mL

No hypersensitivity or contraindications for levonorgestrel-releasing intrauterine system (Mirena)

Ability to comply with endometrial biopsies at specified intervals

Negative serum or urine pregnancy test in premenopausal women and women < 2 years after the onset of menopause

Creatinine < 150 µmol/L (1.7 mg/dL) to be randomised into levonorgestrel-releasing intrauterine system + metformin arm

Exclusion criteria

ECOG PS > 3

Histological type other than endometrioid adenocarcinoma

Pregnant or planning to become pregnant during trial period

Has had prior treatment or undergoing current treatment for endometrial adenocarcinoma or endometrial hyperplasia with atypia

History of pelvic or abdominal radiotherapy

Unable to provide informed consent

Unable or unwilling to complete questionnaires

Congenital or acquired uterine anomaly which distorts the uterine cavity

Acute pelvic inflammatory disease

Conditions associated with increased susceptibility to infections with micro-organisms (e.g. AIDS, leukaemia, intravenous drug abuse) according to medical history

Genital actinomycosis

Current other cancer, except low-grade malignancies that do not require any systemic treatment or treatment to the pelvis

Breastfeeding

Levonorgestrel-releasing intrauterine system inserted > 12 weeks before randomisation/enrolment

Previous use of levonorgestrel-releasing intrauterine system within last 5 years from randomisation/enrolment

Contraindications to both metformin and weight loss

Baseline participant characteristics

Mean age 54.9 (SD 15.5) years in control arm, 52.9 (SD 13.6) years in intervention arm. Mean BMI 46.0 (SD 9.6) kg/m^2 in control arm, 48.6 (SD 9.6) kg/m^2 in intervention arm. Ethnicity data were not provided separately for this group of participants, however, in the study as a whole 60% were of European ethnicity, 5% Indigenous Australian, 10% Pacific Islander, 13% other and 8% declined to answer. All participants had stage 1 endometrioid endometrial cancer and had not undergone any treatment for their disease. Comorbid conditions were recorded as a Charlson Comorbidity Index scores: 0 (23.7% for control, 24.2%) for intervention; 1 (23.7% for control, 21.2% for intervention); 2 (18.4% for control, 30.3% for intervention); 3 (15.8% for control, 15.2% for intervention); 4 (13.2% for control, 6.1% for intervention); 5 (5.3% for control, 3.0% for intervention). ECOG PS were: 0 (65.8% for control, 54.5% for intervention), 1 (26.3% for control, 39.4% for intervention), 2 (7.9% for control, 3.0% for intervention), 3 (0% for control, 3.0% for intervention).

Janda 2021 *(Continued)*

Interventions	Intervention arm Levonorgestrel-intrauterine device plus weight-loss intervention. Participants provided with a voucher for a comprehensive subscription to a weight-loss programme (Weight Watchers) and encouraged to attend the face-to-face group meetings and to use the online tools and social networking opportunities for 6 months. Participants were encouraged to lose 7% bodyweight by 6 months and were called monthly to assess adherence to the weight loss programme and encouragement to increase its active use. Control arm Levonorgestrel-intrauterine device only. Standard, Australian Therapeutic Goods Administration approved device releasing levonorgestrel 52 mg at 20 µg/24 hours inserted into the uterine cavity and left for 6 months. Metformin arm
Outcomes	Primary outcomes Overall survival: no deaths reported in any arm during study. Adverse events: reported in both control arm (6 events) and intervention arm (5 events) Secondary outcomes Recurrence-free survival: not reported. Cancer-specific survival: no cancer-specific deaths reported in any arm during study Weight loss: change in weight from baseline to 6 months reported Cardiovascular and metabolic event frequency: 1 event reported in intervention arm (congestive heart failure). (In addition 3 participants in the control arm experienced chest pain of unknown cause therefore cannot determine if they were cardiovascular related). QoL: not reported. Power Power calculation performed, and sufficient detail provided to allow it to be replicated. Quote: "in the event of a pCR (pathological complete response) within the observation group higher than 45%, the study sample size would also have at least 80% power (95% confidence) to rule out a 60% observation only pCR in favor of a 75% in the M or WL groups; or alternatively also >80% power to rule out a 65% pCR in favor of 80% pCR rate."
Notes	Clinical trials.gov identifier: NCT01686126

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: randomisation stratified by diagnosis (cancer vs hyperplasia), BMI, menopausal status and treatment site. Acknowledged that results would be of "pragmatic signal finding nature" and not necessarily determine whether 1 intervention was better than another as individuals could avoid being randomised to a group if they were already taking metformin or involved in a weight loss programme. Quote: "randomisation was open label (unblinded)" Quote: "All participants received LNG-IUD [levonorgestrel-intrauterine device] and were additionally allocated to either i) OBS [observation]; ii) WL [weight

Janda 2021 *(Continued)*

		loss]; or iii) M [metformin] in 3:3:5 ratio. Randomization was stratified by diagnosis (EAC [endometrial adenocarcinoma] EHA [endometrial hyperplasia with atypia]); BMI (30 kg/m^2, 40 kg/m^2, ≥ 40 kg/m^2); menopausal status; and treatment site. Women with contraindications to M were randomized to OBS versus WL on 1:1 ratio. Similarly, women not eligible for WL were randomized into OBS versus M on 3:5 ratio. The same stratification factors were used as in the three-arm study."
Allocation concealment (selection bias)	Low risk	Comment: allocation concealed using a central telephone system. Quote: "centrally randomized through interactive Voice Response System (NHMRC Clinical Trials Centre, Sydney, Australia)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: due to nature of intervention, unable to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: both pathologists and gynaeoncologists assessing response were blinded for the outcome assessments. Quote: "yes, they were blinded to outcome."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up Entered into study: 38 into observation control arm and 33 into weight loss intervention arm. Withdrew from study: 2 from observation control arm and 2 from weight loss intervention arm. Reasons provided for overall study but not specifically for these 4 participants. Completed the study: 36 in observation control arm and 31 in weight loss intervention arm. Overall < 10% loss to follow-up. No missing data reported. Intention-to-treat analysis Comment: performed for primary and secondary analyses. Quote: "All primary and secondary analyses except where stated, were performed according to the intention-to-treat principle."
Selective reporting (reporting bias)	High risk	Comment: multiple versions of the protocol were published (most recent version 9) and the trial registered prospectively on ClinicalTrials.gov. QoL outcomes not reported.
Other bias	Low risk	Source of funding: (quote): "Funding was received from the Royal Brisbane and Women's Hospital Foundation, Cancer Australia (APP1044900, APP1078121), The University of Queensland (Academic Title Holder Grant), Brisbane Lord Mayors Community Trust, Australia and New Zealand Gynecological Oncology Group (ANZGOG), and Cherish Women's Cancer Foundation." Ethical approval: obtained. Conflicts of interest: disclosed, none relevant to this trial. Quote: "AO reports grants, personal fees, and other funding from Surgical Performance PTY LTD, and grants from Medtronic, not directly related to the sub-

Janda 2021 *(Continued)*

	ject of this manuscript. AO reports consultancy fees from Baxter Healthcare Australia and New Zealand and Astra Zeneca Australia, not directly related to the subject of this manuscript. In addition, AO has a trademark licensed to Surgical Performance Pty Ltd. All other authors declare they have nothing to disclose." Other sources Comment: sample sized increased in accordance with addition of third arm to study. Protocol amended to include weight loss arm after study opened. Only 1 woman randomised prior to approval of amendment. 15 biopsies not available for central review for primary analysis. Analysed at treating hospital only. However, pathology reporting not relevant to this review.

Maxwell-Smith 2019

Study characteristics	
Methods	Design: parallel, 2-arm, open-label randomised controlled trial Setting: multicentre study in Perth, Australia Follow-up: 24 weeks following end of intervention (12 weeks), participants commenced a 12-week maintenance period.
Participants	Number of participants enroled In total, 68 participants randomised; 34 into intervention arm and 34 into control arm. Of these, 11 participants with endometrial cancer and a BMI ≥ 25 kg/m^2 were randomised; 8 into intervention arm and 3 into control arm. Inclusion criteria Stage 1 and 2 colorectal and gynaecological cancer survivors Aged 18–80 years Finished active treatment (surgery, chemotherapy, radiotherapy, or a combination) in the previous 5 years Completing < 150 minutes of moderate–vigorous intensity physical activity per week Comorbidities resulting in increased cardiovascular risk identified through hospital records (i.e. on blood pressure medication or have blood pressure (systolic/diastolic) > 150/90 mmHg, BMI > 28 kg/m^2, hypercholesterolaemia > 5.2 mmol/L) or an American Society of Anesthesiologists score 2 or 3 in the absence of medical records In remission at time of recruitment English-reading and speaking Live in the Perth Metropolitan area Have no surgery planned for the 6 months following recruitment Exclusion criteria Meeting the physical activity guidelines of > 150 minutes of moderate–vigorous intensity physical activity per week

Maxwell-Smith 2019 *(Continued)*

	Have a current diagnosis of a severe psychiatric illness or cardiac abnormalities (those with minor psychiatric diagnoses will be eligible if they are willing and able to participate in the intervention) Severe disabilities including arthritis American Society of Anesthesiologists scores of 1 or 4 Already enroled in a physical activity programme/trial Diagnosed with uterine carcinosarcoma (malignant mixed Müllerian tumours), uterine serous carcinoma or ovarian cancer Baseline participant characteristics These characteristics relate only to the 11 participants with endometrial cancer with a BMI ≥ 25 kg/m^2. Mean age 65.9 (SD 5.7) years, mean BMI 31.9 (SD 4.2) kg/m^2. Ethnicity of participants with endometrial cancer alone was not provided. Within the whole study population, 97.1% were Caucasian (assumed to be white people) and 2.9% Indian. Comorbid conditions included smoking (9.1%), angina/myocardial infarction (18.2%), receiving medication to lower blood pressure (54.5%), systolic hypertension (63.6%), diastolic hypertension (63.6%), hypercholesterolaemia (36.4%), stress (36.4%) and depression (9.1%). ECOG status was not collected by the study authors. All participants had grade 1 endometrioid endometrial cancer, with 72.7% having stage Ia disease and 27.3% having stage Ib disease. All 11 participants had undergone primary surgery for their endometrial cancer with 1 participant undergoing adjuvant radiotherapy, and 1 undergoing both adjuvant chemotherapy and radiotherapy.
Interventions	Intervention arm Wearable technology (Fitbit Alta), in conjunction with instruction on how to perform behaviour, action planning, goal setting and coping planning. Consisted of 3 components • The Fitbit Alta recorded daily steps, moderate–vigorous intensity physical activity accrued in bouts of ≥ 10 minutes (active minutes), and distance and provided automated prompts encouraging participants to accumulate ≥250 steps per hour. • 2-hour group sessions (approximately 11 per group) run by behaviour change specialist in weeks 1 and 4. Emphasis given to reducing bouts of sedentary behaviour and responding to automatic prompts to take steps, in addition to encouraging planned bouts of moderate–vigorous intensity physical activity. Participants were assisted to complete action-planning and goal-setting activities. • 20-minute telephone call during week 8 to provide support and feedback regarding physical activity progress, review goals, action plans and coping-planning strategies. Control arm Printed material on physical activity guidelines and not specifically encouraged to increase their activity.
Outcomes	Primary outcomes Overall survival: no deaths reported in either arm during study. Adverse events: no adverse events reported in either arm during study. Secondary outcomes Recurrence-free survival: not reported. Cancer-specific survival: no cancer-specific deaths reported in either arm during study. Weight loss: change in weight from baseline to 24 weeks reported. Cardiovascular and metabolic event frequency: no events recorded in either arm during study. QoL: not reported.

Maxwell-Smith 2019 *(Continued)*

Quote: "We did intend to assess QoL outcomes using SF12, per the protocol. However, we since learned that the SF12 is licenced to another organisation external to RAND, which permits non-commercial use."

Power

Power calculation performed, and sufficient details provided to allow it to be replicated.

Quote: "To detect a small-to-moderate effect (f = 0.17), as identified in similar designs, a group by time interaction for the primary outcome of MVPA [moderate–vigorous intensity physical activity] with 80% power and an alpha level of 0.05, 56 participants were required (28 per group). We recruited an additional 20% to allow for attrition."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: consecutive randomisation codes using statistical software package. Quote: "an independent statistician who was blinded to the assessments and intervention randomized participants using consecutive randomization codes (STATA v14) with a 1:1 allocation in blocks of 4."
Allocation concealment (selection bias)	Low risk	Comment: independent statistician performed randomisation and allocation. Quote: "an independent statistician who was blinded to the assessments and intervention randomized participants using consecutive randomization codes (STATA v14) with a 1:1 allocation in blocks of 4."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessments performed by personnel blinded to allocation. Quote: "Assessments postrandomization was conducted at St John of God Subiaco Hospital by hospital staff blinded to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up Entered study: 8 into intervention arm and 3 into control arm. Withdrew from study: 0 in intervention arm and 0 in control arm. Completed study: 8 in intervention arm and 3 in control arm. Intention-to-treat analysis Comment: intention-to-treat analyses performed for both activity measures and cardiovascular risk outcomes. Quote: "None of the 7 participants who had missing data across the 3 assessments were endometrial patients."
Selective reporting (reporting bias)	Unclear risk	Comment: protocol published and trial registered prospectively on anzctr.org.au. QoL data not reported.

Maxwell-Smith 2019 *(Continued)*

		Quote: "We did intend to assess QoL outcomes using SF12, per the protocol. However, we since learned that the SF12 is licenced to another organisation external to RAND, which permits non-commercial use"
Other bias	Low risk	Source of funding: "This work was sponsored by a grant from the Tonkinson Colorectal Cancer Research Fund (no. 57838). We acknowledge the small grant from the St John of God Gynecologic Oncology Research Group, Western Australia … Ruth Jiménez-Castuera received a grant from the Junta of Extremadura, Spain, to sponsor her role in the study." Ethical approval: granted. Quote: "The study was approved by the St John of God Human Research Ethics Committee (reference no. 1102)." Conflicts of interest: no conflicts of interest reported. Other sources: none identified.

McCarroll 2014

Study characteristics	
Methods	Design: parallel design, 2-arm, randomised controlled trial Setting: single-centre study in Ohio, USA Used Case Comprehensive Cancer Center (affiliates University Hospitals Case Medical Center and Cleveland Clinic) tumor registry to identify participants. Letter was sent to potential participants describing the study and women were invited to attend an informational session. Follow-up: 12 months. Outcome measures assessed at baseline, 3, 6 and 12 months.
Participants	Number of participants enroled 75 participants enroled; 41 in intervention arm and 34 in control arm Inclusion criteria Histologically confirmed endometrial cancer diagnosed within last 3 years Stage I or II Undergone surgical treatment of endometrial cancer in the form of total abdominal hysterectomy and bilateral salpingo-oophorectomy with/without lymphadenectomy No evidence of disease at time of enrolment ECOG PS 0–2 BMI ≥ 25 kg/m^2 Medical clearance from primary care physician and approval to contact patient by treating gynae-oncologist Exclusion criteria Unable to read consent form Severe depression, dementia or cognitive deficit Unavailable for longitudinal follow-up assessment

McCarroll 2014 *(Continued)*

	Pre-existing medical conditions that prevent participation in unsupervised walking Participation in weight-loss or exercise programme in preceding 6 months Baseline participant characteristics No differences in the baseline characteristics of participants between groups. Mean age 57 (SD 8.6) years in intervention arm, 58.9 (SD 10.9) in control arm. Overall, mean BMI 36.5 kg/m^2; 36.4 kg/m^2 (SD 5.5) in intervention arm and 36.5 kg/m^2 (SD 9.6) in control arm. No ethnicity data were available. Comorbidities: hypertension in 31.7% and diabetes in 17.1% of intervention arm; hypertension in 35.3% and diabetes in 26.5% of control arm. All participants had an ECOG PS 0–2. All participants underwent surgical treatment of their endometrial cancer, on average, 20.7 months earlier. In addition, 39.0% of participants in the intervention arm and 35.3% of participants in the control arm had undergone adjuvant radiotherapy. Details of grade, stage and histological type of endometrial cancer were not provided.
Interventions	Intervention arm 16 group sessions focusing on diet and physical activity over 6 months and an additional 3 face-to-face counselling visits at 3, 6 and 12 months. Feedback and support were provided by a registered dietitian after the end of the group sessions by telephone, email and newsletters. Group topics included physical activity, nutrition and improving diet quality and behaviour modification designed to increase women's self-efficacy. Sessions were 60 min with 8–10 women per group. Participants weighed in private at beginning of each session and weekly food/activity records reviewed. After 6 months when sessions ended, additional feedback and support was provided via newsletters, telephone and email. Topics included holiday recipes, reinforcement of goals for increasing calcium, decreasing sodium and ways to increase physical activity. Intervention followed a stepwise, phased approach using strategies outlined by social cognitive theory, indicating that the optimal intervention for a major behaviour change should focus on establishing short-term goals, enabling the person to build self-efficacy. Control arm Received "Healthy Eating & Physical Activity Across Your Lifespan, Better Health and You" information brochure only. Participants also attended physician counselling sessions at 3, 6 and 12 months, but these visits did not include any lifestyle advice related to weight loss, physical activity or nutrition.
Outcomes	Primary outcomes Overall survival: no deaths reported during 12-month study Adverse events: reported adverse events in both intervention and control arms. Quote: "(Adverse events were reported) as required by the IRB … The true adverse events were all in the intervention group" Second outcomes Recurrence-free survival: not reported Cancer-specific survival: no deaths reported during 12-month study Weight loss: weight change from baseline at 3, 6 and 12 months reported Cardiovascular and metabolic event frequency: no events reported QoL: change in QoL from baseline measured at 3, 6 and 12 months using FACT-G questionnaire at baseline, 3, 6 and 12 months. Power Power calculation performed and sufficient detail provided to allow it to be replicated.

McCarroll 2014 *(Continued)*

	Quote: "Approximately 37 patients per group were needed to provide 80% power to detect a difference between groups in mean weight change from baseline to 12 months of 4.0 kg or greater (alpha= 0.05, two-sided, SD= 6.0; effect size= 0.67) and to assess changes in PA with a similar effect size. Effect sizes of 0.5 are considered medium and 0.8 or greater large."
Notes	This is the definitive RCT following on from the pilot study also included in this review (von Gruenigen 2008).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: block randomisation performed according to baseline BMI. Quote: "Randomization was stratified using block sizes of 6 or 8 by baseline BMI (25.0–39.9 versus > 40)."
Allocation concealment (selection bias)	Unclear risk	Comment: no details of allocation concealment provided by study authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants and personnel not possible due to nature of intervention. Principal investigator involved in delivery of intervention so aware of randomisation. Quote: "Due to the interventions performed by the study team (dietitian, physical therapist, psychologist, etc.), they were able to know who was in each group."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: principal investigator performed outcome assessments and was unblinded to treatment group allocation. This is unlikely to affect weight measurements but may impact upon QoL assessments.
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered into the study: 41 in intervention arm and 34 in control arm Withdrew from study: 6 in intervention arm and 10 in control arm Completed study: 35 in intervention arm and 24 in control arm Reasons for withdrawal from study not provided by study authors. Study was underpowered at 12 months to detect a weight loss of ≥ 4.0 kg in intervention arm. Quote: "Attrition in the trial overall was 21.3%. Six (14.6%) patients in the LI group (intervention) versus 10 (29.4%) in UC (control) did not complete the twelve-month assessments, P = 0.159. Thirty-one (75.6%) participants in the (intervention arm) attended 14 or more of the 16 sessions; mean adherence was 84.1%. Intention-to-treat analysis Comment: analyses conducted according to intention-to-treat protocol; however, only 85.4% of participants in intervention arm and 70.6% of participants in control arm attended 12-month assessments. Missing data were imputed by multiple imputation.
Selective reporting (reporting bias)	Low risk	Comment: protocol not published but trial registered prospectively on ClinicalTrials.gov and all prespecified outcomes reported.

McCarroll 2014 *(Continued)*

Other bias	Low risk	Source of funding: "This research was supported by the American Cancer Society." Ethical approval: obtained Quote: "Institutional review board approval was granted …" Conflicts of interest: no significant conflicts of interest noted.

Mohammad 2019

Study characteristics	
Methods	Design: parallel, 2-arm, randomised controlled trial. Random distribution into 2 attending clinics creating 2 participant groups Setting: single centre study in the USA. Follow-up: 24 months
Participants	Number of participants enroled A total of 106 participants randomised; 62 into intervention arm and 44 into control arm Inclusion criteria Endometrial cancer BMI > 34 kg/m^2 Exclusion criteria Not reported Baseline patient characteristics Mean age not reported. The 'average' BMI was reported as 44 kg/m^2, but it is unknown if this was the median or mean and no SD reported. No ethnicity data were provided. All participants had undergone surgical staging for their endometrial cancer but no further information regarding adjuvant treatment reported. Details of comorbid conditions or the ECOG PS not reported. No information regarding histological subtype, grade or stage of cancer reported. Quote: "The average BMI at consult was 44 kg/m^2 and did not differ between groups, nor did age, stage, chemotherapy, or the rate of open surgery."
Interventions	Intervention arm 6-page cancer-specific nutritional guidelines, 20 minutes of physician-diet counselling at initial consultation. Guidelines suggested daily carbohydrates 40 g, and a shift to plant-based foods dominated by plant fats, with minimal aged cheeses and lean meat. Fasting encouraged. Control arm Standard care. Encouraged to have healthy lifestyle and diet with dietitian referral.
Outcomes	Primary outcomes Overall survival: not reported Adverse events: not reported

Mohammad 2019 *(Continued)*

	Secondary outcomes Recurrence-free survival: not reported Cancer-specific survival: not reported Weight loss: percentage weight loss from baseline at 24 months reported Cardiovascular and metabolic event frequency: not reported QoL: not reported Power Unknown if power calculation performed. Quote: "This study provides a basis for evaluation of the long-term benefits of weight loss."
Notes	Conference abstract provided all above information. We contacted study authors but received no response to requests for more detailed information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: unclear how groups were randomly generated. Quote: "Random distribution of endometrial cancer patients into 2 attending clinics created 2 patient groups."
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided regarding blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered into study: 62 into intervention arm and 44 into control arm. Withdrew from study: 13 participants at 12 months, distribution between arms unknown. Unclear if further withdrawals at 24 months. Completed the study: 93 participants at 12 months, distribution between arms unknown. Unclear if number maintained at 24 months. Missing data: data from 93 participants available at 12 months, unclear if further missing data at 24 months. Intention-to-treat analysis Comment: not performed.
Selective reporting (reporting bias)	Unclear risk	Comment: unable to confirm if protocol published or trial registered prospectively and, therefore, unable to confirm if all prespecified outcomes reported.

Mohammad 2019 *(Continued)*

Other bias	Unclear risk	Comment: all information obtained from a conference abstract; therefore, unable to comment on source of funding, ethical approval, conflicts of interest or any other sources of bias.

Nock 2013

Study characteristics	
Methods	Design: parallel, 2-arm, open-label, randomised trial Setting: multicentre study in USA. Enroled in 'REWARD' lifestyle intervention at University Hospitals Case Medical Center (UHCMC) and the Cleveland Clinic (CCF) Follow-up: 24 weeks. Assessed before and after a 16-week exercise intervention and 12 and 24 weeks after intervention
Participants	Number of participants enroled 100 participants randomised. Enrolment per group not reported. Inclusion criteria Histologically confirmed Stage I endometrial adenocarcinoma, grade 1 or 2, with no adjuvant chemotherapy. Participants eligible from 3 months after completion of treatment but no later than 4 years after completion of treatment. BMI ≥ 30.0 kg/m^2 (obese) Approved to be contacted by the participant's treating gynaecological oncologist Meets screening criteria including successful completion of a cardiopulmonary stress test Receives medical clearance from the participant's primary care physician or gynaecological oncologist to exercise in this study Exclusion criteria Unable to read and provide informed consent. Women currently participating in a structured weight loss or exercise programme in past 6 months or any woman who had had bariatric surgery or was planning to undergo bariatric surgery in next 12 months Did not consent to be in study or who was unavailable for follow-up assessments Pre-existing medical conditions that would be a barrier for participation in supervised exercise Baseline participant characteristics Mean age 59.9 (SD 8.8) years, mean BMI 42.1 (SD 8.2) kg/m^2. No ethnicity data were available. Comorbid conditions and ECOG PS not reported. 86% of participants had only surgical treatment for their endometrial cancer while 14% required surgery and radiation treatment. All participants had stage I, grade 1 or 2 endometrioid adenocarcinoma.
Interventions	'Assisted rate' exercise intervention Cycling on stationary, recumbent exercise bike with motor assistance to maintain pedalling rate 35% greater than their voluntary rate. 45- to 60-minute sessions 3 times per week for 8 weeks. Informational brochure ("Better Health and You," Weight Control Information Network, June, 2004) 'Voluntary rate' exercise intervention

Nock 2013 *(Continued)*

	Cycling on stationary, recumbent exercise bike at preferred pedalling rate for 45–60 minutes, 3 times per week for 8 weeks. Informational brochure ("Better Health and You," Weight Control Information Network, June, 2004)
Outcomes	Primary outcomes Overall survival: not reported Adverse events: not reported Secondary outcomes Recurrence-free survival: not reported Cancer-specific survival: not reported Weight loss: not reported Cardiovascular and metabolic event frequency: not reported QoL: not reported Power Comment: not reported
Notes	ClinicalTrials.gov identifier: NCT01870947 Authors contacted, but no data supplied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information regarding random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded due to nature of intervention. Quote: "masking: none (open label)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information regarding blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up Entered into study: 95 participants. No information provided regarding group allocation. Withdrew from study: no information provided. Completed the study: no information provided. Missing data: no information provided. Intention-to-treat analysis Comment: no information provided.

Nock 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: unable to confirm with study authors regarding publication of protocol. Trial registered prospectively on ClinicalTrials.gov. Unable to comment if all prespecified outcomes reported.
Other bias	Unclear risk	Source of funding: (quote): "This work was financially supported by the National Institutes of Health (NIH) National Cancer Institute (NCI) grant no. R01-CA175100 (awarded to NLN) and by the NIH National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS) grant no. UL1RR024989." Ethical approval: obtained. Quote: "The study was approved by the Institutional Review Support Care Cancer (2020) 28:2311–23192317 Boards of University Hospitals Case Medical Center and the Cleveland Clinic" Conflicts of interest: none declared. Other sources: without further information being provided by authors, unable to confirm the presence of absence of further sources of bias.

von Gruenigen 2008

Study characteristics	
Methods	Design: parallel, prospective, 2-arm, randomised controlled trial Setting: single-centre study in Ohio, USA. Women from in the cancer registry at the Ireland Cancer Center diagnosed in 2001–2004 Follow-up: 24 months
Participants	Number of participants enroled 45 participants enroled; 23 into intervention arm and 22 into control arm Inclusion criteria Histologically confirmed endometrial cancer Stage I or II Undergone surgical treatment of endometrial cancer in the form of total abdominal hysterectomy and bilateral salpingo-oophorectomy with/without lymphadenectomy No evidence of disease at time of enrolment ECOG PS 0–2 BMI > 25 kg/m^2 Exclusion criteria Clear cell or papillary serous histology Baseline participant characteristics No differences in the baseline characteristics between arms. Mean age 54 (SEM 2.0) years in intervention arm, 55.5 (SEM 1.6) years in control arm.

von Gruenigen 2008 *(Continued)*

	Overall, mean BMI 42.3 kg/m^2; 43.5 (SEM 2.1) kg/m^2 in intervention arm, 41.1 (SEM 2.2) kg/m^2 in control arm. Caucasian (assumed to be white people): 100% in intervention arm, 95.4% in control arm. Comorbidities: hypertension 65.2%, diabetes 17.4% and metabolic syndrome 26.1% of participants in intervention arm; hypertension 36.4%, diabetes 27.3% and metabolic syndrome 27.3% of participants in control arm. All participants ECOG PS 0–2. All participants underwent surgical treatment of their endometrial cancer, on average, 2 years earlier. Details of adjuvant treatment and grade, stage and histological type of endometrial cancer not reported.
Interventions	Intervention arm Group sessions based on other nutrition and exercise goals and delivered by a registered dietitian, principal investigator and psychologist for 6 months. Participants encouraged to gradually increase walking or other aerobic activity to 5 days per week for ≥ 45 minutes per session. Reinforcement of content of group sessions provided on an individual basis by principal investigator at 3, 6 and 12 months. Topics included: weight loss readiness and goal-setting, physical activity, portion sizes and food intake per mypyramid.gov, emotional eating/negative thinking, behaviour modification, grocery shopping and reading food labels, relapse prevention, eating out and in social situations, and stress management. Groups met weekly for 6 weeks, every 2 weeks for 1 month and monthly for 3 months. Registered dietitian contacted participants by telephone or newsletter every week that group did not meet. Telephone calls structured in content and included reinforcement and discussion regarding the previous week's topic. Participants given feedback on individual progress towards physical activity and nutrition goals. Pedometers provided to for participant feedback. Control arm Received usual care and provided with a generic booklet on improving health. Individual meetings were held with the principal investigator at 3, 6 and 12 months consisting of counselling regarding overall health concerns rather than a discussion about weight loss and physical activity.
Outcomes	Primary outcomes Overall survival: deaths reported during study (24 months) but insufficient data available to determine hazard ratio. 2 participants deceased: 1 to brain aneurysm and 1 to kidney cancer. Both deaths in control arm. Adverse events: no reported adverse events in either arm. Second outcomes Recurrence-free survival: not reported Cancer-specific survival: deaths reported during study (24 months) but insufficient data available to determine hazard ratio. 2 participants deceased: 1 to brain aneurysm and 1 to kidney cancer. Both deaths in control arm. Weight loss: weight change from baseline to 3, 6, 9, 12 and 24 months reported Cardiovascular and metabolic event frequency: no events reported up to 24 months' follow-up QoL: change in QoL from baseline at 3, 6, 9 and 12 months reported using FACT-G questionnaire using Physical, Functional, Family Social, Emotional Well-being, Fatigue and Endometrial Symptom subscales. Power Power calculation performed, and sufficient detail was provided to allow it to be replicated.

von Gruenigen 2008 *(Continued)*

	Quote: "Approximately 25 patients per group were needed to provide 80% power to detect a difference between groups in mean weight change from baseline to 12 months of 5 kg (11 lb) or greater, representing approximately 5% for an obese female (alpha = 0.05, two-sided, SD = 5.0). Five percent weight change is considered clinically relevant and a recommended goal for weight loss over 6 months."
Notes	Follow-up described as 12 months' duration in publication; however, when contacted, authors provided data for weight change up to 24 months. Pilot study preceding the definitive trial, which is also included in this review (McCarroll 2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: stratified block randomisation based on BMI employed. Quote: "After enrolment, participants were randomly assigned (to intervention or control arm) … Randomization was stratified according to patient BMI (25–39.9 versus 40 kg/m^2) using a stratified blocked randomization scheme."
Allocation concealment (selection bias)	Unclear risk	Comment: no details of allocation concealment provided by study authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants and personnel not possible due to nature of intervention. Principal investigator involved in delivery of intervention so aware of randomisation. Quote: "Due to the interventions performed by the study team (dietitian, Physical therapist, psychologist, etc.), they were able to know who was in each group."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: principal investigator performed outcome assessments and was unblinded to treatment group allocation. This is unlikely to affect weight measurements but may have impacted QoL assessments.
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered into study: 23 in intervention arm, 22 in control arm Withdrew from study: 5 in intervention arm, 2 in control arm Completed study: 17 in intervention arm, 20 in control arm (though data from assessment at 12 months missing for 2 participants in control arm) 2 withdrawals in intervention arm were due to issues with work, the reason for the other 3 withdrawals in this group were not reported. 2 withdrawals from the control arm occurred prior to the first assessment at 3 months and the reasons were not reported. Quote: "Attrition in the trial overall was 16% [2 patients (10%) in the UC [usual care] group versus 5 (22%) in the LI [intervention] group; P = 0.242], therefore 84% completed follow-up assessments. Specifically, 78% of patients [LI: 17/23 (74%), UC: 18/22 (82%)] completed the 12-month assessment time point and there was no difference between groups (P = 0.523)" Intention-to-treat analysis Analyses conducted according to intention-to-treat protocol. However, there were significant missing data; 19% of weight values and 15–19% of QoL data missing. Missing data were imputed using 3 techniques; last and next average (average of last and next known values), previous row mean method and last observation carried forward. All produced similar findings and so only the re-

von Gruenigen 2008 *(Continued)*

		sults obtained using the first approach were included in the journal publication. Quote: "Imputation was done for 19% (35/ 180) of weight values, 10 patients (LI: 6 and UC: 4) had weight values imputed for the final weight. These patients opted to not complete the assessment and values were imputed based on the most recent physician visit, if they had one or were imputed … Imputation was done on between 15–19% of values for the various QoL and eating behavior measures."
Selective reporting (reporting bias)	Low risk	Comment: protocol not published but trial registered prospectively on ClinicalTrials.gov and all prespecified outcomes reported.
Other bias	High risk	Source of funding: "supported by a grant from the Lance Armstrong Foundation." Ethical approval: (quote): "Institutional review board approval was obtained …" Conflicts of interest: no significant conflicts of interest noted. Other sources Study failed to recruit sufficient numbers to meet a priori total in time frame. 1 participant in intervention arm underwent gastric bypass at 9 months after start of intervention and another between 12 and 24 months. Both were included in final analysis.

Yeh 2021

Study characteristics	
Methods	Design: parallel, single-blind, 3-arm, randomised controlled trial named SPIRIT Setting: single-centre study in USA in Baltimore metropolitan area between August 2015 and December 2016 through mass mailing, placement of brochures in doctors' clinics, distribution of flyers in various community settings (e.g. health fairs), direct referral from study physicians, word of mouth, advertisement in local newspapers and online advertising. Follow-up: 12 months. Weights measured at baseline and 3, 6 and 12 months
Participants	Number of participants enroled In total 121 participants randomised; 40 into control arm, 39 into weight loss arm and 42 into metformin arm Of these, 7 had endometrial cancer; 2 in control arm, 3 in weight loss arm and 2 into metformin arm Inclusion criteria Women and men aged ≥ 18 years Prior diagnosis of a solid malignant (including endometrial cancer) Completed surgical, chemotherapy or radiation therapy ≥ 3 months prior to enrolment and anticipated treatment-free lifespan of ≥ 12 months BMI ≥ 25 kg/m^2 and < 400 lbs (181 kg) Internet and telephone access

Yeh 2021 *(Continued)*

	Willingness to change diet, physical activity and weight Exclusion criteria Breastfeeding, pregnant or planning pregnancy within next year Medication-treated diabetes Non-fasting blood glucose ≥ 200 mg/dL or glycated haemoglobin ≥ 7% Current or prior regular use of metformin within past 3 months Significant renal disease or dysfunction defined as estimated glomerular filtration rate < 45 mL/minute/1.73 m^2 Uncontrolled concurrent medical condition likely to limit compliance with the study interventions History of lactic acidosis by self-report Prior or planned bariatric surgery Significant hepatic dysfunction (aspartate aminotransferase/alanine transaminase ≥ 2 × upper limit of normal or reported liver disease) Self-reported mean consumption > 14 alcoholic drink per week Currently enroled or planned to enrol in weight loss programme Haemoglobin < 9 g/dL, platelet count < 100/μL, white blood cell count < 2.5 × 10^9/L Plans to relocate from the area within 1 year Use of prescription weight loss medication(s) (e.g. lorcaserin, topiramate/phentermine, phentermine, liraglutide and bupropion/naltrexone), including off-label use of drugs for weight loss or non-prescription weight loss medications such as orlistat within past 6 months. Baseline participant characteristics For the 7 participants with endometrial cancer, mean age 54 (SD 7.5) years, mean BMI 35.5 (SD 5.0) kg/m^2. Ethnicity data specifically for participants with a history of endometrial cancer were not available. 1 participant was prediabetic and 1 reported a history of angina, arrhythmia and hypertension. Histological type of endometrial cancer not collected; 3 had stage I disease, 1 had stage III disease and 1 had stage IV disease. In 2 participants, the cancer stage was not known. Primary treatment and ECOG PS not reported. Baseline characteristics of participants according to group allocation not reported.
Interventions	Control arm Self-directed weight loss. Meeting with trial team at beginning of study and provision of written information/websites about weight management and, if desired, after final data collection visit at 12 months. Coach-directed behavioural weight loss arm Remote lifestyle coaching intervention-behaviour-based telephonic coaching with web-based support to promote healthy lifestyle and weight loss. Goal was to achieve ≥ 5% weight loss in first 6 months and to maintain these improvements through month 12 by meeting dietary and exercise goals. Specific strategies included increased physical activity, caloric restriction, self-monitoring (diet, exercise and weight), goal setting and problem-solving. Metformin arm Metformin, up to 2000 mg/day. Dosing could be flexible, depending on tolerance, and given 2 or 3 times per day orally with meals for 12 months. Participants received medication-related education and counseling from a study staff member immediately following randomisation.

Yeh 2021 *(Continued)*

Outcomes	Primary outcomes Overall survival: no deaths reported in any arm during study. Adverse events: 1 hospitalisation for heart failure (metformin arm). No other adverse events reported in any arm during study. Secondary outcomes Recurrence-free survival: no known recurrences in any arm during study. Cancer-specific survival: no cancer-specific deaths reported in any arm during study. Weight loss: change in weight loss from baseline to 12 months reported. Cardiovascular and metabolic event frequency: 1 patient had congestive heart failure and was hospitalised (metformin arm). QoL: change in QoL from baseline to 12 months measured, but data were not analysed at time of undertaking this review. Power Power calculation performed, and sufficient detail provided to allow it to be replicated. Quote: "The required sample size for the study was powered for comparing change in IGF-1 at 6 months from baseline between: (1) coach-directed weight loss intervention and self-directed arm and (2) metformin and self-directed arm, respectively, each with 80% power using a 2-sided z-test with α of 0.025. The comparison between the coach-directed and metformin arms was exploratory and not included in sample size and power considerations."
Notes	Clinical Trials.gov identifier: NCT02431676

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: computer-generated algorithm, generated prior to study commencement by a blinded statistician. Quote: "Randomization assignments were computer-generated and stratified according to baseline BMI category (BMI < 30; BMI ≥ 30 kg/m^2) and race (black, non-black)." Quote: "The statistician has never seen participants, did not see randomization arm or outcome data until data analysis stage."
Allocation concealment (selection bias)	Low risk	Comment: computer-generated, randomly selected block sizes of 3 and 6. Quote: "Assignments were generated with equal allocation to the three study arms within randomly selected block sizes of 3 and 6 using a computerized program by the study statistician."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and personnel were unblinded. Quote: "Intervention assignment was not blinded to the trial participants, nor the intervention staff."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessments performed by blinded study and laboratory staff.

Yeh 2021 *(Continued)*

		Quote: "study staff involved in follow-up data collection and lab staff involved in lab measures were masked to the randomization assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered study: 2 in control arm, 3 in weight loss arm and 2 in metformin arm Withdrew from study: 1 withdrew from study between 6 and 12 months. Completed study: 6 participants completed study. Missing data for 1 participant for both laboratory and weight measurements. Intention-to-treat analysis Comment: analyses conducted according to an intention-to-treat protocol. Missing data were imputed by multiple imputation. Quote: "Intervention effects were analyzed using an intention-to-treat approach." Quote: "Sensitivity analysis through multiple imputation based on sensible missing not at random scenarios was conducted to evaluate the robustness of the finding under MAR [missing at random] assumption."
Selective reporting (reporting bias)	High risk	Comment: protocol not published but trial registered prospectively on ClinicalTrials.gov. QoL data were not analysed or reported.
Other bias	Unclear risk	Source of funding: (quote) "This project was supported by the Maryland Cigarette Restitution Fund and Johns Hopkins Sidney Kimmel Comprehensive Cancer Center. Drs. Yeh and Kanarek, were also supported in part by the National Cancer Institute's Cancer Centers Support Grant (5P30CA006973)." Ethical approval: (quote) "The SPIRIT trial was reviewed and approved by an Institutional Review Board at Johns Hopkins University School of Medicine." Conflicts of interest: declared, may have impacted on trial. Quote: "Healthways, Inc. developed the website for the original POWER trial in collaboration with Johns Hopkins investigators (Appel, Dalcin, Jerome). On the basis of POWER trial results, Healthways developed and commercialized a weight-loss intervention program called Innergy. This project used the Innergy website to deliver the weight loss intervention. Under an agreement with Healthways, Johns Hopkins faculty (Appel, Dalcin, Jerome) monitored the Innergy program's content and process (staffing, training, and counseling) and outcomes (engagement and weight loss) to ensure consistency with the original POWER Trial. Johns Hopkins received fees for these services and faculty members (Appel, Dalcin, Jerome) who participated in the consulting services receive a portion of these fees. Johns Hopkins receives royalty on sales of the Innergy program. After completion of this project, Healthways sold the Innergy platform to Sharecare, which ended the relationship with Johns Hopkins. Dr. Maruthur is co-inventor of virtual diabetes prevention program technology; under a license agreement between Johns Hopkins HealthCare Solutions and the Johns Hopkins University, Dr. Maruthur and the University are entitled to royalty distributions related to this technology. This technology/intervention is not discussed in this publication. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies." Other sources: none identified.

Zamorano 2021

Study characteristics	
Methods	Design: parallel, 2-arm, open-label randomised controlled trial Setting: single centre in Washington University in St Louis School of Medicine Gynecologic Oncology Clinic (US) between 18 May 2017 and 31 December 2017 Follow-up: 12 months. Primary study outcome was weight loss at 6 months. Secondary outcomes included weight loss at 12 months.
Participants	Number of participants enroled 80 participants randomised; 40 into SMS text-message-based intervention arm and 40 into enhanced usual care control arm Inclusion criteria Women aged ≥ 18 years and with biopsy-confirmed endometrial cancer BMI ≥ 30 kg/m^2 Must be able to read and speak English Able to give written informed consent Completed prior surgical management and adjuvant endometrial cancer treatment (if indicated) No concurrent or planned chemotherapy or radiotherapy (or both) Could be undergoing hormonal treatment for endometrial cancer ECOG PS 0–2 Life expectancy ≥ 1 year Must have a telephone capable of receiving text messages Exclusion criteria Must not be participating in another formal weight loss programme Must not have any other clinically significant medical disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a participant's ability to give informed consent For participants randomised to intervention arm: No uncontrolled serious medical or psychiatric condition(s) that would affect the patient's ability to participate in the interventional study, e.g. uncontrolled hypertension, symptomatic cardiac disease or severe/uncontrolled depression as indicated by a previously completed 9-item Patient Health Questionnaire score > 9. No diagnoses of any other invasive malignancy other than endometrial cancer or non-melanoma skin cancer that required active treatment currently or within the last 2 years. Baseline participant characteristics Mean age 59 (SD 9.8) years, mean BMI 41.7 (SD 8.7) kg/m^2. In intervention arm, 80% were white, 15% black, 0% Asian and 5% other ethnicity. In control arm, 75% were white, 20% black, 5% Asian and 0% other ethnicity. Comorbidities included coronary artery disease (2.5% intervention, 0 control), diabetes (22.5% intervention, 25% control), hypertension (45% intervention, 67.5% control), hyperlipidaemia (15% intervention, 25% control), arthritis (10% intervention, 25% control) and depression (10% intervention, 12.5% control). All participants had ECOG PS 0–2 and all, except 5 participants, had undergone surgical treatment for their endometrial cancer. Adjuvant treatment was: full pelvic radiotherapy (22.5% intervention, 17.5% control), vaginal vault brachytherapy (25% intervention, 20% control) and chemotherapy (37.5% intervention, 27.5% control).

Zamorano 2021 *(Continued)*

	Histological types and grades of tumour were: endometrioid grade 1–2 (70% intervention, 92.5% control), endometrioid grade 3 (12.5% intervention, 2.5% control), serous (2.5% intervention, 0% control), clear cell (0% intervention, 2.5% control), carcinosarcoma (12.5% intervention, 2.5% control) and mixed endometrioid/serous (2.5% intervention, 0% control). Staging of the tumours were: Ia (56.4% intervention, 71.1% control), Ib (15.4% intervention, 7.9% control), II (0% intervention, 2.6% control), III (20.5% intervention, 15.8% control) and IV (7.7% intervention, 2.6% control).
Interventions	SMS text-message-based intervention arm 6-month text-message-based weight management intervention. BodyTrace scale at baseline + ScaleDown initially (sold at 3 months, n = 16, 1.5-month suspension of randomisation and services) then switch to Balance High Accuracy Digital Body Fat Scale at baseline + Interactive Obesity Treatment Approach (iOTA). ScaleDown: daily weighing, questions via text message, personalised weight loss advice. iOTA: 1-on-1 counselling, tailored behavioural goals, skills training, daily texts. Quote: "Initially, each patient in the intervention group received a BodyTrace scale, which used cellular technology to connect to and transmit information to the third-party vendor, ScaleDown™. ScaleDown™ then used advanced algorithms to monitor trends in weight change trajectories. In response to daily weighing, the system then asked questions via text message and gave each participant personalized weight loss advice. Proprietary algorithms in ScaleDown's™ behavioral phenotyping engine personalized this content, which became more personalized with time. However, three months into participant randomization, ScaleDown™ was sold, and the company was abruptly no longer able to provide services to our participants … New participants randomized to the intervention arm after implementation of iOTA received a Balance High Accuracy Digital Body Fat Scale at the time of enrollment and randomization. This digital scale did not connect directly to iOTA; instead, participants were asked to text their weight to iOTA weekly. A health coach (AL) met with each iOTA participant, either in-person or by phone, to review that individual's health risk assessment and to choose three behavior change goals related to healthy eating and physical activity. Participants had weekly “check-ins” by text message, prompting them to reply with data on their weight and their chosen behavior goals. Participants then immediately received individually tailored self-monitoring feedback messages and motivational strategies. Participants spoke with the health coach at enrollment, at 3-months, and at 6-months to review their progress and select new goals if necessary." Enhanced usual care control arm Participants were provided with handouts based on ACS guideline on healthy eating and exercise and following the initial session received no further input from the research team. Quote: "a brief in-person counseling session by the research assistant and received handouts based on American Cancer Society guidelines on healthy eating and exercise. These materials encouraged weight loss through counting calories, recording dietary intake, and a walking exercise program. Participants' efforts were not reinforced or monitored by study staff."
Outcomes	Primary outcomes Overall survival: no deaths reported in any arm during study. Adverse events: 1 recorded in intervention group. 1 participant felt "overwhelmed" because her health conditions prohibited her from achieving the goals. She did not complete 6-month survey or anthropometric measurements. Secondary outcomes Recurrence-free survival: not reported. Cancer-specific survival: no cancer-specific deaths reported in any arm during study. Weight loss: change in weight from baseline at 12 months reported. Cardiovascular and metabolic event frequency: not reported.

Zamorano 2021 *(Continued)*

QoL: change in QoL from baseline at 6 months reported using SF-12 Physical Health Component change score, SF-12 Mental Health Component change score, PHQ-9 change score, CRBI change score.

Power

Power calculation performed, and sufficient detail provided to allow it to be replicated.

Quote: "Assuming equal variances between the arms, the sample size calculation was based on the effect size, defined as the mean weight loss difference between two groups divided by the pooled standard deviation. By this calculation, 40 patients per group were needed to obtain an 80% power to detect an expected effect size of 0.65, using a 2-sided independent t-test at a 0.05 significance level."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: REDCap database generated a 5-block random allocation sequence and statistician blinded. Quote: "A 5-block random allocation sequence was generated by a member of the statistics team, programmed securely in the REDCap (Research Electronic Data Capture) database, managed by Washington University." Quote: "The randomization was generated randomly by REDCap and was concealed from the statistician."
Allocation concealment (selection bias)	Low risk	Comment: allocation generated by REDCap without prior knowledge of the research co-ordinator enroling participants. Quote: "Patients were enrolled and assigned to an intervention by a research co-ordinator." Quote: "Random allocation sequence was generated by REDCap, so the research coordinator who consented and enrolled the participants was unaware of what the next treatment allocation would be."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of personnel and participants not possible due to nature of intervention. Quote: "This was a prospective, non-blinded, randomized controlled trial."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: research team performing outcome assessments were unblinded. Overall knowing group allocation will not affect objectively measured outcomes (low risk bias), such as weight, but could have an impact on those that are subjectively measured (high risk bias).
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up Entered into study: 40 in intervention arm and 40 in control arm. Withdrew from study: 8 from intervention arm (6 from ScaleDown and 2 from iOTA) and 11 from control arm. Completed study: 32 in intervention arm and 29 in control arm. Missing data: 19 participants did not complete the 6-month survey or measurements. Intention-to-treat analysis

Zamorano 2021 *(Continued)*

		Analyses were conducted according to an intention-to-treat protocol; however, only 80% of intervention arm and 72.5% of control arm attended and completed survey and measurements. Quote: "All data were analyzed with an intention-to-treat approach."
Selective reporting (reporting bias)	Low risk	Comment: protocol not published but trial registered prospectively on ClinicalTrials.gov and all prespecified outcomes reported.
Other bias	High risk	Source of funding: (quote) "(1) Supported (in part by) IRG-18-158-60 from the American Cancer Society. (2) Washington University Institution Just-in-Time Grant for statistical support. (3) The SMS text iOTA intervention was developed with funding from the National Institutes of Health R01DK103760." Ethical approval: (quote) "The Washington University in St. Louis School of Medicine Institutional Review Board approved both the randomized trial and retrospective assessment of non-participants (IRB #201701098, 201,906,064)." Conflicts of interest: (quote) "There are no additional conflicts of interest to disclose by any author." Other sources Comment: change in system from ScaleDown to iOTA 3 months into participant randomisation. Quote: "The main limitation of our study was the necessary modification of the intervention shortly after the trial began. This change forced original participants to alter their method of communication with the program and several were lost to follow up. It also required retraining of staff and may have introduced confounding."

ACS: American Cancer Society; BMI: body mass index; CA-125: cancer antigen 125; COPD: chronic obstructive pulmonary disease; CRBI: Cancer-Related Body Image Scale; ECOG: European Cooperative Oncology Group; ECOG PS: European Cooperative Oncology Group Performance Status; FACT-G: Functional Assessment of Cancer Therapy – General; iOTA: Interactive Obesity Treatment Approach; PHQ-9: 9-item Patient Health Questionnaire; QoL: quality of life; RCT: randomised controlled trial; SD: standard deviation; SEM: standard error of the mean; SF-12: 12-item Short Form.

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

Study	Reason for exclusion
Babatunde 2016	Systematic review rather than randomised controlled trial.
Bantum 2015	Comment: not a randomised controlled trial. Quote: "Participants will attend one-hour hula classes twice a week for six months." Single group assignment interventional trial.
Basen-Engquist 2016	Trial not completed due to lack of funding.
Beck 2015	Comment: wrong patient population Quote: "Obese (Mean BMI = 35.8 [kg/m^2]) female patients (Mean age 58.41) with breast (n = 15), colon (n = 1), and endometrial cancers (n = 1) were recruited and randomly assigned to receive exercise and nutrition intervention without (POWER, n = 10) or with an additional mindfulness component (MORE POWER, n = 7)."
Bell 2021	Comment: wrong study design, not a randomised controlled trial.

Study	Reason for exclusion
	Quote: "Women (n = 22) were enrolled into the BWL [bodyweight loss] program and were compared against a control group."
Cohen 2019	Comment: wrong indication Quote: "We hypothesized that a KD (ketogenic diet) does not negatively affect blood lipid profile compared to a lower-fat diet in ovarian and endometrial cancer patients, and that KD subjects would demonstrate acceptable adherence."
Donnelly 2011	Comment: wrong indication. Quote: "To determine the feasibility and effectiveness of a physical activity (PA) behavioural change intervention in managing cancer-related fatigue (CRF) among gynaecological cancer survivors during and post anti-cancer treatments."
Fasching 2009	Systematic review rather than randomised controlled trial.
Gil 2011	Systematic review rather than randomised controlled trial.
Gorzelitz 2022	Comment: wrong indication. Focus on the benefit of home-based strength training but not weight loss as the endpoint. Quote: "The purpose of this study was to determine the feasibility of home-based muscle strengthening activity in endometrial cancer survivors." Quote: "The primary outcomes of this randomized controlled pilot were feasibility, safety, and acceptability of home-based strength training."
Groarke 2021	Comment: wrong patient population. Author contacted and, although eligible for inclusion, there were no participants with endometrial cancer included in this study.
Haggerty 2016	Comment: not a randomised controlled trial. Quote "Women with obesity (BMI ≥ 30 kg/m^2) and endometrial hyperplasia or Type I endometrial cancer were randomized 1:1 to a technology-based 6-month lifestyle intervention via either telemedicine or text messaging", there was no control arm.
Jernigan 2016	Comment: wrong study design, not a randomised controlled trial. Quote: "Women with stage I-II EC [endometrial cancer] or CAH [complex atypical hyperplasia] with a body mass index (BMI) higher than 30 kg/m^2 were offered a medical bariatric referral (BR); if their BMI was higher than 35 kg/m^2 with an obesity-related comorbidity or higher than 40 kg/m^2 they were also offered a surgical BR."
Koutoukidis 2015	Systematic review rather than randomised controlled trial.
Koutoukidis 2017	Comment: wrong indication Quote: "Aim … (to determine if) Shape-up following cancer treatment programme is more effective than usual care in improving the health-related quality of life of endometrial cancer survivors."
Koutoukidis 2019	Comment: wrong indication. Quote: objective "To explore the effectiveness of a theory-based behavioural lifestyle intervention on health behaviours and quality of life (QoL) in endometrial cancer survivors."
Lin 2016	Systematic review rather than randomised controlled trial.

Study	Reason for exclusion
NCT02575872	Comment: not a randomised controlled trial. Quote: "The study was a pragmatic, wait-list control trial where participants were placed into one of the 2 groups: an immediate intervention group (n = 13) and wait-list (control) intervention group (n = 15) … Each cohort was tested prior to the intervention (baseline), the week after the intervention (post-intervention), and 12 weeks following the completion of the intervention (follow-up)."
Rahimy 2021	Comment: not a randomised controlled trial. Quote: "Participants received a Fitbit Alta and were randomized to receive communication via telephone or electronic methods," no control arm.
Rossi 2016	Comment: wrong indication. Quote: "… aims of this study were to 1) assess the feasibility of a 12-week physical activity intervention for obese socioculturally diverse endometrial cancer survivors in Bronx, NY; 2) determine the probable effectiveness of the intervention on physical activity, waist circumference, physical function and quality of life; and 3) evaluate changes in self-efficacy, outcome expectations, social support, and self-regulation during the 12-week physical activity intervention."
Smits 2015	Systematic review rather than randomised controlled trial.

BMI: body mass index; n: number.

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

ACTRN12621000050853

Study name	Enhancing treatment outcomes after gynaecological cancer (ACUMEN): using exercise to promote health after cancer therapy
Methods	Parallel, unblinded, 2-arm, randomised controlled trial
Participants	Women aged ≥ 18 years, diagnosis of cancer of the ovary, cervix, fallopian tubes, placenta, endometrium, vagina or vulva in the previous 60 months, including early, recurrent, advanced or metastatic cancer. > 1 month after intensive cancer treatment (including surgery, radiotherapy, chemotherapy), with access to the internet, with access to computer/tablet device, be resident in Australia, be willing and able to comply with all study requirements and able to speak and read in English.
Interventions	Control group: standard care and general advice about self-managed exercise, a Fitbit and the Exercise is Medicine guidelines for gynaecological cancer. Participants will be asked to wear the Fitbit device to assess physical activity performed over the study period. Intervention group: 1-on-1 supervision by an accredited exercise physiologists or physiotherapists. Goals will be prioritised and set with the participant and the prescription co-designed with the participant, including strategies for relapse prevention and longer-term maintenance. As part of this process, the 12-week exercise training intervention will adhere to the following principles: 1. Participants will be screened for known disease and risk of adverse events due to exercise with the Adult Pre-Exercise Screening System. 2. The goal is to enhance neuromuscular strength, endurance, balance, flexibility, cardiorespiratory fitness and cardiovascular function. The AEPP will individually tailor exercise to the functional capacity of each participant towards these goals, cognisant of potential restrictions caused by surgical scarring, pain, metastases, lymphoedema, obesity, incontinence or neuropathic problems. 3. Participants will aim for 3 × 60-minute exercise sessions per week, individually prescribed by an accredited exercise physiologist or physiotherapist based on Adult Pre-Exercise Screening System results and the participant.

ACTRN12621000050853 *(Continued)*

Outcomes	Primary outcomes: mean difference on the 36-item Short Form Mental Component Summary scores of health-related quality of life; mean difference on SF-36 Physical Component Summary scores of health-related quality of life. Secondary outcomes: balance, blood markers for steroid hormone modulation – follicle-stimulating hormone, luteinising hormone, oestradiol, progesterone, blood markers of glycaemic modulation (HbA1c), blood markers of inflammatory modulation (assessed by the levels of tumour-necrosing factor-α, IL-2, IL-1β, IL-6 and IL-8), body composition measured via waist–hip ratio with a measuring tape according to WHO STEPwise Approach to Surveillance (STEPS) protocol for consistent measurement, cardiorespiratory fitness (VO_{2peak} and exercise capacity) assessed during a graded cycling test with breath-by-breath gas analysis, duration of physical activity levels as assessed by the Fitbit watch, dynamic upper and lower body muscle strength (chest and leg press respectively using 1 repetition maximum), exercise self-efficacy as measured by the Exercise Self-efficacy Scale, frequency of physical activity levels as assessed by the Fitbit watch and intensity of physical activity levels as assessed by the Fitbit watch.
Starting date	March 2021
Contact information	Sandie McCarthy, The University of Queensland, Australia
Notes	

NCT03095664

Study name	Effect of a lifestyle intervention on nutritional status and prognosis of endometrial cancer survivors
Methods	Parallel, unblinded, 2-arm, randomised controlled trial
Participants	Women aged 20–69 years with history of endometrial cancer stage I–III who are undergoing surgical treatment, who report moderate-to-vigorous physical activity < 150 minutes per week
Interventions	Intervention group. 6 months after surgical treatment, women will attend a counselling programme to promote healthy eating and physical activity. Control group will receive usual care (verbal nutritional counselling after surgical treatment, at discharge).
Outcomes	Primary outcome: overall survival. Secondary outcomes: change in QoL, change in hand grip strength, change in functional capacity (30 second stand chair test, timed Get Up and Go test, 6-minute walk test), change in physical activity behaviour, change in food intake pattern, change in body composition, change in anthropometric status (weight, BMI, waist circumference, hip circumference), disease-free survival.
Starting date	March 2017
Contact information	Gabriela Villaça Chaves, Brazilian National Cancer Institute, Brazil
Notes	

NCT03285152

Study name	A study of ketogenic diet in newly diagnosed overweight or obese endometrial cancer patients

NCT03285152 *(Continued)*

Methods	Parallel, unblinded, 2-arm, randomised controlled trial
Participants	Women aged ≥ 18 years; biopsy-confirmed endometrial cancer stage I–IVA taken at Memorial Sloan Kettering; consented to surgery with a board-certified gynaecology surgeon and have not received any adjuvant treatment; of ECOG PS 0–1; with adequate haematological, hepatic and renal function within 11 days prior to first study treatment; with HbA1c ≤ 7.9%, with BMI ≥ 23 kg/m^2; who agree to consent to the companion genomic profiling study MSK IRB# 12-245; who agree to consent for their tumour samples to be used for generation of cellular research tools such as organoids; who are willing to travel to the Clinical Translational Science Center at Weill Cornell Medical Center weekly and who have the ability to read, write, speak and understand English.
Interventions	Experimental: ketogenic diet. rotating 7-day meal plan prepared the centre at with weekly food pick-up. Meal plan will provide a 3:1 fat:net carbohydrate ratio and calories for weight maintenance (30 kcal/kg for a BMI < 30 kg/m^2 and 25 kcal/kg for a BMI 30 kg/m^2). Active comparator: standard diet. Group will consume their normal diet plan. They will meet with the dietitian from the Centre weekly and receive standard nutritional counselling. Mean intake will be documented through analysing a 3-day intake before and after the 4-week period.
Outcomes	Primary outcome measure: number of participants who complete the study.
Starting date	September 2017
Contact information	Vicky Makker, Memorial Sloan Kettering Cancer Center, USA.
Notes	

NCT04000880

Study name	Adapting multiple behavior interventions that effectively improve cancer survivor health cancer survivor health (AMPLIFY)
Methods	Parallel, single-blind, 3-arm, randomised controlled trial
Participants	People aged ≥ 50 years; resident in continental US; history of multiple myeloma, non-Hodgkin lymphoma, or localised kidney or ovarian cancer; or (localised (includes in situ) through regional) breast, colorectum, endometrium, thyroid or prostate cancer. Have completed primary treatment, completed 8th grade at school, able to read and write English, normal blood pressure (or physician agreement to participate if on treatment), community dwelling, resided in areas with wireless coverage, access to email, BMI ≥ 25 kg/m^2 but < 50 kg/m^2, with a physical activity level < 150 minutes of moderate-to-vigorous activity per week.
Interventions	AMPLIFI will provide participants with a secure website where they receive and participate in educational sessions tailored to their assigned topics for the intervention arm. The website will provide a resource library for static documents, tips of the day, tracking of health behaviours, and goal-setting. Experimental: project 1: diet–exercise Participants will receive and participate in web-based sessions that focus on diet for 6 months, followed by exercise for another 6 months. Participants will be encouraged to track their diet and weight for the first 6 months and to log their data in the intervention website, during the second 6 months they will be asked to log their physical activity data (minutes and step counts). Tailored feedback and goal recommendations will be provided through the website. Participants will also receive access to resources for relevant behavioural topics. All participants will be invited to participate in the secret Facebook group for the project (though participation is optional).

NCT04000880 *(Continued)*

	Experimental: project 2: exercise–diet Participants will receive and participate in web-based sessions that focus on diet for 6 months, followed by exercise for another 6 months. Participants will be encouraged to track their diet and weight for the first 6 months and to log their data in the intervention website, during the second 6 months they will be asked to log their physical activity data (minutes and step counts). Tailored feedback and goal recommendations will be provided through the website. Participants will also receive access to resources for relevant behavioural topics. All participants will be invited to participate in the secret Facebook group for the project (though participation is optional). Experimental: project 3: survivorship topics – combined diet and exercise For the first 6 months of the study, participants will be in the Survivorship Topics group, where they receive health information on topics other than diet and exercise. Participants will then join the intervention, receiving the diet and exercise content simultaneously in combined web-based sessions. Participants will receive and participate in web-based sessions that focus on diet and exercise for 12 months. Participants will be encouraged to track their diet, weight and physical activity data (minutes and step counts). Tailored feedback and goal recommendations will be provided through the website. Participants will also receive access to resources for relevant behavioural topics. All participants will be invited to participate in the secret Facebook group for the project (though participation is optional).
Outcomes	Primary outcomes: change in dietary quality and intake, change in bodyweight, change in physical activity and sleep. Secondary outcomes: change in waist circumference, change in muscle mass, change in physical performance, change in physical activity, change in QoL, change in healthcare utilisation. Other outcomes: change in levels of stress, change in circulating biomarkers, change in comorbidity and symptoms, social support, self-efficacy and barriers for adhering to a caloric restricted diet or increased physical activity, QoL (EQ-5D-5L), health literacy and Ehealth literacy scales (eHEALS), health-related status and PROMIS Cognitive Function + PROMIS Cognitive Abilities – 8a.
Starting date	June 2019
Contact information	Wendy Demark-Wahnefried, University of Alabama at Birmingham, USA
Notes	

NCT04008563

Study name	Bariatric surgery for fertility-sparing treatment of atypical hyperplasia and grade 1 cancer of the endometrium (B-FiERCE)
Methods	Parallel, unblinded, 2-arm, randomised controlled trial
Participants	Women aged 18–41 years, BMI ≥ 35 kg/m^2, with a diagnosis of grade endometrioid endometrial cancer or complex atypical hyperplasia, with clinical stage 1 disease, with an ECOG PS < 2, with a desire for fertility preservation and with no contraindications to progestin intrauterine device.
Interventions	Experimental: bariatric surgery and progestin intrauterine device. Participants will receive a progestin intrauterine device and be referred for bariatric service to undergo bariatric surgery within 3 months of their study consent. No intervention: progestin intrauterine device alone.
Outcomes	Primary outcomes: recruitment rate (to determine proportion of eligible women who agree to participate in study (recruitment rate). Primary outcome will be met, and a full-scale randomised con-

NCT04008563 *(Continued)*

	trolled trial to assess efficacy will be conducted if ≥ 40% recruitment rate is achieved. Patients' reasons for participation or non-participation will be recorded.) Secondary outcomes: completion of bariatric surgery; loss to follow-up rate; completion of Patient Reported Outcome Questionnaires and complete response rate: time to complete response, overall recurrence rate and time to recurrence.
Starting date	July 2019
Contact information	Sarah E Ferguson, University Health Network, Toronto, Canada
Notes	

NCT04783467

Study name	Time restricted eating (TRE) among endometrial cancer patients (TREND)
Methods	Crossover, unblinded, 2-arm, randomised controlled trial
Participants	Women aged ≥ 18 years, with a diagnosis of endometrial cancer of any stage, with clinically overweight or obese (BMI > 25 kg/m^2), ≥ 3 months after cancer surgery or treatment (or both), with a stable weight for 3 months prior to beginning the study (< 4 kg weight loss/gain), have a mobile phone that is able to download a phone App and able to use phone during the day.
Interventions	Experimental: time restricted sating (TRE) schedule. For 6-weeks out of the 16-week randomised dietary crossover study, women will receive prepared frozen lunch and dinner meals as per the control schedule, but will be asked to consume daily meals, snacks and calorie-containing beverages within an 8- to 10-hour period that fits their schedule. The meal plans will be individualised to meet weight maintenance energy requirements. No intervention: control schedule. For 4 weeks out of the 16-week randomised dietary crossover study, women will receive frozen lunch and dinner meals, and a standardised breakfast and snacks menu. The meal plans will be individualised to meet weight maintenance energy requirements. There are no restrictions on timing of eating.
Outcomes	Primary outcomes: proportion of women referred who are consented, attrition as a function of time, percent of scheduled assessments completed, number of TRE-adherent days per week, fidelity of TRE intervention. Secondary outcomes: change in blood pressure, change in waist circumference, change in BMI, change in fasting blood glucose, change in HOMA-IR, change in c-peptide, change in triglycerides, change in HDL-cholesterol and change in high sensitivity C-reactive protein.
Starting date	March 2021
Contact information	Mary Playdon, University of Utah, USA
Notes	

NCT05233059

Study name	FitEx for endometrial cancer survivors
Methods	Parallel, unblinded, 2-arm, randomised controlled trial

NCT05233059 *(Continued)*

Participants	Women aged ≥ 18 years with history of stage I–II endometrial cancer of any histology, who received cancer care at the Carilion Clinic after 1 January 2010, who have a BMI ≥ 30 kg/m^2, who meet the requirements of the Physical Activity Readiness Questionnaire, who do not meet physical activity guidelines (< 150 minutes per week) and who do not have functional limitations that would prevent them from participating in the intervention safely. In addition, healthy volunteers of either gender identified by a participant with endometrial cancer as a member of their support system, aged ≥ 18 years, who meet the requirements of the Physical Activity Readiness Questionnaire and who do not have functional limitations that would prevent them from participating in the intervention safely.
Interventions	Experimental: walking plus yoga: FitEx is an 8-week goal-setting, behaviour tracking, physical activity intervention with a low dose of social support that will be delivered virtually. 30 minutes of optional guided yoga online led by a 500-hour yoga teacher once a week. Accompanied by a yoga-based newsletter. Active comparator: walking: FitEx plus 30 minutes of optional guided movement online led by a 500-hour yoga teacher once a week. Accompanied by a movement-based newsletter.
Outcomes	Primary outcomes: feasibility and acceptability as measured by recruitment rate and programme completion. Secondary outcomes: changes to self-reported physical activity levels as measured by L-Cat questionnaire, changes to QoL as measured by FACT-En questionnaire, changes to Yoga Self-Efficacy as measured by Yoga Self Efficacy questionnaire, self-reported physical activity measured via steps per day on pedometer and changes to Fear of Cancer Recurrence measured by Fear of Cancer Recurrence Inventory questionnaire.
Starting date	February 2022
Contact information	Shannon D Armbruster, Carilion Clinic, USA
Notes	

BMI: body mass index; CA-125: cancer antigen 125; CT: computed tomography; ECOG PS: European Cooperative Oncology Group Performance Status; FACT-En: Functional Assessment of Cancer Therapy – Endometrial; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IGF-1: insulin-like growth factor-1; IGFBP-3: insulin-like growth factor binding protein-3; IL: interleukin; MRI: magnetic resonance imaging; QoL: quality of life; TRE: time-restricted eating; WHO: World Health Organization; VO_{2peak}: peak oxygen consumption.

DATA AND ANALYSES

Comparison 1. Lifestyle intervention versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival (3 months)	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Overall survival (6 months)	5	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Overall survival (12 months)	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Overall survival (24 months)	1	37	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.55]
1.5 Adverse events – musculoskeletal	8	315	Risk Ratio (M-H, Random, 95% CI)	19.03 [1.17, 310.52]
1.6 Adverse events – diarrhoea	8	315	Risk Ratio (M-H, Random, 95% CI)	4.53 [0.23, 90.51]
1.7 Adverse events – exacerbation of asthma	8	315	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.08, 17.80]
1.8 Adverse events – primary lung adenocarcinoma	8	315	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.15, 82.21]
1.9 Adverse events – ovarian hyperstimulation syndrome	8	315	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.15, 82.21]
1.10 Adverse events – abdominal pain	8	315	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.15, 82.21]
1.11 Adverse events – chest pain (unknown cause)	8	315	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 3.08]
1.12 Adverse events – seizure	8	315	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.02, 9.13]
1.13 Adverse events – atrial fibrillation	8	315	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.02, 9.13]
1.14 Adverse events – overwhelmed	8	315	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.12, 64.42]
1.15 Recurrence-free survival (6 months)	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.16 Cancer-specific survival (3 months)	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.17 Cancer-specific survival (6 months)	5	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.18 Cancer-specific survival (12 months)	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.19 Cancer-specific survival (24 months)	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.20 Weight loss (9 weeks)	1	7	Mean Difference (IV, Random, 95% CI)	6.29 [-0.18, 12.76]
1.21 Weight loss stratified by body mass index (BMI) (9 weeks)	1	6	Mean Difference (IV, Random, 95% CI)	6.03 [-0.86, 12.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21.1 BMI < 40 kg/m^2	1	6	Mean Difference (IV, Random, 95% CI)	6.03 [-0.86, 12.92]
1.22 Weight loss (3 months)	1	6	Mean Difference (IV, Random, 95% CI)	5.03 [-2.67, 12.73]
1.23 Weight loss stratified by BMI (3 months)	1	6	Mean Difference (IV, Random, 95% CI)	5.03 [-2.67, 12.73]
1.23.1 BMI < 40 kg/m^2	1	6	Mean Difference (IV, Random, 95% CI)	5.03 [-2.67, 12.73]
1.24 Weight loss (6 months)	5	209	Mean Difference (IV, Random, 95% CI)	-1.39 [-4.04, 1.26]
1.25 Weight loss stratified by BMI (6 months)	4	179	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.97, 0.85]
1.25.1 BMI < 40 kg/m^2	4	88	Mean Difference (IV, Random, 95% CI)	-0.15 [-1.63, 1.32]
1.25.2 BMI ≥ 40 kg/m^2	3	91	Mean Difference (IV, Random, 95% CI)	-4.66 [-9.34, 0.01]
1.26 Weight loss (12 months)	3	152	Mean Difference (IV, Random, 95% CI)	-1.57 [-5.46, 2.31]
1.27 Weight loss stratified by BMI (12 months)	2	90	Mean Difference (IV, Random, 95% CI)	-5.23 [-11.59, 1.12]
1.27.1 BMI < 40 kg/m^2	2	55	Mean Difference (IV, Random, 95% CI)	-4.08 [-11.20, 3.04]
1.27.2 BMI ≥ 40 kg/m^2	2	35	Mean Difference (IV, Random, 95% CI)	-9.76 [-23.84, 4.32]
1.28 Weight loss (24 months)	1	25	Mean Difference (IV, Random, 95% CI)	-18.26 [-38.73, 2.21]
1.29 Weight loss stratified by BMI (24 months)	1	25	Mean Difference (IV, Random, 95% CI)	-25.84 [-81.40, 29.72]
1.29.1 BMI < 40 kg/m^2	1	13	Mean Difference (IV, Random, 95% CI)	2.12 [-20.82, 25.06]
1.29.2 BMI ≥ 40 kg/m^2	1	12	Mean Difference (IV, Random, 95% CI)	-54.58 [-80.97, -28.19]
1.30 Cardiovascular and metabolic event frequency (6 months)	5	211	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.15, 82.21]
1.31 Cardiovascular and metabolic event frequency (12 months)	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

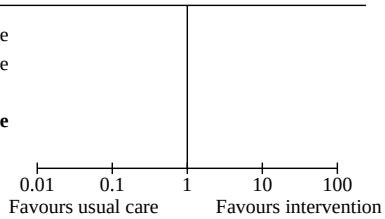
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.32 Quality of life: Functional Assessment of Cancer Therapy – General (FACT-G) (9 weeks)	1	16	Mean Difference (IV, Random, 95% CI)	3.51 [-10.96, 17.98]
1.33 Quality of life stratified by BMI (9 weeks FACT-G)	1	16	Mean Difference (IV, Random, 95% CI)	2.05 [-14.61, 18.71]
1.33.1 BMI < 40 kg/m^2	1	14	Mean Difference (IV, Random, 95% CI)	2.05 [-14.61, 18.71]
1.33.2 BMI ≥ 40 kg/m^2	1	0	Mean Difference (IV, Random, 95% CI)	Not estimable
1.34 Quality of life: FACT-G (3 months)	1	14	Mean Difference (IV, Random, 95% CI)	5.75 [-11.26, 22.76]
1.35 Quality of life stratified by BMI (3 months FACT-G)	1	14	Mean Difference (IV, Random, 95% CI)	4.81 [-15.86, 25.48]
1.35.1 BMI < 40 kg/m^2	1	12	Mean Difference (IV, Random, 95% CI)	4.81 [-15.86, 25.48]
1.35.2 BMI ≥ 40 kg/m^2	1	0	Mean Difference (IV, Random, 95% CI)	Not estimable
1.36 Quality of life: FACT-G (6 months)	2	95	Mean Difference (IV, Random, 95% CI)	2.51 [-5.61, 10.64]
1.37 Quality of life stratified by BMI (6 months FACT-G)	2	95	Mean Difference (IV, Random, 95% CI)	4.69 [1.39, 7.99]
1.37.1 BMI < 40 kg/m^2	2	60	Mean Difference (IV, Random, 95% CI)	4.01 [-5.48, 13.51]
1.37.2 BMI ≥ 40 kg/m^2	2	35	Mean Difference (IV, Random, 95% CI)	4.18 [-0.13, 8.49]
1.38 Quality of life: FACT-G (12 months)	2	89	Mean Difference (IV, Random, 95% CI)	2.77 [-0.65, 6.20]
1.39 Quality of life stratified by BMI (12 months FACT-G)	2	89	Mean Difference (IV, Random, 95% CI)	2.83 [0.15, 5.50]
1.39.1 BMI < 40 kg/m^2	2	56	Mean Difference (IV, Random, 95% CI)	2.90 [-0.40, 6.20]
1.39.2 BMI ≥ 40 kg/m^2	2	33	Mean Difference (IV, Random, 95% CI)	2.68 [-1.90, 7.26]
1.40 Quality of life: 12-item Short Form (SF-12) Physical Health Component (6 months)	1	30	Mean Difference (IV, Random, 95% CI)	-2.29 [-7.34, 2.76]
1.41 Quality of life: SF-12 Physical Health Component (12 months)	1	61	Mean Difference (IV, Random, 95% CI)	-3.50 [-8.85, 1.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.42 Quality of life: SF-12 Mental Health Component (12 months)	1	61	Mean Difference (IV, Random, 95% CI)	3.00 [-2.49, 8.49]
1.43 Quality of life: Cancer-Related Body Image Scale (CRBI) (12 months)	1	61	Mean Difference (IV, Random, 95% CI)	-1.10 [-5.02, 2.82]
1.44 Quality of life: 9-item Patient Health Questionnaire (PHQ-9) (12 months)	1	61	Mean Difference (IV, Random, 95% CI)	0.90 [-1.79, 3.59]

Analysis 1.1. Comparison 1: Lifestyle intervention versus usual care, Outcome 1: Overall survival (3 months)

Study or Subgroup	Interventon Events	Interventon Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

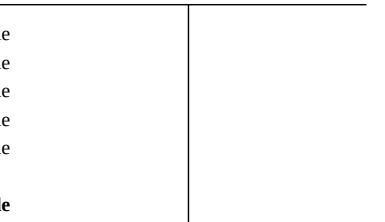
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Lifestyle intervention versus usual care, Outcome 2: Overall survival (6 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Janda 2021	0	31	0	36		Not estimable
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	41	0	28		Not estimable
Yeh 2021	0	3	0	2		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

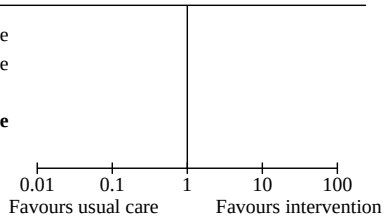
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Lifestyle intervention versus usual care, Outcome 3: Overall survival (12 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
McCarroll 2014	0	35	0	24		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

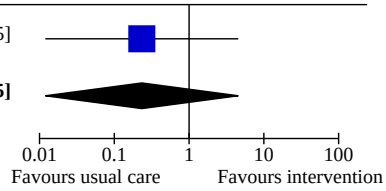
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Lifestyle intervention versus usual care, Outcome 4: Overall survival (24 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
von Gruenigen 2008	0	17	2	20	100.0%	0.23 [0.01 , 4.55]
Total (95% CI)		**17**		**20**	**100.0%**	**0.23 [0.01 , 4.55]**
Total events:	0		2			

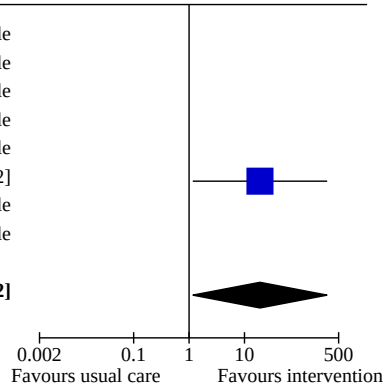
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Lifestyle intervention versus usual care, Outcome 5: Adverse events – musculoskeletal

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	0	36		Not estimable
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	10	31	0	28	100.0%	19.03 [1.17 , 310.52]
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**19.03 [1.17 , 310.52]**
Total events:	10		0			

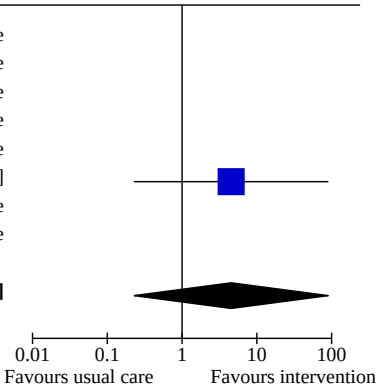
Heterogeneity: Not applicable
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Lifestyle intervention versus usual care, Outcome 6: Adverse events – diarrhoea

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	0	36		Not estimable
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	2	31	0	28	100.0%	4.53 [0.23 , 90.51]
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**4.53 [0.23 , 90.51]**
Total events:	2		0			

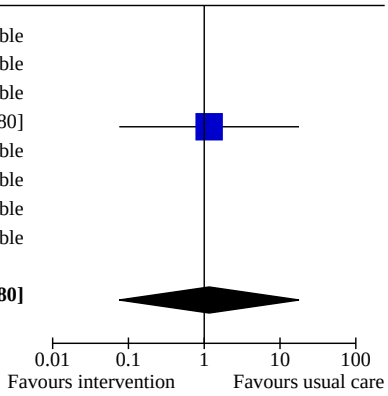
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Lifestyle intervention versus usual care, Outcome 7: Adverse events – exacerbation of asthma

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	1	31	1	36	100.0%	1.16 [0.08 , 17.80]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**1.16 [0.08 , 17.80]**
Total events:	1		1			

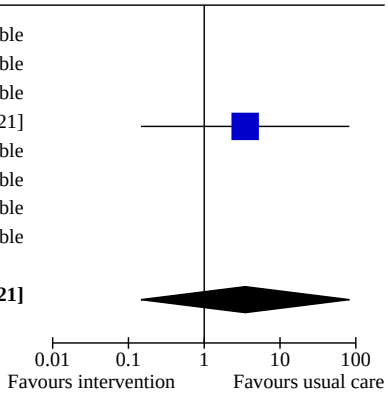
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Lifestyle intervention versus usual care, Outcome 8: Adverse events – primary lung adenocarcinoma

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	1	31	0	36	100.0%	3.47 [0.15 , 82.21]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**3.47 [0.15 , 82.21]**
Total events:	1		0			

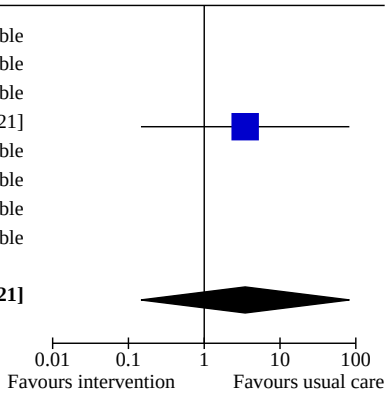
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Lifestyle intervention versus usual care, Outcome 9: Adverse events – ovarian hyperstimulation syndrome

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	1	31	0	36	100.0%	3.47 [0.15 , 82.21]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**3.47 [0.15 , 82.21]**
Total events:	1		0			

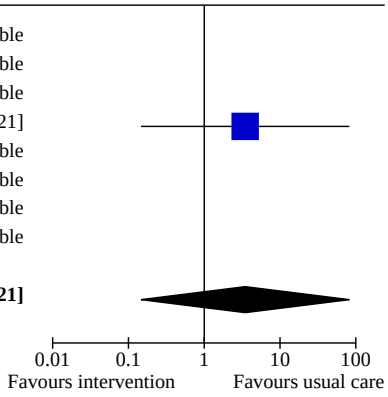
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Lifestyle intervention versus usual care, Outcome 10: Adverse events – abdominal pain

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	1	31	0	36	100.0%	3.47 [0.15 , 82.21]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**3.47 [0.15 , 82.21]**
Total events:	1		0			

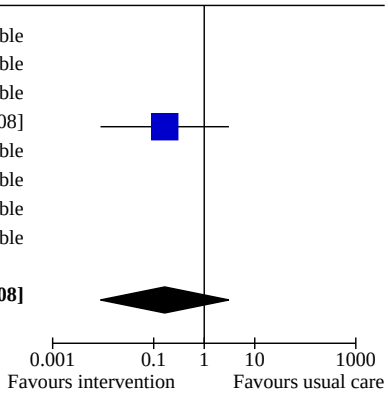
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Lifestyle intervention versus usual care, Outcome 11: Adverse events – chest pain (unknown cause)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	3	36	100.0%	0.17 [0.01 , 3.08]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**0.17 [0.01 , 3.08]**
Total events:	0		3			

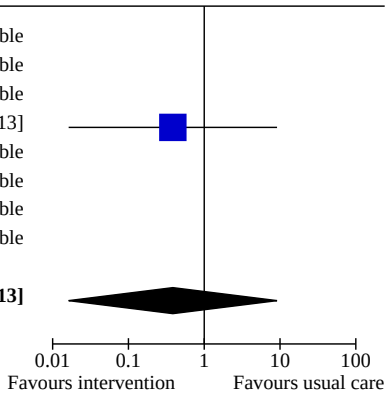
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Lifestyle intervention versus usual care, Outcome 12: Adverse events – seizure

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	1	36	100.0%	0.39 [0.02 , 9.13]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**0.39 [0.02 , 9.13]**
Total events:	0		1			

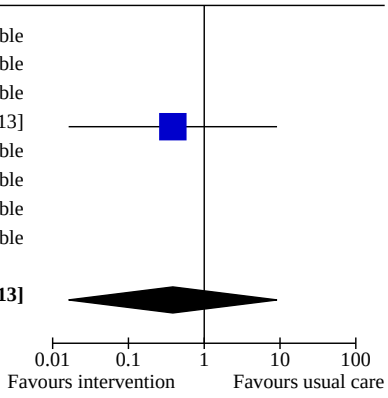
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Lifestyle intervention versus usual care, Outcome 13: Adverse events – atrial fibrillation

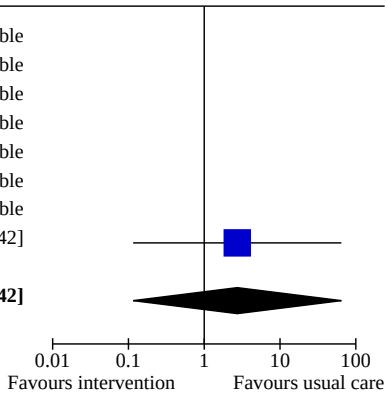
Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	1	36	100.0%	0.39 [0.02 , 9.13]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**168**		**147**	**100.0%**	**0.39 [0.02 , 9.13]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable



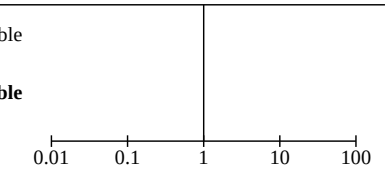
Analysis 1.14. Comparison 1: Lifestyle intervention versus usual care, Outcome 14: Adverse events – overwhelmed

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Janda 2021	0	31	0	36		Not estimable
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	31	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Zamorano 2021	1	32	0	29	100.0%	2.73 [0.12 , 64.42]
Total (95% CI)		**168**		**147**	**100.0%**	**2.73 [0.12 , 64.42]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
Test for subgroup differences: Not applicable						



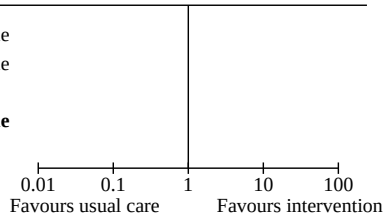
Analysis 1.15. Comparison 1: Lifestyle intervention versus usual care, Outcome 15: Recurrence-free survival (6 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Yeh 2021	0	3	0	2		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.16. Comparison 1: Lifestyle intervention versus usual care, Outcome 16: Cancer-specific survival (3 months)

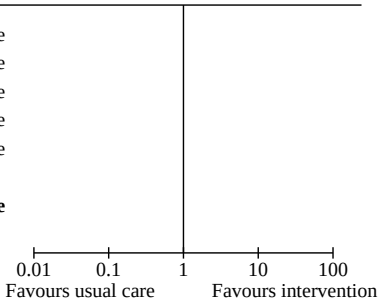
Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Clark 2021	0	18	0	18		Not estimable
Edbrooke 2022	0	10	0	7		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.17. Comparison 1: Lifestyle intervention versus usual care, Outcome 17: Cancer-specific survival (6 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Janda 2021	0	31	0	36		Not estimable
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	41	0	28		Not estimable
Yeh 2021	0	3	0	2		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

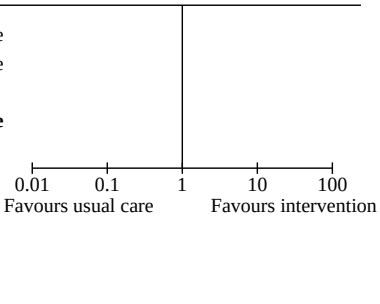
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Lifestyle intervention versus usual care, Outcome 18: Cancer-specific survival (12 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
McCarroll 2014	0	35	0	24		Not estimable
Zamorano 2021	0	32	0	29		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

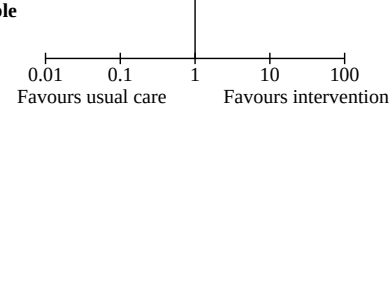
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Lifestyle intervention versus usual care, Outcome 19: Cancer-specific survival (24 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
von Gruenigen 2008	0	17	0	20		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

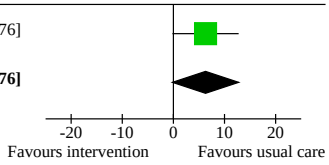
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Lifestyle intervention versus usual care, Outcome 20: Weight loss (9 weeks)

Study or Subgroup	Intervention Mean [kg]	SD [kg]	Total	Usual care Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Edbrooke 2022	0.46	3.42	5	-5.83	4.14	2	100.0%	6.29 [-0.18 , 12.76]
Total (95% CI)			**5**			**2**	**100.0%**	**6.29 [-0.18 , 12.76]**

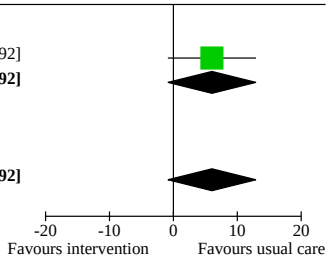
Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Lifestyle intervention versus usual care, Outcome 21: Weight loss stratified by body mass index (BMI) (9 weeks)

Study or Subgroup	Intervention Mean [kg]	SD [kg]	Total	Usual care Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.21.1 BMI < 40 kg/m2								
Edbrooke 2022	0.2	3.9	4	-5.83	4.14	2	100.0%	6.03 [-0.86 , 12.92]
Subtotal (95% CI)			**4**			**2**	**100.0%**	**6.03 [-0.86 , 12.92]**
Total (95% CI)			**4**			**2**	**100.0%**	**6.03 [-0.86 , 12.92]**

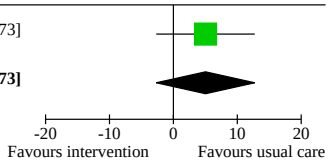
Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)
Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Lifestyle intervention versus usual care, Outcome 22: Weight loss (3 months)

Study or Subgroup	Intervention Mean [kg]	SD [kg]	Total	Usual care Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Edbrooke 2022	0.55	2.78	4	-4.48	5.2	2	100.0%	5.03 [-2.67 , 12.73]
Total (95% CI)			**4**			**2**	**100.0%**	**5.03 [-2.67 , 12.73]**

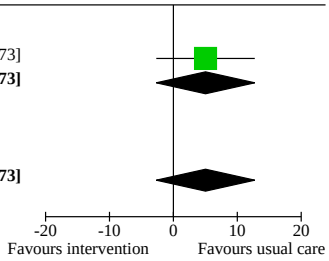
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Lifestyle intervention versus usual care, Outcome 23: Weight loss stratified by BMI (3 months)

Study or Subgroup	Intervention Mean [kg]	SD [kg]	Total	Usual care Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.23.1 BMI < 40 kg/m2								
Edbrooke 2022	0.55	2.78	4	-4.48	5.2	2	100.0%	5.03 [-2.67 , 12.73]
Subtotal (95% CI)			**4**			**2**	**100.0%**	**5.03 [-2.67 , 12.73]**
Total (95% CI)			**4**			**2**	**100.0%**	**5.03 [-2.67 , 12.73]**

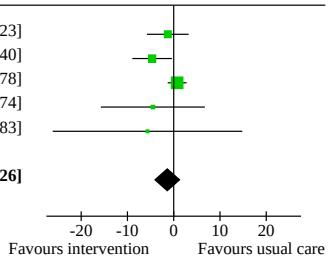
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Lifestyle intervention versus usual care, Outcome 24: Weight loss (6 months)

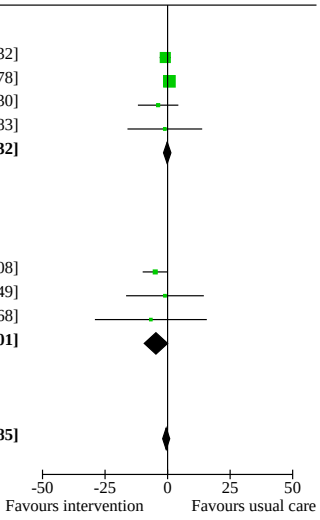
Study or Subgroup	Intervention Mean [kg]	Intervention SD [kg]	Intervention Total	Usual care Mean [kg]	Usual care SD [kg]	Usual care Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Allison 2016	-4.78	7.09	21	-3.5	5.1	9	22.5%	-1.28 [-5.79 , 3.23]
Janda 2021	-7.96	10.94	31	-3.29	5.66	36	24.1%	-4.67 [-8.94 , -0.40]
Maxwell-Smith 2019	-0.53	2.43	8	-1.27	1.02	3	46.6%	0.74 [-1.30 , 2.78]
McCarroll 2014	-3.9	19.348	41	0.6	25.787	28	5.1%	-4.50 [-15.74 , 6.74]
von Gruenigen 2008	-6.25	29.499	16	-0.59	29.636	16	1.6%	-5.66 [-26.15 , 14.83]
Total (95% CI)			**117**			**92**	**100.0%**	**-1.39 [-4.04 , 1.26]**

Heterogeneity: Tau² = 2.84; Chi² = 5.92, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Lifestyle intervention versus usual care, Outcome 25: Weight loss stratified by BMI (6 months)

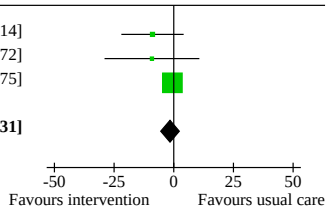
Study or Subgroup	Intervention Mean [kg]	Intervention SD [kg]	Intervention Total	Usual care Mean [kg]	Usual care SD [kg]	Usual care Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.25.1 BMI < 40 kg/m2								
Janda 2021	-3	1.72	4	-2.08	2.37	10	39.6%	-0.92 [-3.16 , 1.32]
Maxwell-Smith 2019	-0.53	2.43	8	-1.27	1.02	3	47.5%	0.74 [-1.30 , 2.78]
McCarroll 2014	-3.82	14.78244	29	-0.036	13.05601	18	3.0%	-3.78 [-11.87 , 4.30]
von Gruenigen 2008	-3	18.33574	8	-1.895	11.32327	8	0.9%	-1.10 [-16.04 , 13.83]
Subtotal (95% CI)			**49**			**39**	**90.9%**	**-0.15 [-1.63 , 1.32]**
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 3 (P = 0.58); I² = 0%								
Test for overall effect: Z = 0.20 (P = 0.84)								
1.25.2 BMI ≥ 40 kg/m2								
Janda 2021	-8.7	11.55	27	-3.76	6.49	26	7.8%	-4.94 [-9.96 , 0.08]
McCarroll 2014	-4.23	15.9546	12	-3.18	20.4041	10	0.8%	-1.05 [-16.59 , 14.49]
von Gruenigen 2008	-3.62	19.84407	8	3.07	25.46078	8	0.4%	-6.69 [-29.06 , 15.68]
Subtotal (95% CI)			**47**			**44**	**9.1%**	**-4.66 [-9.34 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 2 (P = 0.88); I² = 0%								
Test for overall effect: Z = 1.96 (P = 0.05)								
Total (95% CI)			**96**			**83**	**100.0%**	**-0.56 [-1.97 , 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 5.49, df = 6 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.78 (P = 0.44)								
Test for subgroup differences: Chi² = 3.26, df = 1 (P = 0.07), I² = 69.3%								



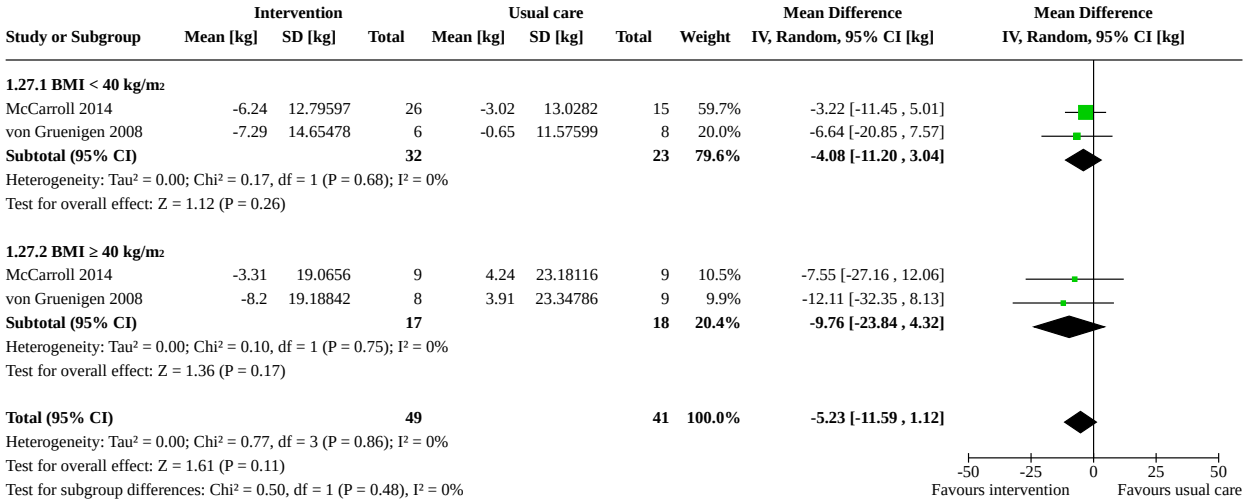
Analysis 1.26. Comparison 1: Lifestyle intervention versus usual care, Outcome 26: Weight loss (12 months)

Study or Subgroup	Intervention Mean [kg]	Intervention SD [kg]	Intervention Total	Usual care Mean [kg]	Usual care SD [kg]	Usual care Total	Weight	Mean Difference IV, Random, 95% CI [kg]
McCarroll 2014	-7.51	19.581	35	1.4	28.2905	24	8.3%	-8.91 [-21.96 , 4.14]
von Gruenigen 2008	-7.51	28.248	14	1.63	28.679	18	3.7%	-9.14 [-29.00 , 10.72]
Zamorano 2021	-0.71	5.23	32	-0.15	3.95	29	88.0%	-0.56 [-2.87 , 1.75]
Total (95% CI)			**81**			**71**	**100.0%**	**-1.57 [-5.46 , 2.31]**

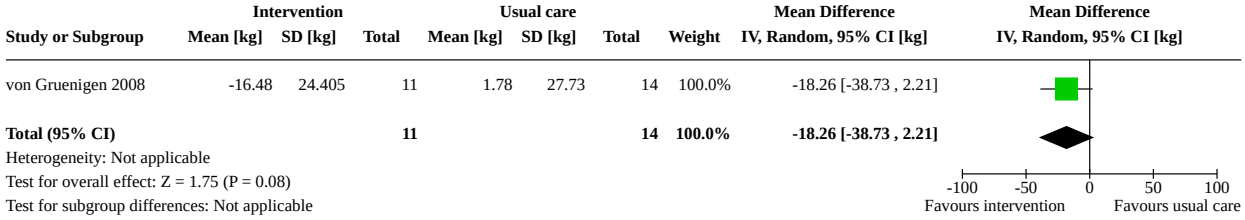
Heterogeneity: Tau² = 3.08; Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



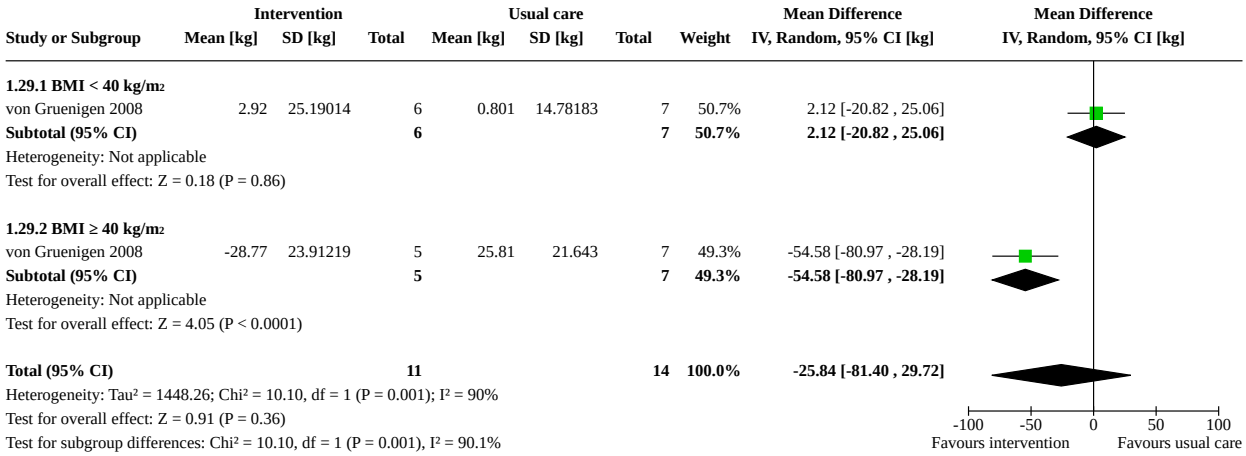
Analysis 1.27. Comparison 1: Lifestyle intervention versus usual care, Outcome 27: Weight loss stratified by BMI (12 months)



Analysis 1.28. Comparison 1: Lifestyle intervention versus usual care, Outcome 28: Weight loss (24 months)



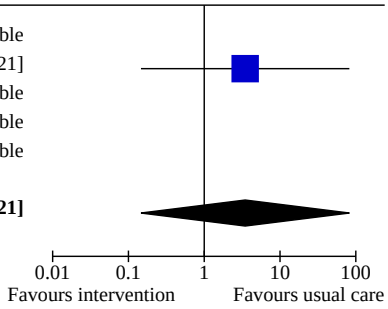
Analysis 1.29. Comparison 1: Lifestyle intervention versus usual care, Outcome 29: Weight loss stratified by BMI (24 months)



Analysis 1.30. Comparison 1: Lifestyle intervention versus usual care, Outcome 30: Cardiovascular and metabolic event frequency (6 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Allison 2016	0	22	0	10		Not estimable
Janda 2021	1	31	0	36	100.0%	3.47 [0.15 , 82.21]
Maxwell-Smith 2019	0	8	0	3		Not estimable
McCarroll 2014	0	41	0	28		Not estimable
von Gruenigen 2008	0	16	0	16		Not estimable
Total (95% CI)		**118**		**93**	**100.0%**	**3.47 [0.15 , 82.21]**
Total events:	1		0			

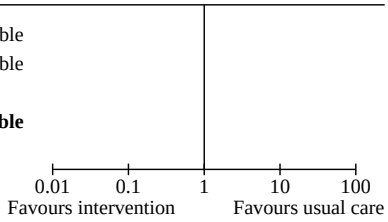
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1: Lifestyle intervention versus usual care, Outcome 31: Cardiovascular and metabolic event frequency (12 months)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
McCarroll 2014	0	34	0	24		Not estimable
von Gruenigen 2008	0	17	0	18		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

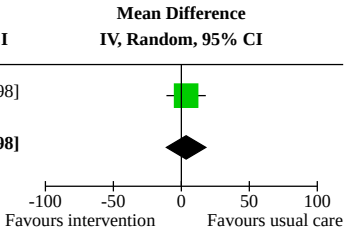
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1: Lifestyle intervention versus usual care, Outcome 32: Quality of life: Functional Assessment of Cancer Therapy – General (FACT-G) (9 weeks)

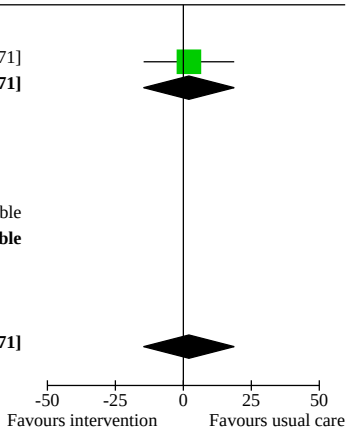
Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Random, 95% CI
Edbrooke 2022	-3.8	13.23	9	-7.31	15.67	7	100.0%	3.51 [-10.96 , 17.98]
Total (95% CI)			**9**			**7**	**100.0%**	**3.51 [-10.96 , 17.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



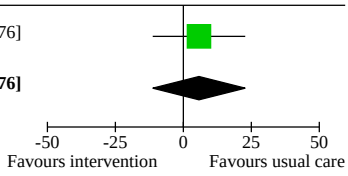
Analysis 1.33. Comparison 1: Lifestyle intervention versus usual care, Outcome 33: Quality of life stratified by BMI (9 weeks FACT-G)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.33.1 BMI < 40 kg/m2								
Edbrooke 2022	-4.15	14.1	8	-6.2	16.86	6	100.0%	2.05 [-14.61 , 18.71]
Subtotal (95% CI)			**8**			**6**	**100.0%**	**2.05 [-14.61 , 18.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.33.2 BMI ≥ 40 kg/m2								
Edbrooke 2022	-1	0	1	-14	0	1		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**9**			**7**	**100.0%**	**2.05 [-14.61 , 18.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
Test for subgroup differences: Not applicable								



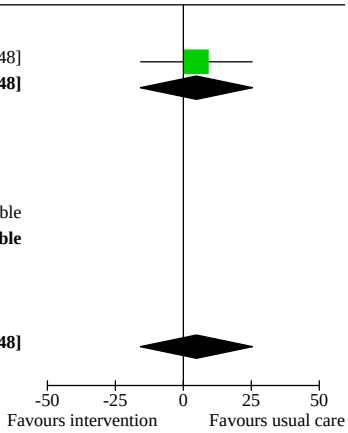
Analysis 1.34. Comparison 1: Lifestyle intervention versus usual care, Outcome 34: Quality of life: FACT-G (3 months)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Edbrooke 2022	-3.25	7.37	8	-9	20.28	6	100.0%	5.75 [-11.26 , 22.76]
Total (95% CI)			**8**			**6**	**100.0%**	**5.75 [-11.26 , 22.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Test for subgroup differences: Not applicable								

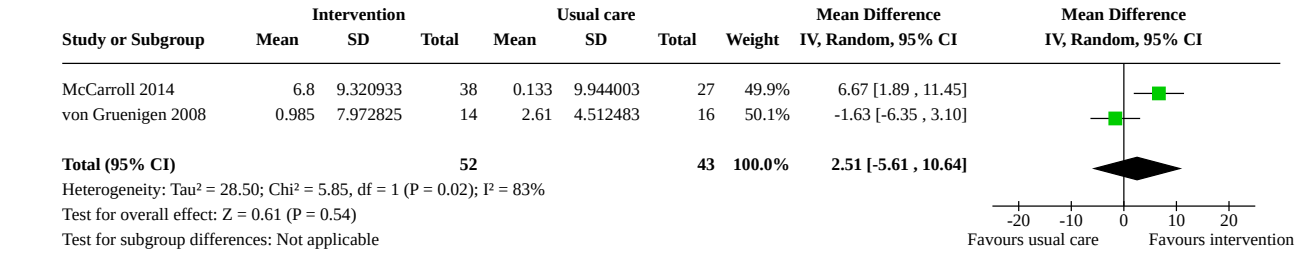


Analysis 1.35. Comparison 1: Lifestyle intervention versus usual care, Outcome 35: Quality of life stratified by BMI (3 months FACT-G)

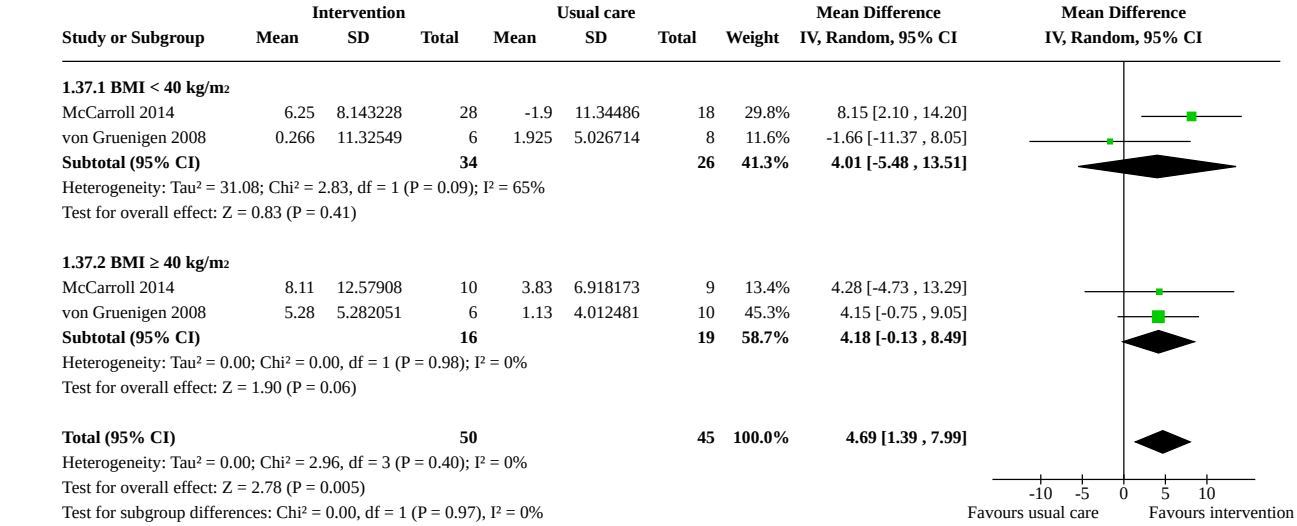
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.35.1 BMI < 40 kg/m2								
Edbrooke 2022	-3.79	7.79	7	-8.6	22.65	5	100.0%	4.81 [-15.86 , 25.48]
Subtotal (95% CI)			**7**			**5**	**100.0%**	**4.81 [-15.86 , 25.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.65)								
1.35.2 BMI ≥ 40 kg/m2								
Edbrooke 2022	0.5	0	1	-11	0	1		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**8**			**6**	**100.0%**	**4.81 [-15.86 , 25.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.65)								
Test for subgroup differences: Not applicable								



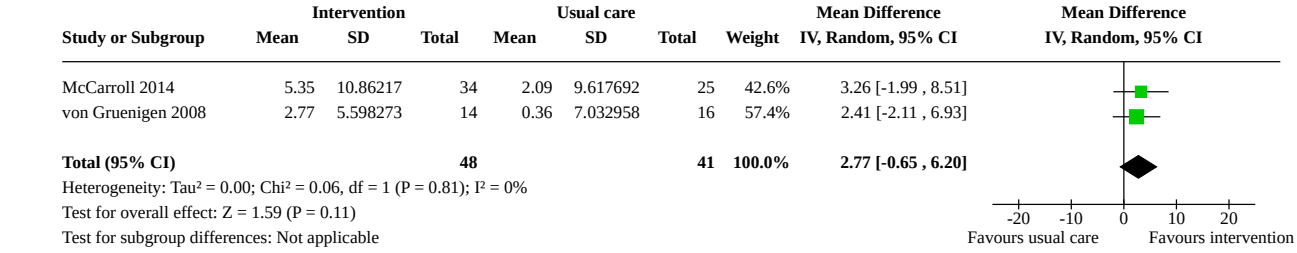
Analysis 1.36. Comparison 1: Lifestyle intervention versus usual care, Outcome 36: Quality of life: FACT-G (6 months)



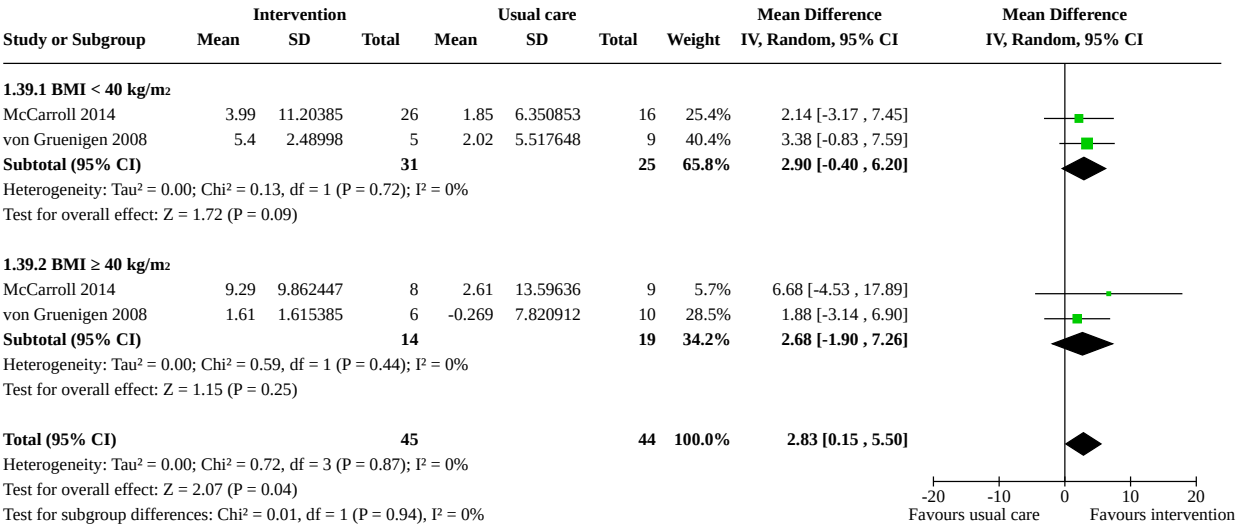
Analysis 1.37. Comparison 1: Lifestyle intervention versus usual care, Outcome 37: Quality of life stratified by BMI (6 months FACT-G)



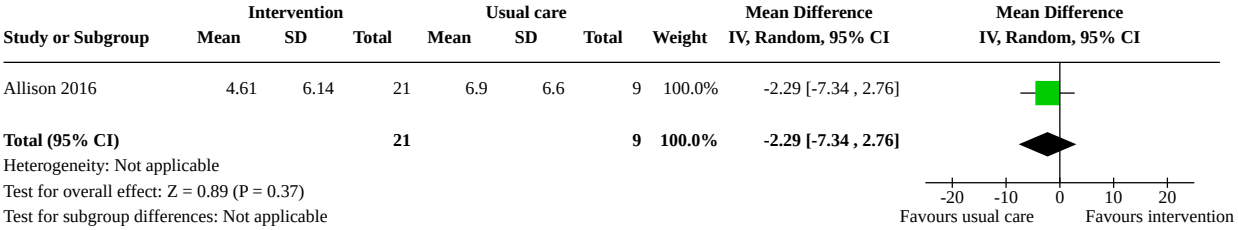
Analysis 1.38. Comparison 1: Lifestyle intervention versus usual care, Outcome 38: Quality of life: FACT-G (12 months)



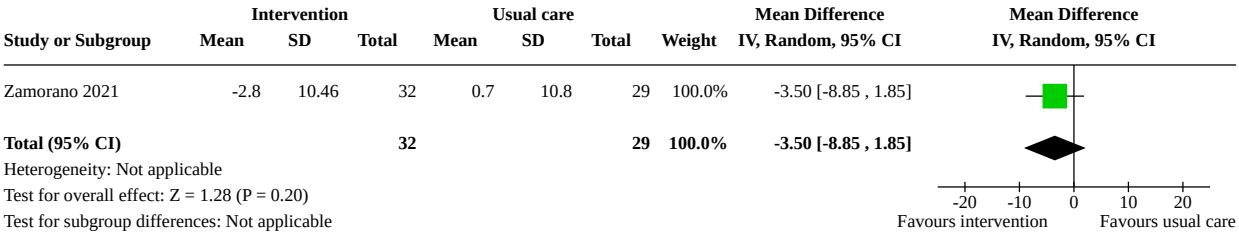
Analysis 1.39. Comparison 1: Lifestyle intervention versus usual care, Outcome 39: Quality of life stratified by BMI (12 months FACT-G)



Analysis 1.40. Comparison 1: Lifestyle intervention versus usual care, Outcome 40: Quality of life: 12-item Short Form (SF-12) Physical Health Component (6 months)



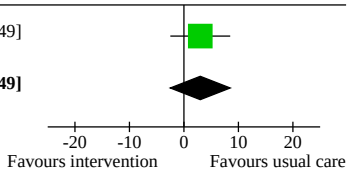
Analysis 1.41. Comparison 1: Lifestyle intervention versus usual care, Outcome 41: Quality of life: SF-12 Physical Health Component (12 months)



Analysis 1.42. Comparison 1: Lifestyle intervention versus usual care, Outcome 42: Quality of life: SF-12 Mental Health Component (12 months)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Zamorano 2021	3.5	12.1	32	0.5	9.76	29	100.0%	3.00 [-2.49 , 8.49]
Total (95% CI)			**32**			**29**	**100.0%**	**3.00 [-2.49 , 8.49]**

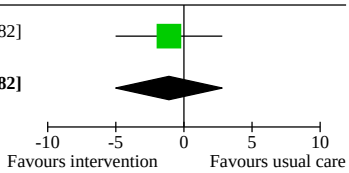
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.43. Comparison 1: Lifestyle intervention versus usual care, Outcome 43: Quality of life: Cancer-Related Body Image Scale (CRBI) (12 months)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Zamorano 2021	-1.8	8.69	32	-0.7	6.88	29	100.0%	-1.10 [-5.02 , 2.82]
Total (95% CI)			**32**			**29**	**100.0%**	**-1.10 [-5.02 , 2.82]**

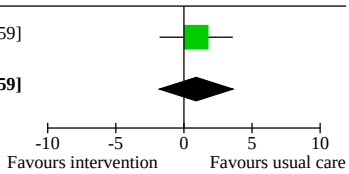
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 1.44. Comparison 1: Lifestyle intervention versus usual care, Outcome 44: Quality of life: 9-item Patient Health Questionnaire (PHQ-9) (12 months)

Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Zamorano 2021	-0.6	5.17	32	-1.5	5.51	29	100.0%	0.90 [-1.79 , 3.59]
Total (95% CI)			**32**			**29**	**100.0%**	**0.90 [-1.79 , 3.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Authors' responses to additional information request

Study	Principal Investigator contacted	Additional information requested	Answers provided
Allison 2016	Kelly Allison	Randomisation process	"The coordinating center used a computer generated algorithm to produce the randomization envelopes for each clinical site, with the general parameters of randomizing 1:1:1 across the three conditions. The envelopes are then chosen sequentially as each participant was enrolled."
		Blinding process	"There was no blinding. The outcome assessments were conducted by study coordinators and trained medical personnel (for blood draws, DEXA [dual-energy X-ray absorptiometry]). The coordinators knew which condition

Table 1. Authors' responses to additional information request *(Continued)*

	the participants were in, but other medical personnel were not informed."
How was the study analysed?	"Given we only had pre–post assessment data and our main analyses used paired t-tests and correlations, we were unable to do intention-to treat analyses."
Exclusion criteria	"Exclusion criteria included: age less than 18, current or recent participation in a weight loss program or use of weight loss medications; uncontrolled serious medical or psychiatric condition(s) that would affect the patient's ability to participate in the interventional study; invasive malignancy other than EC or non-melanoma skin cancer which required active treatment currently or within the last 5 years, or current pregnancy."
How was missing data dealt with?	"Given the pre–post assessment design, were excluded participants for variables that were not completed."
Baseline characteristics	See Allison 2016 under Characteristics of included studies section. Data on comorbidities, performance status and type of endometrial cancer were not provided.
Duration of study intervention	"6 months."
Was a power calculation performed?	"No – From the grant: The purpose will be to provide estimates for the size of an intervention effect achievable by the experimental intervention in order to power and justify a grant application for a full-scale trial of a weight loss program in women with endometrial cancer. With a sample size of 30 participants per group, the true difference in mean weight loss between the groups can be estimated with a 95% confidence interval size of ±0.50σ, where σ is the population standard deviation of weight loss, assumed in this calculation to be the same in each of the two intervention groups and the control group. We will assess the comparability of variance across the groups and do exploratory analyses of possibly variance-stabilizing transformations. Because this is a pilot study to derive parameters to design an appropriately-powered study, hypothesis testing is not a primary goal of the statistical analysis of the data, although p-values will be calculated."
Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses. No data provided on adverse events, recurrence-free and cancer-specific survival.
Funding source	"Cross-TREC study funded by NCI U54-CA155850 – University of Pennsylvania; U54 CA155626 – Harvard University; U54 CA155496CC – Washington University; U01 CA116850 – Fred Hutchinson Cancer Research Center."

Table 1. Authors' responses to additional information request *(Continued)*

		Conflicts of interest	None declared.
Cohen 2018	Caroline Cohen	Single- or multicentre study?	Single centre.
		Any deviation from inclusion/exclusion criteria on ClinicalTrials.gov website?	"No."
		How many of the original 73 participants had endometrial cancer?	"Data re: all 73 randomized is not available. Of 57 who completed baseline testing, 23 had endometrial cancer."
		With a BMI ≥ 25?	18.
		Who completed the trial?	13.
		Reasons for non-attendance at follow-up visits?	"Reasons for withdrawal of patients with endometrial cancer (BMI >25) included: decision to enter hospice care, deceased, family emergency, planned surgery, and lost to follow-up."
		Baseline characteristics	See Cohen 2018 under Characteristics of included studies table. Data on histological type, ECOG status and primary treatment modality were not provided.
		Had trial participants completed their primary treatment or still undergoing?	"All participants had completed their first treatment. 2 participants were receiving concurrent treatment, but it was the third treatment for both. "
		Was the computer-generated blocked randomisation scheme created prior to study commencement?	"Yes."
		Methods of group allocation concealment	"Research team members were provided only with subject IDs and demographics as needed to complete measurements/analyses."
		Blinding of outcome measurements	"Study coordinator, physician, and dietitian were aware of assignment, but DXA technicians, nursing staff, and laboratory staff were blinded."
		Prospectively published protocol?	"No."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses. Standard deviation not provided for QoL data, therefore unable to include in analyses. No data provided on cancer-specific or recurrence-free survival, adverse events and cardiovascular and metabolic event frequency.
Edbrooke 2022	Lara Edbrooke	Single- or multicentre study?	Single – Peter Mac Callum Cancer Centre.

Table 1. Authors' responses to additional information request *(Continued)*

		How many participants had a BMI ≥ 25? In each group?	"17/22 (77%)" "Intervention: 10; Usual Care: 7."
		Baseline characteristics	See Edbrooke 2022 under Characteristics of included studies table. Data on comorbidities was provided as "Colinet co-morbidity score (median (IQR)) 6 (1, 8)". Further breakdown of ECOG score was not provided- "We did not collect further details as this was only used to screen out patients with an ECOG of 3 or 4."
		Power calculation?	"No this was a pilot RCT with a pragmatic sample size."
		Methods of group allocation concealment	"An independent statistician created the randomisation table and this was uploaded into the trial REDCap database. Randomisation was performed using the randomisation module within the REDCap database and managed by an independent data manager."
		Prospectively published protocol?	"No. The trial protocol was only published on the trial registration website (ANZCTRN: 12619000631101)."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses. No data provided on cardiovascular and metabolic event frequency. Quote: "assessment of weight (measured in kg) was impacted by restrictions on face-to-face appointments during the COVID-19 pandemic and participants declining to attend hospital follow-up appointments. Some weights were measured and some were patient-reported."
		Source of funding	"The study was funded by the Peter MacCallum Cancer Foundation."
		Any conflicts of interest?	"No."
Janda 2021	Andreas Obermair	Baseline characteristics	See Janda 2021 under Characteristics of included studies table. Comorbidity data provided as the Charlson Comorbidity Index.
		Methods of group allocation concealment	"Randomisation was open label (unblinded), allocation was concealed by using a central telephone system."
		Were the pathologists or gynae-oncologists assessing response blinded for the outcome assessments?	"Yes, they were blinded to outcome."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency,	See Data and analyses. No data provided on cardiovascular and metabolic event frequency, QoL and "survival data not collected."

Table 1. Authors' responses to additional information request *(Continued)*

		change in QoL from baseline	
Maxwell-Smith 2019	Chloe Maxwell-Smith	Baseline characteristics	See Maxwell-Smith 2019 under Characteristics of included studies table. ECOG status not reported. Quote: "Screening ensured that all patients recruited were without physical ailments, such that they were able to engage in the recommended level of MVPA. In any difficult situations, the patient's specialist or GP was consulted."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses. No survival or QoL data provided "Unfortunately I don't believe we can provide data on QOL. We did intend to assess QoL outcomes using SF-12, per the protocol. However, we since learned that the SF-12 is licenced to another organisation external to RAND, which permits non-commercial use. We did measure some very brief outcomes on depression and stress as part of a measure of cardiovascular risk. However, these were only binary (y/n) responses."
McCarroll 2014	Michele McCarroll	Single- or multicentre study?	Single centre.
		Reasons for non-attendance at follow-up visits	None provided.
		Methods of group allocation concealment	"Physician counseling was standardized. Clinical guidelines for professionals on the identification, evaluation, and treatment of overweight and obesity in adults, according to the NIH should include dietary therapy, behavior therapy, and an increase in physical activity. They recommend that the clinician and the patient devise goals and a treatment strategy for weight loss with periodic weight checks. A guideline for physicians consisting of a laminated 3 × 5 card was given to all treating physicians as a reminder of patient teaching points. Due to the interventions performed by the study team (dietitian, Physical therapist, psychologist, etc.), they were able to know who was in each group."
		Prospectively published protocol?	"No."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses.
von Gruenigen 2008	Michele McCarrroll	Single- or multicentre study?	Single centre.

Table 1. Authors' responses to additional information request *(Continued)*

		Reasons for non-attendance at follow-up visits	None provided.
		Methods of group allocation concealment	"Physician counselling was standardized. Clinical guidelines for professionals on the identification, evaluation, and treatment of overweight and obesity in adults, according to the NIH should include dietary therapy, behavior therapy, and an increase in physical activity. They recommend that the clinician and the patient devise goals and a treatment strategy for weight loss with periodic weight checks. A guideline for physicians consisting of a laminated 3 × 5 card was given to all treating physicians as a reminder of patient teaching points. Due to the interventions performed by the study team (dietitian, Physical therapist, psychologist, etc.), they were able to know who was in each group."
		Prospectively published protocol?	No.
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses.
Yeh 2021	Jessica Yeh	Single- or multicentre study?	Single centre.
		Baseline characteristics	See Yeh 2021 under Characteristics of included studies table. Data on histological type, ECOG status and primary treatment modality were not provided.
		Prospectively published protocol?	"We did not publish a manuscript, but there was a study protocol pre-approved by IRB. This protocol was posted in ClinicalTrials.gov."
		Was the randomisation sequence performed prior to study commencement?	"Yes; computer generated."
		Was the statistician who generated the randomisation sequence blinded? And if so, could you provide information on how?	"Yes. The statistician has never seen participants, did not see randomization arm or outcome data until data analysis stage. Data collection staff were blinded by randomization arm."
		Was the allocation performed next in sequence, and who performed it?	"Computer generated sequence. Study coordinator checked eligibility and then randomized participants."
		Results – overall survival, adverse events, recurrence-free survival,	See Data and analyses. No standard deviation provided for weight loss data therefore unable to include in analyses. QoL data not provided (not yet analysed).

Table 1. Authors' responses to additional information request *(Continued)*

		cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	
Zamorano 2021	Abigail Zamorano	Could you provide the breakdown of the reasons for non-attendance in the control vs intervention of participants at each of the study visit time points?	"19 patients did not complete the six-month survey or measurements: 8 in the intervention arm (6 from ScaleDown™ and 2 from iOTA) and 11 in the enhanced usual care arm. Reasons included: needing no scheduled follow-up with the gynecologic oncology provider at our institution and being unable to come for "research only visits" (n=2), living "too far away" to come for visits (n=6), feeling "overwhelmed" and that her health conditions prohibited her from achieving the goals set by iOTA (n=1), choosing not to complete surveys or have anthropometric measurements taken at the follow-up visit (n=2), and being unable to be contacted (n=7). Three intervention patients discontinued participation at the time of transition from ScaleDown™ to iOTA."
		Baseline characteristics	See Zamorano 2021 under Characteristics of included studies table.
		Methods of group allocation concealment	"Random allocation sequence was generated by REDCap, so the research coordinator who consented and enrolled the participants was unaware of what the next treatment allocation would be."
		Randomisation process	"The randomization was generated randomly by REDCap and was concealed from the statistician."
		Outcome allocation concealment?	"None."
		Prospectively published protocol?	"No."
		Results – overall survival, adverse events, recurrence-free survival, cancer-specific survival, weight loss from baseline, cardiovascular and metabolic event frequency, change in QoL from baseline	See Data and analyses. Data was provided on weight loss stratified by BMI at 12 months; however number of participants with BMI < 40 kg/m^2 and BMI ≥ 40 kg/m^2 not supplied and, therefore, could not be included in the analyses. Data not provided on cardiovascular and metabolic event frequency.

Further information was requested from the authors of Clark 2021; Mohammad 2019; Nock 2013; however no data were received. The author of Allison 2016 was re-contacted for further data for this review update but no response was received.,
BMI: body mass index; ECOG: European Cooperative Oncology Group; GP: general practitioner; IQR: interquartile range; iOTA: Interactive Obesity Treatment Approach; IRB: Institutional Review Board; MVPA: moderate–vigorous intensity physical activity; n: number; QoL: quality of life; RCT: randomised controlled trial; SF-12: 12-item Short Form.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Uterine Neoplasms] explode all trees
#2 ((uterus or uterine or endometri* or womb or corpus uteri) near5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*))
#3 #1 or #2
#4 MeSH descriptor: [Body Mass Index] this term only
#5 BMI
#6 MeSH descriptor: [Obesity] explode all trees
#7 MeSH descriptor: [Body Weight] explode all trees
#8 MeSH descriptor: [Adiposity] this term only
#9 obese or obesity or overweight or weight or adiposity or excess body fat
#10 4 or 5 or 6 or 7 or 8 or 9
#11 #3 and #10

Appendix 2. MEDLINE OvidSP search strategy

1. exp Uterine Neoplasms/
2. ((uterus or uterine or endometri* or womb or corpus uteri) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. body mass index/
5. BMI.mp.
6. exp obesity/
7. exp body weight/
8. Adiposity/
9. (obese or obesity or overweight or weight or adiposity or excess body fat).mp.
10. 4 or 5 or 6 or 7 or 8 or 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.
14. placebo.ab.
15. clinical trials as topic.sh.
16. randomly.ab.
17. trial.ti.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 10 and 18

Appendix 3. Embase OvidSP search strategy

1. exp uterus cancer/
2. ((uterus or uterine or endometri* or womb or corpus uteri) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. body mass/
5. BMI.mp.
6. exp obesity/
7. exp body weight/
8. (obese or obesity or overweight or weight or adiposity or excess body fat).mp.
9. 4 or 5 or 6 or 7 or 8
10. crossover procedure/
11. double-blind procedure/
12. randomized controlled trial/
13. single-blind procedure/
14. random*.mp.
15. factorial*.mp.
16. (crossover* or cross over* or cross-over*).mp.
17. placebo*.mp.
18. (double* adj blind*).mp.
19. (singl* adj blind*).mp.
20. assign*.mp.

21. allocat*.mp.
22. volunteer*.mp.
23. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 3 and 9 and 23

WHAT'S NEW

Date	Event	Description
24 March 2023	New search has been performed	This is an updated version of the original Cochrane Review published in Issue 2, 2018. Heather Agnew was added to the authorship team while Michelle MacKintosh, Neil Ryan, Richard Edmondson and James Duffy were removed. For handsearching of other resources, we did not search the link www.controlled-trials.com/rct as this is a duplicate for ISRCTN. In addition, we searched PsycINFO- a database covering the behavioural and social sciences in the field of psychology, to broaden our search. We identified nine new RCTs and combined these with the three RCTs identified in the original review. These 12 completed RCTs were included in this update, randomising 610 overweight and obese women with a history of endometrial cancer.
24 March 2023	New citation required but conclusions have not changed	Since the last version of this review none of the new relevant studies have provided additional information to change the conclusions.

HISTORY

Protocol first published: Issue 1, 2017
Review first published: Issue 1, 2018

CONTRIBUTIONS OF AUTHORS

Study conception and design: SK and EC; alongside the other authors in the original review (Michelle MacKintosh, Neil Ryan, Richard Edmondson and James Duffy).

Acquisition of data: HA and SK.

Analysis and interpretation: HA, SK and EC.

Drafting of the manuscript: HA, SK and EC.

Review and approval: HA, SK and EC.

DECLARATIONS OF INTEREST

HA: none.

SK: none.

EC: none.

SOURCES OF SUPPORT

Internal sources

- Cochrane Review Support Programme, UK

Prof Emma Crosbie was awarded funding via the Cochrane Review Support Programme to expedite the completion of this original version of this review which is a priority topic area.

External sources

- National Institute for Health Research Clinician Scientist Fellowship, UK

  Prof Emma Crosbie is supported by a National Institute for Health and Care Research (NIHR) Advanced Fellowship (NIHR300650) and the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007).

  The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
- National Institute of Health Research Academic Clinical Lecturer, UK

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- Wellbeing of Women, UK

  Dr Sarah Kitson is in receipt of a Wellbeing of Women postdoctoral research fellowship PRF 101.
- Manchester University NHS Foundation Trust, UK

  Dr Heather Agnew is supported by the Manchester University NHS Foundation Trust clinical research fellowship.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes in authorship from the protocol to this review update include the addition of Heather Agnew, and removal of Michelle MacKintosh, Neil Ryan, Richard Edmondson and James Duffy. Both Sarah Kitson and Emma Crosbie have been involved in the protocol, original review and this update.

For handsearching of other resources, we did not search www.controlled-trials.com/rct as this is a duplicate for ISRCTN. In addition, we searched PsycINFO – a database covering the behavioural and social sciences in the field of psychology, to broaden our search.

For the outcomes of overall survival and cancer-specific survival insufficient data were available from published reports or correspondence with study authors to allow the calculation of hazard ratios. Instead, we presented survival as a dichotomous outcome and calculated the risk ratio for survival instead. Depending on the assembled research, the study authors had planned to organise the data by population and, within the data categories, to explore the main comparisons of the review. Due to the small number of studies and participants included in the review this was not possible.

INDEX TERMS

Medical Subject Headings (MeSH)

*COVID-19 [complications]; *Endometrial Neoplasms [therapy]; Obesity [complications] [therapy]; Overweight [complications] [therapy]; Weight Loss

MeSH check words

Female; Humans