SUPPLEMENTARY FILE 1:

Review Protocol

What is the evidence that overweight breast cancer survivors can lose weight and which interventions are most successful? A systematic review of reviews

Rationale:

Breast cancer is the commonest cancer in the UK, with 54,000 cases diagnosed each year. Breast cancer survivors are the largest group of cancer survivors, with 500,000 patients living in the UK following breast cancer. Over 30% of patients diagnosed with a new breast cancer are obese. Breast cancer survivors who are overweight (Body mass Index or BMI 25-29.9) or obese (BMI>30) have poorer outcomes than those with a normal BMI <25; with higher recurrence rates, poorer response to treatment and increased secondary cancer rates. (1) (3) A recent meta-analysis concluded that women with obesity have a one third increased risk of breast cancer related mortality and a 41% increased risk of overall mortality compared to women with breast cancer who have a normal weight. (2) Weight loss interventions have been shown to be safe and feasible in breast cancer survivors. This systematic review of reviews will explore the potential magnitude of weight loss that breast cancer survivors can achieve through physical activity, dietary modification and/or surgical interventions, and assess which interventions are the most effective in facilitating weight loss.

Registration:

This review of reviews has been registered on PROSPERO (International Prospective Register of Systematic Reviews) (19th October CRD42021283481)

Aims/objectives:

1. To summarise the evidence regarding the impact of weight loss interventions in breast cancer survivors from 1990 to present in terms of amount of weight loss, and the effectiveness of the interventions
2. To look at clinical outcomes including survival or breast cancer recurrence, biomarkers, and psychosocial outcomes, including Patient-Reported Outcome Measures (PROMs), general and health-related quality of life, and functional status
3. To see if any particular weight loss interventions is preferably dependent on body mass index
4. To identify any gaps in the literature where it may be appropriate to undertake further targeted systematic reviews

Systematic review of reviews:

Reviews of reviews are designed to synthesise evidence from multiple systematic reviews of interventions into a single review. They do not repeat the searches, assessment of eligibility, assessment of risk of bias or meta-analysis from included reviews, nor do they aim to extract additional outcomes from studies, but they are a useful tool to assess the limitations of included reviews, and where possible, include meta-analyses across reviews to provide indirect comparisons of the effects of different interventions on a specific outcome or range of outcomes. This is particularly useful when a large number of systematic reviews may exist for a given topic, as an overview of relevant reviews allows the findings of separate reviews to be compared and contrasted.

Inclusion/exclusion criteria:

Inclusion criteria: All systematic reviews of weight loss interventions in adult female breast cancer survivors, published in the English language from 1990 to date, in which weight loss or percentage
reduction in BMI or body weight is reported as a main outcome, to include trials, randomised and non-randomised, feasibility studies, cohort and case control studies.

Exclusion criteria: Publications not in English; Animal studies; Study population was not breast cancer survivors or women or adults 18 and over, Publications prior to 1990, narrative reviews with unsystematic methodologies, editorials, opinion pieces, commentaries, letters, meeting abstracts or conference proceedings.

**PICO**

Participants: Adult breast cancer survivors who are female and 18 years or older who have been involved in weight loss intervention following initial breast cancer diagnosis or secondary breast cancer diagnosis. Studies included will be trials, randomised and no randomised and cohort and case control studies.

Interventions: Physical activity interventions (whether individually-targeted or in a group), dietary modifications such as referral to dietician or weight loss support group such as Weight Watchers, Slimming World, bariatric surgery such as laparoscopic sleeve gastrectomy, gastric band or bypass surgery

Comparators: Adult breast cancer survivors who are female and 18 year or older who have not had physical activity or dietary modifications, or have had lifestyle intervention alone. Comparison groups comprising lifestyle intervention alone would be relevant only for interventions relating to bariatric surgery and would include physical activity or dietary modifications as detailed in the intervention.

Outcomes: All eligible reviews must report weight loss measured as a reduction in BMI or weight in pounds/kg or in waist circumference or as a percentage (%) of body weight loss.

Other outcome measures of interest include psycho-social measures, survival or cancer recurrence rates, biomarkers if recorded within the study, PROMs, including general and health-related quality of life, functional status.

**Search strategy**

Relevant systematic reviews will be identified through searching electronic bibliographic databases, and the manual checking of the reference list of each systematic review which meets the eligibility criteria for the review of reviews. For the electronic databases, searches will be limited to reviews published during or after 1990, and reviews written in the English language. The rationale for imposing these limits comes from initial scoping searches that suggested that little or no systematic review evidence about the effectiveness of weight loss interventions for breast cancer survivors predates the year 1990. It is also expected that the vast majority of systematic reviews focusing on this topic will have been published in English, even if individual reviews included primary research written in languages other than English. No reviews will be excluded on the basis of the language of their source material.

The following electronic databases will be searched:

- Medline (Medline database and Medline in process)
- Embase
- CINAHL
- PsycINFO
- Cochrane Library (including the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects (DARE))
Other strategies will include checking the reference list of included reviews for further studies not found via database searching, and a search of PROSPERO will be undertaken to ensure that we will not be duplicating other planned systematic review research that is yet to be published.

**Search terms**

The databases will be searched using a search strategy focusing on terms related to Breast neoplasms and Weight loss or Obesity or Exercise or Physical Activity or Lifestyle or Diet, with an English language and review/systematic review filter applied. MESH terms used breast neoplasm, weight loss, obesity, exercise, lifestyle, diet, review and systematic review. Other terms used as main headings: weight loss, physical activity and lifestyle. Search strategy for Medline attached in Appendix 1.

**Study selection**

Literature search results will be uploaded into Rayyan and duplicates removed. Two independent reviewers (BL, SD) will screen titles and abstracts for relevance against the above inclusion/exclusion criteria. Where both reviewers agree that a review is not relevant, it will be excluded. Where both reviewers agree that a review should be included, full text copies of the review will be obtained, and the paper will be taken forward for full text screening. Where reviewers disagree in their assessment of the eligibility of a title/abstract, this will be resolved by discussion until consensus is reached, or (if necessary), by the independent assessment of a third reviewer.

Articles will first screened by title and abstract, then full text and then data extraction will be performed.

In addition to systematic reviews, our search criteria may return other reviews of reviews, and these reviews of reviews may overlap in terms of the source systematic reviews that they include. We will treat these separately during the analysis phase to avoid including the same systematic reviews multiple times and potentially inflating or over-estimating estimates of intervention effectiveness.

**Data extraction**

Once the list of relevant references has been agreed and full copies of the manuscripts have been obtained, data on the population characteristics, interventions being assessed and outcomes will be extracted from each eligible review using a standardised data extraction form. Data extraction will include Authors, Year of publication, Country of publication, Study types included in review or Review Characteristics, Overall review question and Methodological Characteristics, Study population, detailed description of intervention and follow-up regime and Primary and Secondary Outcomes. One reviewer will undertake the data extraction, which will be checked against the original manuscript by a second reviewer. All disagreements will be resolved by discussion or through arbitration by an additional reviewer.

**Quality assessment**

Two reviewers (BL, SD) will assess the quality of systematic reviews and meta-analyses using the critical appraisal tool-based tool Joanna Briggs Institute (JBI) Critical Appraisal Checklist. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. JBI has 11 criteria against which reviews are appraised including appropriateness of the review question, inclusion criteria and search strategy. Also how the critical appraisal was done and by who and what methods were used to minimise data extraction errors and likelihood of publication bias. Full details of JBI can be found in Appendix 2.

Two reviewers (BL, SD) will be involved in the quality assessment. Any disagreements between the two reviewers over quality assessment in particular studies will be resolved through consultation with an additional reviewer.
Analysis

In this review of reviews our goal is to evaluate the ability of overweight and obese breast cancer survivors to lose weight and the relative/combined effectiveness of different weight loss interventions. Ideally, we would seek to generate pooled estimates of intervention effects, but it is likely that differences in data quality and study heterogeneity within included systematic reviews will make synthesis impossible. If this is the case, we will undertake a narrative synthesis which will comprise a review of participants, interventions, and outcomes, with a particular focus on the characteristics of effective interventions. If there is sufficient homogeneity between reviews, statistical pooling of estimates of intervention effects will be carried out.

References

1. Feigelsen HS et al BMI and Risk of Second Cancer among women with Breast Cancer JNCI J Nat Cancer Inst 2021 00(0):djab053 doi.10.1093/jnci/djab053


3. Lee K et al The Impact of Obesity on Breast Cancer Diagnosis and Treatment Current Oncology Reports 2019 21:41