

# **Impact of lifestyle interventions on body weight and mortality: a meta-analysis of randomized controlled trials**

## **Study Protocol**

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## Background and Aim

Obesity has become a major public health issue with rates tripling between 1975 and 2016. In 2016 more than 2.1 billion people – nearly 30% of the world's population – were either obese ( $\text{BMI} \geq 30$  kg/m<sup>2</sup>) or overweight ( $25 \leq \text{BMI} < 30$  kg/m<sup>2</sup>).<sup>1</sup> Obesity is associated with increased risk of the metabolic syndrome, diabetes, heart failure, ischaemic heart disease, cancer, musculoskeletal disorder and premature death. Randomised studies show that intentional weight loss is associated with improvements in insulin resistance,<sup>2</sup> blood pressure,<sup>3</sup> and some cancers,<sup>4-6</sup> but effects on mortality are uncertain.

The most effective therapy at an individual level is bariatric surgery which achieves substantial and sustained weight loss and is associated with reduction of heart failure,<sup>7</sup> diabetes,<sup>8</sup> risk factors for coronary heart disease<sup>9</sup> and cancer.<sup>4-6</sup> Medications have not provided a safe and effective treatment. The mainstay of most guidelines remains lifestyle change to prevent or treat overweight and obesity.

Losing weight through lifestyle is a class 1A recommendation in both European and American cardiology,<sup>10-12</sup> diabetes<sup>13,14</sup> and as cancer guidelines<sup>15</sup> to prevent disease. These recommendations are predicated on the assumption that lifestyle advice achieves meaningful and sustained weight loss; and that this in turn is associated with reduced morbidity and mortality. Most guidelines do not stipulate precisely on how intensive lifestyle interventions have to be to be effective.

A previous meta-analysis<sup>16</sup> has shown that weight loss through lifestyle achieves modest weight loss and a non-significant reduction in mortality. However, this study has not evaluated the intensity and duration of lifestyle interventions required to achieve sustained weight loss that impacts mortality.

The aim of this meta-analysis is to investigate the efficacy of lifestyle interventions on weight loss and mortality. It will also examine the dose of intervention required to achieve significant weight loss.

## Methods

The search of these electronic databases to obtain suitable studies is carried out by two reviewers. Any queries arising around the suitability of a particular study for inclusion was resolved by discussion with all 3 reviewers. Methodological and appropriate quantitative data will be extracted and compiled in an electronic database from all included studies on three separate occasions independently by 2 reviewers to ensure accuracy. If relevant data was not presented in a study, the corresponding study authors were contacted in attempt to obtain the missing data. The Jadad score of each study will be calculated to assess the quality of the randomized controlled trial. Questions arising during data extraction were resolved by consensus between 3 reviewers [Search Criteria](#)

Inclusion criteria include:

1. Published in 1980 or later
2. At least one study arm is a lifestyle-modification only intervention designed for weight loss
3. Presence of a non-weight loss control group (therefore involving the provision of usual care, generic healthy lifestyle information or a non-weight loss intervention such as the prescription of exercise or salt modification only)
4. Study population is overweight or obese (mean BMI  $\geq 25$  kg/m<sup>2</sup>)
5. Study population are adults
6. Total study sample contains at least 100 participants
7. Follow-up of at least one year
8. Reporting of weight change and mortality data

Exclusion criteria include:

1. Intervention partly or wholly involves pharmacological or surgical therapy
2. Inadequate availability of data to allow for the calculation of weight changes with associated standard deviation and number of deaths
3. All study groups are prescribed specific diets, or the control group receives some targeted support specifically aimed at weight loss

Full Search Strategy for MEDLINE database

Three separate types of searches are undertaken on multiple occasions from November 16<sup>th</sup> 2016 through until 20 April 2018 using the keywords

1. weight AND mortality
2. weight AND lifestyle
3. lifestyle AND weight AND (coronary OR heart OR cardiovascular)

with the search limits of clinical trials only, humans studies only and publications only from 1990 onwards considered. Search 1 and 2 broadly aimed to identify relevant studies in general populations, and search 3 broadly aimed to elicit appropriate studies in coronary heart disease populations.

Duplicates between the three searches were removed.

The search details are as follows:

1. ("weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])
2. ("weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) AND ("life style"[MeSH Terms] OR ("life"[All Fields] AND "style"[All Fields]) OR "life style"[All Fields] OR "lifestyle"[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])

3. ("life style"[MeSH Terms] OR ("life"[All Fields] AND "style"[All Fields]) OR "life style"[All Fields] OR "lifestyle"[All Fields]) AND ("weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields]) AND (("heart"[MeSH Terms] OR "heart"[All Fields] OR "coronary"[All Fields]) OR ("heart"[MeSH Terms] OR "heart"[All Fields]) OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields])) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])

Following the above three searches, more focussed searches using more specific and descriptive keywords such as “weight loss” AND “lifestyle intervention” were carried out in the CENTRAL and Science Direct databases to discover any other appropriate studies not found in the broad MEDLINE search.

### Statistical Analyses

All data will be compiled into a spreadsheet using Microsoft Excel 2010 software, and will be meta-analyses using the Review Manager 5.3 software. Statistical calculation support will be derived from the Cochrane Handbook of Systematic Reviews for Interventions 2011.

Details of the statistical methods ultimately used to derive standard deviations, weights and mortalities are outlined below:

**Standard deviations:** Standard deviations were taken directly from the studies. In situations where standard deviations were not directly presented in the study itself, the values were estimated from standard errors, confidence intervals, interquartile ranges and p-values using information provided in chapters 7 and 16 of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. In situations where only baseline and final standard deviations for weight change were provided, the composite standard deviation for weight change was estimated using formulae presented in the Cochrane handbook (with a conservative correlation coefficient value of 0.5 used in such calculations). In one case (Roumen 2011), the standard deviations were imputed from another report (Roumen 2008) on the same trial that had undertaken a subgroup completers analysis for the same study population. This was deemed appropriate as the completers analysis used the same trial protocol as the full analysis in Roumen 2011, and because the weight changes reported in the two papers were similar to one another.

**Weight changes:** Weight changes are taken directly or indirectly determined using baseline and final weights presented in the studies, and converted into SI units where necessary. In Shea 2010, Fitzgibbon 2010, Rejeski 2011, Gabriel 2011, Wadden 1992, Whelton 1992 in which weight loss data was reported at eighteen months (and in one study, Ma 2013, where it was reported at fifteen months) instead of at one or two years of follow-up, the value presented at fifteen or eighteen months was conservatively taken to be the weight change value at one year follow-up.

**Mortality:** The number of deaths is taken directly from the studies or indirectly calculated when the mortality rate was presented instead of raw death figures. In one particular study (Whelton 1992) in which there was multiple study arms, the mortality data was not stratified to just the weight-loss intervention and control study groups; thus the mortality data meta-analysis uses a larger sample size

compared to the corresponding sample size used for the same study in the weight-change meta-analysis.

If any of the above data was missing, study authors were contacted where appropriate.

Mean number of interventions across studies will be calculated. Subgroup analysis will be done to assess effects on weight loss based on number of interventions (< and > than mean interventions), also effects on mortality be assessed by < and >; than mean interventions and < and > mean weight loss achieved.

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