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Intensity and duration of lifestyle interventions for long term weight loss and association with mortality: a meta-analysis of randomised trials.

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18 Abstract

Objectives

20 To evaluate the importance of the frequency and duration of lifestyle interventions for

21 achieving weight loss over \geq one year, and associations with all-cause mortality.

22 Design

Meta-analysis of randomised trials published in English-language journals from 1980 to June
 2018 that assessed lifestyle compared to control interventions on weight loss, and which
 included ≥100 subjects and reported weight change and mortality for ≥ one year.

Results

31 randomised trials with a total of 20 816 overweight or obese participants were included. 70% of participants had cardiometabolic risk factors. The difference in body weight between lifestyle intervention and control arms at 1 year was -3.65, 95% confidence interval (CI) -4.66, -2.65 kg, and at 3 years was -2.45, 95% CI-3.73, -1.17kg. Weight loss at one year was greater in studies with more compared to fewer interventions (>vs \leq 28 /year (-4.53 [IQR -5.93, -3.12] kg vs -2.38 [-3.98, -0.78] kg, p=0.001). There were 593 deaths (~0.3%/year). The odds ratio for mortality for weight loss interventions compared to the controls was 0.86 (95% CI 0.74, 1.01), p=0.09.

35 Conclusion

In predominantly healthy populations with risk factors lifestyle interventions which are
frequent and sustained on average achieve modest weight loss, and a small decrease in allcause mortality. There was insufficient evidence to reliably evaluate the benefits of shorter
and less intense lifestyle interventions, or benefits in persons with known cardiovascular
disease or cancer.

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| 41 | Prospero registration number CRD42018095067 |
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| 44 | Strengths and Limitations of study |
| 45 | Previous meta-analysis of randomised trials of lifestyle interventions have not considered the |
| 46 | level of intervention needed to achieve clinically meaningful weight loss. |
| 47 | It was not possible for treatment allocation to be blinded. |
| 48 | There was wide variation in the type of lifestyle advice. It was not possible to assess which |
| 49 | type of lifestyle advice is the most effective. |
| 50 | Individual characteristics such as adherence to randomised treatments could not be |
| 51 | evaluated. |
| 52 | Mortality was low, so the statistical power to assess modest differences in mortality was also |
| 53 | low. |
| 54 | There is limited data on effects of lifestyle interventions for weight loss in patients with |
| 55 | cardiovascular disease or cancer. |
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57 Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m²) or overweight (25≤BMI<30 kg/m²).(1) International guidelines in cardiology.(2-4) diabetes (5, 6) and cancer (7) recommend changing lifestyle related factors for management of overweight and obesity. These lifestyle recommendations (2-4, 7-10) are largely based on data from observational epidemiological studies in which obesity was associated with an increased risk of metabolic syndrome, diabetes, arthritis, heart disease and/or cancer. (11-16) However, observational studies do not provide reliable information on whether lifestyle interventions should be recommended in obese people, and several relevant questions remained unanswered: Do lifestyle interventions lead to weight reduction, if so by how much, and is this maintained over time? What level of lifestyle intervention is needed, how long should these interventions be continued, and do lifestyle interventions which target weight reduction improve health and lower the mortality risk? The aim of this meta-analysis was to determine whether published randomised trials of lifestyle interventions for weight loss provide evidence on whether the dose of lifestyle intervention influences the effectiveness of longer term weight reduction, or mortality.

73 Methods

PRISMA guidelines on reporting systematic reviews and meta-analyses of studies were
used throughout the planning, conduct and interpretation of this meta-analysis. A review
protocol was designed, and is available in the supplementary text.

51 77 **Stud**

Study Search and inclusion criteria

Searches of MEDLINE, CENTRAL, Google and Science Direct databases alongside
reference lists of appropriate articles and meta-analyses were performed for any reports on
randomized clinical trials that assessed lifestyle intervention on weight loss published in
English-language journals from 1980 to June 2018. Key words used in searches to identify

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studies included "weight", "lifestyle", "hypocaloric", "diet", "mortality", "coronary", "heart" and "cardiovascular". Articles retrieved using this search string were then limited to trials including weight loss and non-weight loss arms, a trial duration (weight loss and maintenance phase) \geq 12 months, and mortality data by intervention group. Eligible studies were randomised control studies longer than 1 year with \geq 100 overweight and obese adults (BMI ≥25kg/m2) participants randomised to an intentional weight-loss lifestyle intervention and had an appropriate control group. Studies were only included if the control group received normal care – which could include standard healthy lifestyle information – but had no specific advice to achieve weight loss. The intervention arm needed to have intent for weight loss, mainly through the promotion of a hypocaloric diet, and had to include \geq 1 face to face intervention. Participants could be healthy or have established cardiovascular disease (CVD). Studies were excluded if both groups were prescribed specific diets (such as high-protein diets, OPTIFAST), included pharmacotherapy or surgery for weight loss or if the intervention was 'self- help'. Studies with >5% lost to follow up were also excluded to reduce the risk of bias.(17) For mortality, eligible studies were required to report mortality data explicitly either in the CONSORT diagram, as an outcome measure or as an adverse event (studies reporting "no adverse events" was taken to mean that no deaths occurred, but studies reporting "no adverse events related to intervention" without specifying the nature of these adverse events were excluded). Studies also were required to present sufficient data in order for calculations of mean weight changes in kilograms. The search of these electronic databases to obtain suitable studies was carried out by two reviewers (NS, JB). Any gueries arising around the suitability of a particular study for inclusion was resolved by discussion with all reviewers (NS, JB and RS). In some situations, multiple papers reporting on the same clinical trial were used if each individual paper did not provide all required data and qualitative information on the study. Methodological and

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appropriate quantitative data was extracted and compiled in an electronic database from all
included studies on three separate occasions independently by two reviewers (NS, JB) to
ensure accuracy.

Baseline data extracted included study sample size, mean study population age and BMI,
duration of intervention and follow-up, and percentage of women in the study sample. Each
study's intervention was also categorised into levels of intensity depending on the number
and frequency of dietary interventions. An 'individual session' was defined as an
intervention delivered one to one by a dietician/lifestyle coach/physician. A 'face to face'
intervention was delivered in person. 'Remote interventions' were those delivered by
telephone, emails or web based programs.

Follow-up data included mean weight or weight loss at each follow-up time after one year, and all-cause mortality. If relevant data was not presented in a study, the corresponding study authors were contacted. Questions arising during data extraction were resolved by consensus between reviewers (NS, JB and RS). Outcome measures are weight loss achieved at 1, 2 and 3 years, intensity of intervention required to achieve weight loss and mortality. Weight loss at 1 year was the primary outcome. If not reported, the first weight recorded after the first year was used. (18-23)

125 The Jadad score of each study was also calculated to assess the quality of the randomised126 controlled trial.(24)

⁰ 128 **Statistical Analyses**

The inverse-variance method was used to pool mean differences for weight in kilograms and
 odds ratio for mortality to yield an overall effect size with 95% confidence intervals. For
 studies where standard deviations (SD) or confidence intervals were not available despite
 contacting authors, the mean SD for all other studies was used. Standard error or

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| 3 4 | 133 | confidence intervals were converted to standard deviation using standard statistical formulae |
| 5 6 7 | 134 | presented in the Cochrane Handbook for Systematic Reviews of Interventions 2011. |
| 8 9 | 135 | Each meta-analysis was assessed for heterogeneity by a Chi square test and I ² statistic. A |
| 10 11 | 136 | fixed effects model was used when heterogeneity was not present ($I^2=0\%$) and a random |
| 12 13 | 137 | effects model was used when statistical heterogeneity (I²≥1%) was present. The meta- |
| 14 15 | 138 | analysis was also repeated using a fixed effects model to assess the effects of small studies |
| 16 17 | 139 | on results.(25) A p-value of <0.05 was considered statistically significant. Studies are |
| 18 19 20 | 140 | presented in Forrest plots in order of statistical power. |
| 21 22 | 141 | For weight loss at 1 year and all-cause mortality, analysis was stratified at the mean baseline |
| 23 24 25 | 142 | body mass index (BMI), the median number of interventions (\leq 28; >28 interventions), and |
| 25 26 27 | 143 | the whether intentions were frontloaded (< or \ge 75% interventions in first 6 months). For |
| 28 29 | 144 | weight loss over the length of follow up, subgroup analysis was done for mean study BMI |
| 30 31 | 145 | (25-29, 30-35 and >35), age (40-49, 50-59 and ≥60) and number of interventions per year (≤ |
| 32 33 34 | 146 | 6, 7-12, 13-24, and ≥25). |
| 35 36 | 147 | Sensitivity analysis was undertaken to assess effects of studies that deviated significantly |
| 37 38 | 148 | from the standard error of the total study result or studies where baseline values differed |
| 39 40 41 | 149 | significantly from the mean baseline. Funnel plots were used to assess for publication bias. |
| 42 43 | 150 | The statistical analyses were performed using RevMan software version 5.2 (The Nordic |
| 44 45 | 151 | Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed |
| 46 47 48 | 152 | guidelines suggested by Wang. (26) |
| 49 50 51 | 153 | |
| 52 53 54 55 56 57 58 59 60 | 154 | |

Results

From a review of 5654 titles and abstracts, 31 randomised trials with a total of 20 563 participants met inclusion criteria. The most common reasons for excluding studies were duplicate reports, sample size <100, duration of follow-up <1 year, and no reporting of mortality (Figure 2). One study, reported separate outcomes for the face to face and remote intervention (27), and another reported separate outcomes for control, diet, exercise, and both diet and exercise(18). These are reported separately for a total of 34 studies. 70% of study participants had cardiometabolic risk factors. No study was found in patients with established cardiovascular disease, although 14% of participants in the Look AHEAD trial had cardiac disease (28).

Included studies are summarised in Table 1. Most studies were small and only four studies had sample sizes > 1000 in each arm. (28-32) One study (18) reported outcomes and weight only at 6 years and this study is included only in the mortality analysis. The Da Qing study, (33) did not report summary measures of weight loss by randomised group, so also could only be included in mortality analysis. The majority of included studies were of modest quality, with an average Jadad score of 3.1 (± 0.9). The Look AHEAD trial (28) was both the largest study and had the longest follow up.

41
42172Lifestyle interventions evaluated

There were large variations in types of intervention (individual or group), mode of interventions (face to face or remote), timing of interventions and frequency of interventions between studies described in Table 2. In some studies, the number of interventions provided was dependent on an individual study participant's response to the weight loss program, so it was not possible to accurately describe the dose of intervention for every study. For these studies, the average number of interventions was extrapolated based on the assumption that there was a normal distribution of extra interventions within the study.

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There was also large variety in the frequency, mode and timing of interventions across all studies with no standard approach (Table 2). The median number of interventions during the first year was 28 (IQR 12 to 37). In most studies there were more interventions during the first 6 months, median 18 (IQR 10 to 24) interventions. 14 studies report intervention beyond 1 year and for these the median number of interventions in year 2 was 5 (IQR 4 to 12). Few studies reported weight outcomes beyond 3 years.

7 186 Effect of lifestyle interventions on body weight

Effects on body weight are shown in Figure 3, Table 3 and Supplemental Figures available in the supplemental document. 28 of the included studies reported weight loss at one year, 13 at two years and 8 at three years. For studies which did not report weight loss at 1 year, the first reported weight after 1 year was used to assess the relationship with median number of interventions and total weight loss.(19, 21, 23)

The weighted mean difference in body weight between intervention and control groups was
-3.68, (% CI -4.70, -2.66) kg at 1 year. This difference decreased over time and at year 3
was -2.45 (-3.73, -1.17) kg. Funnel plots do not suggest publication bias.

 38_{88}^{7} 195Weight loss for studies with > than the median of 28 interventions /year was -4.53 [-5.93, - 39_{40}^{7} 1963.12] kg, and with ≤28 interventions was -2.38 [-3.98, -0.78] kg, p=0.001. A dose response 41_{42}^{7} 197was also evident, with increasing number of interventions associated with greater weight 198_{44}^{7} 198loss (Table 3). For all studies the average weight loss per lifestyle intervention session at 199_{45}^{7} one year compared to controls was ~0.13kg.

9 200 Effects of lifestyle intervention on mortality

Effects on mortality are presented in Figure 4, Table 3 and the supplemental document. In
eight studies there were no deaths during follow up. For all studies combined there were
593 deaths, during a weighted average follow-up of 9.2 years, equivalent to an average
mortality rate of 0.3%/year. Mortality was non-significantly lower in the intervention
compared to the control group, odds ratio 0.86 (0.73, 1.02), p=0.09. The number of

interventions in the first year and weight loss achieved in the first year were not associated

 with mortality (Table 3). There were too few deaths in studies with low interventions rates to confidently evaluate effects of dose of the intervention on mortality. There was no difference in mortality based on < or \ge 75% interventions in first 6 months, median age of participants or presence of co morbidities (Table 3). Importance of the Look AHEAD study The Look AHEAD study (28) contributed 25% of people to the meta-analysis and accounted for 63% of deaths. This trial randomised 5145 overweight or obese patients with type 2 diabetes, 14% also had established heart disease, 60% were women and the mean age was 59 years. (34, 35) The lifestyle intervention included weekly face to face meetings for the first 6 months, meetings 3 times a month for the next 6 months and then monthly until the end of study. Patients were followed for median 9.6 years (interguartile range, 8.9 to 10.3). A clinically meaningful 5-10% weight loss was achieved. The hazard ratio for all-cause mortality was 0.85 (95%CI 0.69–1.04; p = 0.11). Estimated effects on mortality and body weight in the Look AHEAD trial (28) were similar to those observed in all other studies combined (Table 3). **Discussion** There are three important conclusions from this meta-analysis. First, lifestyle interventions compared to 'usual' care result in a modest reduction in body weight, on average ~3.6kg at one year, with about 2/3 of this sustained after 2-3 years. Weight loss was slightly greater in very obese and obese persons compared to overweight, but was still on average < 5% of body weight for all groups. Second, the weight reduction was observed with frequent lifestyle interventions sustained over a year or more. There is limited evidence on whether shorter simpler interventions are beneficial. Third, lifestyle interventions were associated

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| 4 | 231 | with a modest reduction in all-cause mortality, (point estimate ~14%), but with wide |
| 5 6 | 232 | confidence intervals, so there is uncertainty on whether this benefit is real. |
| 7 8 | 233 | |
| 9 10 | 234 | Previous meta-analyses also reported that lifestyle interventions result in a modest weight |
| 11 12 | 235 | loss, and a small but not statistically significant reduction in all-cause mortality.(36, 37) |
| 13 14 | 236 | These meta-analyses did not evaluate the importance of the intensity and duration of the |
| 15 16 17 | 237 | lifestyle interventions. In most studies there was a substantial effort for the lifestyle |
| 18 19 | 238 | intervention group, with a median of 28 interventions over the first year. Comparison across |
| 20 21 | 239 | studies suggests more interventions were associated with greater weight loss at one year, |
| 22 23 | 240 | but no studies directly compared different intervention intensities or durations. There was |
| 24 25 | 241 | limited data on the efficacy of shorter lifestyle interventions, or whether simple lifestyle |
| 26 27 | 242 | advice from a health practitioner is effective. Most studies were small, and lifestyle |
| 28 29 | 243 | interventions varied markedly. However it was not possible to confidently evaluate the |
| 30 31 | 244 | impact of difference types of lifestyle advice or the relative strengths of face to face |
| 32 33 | 245 | compared to remote interventions. |
| 34 35 36 | 246 | |
| 37 38 | 247 | This analysis provides insights on why obtaining reliable information on the impact of lifestyle |
| 39 40 | 248 | interventions on mortality are so difficult. The meta-analysis included randomised data from |
| 41 42 | 249 | over 20,000 patients with ~190,000 patient-years of follow-up. However the mortality rate |
| 43 44 | 250 | was only 0.3%/ year, and only three studies (28, 30, 38) reported more than 10 deaths. |
| 45 46 | 251 | Modest mortality benefits of sustained weight reduction may be expected to occur during |
| 47 48 | 252 | longer follow-up. This is consistent with results of the Look AHEAD (28) study which |
| 49 50 51 | 253 | followed patients for nearly 10 years. The 14% reduction for all-cause mortality was similar |
| 52 53 | 254 | to all other studies combined, supporting the conclusion that this mortality reduction is real. |
| 54 55 | 255 | Although this was of borderline statistical significance, this modest mortality benefit is |
| 56 57 | 256 | consistent with observational studies which report that bariatric surgery is associated with |
| 58 59 60 | 257 | lower all-cause, cardiovascular and cancer-related mortality.(39) However, compared to |
| | | |

lifestyle interventions bariatric surgery results in much larger and sustained reductions in body weight. (40)

 Findings from this study are relevant to clinical practice guidelines on interventions for weight loss. Although lifestyle interventions are associated with lower body weight and a probable small reduction in mortality, there is only reliable evidence for very comprehensive programmes which include many interactions sustained over months. There is limited evidence that the shorter and simpler interventions, more typical of usual clinical practice, have any benefit. Also we were unable to evaluate whether weight loss is maintained after cessation of the lifestyle intervention, because most studies did not report this. The efficacy of lifestyle programs in the 'real word' is likely to be less than for volunteers in clinical trials, who are generally highly motivated. These observations are important to inform realistic expectations on the likelihood and amount of weight loss, which may be much less than 'expected' by many clinicians and patients. iez

Study limitations

Individual participant data was not available and this limits the ability to address several important questions. It is likely that some individuals in the studies loose significant weight, while others loose none. However this could not be reliably evaluated from summary data. It was also not possible to evaluate the benefit of weight loss in subgroups of individuals who lost the most weight. It is not clear whether weight loss is dependent on individual participant characteristics such as body mass index, gender, age and ethnicity. Most studies did not provide information on food consumed or exercise performed, and it was not possible to assess adherence to randomised treatments, or to compare different types of lifestyle intervention. It was not possible to compare the nature of the interventions and type of lifestyle advice given.

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| 5 | 285 | Conclusion |
| 6 7 | 200 | |
| 8 | | |
| 9 | 286 | Lifestyle programs with frequent patient interactions sustained over a year or more achieve |
| 10 11 | 007 | |
| 12 | 287 | modest weight loss. This level of intervention may be unrealistic for most medical practices. |
| 13 14 | 288 | There is a modest but non-significant reduction in mortality with lifestyle programs, but |
| 15 | 289 | limited data on whether lifestyle interventions for obesity decrease mortality in persons at |
| 16 17 | 209 | |
| 18 | 290 | higher risk because of cancer, heart failure or ischaemic heart disease. |
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| 4 5 6 7 | 474 475 476 | weight and fat mass loss and increased physical activity on physical function in overweight, postmenopausal women: results from the Women on the Move Through Activity and Nutrition study. Menopause (New York, NY). 2011;18(7):759-65. |
| 8 9 10 | 477 | |
| 10 11 12 13 14 15 16 17 18 9 21 22 23 24 26 27 28 29 31 23 34 35 37 38 9 40 41 23 445 467 48 9 01 22 34 55 57 58 9 60 | 478 | |

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| 79 30 Table 1: Ba 31 | eseline characteristic of | 31 studies | s included in | n mortalit | y meta-ana | lysis. | /bmjopen-2019-029966 on 18 Aug | | | |
| Name of Study | Target population | Sample | Women | Mean | Mean | Mean | Intervention | Follow- | Deaths | Jada |
| | 4 | size | number | ВМІ | initial | age | duration | up | | scor |
| | | N | (%) | (kg/m²) | weight | (years) | (years) | duration | | |
| | | | | | (kg) | | aded fr | (years) | | |
| Summary | | 615 | 346 (56) | 32.5 | 87.2 | 53.8 | 2.39 | 2.49 | 19 | 3.1 |
| statistic weighted mean | | | | rel | 10 | | (years) (years) 2 ^{ttp://bmjopen.bmj.com/5} April 17, 5 | | | |
| ACHIEVE (41) | Overweight/obese with mental illness | 291 | 146 (50) | 36.3 | 102.7 | 45.3 | iom 40 April 17 | 1.5 | 5 | 3 |
| ADAPT (29) | Overweight/obese knee osteoarthritic older persons | 318 | 229 (72) | 34.3 | 93.8 | 68.5 | 7, 2024 by guest. Protected by copyright. | 1.5 (8 for mortality) | 45 | 2 |
| ALIFE@WORK 19) | Overweight/obese | 1386 | 457 (33) | 29.6 | 92.1 | 43 | olected by co | 2 | 3 | 4 |

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| | | | | | | | 1-2019-(| | | 19 |
| BE-WELL(20) | Obese asthmatics | 330 | 234 (71) | 37.5 | 104.2 | 47.6 | /bmjopen-2019-029 9 66 on | 1 | 0 | 3 |
| CLIP (42) | Overweight/obese older with limited mobility and cardiovascular disease or dysfunction | 288 | 193 (67) | 32.8 | 91.9 | 67.1 | n 182 August 2019. Downloaded from http 200 mjopen.bmj.com | 1.5 | 3 | 1 |
| Da Qing (33) | Impaired glucose tolerance | 530 | 244 (46) | 25.8 | _ | 45 | baded from ht | 6 | 11 | 2 |
| DPP (43) | Overweight/obese with elevated fasting glucose | 2161 | 1491 (69) | 34.1 | 94.2 | 50.4 | p 20 20 mjopen.bmj.co | 2.8 | 8 | 2 |
| EDIPS-Newcastle (44) | Overweight/obese with impaired glucose tolerance | 102 | 61 (60) | 33.8 | 92 | 57.1 | Fon April 17, 202 | 3.1 | 3 | 4 |
| E-LITE (45) | Overweight/obese persons with pre- diabetes or metabolic syndrome | 241 | 113 (47) | 32 | 93.8 | 52.9 | 45 guest. Protected by copyright. | 1.25 | 0 | 3 |

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|-------------|--|-----|-----------|----------|-------|------|--|-----|---|---|
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| HEALTH | Overweight and obese | 377 | 279 (74) | 32 | 125.2 | 45 | 029966 | 1 | 0 | 4 |
| TRACK(32) | Australians | | | | | | 6 on 18 | | | |
| HCP (21) | Hypertension | 118 | 42 (36) | - | 77 | 56 | 3 Astgust 2018. | 4 | 3 | 3 |
| IDEA (46) | Overweight/obese with | 454 | 327 (72) | 33.6 | 93 | 66 | 20 tab. Do | 1.5 | 0 | 4 |
| | osteoarthritis knee | 0/ | | | | | wnload | | | |
| IDPP-1 (47) | Indian and Pakistani origin with impaired | 269 | 62 (23) | 26 | _ | 45.6 | And from ht | 2.5 | 2 | 3 |
| | glucose tolerance | | | r | | | tp://bm | | | |
| LEAN (22) | Overweight/obese women with treated | 100 | 100 (100) | 33.1 | 87.5 | 59 | jo 5 Ogen.bmj. | 1 | 0 | 5 |
| | breast cancer | | | | 4 | | com/ on / | | | |
| LISA (48) | Overweight/obese post- menopausal women | 338 | 338 (100) | 31.3 | 82 | 61 | Downloaded from http://bmjoeen.bmj.com/ on April 17, 2024 by guest. Protected by copyright | 2 | 2 | 3 |
| | with breast cancer history who are | | | | | | 14 by gues | | | |
| | currently taking | | | | | | t. Protecte | | | |
| | letrozole | | | | | | ¢d by c | | | |

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| Look AHEAD (49) | Overweight/obese with type 2 diabetes | 5145 | 3087 (60) | 36 | 101 | 58.8 | /bmjopen-2019-02666 on 18 | 9.6 | 376 | 3 |
| NEW (50) | Overweight/obese post- menopausal women | 439 | 439 (100) | 30.9 | 83.6 | 58 | August 2019. | 1 | 1 | 4 |
| ORBIT(51) | Obese African- American women | 213 | 213(100) | 39.2 | 104.9 | 46 | 5 Cownloaded | 1.5 | 1 | 4 |
| Patrick (52) | Overweight/obese men | 441 | 0 (0) | 34.2 | 104.7 | 43.9 | from | 1 | 2 | 4 |
| PODOSA(53) | Indian or Pakistani- origin with impaired glucose tolerance test | 171 | 92 (54) | 30.5 | 80.3 | 52.5 | http://bmjopen.bmj.coxh/ on April 17, | 3 | 1 | 4 |
| POWER(27) | Obese with cardiovascular risk factors | 415 | 266 (64) | 36.6 | 103.4 | 54 | | 2 | 0 | 2 |
| SLIM (54) | Impaired glucose tolerance | 147 | 72 (49) | 29.8 | 85.5 | 56.9 | 20社 by guest. | 4.1 | 1 | 2 |
| STRIDE (55) | Overweight/obese taking antipsychotic | 200 | 144 (72) | 38.3 | 107.7 | 47.2 | . Protected by copyright. | 1 | 2 | 4 |

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| | agents | | | | | |)29966 | | | |
| Swedish Bjorknas | Metabolic syndrome | 145 | 83 (57) | 29.8 | 85.8 | 54.4 | 0 f 771 8 | 3 | 0 | 4 |
| (56) | | | | | | | 3 Augu | | | |
| TAIM (57) | Overweight/obese | 200 | 102 (51) | | 87.7 | 48.3 | st 435 | 4.5 | 2 | 4 |
| | hypertensive | | | | | | om 8 August 2019. Downloaded from | | | |
| TOHP I (58) | Normal to high blood | 564 | 180(32) | 29.5 | 89.8 | 42.8 | 125 | 1.5 | 2 | 2 |
| | pressure | | | | | | ad from | | | |
| TOHP II (59) | Overweight/obese | 2382 | 810 (34) | 30.9 | 93.6 | 43.6 | http:// | 3 | 12 | 2 |
| | persons that are | | | ro. | | | 'bmjop | | | |
| | normo- or hypertensive | | | SI SI | | | http://bmjopen.bmj.com/on April 17, 2024 by | | | |
| TONE (38) | Overweight/obese | 585 | 304 (52) | 31.2 | 87.8 | 65.5 | 25 | 2.5 | 101 | 4 |
| | elderly hypertensive | | | | | 0. | on Ap | (12 | | |
| | persons | | | | | $\neg \gamma$ | oril 17, 2 | mortality) | | |
| Trento (23) | type 2 diabetes | 112 | 50 (45) | 28.8 | 77.8 | 61.5 | 0224 b | 2 | 4 | 3 |
| /illareal (60) | Older obese | 107 | 67 (63) | 37.2 | 100.8 | 69.7 | y guest. | 1 | 0 | 2 |
| WOMAN (61) | Overweight/obese post- | 508 | 508 (100) | 30.8 | 81.7 | 57 | 1. PP | 4 | 3 | 3 |
| | menopausal women | | | | | | Protected by | | | |
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Table 2: Frequency and mode of contact of lifestyle intervention.

The type of contact refers to whether trial participants received individual (I) or group (G), and mode of cont

| Study name | Type of contact | Mode of contact | Number of dietary | Numbes of dietary | Proportion of first | |
|----------------|-----------------------|---------------------------|-------------------|--|-----------------------|--|
| Year Published | | 6 | interventions | interventions | year interventions in | |
| | | No | in year 1 | in sear 2 | first 6 months (%) | |
| | Individual= 7 | Face to face =11 | | http:// | | |
| All studies | Group only = 5 | Remote = 3 | 27.5 | 3.96 | 66 | |
| | Group + individual=19 | Face to face + remote= 17 | 1 | pen.bm | | |
| ACHIEVE | G,I | F | 30 | ttp://b ra; open.bmj.com/ on | 80 | |
| ADAPT | G,I | F,R | 33 | April 1 | 64 | |
| ALIFE@WORK | 1 | R | 10 | April 17, 2024 by guest. Protected by copyright. | 100 | |
| BE-WELL | G,I | F,R | 18 | by gues | 83 | |
| CLIP | G,I | F,R | 36 | st. Prote | 67 | |
| Da Qing | G,I | F | 16 | ed b | 80 | |

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| DPP | G, I | F,R | 22 | 029962 6 0 | 73 |
| EDIPS-Newcastle | G,I | F | 8 | | 75 |
| E-LITE | G,I | F,R | 38 | 18 August 2019. Bownloaded from http://Emjopen.bmj.com/ on APHil 17 | 61 |
| HEALTH TRACK | | F,R | 6 | 9. D6 ¥ | 50 |
| HCP | | F | 12 | oaded | 75 |
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| IDPP-1 | I | F,R | 15 | 2:/bu | 53 |
| LEAN | I | F,R | 11 | n.bm | 100 |
| LISA | I | R | 31 | en e | 87 |
| Look Ahead | G,I | F,R | 42 | App4 | 57 |
| NEW | G,I | F,R | 32 | | 63 |
| ORBIT | G,I | F,R | 110 | by guest | 56 |
| Patrick | I | R | 52 | 2024 by guest. Protected by copyright. | 50 |
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| 1 2 | | | | |
| 3 4 5 | POWER | G,I | F,R | |
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| | POWER | G,I | F,R | 39 | 29968 60 | 77 |
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| | STRIDE | G,I | F,R | 36 | 18 August 2019. Bownloaded from http://bmjopen.bmj.com/ on April 17 | 67 |
| | Swedish Bjorknas | G | F | 12 | 9. 05 % | 58 |
| | TAIM | G,I | F | 17 | oaded | 71 |
| | TOHP I | G,I | F,R | 26 | from http | 77 |
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| | TONE | G,I | F | 28 | | 71 |
| | Trento | G | F | 4 | cont on | 50 |
| | Villareal | G | F | 52 | April 17 | 50 |
| | WOMAN | G | F | 40 | | 50 |
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Table 3: Association with intervention intensity with weight loss achieved and mortality.

| Table 3: Association | ı with interver | tion intensity | BMJ Open with weight loss ac | hieved and | mortality. | /bmjopen-2019-029966 on | F 26 |
|--|------------------------|--|--|------------|------------------------|--|--|
| | | Weight change (final reported) ⁺ | | | | 18 August 2019. Downloade | |
| Characteristic | N studies [#] | Weight of study (%) | Mean difference Random effect model (kg) (95%CI) | N studies | Weight of study (%) | total deaths from http://bmjopen.bmj.com/ | Odds ratio Fixed effect model (95%Cl) |
| Number of Interventions per year | | | | | only | on April 17, 2024 b | L |
| ≤ 6 | 3 | 9 | -0.84 [-1.40, -0.28] | 3 | 1 | V 5/510 | 1.45 [0.22, 9.40] |
| 7-12 | 6 | 17 | -2.04 | 6 | 2 | Protected by copyright. | 1.34 |

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| | | | [-3.24, -0.84] | | | 19-02 <u>9966</u> | [0.35, 5.16 |
| 13-24 | 4 | 15 | -2.46 | 6 | 4 | ⁹ 23/3490 | 1.20 |
| | | | [-5.59, 0.67] | | | 3 Aug | [0.49, 2.96 |
| | | | | | | on 23/3490 n 18 August 2019 | |
| ≥ 25 | 18 | 60 | -3.53 | 18 | 93 | | 0.84 |
| | | | [-4.13, -2.92] | | | vnloa | [0.71, 1.00 |
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| BMI* | | | N/2 | | | Biopension 23/3890 | |
| 25-29 | 6 | 19 | -1.37 | 8 | 11 | <u>23/3890</u> | 1.58 |
| 20 23 | Ŭ | 10 | | Ū | | | |
| | | | [-2.82, 0.09] | | | | [0.64, 3.9 |
| 30- 35 | 16 | 48 | -3.09 | 14 | 22 | 9 136/8374 | 0.93 |
| | | | [-4.06, -2.11] | | | 136/8374 9 4 5 5 5 5 5 5 5 5 5 5 5 5 5 | [0.65, 1.33 |
| > 35 | 7 | 23 | -4.04 | 7 | 67 | | 0.86 |
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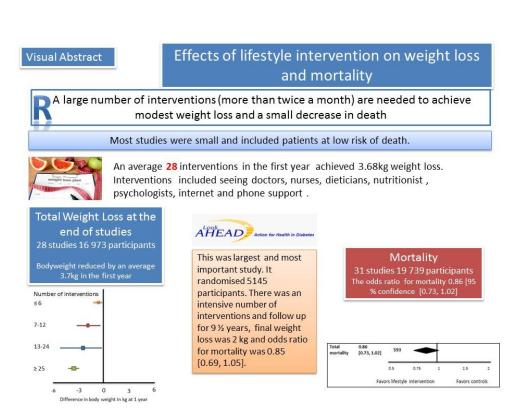
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| • | 506 | Supplementary document 1: Protocol | |
| | 507 | Supplementary document 2: supplementary figures. | |
| I | | Key message box | |
| | | An average 28 interventions (more than twice a month) in the first year achieved 3.67kg weight loss with a small decrease in mortalit Interventions included seeing doctors, nurses, dieticians, nutritionist, and psychologists. | y. |
| | | • There was less than 1kg weight loss when patients had <6 weight loss lifestyle interventions per yea | |
| | | • The level of intervention in these studies is not realistic and suggests that we are setting patients up $\frac{R}{20}$ fail when simple advice to los | e |
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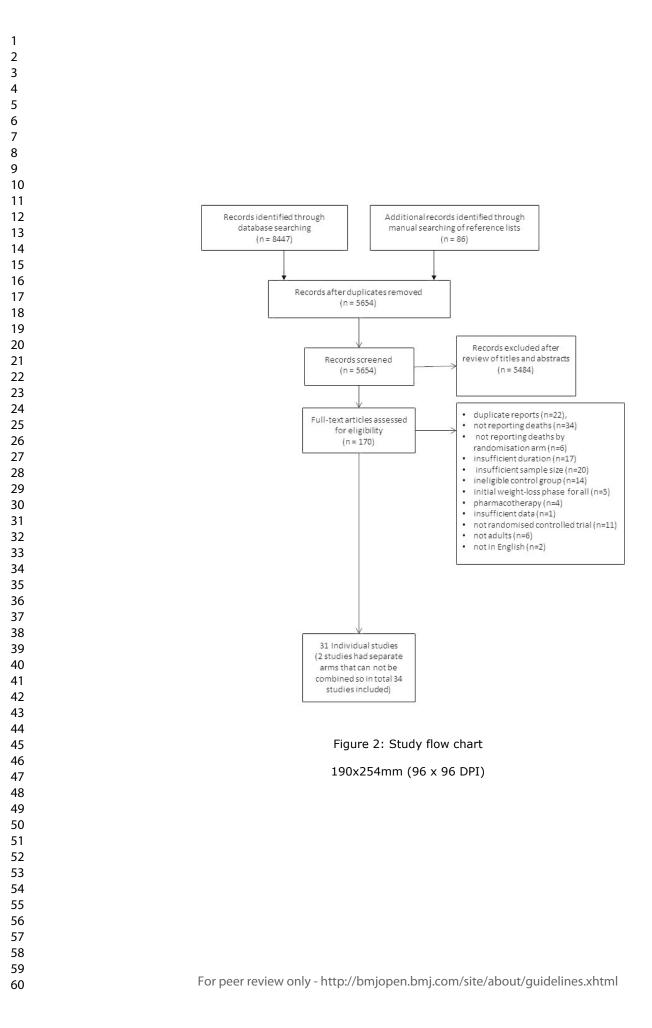
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I² (%) P value

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| 6 | | | | | | | |
| 7 | | Number | N | N | Mean difference in Kg | 1 | l ² (%) |
| | | studies | Intervention | control | (95% CI) | | |
| 8 | BMI | | | | | | |
| 9 | BMI | 4 | 586 | 539 | -2.23 [-4.43, -0.03] | | 94 |
| 10 | (26-29kg/m ²) | 4 | 200 | 223 | -2.25 [-4.45, -0.05] | | 94 |
| 11 | BMI | | | | | | |
| 12 | (30- 35kg/m ²) | 15 | 4809 | 4543 | -3.60 [-4.85, -2.36] | -8- | 96 |
| 13 | | | | | | | |
| 14 | BMI >35kg/m ²) | 7 | 3421 | 3280 | -4.64 [-6.88, -2.40] | | 94 |
| 15 | | | | | | | |
| 16 | Interventions | | | | | | |
| | ≤28 | | | | | | |
| 17 | intervention in first year | 13 | 3744 | 3663 | -2.38 [-3.98, -0.78] | | 97 |
| 18 | > 28 | | | | | | |
| 19 | interventions in first year | 17 | 4860 | 4676 | -4.53 [-5.93, -3.12] | | 95 |
| 20 | < 75% of all | | | | | | |
| 21 | intervention | 18 | 7043 | 6863 | -3.95 [-5.34, -2.57] | | 98 |
| 22 | in first 6 months | | | | | | |
| 23 | > 75% of all | | | | | | |
| 24 | intervention in first 6 | 9 | 1561 | 1338 | -3.31 [-4.46,-2.17] | | 80 |
| | months | | | | | - | |
| 25 | Total weight | | | | | | |
| 26 | loss at 1 year | 28 | 8665 | 8308 | -3.67 [-4.69, -2.76] | • | 97 |
| 27 | | | | | -9 | -6 -3 0 | 3 |
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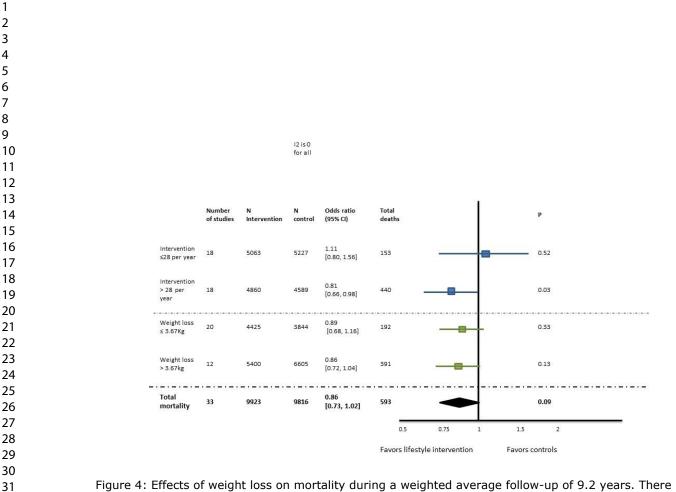


Figure 4: Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I2=0).

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

Study Protocol

ο ingh **Navneet Singh Jocelyne Benatar Ralph Stewart**

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 (BMI≥30 kg/m2) or overweight (25 < BMI < 30 kg/m2).¹ 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,² blood pressure, ³ and some cancers,⁴⁻⁶ 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, ⁷ diabetes,⁸ risk factors for coronary heart disease ⁹ and cancer. ⁴⁶ 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, ¹⁰⁻¹² diabetes ^{13, 14} and as cancer guidelines¹⁵ 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-analysis¹⁶ 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 $BMI \ge 25 kg/m^2$)
- 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 16th 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 metaanalyses 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 metaanalysis.

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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Supplementary document 2

Supplementary figures

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Figure 1a: Weight loss at 1 year

| | Lifestyle | e intervei | ntion | C | ontrol | | | Mean Difference | Mean Difference |
|---------------------------|-----------|------------|-------|--------|--------|-------|--------|-----------------------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 1.8% | -3.85 [-9.40, 1.70] | |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | 23.4 | 150 | 2.3% | -7.95 [-12.45, -3.45] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 3.1% | -2.16 [-5.01, 0.69] | |
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 3.2% | -3.50 [-6.03, -0.97] | |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 3.2% | -2.99 [-5.50, -0.48] | 2 |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 3.3% | -2.31 [-4.76, 0.14] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 3.4% | -6.55 [-8.84, -4.26] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 3.4% | -1.90 [-4.12, 0.32] | |
| ACHIEVE 2013 | -2.8 | 7.96 | 144 | -0.4 | 9.28 | 147 | 3.5% | -2.40 [-4.39, -0.41] | |
| CLIP 2011 | -4.8 | 7.5 | 93 | -1.4 | 5.1 | 97 | 3.6% | -3.40 [-5.23, -1.57] | |
| ORBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 3.6% | -2.77 [-4.54, -1.00] | |
| POWER (remote) 2011 | -6.1 | 8.22 | 138 | -1.1 | 5.87 | 138 | 3.6% | -5.00 [-6.69, -3.31] | |
| POWER (face to face) 2011 | -5.8 | 8.22 | 139 | -1.1 | 5.87 | 138 | 3.6% | -4.70 [-6.38, -3.02] | |
| Villareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 3.7% | -8.83 [-10.39, -7.28] | |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 3.7% | -3.40 [-4.81, -1.99] | |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 3.8% | -1.86 [-3.09, -0.63] | |
| LISA 2014 | -4.5 | 5.4 | 171 | -0.6 | 5.7 | 167 | 3.8% | -3.90 [-5.08, -2.72] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 3.9% | -1.30 [-2.41, -0.19] | |
| WOMAN2011 | -7.8 | 7.1 | 253 | -1.6 | 5.5 | 255 | 3.9% | -6.20 [-7.31, -5.09] | |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 3.9% | -3.00 [-3.98, -2.02] | and the second sec |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 3.9% | -0.81 [-1.73, 0.11] | |
| TOHP 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 3.9% | -3.90 [-4.74, -3.06] | 1. 1. |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 3.9% | -0.70 [-1.53, 0.13] | |
| TONE 1998 | -4.73 | 4.67 | 294 | -1.14 | 3.65 | 291 | 4.0% | -3.59 [-4.27, -2.91] | + |
| Look AHEAD 2013 | -9.2 | 10.2 | 2570 | -1.2 | 10.3 | 2575 | 4.0% | -8.00 [-8.56, -7.44] | + |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 4.0% | -0.40 [-0.89, 0.09] | + |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 4.0% | -6.40 [-6.80, -6.00] | + |
| TOHP II 1997 | -2.1 | 5.7 | 1192 | 0.55 | 4.25 | 1190 | 4.0% | -2.65 [-3.05, -2.25] | + |
| Total (95% CI) | | | 8518 | | | 8246 | 100.0% | -3.68 [-4.70, -2.66] | • |

Heterogeneity: Tau² = 6.71; Chi² = 799.58, df = 27 (P < 0.00001); l² = 97% Test for overall effect: Z = 7.07 (P < 0.00001)

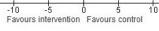
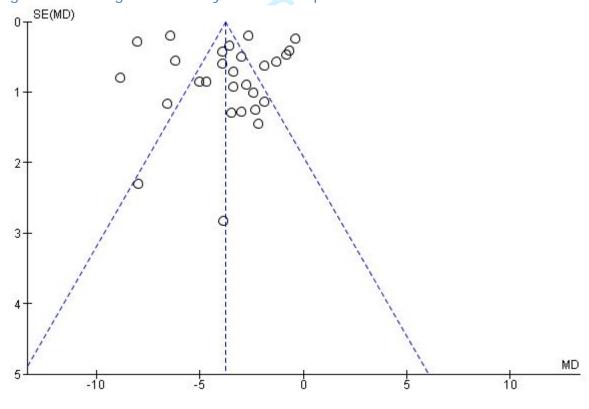


Figure 1b : Weight loss at 1 year- funnel plot



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Figure 2a: Weight loss at 2 years

| tudy or Subgroup | Lifestyle | interven SD | Total | Mean | ontrol SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% Cl |
|--|--------------------------|----------------|-------|----------|---------------------------------------|-------------|--------|---------------------------------------|---------------------------------------|
| rento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 2.7% | -0.30 [-7.61, 7.01] | |
| wedish Bjorknas 2009 | -3.15 | 14.9 | 71 | 0.6 | 18.3 | 74 | 3.9% | -3.75 [-9.17, 1.67] | |
| OWER (face to face) 2011 | -5.1 | 8.83 | 138 | -0.8 | 8.22 | 138 | 7.6% | -4.30 [-6.31, -2.29] | |
| OWER (remote) 2011 | -4.6 | 8.8 | 139 | -0.8 | 8.2 | 138 | 7.6% | -3.80 [-5.80, -1.80] | |
| LIM 2011 | -0.85 | 4.34 | 74 | -0.76 | 3.26 | 73 | 8.4% | -0.09 [-1.33, 1.15] | + |
| ISA 2014 | -3.1 | 6.2 | 171 | -0.3 | 5.3 | 167 | 8.4% | -2.80 [-4.03, -1.57] | + |
| ODOSA 2014 | -0.78 | 3.43 | 85 | 0.13 | 3.24 | 86 | 8.6% | -0.91 [-1.91, 0.09] | - |
| AIM 1993 | -2.2 | 3.25 | 100 | -0.4 | 3.25 | 100 | 8.7% | -1.80 [-2.70, -0.90] | - |
| LIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 8.7% | -0.63 [-1.48, 0.22] | - |
| ONE 1998 | -3.83 | 5.16 | 294 | -0.468 | 3.92 | 291 | 8.8% | -3.36 [-4.10, -2.62] | + |
| ook AHEAD 2013 | -7.1 | 10.2 | 2570 | -1.4 | | 2575 | 8.8% | -5.70 [-6.26, -5.14] | - |
|)PP-1 2006 | 0.3 | 1.62 | 133 | 0.65 | 2.9 | 136 | 8.8% | -0.35 [-0.91, 0.21] | - |
| PP2002 | -5.4 | 5.48 | 1079 | | 0.997 | | 8.9% | -5.40 [-5.73, -5.07] | |
| otal (95% CI) | | | 5836 | | | 5376 | 100.0% | -2.62 [-4.05, -1.18] | • |
| leterogeneity: Tau ² = 5.96; Ch | ni ^z = 419.85 | , df = 12 i | | 0001); P | = 97% | | | - | |
| est for overall effect: Z = 3.58 | | | | 100 | | | | | -20 -10 0 10 20 |
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| igure 2b: Weig | JIL IO: | 55 al | z yt | al 2. | - Iui | ше | i più | ι | |
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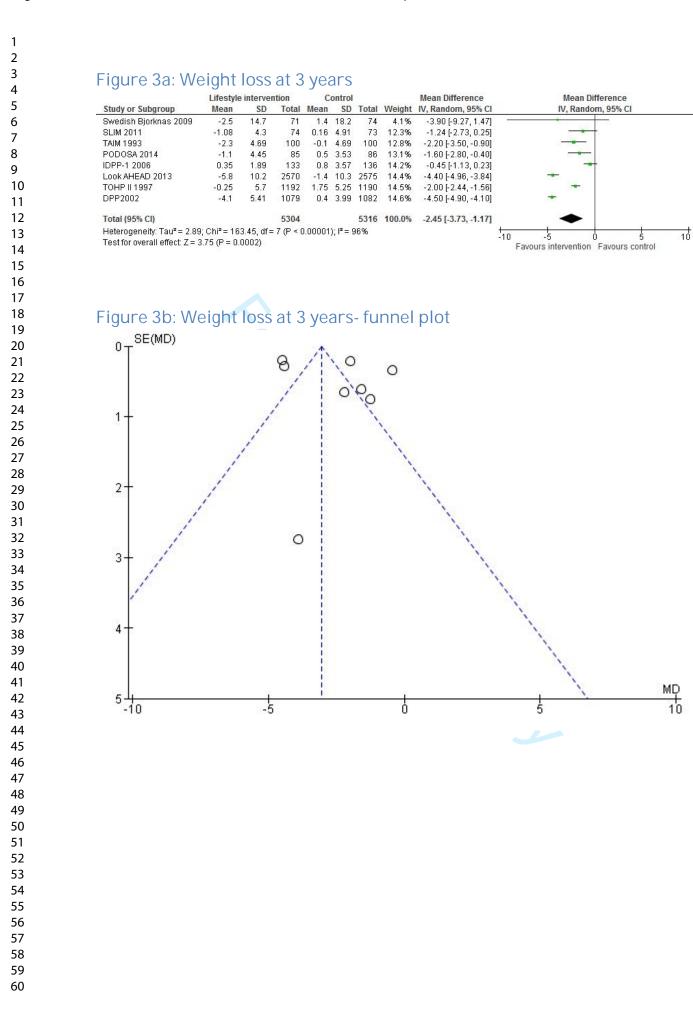


Figure 4a: Weight loss achieved by end of study

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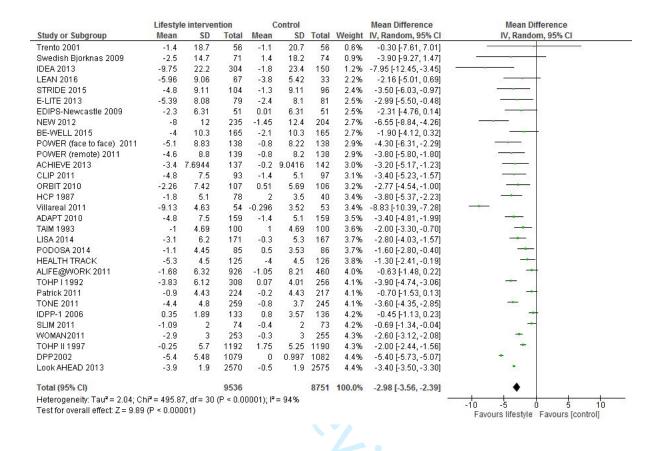


Figure 4b: Weight loss achieved by end of study-funnel plots

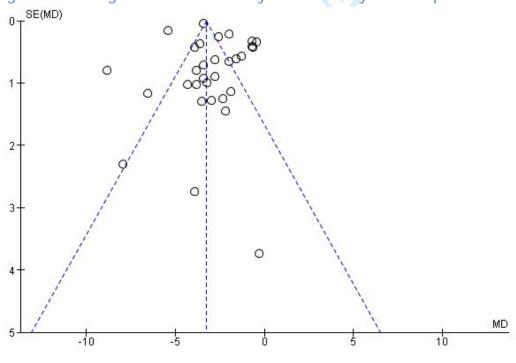


Figure 5a: Weight loss !interventions/year

| | Lifestyle | interver | ntion | C | ontrol | | | Mean Difference | Mean Difference |
|--|-------------------------|-----------|---------|--------|----------------------|-------|--------|----------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 3.0% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 4.1% | -3.85 [-9.40, 1.70] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 6.5% | -2.16 [-5.01, 0.69] | 10-10-10-10-10-10-10-10-10-10-10-10-10-1 |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 6.9% | -2.31 [-4.76, 0.14] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 7.1% | -1.90 [-4.12, 0.32] | |
| HCP 1987 | -1.8 | 5.1 | 78 | 2 | 3.5 | 40 | 7.7% | -3.80 [-5.37, -2.23] | |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 7.9% | -1.86 [-3.09, -0.63] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 8.0% | -1.30 [-2.41, -0.19] | _ |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 8.0% | -3.00 [-3.98, -2.02] | |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 8.1% | -0.81 [-1.73, 0.11] | |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 8.1% | -0.63 [-1.48, 0.22] | |
| TOHP 1 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 8.1% | -3.90 [-4.74, -3.06] | |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 8.2% | -0.40 [-0.89, 0.09] | - |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 8.2% | -6.40 [-6.80, -6.00] | a t a |
| Total (95% CI) | | | 3318 | | | 2738 | 100.0% | -2.38 [-3.98, -0.78] | • |
| Heterogeneity: Tau ² = 8.01 | ; Chi ² = 45 | 0.59, df= | 13 (P < | 0.0000 | 1); l ² = | 97% | | 1 | |
| Test for overall effect: Z = 2 | .92 (P = 0.) | 003) | | | | | | | -10 -5 0 5 10 Favours [experimental] Favours [control] |

Figure 5b: Weight loss >28 interventions/year

| le interve SD 22.2 15.8 9.11 8.08 122 7.96 7.42 8.22 8.22 4.63 7.5 5.4 7.1 4.43 | ntion Total 304 93 104 79 235 137 107 138 139 54 159 171 253 | Mean -1.8 -0.849 -1.3 -2.4 -1.45 -0.4 0.51 -1.1 -1.1 -0.296 -1.4 -0.6 | 23.4 14.7 9.11 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | Total 150 97 96 81 204 142 106 138 138 | Weight 4.0% 4.1% 5.5% 5.5% 5.7% 5.8% 6.0% 6.1% 6.2% 6.2% 6.4% | -6.25 [-10.59, -1.91] -3.50 [-6.03, -0.97] -2.99 [-5.50, -0.48] -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] | Mean Difference IV, Random, 95% Cl |
|--|--|---|---|---|--|---|--|
| 22.2 15.8 9.11 8.08 12 7.96 7.42 8.22 8.22 8.22 4.63 7.5 5.4 7.1 | 304 93 104 79 235 137 107 138 139 54 159 171 | -1.8 -0.849 -1.3 -2.4 -1.45 -0.4 0.51 -1.1 -1.1 -0.296 -1.4 -0.6 | 23.4 14.7 9.11 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | 150 97 96 81 204 142 106 138 138 53 159 | 4.0% 4.1% 5.5% 5.5% 5.7% 5.8% 6.0% 6.1% 6.1% 6.2% 6.2% | -7.95 [-12.45, -3.45] -6.25 [-10.59, -1.91] -3.50 [-6.03, -0.97] -2.99 [-5.50, -0.48] -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | IV, Random, 95% Cl |
| 15.8 9.11 8.08 12 7.96 7.42 8.22 8.22 8.22 4.63 7.5 5.4 7.1 | 93 104 79 235 137 107 138 139 54 159 171 | -0.849 -1.3 -2.4 -1.45 -0.4 0.51 -1.1 -0.296 -1.4 -0.6 | 14.7 9.11 8.1 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | 97 96 81 204 142 106 138 138 53 159 | 4.1% 5.5% 5.7% 5.8% 6.0% 6.1% 6.1% 6.2% 6.2% | -6.25 [-10.59, -1.91] -3.50 [-6.03, -0.97] -2.99 [-5.50, -0.48] -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | <u>+</u> +++++++++++++++++++++++++++++++++++ |
| 9.11 8.08 12 7.96 7.42 8.22 8.22 4.63 7.5 5.4 7.1 | 104 79 235 137 107 138 139 54 159 171 | -1.3 -2.4 -1.45 -0.4 0.51 -1.1 -1.1 -0.296 -1.4 -0.6 | 9.11 8.1 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | 96 81 204 142 106 138 138 53 159 | 5.5% 5.5% 5.7% 6.0% 6.1% 6.1% 6.2% 6.2% | -3.50 [-6.03, -0.97] -2.99 [-5.50, -0.48] -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 8.08 12 7.96 7.42 8.22 8.22 4.63 7.5 5.4 7.1 | 79 235 137 107 138 139 54 159 171 | -2.4 -1.45 -0.4 0.51 -1.1 -0.296 -1.4 -0.6 | 8.1 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | 81 204 142 106 138 138 53 159 | 5.5% 5.7% 5.8% 6.0% 6.1% 6.2% 6.2% | -2.99 [-5.50, -0.48] -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 12 7.96 7.42 8.22 8.22 4.63 7.5 5.4 7.1 | 235 137 107 138 139 54 159 171 | -1.45 -0.4 0.51 -1.1 -1.1 -0.296 -1.4 -0.6 | 12.4 9.28 5.69 5.87 5.87 3.52 5.1 | 204 142 106 138 138 53 159 | 5.7% 5.8% 6.0% 6.1% 6.1% 6.2% | -6.55 [-8.84, -4.26] -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 7.96 7.42 8.22 8.22 4.63 7.5 5.4 7.1 | 137 107 138 139 54 159 171 | -0.4 0.51 -1.1 -1.1 -0.296 -1.4 -0.6 | 9.28 5.69 5.87 5.87 3.52 5.1 | 142 106 138 138 53 159 | 5.8% 6.0% 6.1% 6.1% 6.2% 6.2% | -2.40 [-4.43, -0.37] -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 7.42 8.22 8.22 4.63 7.5 5.4 7.1 | 107 138 139 54 159 171 | 0.51 -1.1 -0.296 -1.4 -0.6 | 5.69 5.87 5.87 3.52 5.1 | 106 138 138 53 159 | 6.0% 6.1% 6.1% 6.2% 6.2% | -2.77 [-4.54, -1.00] -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 8.22 8.22 4.63 7.5 5.4 7.1 | 138 139 54 159 171 | -1.1 -1.1 -0.296 -1.4 -0.6 | 5.87 5.87 3.52 5.1 | 138 138 53 159 | 6.1% 6.1% 6.2% 6.2% | -4.70 [-6.39, -3.01] -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 8.22 4.63 7.5 5.4 7.1 | 139 54 159 171 | -1.1 -0.296 -1.4 -0.6 | 5.87 3.52 5.1 | 138 53 159 | 6.1% 6.2% 6.2% | -5.00 [-6.68, -3.32] -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | - <u>+</u> |
| 4.63 7.5 5.4 7.1 | 54 159 171 | -0.296 -1.4 -0.6 | 3.52 5.1 | 53 159 | 6.2% 6.2% | -8.83 [-10.39, -7.28] -3.40 [-4.81, -1.99] | |
| 7.5 5.4 7.1 | 159 171 | -1.4 -0.6 | 5.1 | 159 | 6.2% | -3.40 [-4.81, -1.99] | |
| 5.4 7.1 | 171 | -0.6 | | | | | |
| 7.1 | | | 5.7 | 167 | 6.4% | -3.90 [-5.08, -2.72] | |
| | 253 | | | | | | |
| 4 4 3 | | -1.6 | 5.5 | 255 | 6.4% | -6.20 [-7.31, -5.09] | |
| 1.10 | 224 | -0.2 | 4.43 | 217 | 6.5% | -0.70 [-1.53, 0.13] | |
| 4.8 | 259 | -0.8 | 3.7 | 245 | 6.5% | -3.60 [-4.35, -2.85] | |
| 10.2 | 2570 | -1.2 | 10.3 | 2575 | 6.6% | -8.00 [-8.56, -7.44] | + |
| 5.7 | 1192 | 1.75 | 5.25 | 1190 | 6.6% | -2.00 [-2.44, -1.56] | 1 |
| | 6218 | | | 6013 | 100.0% | -4.53 [-5.93, -3.12] | • |
| 5, df = 16 | (P < 0.0 | 10001); P | ² = 969 | 6 | | 1 | |
| 001) | 8 | 100 | | | | | -10 -5 0 5 10 Favours [experimental] Favours [control] |
| | 5.7 5, df = 16 | 5.7 1192 6218 5, df = 16 (P < 0.0 | 5.7 1192 1.75 6218 5, df = 16 (P < 0.00001); F | 5.7 1192 1.75 5.25 6218 5, df = 16 (P < 0.00001); I ^a = 969 | 5.7 1192 1.75 5.25 1190 6218 6013 5, df = 16 (P < 0.00001); I ² = 96% | 5.7 1192 1.75 5.25 1190 6.6% 6218 6013 100.0% 5, df= 16 (P < 0.00001); I ^z = 96% | 5.7 1192 1.75 5.25 1190 6.6% -2.00 [-2.44, -1.56] 6218 6013 100.0% -4.53 [-5.93, -3.12] 5, df = 16 (P < 0.00001); I² = 96% |

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Figure 6a: Total mortality

| and the second | Events | ention Total | Contro Events | | Weight | Odds Ratio IV, Fixed, 95% CI | Odds Ratio IV, Fixed, 95% Cl |
|--|------------|-----------------|------------------|------|--------|---------------------------------|--|
| Swedish Bjorknas 2009 | 0 | 71 | 0 | 74 | | Not estimable | |
| POWER (remote) 2011 | 0 | 138 | 0 | 138 | | Not estimable | |
| POWER (face to face) 2011 | 0 | 139 | 0 | 138 | | Not estimable | |
| /illareal 2011 | Ō | 54 | Ō | 53 | | Not estimable | |
| E-LITE 2013 | 0 | 160 | 0 | 81 | | Not estimable | |
| 3E-WELL 2015 | Ō | 165 | 0 | 165 | | Not estimable | |
| EAN 2016 | ō | 67 | Ō | 33 | | Not estimable | |
| HEALTH TRACK | Ő | 125 | Ö | 126 | | Not estimable | |
| DEA 2013 | 0 | 304 | 0 | 150 | | | |
| | 0 | 74 | 1 | | 0.20 | Not estimable | |
| 3LIM 2011 | | | | 73 | 0.3% | 0.32 [0.01, 8.09] | |
| PODOSA 2014 | 0 | 85 | 1 | 86 | 0.3% | 0.33 [0.01, 8.30] | 215 |
| DRBIT 2010 | 1 | 107 | 0 | 106 | 0.3% | 3.00 [0.12, 74.48] | |
| VEW 2012 | 0 | 235 | 1 | 204 | 0.3% | 0.29 [0.01, 7.11] | 10 10 10 |
| AIM 1993 | 2 | 100 | 0 | 100 | 0.3% | 5.10 [0.24, 107.62] | |
| Patrick 2011 | 2 | 224 | 0 | 130 | 0.3% | 2.93 [0.14, 61.55] | 2 |
| ICP 1987 | 3 | 78 | 0 | 40 | 0.3% | 3.75 [0.19, 74.50] | |
| Da Qing (exercise) 1997 | 5 | 126 | 0 | 141 | | 12.81 [0.70, 234.04] | |
| STRIDE 2015 | 1 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| | 1 | 133 | 1 | 136 | | | <u> </u> |
| DPP-1 2006 | | | | | 0.4% | 1.02 [0.06, 16.52] | |
| ISA 2014 | 1 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | |
| OHP 1992 | 1 | 308 | 1 | 993 | 0.4% | 3.23 [0.20, 51.81] | 20 |
| DIPS-Newcastle 2009 | 2 | 51 | 1 | 51 | 0.5% | 2.04 [0.18, 23.24] | |
| CLIP 2011 | 1 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| VOMAN2011 | 1 | 253 | 2 | 255 | 0.5% | 0.50 [0.05, 5.57] | |
| LIFE@WORK 2011 | 2 | 926 | 1 | 460 | 0.5% | 0.99 [0.09, 10.99] | |
| Trento 2001 | 3 | 56 | 1 | 56 | 0.6% | 3.11 [0.31, 30.88] | |
| CHIEVE 2013 | 2 | 144 | 3 | 147 | 0.9% | 0.68 [0.11, 4.11] | |
| | | | | | | | 20 20 20 C |
| Da Qing (no exercise) 1997 | 3 | 133 | 3 | 130 | 1.1% | 0.98 [0.19, 4.93] | |
| DPP2002 | 3 | 1079 | | 1082 | 1.4% | 0.60 [0.14, 2.52] | and the second sec |
| OHP II 1997 | 7 | 1192 | | 1190 | 2.2% | 1.40 [0.44, 4.42] | |
| ADAPT 2010 | 15 | 159 | 30 | 159 | 6.6% | 0.45 [0.23, 0.87] | |
| ONE 2011 | 49 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | |
| ook AHEAD 2013 | 174 | 2570 | 202 | 2575 | 65.5% | 0.85 [0.69, 1.05] | |
| | | | | | | | |
| otal (95% CI) | | 9923 | | 9816 | 100.0% | 0.86 [0.73, 1.02] | • |
| otal events | 279 | | 314 | | | | |
| | (P = 0.09) | | | | | | 0.005 0.1 1 10 2 Favours intervention Favours control |
| | (P = 0.09) | | | | | | |
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| igure 6a: Tota 0 - ^{SE(log[OR])} 0.5 - 1 - | | | 0 | 0 0 | D''' | 0 | |
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| igure 6a: Tota 0 - ^{SE(log[OR])} 0.5 - 1 - | | | 0 | 0 0 | D''' | 0 | |
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| igure 6a: Tota 0 _ ^{SE(log[OR])} 1.5 | | | 0 | 0 0 | D''' | 0 | Favours intervention Favours control |
| igure 6a: Tota 0 - ^{SE(log[OR])} 0.5 - 1 - | | | 0 | 0 0 | D''' | | |

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Figure 7a: Mortality !28 – interventions per year

| | Lifestyle interv | ention | Cont | rol | | Odds Ratio | Odds Ratio |
|--|---------------------------------|--------|--------|-------|--------|----------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| LEAN 2016 | 0 | 67 | 0 | 33 | | Not estimable | |
| HEALTH TRACK | 0 | 125 | 0 | 126 | | Not estimable | |
| Swedish Bjorknas 2009 | 0 | 71 | 0 | 74 | | Not estimable | |
| BE-WELL 2015 | 0 | 165 | 0 | 165 | | Not estimable | |
| Da Qing (exercise) 1997 | 5 | 126 | 0 | 141 | 2.6% | 12.81 [0.70, 234.04] | 27 (d) |
| TOHP 1992 | 1 | 308 | 1 | 993 | 2.7% | 3.23 [0.20, 51.81] | |
| TAIM 1993 | 2 | 100 | 0 | 100 | 2.8% | 5.10 [0.24, 107.62] | 20 |
| HCP 1987 | 3 | 78 | 0 | 40 | 3.7% | 3.75 [0.19, 74.50] | · · · · · · · · · · · · · · · · · · · |
| Trento 2001 | 3 | 56 | 1 | 56 | 5.5% | 3.11 [0.31, 30.88] | 2 |
| EDIPS-Newcastle 2009 | 2 | 51 | 1 | 51 | 5.6% | 2.04 [0.18, 23.24] | |
| IDPP-1 2006 | 1 | 133 | 1 | 136 | 5.7% | 1.02 [0.06, 16.52] | Z |
| ALIFE@WORK 2011 | 2 | 926 | 1 | 460 | 7.8% | 0.99 [0.09, 10.99] | |
| PODOSA 2014 | 0 | 85 | 1 | 86 | 8.6% | 0.33 [0.01, 8.30] | |
| SLIM 2011 | 0 | 74 | 1 | 73 | 8.7% | 0.32 [0.01, 8.09] | |
| Da Qing (no exercise) 1997 | 3 | 133 | 3 | 130 | 17.3% | 0.98 [0.19, 4.93] | 2 |
| DPP2002 | 3 | 1079 | 5 | 1082 | 29.0% | 0.60 [0.14, 2.52] | |
| Total (95% CI) | | 3577 | | 3746 | 100.0% | 1.53 [0.83, 2.81] | - |
| Total events | 25 | | 15 | | | | |
| Heterogeneity: Chi ² = 7.59, df | = 11 (P = 0.75); I ² | = 0% | | | | | |
| Test for overall effect: Z = 1.37 | (P = 0.17) | | | | | | 0.01 0.1 1 10 11 Favours [experimental] Favours [control] |

Figure 7b: Mortality >28 – interventions per year

| - | Lifestyle interv | ention | Cont | Io | | Odds Ratio | Odds Ratio |
|--|---------------------|--------|------|-------------|--------|--------------------|--|
| Study or Subgroup | Events | | | State State | Weight | M-H, Fixed, 95% Cl | |
| E-LITE 2013 | 0 | 160 | 0 | 81 | | Not estimable | |
| IDEA 2013 | 0 | 304 | 0 | 150 | | Not estimable | |
| POWER (face to face) 2011 | 0 | 139 | 0 | 138 | | Not estimable | |
| POWER (remote) 2011 | 0 | 138 | 0 | 138 | | Not estimable | |
| Villareal 2011 | 0 | 54 | 0 | 53 | | Not estimable | |
| ORBIT 2010 | 1 | 107 | 0 | 106 | 0.2% | 3.00 [0.12, 74.48] | |
| Patrick 2011 | 2 | 224 | 0 | 130 | 0.2% | 2.93 [0.14, 61.55] | |
| LISA 2014 | 1 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | 2 |
| STRIDE 2015 | 1 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| CLIP 2011 | 1 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| NEW 2012 | 0 | 235 | 1 | 204 | 0.6% | 0.29 [0.01, 7.11] | · · · · · · · · · · · · · · · · · · · |
| WOMAN2011 | 1 | 253 | 2 | 255 | 0.7% | 0.50 [0.05, 5.57] | |
| ACHIEVE 2013 | 2 | 144 | 3 | 147 | 1.1% | 0.68 [0.11, 4.11] | |
| TOHP II 1997 | 7 | 1192 | 5 | 1190 | 1.8% | 1.40 [0.44, 4.42] | |
| ADAPT 2010 | 15 | 159 | 30 | 159 | 9.9% | 0.45 [0.23, 0.87] | |
| TONE 2011 | 49 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | a |
| Look AHEAD 2013 | 174 | 2570 | 202 | 2575 | 68.5% | 0.85 [0.69, 1.05] | = |
| Total (95% CI) | | 6346 | | 6070 | 100.0% | 0.84 [0.70, 1.00] | • |
| Total events | 254 | | 299 | | | | |
| Heterogeneity: Chi ² = 6.33, df | /= 11 (P = 0.85); P | ²= 0% | | | | | |
| Test for overall effect: Z = 2.01 | 1 (P = 0.04) | | | | | | 0.01 0.1 1 10 10 Favours [experimental] Favours [control] |
| | | | | | | | Favours (experimental) Favours (control) |
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PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|---|--------------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Registration page 3 |
| | | °Ch | Supplementar protocol |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4,5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5,6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (for soprisk ratio difference in means) es. xhtml | 7 |

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| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | 7 |
|-------------------------------|----|--|---|
| | | Page 1 of 2 | 1 |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 1 and supplementary figures Pages 9,10 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each | Supplementary |
| | | intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures 3-5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Supplementary figures, table 1 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Table 2 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Pages 10,11,12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 12 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | [Page 12 |



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| 5 Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |
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| From: Moher D, Liber 0 doi:10.1371/journal.pm | ati A, Tetzlaff J, Ali ed1000097 | tman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PL | oS Med 6(7): e1000097. |
| 1 | | For more information, visit: www.prisma-statement.org. Page 2 of 2 | |
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BMJ Open

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Intensity and duration of lifestyle interventions for long term weight loss and association with mortality: a meta-analysis of randomised trials.

| Journal: | BMJ Open |
|--------------------------------------|--|
| Manuscript ID | bmjopen-2019-029966.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 29-May-2019 |
| Complete List of Authors: | Singh, Navneet; The University of Auckland, School of medicine Stewart, RA; Auckland City Hospital, Green Lane Cardiovascular Service Benatar, Jocelyne; Auckland City Hospital, Green Lane Cardiovascular Services |
| Primary Subject Heading : | Nutrition and metabolism |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | NUTRITION & DIETETICS, weight loss, lifestyle interventions |
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| 21 | 6 | Navneet Singh ¹ , Ralph AH Stewart ² , Jocelyne R Benatar ² * |
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| 24 | 7 | |
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| 26 27 | | |
| 27 28 | 8 | 1 School of Medicine, The University of Auckland, Auckland, New Zealand |
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| 30 | 9 | 2 Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New |
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| 45 | 14 | Corresponding author: Dr Jocelyne Benatar Jbenatar@adhb.govt.nz |
| 46 47 | | |
| 47 48 | • – | |
| 49 | 15 | All authors contributed to this work and have no competing interests. |
| 50 | | |
| 51 52 | 16 | This study was not funded. |
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18 Abstract

19 Objectives

- 20 To evaluate the importance of the frequency and duration of lifestyle interventions for
- 21 achieving weight loss over \geq one year, and associations with all-cause mortality.

22 Design

- 23 Meta-analysis of randomised trials using PRISMA guidelines and RevMan software version
- 24 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

25 Data sources

MEDLINE, CENTRAL, Google and Science Direct databases alongside reference lists of
 appropriate articles and meta-analyses.

28 Eligibility Criteria

- 29 Randomised studies published in English-language journals from 1980 to June 2018 that
- 30 assessed lifestyle compared to control interventions on weight loss, and which included
- \geq 100 subjects and reported weight change and mortality for \geq one year.

32 Data extraction and synthesis

Two independent reviewers extracted data and assessed risk of bias. Data were pooled
using the generic inverse-variance method and expressed as mean differences (MD) with
95% CI and odds ratio with 95%CI as appropriate. Heterogeneity was assessed (Cochran Q
statistic) and quantified (I2 statistic). The GRADE score was used to assess the certainty of
the evidence

| 39 | Results |
|----|--|
| 40 | 31 randomised trials with a total of 20 816 overweight or obese participants were included. |
| 41 | 70% of participants had cardiometabolic risk factors. Body weight was lower for lifestyle |
| 42 | intervention compared to the control at 1 year (3.63 kg, 95% confidence interval (CI) 4.67, |
| 43 | 2.58), and at 3 years (2.45 kg, 95% CI 3.73, 1.17). Weight loss at one year was greater in |
| 44 | studies with > 28 compared to \leq 28 interventions per year (4.50 kg, 95%Cl 5.97, 3.03 vs |
| 45 | 2.38, 95%CI 3.98, 0.78 kg, p=0.001). In all studies there were 593 deaths (~0.3%/year). The |
| 46 | odds ratio for mortality for weight loss interventions compared to the controls was 0.86 (95% |
| 47 | CI 0.73, 1.02), p=0.09. |
| 48 | Conclusion |
| 49 | In predominantly healthy populations with risk factors, there is a dose response with number |
| 50 | of lifestyle interventions and weight loss. Frequent and sustained interventions are needed to |
| 51 | achieve a clinically significant 5% weight loss. There was insufficient evidence to reliably |
| 52 | evaluate the benefits in persons with known cardiovascular disease or cancer. |
| 53 | |
| 54 | Prospero registration number: CRD42018095067 |
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|--|----|---|
| 2 3 4 | 56 | |
| 5 6 | 57 | Strengths and Limitations of study |
| 7 8 9 | 58 | Previous meta-analyses of randomised trials of lifestyle interventions have not |
| 9 10 11 | 59 | considered the level of intervention needed to achieve clinically meaningful (>5%) |
| 12 13 | 60 | weight loss. There was wide variation in the type of lifestyle advice, but it was not |
| 14 15 | 61 | possible to assess which type of lifestyle advice is most effective. |
| 16 17 | 62 | • Most evidence is in middle aged people (age 50 -60) with cardiometabolic risk |
| 18 19 | 63 | factors. There is limited data on effects of lifestyle interventions for weight loss in |
| 20 21 | 64 | older patients and those with cardiovascular disease or cancer. |
| 22 23 | 65 | Lifestyle interventions for weight loss may reduce mortality if sustained. However in |
| 24 25 26 | 66 | most studies the duration of the intervention and follow-up were too short and |
| 20 27 28 | 67 | mortality too low to allow a reliable assessment. |
| 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 | 68 | |
| 59 60 | | |

69 Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m²) or overweight (25≤BMI<30 kg/m²).(1) International guidelines in cardiology.(2-4) diabetes (5, 6) and cancer (7) recommend changing lifestyle related factors for management of overweight and obesity. These lifestyle recommendations (2-4, 7-10) are largely based on data from observational epidemiological studies in which obesity was associated with an increased risk of metabolic syndrome, diabetes, arthritis, heart disease and/or cancer. (11-16) However, observational studies do not provide reliable information on whether lifestyle interventions should be recommended in obese people, and several relevant questions remained unanswered: Do lifestyle interventions lead to weight reduction, if so, by how much, and is this maintained over time? What level of lifestyle intervention is needed, how long should these interventions be continued, and do lifestyle interventions which target weight reduction improve health and lower the mortality risk? The aim of this meta-analysis was to determine whether published randomised trials of lifestyle interventions for weight loss provide evidence on whether the dose of lifestyle intervention influences the effectiveness of longer term weight reduction, or mortality.

85 Methods

PRISMA guidelines on reporting systematic reviews and meta-analyses of studies were
used throughout the planning, conduct and interpretation of this meta-analysis. A review
protocol was designed, and is available in the supplementary text.

89 There was no patient or public Involvement in this study

90 Study Search and inclusion criteria

91 The full strategy is described in Supplementary document 1, the protocol. Searches of
92 MEDLINE, CENTRAL, Google and Science Direct databases alongside reference lists of

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appropriate articles and meta-analyses were performed for any reports on randomized
clinical trials that assessed lifestyle intervention on weight loss published in Englishlanguage journals from 1980 to June 2018. Key words used in searches to identify studies
included "weight", "lifestyle", "hypocaloric", "diet", "mortality", "coronary", "heart" and
"cardiovascular". Articles retrieved using this search string were then limited to trials
including weight loss and non-weight loss arms, a trial duration (weight loss and
maintenance phase) ≥12 months, and mortality data by intervention group.

Eligible studies were randomised control studies longer than 1 year with ≥ 100 overweight and obese adults (BMI ≥ 25 kg/m2) participants randomised to an intentional weight-loss lifestyle intervention and had an appropriate control group. Studies were only included if the control group received normal care – which could include standard healthy lifestyle information – but had no specific advice to achieve weight loss. The intervention arm needed to have intent for weight loss, mainly through the promotion of a hypocaloric diet, and had to include ≥ 1 face to face intervention. Participants could be healthy or have established cardiovascular disease (CVD). Studies were excluded if both groups were prescribed specific diets (such as high-protein diets, OPTIFAST), included pharmacotherapy or surgery for weight loss or if the intervention was 'self- help'. Studies with >5% lost to follow up were also excluded to reduce the risk of bias.(17)

For mortality, eligible studies were required to report mortality data explicitly either in the CONSORT diagram, as an outcome measure or as an adverse event (studies reporting "no adverse events" was taken to mean that no deaths occurred, but studies reporting "no adverse events related to intervention" without specifying the nature of these adverse events were excluded). Studies also were required to present sufficient data in order for calculations of mean weight changes in kilograms.

 $\frac{16}{17}$ The search of these electronic databases to obtain suitable studies was carried out by two reviewers (NS, JB). Any queries arising around the suitability of a particular study for Page 7 of 53

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inclusion was resolved by discussion with all reviewers (NS, JB and RS). In some situations, multiple papers reporting on the same clinical trial were used if each individual paper did not provide all required data and qualitative information on the study. Methodological and appropriate guantitative data was extracted and compiled in an electronic database from all included studies on three separate occasions independently by two reviewers (NS, JB). Baseline data extracted included study sample size, mean age and BMI, duration of intervention and follow-up, and percentage of women. Each study's intervention was also categorised into levels of intensity depending on the number and frequency of dietary interventions. An 'individual session' was defined as an intervention delivered one to one by a dietician/lifestyle coach/physician. A 'face to face' intervention was delivered in person. 'Remote interventions' were those delivered by telephone, emails or web based programs. In one study which reported two interventions, but used the same control group, the face to face intervention, which was more intensive compared to the remote intervention, was used in the meta-analysis. (18) Follow-up data included mean weight or weight loss at each follow-up time after one year, and all-cause mortality. If relevant data was not presented in a study, the corresponding study authors were contacted. Questions arising during data extraction were resolved by consensus between reviewers (NS, JB and RS). Outcome measures are weight loss achieved at 1, 2 and 3 years, weight loss achieved at the end of study, intensity of intervention required to achieve weight loss and mortality. Weight loss at 1 year was the primary outcome. If not reported, the first weight recorded after the first year was used. (19-24)

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142 Grading the evidence

The grading of Recommendations Assessment, Development, and Evaluation (GRADE)
approach was used to assess the certainty of the evidence. (25) Evidence was graded as
high, moderate, low or very low quality. The included RCTs were graded as high-quality
evidence by default and downgraded based on the following criteria; risk of bias,
inconsistency, indirectness, imprecision and publication bias.

148 Statistical Analyses

interventions was calculated.

The inverse-variance method was used to pool mean differences for weight in kilograms and odds ratio for mortality to yield an overall effect size with 95% confidence intervals. For studies where standard deviations (SD) or confidence intervals were not available despite contacting authors, the mean SD for all other studies was used. Standard error or confidence intervals were converted to standard deviation using standard statistical formulae presented in the Cochrane Handbook for Systematic Reviews of Interventions 2011. Each meta-analysis was assessed for heterogeneity by a Chi square test and I² statistic. A fixed effects model was used when heterogeneity was not present ($I^2=0\%$) and a random effects model was used when statistical heterogeneity (I²≥1%) was present. The meta-

analysis was also repeated using a fixed effects model to assess the effects of small studies
on results.(26) A p-value of <0.05 was considered statistically significant. Studies are
presented in Forest plots in order of statistical power. A weighted average for weight loss per

For weight loss at 1 year and all-cause mortality, analysis was stratified at the mean baseline body mass index (BMI), the median number of interventions (≤ 28 ; >28 interventions), and the whether intentions were frontloaded (< or $\geq 75\%$ interventions in first 6 months). For weight loss over the length of follow up, subgroup analysis was done for mean study BMI (25-29, 30-35 and >35), age (40-49, 50-59 and ≥ 60) and number of interventions per year (\leq 6, 7-12, 13-24, and ≥ 25).

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| 2 3 | 160 | Sonaitivity analysis was undertaken to assess offects of studies that deviated significantly |
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| 4 | 168 | Sensitivity analysis was undertaken to assess effects of studies that deviated significantly |
| 5 6 | 169 | from the standard error of the total study result or studies where baseline values differed |
| 7 8 9 | 170 | significantly from the mean baseline. Funnel plots were used to assess for publication bias. |
| 10 11 | 171 | The statistical analyses were performed using RevMan software version 5.2 (The Nordic |
| 12 13 | 172 | Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed |
| 14 15 16 | 173 | guidelines suggested by Wang. (27) |
| 17 18 | 174 | A regression analysis evaluated the relationship between the number of interventions/study |
| 19 20 | 175 | and weight loss using Statistical Analysis Software (SAS). Intervention doses more than 3 |
| 21 22 | 176 | standard deviations above the mean were considered outliers, and were removed from the |
| 23 24 25 | 177 | analysis. (28) |
| 26 27 | 178 | standard deviations above the mean were considered outliers, and were removed from the analysis. (28) |
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Results

From a review of 5654 titles and abstracts, 31 randomised trials with a total of 20 563 participants met inclusion criteria. The most common reasons for excluding studies were duplicate reports, sample size <100, duration of follow-up <1 year, and no reporting of mortality (Figure 1). In one study, there was a factorial design where a control group was compared to diet alone, and exercise compared to exercise and diet. (18) These two comparisons are reported separately for a total of 32 studies. 70% of study participants had cardio-metabolic risk factors. No study was found in patients with established cardiovascular disease, although 14% of participants in the Look AHEAD trial had cardiac disease. (29)

Included studies are summarised in Table 1. Most studies were small and only four studies
had sample sizes > 1000 in each arm. (29-32) One study reported outcomes and weight
only at 6 years and this study is included only in the mortality analysis. (19) The Da Qing
study, (19) did not report summary measures of weight loss by randomised group, so also
could only be included in mortality analysis. The Look AHEAD trial (29) was both the largest
study and had the longest follow up. The GRADE score for both the weight loss and
mortality metaanalysis were high.

³⁹ 196 **Lifestyle interventions evaluated**

1197There were large variations in types (individual or group), mode of (face to face or remote),3198timing and frequency of interventions between studies described in Table 2. In some studies,5199the number of interventions provided was dependent on an individual study participant's7200response to the weight loss program, so it was not possible to accurately describe the dose901of intervention for every study. For these studies, the average number of interventions was202extrapolated based on the assumption that there was a normal distribution of extra4203interventions within the study.

The median number of interventions during the first year was 28 (IQR 12 to 37). In most
 studies there were more interventions during the first 6 months, median 18 (IQR 10 to 24)

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beyond 3 years.

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interventions. 14 studies report intervention beyond 1 year and for these the median number

of interventions in year 2 was 5 (IQR 4 to 12). Few studies reported weight outcomes

Effect of lifestyle interventions on body weight For all studies the average weight loss per lifestyle intervention session at one year compared to controls was ~0.13kg (95% CI 0.19, -0.07). Effects on body weight are shown in Figure 2, Table 3 and Supplemental Figures in Supplemental document 2. 27 of the included studies reported weight loss at one year, 12 at two years and 8 at three years. For studies which did not report weight loss at 1 year, the first reported weight after 1 year was used to assess the relationship with median number of interventions and total weight loss.(20, 22, 24) Weight loss was greater in the intervention group compared to the control group (3.63kg, 95% CI 4.67,2.58) at 1 year. This difference decreased over time and at year 3 was 2.45kg (95%CI 3.73, 1.17). Funnel plots do not suggest publication bias. Weight loss for studies with more than the median of 28 interventions /year was 4.50kg (95% CI 5.97, 3.03), and ≤28 interventions/year was 2.38 kg (95%CI 3.98, 0.78), p=0.001. Weight loss is presented by the number of interventions/study in Table 3. The estimated difference in weight loss between studies using the regression model was 0.6 kg (95% CI 0.23, 1.4) for each additional 10 interventions. Effects of lifestyle intervention on mortality Effects on mortality are presented in Figure 3, Table 3 and Supplemental document 2. In eight studies there were no deaths during follow up. For all studies combined there were 593 deaths, during a weighted average follow-up of 9.2 years, equivalent to an average mortality rate of 0.3%/year. Mortality was non-significantly lower in the intervention compared to the control group, odds ratio 0.86 (95% CI 0.73, 1.02), p=0.09. The number of interventions in the first year and weight loss achieved in the first year were not associated

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with mortality (Table 3). There were too few deaths to confidently evaluate possible differences in the relationship between study characteristics and mortality (Table 3).

Importance of the Look AHEAD study

The Look AHEAD study (29) contributed 25% of people to the meta-analysis and accounted for 63% of deaths. This trial randomised 5145 overweight or obese patients with type 2 diabetes, 14% also had established heart disease, 60% were women and the mean age was 59 years. The lifestyle intervention included weekly face to face meetings for the first 6 months, meetings 3 times a month for the next 6 months and then monthly until the end of study. Patients were followed for median 9.6 years (interquartile range, 8.9 to 10.3). A clinically meaningful 5-10% weight loss was achieved. The hazard ratio for all-cause mortality was 0.85 (95%Cl 0.69, 1.04; p = 0.11). Estimated effects on mortality and body weight in the Look AHEAD trial (29) were similar to those observed in all other studies combined (Table 3). ez.e

Discussion

There are four important conclusions from this meta-analysis (Box1). First, most studies were done in people aged 50-60 with cardiometabolic risk factors (Table 3). There were few studies in the elderly or in those with established cardiovascular or other diseases. Second lifestyle interventions compared to 'usual' care result in a modest reduction in body weight, on average ~3.6kg at one year, with about 2/3 of this sustained after 2-3 years. Weight loss was slightly greater in very obese and obese persons compared to overweight, but was still on average < 5% of body weight for all groups. Third, there was probably a dose response with greater weight loss with more frequent lifestyle interventions. Clinically meaningful >5% weight loss, as defined by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society, (33) was achieved with >28 interventions over one year, but not for shorter interventions. Fourth, lifestyle interventions

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were associated with a modest reduction in all-cause mortality, (point estimate ~14%), but
with wide confidence intervals. This estimate is similar to a previous meta-analyses which
reported that lifestyle interventions decreased all-cause mortality (RR = 0.85; 95%CI: 0.73–
1.00 and 0.82, 95% CI 0.71 to 0.95).(34, 35), but these meta-analyses did not evaluate the
importance of the intensity and duration of the lifestyle interventions.

In most studies there was a substantial effort for the lifestyle intervention group, with a median of 28 interventions over the first year. Comparison across studies suggests more interventions were associated with greater weight loss at one year, but no studies directly compared different intervention intensities or durations. There was limited data on the efficacy of shorter lifestyle interventions, or whether simple lifestyle advice from a health practitioner is effective. Most studies included relatively small numbers of participants, and lifestyle interventions varied markedly. It was not possible to confidently evaluate the impact of different types of lifestyle advice or the relative strengths of face to face compared to remote interventions.

This analysis provides insights on why obtaining reliable information on the impact of lifestyle
interventions on mortality is so difficult. The meta-analysis included randomised data from
over 20,000 patients with ~190,000 patient-years of follow-up. However the mortality rate
was only 0.3%/ year, and only three studies (29, 30, 36) reported more than 10 deaths.
There were also too few deaths in studies with fewer interventions, in healthy populations
and in people younger than 50 to reliably evaluate the effects in these groups. Modest
mortality benefits of sustained weight reduction may be expected to occur during longer
follow-up. In the Look AHEAD (29) study which followed patients for nearly 10 years, the
14% reduction in all-cause mortality was similar to all other studies combined, supporting the
conclusion that this mortality reduction is real. Although of borderline statistical significance,
this modest mortality benefit is consistent with observational studies which report that

285 mortality.(37) However, compared to lifestyle interventions bariatric surgery results in much
286 larger and sustained reductions in body weight. (38)

Findings from this study are relevant to clinical practice guidelines on interventions for weight loss. Although lifestyle interventions are associated with lower body weight and a probable small reduction in mortality, there is only reliable evidence for very comprehensive programmes which include many interactions sustained over months. There is limited evidence that shorter and simpler interventions, more typical of usual clinical practice, have a clinically meaningful benefit.(39) Also we were unable to evaluate whether weight loss is maintained after cessation of the lifestyle intervention, because most studies did not report outcomes after the intervention stops. The efficacy of lifestyle programs in the 'real word' is likely to be less than for volunteers in clinical trials who are generally highly motivated. These observations are important to inform realistic expectations on weight loss with lifestyle interventions, which may be much less than 'expected' by many clinicians and patients.

300 Study limitations

Individual participant data was not available and this limits the ability to address several important guestions. It is possible some individuals loose significant weight, while others loose none, but this could not be reliably evaluated from summary data. It was also not possible to evaluate the benefit of weight loss in subgroups of individuals who lost the most weight. It is not clear the degree to which weight loss is dependent on individual participant characteristics such as body mass index, gender, age and ethnicity. Most studies did not provide information on food consumed or exercise performed, and it was not possible to assess adherence to randomised treatments, or to compare different types of lifestyle intervention. It was not possible to compare the nature of the interventions and type of lifestyle advice given. Intensive lifestyle interventions have been reported to reduce

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| 2 3 4 | 311 | progression of diabetes and to be cost effective.(40) The current meta-analysis did not |
| 5 6 | 312 | assess other potential health benefits of weight loss such as reducing progression to |
| 7 8 | 313 | diabetes. |
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| 12 13 14 | 315 | Conclusion |
| 15 16 17 | 316 | Lifestyle programs with frequent patient interactions sustained over a year or more can |
| 18 19 | 317 | achieve clinically meaningful weight loss, and this may lower mortality during long term |
| 20 21 | 318 | follow-up. However the benefits of less frequent interventions over shorter durations in body |
| 22 23 | 319 | weight are more modest and long term benefits to mortality risk are uncertain. Because |
| 24 25 | 320 | there is limited data from randomised trials, it is uncertain whether lifestyle interventions for |
| 26 27 28 | 321 | obesity decrease mortality in persons with cancer, heart failure or ischaemic heart disease. |
| 29 30 31 | 322 | |
| 32 33 34 | 323 | Figure 1: Study flow chart |
| 35 36 37 | 324 | Figure 2: Effects of lifestyle intervention on weight loss at 1 year. |
| 38 39 | 325 | Figure 3: Effects of weight loss on mortality during a weighted average follow-up of 9.2 |
| 40 41 42 | 326 | years. There is no heterogeneity for all (I ² =0). |
| 43 44 45 | 327 | Supplementary document 1: Protocol (includes search strategy) |
| 46 47 48 | 328 | Supplementary document 2: Supplementary figures. |
| 49 50 | 329 | Patient consent: Not required. |
| 51 52 53 | 330 | Contributor statement: |
| 54 55 56 | 331 | NS, RS and JB: conception of study, adjudication inclusion of studies, draft version |
| 57 58 | 332 | manuscript. NS and JB: electronic database searches, data extraction, performed the |
| 59 60 | 333 | analysis. RS and JB wrote the subsequent and final versions of manuscript in consultation |

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- 334 with NS, JB: regression model, designed the figures and tables. All authors discussed the
- 335 results and commented on the manuscript.
- **Competing interests**: nil
- 337 Funding: Nil

- 338 Data sharing statement No additional data available
 - Key message box
 - An average 28 interventions (more than twice a month) in the first year achieved 3.67kg weight loss at one year. Interventions included seeing doctors, nurses, dieticians, nutritionist, and psychologists.
 - Evidence that weight loss reduces mortality is from large, long term studies with frequent interventions in middle aged patients with cardiometabolic risk factors.
 - The effectiveness of simple lifestyle advice by medical practitioners or a limited

number of interventions to achieve sustained weight loss is uncertain.

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Table 1: Baseline characteristic of 31 studies included in mortality meta-analysis.

| 524 |
|-----|
| 525 |

| Name of Study | Target population | Sample | Women | Mean | Mean | Mean | Intervention | Follow- | Death |
|---------------|--------------------------------------|--------|----------|---------|---------|---------|--------------|------------|-------|
| | L | size | number | ВМІ | initial | age | duration | up | |
| | | N | (%) | (kg/m²) | weight | (years) | (years) | duration | |
| | | | 2 | | (kg) | | | (years) | |
| Summary | | 615 | 346 (56) | 32.5 | 87.2 | 53.8 | 2.39 | 2.49 | 19 |
| statistic | | | | 1- | | | | | |
| weighted mean | | | | 191 | i | | | | |
| | | | | 4 | 101 | | | | |
| ACHIEVE (41) | Overweight/obese with mental illness | 291 | 146 (50) | 36.3 | 102.7 | 45.3 | 1.5 | 1.5 | 5 |
| ADAPT (42) | Overweight/obese knee | 318 | 229 (72) | 34.3 | 93.8 | 68.5 | 1.5 | 1.5 | 45 |
| | osteoarthritic older | | | | | | | (8 for | |
| | persons | | | | | | | mortality) | |
| ALIFE@WORK | Overweight/obese | 1386 | 457 (33) | 29.6 | 92.1 | 43 | 0.5 | 2 | 3 |
| (20) | | | | | | | | | |

| BE-WELL(21) | Obese asthmatics | 330 | 234 (71) | 37.5 | 104.2 | 47.6 | 1 | 1 | 0 |
|-----------------|---------------------------|------|-----------|------------|-------|------|------|------|----|
| CLIP (43) | Overweight/obese older | 288 | 193 (67) | 32.8 | 91.9 | 67.1 | 1.5 | 1.5 | 3 |
| | with limited mobility and | | | | | | | | |
| | cardiovascular disease | | | | | | | | |
| | or dysfunction | 0 | | | | | | | |
| Da Qing (19) | Impaired glucose | 530 | 244 (46) | 25.8 | _ | 45 | 6 | 6 | 11 |
| | tolerance | | | | | | | | |
| DPP (31) | Overweight/obese with | 2161 | 1491 (69) | 34.1 | 94.2 | 50.4 | 2.8 | 2.8 | 8 |
| | elevated fasting | | | <u>(6)</u> | • | | | | |
| | glucose | | | | 0 | | | | |
| EDIPS-Newcastle | Overweight/obese with | 102 | 61 (60) | 33.8 | 92 | 57.1 | 3.1 | 3.1 | 3 |
| (44) | impaired glucose | | | | | 0h | | | |
| | tolerance | | | | | | | | |
| E-LITE (45) | Overweight/obese | 241 | 113 (47) | 32 | 93.8 | 52.9 | 1.25 | 1.25 | 0 |
| | persons with pre- | | | | | | | | |
| | diabetes or metabolic | | | | | | | | |
| | syndrome | | | | | | | | |

| HEALTH TRACK | Overweight and obese | 377 | 279 (74) | 32 | 125.2 | 45 | 1 | 1 | 0 |
|--------------|------------------------|-----|-----------|------|-------|------|-----|-----|---|
| 32) | Australians | | | | | | | | |
| HCP (22) | Hypertension | 118 | 42 (36) | - | 77 | 56 | 4 | 4 | 3 |
| DEA (46) | Overweight/obese with | 454 | 327 (72) | 33.6 | 93 | 66 | 1.5 | 1.5 | 0 |
| | osteoarthritis knee | 0 | | | | | | | |
| DPP-1 (47) | Indian and Pakistani | 269 | 62 (23) | 26 | _ | 45.6 | 2.5 | 2.5 | 2 |
| | origin with impaired | | 6 | | | | | | |
| | glucose tolerance | | | k | | | | | |
| EAN (23) | Overweight/obese | 100 | 100 (100) | 33.1 | 87.5 | 59 | 0.5 | 1 | 0 |
| | women with treated | | | | 0 | | | | |
| | breast cancer | | | | -4 | | | | |
| -ISA (48) | Overweight/obese post- | 338 | 338 (100) | 31.3 | 82 | 61 | 2 | 2 | 2 |
| | menopausal women | | | | | | | | |
| | with breast cancer | | | | | | | | |
| | history who are | | | | | | | | |
| | currently taking | | | | | | | | |
| | letrozole | | | | | | | | |

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| Look AHEAD (29) | Overweight/obese with | 5145 | 3087 (60) | 36 | 101 | 58.8 | 9.6 | 9.6 | 376 |
|-----------------|------------------------|------|-----------|------|-------|--------|-----|-----|-----|
| | type 2 diabetes | | | | | | | | |
| NEW (49) | Overweight/obese post- | 439 | 439 (100) | 30.9 | 83.6 | 58 | 1 | 1 | 1 |
| | menopausal women | | | | | | | | |
| ORBIT(28) | Obese African- | 213 | 213(100) | 39.2 | 104.9 | 46 | 1.5 | 1.5 | 1 |
| | American women | Or, | | | | | | | |
| Patrick (50) | Overweight/obese men | 441 | 0 (0) | 34.2 | 104.7 | 43.9 | 1 | 1 | 2 |
| PODOSA (51) | Indian or Pakistani- | 171 | 92 (54) | 30.5 | 80.3 | 52.5 | 3 | 3 | 1 |
| | origin with impaired | | | ro. | | | | | |
| | glucose tolerance test | | | | | | | | |
| POWER (18) | Obese with | 276 | 176 (64) | 36.6 | 103.4 | 54 | 2 | 2 | 0 |
| | cardiovascular risk | | | | | 0. | | | |
| | factors | | | | | \sim | 1. | | |
| SLIM (52) | Impaired glucose | 147 | 72 (49) | 29.8 | 85.5 | 56.9 | 4.1 | 4.1 | 1 |
| | tolerance | | | | | | | | |
| STRIDE (53) | Overweight/obese | 200 | 144 (72) | 38.3 | 107.7 | 47.2 | 1 | 1 | 2 |
| | taking antipsychotic | | | | | | | | |

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| | agents | | | | | | | | |
|--------------------------|--|------|-----------|------|-------|------|-----|-------------------|-----|
| Swedish Bjorknas (54) | Metabolic syndrome | 145 | 83 (57) | 29.8 | 85.8 | 54.4 | 3 | 3 | 0 |
| . , | - | | | | | | | | |
| TAIM (55) | Overweight/obese hypertensive | 200 | 102 (51) | - | 87.7 | 48.3 | 4.5 | 4.5 | 2 |
| TOHP I (56) | Normal to high blood | 564 | 180(32) | 29.5 | 89.8 | 42.8 | 1.5 | 1.5 | 2 |
| | pressure | | | | | | | | |
| TOHP II (57) | Overweight/obese | 2382 | 810 (34) | 30.9 | 93.6 | 43.6 | 3 | 3 | 12 |
| | persons that are normo- or hypertensive | | | | | | | | |
| TONE (30) | Overweight/obese | 585 | 304 (52) | 31.2 | 87.8 | 65.5 | 2.5 | 2.5 | 101 |
| | elderly hypertensive | | | | | 00 | 1. | (12 mortality) | |
| Transfer (0.4) | | 440 | | 00.0 | 77.0 | 04.5 | | | |
| Trento (24) | type 2 diabetes | 112 | 50 (45) | 28.8 | 77.8 | 61.5 | 2 | 2 | 4 |
| Villareal (58) | Older obese | 107 | 67 (63) | 37.2 | 100.8 | 69.7 | 1 | 1 | 0 |
| WOMAN (59) | Overweight/obese post- menopausal women | 508 | 508 (100) | 30.8 | 81.7 | 57 | 3 | 4 | 3 |

Table 2: Frequency and mode of contact of lifestyle intervention.

529 The type of contact refers to whether trial participants received individual (I) or group (G), and mode of contact outlines whether participants

530 received interventions remotely by internet, email or over the phone (R) or face to face (F).

| Study name | Type of contact | Mode of contact | Number of dietary | Number of dietary | Proportion of first |
|-----------------|-----------------------|---------------------------|-------------------|-------------------|-----------------------|
| Year Published | | | interventions | interventions | year interventions in |
| | | 20 | in year 1 | in year 2 | first 6 months (%) |
| | Individual= 7 | Face to face =11 | | | |
| All studies | Group only = 5 | Remote = 3 | 27.5 | 3.96 | 66 |
| | Group + individual=19 | Face to face + remote= 17 | | | |
| ACHIEVE (41) | G,I | F | 30 | х | 80 |
| ADAPT (42) | G,I | F,R | 33 | x | 64 |
| ALIFE@WORK (20) | I | R | 10 | 0 | 100 |
| BE-WELL (21) | G,I | F,R | 18 | X | 83 |
| CLIP (43) | G,I | F,R | 36 | x | 67 |
| Da Qing (19) | G,I | F | 16 | 4 | 80 |

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| 0 | - |
|---|---|
| Z | 1 |

| DPP (31) | G, I | F,R | 22 | 12 | 73 |
|----------------------|------|-----|-----|----|-----|
| EDIPS-Newcastle (44) | G,I | F | 8 | х | 75 |
| E-LITE (45) | G,I | F,R | 38 | x | 61 |
| HEALTH TRACK (32) | 4 | F,R | 6 | 6 | 50 |
| HCP (22) | | F | 12 | 4 | 75 |
| IDEA (46) | G,I | F,R | 39 | x | 62 |
| IDPP-1 (47) | I | F,R | 15 | 14 | 53 |
| LEAN (23) | I | F,R | 11 | X | 100 |
| LISA (48) | I | R | 31 | 4 | 87 |
| Look AHEAD (29) | G,I | F,R | 42 | 24 | 57 |
| NEW (49) | G,I | F,R | 32 | x | 63 |
| ORBIT (28) | G,I | F,R | 110 | x | 56 |
| Patrick (50) | I | R | 52 | X | 50 |
| PODOSA (51) | G | F | 7 | 4 | 71 |

| 28 | |
|----|--|
| | |

| POWER (18) | G,I | F | 39 | 18 | 77 |
|-----------------------|-----------------|----------------------------------|---------------------------|----|----|
| SLIM (52) | G,I | F,R | 5 | 4 | 60 |
| STRIDE (53) | G,I | F,R | 36 | x | 67 |
| Swedish Bjorknas (54) | G | F | 12 | 5 | 58 |
| TAIM (55) | G,I | F | 17 | 8 | 71 |
| TOHP I (56) | G,I | F,R | 26 | X | 77 |
| TOHP II (57) | G,I | F,R | 28 | X | 68 |
| TONE (30) | G,I | F | 28 | 12 | 71 |
| Trento (24) | G | F | 4 | 4 | 50 |
| Villareal (58) | G | F | 52 | x | 50 |
| WOMAN (59) | G | F | 40 | 12 | 50 |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | For peer review | v only - http://bmjopen.bmj.com/ | site/about/quidelines.vht | ml | |

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Table 3: Association with intervention intensity with weight loss achieved and mortality.

| | | Weight lo | SS | | | Mortality | |
|--|------------------------|--------------------|--|-----------|--------------------|---|---|
| | (from b | aseline and fi | nal reported)* | | | | |
| Characteristic | N studies [#] | Weight of study | Mean difference Random effect model (kg) (95%CI) | N studies | Weight of study | total deaths /total patients (mortality rate) | Odds ratio Fixed effec model (95%Cl) |
| Number of Interventions per year | | | | ien. | | | |
| ≤ 6 | 3 | 9 % | 0.84 [0.28, 1.40] | 3 | 1% | 5/510 (1.0%) | 1.45 [0.22, 9.40] |
| 7-12 | 6 | 17% | 2.04 [0.84,3.24] | 6 | 2% | 10/2022 (0.5%) | 1.34 [0.35, 5.16] |
| 13-24 | 4 | 15% | 2.46 [0.67,5.59] | 6 | 4% | 23/3490 (0.7%) | 1.20 [0.49, 2.96] |

| ≥ 25 | 17 | 60% | 3.53 | 17 | 93% | 555/13578 | 0.84 |
|------------------------|----|-----|---------------|----|-----|-----------|--------------|
| | | | [2.92, 4.13] | | | (4.1%) | [0.71, 1.00] |
| BMI* | | | | | | | |
| 25-29 | 6 | 19% | 1.37 | 8 | 11% | 23/3890 | 1.58 |
| | | | [-0.09, 2.82] | | | (0.6%) | [0.64, 3.90] |
| 30- 35 | 16 | 48% | 3.09 | 14 | 22% | 136/8374 | 0.93 |
| | | | [2.11, 4.06] | | | (1.6%) | [0.65, 1.33] |
| > 35 | 6 | 23% | 4.04 | 6 | 67% | 384/6370 | 0.86 |
| | | | [2.47, 5.61] | | | (6%) | [0.69, 1.05] |
| Comorbidities | | | V | 0 | | | |
| Cardiometabolic risk | 16 | 56% | 2.86 | 18 | 90% | 529/14311 | 0.90 |
| factor present | | | [2.10, 3.63] | | | (3.7%) | [0.75, 1.08] |
| Healthy population | 8 | 29% | 3.03 | 8 | 3% | 12/3458 | 1.23 |
| | | | [1.53, 4.52] | | | (0.3%) | [0.39, 3.89] |
| Other (arthritis, | 4 | 9% | 3.35 | 4 | 2% | 7 /1275 | 0.74 |
| asthma mental illness) | | | [2.18, 4.52] | | | (0.6%) | [0.16, 3.37] |

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| Cancer | 2 | 6% | 2.70 | 2 | 6% | 2/438 | 0.98 |
|-------------------|----|------|--------------|-----|------|-----------|-------------|
| | | | [1.57, 3.83] | | | (0.5%) | [0.06, 15.7 |
| Age | | | | | | | |
| 40-49 | 12 | 47% | 2.29 | 14 | 9% | 50/9868 | 1.28 |
| | | | [0.97, 3.61] | | | (0.5%) | [0.71, 2.30 |
| 50-59 | 12 | 39% | 3.27 | 12 | 69% | 396/9691 | 0.84 |
| | | | [2.38, 4.15] | | | (3.8%) | [0.69, 1.04 |
| >60 | 7 | 14% | 4.50 | 7 | 22% | 155/2202 | 0.78 |
| | | | [2.76, 6.25] | | | (7.0%) | [0.55, 1.10 |
| | | | | -1/ | | | |
| Look AHEAD | 1 | 4% | 3.40 | 1 | 65% | 376/5145 | 0.85 |
| | | | [3.30, 3.50] | | | (7.3%) | [0.69, 1.05 |
| All other studies | 29 | 96% | 3.01 | 32 | 35% | 207/14455 | 0.88 |
| | | | [2.23, 3.79] | | | (1.4%) | [0.66, 1.17 |
| Total | 30 | 100% | 2.95 | 32 | 100% | 593/19463 | 0.86 |
| | | | [2.35, 3.55] | | | (3.1%) | [0.73, 1.02 |

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536 *TAIM and HCP excluded for BMI

- 537 # Da Quing excluded for all weight loss
- 538 + P<0.0001 for all

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| 1 | |
|----------------|-----|
| 2 3 4 | 539 |
| 5 6 7 | 540 |
| 8 9 10 | 541 |
| 11 12 13 | |
| 14 15 16 | |
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| 23 24 25 | |
| 26 27 28 | |
| 29 30 31 | |
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| 59 60 | |

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Additional records identified through

manual searching of reference lists

(n = 86)

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• (n=11)

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Records excluded after

review of titles and abstracts

(n = 5484)

duplicate reports (n=22)

not reporting deaths (n=34)

not reporting deaths by

randomisation arm (n=6)

insufficient duration (n=17)

insufficient data (n=1)

not adults (n=6)

not in English (n=2)

insufficient sample size (n=20)

ineligible control group (n=14)

not randomised controlled trial

initial weight-loss phase for all (n=5) pharmacotherapy (n=4)

Records identified through

database searching

(n = 8447)

Records after duplicates removed

(n = 5654)

Records screened

(n = 5654)

Full-text articles assessed

for eligibility

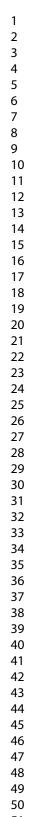
(n = 170)

31 Individual studies

(1 studies had separate

arms that can not be

combined so in total 32 studies included)







Study flow chart

67x90mm (300 x 300 DPI)

60

I² (%) P value

0.05

< 0.0001

< 0.0001

<0.0001

< 0.0001

< 0.0001

<0.0001

<0.0001

94

96

94

97

95

98

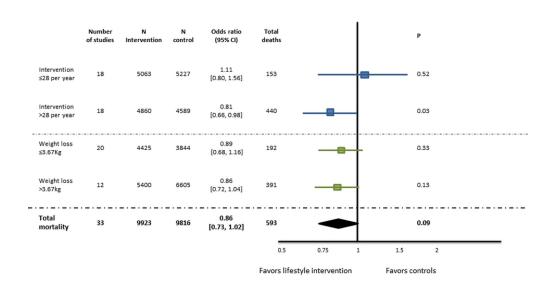
80

97

Favors controls

6

| | Number studies | N Intervention | N control | Mean difference in Kg (95% Cl) | | I |
|---|-------------------|-------------------|--------------|-----------------------------------|---------------------|-------|
| BMI | | | | | | |
| BMI (26-29kg/m²) BMI | 4 | 586 | 539 | -2.23 [-4.43, -0.03] | | |
| (30- 35kg/m ²) | 15 | 4809 | 4543 | -3.60 [-4.85, -2.36] | | |
| >35kg/m ²) | 7 | 3421 | 3280 | -4.64 [-6.88, -2.40] | | |
| Interventions | | | | | | |
| ≤28 intervention in first year | 13 | 3318 | 2738 | -2.38 [-3.98, -0.78] | | |
| >28 interventions in first year | 17 | 6079 | 5875 | -4.50 [-5.97, -3.03] | | |
| <75% of all intervention in first 6 months | 18 | 7043 | 6863 | -3.95 [-5.34, -2.57] | | |
| >75% of all intervention in first 6 months | 9 | 1561 | 1338 | -3.31 [-4.46,-2.17] | | |
| fotal weight oss at 1 year | 27 | 8380 | 8108 | -3.63 [-4.67, -2.58] | ٠ | |
| | | | | -9 | -6 -3 | 0 |
| | | Effects of | | | n on weight loss at | 1 yea |
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Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I2=0).

81x60mm (300 x 300 DPI)

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

Study Protocol

JI **Navneet Singh Jocelyne Benatar Ralph Stewart**

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 (BMI \geq 30 kg/m2) or overweight (25 \leq BMI<30 kg/m2). ¹ 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,² blood pressure, ³ and some cancers,⁴⁻⁶ 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, ⁷ diabetes,⁸ risk factors for coronary heart disease ⁹ and cancer. ⁴⁻⁶ 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, ¹⁰⁻¹² diabetes ^{13, 14} and as cancer guidelines¹⁵ 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-analysis¹⁶ 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 <u>Search Criteria</u>

 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≥25kg/m²)
- 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 16th 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 metaanalyses 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 metaanalysis.

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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15. Society AC. ACS Guidelines for Nutrition and Physical Activity. April 13, 2017 2017. https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activitycancer-prevention/guidelines.html (accessed 12 April 2018).

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Figure 1a: Weight loss at 1 year

| | Lifestyle | | | | ontrol | | | Mean Difference | Mean Difference |
|---------------------------|-----------|------|-------|--------|--------|-------|--------|-----------------------|--------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 1.9% | -3.85 [-9.40, 1.70] | |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | | 150 | 2.4% | -7.95 [-12.45, -3.45] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 3.2% | -2.16 [-5.01, 0.69] | |
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 3.4% | -3.50 [-6.03, -0.97] | <u> </u> |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 3.4% | -2.99 [-5.50, -0.48] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 3.4% | -2.31 [-4.76, 0.14] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 3.5% | -6.55 [-8.84, -4.26] | <u> </u> |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 3.5% | -1.90 [-4.12, 0.32] | |
| ACHIEVE 2013 | -2.8 | 7.96 | 144 | -0.4 | 9.28 | 147 | 3.6% | -2.40 [-4.39, -0.41] | |
| CLIP 2011 | -4.8 | 7.5 | 93 | -1.4 | 5.1 | 97 | 3.7% | -3.40 [-5.23, -1.57] | <u> </u> |
| ORBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 3.7% | -2.77 [-4.54, -1.00] | _ |
| POWER (face to face) 2011 | -5.8 | 8.22 | 139 | -1.1 | 5.87 | 138 | 3.8% | -4.70 [-6.38, -3.02] | _ — |
| Villareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 3.8% | -8.83 [-10.39, -7.28] | <u> </u> |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 3.9% | -3.40 [-4.81, -1.99] | <u> </u> |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 4.0% | -1.86 [-3.09, -0.63] | |
| LISA 2014 | -4.5 | 5.4 | 171 | -0.6 | 5.7 | 167 | 4.0% | -3.90 [-5.08, -2.72] | <u> </u> |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 4.0% | -1.30 [-2.41, -0.19] | |
| WOMAN2011 | -7.8 | 7.1 | 253 | -1.6 | 5.5 | 255 | 4.0% | -6.20 [-7.31, -5.09] | |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 4.0% | -3.00 [-3.98, -2.02] | |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 4.1% | -0.81 [-1.73, 0.11] | |
| TOHP 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 4.1% | -3.90 [-4.74, -3.06] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 4.1% | -0.70 [-1.53, 0.13] | |
| TONE 1998 | -4.73 | 4.67 | 294 | -1.14 | 3.65 | 291 | 4.1% | -3.59 [-4.27, -2.91] | - |
| Look AHEAD 2013 | -9.2 | 10.2 | 2570 | -1.2 | 10.3 | 2575 | 4.1% | -8.00 [-8.56, -7.44] | + |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 4.1% | -0.40 [-0.89, 0.09] | |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 4.2% | -6.40 [-6.80, -6.00] | + |
| TOHP II 1997 | -2.1 | 5.7 | 1192 | 0.55 | 4.25 | 1190 | 4.2% | -2.65 [-3.05, -2.25] | + |
| Total (95% CI) | | | 8380 | | | 8108 | 100.0% | -3.63 [-4.67, -2.58] | ▲ |

Test for overall effect: Z = 6.81 (P < 0.00001)

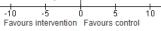


Figure 1b : Weight loss at 1 year- funnel plot

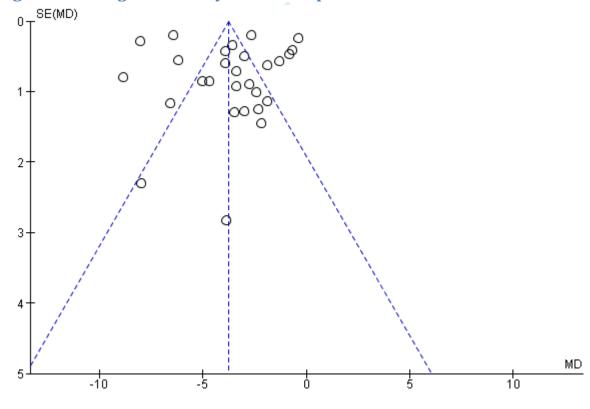


Figure 2a: Weight loss at 2 years

| 0 | 0 | | | | | | | | |
|---|---------------|----------|----------|-----------------------|---------|-------|--------|----------------------|--------------------------------------|
| | Lifestyle | intervei | ntion | C | Control | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 2.9% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -3.15 | 14.9 | 71 | 0.6 | 18.3 | 74 | 4.3% | -3.75 [-9.17, 1.67] | - _+ |
| POWER (face to face) 2011 | -5.1 | 8.83 | 138 | -0.8 | 8.22 | 138 | 8.3% | -4.30 [-6.31, -2.29] | |
| SLIM 2011 | -0.85 | 4.34 | 74 | -0.76 | 3.26 | 73 | 9.1% | -0.09 [-1.33, 1.15] | + |
| LISA 2014 | -3.1 | 6.2 | 171 | -0.3 | 5.3 | 167 | 9.1% | -2.80 [-4.03, -1.57] | |
| PODOSA 2014 | -0.78 | 3.43 | 85 | 0.13 | 3.24 | 86 | 9.3% | -0.91 [-1.91, 0.09] | |
| TAIM 1993 | -2.2 | 3.25 | 100 | -0.4 | 3.25 | 100 | 9.4% | -1.80 [-2.70, -0.90] | + |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 9.4% | -0.63 [-1.48, 0.22] | * |
| TONE 1998 | -3.83 | 5.16 | 294 | -0.468 | 3.92 | 291 | 9.5% | -3.36 [-4.10, -2.62] | + |
| Look AHEAD 2013 | -7.1 | 10.2 | 2570 | -1.4 | 10.3 | 2575 | 9.6% | -5.70 [-6.26, -5.14] | • |
| IDPP-1 2006 | 0.3 | 1.62 | 133 | 0.65 | 2.9 | 136 | 9.6% | -0.35 [-0.91, 0.21] | + |
| DPP2002 | -5.4 | 5.48 | 1079 | 0 | 0.997 | 1082 | 9.6% | -5.40 [-5.73, -5.07] | • |
| Total (95% CI) | | | 5697 | | | 5238 | 100.0% | -2.52 [-4.02, -1.01] | • |
| Heterogeneity: Tau ² = 6.07; (| | | (P < 0.0 | 0001); I ^z | = 97% | | | - | -20 -10 0 10 20 |
| Test for overall effect: Z = 3.2 | 8 (P = 0.001) |) | | | | | | | Favours intervention Favours control |



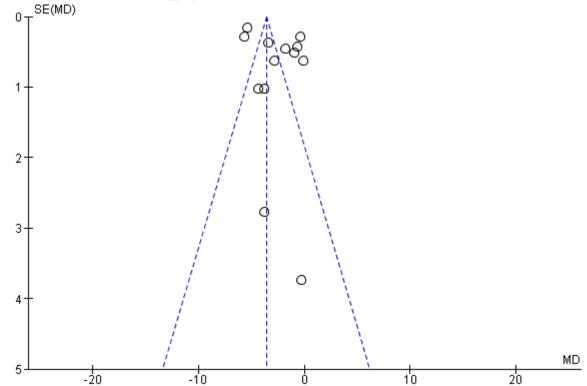


Figure 3a: Weight loss at 3 years

| 0 | 0 | | | | | | | | |
|--|--------------|------------|----------|---------|--------------|-------|--------|----------------------|---|
| | Lifestyle | e interven | tion | С | ontrol | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Swedish Bjorknas 2009 | -2.5 | 14.7 | 71 | 1.4 | 18.2 | 74 | 4.1% | -3.90 [-9.27, 1.47] | |
| SLIM 2011 | -1.08 | 4.3 | 74 | 0.16 | 4.91 | 73 | 12.3% | -1.24 [-2.73, 0.25] | |
| TAIM 1993 | -2.3 | 4.69 | 100 | -0.1 | 4.69 | 100 | 12.8% | -2.20 [-3.50, -0.90] | _ |
| PODOSA 2014 | -1.1 | 4.45 | 85 | 0.5 | 3.53 | 86 | 13.1% | -1.60 [-2.80, -0.40] | |
| IDPP-1 2006 | 0.35 | 1.89 | 133 | 0.8 | 3.57 | 136 | 14.2% | -0.45 [-1.13, 0.23] | -=+ |
| Look AHEAD 2013 | -5.8 | 10.2 | 2570 | -1.4 | 10.3 | 2575 | 14.4% | -4.40 [-4.96, -3.84] | - |
| TOHP 1997 | -0.25 | 5.7 | 1192 | 1.75 | 5.25 | 1190 | 14.5% | -2.00 [-2.44, -1.56] | + |
| DPP2002 | -4.1 | 5.41 | 1079 | 0.4 | 3.99 | 1082 | 14.6% | -4.50 [-4.90, -4.10] | + |
| Total (95% CI) | | | 5304 | | | 5316 | 100.0% | -2.45 [-3.73, -1.17] | ◆ |
| Heterogeneity: Tau ² = 2.89 | 3; Chi² = 16 | 3.45, df= | 7 (P < 0 | 0.00001 |); $ ^2 = 9$ | 36% | | | |
| Test for overall effect: Z = 3 | | • | | | | | | | -10 -5 0 5 10 Favours intervention Favours control |
| | | | | | | | | | |

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Figure 3b: Weight loss at 3 years- funnel plot

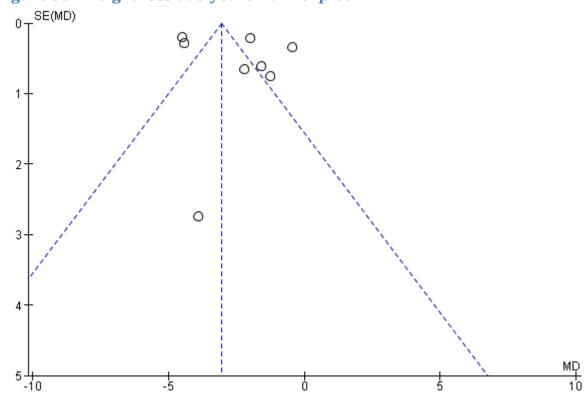


Figure 4a: Weight loss achieved by end of study

| | - | e interver | | | Control | | | Mean Difference | Mean Difference |
|---|-------|------------|----------|-------------------|---------|------|--------|-----------------------|--------------------|
| Study or Subgroup | Mean | SD | Total | Mean | | | - | IV, Random, 95% CI | IV, Random, 95% CI |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 0.6% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -2.5 | 14.7 | 71 | 1.4 | 18.2 | 74 | 1.0% | -3.90 [-9.27, 1.47] | |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | 23.4 | 150 | 1.3% | -7.95 [-12.45, -3.45] | • |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 2.2% | -2.16 [-5.01, 0.69] | |
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 2.5% | -3.50 [-6.03, -0.97] | |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 2.5% | -2.99 [-5.50, -0.48] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 2.6% | -2.31 [-4.76, 0.14] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 2.7% | -6.55 [-8.84, -4.26] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 2.8% | -1.90 [-4.12, 0.32] | |
| POWER (face to face) 2011 | -5.1 | 8.83 | 138 | -0.8 | 8.22 | 138 | 3.0% | -4.30 [-6.31, -2.29] | |
| ACHIEVE 2013 | -3.4 | 7.6944 | 137 | -0.2 | 9.0416 | 142 | 3.1% | -3.20 [-5.17, -1.23] | — <u> </u> |
| CLIP 2011 | -4.8 | 7.5 | 93 | -1.4 | 5.1 | 97 | 3.2% | -3.40 [-5.23, -1.57] | _ - |
| ORBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 3.3% | -2.77 [-4.54, -1.00] | _ |
| HCP 1987 | -1.8 | 5.1 | 78 | 2 | 3.5 | 40 | 3.5% | -3.80 [-5.37, -2.23] | |
| Villareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 3.5% | -8.83 [-10.39, -7.28] | _ |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 3.6% | -3.40 [-4.81, -1.99] | |
| TAIM 1993 | -1 | 4.69 | 100 | 1 | 4.69 | 100 | 3.7% | -2.00 [-3.30, -0.70] | |
| LISA 2014 | -3.1 | 6.2 | 171 | -0.3 | 5.3 | 167 | 3.8% | -2.80 [-4.03, -1.57] | |
| PODOSA 2014 | -1.1 | 4.45 | 85 | 0.5 | 3.53 | 86 | 3.8% | -1.60 [-2.80, -0.40] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 3.9% | -1.30 [-2.41, -0.19] | |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 4.2% | -0.63 [-1.48, 0.22] | -+ |
| TOHP 1 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 4.2% | -3.90 [-4.74, -3.06] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 4.2% | -0.70 [-1.53, 0.13] | |
| TONE 2011 | -4.4 | 4.8 | 259 | -0.8 | 3.7 | 245 | 4.3% | -3.60 [-4.35, -2.85] | - |
| IDPP-1 2006 | 0.35 | 1.89 | 133 | 0.8 | 3.57 | 136 | 4.3% | -0.45 [-1.13, 0.23] | -+- |
| SLIM 2011 | -1.09 | 2 | 74 | -0.4 | 2 | 73 | 4.3% | -0.69 [-1.34, -0.04] | - |
| WOMAN2011 | -2.9 | 3 | 253 | -0.3 | 3 | 255 | 4.4% | -2.60 [-3.12, -2.08] | + |
| TOHP II 1997 | -0.25 | 5.7 | 1192 | 1.75 | | 1190 | 4.4% | -2.00 [-2.44, -1.56] | + |
| DPP2002 | -5.4 | 5.48 | 1079 | 0 | 0.997 | | 4.5% | -5.40 [-5.73, -5.07] | + |
| Look AHEAD 2013 | -3.9 | 1.9 | 2570 | -0.5 | | 2575 | 4.5% | -3.40 [-3.50, -3.30] | • |
| Total (95% CI) | | | 9397 | | | 8613 | 100.0% | -2.95 [-3.55, -2.35] | • |
| Heterogeneity: Tau ^z = 2.06; CH Test for overall effect: Z = 9.64 | | • | (P < 0.0 | 0001); I ² | = 94% | | | | -10 -5 0 5 10 |

Figure 4b: Weight loss achieved by end of study- funnel plots

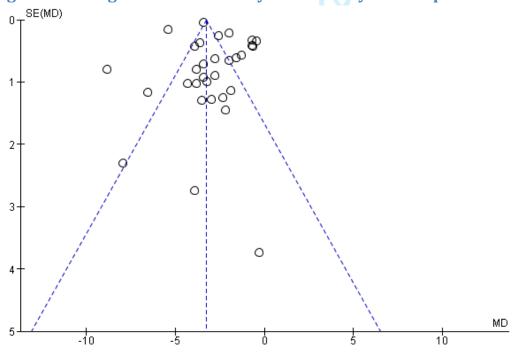


Figure 5a: Weight loss ≤28 interventions/year

| 0 | 0 | | | | | | | 15 | |
|--|--------------|------------|---------|--------|----------|-------|--------|----------------------|--|
| | Lifestyle | e interven | ition | С | ontrol | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 3.0% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 4.1% | -3.85 [-9.40, 1.70] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 6.5% | -2.16 [-5.01, 0.69] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 6.9% | -2.31 [-4.76, 0.14] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 7.1% | -1.90 [-4.12, 0.32] | |
| HCP 1987 | -1.8 | 5.1 | 78 | 2 | 3.5 | 40 | 7.7% | -3.80 [-5.37, -2.23] | _ — |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 7.9% | -1.86 [-3.09, -0.63] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 8.0% | -1.30 [-2.41, -0.19] | |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 8.0% | -3.00 [-3.98, -2.02] | |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 8.1% | -0.81 [-1.73, 0.11] | |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 8.1% | -0.63 [-1.48, 0.22] | |
| TOHP 1 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 8.1% | -3.90 [-4.74, -3.06] | |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 8.2% | -0.40 [-0.89, 0.09] | |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 8.2% | -6.40 [-6.80, -6.00] | + |
| Total (95% CI) | | | 3318 | | | 2738 | 100.0% | -2.38 [-3.98, -0.78] | ◆ |
| Heterogeneity: Tau ² = 8.01 | ; Chi² = 45 | 0.59, df= | 13 (P < | 0.0000 | 1); l² = | 97% | | - | |
| Test for overall effect: Z = 2 | 2.92 (P = 0. | 003) | | | | | | | Favours [experimental] Favours [control] |
| | | | | | | | | | r avours [experimental] i avours [control] |

Figure 5b: Weight loss >28 interventions/year

| | Lifestyle | | ntion | | ontrol | | | Mean Difference | Mean Difference |
|---|-----------|------|----------|-----------|--------|-------|--------|-----------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| DEA 2013 | -9.75 | 22.2 | 304 | -1.8 | 23.4 | 150 | 4.2% | -7.95 [-12.45, -3.45] | _ |
| CLIP 2011 | -7.1 | 15.8 | 93 | -0.849 | 14.7 | 97 | 4.4% | -6.25 [-10.59, -1.91] | |
| 3TRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 5.8% | -3.50 [-6.03, -0.97] | |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 5.9% | -2.99 [-5.50, -0.48] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 6.0% | -6.55 [-8.84, -4.26] | |
| CHIEVE 2013 | -2.8 | 7.96 | 137 | -0.4 | 9.28 | 142 | 6.2% | -2.40 [-4.43, -0.37] | |
| DRBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 6.4% | -2.77 [-4.54, -1.00] | |
| POWER (face to face) 2011 | -5.8 | 8.22 | 138 | -1.1 | 5.87 | 138 | 6.5% | -4.70 [-6.39, -3.01] | |
| /illareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 6.5% | -8.83 [-10.39, -7.28] | |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 6.6% | -3.40 [-4.81, -1.99] | |
| JSA 2014 | -4.5 | 5.4 | 171 | -0.6 | 5.7 | 167 | 6.8% | -3.90 [-5.08, -2.72] | - |
| WOMAN2011 | -7.8 | 7.1 | 253 | -1.6 | 5.5 | 255 | 6.8% | -6.20 [-7.31, -5.09] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 6.9% | -0.70 [-1.53, 0.13] | - |
| FONE 1998 | -4.4 | 4.8 | 259 | -0.8 | 3.7 | 245 | 6.9% | -3.60 [-4.35, -2.85] | + |
| .ook AHEAD 2013 | -9.2 | 10.2 | 2570 | -1.2 | 10.3 | 2575 | 7.0% | -8.00 [-8.56, -7.44] | - |
| TOHP II 1997 | -0.25 | 5.7 | 1192 | 1.75 | 5.25 | 1190 | 7.0% | -2.00 [-2.44, -1.56] | • |
| otal (95% CI) | | | 6079 | | | 5875 | 100.0% | -4.50 [-5.97, -3.03] | • |
| Heterogeneity: Tau ^z = 7.96; Ch Fest for overall effect: Z = 6.00 | | | (P < 0.0 | 0001); I² | = 96% | b | | - | -20 -10 0 10 20 Favours [experimental] Favours [control] |
| | | | | | | | | | |
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4 5

Figure 6a: Total mortality

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| Villareal 2011 0 BE-WELL 2015 0 IDEA 2013 0 HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 1000 71 139 54 165 304 125 160 67 74 85 107 235 100 | Events 0 0 0 0 0 0 0 0 1 1 | 74 138 53 165 150 126 81 33 | Weight | IV, Fixed, 95% CI Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable Not estimable | IV, Fixed, 95% Cl |
|---|--|--|--|--------|--|-------------------|
| POWER (face to face) 2011 0 Villareal 2011 0 BE-WELL 2015 0 IDEA 2013 0 HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP 11992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 139 54 165 304 125 160 67 74 85 107 235 | 0 0 0 0 0 0 1 | 138 53 165 150 126 81 33 | | Not estimable Not estimable Not estimable Not estimable Not estimable | |
| Villareal 2011 0 BE-WELL 2015 0 IDEA 2013 0 HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 54 165 304 125 160 67 74 85 107 235 | 0 0 0 0 0 1 | 53 165 150 126 81 33 | | Not estimable Not estimable Not estimable Not estimable | |
| BE-WELL 2015 0 IDEA 2013 0 HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 165 304 125 160 67 74 85 107 235 | 0 0 0 0 1 | 165 150 126 81 33 | | Not estimable Not estimable Not estimable | |
| IDEA 2013 0 HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP 11992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 304 125 160 67 74 85 107 235 | 0 0 0 0 1 | 150 126 81 33 | | Not estimable Not estimable | |
| HEALTH TRACK 0 E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP 11992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 125 160 67 74 85 107 235 | 0 0 0 1 | 126 81 33 | | Not estimable | |
| E-LITE 2013 0 LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 160 67 74 85 107 235 | 0 0 1 | 81 33 | | | |
| LEAN 2016 0 SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 67 74 85 107 235 | 0 1 | 33 | | Not estimable | |
| SLIM 2011 0 PODOSA 2014 0 ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 74 85 107 235 | 1 | | | 1101 000011100010 | |
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| ORBIT 2010 1 NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP 11992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 107 235 | 1 | 73 | 0.3% | 0.32 [0.01, 8.09] | |
| NEW 2012 0 TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 MOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 235 | | 86 | 0.3% | 0.33 [0.01, 8.30] | |
| TAIM 1993 2 Patrick 2011 2 HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | | 0 | 106 | 0.3% | 3.00 [0.12, 74.48] | |
| Patrick 2011 2 HCP 1987 3 Da Ging (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALFE @WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 100 | 1 | 204 | 0.3% | 0.29 [0.01, 7.11] | |
| HCP 1987 3 Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | .00 | 0 | 100 | 0.3% | 5.10 [0.24, 107.62] | |
| Da Qing (exercise) 1997 5 STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 224 | 0 | 130 | 0.3% | 2.93 [0.14, 61.55] | |
| STRIDE 2015 1 IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 78 | 0 | 40 | 0.3% | 3.75 [0.19, 74.50] | |
| IDPP-1 2006 1 LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 126 | 0 | 141 | 0.3% | 12.81 [0.70, 234.04] | |
| LISA 2014 1 TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 MUMAN2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| TOHP I 1992 1 EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 133 | 1 | 136 | 0.4% | 1.02 [0.06, 16.52] | |
| EDIPS-Newcastle 2009 2 CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | |
| CLIP 2011 1 WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 308 | 1 | 993 | 0.4% | 3.23 [0.20, 51.81] | |
| WOMAN2011 1 ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 51 | 1 | 51 | 0.5% | 2.04 [0.18, 23.24] | |
| ALIFE@WORK 2011 2 Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| Trento 2001 3 ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 253 | 2 | 255 | 0.5% | 0.50 [0.05, 5.57] | |
| ACHIEVE 2013 2 Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 926 | 1 | 460 | 0.5% | 0.99 [0.09, 10.99] | |
| Da Qing (no exercise) 1997 3 DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 56 | 1 | 56 | 0.6% | 3.11 [0.31, 30.88] | |
| DPP2002 3 TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 144 | 3 | 147 | 0.9% | 0.68 [0.11, 4.11] | |
| TOHP II 1997 7 ADAPT 2010 15 TONE 2011 49 | 133 | 3 | 130 | 1.1% | 0.98 [0.19, 4.93] | |
| ADAPT 2010 15 TONE 2011 49 | 1079 | 5 | 1082 | 1.4% | 0.60 [0.14, 2.52] | |
| TONE 2011 49 | 1192 | 5 | 1190 | 2.2% | 1.40 [0.44, 4.42] | _ |
| | 159 | 30 | 159 | 6.6% | 0.45 [0.23, 0.87] | |
| Look AHEAD 2013 174 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | - |
| E0010A11EAD 2013 | 2570 | 202 | 2575 | 65.5% | 0.85 [0.69, 1.05] | - |
| Total (95% CI) | 9785 | | 9678 | 100.0% | 0.86 [0.73, 1.02] | • |
| Total events 279 | | 314 | | | | |
| Heterogeneity: Chi ² = 15.54, df = 23 (P = 0.87 | | | | | | 0.005 0.1 1 10 2 |

Figure 6a: Total mortality- funnel plots

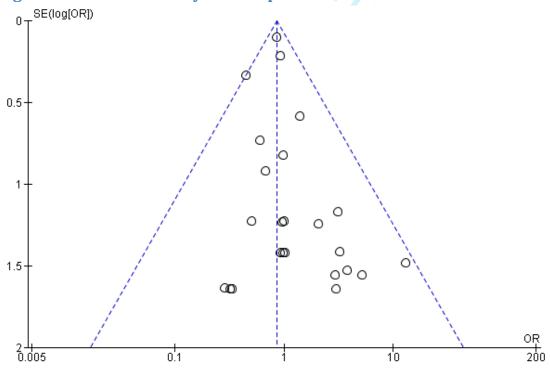


Figure 7a: Mortality ≤ 28 – interventions per year

| | Lifestyle interv | ention | Contr | ol | | Odds Ratio | Odds Ratio |
|--|---------------------------------|--------|--------|-------|--------|----------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| LEAN 2016 | 0 | 67 | 0 | 33 | | Not estimable | |
| HEALTH TRACK | 0 | 125 | 0 | 126 | | Not estimable | |
| Swedish Bjorknas 2009 | 0 | 71 | 0 | 74 | | Not estimable | |
| BE-WELL 2015 | 0 | 165 | 0 | 165 | | Not estimable | |
| Da Qing (exercise) 1997 | 5 | 126 | 0 | 141 | 2.6% | 12.81 [0.70, 234.04] | |
| TOHP 1992 | 1 | 308 | 1 | 993 | 2.7% | 3.23 [0.20, 51.81] | |
| TAIM 1993 | 2 | 100 | 0 | 100 | 2.8% | 5.10 [0.24, 107.62] | |
| HCP 1987 | 3 | 78 | 0 | 40 | 3.7% | 3.75 [0.19, 74.50] | |
| Trento 2001 | 3 | 56 | 1 | 56 | 5.5% | 3.11 [0.31, 30.88] | |
| EDIPS-Newcastle 2009 | 2 | 51 | 1 | 51 | 5.6% | 2.04 [0.18, 23.24] | |
| IDPP-1 2006 | 1 | 133 | 1 | 136 | 5.7% | 1.02 [0.06, 16.52] | |
| ALIFE@WORK 2011 | 2 | 926 | 1 | 460 | 7.8% | 0.99 [0.09, 10.99] | |
| PODOSA 2014 | 0 | 85 | 1 | 86 | 8.6% | 0.33 [0.01, 8.30] | |
| SLIM 2011 | 0 | 74 | 1 | 73 | 8.7% | 0.32 [0.01, 8.09] | |
| Da Qing (no exercise) 1997 | 3 | 133 | 3 | 130 | 17.3% | 0.98 [0.19, 4.93] | |
| DPP2002 | 3 | 1079 | 5 | 1082 | 29.0% | 0.60 [0.14, 2.52] | |
| Total (95% CI) | | 3577 | | 3746 | 100.0% | 1.53 [0.83, 2.81] | • |
| Total events | 25 | | 15 | | | | |
| Heterogeneity: Chi ² = 7.59, df = | = 11 (P = 0.75); I ² | = 0% | | | | | |
| Test for overall effect: Z = 1.37 | (P = 0.17) | | | | | | 0.01 0.1 1 10 100 Favours [experimental] Favours [control] |

Figure 7b: Mortality >28 – interventions per year

| | Lifestyle interv | ention | Cont | rol | | Odds Ratio | Odds Ratio |
|--|---------------------------------|--------|--------|-------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% CI |
| IDEA 2013 | 0 | 304 | 0 | 150 | | Not estimable | |
| E-LITE 2013 | 0 | 160 | 0 | 81 | | Not estimable | |
| POWER (face to face) 2011 | 0 | 139 | 0 | 138 | | Not estimable | |
| Villareal 2011 | 0 | 54 | 0 | 53 | | Not estimable | |
| ORBIT 2010 | 1 | 107 | 0 | 106 | 0.2% | 3.00 [0.12, 74.48] | |
| Patrick 2011 | 2 | 224 | 0 | 130 | 0.2% | 2.93 [0.14, 61.55] | |
| LISA 2014 | 1 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | |
| STRIDE 2015 | 1 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| CLIP 2011 | 1 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| NEW 2012 | 0 | 235 | 1 | 204 | 0.6% | 0.29 [0.01, 7.11] | |
| WOMAN2011 | 1 | 253 | 2 | 255 | 0.7% | 0.50 [0.05, 5.57] | |
| ACHIEVE 2013 | 2 | 144 | 3 | 147 | 1.1% | 0.68 [0.11, 4.11] | |
| TOHP II 1997 | 7 | 1192 | 5 | 1190 | 1.8% | 1.40 [0.44, 4.42] | |
| ADAPT 2010 | 15 | 159 | 30 | 159 | 9.9% | 0.45 [0.23, 0.87] | - _ |
| TONE 2011 | 49 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | _ _ |
| Look AHEAD 2013 | 174 | 2570 | 202 | 2575 | 68.5% | 0.85 [0.69, 1.05] | |
| Total (95% CI) | | 6208 | | 5932 | 100.0% | 0.84 [0.70, 1.00] | • |
| Total events | 254 | | 299 | | | | |
| Heterogeneity: Chi ² = 6.33, df | = 11 (P = 0.85); I ² | = 0% | | | | | |
| Test for overall effect: Z = 2.01 | (P = 0.04) | | | | | | Favours [experimental] Favours [control] |
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| 1 2 3 | PRISMA 20 | 009 | Checklist | | | | |
|-------------|---------------|-----|---|--|--|--|--|
| 4 5 6 | Section/topic | # | Checklist item | | | | |
| 7 | 7 TITLE | | | | | | |
| 8 9 | Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | | | | |

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|------------------------------------|----|---|------------------------|
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Registration page 3 |
| 5 | | °Ch. | Supplementary protocol |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4,5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5,6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (la goprisk) ratio of the rease in manuals) es. xhtml | 7 |

Reported on page #



PRISMA 2009 Checklist

| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis. | 7 |
|-------------------------------|----|--|---|
| | | Page 1 of 2 | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 1 and supplementary figures Pages 9,10 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Supplementar figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures 3-5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Supplementary |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Table 2 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Pages 10,11,12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 12 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | [Page 12 |

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PRISMA 2009 Checklist

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| 4 FUNDING | | | |
| 5 6 Funding 7 | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |
| 8 9 <i>From:</i> Moher D, Li 10 doi:10.1371/journal. | berati A, Tetzlaff J, Altr pmed1000097 | nan DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Pr Page 2 of 2 Page 2 of 2 | _oS Med 6(7): e1000097. |
| 11 | | For more information, visit: <u>www.prisma-statement.org</u> . | |
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BMJ Open

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Intensity and duration of lifestyle interventions for long term weight loss and association with mortality: a meta-analysis of randomised trials.

| Journal: | BMJ Open |
|--------------------------------------|--|
| Manuscript ID | bmjopen-2019-029966.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 21-Jul-2019 |
| Complete List of Authors: | Singh, Navneet; The University of Auckland, School of medicine Stewart, RA; Auckland City Hospital, Green Lane Cardiovascular Service Benatar, Jocelyne; Auckland City Hospital, Green Lane Cardiovascular Services |
| Primary Subject Heading : | Nutrition and metabolism |
| Secondary Subject Heading: | Evidence based practice |
| Keywords: | NUTRITION & DIETETICS, weight loss, lifestyle interventions |
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| 21 | 6 | Navneet Singh ¹ , Ralph AH Stewart ² , Jocelyne R Benatar ² * |
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| 27 28 | 8 | 1 School of Medicine, The University of Auckland, Auckland, New Zealand |
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| 49 | 15 | All authors contributed to this work and have no competing interests. |
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| 51 52 | 16 | This study was not funded. |
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18 Abstract

19 Objectives

- 20 To evaluate the importance of the frequency and duration of lifestyle interventions for
- 21 achieving weight loss over \geq one year, and associations with all-cause mortality.

22 Design

- 23 Meta-analysis of randomised trials using PRISMA guidelines and RevMan software version
- 24 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

25 Data sources

MEDLINE, CENTRAL, Google and Science Direct databases alongside reference lists of
 appropriate articles and meta-analyses.

28 Eligibility Criteria

- 29 Randomised studies published in English-language journals from 1980 to June 2018 that
- 30 assessed lifestyle compared to control interventions on weight loss, and which included
- \geq 100 subjects and reported weight change and mortality for \geq one year.

32 Data extraction and synthesis

Two independent reviewers extracted data and assessed risk of bias. Data were pooled
using the generic inverse-variance method and expressed as mean differences (MD) with
95% CI and odds ratio with 95%CI as appropriate. Heterogeneity was assessed (Cochran Q
statistic) and quantified (I2 statistic). The GRADE score was used to assess the certainty of
the evidence

Results

CI 0.73, 1.02), p=0.09.

Conclusion

31 randomised trials with a total of 20 816 overweight or obese participants were included.

70% of participants had cardiometabolic risk factors. Body weight was lower for lifestyle

intervention compared to the control at 1 year (3.63 kg, 95% confidence interval (CI) 2.58,

4.67), and at 3 years (2.45 kg, 95% CI 1.17, 3.73). Weight loss at one year was greater in

2.38, 95%CI 0.78, 3.98 kg, p=0.001). In all studies there were 593 deaths (~0.3%/year). The

odds ratio for mortality for weight loss interventions compared to the controls was 0.86 (95%

In predominantly healthy populations with risk factors, there is a dose response with number

of lifestyle interventions and weight loss. Frequent and sustained interventions are needed to

achieve a clinically significant 5% weight loss. There was insufficient evidence to reliably

evaluate the benefits in persons with known cardiovascular disease or cancer.

Prospero registration number: CRD42018095067

studies with > 28 compared to \leq 28 interventions per year (4.50 kg, 95%Cl 3.03, 5.97 vs

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| 2 3 4 | 56 | |
| 5 6 | 57 | Strengths and Limitations of study |
| 7 8 9 | 58 | Previous meta-analyses of randomised trials of lifestyle interventions have not |
| 9 10 11 | 59 | considered the level of intervention needed to achieve clinically meaningful (>5%) |
| 12 13 | 60 | weight loss. There was wide variation in the type of lifestyle advice, but it was not |
| 14 15 | 61 | possible to assess which type of lifestyle advice is most effective. |
| 16 17 | 62 | • Most evidence is in middle aged people (age 50 -60) with cardiometabolic risk |
| 18 19 | 63 | factors. There is limited data on effects of lifestyle interventions for weight loss in |
| 20 21 | 64 | older patients and those with cardiovascular disease or cancer. |
| 22 23 | 65 | Lifestyle interventions for weight loss may reduce mortality if sustained. However in |
| 24 25 26 | 66 | most studies the duration of the intervention and follow-up were too short and |
| 27 | 67 | mortality too low to allow a reliable assessment. |
| 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 | 68 | |
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69 Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m²) or overweight (25≤BMI<30 kg/m²).(1) International guidelines in cardiology.(2-4) diabetes (5, 6) and cancer (7) recommend changing lifestyle related factors for management of overweight and obesity. These lifestyle recommendations (2-4, 7-10) are largely based on data from observational epidemiological studies in which obesity was associated with an increased risk of metabolic syndrome, diabetes, arthritis, heart disease and/or cancer. (11-16) However, observational studies do not provide reliable information on whether lifestyle interventions should be recommended in obese people, and several relevant questions remained unanswered: Do lifestyle interventions lead to weight reduction, if so, by how much, and is this maintained over time? What level of lifestyle intervention is needed, how long should these interventions be continued, and do lifestyle interventions which target weight reduction improve health and lower the mortality risk? The aim of this meta-analysis was to determine whether published randomised trials of lifestyle interventions for weight loss provide evidence on whether the dose of lifestyle intervention influences the effectiveness of longer term weight reduction, or mortality.

85 Methods

PRISMA guidelines on reporting systematic reviews and meta-analyses of studies were
used throughout the planning, conduct and interpretation of this meta-analysis. A review
protocol was designed, and is available in the supplementary text.

89 There was no patient or public Involvement in this study

90 Study Search and inclusion criteria

91 The full strategy is described in Supplementary document 1, the protocol. Searches of
92 MEDLINE, CENTRAL, Google and Science Direct databases alongside reference lists of

appropriate articles and meta-analyses were performed for any reports on randomized
clinical trials that assessed lifestyle intervention on weight loss published in Englishlanguage journals from 1980 to June 2018. Key words used in searches to identify studies
included "weight", "lifestyle", "hypocaloric", "diet", "mortality", "coronary", "heart" and
"cardiovascular". Articles retrieved using this search string were then limited to trials
including weight loss and non-weight loss arms, a trial duration (weight loss and
maintenance phase) ≥12 months, and mortality data by intervention group.

Eligible studies were randomised control studies longer than 1 year with ≥ 100 overweight and obese adults (BMI ≥ 25 kg/m2) participants randomised to an intentional weight-loss lifestyle intervention and had an appropriate control group. Studies were only included if the control group received normal care – which could include standard healthy lifestyle information – but had no specific advice to achieve weight loss. The intervention arm needed to have intent for weight loss, mainly through the promotion of a hypocaloric diet, and had to include ≥ 1 face to face intervention. Participants could be healthy or have established cardiovascular disease (CVD). Studies were excluded if both groups were prescribed specific diets (such as high-protein diets, OPTIFAST), included pharmacotherapy or surgery for weight loss or if the intervention was 'self- help'. Studies with >5% lost to follow up were also excluded to reduce the risk of bias.(17)

For mortality, eligible studies were required to report mortality data explicitly either in the CONSORT diagram, as an outcome measure or as an adverse event (studies reporting "no adverse events" was taken to mean that no deaths occurred, but studies reporting "no adverse events related to intervention" without specifying the nature of these adverse events were excluded). Studies also were required to present sufficient data in order for calculations of mean weight changes in kilograms.

 $\frac{16}{17}$ The search of these electronic databases to obtain suitable studies was carried out by two reviewers (NS, JB). Any queries arising around the suitability of a particular study for Page 7 of 53

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inclusion was resolved by discussion with all reviewers (NS, JB and RS). In some situations, multiple papers reporting on the same clinical trial were used if each individual paper did not provide all required data and qualitative information on the study. Methodological and appropriate guantitative data was extracted and compiled in an electronic database from all included studies on three separate occasions independently by two reviewers (NS, JB). Baseline data extracted included study sample size, mean age and BMI, duration of intervention and follow-up, and percentage of women. Each study's intervention was also categorised into levels of intensity depending on the number and frequency of dietary interventions. An 'individual session' was defined as an intervention delivered one to one by a dietician/lifestyle coach/physician. A 'face to face' intervention was delivered in person. 'Remote interventions' were those delivered by telephone, emails or web based programs. In one study which reported two interventions, but used the same control group, the face to face intervention, which was more intensive compared to the remote intervention, was used in the meta-analysis. (18) Follow-up data included mean weight or weight loss at each follow-up time after one year, and all-cause mortality. If relevant data was not presented in a study, the corresponding study authors were contacted. Questions arising during data extraction were resolved by consensus between reviewers (NS, JB and RS). Outcome measures are weight loss achieved at 1, 2 and 3 years, weight loss achieved at the end of study, intensity of intervention required to achieve weight loss and mortality. Weight loss at 1 year was the primary outcome. If not reported, the first weight recorded after the first year was used. (19-24)

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142 Grading the evidence

The grading of Recommendations Assessment, Development, and Evaluation (GRADE)
approach was used to assess the certainty of the evidence. (25) Evidence was graded as
high, moderate, low or very low quality. The included RCTs were graded as high-quality
evidence by default and downgraded based on the following criteria; risk of bias,
inconsistency, indirectness, imprecision and publication bias.

148 Statistical Analyses

The inverse-variance method was used to pool mean differences for weight in kilograms and odds ratio for mortality to yield an overall effect size with 95% confidence intervals. For studies where standard deviations (SD) or confidence intervals were not available despite contacting authors, the mean SD for all other studies was used. Standard error or confidence intervals were converted to standard deviation using standard statistical formulae presented in the Cochrane Handbook for Systematic Reviews of Interventions 2011. Each meta-analysis was assessed for heterogeneity by a Chi square test and I² statistic. A fixed effects model was used when heterogeneity was not present ($I^2 < 1\%$) and a random effects model was used when statistical heterogeneity $(l^2 \ge 1\%)$ was present. The meta-

analysis was also repeated using a fixed effects model to assess the effects of small studies
on results.(26) A p-value of <0.05 was considered statistically significant. Studies are
presented in Forest plots in order of statistical power. A weighted average for weight loss per

5 161 interventions was calculated.

For weight loss at 1 year and all-cause mortality, analysis was stratified by the mean baseline body mass index (BMI), the median number of interventions (≤ 28 ; >28 interventions), and whether intentions were frontloaded (< or \geq 75% interventions in first 6 months). For weight loss over the length of follow up, subgroup analysis was done for mean study BMI (25-29, 30-35 and >35), age (40-49, 50-60 and \geq 60) and number of interventions per year (≤ 6 , 7-12, 13-24, and \geq 25).

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| 2 3 | 160 | Sonaitivity analysis was undertaken to assess offects of studies that deviated significantly |
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| 4 | 168 | Sensitivity analysis was undertaken to assess effects of studies that deviated significantly |
| 5 6 | 169 | from the standard error of the total study result or studies where baseline values differed |
| 7 8 9 | 170 | significantly from the mean baseline. Funnel plots were used to assess for publication bias. |
| 10 11 | 171 | The statistical analyses were performed using RevMan software version 5.2 (The Nordic |
| 12 13 | 172 | Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed |
| 14 15 16 | 173 | guidelines suggested by Wang. (27) |
| 17 18 | 174 | A regression analysis evaluated the relationship between the number of interventions/study |
| 19 20 | 175 | and weight loss using Statistical Analysis Software (SAS). Intervention doses more than 3 |
| 21 22 | 176 | standard deviations above the mean were considered outliers, and were removed from the |
| 23 24 25 | 177 | analysis. (28) |
| 26 27 | 178 | standard deviations above the mean were considered outliers, and were removed from the analysis. (28) |
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Results

From a review of 5654 titles and abstracts, 31 randomised trials with a total of 20 563 participants met inclusion criteria. The most common reasons for excluding studies were duplicate reports, sample size <100, duration of follow-up <1 year, and no reporting of mortality (Figure 1). In one study, there was a factorial design where a control group was compared to diet alone, and exercise compared to exercise and diet. (18) These two comparisons are reported separately for a total of 32 studies. 70% of study participants had cardio-metabolic risk factors. No study was found in patients with established cardiovascular disease, although 14% of participants in the Look AHEAD trial had cardiac disease. (29)

Included studies are summarised in Table 1. Most studies were small and only four studies
had sample sizes > 1000 in each arm. (29-32) One study reported outcomes and weight
only at 6 years and this study is included only in the mortality analysis. (19) The Da Qing
study, (19) did not report summary measures of weight loss by randomised group, so also
could only be included in mortality analysis. The Look AHEAD trial (29) was both the largest
study and had the longest follow up. The GRADE scores for both the weight loss and
mortality metaanalysis were high.

³⁹ 196 Lifestyle interventions evaluated

As described in Table 2, there were large variations in types (individual or group), mode of (face to face or remote), timing and frequency of interventions between studies. In some studies, the number of interventions provided was dependent on an individual study participant's response to the weight loss program, so it was not possible to accurately describe the dose of intervention for every study. For these studies, the average number of interventions was extrapolated based on the assumption that there was a normal distribution of extra interventions within the study.

The median number of interventions during the first year was 28 (IQR 12 to 37). In most
 studies there were more interventions during the first 6 months, median 18 (IQR 10 to 24)

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| 2 3 4 | 206 | interventions. 14 studies reported intervention beyond 1 year and for these the median |
|----------------|-----|--|
| 5 6 | 207 | number of interventions in year 2 was 5 (IQR 4 to 12). Few studies reported weight |
| 7 8 9 | 208 | outcomes beyond 3 years. |
| 10 11 | 209 | Effect of lifestyle interventions on body weight |
| 12 13 | 210 | For all studies the average weight loss per lifestyle intervention session at one year |
| 14 15 | 211 | compared to controls was 0.13kg (95% CI 0.19, -0.07). Effects on body weight are shown in |
| 16 17 | 212 | Figure 2, Table 3 and Supplemental Figures in Supplemental document 2. 27 of the |
| 18 19 20 | 213 | included studies reported weight loss at one year, 12 at two years and 8 at three years. For |
| 20 21 22 | 214 | studies which did not report weight loss at 1 year, the first reported weight after 1 year was |
| 23 24 | 215 | used to assess the relationship with median number of interventions and total weight |
| 25 26 | 216 | loss.(20, 22, 24) |
| 27 28 29 | 217 | Weight loss was greater in the intervention group compared to the control group (3.63kg, |
| 29 30 31 | 218 | 95% CI 2.58,4.67 at 1 year. This difference decreased over time and at year 3 was 2.45kg |
| 32 33 34 | 219 | (95%CI 1.17, 3.73). Funnel plots do not suggest publication bias. |
| 35 36 | 220 | Weight loss for studies with more than the median of 28 interventions /year was 4.50kg (95% |
| 37 38 | 221 | CI 3.03, 5.97), and ≤28 interventions/year was 2.38 kg (95%CI 0.78, 3.98), p=0.001. Weight |
| 39 40 | 222 | loss is presented by the number of interventions/study in Table 3. The estimated difference |
| 41 42 | 223 | in weight loss between studies using the regression model was 0.6 kg (95% CI 0.23, 1.4) for |
| 43 44 45 | 224 | each additional 10 interventions. |
| 46 47 48 | 225 | Effects of lifestyle intervention on mortality |
| 49 50 | 226 | Effects on mortality are presented in Figure 3, Table 3 and Supplemental document 2. In |
| 51 52 | 227 | eight studies there were no deaths during follow up. For all studies combined there were |
| 53 54 | 228 | 593 deaths, during a weighted average follow-up of 9.2 years, equivalent to an average |
| 55 56 | 229 | mortality rate of 0.3%/year. Mortality was non-significantly lower in the intervention |
| 57 58 | 230 | compared to the control group, odds ratio 0.86 (95% CI 0.73, 1.02), p=0.09. The number of |
| 59 60 | 231 | interventions in the first year and weight loss achieved in the first year were not associated |

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with mortality (Table 3). There were too few deaths to confidently evaluate possible differences in the relationship between study characteristics and mortality (Table 3).

Importance of the Look AHEAD study

The Look AHEAD study (29) contributed 25% of people to the meta-analysis and accounted for 63% of deaths. This trial randomised 5145 overweight or obese patients with type 2 diabetes, 14% also had established heart disease, 60% were women and the mean age was 59 years. The lifestyle intervention included weekly face to face meetings for the first 6 months, meetings 3 times a month for the next 6 months and then monthly until the end of study. Patients were followed for median 9.6 years (interquartile range, 8.9 to 10.3). A clinically meaningful 5-10% weight loss was achieved. The hazard ratio for all-cause mortality was 0.85 (95%Cl 0.69, 1.04; p = 0.11). Estimated effects on mortality and body weight in the Look AHEAD trial (29) were similar to those observed in all other studies combined (Table 3). ez.e

Discussion

There are four important conclusions from this meta-analysis (Box1). First, most studies were conducted in people aged 50-60 with cardiometabolic risk factors (Table 3). There were few studies in the elderly or in those with established cardiovascular or other diseases. Second lifestyle interventions compared to 'usual' care result in a modest reduction in body weight, on average 3.63kg at one year, with about 2/3 of this sustained after 2-3 years. Weight loss was slightly greater in very obese and obese persons compared to overweight, but was still on average < 5% of body weight for all groups. Third, there was probably a dose response with greater weight loss with more frequent lifestyle interventions. Clinically meaningful >5% weight loss, as defined by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society, (33) was achieved with >28 interventions over one year, but not for shorter interventions. Fourth,

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258 lifestyle interventions were associated with a modest reduction in all-cause mortality, (point 259 estimate ~14%), but with wide confidence intervals. This estimate is similar to a previous 260 meta-analyses which reported that lifestyle interventions decreased all-cause mortality (RR 261 = 0.85; 95%CI: 0.73-1.00 and 0.82, 95% CI 0.71 to 0.95).(34, 35), but these meta-analyses 262 did not evaluate the importance of the intensity and duration of the lifestyle interventions.

In most studies there was a substantial effort for the lifestyle intervention group, with a median of 28 interventions over the first year. Comparison across studies suggests more interventions were associated with greater weight loss at one year, but no studies directly compared different intervention intensities or durations. There was limited data on the efficacy of shorter lifestyle interventions, or whether simple lifestyle advice from a health practitioner is effective. Most studies included relatively small numbers of participants, and lifestyle interventions varied markedly. It was not possible to confidently evaluate the impact of different types of lifestyle advice or the relative strengths of face to face compared to remote interventions.

This analysis provides insights on why obtaining reliable information on the impact of lifestyle
interventions on mortality is so difficult. The meta-analysis included randomised data from
over 20,000 patients with ~190,000 patient-years of follow-up. However the mortality rate
was only 0.3%/ year, and only three studies (29, 30, 36) reported more than 10 deaths.
There were also too few deaths in studies with fewer interventions, in healthy populations
and in people younger than 50 to reliably evaluate the effects in these groups. Modest
mortality benefits of sustained weight reduction may be expected to occur during longer
follow-up. In the Look AHEAD (29) study which followed patients for nearly 10 years, the
14% reduction in all-cause mortality was similar to all other studies combined, supporting the
conclusion that this mortality reduction is real. Although of borderline statistical significance,
this modest mortality benefit is consistent with observational studies which report that
bariatric surgery is associated with lower all-cause, cardiovascular and cancer-related

285 mortality.(37) However, compared to lifestyle interventions bariatric surgery results in much
286 larger and sustained reductions in body weight. (38)

Findings from this study are relevant to clinical practice guidelines on interventions for weight loss. Although lifestyle interventions are associated with lower body weight and a probable small reduction in mortality, there is only reliable evidence for very comprehensive programmes which include many interactions sustained over months. There is limited evidence that shorter and simpler interventions, more typical of usual clinical practice, have a clinically meaningful benefit.(39) Also we were unable to evaluate whether weight loss is maintained after cessation of the lifestyle intervention, because most studies did not report outcomes after the intervention stops. The efficacy of lifestyle programs in the 'real word' is likely to be less than for volunteers in clinical trials who are generally highly motivated. These observations are important to inform realistic expectations on weight loss with lifestyle interventions, which may be much less than 'expected' by many clinicians and patients.

300 Study limitations

Individual participant data was not available and this limits the ability to address several important questions. It is possible some individuals lose significant weight, while others lose none, but this could not be reliably evaluated from summary data. It was also not possible to evaluate the benefit of weight loss in subgroups of individuals who lost the most weight. It is not clear the degree to which weight loss is dependent on individual participant characteristics such as body mass index, gender, age and ethnicity. Most studies did not provide information on food consumed or exercise performed, and it was not possible to assess adherence to randomised treatments, or to compare different types of lifestyle intervention. It was not possible to compare the nature of the interventions and type of lifestyle advice given. Intensive lifestyle interventions have been reported to reduce

| 1 | | |
|----------------|-----|---|
| 2 3 4 | 311 | progression of diabetes and to be cost effective.(40) The current meta-analysis did not |
| 5 6 | 312 | assess other potential health benefits of weight loss such as reducing progression to |
| 7 8 | 313 | diabetes. |
| 9 10 11 | 314 | |
| 12 13 14 | 315 | Conclusion |
| 15 16 17 | 316 | Lifestyle programs with frequent patient interactions sustained over a year or more can |
| 18 19 | 317 | achieve clinically meaningful weight loss, and this may lower mortality during long term |
| 20 21 | 318 | follow-up. However the benefits of less frequent interventions over shorter durations in body |
| 22 23 | 319 | weight are more modest and long term benefits to mortality risk are uncertain. Because |
| 24 25 | 320 | there is limited data from randomised trials, it is uncertain whether lifestyle interventions for |
| 26 27 28 | 321 | obesity decrease mortality in persons with cancer, heart failure or ischaemic heart disease. |
| 29 30 31 | 322 | |
| 32 33 34 | 323 | Figure 1: Study flow chart |
| 35 36 37 | 324 | Figure 2: Effects of lifestyle intervention on weight loss at 1 year. |
| 38 39 | 325 | Figure 3: Effects of weight loss on mortality during a weighted average follow-up of 9.2 |
| 40 41 42 | 326 | years. There is no heterogeneity for all (I ² =0). |
| 43 44 45 | 327 | Supplementary document 1: Protocol (includes search strategy) |
| 46 47 48 | 328 | Supplementary document 2: Supplementary figures. |
| 49 50 | 329 | Patient consent: Not required. |
| 51 52 53 | 330 | Contributor statement: |
| 54 55 56 | 331 | NS, RS and JB: conception of study, adjudication inclusion of studies, draft version |
| 57 58 | 332 | manuscript. NS and JB: electronic database searches, data extraction, performed the |
| 59 60 | 333 | analysis. RS and JB wrote the subsequent and final versions of manuscript in consultation |

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- 334 with NS, JB: regression model, designed the figures and tables. All authors discussed the
- 335 results and commented on the manuscript.
- **Competing interests**: nil
- 337 Funding: Nil

 338 Data sharing statement No additional data available

Box 1 :Key message box

- An average 28 interventions (more than twice a month) in the first year achieved 3.63kg weight loss at one year. Interventions included seeing doctors, nurses, dieticians, nutritionist, and psychologists.
- Evidence that weight loss reduces mortality is from large, long term studies with frequent interventions in middle aged patients with cardiometabolic risk factors.
- The effectiveness of simple lifestyle advice by medical practitioners or a limited number of interventions to achieve sustained weight loss is uncertain.

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Table 1: Baseline characteristic of 31 studies included in mortality meta-analysis.

| 524 |
|-----|
| 525 |

| Name of Study | Target population | Sample | Women | Mean | Mean | Mean | Intervention | Follow- | Death |
|---------------|--------------------------------------|--------|----------|---------|---------|---------|--------------|------------|-------|
| | L | size | number | ВМІ | initial | age | duration | up | |
| | | N | (%) | (kg/m²) | weight | (years) | (years) | duration | |
| | | | 2 | | (kg) | | | (years) | |
| Summary | | 615 | 346 (56) | 32.5 | 87.2 | 53.8 | 2.39 | 2.49 | 19 |
| statistic | | | | 1- | | | | | |
| weighted mean | | | | 191 | i | | | | |
| | | | | 4 | 101 | | | | |
| ACHIEVE (41) | Overweight/obese with mental illness | 291 | 146 (50) | 36.3 | 102.7 | 45.3 | 1.5 | 1.5 | 5 |
| ADAPT (42) | Overweight/obese knee | 318 | 229 (72) | 34.3 | 93.8 | 68.5 | 1.5 | 1.5 | 45 |
| | osteoarthritic older | | | | | | | (8 for | |
| | persons | | | | | | | mortality) | |
| ALIFE@WORK | Overweight/obese | 1386 | 457 (33) | 29.6 | 92.1 | 43 | 0.5 | 2 | 3 |
| (20) | | | | | | | | | |

| BE-WELL(21) | Obese asthmatics | 330 | 234 (71) | 37.5 | 104.2 | 47.6 | 1 | 1 | 0 |
|-----------------|---------------------------|------|-----------|------------|-------|------|------|------|----|
| CLIP (43) | Overweight/obese older | 288 | 193 (67) | 32.8 | 91.9 | 67.1 | 1.5 | 1.5 | 3 |
| | with limited mobility and | | | | | | | | |
| | cardiovascular disease | | | | | | | | |
| | or dysfunction | 0 | | | | | | | |
| Da Qing (19) | Impaired glucose | 530 | 244 (46) | 25.8 | _ | 45 | 6 | 6 | 11 |
| | tolerance | | | | | | | | |
| DPP (31) | Overweight/obese with | 2161 | 1491 (69) | 34.1 | 94.2 | 50.4 | 2.8 | 2.8 | 8 |
| | elevated fasting | | | <u>(6)</u> | • | | | | |
| | glucose | | | | 0 | | | | |
| EDIPS-Newcastle | Overweight/obese with | 102 | 61 (60) | 33.8 | 92 | 57.1 | 3.1 | 3.1 | 3 |
| (44) | impaired glucose | | | | | 0h | | | |
| | tolerance | | | | | | | | |
| E-LITE (45) | Overweight/obese | 241 | 113 (47) | 32 | 93.8 | 52.9 | 1.25 | 1.25 | 0 |
| | persons with pre- | | | | | | | | |
| | diabetes or metabolic | | | | | | | | |
| | syndrome | | | | | | | | |

| HEALTH TRACK | Overweight and obese | 377 | 279 (74) | 32 | 125.2 | 45 | 1 | 1 | 0 |
|--------------|------------------------|-----|-----------|------|-------|------|-----|-----|---|
| 32) | Australians | | | | | | | | |
| HCP (22) | Hypertension | 118 | 42 (36) | - | 77 | 56 | 4 | 4 | 3 |
| DEA (46) | Overweight/obese with | 454 | 327 (72) | 33.6 | 93 | 66 | 1.5 | 1.5 | 0 |
| | osteoarthritis knee | 0 | | | | | | | |
| DPP-1 (47) | Indian and Pakistani | 269 | 62 (23) | 26 | _ | 45.6 | 2.5 | 2.5 | 2 |
| | origin with impaired | | 6 | | | | | | |
| | glucose tolerance | | | k | | | | | |
| EAN (23) | Overweight/obese | 100 | 100 (100) | 33.1 | 87.5 | 59 | 0.5 | 1 | 0 |
| | women with treated | | | | 0 | | | | |
| | breast cancer | | | | -4 | | | | |
| -ISA (48) | Overweight/obese post- | 338 | 338 (100) | 31.3 | 82 | 61 | 2 | 2 | 2 |
| | menopausal women | | | | | | | | |
| | with breast cancer | | | | | | | | |
| | history who are | | | | | | | | |
| | currently taking | | | | | | | | |
| | letrozole | | | | | | | | |

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| Look AHEAD (29) | Overweight/obese with | 5145 | 3087 (60) | 36 | 101 | 58.8 | 9.6 | 9.6 | 376 |
|-----------------|------------------------|------|-----------|------|-------|--------|-----|-----|-----|
| | type 2 diabetes | | | | | | | | |
| NEW (49) | Overweight/obese post- | 439 | 439 (100) | 30.9 | 83.6 | 58 | 1 | 1 | 1 |
| | menopausal women | | | | | | | | |
| ORBIT(28) | Obese African- | 213 | 213(100) | 39.2 | 104.9 | 46 | 1.5 | 1.5 | 1 |
| | American women | Or, | | | | | | | |
| Patrick (50) | Overweight/obese men | 441 | 0 (0) | 34.2 | 104.7 | 43.9 | 1 | 1 | 2 |
| PODOSA (51) | Indian or Pakistani- | 171 | 92 (54) | 30.5 | 80.3 | 52.5 | 3 | 3 | 1 |
| | origin with impaired | | | ro. | | | | | |
| | glucose tolerance test | | | | | | | | |
| POWER (18) | Obese with | 276 | 176 (64) | 36.6 | 103.4 | 54 | 2 | 2 | 0 |
| | cardiovascular risk | | | | | 0. | | | |
| | factors | | | | | \sim | 1. | | |
| SLIM (52) | Impaired glucose | 147 | 72 (49) | 29.8 | 85.5 | 56.9 | 4.1 | 4.1 | 1 |
| | tolerance | | | | | | | | |
| STRIDE (53) | Overweight/obese | 200 | 144 (72) | 38.3 | 107.7 | 47.2 | 1 | 1 | 2 |
| | taking antipsychotic | | | | | | | | |

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| | agents | | | | | | | | |
|--------------------------|--|------|-----------|------|-------|------|-----|-------------------|-----|
| Swedish Bjorknas (54) | Metabolic syndrome | 145 | 83 (57) | 29.8 | 85.8 | 54.4 | 3 | 3 | 0 |
| . , | - | | | | | | | | |
| TAIM (55) | Overweight/obese hypertensive | 200 | 102 (51) | - | 87.7 | 48.3 | 4.5 | 4.5 | 2 |
| TOHP I (56) | Normal to high blood | 564 | 180(32) | 29.5 | 89.8 | 42.8 | 1.5 | 1.5 | 2 |
| | pressure | | | | | | | | |
| TOHP II (57) | Overweight/obese | 2382 | 810 (34) | 30.9 | 93.6 | 43.6 | 3 | 3 | 12 |
| | persons that are normo- or hypertensive | | | | | | | | |
| TONE (30) | Overweight/obese | 585 | 304 (52) | 31.2 | 87.8 | 65.5 | 2.5 | 2.5 | 101 |
| | elderly hypertensive | | | | | 00 | 1. | (12 mortality) | |
| Transfer (0.4) | | 440 | | 00.0 | 77.0 | 04.5 | | | |
| Trento (24) | type 2 diabetes | 112 | 50 (45) | 28.8 | 77.8 | 61.5 | 2 | 2 | 4 |
| Villareal (58) | Older obese | 107 | 67 (63) | 37.2 | 100.8 | 69.7 | 1 | 1 | 0 |
| WOMAN (59) | Overweight/obese post- menopausal women | 508 | 508 (100) | 30.8 | 81.7 | 57 | 3 | 4 | 3 |

Table 2: Frequency and mode of contact of lifestyle intervention.

529 The type of contact refers to whether trial participants received individual (I) or group (G), and mode of contact outlines whether participants

530 received interventions remotely by internet, email or over the phone (R) or face to face (F).

| Study name | Type of contact | Mode of contact | Number of dietary | Number of dietary | Proportion of first |
|-----------------|-----------------------|---------------------------|-------------------|-------------------|-----------------------|
| Year Published | | | interventions | interventions | year interventions in |
| | | 20 | in year 1 | in year 2 | first 6 months (%) |
| | Individual= 7 | Face to face =11 | | | |
| All studies | Group only = 5 | Remote = 3 | 27.5 | 3.96 | 66 |
| | Group + individual=19 | Face to face + remote= 17 | | | |
| ACHIEVE (41) | G,I | F | 30 | x | 80 |
| ADAPT (42) | G,I | F,R | 33 | x | 64 |
| ALIFE@WORK (20) | I | R | 10 | 0 | 100 |
| BE-WELL (21) | G,I | F,R | 18 | X | 83 |
| CLIP (43) | G,I | F,R | 36 | x | 67 |
| Da Qing (19) | G,I | F | 16 | 4 | 80 |

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| DPP (31) | G, I | F,R | 22 | 12 | 73 |
|----------------------|------|-----|-----|----|-----|
| EDIPS-Newcastle (44) | G,I | F | 8 | х | 75 |
| E-LITE (45) | G,I | F,R | 38 | x | 61 |
| HEALTH TRACK (32) | 4 | F,R | 6 | 6 | 50 |
| HCP (22) | | F | 12 | 4 | 75 |
| IDEA (46) | G,I | F,R | 39 | x | 62 |
| IDPP-1 (47) | I | F,R | 15 | 14 | 53 |
| LEAN (23) | I | F,R | 11 | X | 100 |
| LISA (48) | I | R | 31 | 4 | 87 |
| Look AHEAD (29) | G,I | F,R | 42 | 24 | 57 |
| NEW (49) | G,I | F,R | 32 | x | 63 |
| ORBIT (28) | G,I | F,R | 110 | x | 56 |
| Patrick (50) | I | R | 52 | X | 50 |
| PODOSA (51) | G | F | 7 | 4 | 71 |

| 28 | |
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| POWER (18) | G,I | F | 39 | 18 | 77 |
|-----------------------|-----------------|----------------------------------|---------------------------|----|----|
| SLIM (52) | G,I | F,R | 5 | 4 | 60 |
| STRIDE (53) | G,I | F,R | 36 | x | 67 |
| Swedish Bjorknas (54) | G | F | 12 | 5 | 58 |
| TAIM (55) | G,I | F | 17 | 8 | 71 |
| TOHP I (56) | G,I | F,R | 26 | X | 77 |
| TOHP II (57) | G,I | F,R | 28 | X | 68 |
| TONE (30) | G,I | F | 28 | 12 | 71 |
| Trento (24) | G | F | 4 | 4 | 50 |
| Villareal (58) | G | F | 52 | x | 50 |
| WOMAN (59) | G | F | 40 | 12 | 50 |
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Table 3: Association with intervention intensity with weight loss achieved and mortality.

| | | Weight lo | SS | | | Mortality | |
|--|------------------------|----------------------|--|-----------|----------------------|---|--|
| | (from b | aseline and fi | nal reported)* | | | | |
| Characteristic | N studies [#] | Weight of studies | Mean difference Random effect model (kg) (95%CI) | N studies | Weight of studies | total deaths /total patients (mortality rate) | Odds ratio Fixed effect model (95%Cl) |
| Number of Interventions per year | | | | en. | | | |
| ≤ 6 | 3 | 9 % | 0.84 [0.28, 1.40] | 3 | 1% | 5/510 (1.0%) | 1.45 [0.22, 9.40] |
| 7-12 | 6 | 17% | 2.04 [0.84,3.24] | 6 | 2% | 10/2022 (0.5%) | 1.34 [0.35, 5.16] |
| 13-24 | 4 | 15% | 2.46 [0.67,5.59] | 6 | 4% | 23/3490 (0.7%) | 1.20 [0.49, 2.96] |

| ≥ 25 | 17 | 60% | 3.53 | 17 | 93% | 555/13578 | 0.84 |
|------------------------|----|-----|---------------|----|-----|-----------|--------------|
| | | | [2.92, 4.13] | | | (4.1%) | [0.71, 1.00] |
| BMI* | | | | | | | |
| 25-29 | 6 | 19% | 1.37 | 8 | 11% | 23/3890 | 1.58 |
| | | | [-0.09, 2.82] | | | (0.6%) | [0.64, 3.90] |
| 30- 35 | 16 | 48% | 3.09 | 14 | 22% | 136/8374 | 0.93 |
| | | | [2.11, 4.06] | | | (1.6%) | [0.65, 1.33] |
| > 35 | 6 | 23% | 4.04 | 6 | 67% | 384/6370 | 0.86 |
| | | | [2.47, 5.61] | | | (6%) | [0.69, 1.05] |
| Comorbidities | | | V | 0 | | | |
| Cardiometabolic risk | 16 | 56% | 2.86 | 18 | 90% | 529/14311 | 0.90 |
| factor present | | | [2.10, 3.63] | | | (3.7%) | [0.75, 1.08] |
| Healthy population | 8 | 29% | 3.03 | 8 | 3% | 12/3458 | 1.23 |
| | | | [1.53, 4.52] | | | (0.3%) | [0.39, 3.89] |
| Other (arthritis, | 4 | 9% | 3.35 | 4 | 2% | 7 /1275 | 0.74 |
| asthma mental illness) | | | [2.18, 4.52] | | | (0.6%) | [0.16, 3.37] |

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| Cancer | 2 | 6% | 2.70 | 2 | 6% | 2/438 | 0.98 |
|-------------------|----|------|--------------|-----|------|-----------|-------------|
| | | | [1.57, 3.83] | | | (0.5%) | [0.06, 15.7 |
| Age | | | | | | | |
| 40-49 | 12 | 47% | 2.29 | 14 | 9% | 50/9868 | 1.28 |
| | | | [0.97, 3.61] | | | (0.5%) | [0.71, 2.30 |
| 50-59 | 12 | 39% | 3.27 | 12 | 69% | 396/9691 | 0.84 |
| | | | [2.38, 4.15] | | | (3.8%) | [0.69, 1.04 |
| >60 | 7 | 14% | 4.50 | 7 | 22% | 155/2202 | 0.78 |
| | | | [2.76, 6.25] | | | (7.0%) | [0.55, 1.10 |
| | | | | -1/ | | | |
| Look AHEAD | 1 | 4% | 3.40 | 1 | 65% | 376/5145 | 0.85 |
| | | | [3.30, 3.50] | | | (7.3%) | [0.69, 1.05 |
| All other studies | 29 | 96% | 3.01 | 32 | 35% | 207/14455 | 0.88 |
| | | | [2.23, 3.79] | | | (1.4%) | [0.66, 1.17 |
| Total | 30 | 100% | 2.95 | 32 | 100% | 593/19463 | 0.86 |
| | | | [2.35, 3.55] | | | (3.1%) | [0.73, 1.02 |

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536 *TAIM and HCP excluded for BMI

- 537 # Da Quing excluded for all weight loss
- 538 + P<0.0001 for all

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Additional records identified through

manual searching of reference lists

(n = 86)

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Records excluded after

review of titles and abstracts

(n = 5484)

duplicate reports (n=22)

not reporting deaths (n=34)

not reporting deaths by

randomisation arm (n=6)

insufficient duration (n=17)

insufficient data (n=1)

not adults (n=6)

not in English (n=2)

insufficient sample size (n=20)

ineligible control group (n=14)

not randomised controlled trial

initial weight-loss phase for all (n=5) pharmacotherapy (n=4)

Records identified through

database searching

(n = 8447)

Records after duplicates removed

(n = 5654)

Records screened

(n = 5654)

Full-text articles assessed

for eligibility

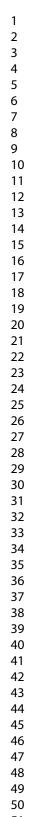
(n = 170)

31 Individual studies

(1 studies had separate

arms that can not be

combined so in total 32 studies included)







Study flow chart

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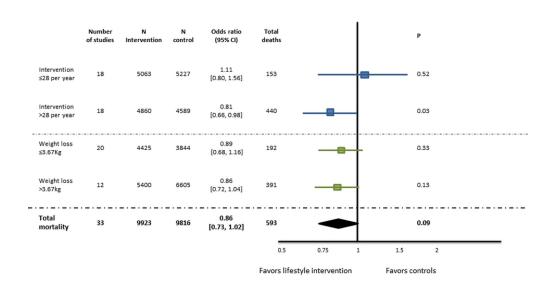
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Favors controls

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| $\frac{Number}{studies} \frac{N}{intervention} \frac{N}{control} \frac{Mean difference in Kg}{(95% CI)}$ Al Al Al Al Al Cossig(m ²) 4 586 539 -2.23 [-4.43, -0.03] Al Al Cossig(m ²) 15 4809 4543 -3.60 [-4.85, -2.36] Al Al Al Cossig(m ²) 15 4809 4543 -3.60 [-4.85, -2.36] Al Al Al Al Cossig(m ²) 15 4809 4543 -3.60 [-4.85, -2.36] Al Al Al Al Al Al Cossig(m ²) 15 4809 4543 -3.60 [-4.85, -2.36] Al Al Al Al Al Al Al Al Al Al |
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Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I2=0).

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

Study Protocol

JI **Navneet Singh Jocelyne Benatar Ralph Stewart**

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 (BMI \geq 30 kg/m2) or overweight (25 \leq BMI<30 kg/m2). ¹ 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,² blood pressure, ³ and some cancers,⁴⁻⁶ 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, ⁷ diabetes,⁸ risk factors for coronary heart disease ⁹ and cancer. ⁴⁻⁶ 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, ¹⁰⁻¹² diabetes ^{13, 14} and as cancer guidelines¹⁵ 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-analysis¹⁶ 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 <u>Search Criteria</u>

 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≥25kg/m²)
- 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 16th 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 metaanalyses 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 metaanalysis.

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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Figure 1a: Weight loss at 1 year

| | Lifestyle | | | | ontrol | | | Mean Difference | Mean Difference |
|---------------------------|-----------|------|-------|--------|--------|-------|--------|-----------------------|--------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 1.9% | -3.85 [-9.40, 1.70] | |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | | 150 | 2.4% | -7.95 [-12.45, -3.45] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 3.2% | -2.16 [-5.01, 0.69] | |
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 3.4% | -3.50 [-6.03, -0.97] | <u> </u> |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 3.4% | -2.99 [-5.50, -0.48] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 3.4% | -2.31 [-4.76, 0.14] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 3.5% | -6.55 [-8.84, -4.26] | <u> </u> |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 3.5% | -1.90 [-4.12, 0.32] | |
| ACHIEVE 2013 | -2.8 | 7.96 | 144 | -0.4 | 9.28 | 147 | 3.6% | -2.40 [-4.39, -0.41] | |
| CLIP 2011 | -4.8 | 7.5 | 93 | -1.4 | 5.1 | 97 | 3.7% | -3.40 [-5.23, -1.57] | <u> </u> |
| ORBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 3.7% | -2.77 [-4.54, -1.00] | _ |
| POWER (face to face) 2011 | -5.8 | 8.22 | 139 | -1.1 | 5.87 | 138 | 3.8% | -4.70 [-6.38, -3.02] | _ — |
| Villareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 3.8% | -8.83 [-10.39, -7.28] | <u> </u> |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 3.9% | -3.40 [-4.81, -1.99] | <u> </u> |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 4.0% | -1.86 [-3.09, -0.63] | |
| LISA 2014 | -4.5 | 5.4 | 171 | -0.6 | 5.7 | 167 | 4.0% | -3.90 [-5.08, -2.72] | <u> </u> |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 4.0% | -1.30 [-2.41, -0.19] | |
| WOMAN2011 | -7.8 | 7.1 | 253 | -1.6 | 5.5 | 255 | 4.0% | -6.20 [-7.31, -5.09] | |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 4.0% | -3.00 [-3.98, -2.02] | |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 4.1% | -0.81 [-1.73, 0.11] | |
| TOHP 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 4.1% | -3.90 [-4.74, -3.06] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 4.1% | -0.70 [-1.53, 0.13] | |
| TONE 1998 | -4.73 | 4.67 | 294 | -1.14 | 3.65 | 291 | 4.1% | -3.59 [-4.27, -2.91] | - |
| Look AHEAD 2013 | -9.2 | 10.2 | 2570 | -1.2 | 10.3 | 2575 | 4.1% | -8.00 [-8.56, -7.44] | + |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 4.1% | -0.40 [-0.89, 0.09] | |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 4.2% | -6.40 [-6.80, -6.00] | + |
| TOHP II 1997 | -2.1 | 5.7 | 1192 | 0.55 | 4.25 | 1190 | 4.2% | -2.65 [-3.05, -2.25] | + |
| Total (95% CI) | | | 8380 | | | 8108 | 100.0% | -3.63 [-4.67, -2.58] | ▲ |

Test for overall effect: Z = 6.81 (P < 0.00001)

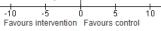


Figure 1b : Weight loss at 1 year- funnel plot

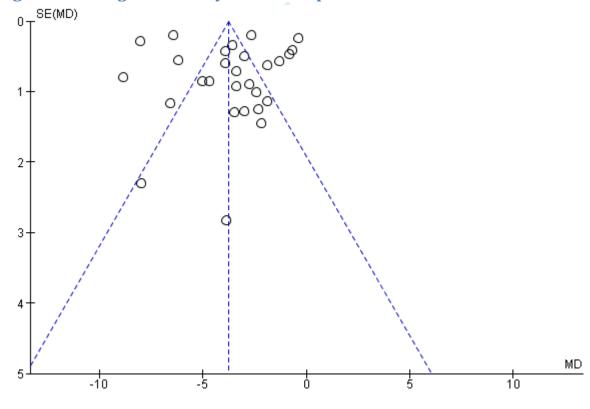


Figure 2a: Weight loss at 2 years

| 0 | 0 | | | | | | | | |
|---|---------------|----------|----------|-----------------------|---------|-------|--------|----------------------|--------------------------------------|
| | Lifestyle | intervei | ntion | C | Control | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 2.9% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -3.15 | 14.9 | 71 | 0.6 | 18.3 | 74 | 4.3% | -3.75 [-9.17, 1.67] | |
| POWER (face to face) 2011 | -5.1 | 8.83 | 138 | -0.8 | 8.22 | 138 | 8.3% | -4.30 [-6.31, -2.29] | |
| SLIM 2011 | -0.85 | 4.34 | 74 | -0.76 | 3.26 | 73 | 9.1% | -0.09 [-1.33, 1.15] | + |
| LISA 2014 | -3.1 | 6.2 | 171 | -0.3 | 5.3 | 167 | 9.1% | -2.80 [-4.03, -1.57] | |
| PODOSA 2014 | -0.78 | 3.43 | 85 | 0.13 | 3.24 | 86 | 9.3% | -0.91 [-1.91, 0.09] | |
| TAIM 1993 | -2.2 | 3.25 | 100 | -0.4 | 3.25 | 100 | 9.4% | -1.80 [-2.70, -0.90] | + |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 9.4% | -0.63 [-1.48, 0.22] | * |
| TONE 1998 | -3.83 | 5.16 | 294 | -0.468 | 3.92 | 291 | 9.5% | -3.36 [-4.10, -2.62] | + |
| Look AHEAD 2013 | -7.1 | 10.2 | 2570 | -1.4 | 10.3 | 2575 | 9.6% | -5.70 [-6.26, -5.14] | • |
| IDPP-1 2006 | 0.3 | 1.62 | 133 | 0.65 | 2.9 | 136 | 9.6% | -0.35 [-0.91, 0.21] | + |
| DPP2002 | -5.4 | 5.48 | 1079 | 0 | 0.997 | 1082 | 9.6% | -5.40 [-5.73, -5.07] | • |
| Total (95% CI) | | | 5697 | | | 5238 | 100.0% | -2.52 [-4.02, -1.01] | • |
| Heterogeneity: Tau ² = 6.07; (| | | (P < 0.0 | 0001); I ^z | = 97% | | | - | -20 -10 0 10 20 |
| Test for overall effect: Z = 3.2 | 8 (P = 0.001) |) | | | | | | | Favours intervention Favours control |



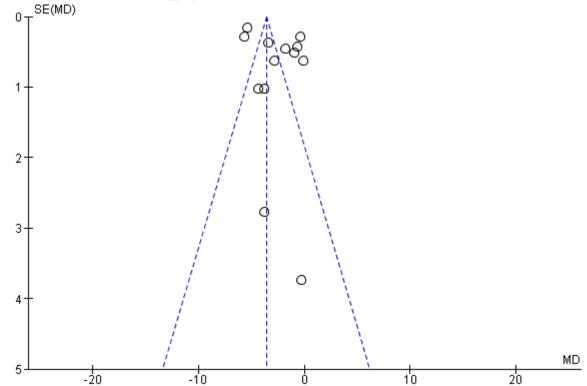


Figure 3a: Weight loss at 3 years

| 0 | 0 | | | | | | | | |
|--|--------------------------|------------|----------|---------|--------------|-------|--------|----------------------|---|
| | Lifestyle | e interven | tion | С | ontrol | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Swedish Bjorknas 2009 | -2.5 | 14.7 | 71 | 1.4 | 18.2 | 74 | 4.1% | -3.90 [-9.27, 1.47] | |
| SLIM 2011 | -1.08 | 4.3 | 74 | 0.16 | 4.91 | 73 | 12.3% | -1.24 [-2.73, 0.25] | |
| TAIM 1993 | -2.3 | 4.69 | 100 | -0.1 | 4.69 | 100 | 12.8% | -2.20 [-3.50, -0.90] | _ |
| PODOSA 2014 | -1.1 | 4.45 | 85 | 0.5 | 3.53 | 86 | 13.1% | -1.60 [-2.80, -0.40] | |
| IDPP-1 2006 | 0.35 | 1.89 | 133 | 0.8 | 3.57 | 136 | 14.2% | -0.45 [-1.13, 0.23] | -=+ |
| Look AHEAD 2013 | -5.8 | 10.2 | 2570 | -1.4 | 10.3 | 2575 | 14.4% | -4.40 [-4.96, -3.84] | - |
| TOHP 1997 | -0.25 | 5.7 | 1192 | 1.75 | 5.25 | 1190 | 14.5% | -2.00 [-2.44, -1.56] | + |
| DPP2002 | -4.1 | 5.41 | 1079 | 0.4 | 3.99 | 1082 | 14.6% | -4.50 [-4.90, -4.10] | + |
| Total (95% CI) | | | 5304 | | | 5316 | 100.0% | -2.45 [-3.73, -1.17] | ◆ |
| Heterogeneity: Tau ² = 2.89 | 3; Chi ² = 16 | 3.45, df= | 7 (P < 0 | 0.00001 |); $ ^2 = 9$ | 36% | | | |
| Test for overall effect: Z = 3 | | • | • | | | | | | -10 -5 0 5 10 Favours intervention Favours control |
| | | | | | | | | | |

BMJ Open

Figure 3b: Weight loss at 3 years- funnel plot

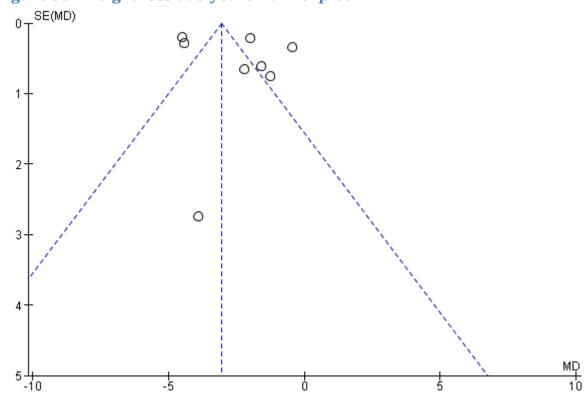


Figure 4a: Weight loss achieved by end of study

| | - | e interver | | | Control | | | Mean Difference | Mean Difference |
|---|-------|------------|----------|-------------------|---------|------|--------|-----------------------|--------------------|
| Study or Subgroup | Mean | SD | Total | Mean | | | - | IV, Random, 95% CI | IV, Random, 95% CI |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 0.6% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -2.5 | 14.7 | 71 | 1.4 | 18.2 | 74 | 1.0% | -3.90 [-9.27, 1.47] | |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | 23.4 | 150 | 1.3% | -7.95 [-12.45, -3.45] | • |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 2.2% | -2.16 [-5.01, 0.69] | |
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 2.5% | -3.50 [-6.03, -0.97] | |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 2.5% | -2.99 [-5.50, -0.48] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 2.6% | -2.31 [-4.76, 0.14] | |
| NEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 2.7% | -6.55 [-8.84, -4.26] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 2.8% | -1.90 [-4.12, 0.32] | |
| POWER (face to face) 2011 | -5.1 | 8.83 | 138 | -0.8 | 8.22 | 138 | 3.0% | -4.30 [-6.31, -2.29] | |
| ACHIEVE 2013 | -3.4 | 7.6944 | 137 | -0.2 | 9.0416 | 142 | 3.1% | -3.20 [-5.17, -1.23] | — <u> </u> |
| CLIP 2011 | -4.8 | 7.5 | 93 | -1.4 | 5.1 | 97 | 3.2% | -3.40 [-5.23, -1.57] | _ - |
| ORBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 3.3% | -2.77 [-4.54, -1.00] | _ |
| HCP 1987 | -1.8 | 5.1 | 78 | 2 | 3.5 | 40 | 3.5% | -3.80 [-5.37, -2.23] | |
| Villareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 3.5% | -8.83 [-10.39, -7.28] | _ |
| ADAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 3.6% | -3.40 [-4.81, -1.99] | |
| TAIM 1993 | -1 | 4.69 | 100 | 1 | 4.69 | 100 | 3.7% | -2.00 [-3.30, -0.70] | |
| LISA 2014 | -3.1 | 6.2 | 171 | -0.3 | 5.3 | 167 | 3.8% | -2.80 [-4.03, -1.57] | |
| PODOSA 2014 | -1.1 | 4.45 | 85 | 0.5 | 3.53 | 86 | 3.8% | -1.60 [-2.80, -0.40] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 3.9% | -1.30 [-2.41, -0.19] | |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 4.2% | -0.63 [-1.48, 0.22] | -+ |
| TOHP 1 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 4.2% | -3.90 [-4.74, -3.06] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 4.2% | -0.70 [-1.53, 0.13] | |
| TONE 2011 | -4.4 | 4.8 | 259 | -0.8 | 3.7 | 245 | 4.3% | -3.60 [-4.35, -2.85] | - |
| IDPP-1 2006 | 0.35 | 1.89 | 133 | 0.8 | 3.57 | 136 | 4.3% | -0.45 [-1.13, 0.23] | -+- |
| SLIM 2011 | -1.09 | 2 | 74 | -0.4 | 2 | 73 | 4.3% | -0.69 [-1.34, -0.04] | - |
| WOMAN2011 | -2.9 | 3 | 253 | -0.3 | 3 | 255 | 4.4% | -2.60 [-3.12, -2.08] | + |
| TOHP II 1997 | -0.25 | 5.7 | 1192 | 1.75 | | 1190 | 4.4% | -2.00 [-2.44, -1.56] | + |
| DPP2002 | -5.4 | 5.48 | 1079 | 0 | 0.997 | | 4.5% | -5.40 [-5.73, -5.07] | + |
| Look AHEAD 2013 | -3.9 | 1.9 | 2570 | -0.5 | | 2575 | 4.5% | -3.40 [-3.50, -3.30] | • |
| Total (95% CI) | | | 9397 | | | 8613 | 100.0% | -2.95 [-3.55, -2.35] | • |
| Heterogeneity: Tau ^z = 2.06; CH Test for overall effect: Z = 9.64 | | • | (P < 0.0 | 0001); I r | = 94% | | | | -10 -5 0 5 10 |

Figure 4b: Weight loss achieved by end of study- funnel plots

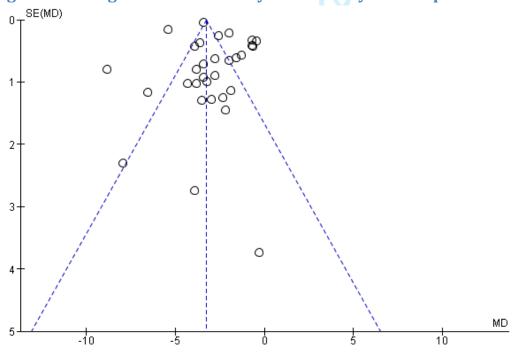


Figure 5a: Weight loss ≤28 interventions/year

| 0 | 0 | | | | | | | 15 | |
|--|--------------|------------|---------|--------|----------|-------|--------|----------------------|--|
| | Lifestyle | e interven | ition | С | ontrol | | | Mean Difference | Mean Difference |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| Trento 2001 | -1.4 | 18.7 | 56 | -1.1 | 20.7 | 56 | 3.0% | -0.30 [-7.61, 7.01] | |
| Swedish Bjorknas 2009 | -3.05 | 15.3 | 71 | 0.8 | 18.7 | 74 | 4.1% | -3.85 [-9.40, 1.70] | |
| LEAN 2016 | -5.96 | 9.06 | 67 | -3.8 | 5.42 | 33 | 6.5% | -2.16 [-5.01, 0.69] | |
| EDIPS-Newcastle 2009 | -2.3 | 6.31 | 51 | 0.01 | 6.31 | 51 | 6.9% | -2.31 [-4.76, 0.14] | |
| BE-WELL 2015 | -4 | 10.3 | 165 | -2.1 | 10.3 | 165 | 7.1% | -1.90 [-4.12, 0.32] | |
| HCP 1987 | -1.8 | 5.1 | 78 | 2 | 3.5 | 40 | 7.7% | -3.80 [-5.37, -2.23] | _ — |
| SLIM 2011 | -2.47 | 3.69 | 74 | -0.61 | 3.92 | 73 | 7.9% | -1.86 [-3.09, -0.63] | |
| HEALTH TRACK | -5.3 | 4.5 | 125 | -4 | 4.5 | 126 | 8.0% | -1.30 [-2.41, -0.19] | |
| TAIM 1993 | -3.7 | 3.52 | 100 | -0.7 | 3.52 | 100 | 8.0% | -3.00 [-3.98, -2.02] | |
| PODOSA 2014 | -1.05 | 3.13 | 85 | -0.24 | 3.03 | 86 | 8.1% | -0.81 [-1.73, 0.11] | |
| ALIFE@WORK 2011 | -1.68 | 6.32 | 926 | -1.05 | 8.21 | 460 | 8.1% | -0.63 [-1.48, 0.22] | |
| TOHP 1 1992 | -3.83 | 6.12 | 308 | 0.07 | 4.01 | 256 | 8.1% | -3.90 [-4.74, -3.06] | |
| IDPP-1 2006 | 0.2 | 1.08 | 133 | 0.6 | 2.68 | 136 | 8.2% | -0.40 [-0.89, 0.09] | |
| DPP2002 | -6.8 | 5.48 | 1079 | -0.4 | 3.99 | 1082 | 8.2% | -6.40 [-6.80, -6.00] | + |
| Total (95% CI) | | | 3318 | | | 2738 | 100.0% | -2.38 [-3.98, -0.78] | ◆ |
| Heterogeneity: Tau ² = 8.01 | ; Chi² = 45 | 0.59, df= | 13 (P < | 0.0000 | 1); l² = | 97% | | - | |
| Test for overall effect: Z = 2 | 2.92 (P = 0. | 003) | | | | | | | Favours [experimental] Favours [control] |
| | | | | | | | | | r avours [experimental] i avours [control] |

Figure 5b: Weight loss >28 interventions/year

| | Lifestyle | interve | ntion | C | ontrol | | | Mean Difference | Mean Difference |
|---|-----------|---------|----------|-----------|--------|-------|--------|-----------------------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| IDEA 2013 | -9.75 | 22.2 | 304 | -1.8 | 23.4 | 150 | 4.2% | | (´ |
| CLIP 2011 | -7.1 | 15.8 | 93 | -0.849 | 14.7 | 97 | 4.4% | -6.25 [-10.59, -1.91] | (|
| STRIDE 2015 | -4.8 | 9.11 | 104 | -1.3 | 9.11 | 96 | 5.8% | -3.50 [-6.03, -0.97] | _ |
| E-LITE 2013 | -5.39 | 8.08 | 79 | -2.4 | 8.1 | 81 | 5.9% | -2.99 [-5.50, -0.48] | |
| JEW 2012 | -8 | 12 | 235 | -1.45 | 12.4 | 204 | 6.0% | -6.55 [-8.84, -4.26] | |
| CHIEVE 2013 | -2.8 | 7.96 | 137 | -0.4 | 9.28 | 142 | 6.2% | -2.40 [-4.43, -0.37] | |
| DRBIT 2010 | -2.26 | 7.42 | 107 | 0.51 | 5.69 | 106 | 6.4% | -2.77 [-4.54, -1.00] | |
| OWER (face to face) 2011 | -5.8 | 8.22 | 138 | -1.1 | 5.87 | 138 | 6.5% | -4.70 [-6.39, -3.01] | - |
| /illareal 2011 | -9.13 | 4.63 | 54 | -0.296 | 3.52 | 53 | 6.5% | -8.83 [-10.39, -7.28] | |
| DAPT 2010 | -4.8 | 7.5 | 159 | -1.4 | 5.1 | 159 | 6.6% | -3.40 [-4.81, -1.99] | |
| JSA 2014 | -4.5 | 5.4 | 171 | -0.6 | 5.7 | 167 | 6.8% | -3.90 [-5.08, -2.72] | - |
| VOMAN2011 | -7.8 | 7.1 | 253 | -1.6 | 5.5 | 255 | 6.8% | -6.20 [-7.31, -5.09] | |
| Patrick 2011 | -0.9 | 4.43 | 224 | -0.2 | 4.43 | 217 | 6.9% | -0.70 [-1.53, 0.13] | - |
| FONE 1998 | -4.4 | 4.8 | 259 | -0.8 | 3.7 | 245 | 6.9% | -3.60 [-4.35, -2.85] | + |
| ook AHEAD 2013. | -9.2 | 10.2 | 2570 | -1.2 | 10.3 | 2575 | 7.0% | -8.00 [-8.56, -7.44] | • |
| TOHP II 1997 | -0.25 | 5.7 | 1192 | 1.75 | 5.25 | 1190 | 7.0% | -2.00 [-2.44, -1.56] | • |
| otal (95% CI) | | | 6079 | | | 5875 | 100.0% | -4.50 [-5.97, -3.03] | • |
| Heterogeneity: Tau² = 7.96; CH Fest for overall effect: Z = 6.00 | | | (P < 0.0 | 0001); I² | = 96% | þ | | - | -20 -10 0 10 20 Favours [experimental] Favours [control] |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

4 5

Figure 6a: Total mortality

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| 58 | |
| 59 60 | |
| 00 | |

| | Lifestyle interv | | Conti | | | Odds Ratio | Odds Ratio |
|--|--------------------|-------|--------|-------|--------|----------------------|---------------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Swedish Bjorknas 2009 | 0 | 71 | 0 | 74 | | Not estimable | |
| POWER (face to face) 2011 | 0 | 139 | 0 | 138 | | Not estimable | |
| Villareal 2011 | 0 | 54 | 0 | 53 | | Not estimable | |
| BE-WELL 2015 | 0 | 165 | 0 | 165 | | Not estimable | |
| IDEA 2013 | 0 | 304 | 0 | 150 | | Not estimable | |
| HEALTH TRACK | 0 | 125 | 0 | 126 | | Not estimable | |
| E-LITE 2013 | 0 | 160 | 0 | 81 | | Not estimable | |
| LEAN 2016 | 0 | 67 | 0 | 33 | | Not estimable | |
| SLIM 2011 | 0 | 74 | 1 | 73 | 0.3% | 0.32 [0.01, 8.09] | |
| PODOSA 2014 | 0 | 85 | 1 | 86 | 0.3% | 0.33 [0.01, 8.30] | |
| ORBIT 2010 | 1 | 107 | 0 | 106 | 0.3% | 3.00 [0.12, 74.48] | |
| NEW 2012 | 0 | 235 | 1 | 204 | 0.3% | 0.29 [0.01, 7.11] | |
| TAIM 1993 | 2 | 100 | 0 | 100 | 0.3% | 5.10 [0.24, 107.62] | |
| Patrick 2011 | 2 | 224 | 0 | 130 | 0.3% | 2.93 [0.14, 61.55] | |
| HCP 1987 | 3 | 78 | 0 | 40 | 0.3% | 3.75 [0.19, 74.50] | |
| Da Qing (exercise) 1997 | 5 | 126 | 0 | 141 | 0.3% | 12.81 [0.70, 234.04] | · · · · · · · · · · · · · · · · · · · |
| STRIDE 2015 | 1 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| IDPP-1 2006 | 1 | 133 | 1 | 136 | 0.4% | 1.02 [0.06, 16.52] | |
| LISA 2014 | 1 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | |
| TOHP 1992 | 1 | 308 | 1 | 993 | 0.4% | 3.23 [0.20, 51.81] | |
| EDIPS-Newcastle 2009 | 2 | 51 | 1 | 51 | 0.5% | 2.04 [0.18, 23.24] | |
| CLIP 2011 | 1 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| WOMAN2011 | 1 | 253 | 2 | 255 | 0.5% | 0.50 [0.05, 5.57] | |
| ALIFE@WORK 2011 | 2 | 926 | 1 | 460 | 0.5% | 0.99 [0.09, 10.99] | |
| Trento 2001 | 3 | 56 | 1 | 56 | 0.6% | 3.11 [0.31, 30.88] | |
| ACHIEVE 2013 | 2 | 144 | 3 | 147 | 0.9% | 0.68 [0.11, 4.11] | |
| Da Qing (no exercise) 1997 | 3 | 133 | 3 | 130 | 1.1% | 0.98 [0.19, 4.93] | |
| DPP2002 | 3 | 1079 | 5 | 1082 | 1.4% | 0.60 [0.14, 2.52] | |
| TOHP 1997 | 7 | 1192 | 5 | 1190 | 2.2% | 1.40 [0.44, 4.42] | _ |
| ADAPT 2010 | 15 | 159 | 30 | 159 | 6.6% | 0.45 [0.23, 0.87] | _ |
| TONE 2011 | 49 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | - |
| Look AHEAD 2013 | 174 | 2570 | 202 | 2575 | 65.5% | 0.85 [0.69, 1.05] | • |
| Total (95% CI) | | 9785 | | 9678 | 100.0% | 0.86 [0.73, 1.02] | • |
| Total events | 279 | | 314 | | | | |
| Heterogeneity: Chi ² = 15.54, c | f = 23 (P = 0.87); | ²=0% | | | | | 0.005 0.1 1 10 2 |
| Test for overall effect: Z = 1.71 | (P = 0.09) | | | | | | Favours intervention Favours control |

Figure 6a: Total mortality- funnel plots

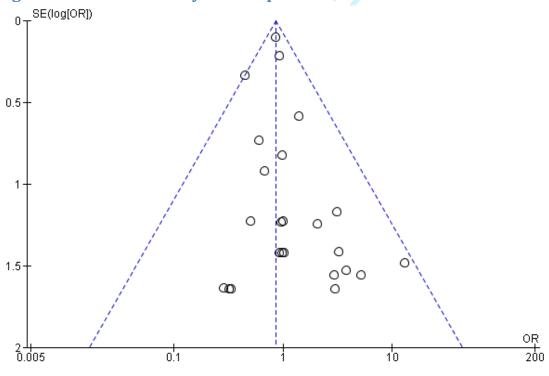


Figure 7a: Mortality ≤ 28 – interventions per year

| | Lifestyle interv | ention | Cont | ol | | Odds Ratio | Odds Ratio |
|--|--------------------|--------|--------|-------|--------|----------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| LEAN 2016 | 0 | 67 | 0 | 33 | | Not estimable | |
| HEALTH TRACK | 0 | 125 | 0 | 126 | | Not estimable | |
| Swedish Bjorknas 2009 | 0 | 71 | 0 | 74 | | Not estimable | |
| BE-WELL 2015 | 0 | 165 | 0 | 165 | | Not estimable | |
| Da Qing (exercise) 1997 | 5 | 126 | 0 | 141 | 2.6% | 12.81 [0.70, 234.04] | |
| TOHP 1992 | 1 | 308 | 1 | 993 | 2.7% | 3.23 [0.20, 51.81] | |
| TAIM 1993 | 2 | 100 | 0 | 100 | 2.8% | 5.10 [0.24, 107.62] | |
| HCP 1987 | 3 | 78 | 0 | 40 | 3.7% | 3.75 [0.19, 74.50] | |
| Trento 2001 | 3 | 56 | 1 | 56 | 5.5% | 3.11 [0.31, 30.88] | |
| EDIPS-Newcastle 2009 | 2 | 51 | 1 | 51 | 5.6% | 2.04 [0.18, 23.24] | |
| IDPP-1 2006 | 1 | 133 | 1 | 136 | 5.7% | 1.02 [0.06, 16.52] | |
| ALIFE@WORK 2011 | 2 | 926 | 1 | 460 | 7.8% | 0.99 [0.09, 10.99] | |
| PODOSA 2014 | 0 | 85 | 1 | 86 | 8.6% | 0.33 [0.01, 8.30] | |
| SLIM 2011 | 0 | 74 | 1 | 73 | 8.7% | 0.32 [0.01, 8.09] | |
| Da Qing (no exercise) 1997 | 3 | 133 | 3 | 130 | 17.3% | 0.98 [0.19, 4.93] | |
| DPP2002 | 3 | 1079 | 5 | 1082 | 29.0% | 0.60 [0.14, 2.52] | |
| Total (95% CI) | | 3577 | | 3746 | 100.0% | 1.53 [0.83, 2.81] | • |
| Total events | 25 | | 15 | | | | |
| Heterogeneity: Chi ² = 7.59, df = | = 11 (P = 0.75); P | = 0% | | | | | |
| Test for overall effect: Z = 1.37 | (P = 0.17) | | | | | | 0.01 0.1 1 10 100 Favours [experimental] Favours [control] |

Figure 7b: Mortality >28 – interventions per year

| | Lifestyle interv | ention | Contr | ol | | Odds Ratio | Odds Ratio |
|-------------------------------------|---------------------------------|--------|--------|-------|--------|--------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| IDEA 2013 | 0 | 304 | 0 | 150 | | Not estimable | |
| E-LITE 2013 | 0 | 160 | 0 | 81 | | Not estimable | |
| POWER (face to face) 2011 | 0 | 139 | 0 | 138 | | Not estimable | |
| Villareal 2011 | 0 | 54 | 0 | 53 | | Not estimable | |
| ORBIT 2010 | 1 | 107 | 0 | 106 | 0.2% | 3.00 [0.12, 74.48] | |
| Patrick 2011 | 2 | 224 | 0 | 130 | 0.2% | 2.93 [0.14, 61.55] | |
| LISA 2014 | 1 | 171 | 1 | 167 | 0.4% | 0.98 [0.06, 15.74] | |
| STRIDE 2015 | 1 | 104 | 1 | 96 | 0.4% | 0.92 [0.06, 14.95] | |
| CLIP 2011 | 1 | 98 | 2 | 190 | 0.5% | 0.97 [0.09, 10.82] | |
| NEW 2012 | 0 | 235 | 1 | 204 | 0.6% | 0.29 [0.01, 7.11] | |
| WOMAN2011 | 1 | 253 | 2 | 255 | 0.7% | 0.50 [0.05, 5.57] | |
| ACHIEVE 2013 | 2 | 144 | 3 | 147 | 1.1% | 0.68 [0.11, 4.11] | |
| TOHP II 1997 | 7 | 1192 | 5 | 1190 | 1.8% | 1.40 [0.44, 4.42] | |
| ADAPT 2010 | 15 | 159 | 30 | 159 | 9.9% | 0.45 [0.23, 0.87] | - _ |
| TONE 2011 | 49 | 294 | 52 | 291 | 15.8% | 0.92 [0.60, 1.41] | _ _ |
| Look AHEAD 2013 | 174 | 2570 | 202 | 2575 | 68.5% | 0.85 [0.69, 1.05] | |
| Total (95% CI) | | 6208 | | 5932 | 100.0% | 0.84 [0.70, 1.00] | • |
| Total events | 254 | | 299 | | | | |
| Heterogeneity: Chi2 = 6.33, df | = 11 (P = 0.85); I ² | = 0% | | | | | |
| Test for overall effect: $Z = 2.01$ | (P = 0.04) | | | | | | Favours [experimental] Favours [control] |
| | | | | | | | |

PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Registration page 3 Supplementary protocol |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4,5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5,6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (for gopriskoration difference in means) es. xhtml | 7 |

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| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis. | 7 |
|-------------------------------|----|--|---|
| | | Page 1 of 2 | |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 1 and supplementary figures Pages 9,10 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Supplementar figures |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figures 3-5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Supplementary |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Table 2 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Pages 10,11,12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 12 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | [Page 12 |

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| 3 | | |
|--|--|--------------------------|
| ⁴ FUNDING | | |
| 5 6 Funding 7 | 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |
| 8 9 <i>From:</i> Moher D, Liberati 10 doi:10.1371/journal.pmed | A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement For more information, visit: www.prisma-statement.org. Page 2 of 2 | PLoS Med 6(7): e1000097. |
| 11 | For more information, visit: <u>www.prisma-statement.org</u> . | |
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