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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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Abstract

Objectives

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

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 ≤ 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.

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 all-cause 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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Strengths and Limitations of study

- Previous meta-analysis of randomised trials of lifestyle interventions have not considered the level of intervention needed to achieve clinically meaningful weight loss.
- It was not possible for treatment allocation to be blinded.
- There was wide variation in the type of lifestyle advice. It was not possible to assess which type of lifestyle advice is the most effective.
- Individual characteristics such as adherence to randomised treatments could not be evaluated.
- Mortality was low, so the statistical power to assess modest differences in mortality was also low.
- There is limited data on effects of lifestyle interventions for weight loss in patients with cardiovascular disease or cancer.

Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m^2) or overweight (25≤BMI<30 kg/m^2).(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.

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.

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

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 ≥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 ≥ 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 queries 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

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)

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

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 I^2 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 (I^2≥1%) was present. The meta-analysis was also repeated using a fixed effects model to assess the effects of small studies on results.(25) A p-value of <0.05 was considered statistically significant. Studies are presented in Forrest plots in order of statistical power.

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 ≥ 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 (≤ 6, 7-12, 13-24, and ≥25).

Sensitivity analysis was undertaken to assess effects of studies that deviated significantly from the standard error of the total study result or studies where baseline values differed significantly from the mean baseline. Funnel plots were used to assess for publication bias.

The statistical analyses were performed using RevMan software version 5·2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed guidelines suggested by Wang. (26)

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.

Lifestyle 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.

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.

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.

Weight loss for studies with > than the median of 28 interventions /year was -4.53 [-5.93, -3.12] kg, and with ≤28 interventions was -2.38 [-3.98, -0.78] kg, p=0.001. A dose response was also evident, with increasing number of interventions associated with greater weight loss (Table 3). For all studies the average weight loss per lifestyle intervention session at one year compared to controls was ~0.13kg.

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 ≥ 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 (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%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

with a modest reduction in all-cause mortality, (point estimate ~14%), but with wide confidence intervals, so there is uncertainty on whether this benefit is real.

Previous meta-analyses also reported that lifestyle interventions result in a modest weight loss, and a small but not statistically significant reduction in all-cause mortality.(36, 37) 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 were small, and lifestyle interventions varied markedly. However it was not possible to confidently evaluate the impact of difference 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 are 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 (28, 30, 38) reported more than 10 deaths. Modest mortality benefits of sustained weight reduction may be expected to occur during longer follow-up. This is consistent with results of the Look AHEAD (28) study which followed patients for nearly 10 years. The 14% reduction for all-cause mortality was similar to all other studies combined, supporting the conclusion that this mortality reduction is real. Although this was 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 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.

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.

Conclusion

Lifestyle programs with frequent patient interactions sustained over a year or more achieve modest weight loss. This level of intervention may be unrealistic for most medical practices. There is a modest but non-significant reduction in mortality with lifestyle programs, but limited data on whether lifestyle interventions for obesity decrease mortality in persons at higher risk because of cancer, heart failure or ischaemic heart disease.

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

Name of Study	Target population	Sample size N	Women number (%)	Mean BMI (kg/m²)	Mean initial weight (kg)	Mean age (years)	Intervention duration (years)	Follow-up duration (years)	Deaths	Jadad score
Summary statistic weighted mean		**615**	**346 (56)**	**32.5**	**87.2**	**53.8**	**2.39**	**2.49**	**19**	**3.1**
ACHIEVE (41)	Overweight/obese with mental illness	291	146 (50)	36.3	102.7	45.3	1.5	1.5	5	3
ADAPT (29)	Overweight/obese knee osteoarthritic older persons	318	229 (72)	34.3	93.8	68.5	2	1.5 (8 for mortality)	45	2
ALIFE@WORK (19)	Overweight/obese	1386	457 (33)	29.6	92.1	43	0.5	2	3	4

BE-WELL(20)	Obese asthmatics	330	234 (71)	37.5	104.2	47.6		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	12.5	1.5	3	1
Da Qing (33)	Impaired glucose tolerance	530	244 (46)	25.8	_	45	6	6	11	2
DPP (43)	Overweight/obese with elevated fasting glucose	2161	1491 (69)	34.1	94.2	50.4	2.8	2.8	8	2
EDIPS-Newcastle (44)	Overweight/obese with impaired glucose tolerance	102	61 (60)	33.8	92	57.1	3.1	3.1	3	4
E-LITE (45)	Overweight/obese persons with pre-diabetes or metabolic syndrome	241	113 (47)	32	93.8	52.9	1.25	1.25	0	3

HEALTH TRACK(32)	Overweight and obese Australians	377	279 (74)	32	125.2	45		1	0	4
HCP (21)	Hypertension	118	42 (36)	-	77	56		4	3	3
IDEA (46)	Overweight/obese with osteoarthritis knee	454	327 (72)	33.6	93	66		1.5	0	4
IDPP-1 (47)	Indian and Pakistani origin with impaired glucose tolerance	269	62 (23)	26	_	45.6		2.5	2	3
LEAN (22)	Overweight/obese women with treated breast cancer	100	100 (100)	33.1	87.5	59		1	0	5
LISA (48)	Overweight/obese post-menopausal women with breast cancer history who are currently taking letrozole	338	338 (100)	31.3	82	61		2	2	3

Look AHEAD (49)	Overweight/obese with type 2 diabetes	5145	3087 (60)	36	101	58.8	9.6	9.6	376	3
NEW (50)	Overweight/obese post-menopausal women	439	439 (100)	30.9	83.6	58	1	1	1	4
ORBIT(51)	Obese African-American women	213	213(100)	39.2	104.9	46	1.5	1.5	1	4
Patrick (52)	Overweight/obese men	441	0 (0)	34.2	104.7	43.9	1	1	2	4
PODOSA(53)	Indian or Pakistani-origin with impaired glucose tolerance test	171	92 (54)	30.5	80.3	52.5	3	3	1	4
POWER(27)	Obese with cardiovascular risk factors	415	266 (64)	36.6	103.4	54	2	2	0	2
SLIM (54)	Impaired glucose tolerance	147	72 (49)	29.8	85.5	56.9	4.1	4.1	1	2
STRIDE (55)	Overweight/obese taking antipsychotic	200	144 (72)	38.3	107.7	47.2	1	1	2	4

	agents									
Swedish Bjorknas (56)	Metabolic syndrome	145	83 (57)	29.8	85.8	54.4	2	3	0	4
TAIM (57)	Overweight/obese hypertensive	200	102 (51)	_	87.7	48.3	4.5	4.5	2	4
TOHP I (58)	Normal to high blood pressure	564	180(32)	29.5	89.8	42.8	1.5	1.5	2	2
TOHP II (59)	Overweight/obese persons that are normo- or hypertensive	2382	810 (34)	30.9	93.6	43.6	3	3	12	2
TONE (38)	Overweight/obese elderly hypertensive persons	585	304 (52)	31.2	87.8	65.5	2.5	2.5 (12 mortality)	101	4
Trento (23)	type 2 diabetes	112	50 (45)	28.8	77.8	61.5	2	2	4	3
Villareal (60)	Older obese	107	67 (63)	37.2	100.8	69.7	1	1	0	2
WOMAN (61)	Overweight/obese post-menopausal women	508	508 (100)	30.8	81.7	57	4	4	3	3

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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 contact outlines whether participants received interventions remotely by internet, email or over the phone (R) or face to face (F).

Study name Year Published	Type of contact	Mode of contact	Number of dietary interventions in year 1	Number of dietary interventions in year 2	Proportion of first year interventions in first 6 months (%)
All studies	***Individual= 7*** ***Group only = 5*** ***Group + individual=19***	***Face to face =11*** ***Remote = 3*** ***Face to face + remote= 17***	***27.5***	***x.96***	***66***
ACHIEVE	G,I	F	30	x	80
ADAPT	G,I	F,R	33	x	64
ALIFE@WORK	I	R	10	0	100
BE-WELL	G,I	F,R	18	x	83
CLIP	G,I	F,R	36	x	67
Da Qing	G,I	F	16	4	80

DPP	G, I	F,R	22	72	73
EDIPS-Newcastle	G,I	F	8	x	75
E-LITE	G,I	F,R	38	x	61
HEALTH TRACK	I	F,R	6	6	50
HCP	I	F	12	4	75
IDEA	G,I	F,R	39	x	62
IDPP-1	I	F,R	15	74	53
LEAN	I	F,R	11	x	100
LISA	I	R	31	4	87
Look Ahead	G,I	F,R	42	24	57
NEW	G,I	F,R	32	x	63
ORBIT	G,I	F,R	110	x	56
Patrick	I	R	52	x	50
PODOSA	G	F	7	4	71

POWER	G,I	F,R	39	78	77
SLIM	G,I	F,R	5	14	60
STRIDE	G,I	F,R	36	x	67
Swedish Bjorknas	G	F	12	5	58
TAIM	G,I	F	17	8	71
TOHP I	G,I	F,R	26	x	77
TOHP II	G,I	F,R	28	x	68
TONE	G,I	F	28	12	71
Trento	G	F	4	4	50
Villareal	G	F	52	x	50
WOMAN	G	F	40	12	50

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

	Weight change (final reported)+			Mortality			
Characteristic	**N studies#**	**Weight of study (%)**	**Mean difference Random effect model (kg) (95%CI)**	**N studies**	**Weight of study (%)**	**total deaths /total patients**	**Odds ratio Fixed effect model (95%CI)**
Number of Interventions per year							
≤ *6*	3	9	-0.84 [-1.40, -0.28]	3	1	5/510	1.45 [0.22, 9.40]
7-12	6	17	-2.04	6	2	10/2022	1.34

			[-3.24, -0.84]				[0.35, 5.16]
13-24	4	15	-2.46 [-5.59, 0.67]	6	4	23/3490	1.20 [0.49, 2.96]
≥ 25	18	60	-3.53 [-4.13, -2.92]	18	93	555/13717	0.84 [0.71, 1.00]
BMI*							
25-29	6	19	-1.37 [-2.82, 0.09]	8	11	23/3890	1.58 [0.64, 3.90]
30- 35	16	48	-3.09 [-4.06, -2.11]	14	22	136/8374	0.93 [0.65, 1.33]
> 35	7	23	-4.04 [-5.61, -2.47]	7	67	384/6509	0.86 [0.69, 1.05]
Comorbidities							
Cardiometabolic risk factor present	17	56	-2.86 [-3.63, -2.10]	19	90	529/14450	0.90 [0.75, 1.08]

Healthy population	8	29	-3.03 [-4.52, -1.53]	8	3	12/3458	1.23 [0.39, 3.89]
Other (arthritis, asthma mental illness)	4	9	-3.35 [-4.52, -2.18]	4	2	7 /1275	0.74 [0.16, 3.37]
Cancer	2	6	-2.70 [-3.83, -1.57]	2	6	2/438	0.98 [0.06, 15.74]
Age							
40-49	12	47	-2.29 [-3.61, -0.97]	14	9	50/9868	1.28 [0.71, 2.30]
50-59	13	39	-3.27 [-4.15, -2.38]	13	69	396/9830	0.84 [0.69, 1.04]
>60	7	14	-4.50 [-6.25, -2.76]	7	22	155/2202	0.78 [0.55, 1.10]

Look AHEAD	1	4	-3.40 [-3.50, -3.30]	1	65	376/5145	0.85 [0.69, 1.05]
All other studies	30	96	-3.01 [-3.79, -2.23]	32	35	207/14594	0.88 [0.66, 1.17]
Total	**31**	**100**	**-2.98 [-3.56, -2.39]**	**33**	**100**	**593/19739**	**0.86 [0.73, 1.02]**

*TAIM and HCP excluded for BMI

Da Quing excluded for all weight loss

+ P<0.0001 for all

Figure 1: Visual abstract

Figure 2: Study flow chart

Figure 3: Effects of lifestyle intervention on weight loss at 1 year.

Figure 4: Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I^2=0).

Supplementary document 1: Protocol

Supplementary document 2: supplementary figures.

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 mortality. Interventions included seeing doctors, nurses, dieticians, nutritionist, and psychologists. • There was less than 1kg weight loss when patients had <6 weight loss lifestyle interventions per year. • The level of intervention in these studies is not realistic and suggests that we are setting patients up to fail when simple advice to lose

weight is given.

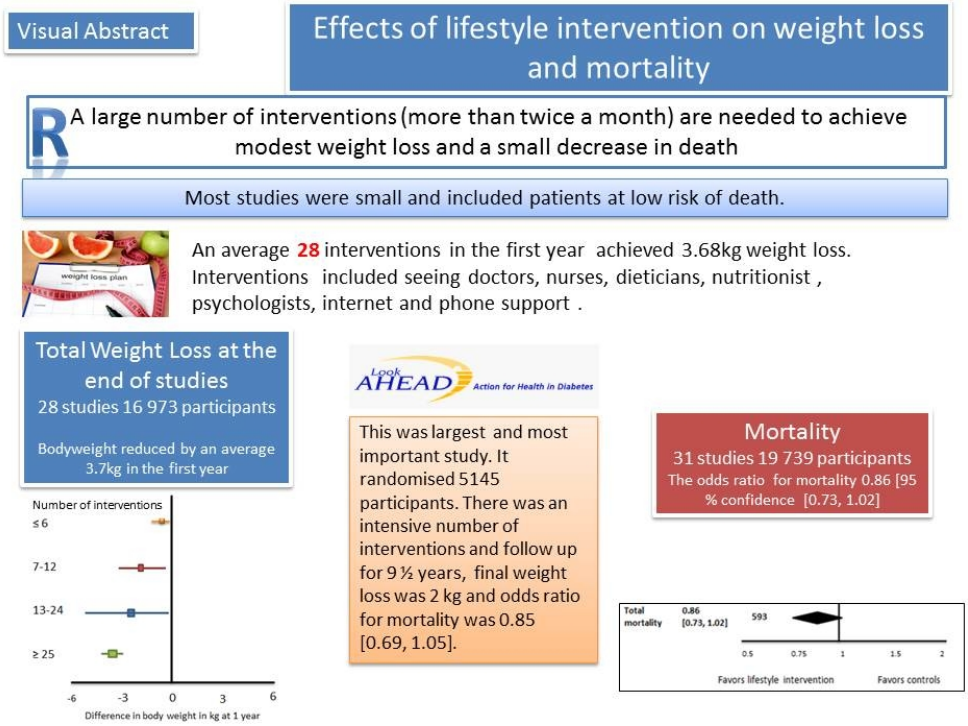

Figure 1: Visual abstract

254x190mm (96 x 96 DPI)

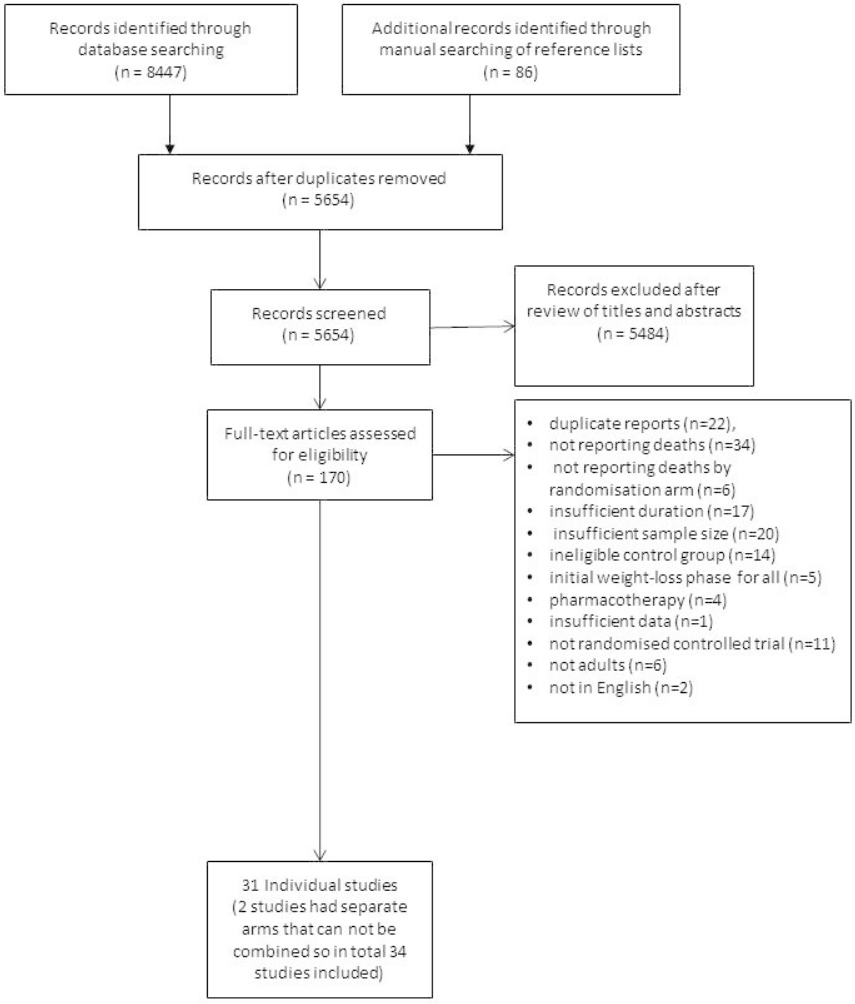

Figure 2: Study flow chart

190x254mm (96 x 96 DPI)

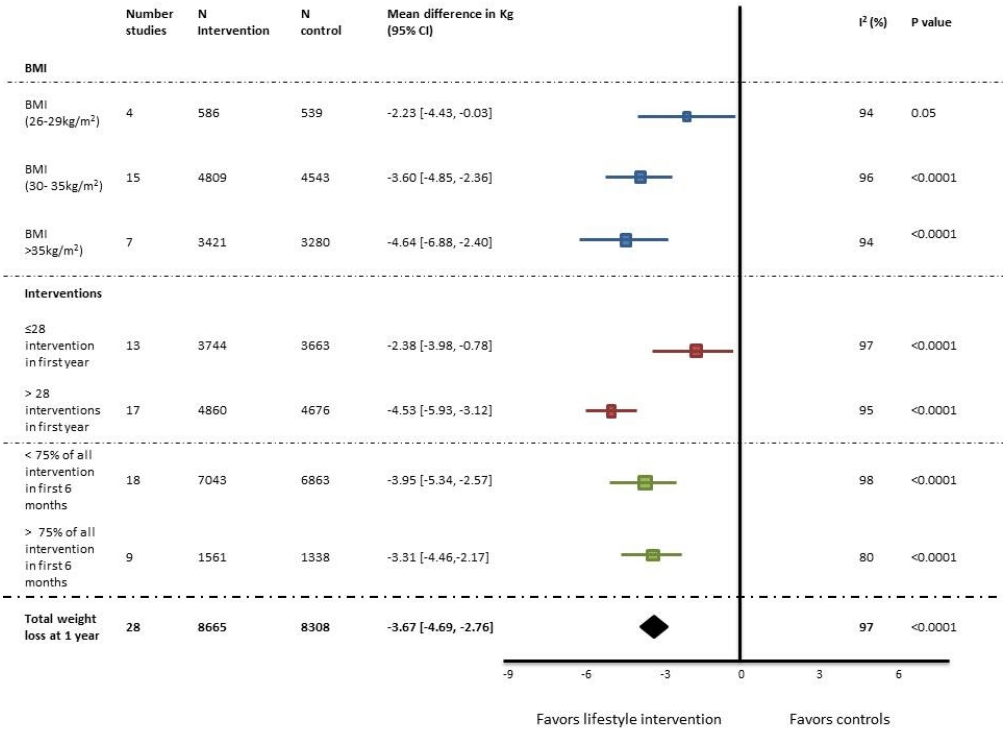

Figure 3: Effects of lifestyle intervention on weight loss at 1 year.

254x190mm (96 x 96 DPI)

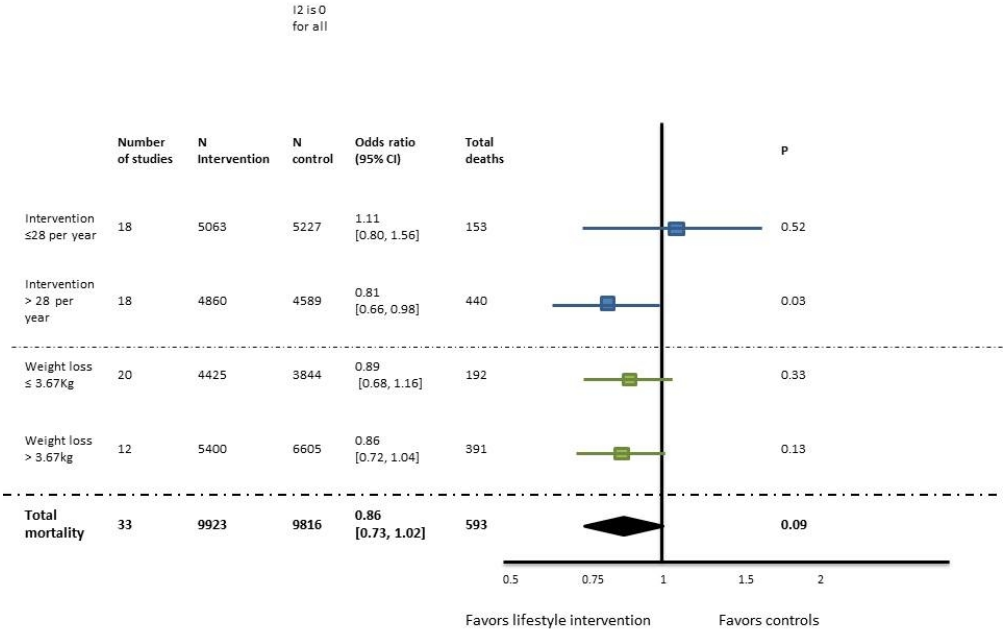

Figure 4: Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I2=0).

254x190mm (96 x 96 DPI)

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

Study Protocol

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. [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 guidelines[15] to prevent disease. These recommendations are predicated on the assumption that lifestyle advice achieves meaningful and sustained weight loss; and that this in turn is associated with reduced morbidity and mortality. Most guidelines do not stipulate precisely on how intensive lifestyle interventions have to be to be effective.

A previous meta-analysis[16] 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≥25kg/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 1and 2 broadly aimed to identify relevant studies in general populations, and search 3 broadly aimed to elicit appropriate studies in coronary heart disease populations. Duplicates between the three searches were removed.

The search details are as follows:

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

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

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

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

Statistical Analyses

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

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

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

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

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

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

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

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

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Supplementary document 2

Supplementary figures

Figure 1a: Weight loss at 1 year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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]
PODOSA 2014	-1.05	3.13	85	-0.24	3.03	86	3.9%	-0.81 [-1.73, 0.11]
TOHP I 1992	-3.83	6.12	308	0.07	4.01	256	3.9%	-3.90 [-4.74, -3.06]
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); I² = 97%
Test for overall effect: Z = 7.07 (P < 0.00001)

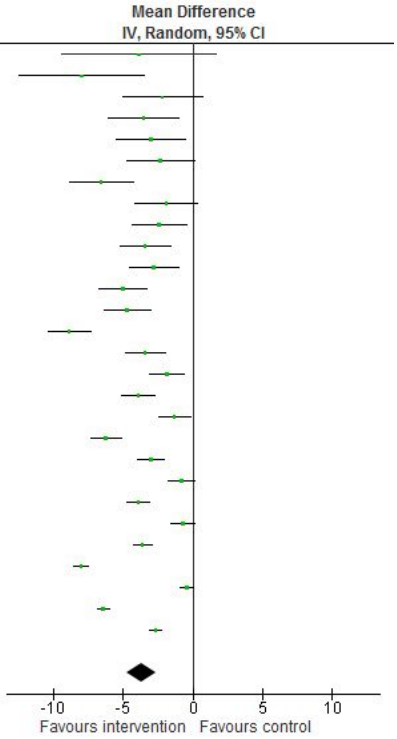


Figure 1b : Weight loss at 1 year- funnel plot

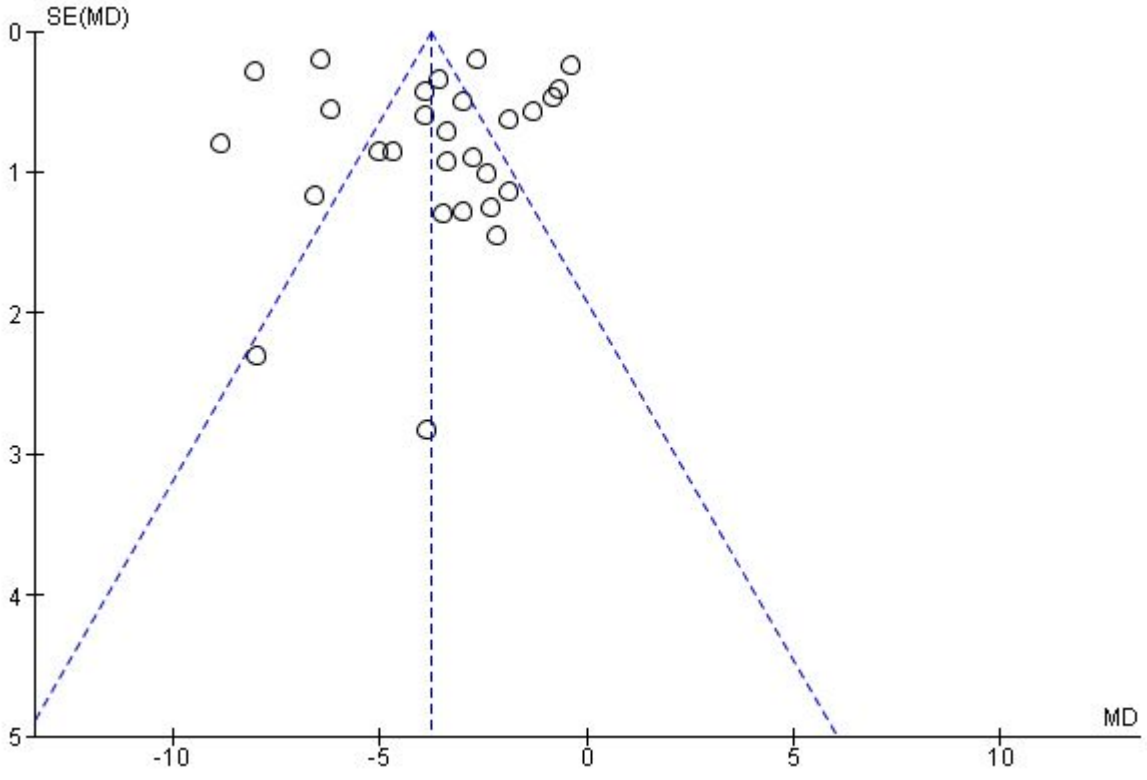


Figure 2a: Weight loss at 2 years

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Trento 2001	-1.4	18.7	56	-1.1	20.7	56	2.7%	-0.30 [-7.61, 7.01]
Swedish Bjorknas 2009	-3.15	14.9	71	0.6	18.3	74	3.9%	-3.75 [-9.17, 1.67]
POWER (face to face) 2011	-5.1	8.83	138	-0.8	8.22	138	7.6%	-4.30 [-6.31, -2.29]
POWER (remote) 2011	-4.6	8.8	139	-0.8	8.2	138	7.6%	-3.80 [-5.80, -1.80]
SLIM 2011	-0.85	4.34	74	-0.76	3.26	73	8.4%	-0.09 [-1.33, 1.15]
LISA 2014	-3.1	6.2	171	-0.3	5.3	167	8.4%	-2.80 [-4.03, -1.57]
PODOSA 2014	-0.78	3.43	85	0.13	3.24	86	8.6%	-0.91 [-1.91, 0.09]
TAIM 1993	-2.2	3.25	100	-0.4	3.25	100	8.7%	-1.80 [-2.70, -0.90]
ALIFE@WORK 2011	-1.68	6.32	926	-1.05	8.21	460	8.7%	-0.63 [-1.48, 0.22]
TONE 1998	-3.83	5.16	294	-0.468	3.92	291	8.8%	-3.36 [-4.10, -2.62]
Look AHEAD 2013	-7.1	10.2	2570	-1.4	10.3	2575	8.8%	-5.70 [-6.26, -5.14]
IDPP-1 2006	0.3	1.62	133	0.65	2.9	136	8.8%	-0.35 [-0.91, 0.21]
DPP2002	-5.4	5.48	1079	0	0.997	1082	8.9%	-5.40 [-5.73, -5.07]
Total (95% CI)			**5836**			**5376**	**100.0%**	**-2.62 [-4.05, -1.18]**

Heterogeneity: Tau² = 5.96; Chi² = 419.85, df = 12 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.58 (P = 0.0003)

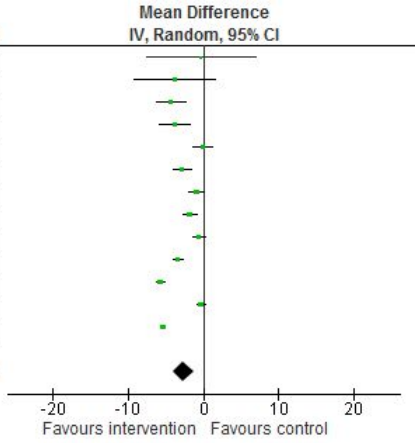


Figure 2b: Weight loss at 2 years- funnel plot

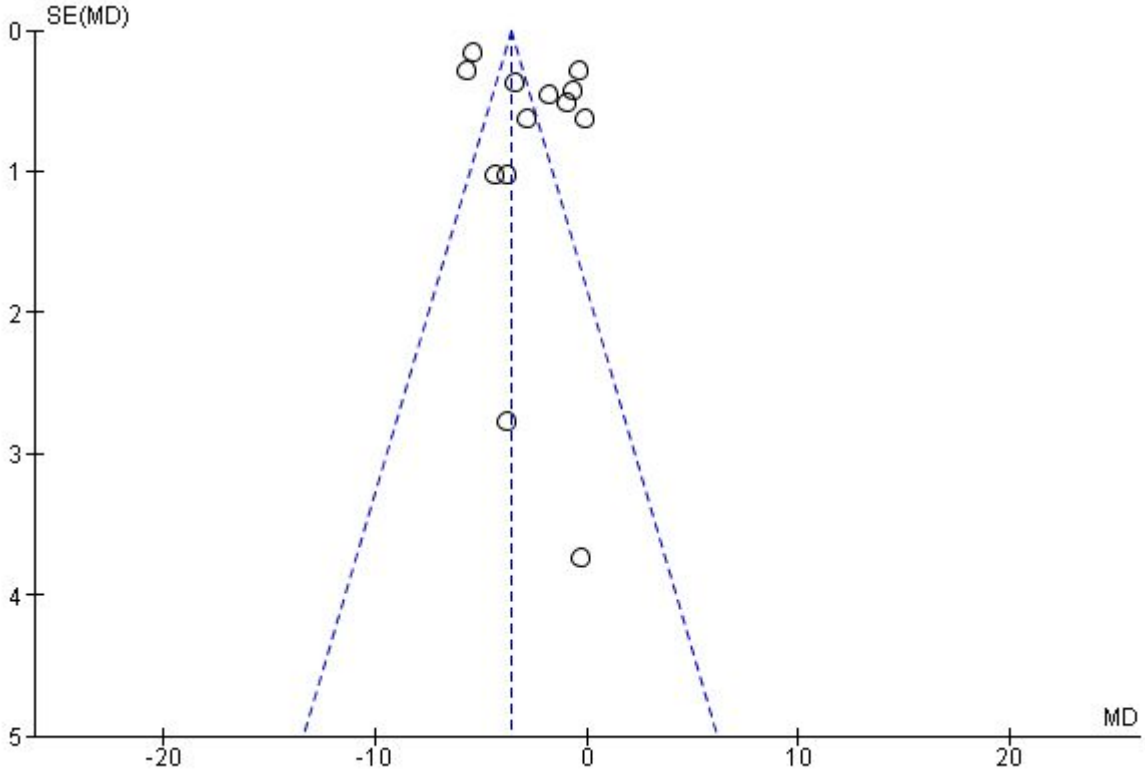


Figure 3a: Weight loss at 3 years

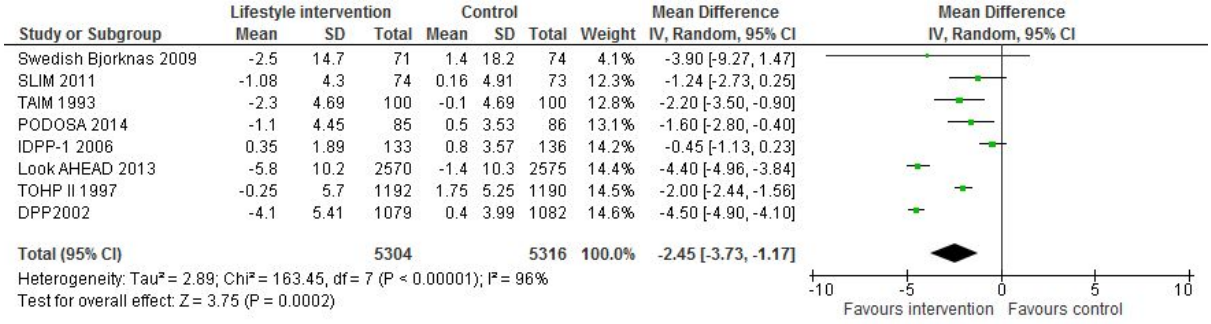


Figure 3b: Weight loss at 3 years- funnel plot

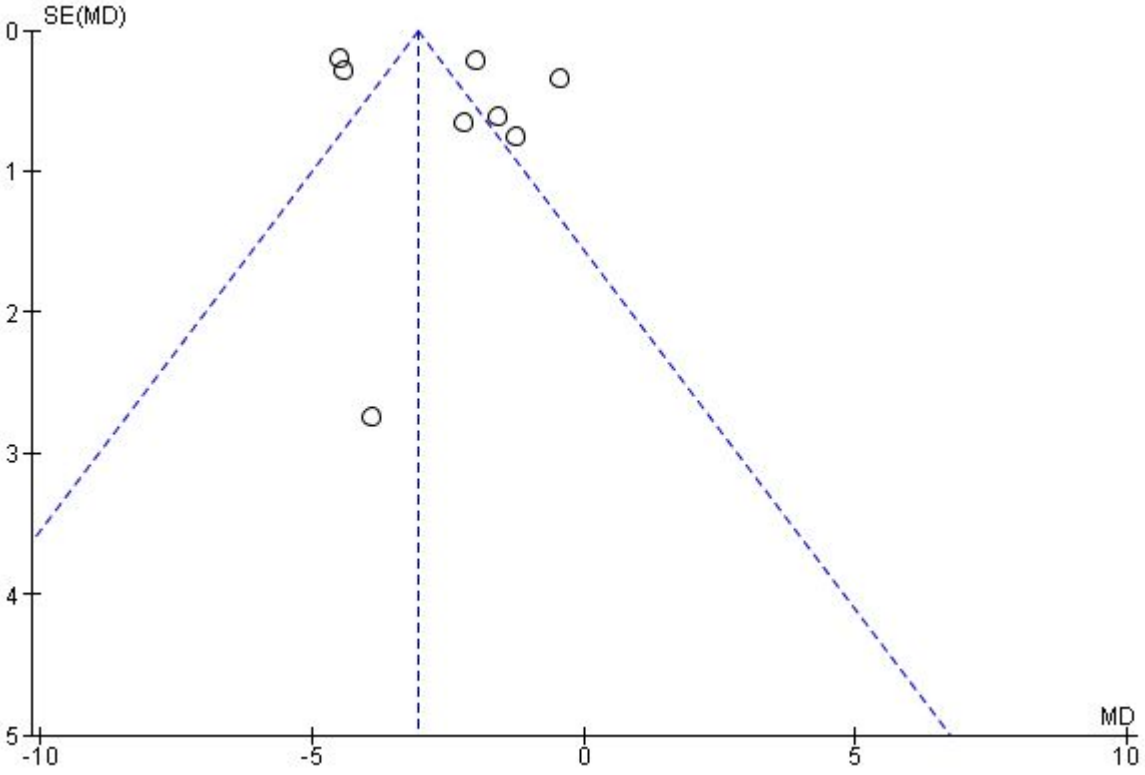
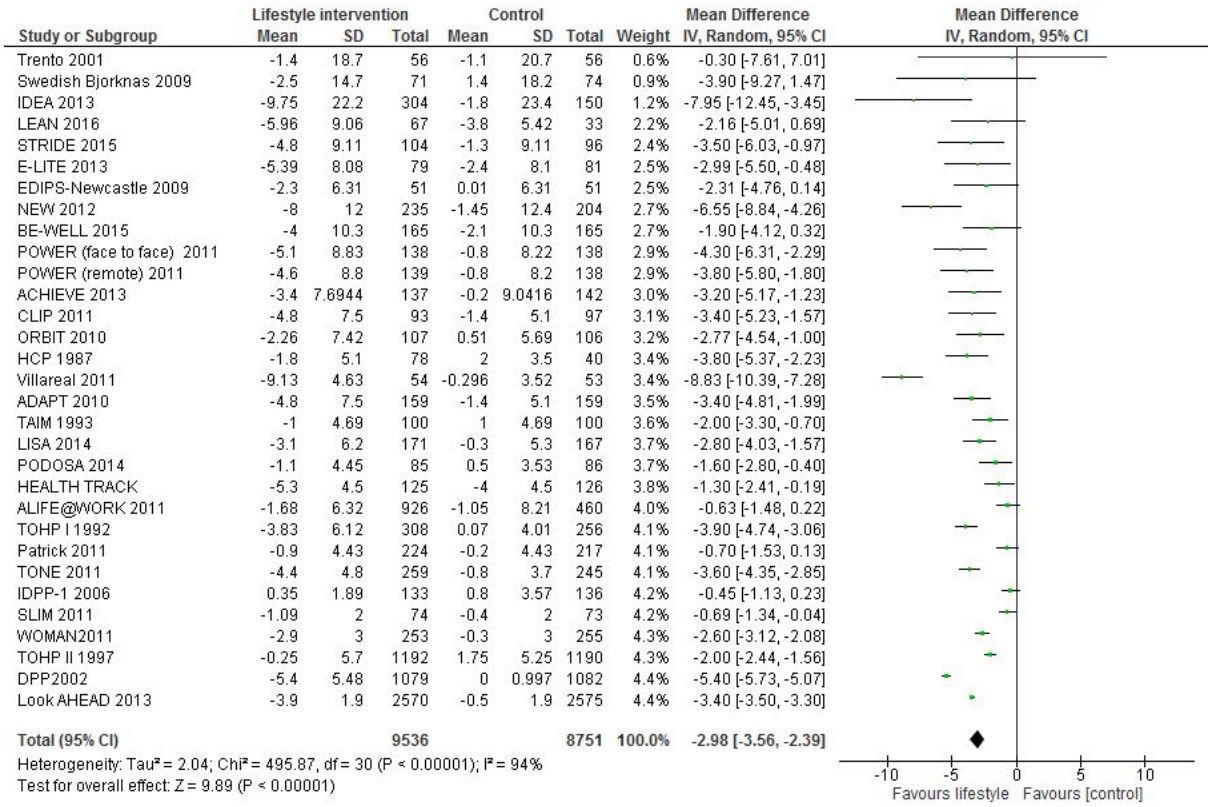


Figure 4a: Weight loss achieved by end of study



Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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	0.9%	-3.90 [-9.27, 1.47]
IDEA 2013	-9.75	22.2	304	-1.8	23.4	150	1.2%	-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	2.4%	-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	2.5%	-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	2.7%	-1.90 [-4.12, 0.32]
POWER (face to face) 2011	-5.1	8.83	138	-0.8	8.22	138	2.9%	-4.30 [-6.31, -2.29]
POWER (remote) 2011	-4.6	8.8	139	-0.8	8.2	138	2.9%	-3.80 [-5.80, -1.80]
ACHIEVE 2013	-3.4	7.6944	137	-0.2	9.0416	142	3.0%	-3.20 [-5.17, -1.23]
CLIP 2011	-4.8	7.5	93	-1.4	5.1	97	3.1%	-3.40 [-5.23, -1.57]
ORBIT 2010	-2.26	7.42	107	0.51	5.69	106	3.2%	-2.77 [-4.54, -1.00]
HCP 1987	-1.8	5.1	78	2	3.5	40	3.4%	-3.80 [-5.37, -2.23]
Villareal 2011	-9.13	4.63	54	-0.296	3.52	53	3.4%	-8.83 [-10.39, -7.28]
ADAPT 2010	-4.8	7.5	159	-1.4	5.1	159	3.5%	-3.40 [-4.81, -1.99]
TAIM 1993	-1	4.69	100	1	4.69	100	3.6%	-2.00 [-3.30, -0.70]
LISA 2014	-3.1	6.2	171	-0.3	5.3	167	3.7%	-2.80 [-4.03, -1.57]
PODOSA 2014	-1.1	4.45	85	0.5	3.53	86	3.7%	-1.60 [-2.80, -0.40]
HEALTH TRACK	-5.3	4.5	125	-4	4.5	126	3.8%	-1.30 [-2.41, -0.19]
ALIFE@WORK 2011	-1.68	6.32	926	-1.05	8.21	460	4.0%	-0.63 [-1.48, 0.22]
TOHP I 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 2011	-4.4	4.8	259	-0.8	3.7	245	4.1%	-3.60 [-4.35, -2.85]
IDPP-1 2006	0.35	1.89	133	0.8	3.57	136	4.2%	-0.45 [-1.13, 0.23]
SLIM 2011	-1.09	2	74	-0.4	2	73	4.2%	-0.69 [-1.34, -0.04]
WOMAN2011	-2.9	3	253	-0.3	3	255	4.3%	-2.60 [-3.12, -2.08]
TOHP II 1997	-0.25	5.7	1192	1.75	5.25	1190	4.3%	-2.00 [-2.44, -1.56]
DPP2002	-5.4	5.48	1079	0	0.997	1082	4.4%	-5.40 [-5.73, -5.07]
Look AHEAD 2013	-3.9	1.9	2570	-0.5	1.9	2575	4.4%	-3.40 [-3.50, -3.30]
Total (95% CI)			9536			8751	100.0%	-2.98 [-3.56, -2.39]

Heterogeneity: Tau² = 2.04; Chi² = 495.87, df = 30 (P < 0.00001); I² = 94%
Test for overall effect: Z = 9.89 (P < 0.00001)

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

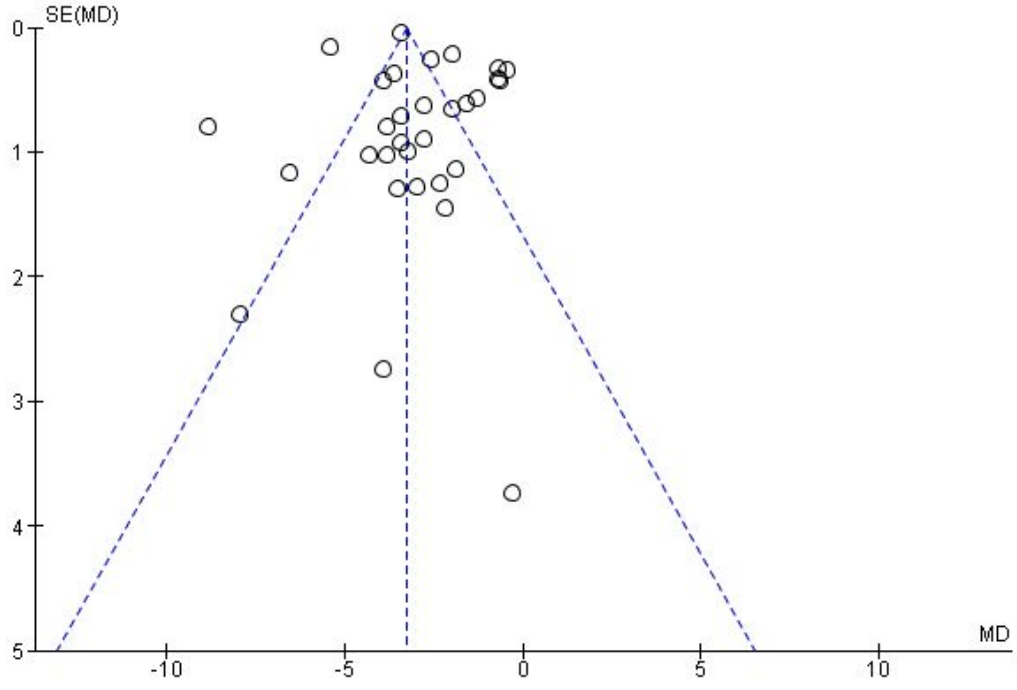


Figure 5a: Weight loss ≤28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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 I 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: Tau² = 8.01; Chi² = 450.59, df = 13 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.92 (P = 0.003)

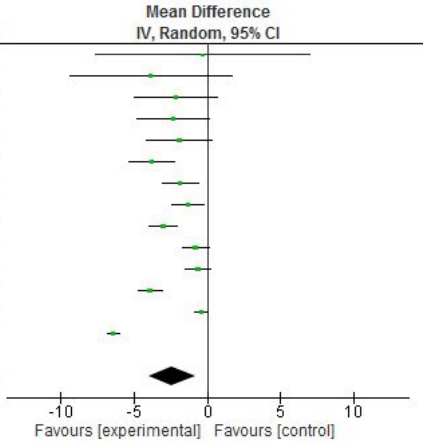


Figure 5b: Weight loss >28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
IDEA 2013	-9.75	22.2	304	-1.8	23.4	150	4.0%	-7.95 [-12.45, -3.45]
CLIP 2011	-7.1	15.8	93	-0.849	14.7	97	4.1%	-6.25 [-10.59, -1.91]
STRIDE 2015	-4.8	9.11	104	-1.3	9.11	96	5.5%	-3.50 [-6.03, -0.97]
E-LITE 2013	-5.39	8.08	79	-2.4	8.1	81	5.5%	-2.99 [-5.50, -0.48]
NEW 2012	-8	12	235	-1.45	12.4	204	5.7%	-6.55 [-8.84, -4.26]
ACHIEVE 2013	-2.8	7.96	137	-0.4	9.28	142	5.8%	-2.40 [-4.43, -0.37]
ORBIT 2010	-2.26	7.42	107	0.51	5.69	106	6.0%	-2.77 [-4.54, -1.00]
POWER (face to face) 2011	-5.8	8.22	138	-1.1	5.87	138	6.1%	-4.70 [-6.39, -3.01]
POWER (remote) 2011	-6.1	8.22	139	-1.1	5.87	138	6.1%	-5.00 [-6.68, -3.32]
Villareal 2011	-9.13	4.63	54	-0.296	3.52	53	6.2%	-8.83 [-10.39, -7.28]
ADAPT 2010	-4.8	7.5	159	-1.4	5.1	159	6.2%	-3.40 [-4.81, -1.99]
LISA 2014	-4.5	5.4	171	-0.6	5.7	167	6.4%	-3.90 [-5.08, -2.72]
WOMAN2011	-7.8	7.1	253	-1.6	5.5	255	6.4%	-6.20 [-7.31, -5.09]
Patrick 2011	-0.9	4.43	224	-0.2	4.43	217	6.5%	-0.70 [-1.53, 0.13]
TONE 1998	-4.4	4.8	259	-0.8	3.7	245	6.5%	-3.60 [-4.35, -2.85]
Look AHEAD 2013	-9.2	10.2	2570	-1.2	10.3	2575	6.6%	-8.00 [-8.56, -7.44]
TOHP II 1997	-0.25	5.7	1192	1.75	5.25	1190	6.6%	-2.00 [-2.44, -1.56]
Total (95% CI)			**6218**			**6013**	**100.0%**	**-4.53 [-5.93, -3.12]**

Heterogeneity: Tau² = 7.72; Chi² = 406.15, df = 16 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.32 (P < 0.00001)

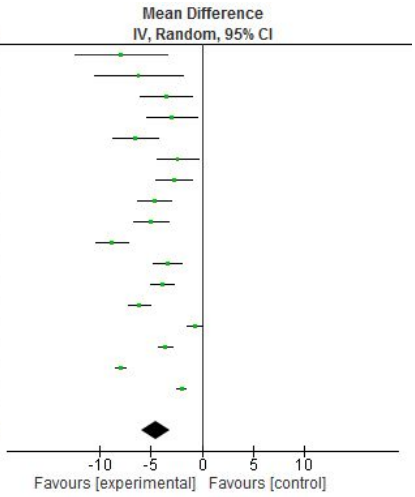
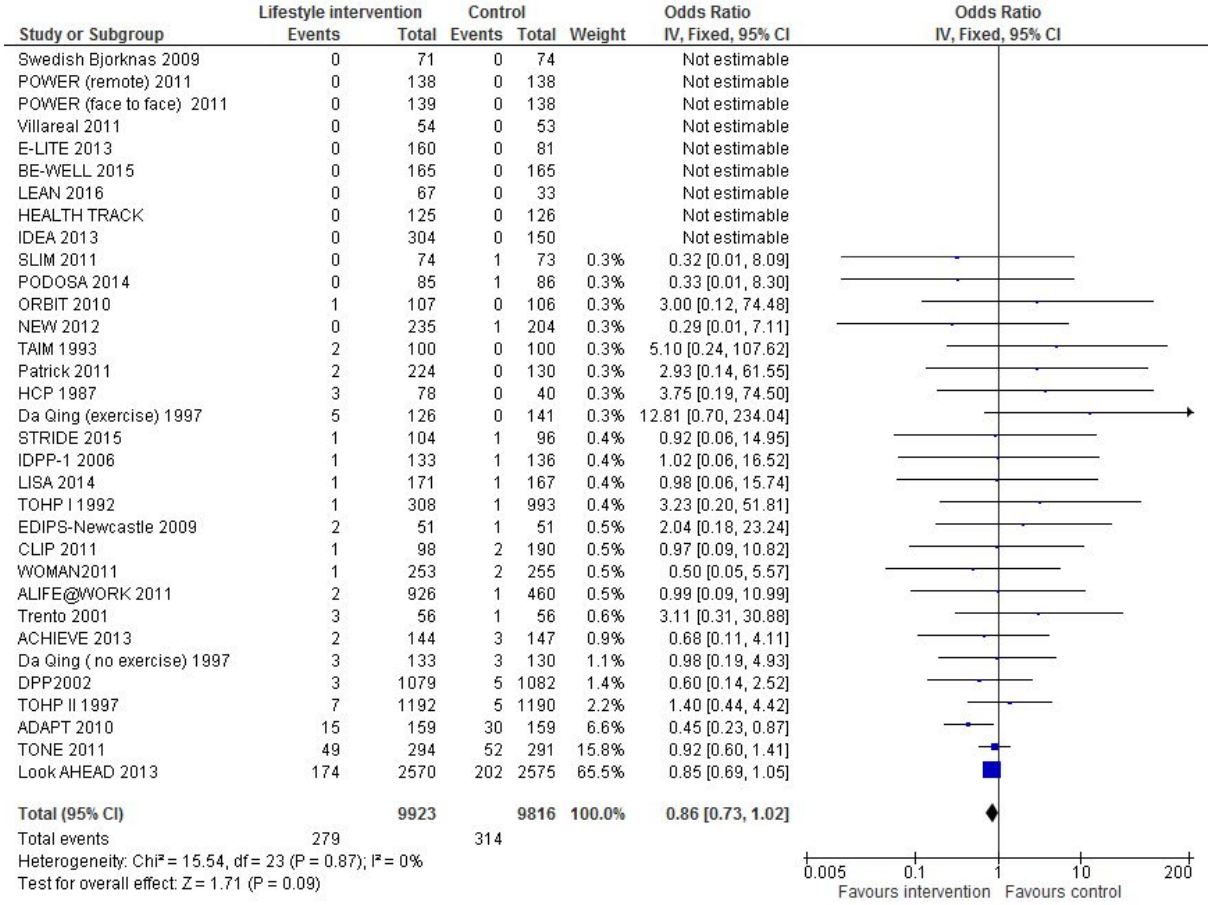


Figure 6a: Total mortality



Study or Subgroup	Lifestyle intervention Events	Total	Control Events	Total	Weight	Odds Ratio IV, Fixed, 95% CI
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
Villareal 2011	0	54	0	53		Not estimable
E-LITE 2013	0	160	0	81		Not estimable
BE-WELL 2015	0	165	0	165		Not estimable
LEAN 2016	0	67	0	33		Not estimable
HEALTH TRACK	0	125	0	126		Not estimable
IDEA 2013	0	304	0	150		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 I 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 II 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)		**9923**		**9816**	**100.0%**	**0.86 [0.73, 1.02]**
Total events	279		314			

Heterogeneity: Chi² = 15.54, df = 23 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

Figure 6a: Total mortality- funnel plots

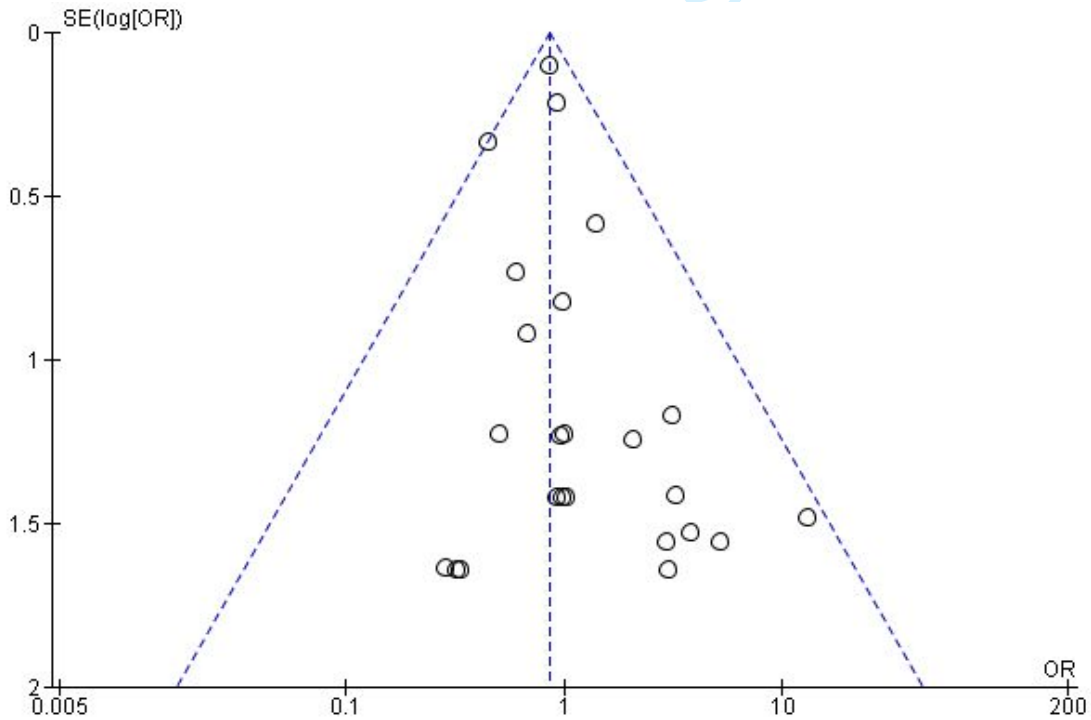


Figure 7a: Mortality !28 – interventions per year

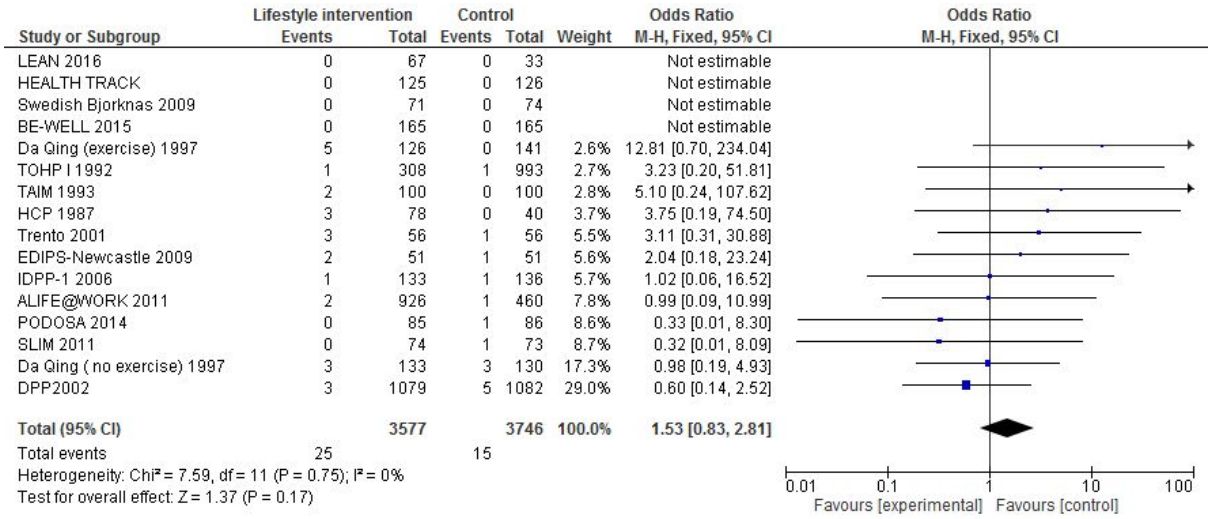
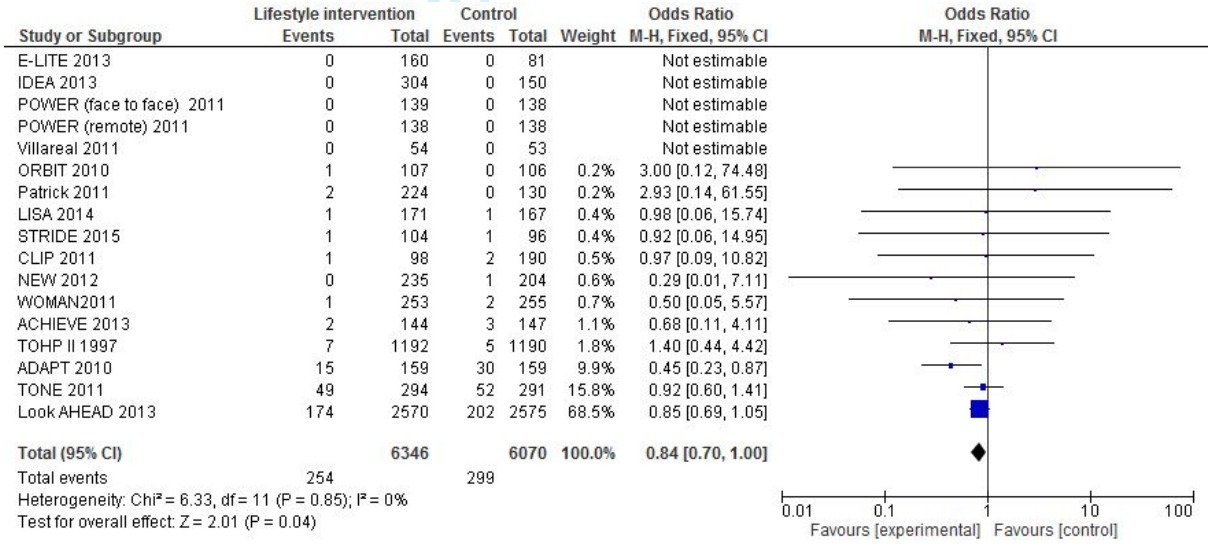


Figure 7b: Mortality >28 – interventions per year



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 (e.g., risk ratio, difference in means).	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

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.	Supplementary 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

PRISMA 2009 Checklist

FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

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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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Evidence based practice
Keywords:	NUTRITION & DIETETICS, weight loss, lifestyle interventions

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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Total word count: 6551 words

Abstract

Objectives

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

Design

Meta-analysis of randomised trials using PRISMA guidelines and RevMan software version 5·2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Data sources

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

Eligibility Criteria

Randomised studies 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.

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

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) 4.67, 2.58), and at 3 years (2.45 kg, 95% CI 3.73, 1.17). Weight loss at one year was greater in studies with > 28 compared to ≤ 28 interventions per year (4.50 kg, 95%CI 5.97, 3.03 vs 2.38, 95%CI 3.98, 0.78 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% CI 0.73, 1.02), p=0.09.

Conclusion

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

Strengths and Limitations of study

- Previous meta-analyses of randomised trials of lifestyle interventions have not considered the level of intervention needed to achieve clinically meaningful (>5%) weight loss. There was wide variation in the type of lifestyle advice, but it was not possible to assess which type of lifestyle advice is most effective.
- Most evidence is in middle aged people (age 50 -60) with cardiometabolic risk factors. There is limited data on effects of lifestyle interventions for weight loss in older patients and those with cardiovascular disease or cancer.
- Lifestyle interventions for weight loss may reduce mortality if sustained. However in most studies the duration of the intervention and follow-up were too short and mortality too low to allow a reliable assessment.

Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m^2) or overweight (25≤BMI<30 kg/m^2).(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.

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.

There was no patient or public Involvement in this study

Study Search and inclusion criteria

The full strategy is described in Supplementary document 1, the protocol. 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 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 ≥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 ≥ 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 queries 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 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).

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)

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.

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 I^2 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 (I^2≥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 interventions was calculated.

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 ≥ 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 (≤ 6, 7-12, 13-24, and ≥25).

Sensitivity analysis was undertaken to assess effects of studies that deviated significantly from the standard error of the total study result or studies where baseline values differed significantly from the mean baseline. Funnel plots were used to assess for publication bias.

The statistical analyses were performed using RevMan software version 5·2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed guidelines suggested by Wang. (27)

A regression analysis evaluated the relationship between the number of interventions/study and weight loss using Statistical Analysis Software (SAS). Intervention doses more than 3 standard deviations above the mean were considered outliers, and were removed from the analysis. (28)

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.

Lifestyle interventions evaluated

There were large variations in types (individual or group), mode of (face to face or remote), timing 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.

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.

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

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%CI 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).

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

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 bariatric surgery is associated with lower all-cause, cardiovascular and cancer-related

mortality.(37) However, compared to lifestyle interventions bariatric surgery results in much 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.

Study limitations

Individual participant data was not available and this limits the ability to address several important questions. 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

progression of diabetes and to be cost effective.(40) The current meta-analysis did not assess other potential health benefits of weight loss such as reducing progression to diabetes.

Conclusion

Lifestyle programs with frequent patient interactions sustained over a year or more can achieve clinically meaningful weight loss, and this may lower mortality during long term follow-up. However the benefits of less frequent interventions over shorter durations in body weight are more modest and long term benefits to mortality risk are uncertain. Because there is limited data from randomised trials, it is uncertain whether lifestyle interventions for obesity decrease mortality in persons with cancer, heart failure or ischaemic heart disease.

Figure 1: Study flow chart

Figure 2: Effects of lifestyle intervention on weight loss at 1 year.

Figure 3: Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I^2=0).

Supplementary document 1: Protocol (includes search strategy)

Supplementary document 2: Supplementary figures.

Patient consent: Not required.

Contributor statement:

NS, RS and JB: conception of study, adjudication inclusion of studies, draft version manuscript. NS and JB: electronic database searches, data extraction, performed the analysis. RS and JB wrote the subsequent and final versions of manuscript in consultation

with NS, JB: regression model, designed the figures and tables. All authors discussed the results and commented on the manuscript.

Competing interests: nil

Funding: Nil

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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524 **Table 1: Baseline characteristic of 31 studies included in mortality meta-analysis.**
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Name of Study	Target population	Sample size N	Women number (%)	Mean BMI (kg/m²)	Mean initial weight (kg)	Mean age (years)	Intervention duration (years)	Follow-up duration (years)	Deaths
Summary statistic weighted mean		**615**	**346 (56)**	**32.5**	**87.2**	**53.8**	**2.39**	**2.49**	**19**
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 osteoarthritic older persons	318	229 (72)	34.3	93.8	68.5	1.5	1.5 (8 for mortality)	45
ALIFE@WORK (20)	Overweight/obese	1386	457 (33)	29.6	92.1	43	0.5	2	3

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

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

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

	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 pressure	564	180(32)	29.5	89.8	42.8	1.5	1.5	2
TOHP II (57)	Overweight/obese persons that are normo- or hypertensive	2382	810 (34)	30.9	93.6	43.6	3	3	12
TONE (30)	Overweight/obese elderly hypertensive persons	585	304 (52)	31.2	87.8	65.5	2.5	2.5 (12 mortality)	101
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

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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 contact outlines whether participants received interventions remotely by internet, email or over the phone (R) or face to face (F).

Study name Year Published	Type of contact	Mode of contact	Number of dietary interventions in year 1	Number of dietary interventions in year 2	Proportion of first year interventions in first 6 months (%)
All studies	***Individual= 7*** ***Group only = 5*** ***Group + individual=19***	***Face to face =11*** ***Remote = 3*** ***Face to face + remote= 17***	***27.5***	***3.96***	***66***
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

DPP (31)	G, I	F,R	22	12	73
EDIPS-Newcastle (44)	G,I	F	8	x	75
E-LITE (45)	G,I	F,R	38	x	61
HEALTH TRACK (32)	I	F,R	6	6	50
HCP (22)	I	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

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

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

	Weight loss (from baseline and final reported)+			Mortality			
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 effect model (95%CI)**
Number of Interventions per year							
≤ 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 [2.92, 4.13]	17	93%	555/13578 (4.1%)	0.84 [0.71, 1.00]
BMI*							
25-29	6	19%	1.37 [-0.09, 2.82]	8	11%	23/3890 (0.6%)	1.58 [0.64, 3.90]
30- 35	16	48%	3.09 [2.11, 4.06]	14	22%	136/8374 (1.6%)	0.93 [0.65, 1.33]
> 35	6	23%	4.04 [2.47, 5.61]	6	67%	384/6370 (6%)	0.86 [0.69, 1.05]
Comorbidities							
Cardiometabolic risk factor present	16	56%	2.86 [2.10, 3.63]	18	90%	529/14311 (3.7%)	0.90 [0.75, 1.08]
Healthy population	8	29%	3.03 [1.53, 4.52]	8	3%	12/3458 (0.3%)	1.23 [0.39, 3.89]
Other (arthritis, asthma mental illness)	4	9%	3.35 [2.18, 4.52]	4	2%	7 /1275 (0.6%)	0.74 [0.16, 3.37]

Cancer	2	6%	2.70 [1.57, 3.83]	2	6%	2/438 (0.5%)	0.98 [0.06, 15.74]
Age							
40-49	12	47%	2.29 [0.97, 3.61]	14	9%	50/9868 (0.5%)	1.28 [0.71, 2.30]
50-59	12	39%	3.27 [2.38, 4.15]	12	69%	396/9691 (3.8%)	0.84 [0.69, 1.04]
>60	7	14%	4.50 [2.76, 6.25]	7	22%	155/2202 (7.0%)	0.78 [0.55, 1.10]
Look AHEAD	1	4%	3.40 [3.30, 3.50]	1	65%	376/5145 (7.3%)	0.85 [0.69, 1.05]
All other studies	29	96%	3.01 [2.23, 3.79]	32	35%	207/14455 (1.4%)	0.88 [0.66, 1.17]
Total	**30**	**100%**	**2.95 [2.35, 3.55]**	**32**	**100%**	**593/19463 (3.1%)**	**0.86 [0.73, 1.02]**

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*TAIM and HCP excluded for BMI

Da Quing excluded for all weight loss

+ P<0.0001 for all

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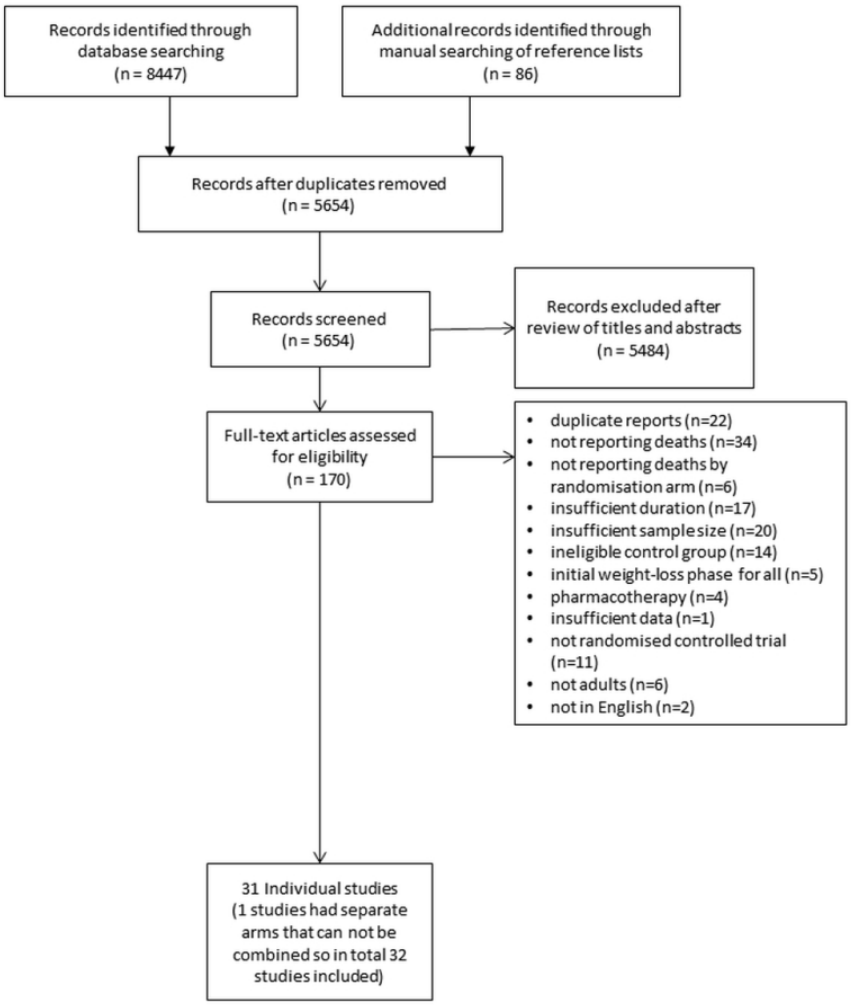
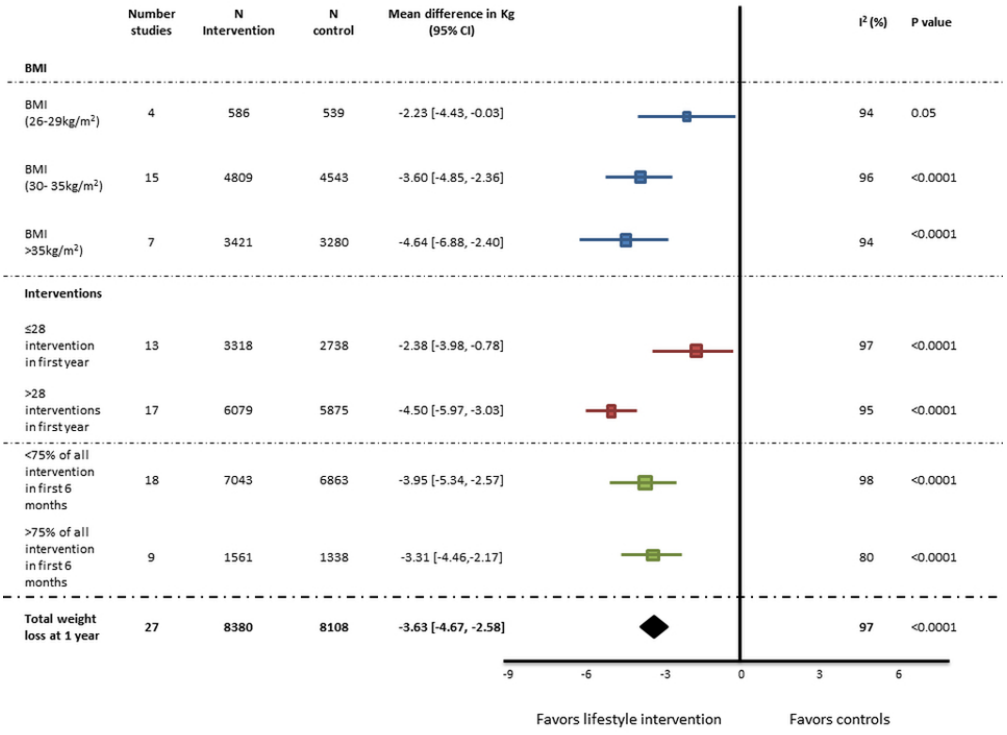


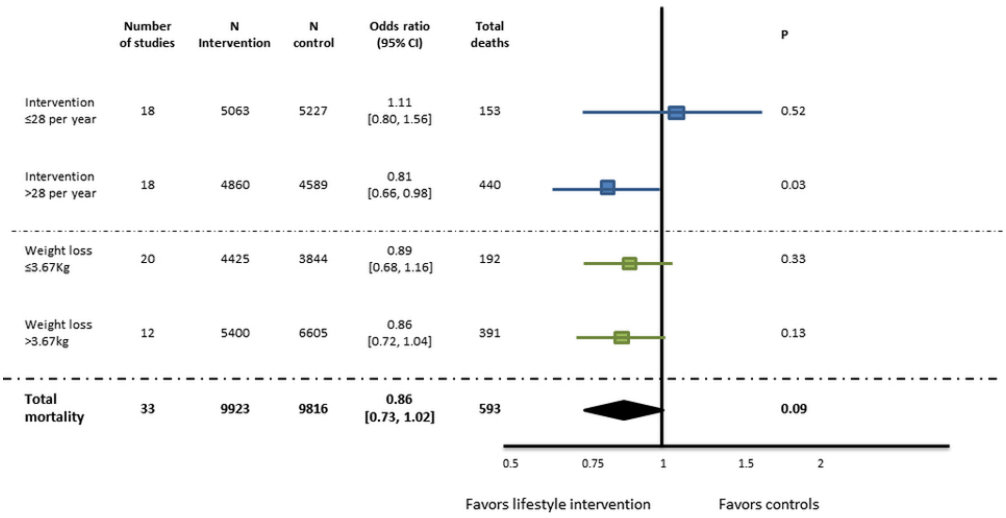
Study flow chart

67x90mm (300 x 300 DPI)



Effects of lifestyle intervention on weight loss at 1 year.

81x60mm (300 x 300 DPI)



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)

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

Study Protocol

Navneet Singh

Jocelyne Benatar

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Background and Aim

Obesity has become a major public health issue with rates tripling between 1975 and 2016. In 2016 more than 2.1 billion people – nearly 30% of the world's population – were either obese (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. [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 guidelines[15] to prevent disease. These recommendations are predicated on the assumption that lifestyle advice achieves meaningful and sustained weight loss; and that this in turn is associated with reduced morbidity and mortality. Most guidelines do not stipulate precisely on how intensive lifestyle interventions have to be to be effective.

A previous meta-analysis[16] 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≥25kg/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 1and 2 broadly aimed to identify relevant studies in general populations, and search 3 broadly aimed to elicit appropriate studies in coronary heart disease populations. Duplicates between the three searches were removed.

The search details are as follows:

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

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

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

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

Statistical Analyses

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

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

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

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

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

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

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

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

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Supplementary document 2

Supplementary figures

Figure 1a: Weight loss at 1 year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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	23.4	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]
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]
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]
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]
ADAPT 2010	-4.8	7.5	159	-1.4	5.1	159	3.9%	-3.40 [-4.81, -1.99]
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]
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 I 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]**

Heterogeneity: Tau² = 6.78; Chi² = 797.51, df = 26 (P < 0.00001); I² = 97%
Test for overall effect: Z = 6.81 (P < 0.00001)

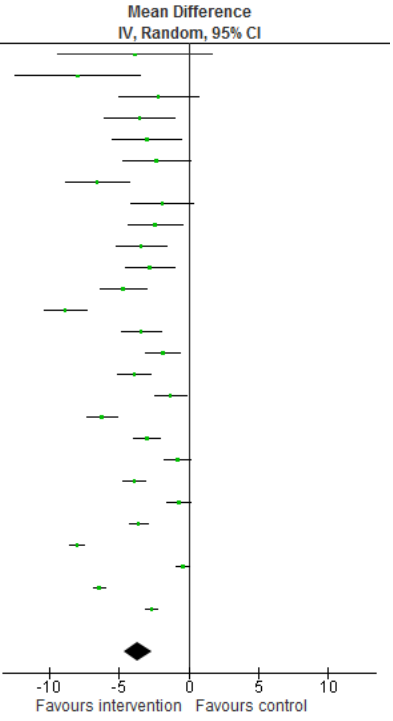


Figure 1b : Weight loss at 1 year- funnel plot

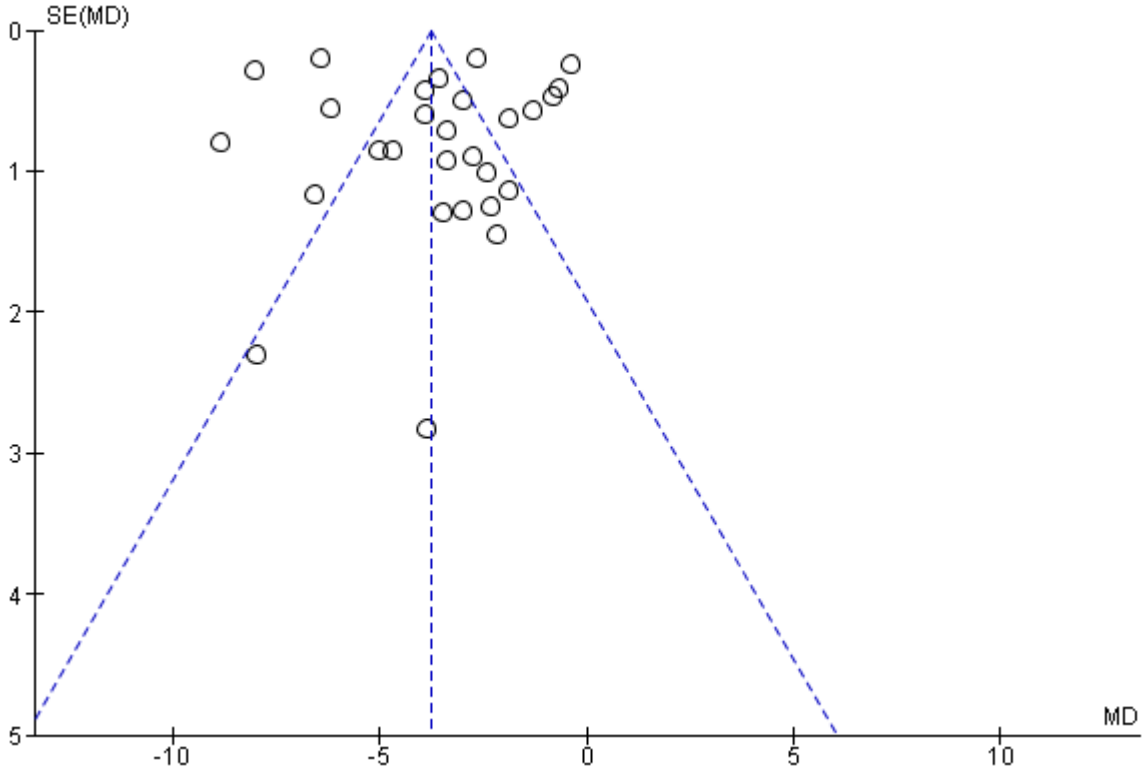


Figure 2a: Weight loss at 2 years

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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: Tau² = 6.07; Chi² = 419.82, df = 11 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.28 (P = 0.001)

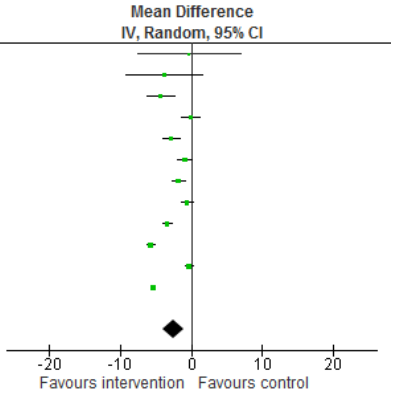


Figure 2b: Weight loss at 2 years- funnel plot

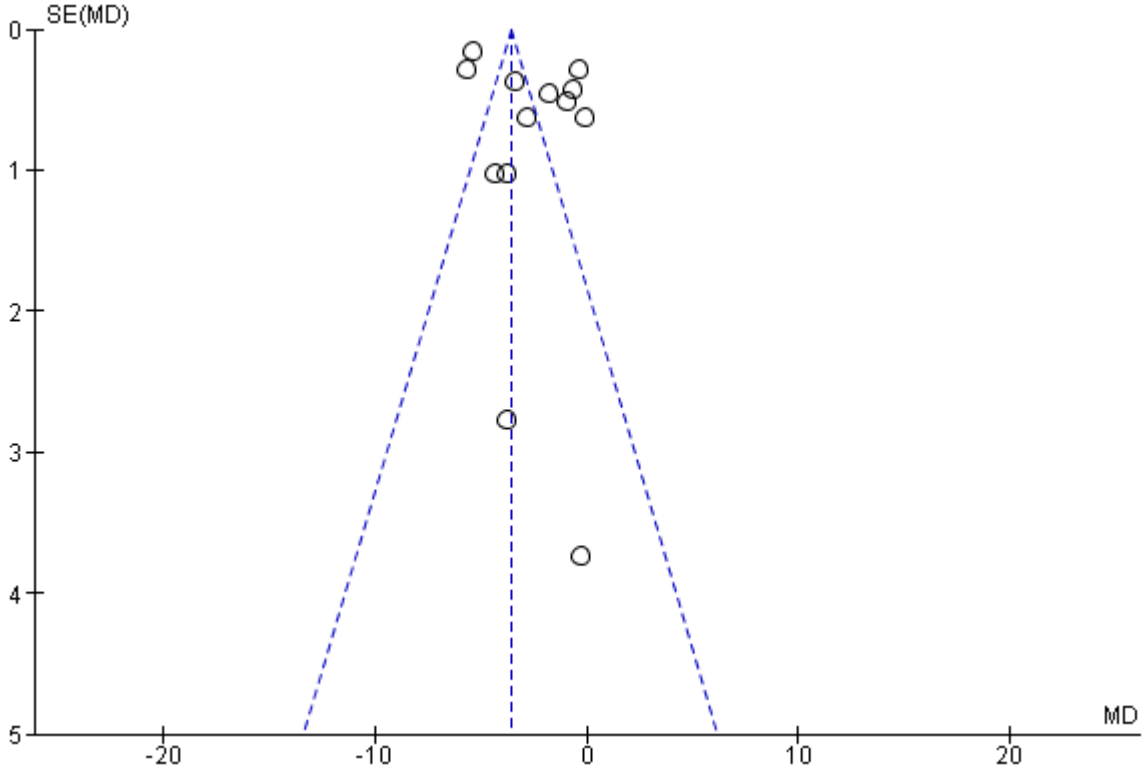


Figure 3a: Weight loss at 3 years

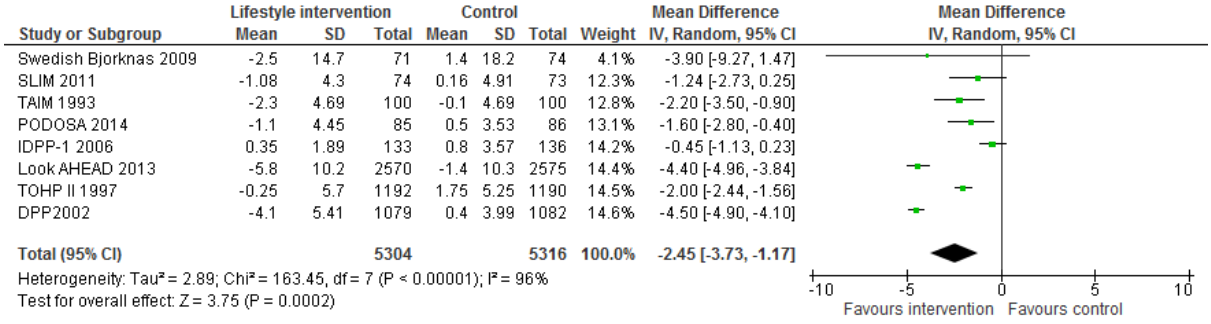


Figure 3b: Weight loss at 3 years- funnel plot

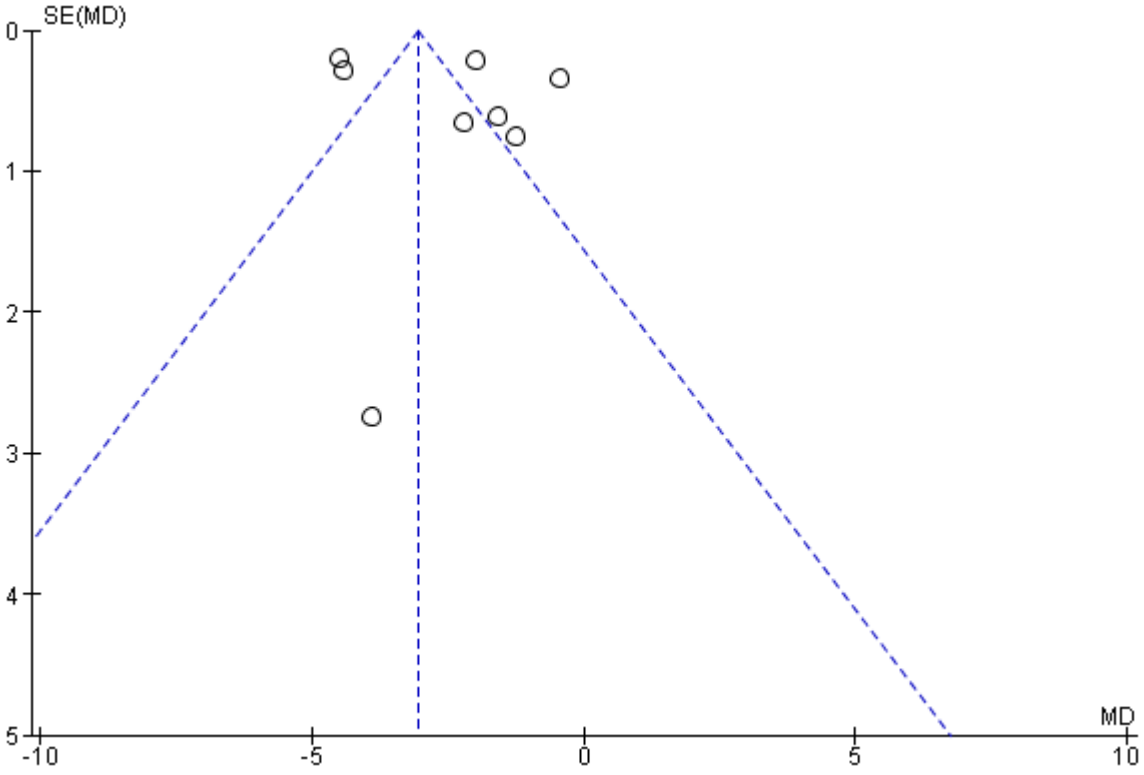
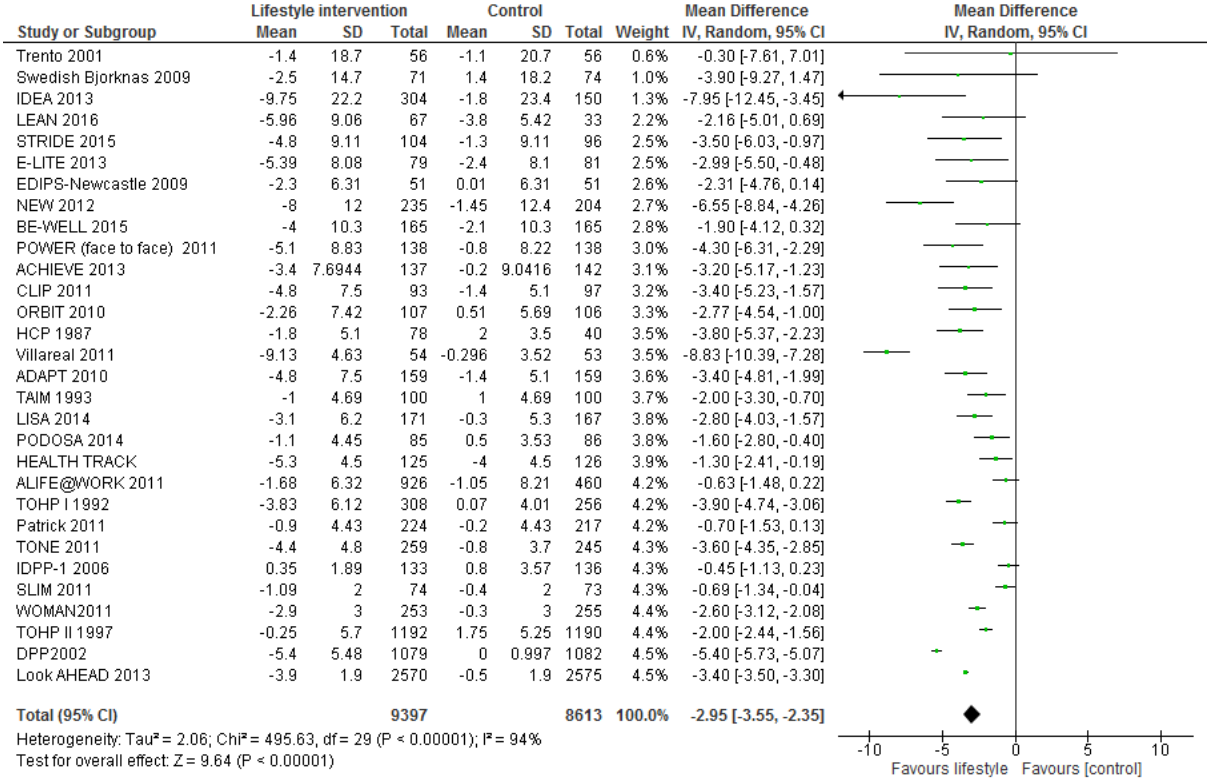


Figure 4a: Weight loss achieved by end of study



Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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 I 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	5.25	1190	4.4%	-2.00 [-2.44, -1.56]
DPP2002	-5.4	5.48	1079	0	0.997	1082	4.5%	-5.40 [-5.73, -5.07]
Look AHEAD 2013	-3.9	1.9	2570	-0.5	1.9	2575	4.5%	-3.40 [-3.50, -3.30]
Total (95% CI)			9397			8613	100.0%	-2.95 [-3.55, -2.35]

Heterogeneity: Tau² = 2.06; Chi² = 495.63, df = 29 (P < 0.00001); I² = 94%
Test for overall effect: Z = 9.64 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
Favours lifestyle Favours [control]

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

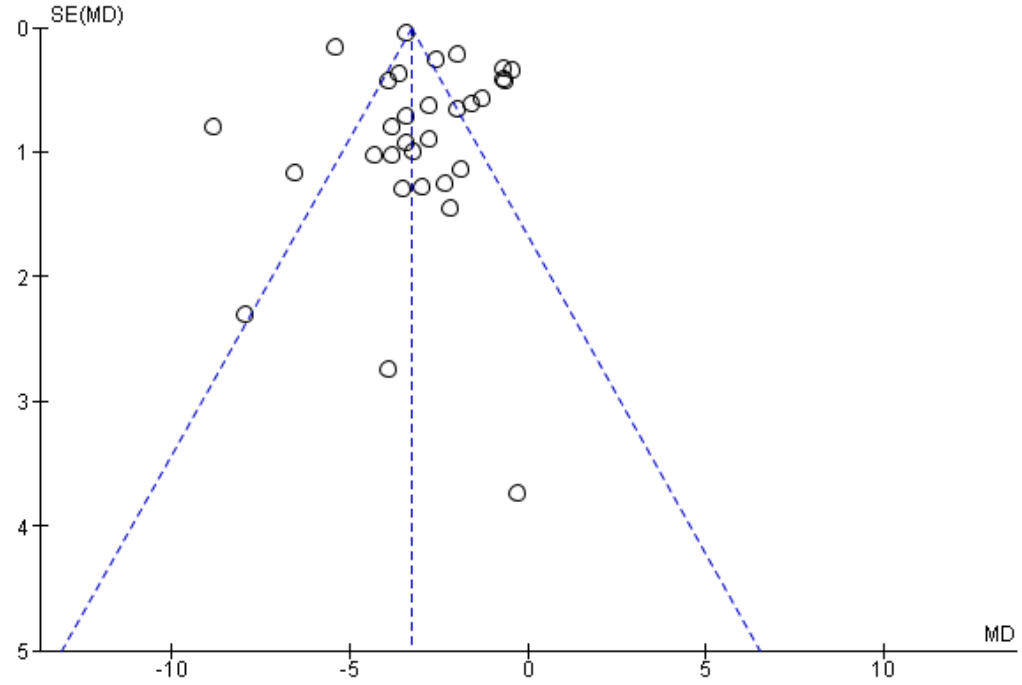


Figure 5a: Weight loss ≤28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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 I 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: Tau² = 8.01; Chi² = 450.59, df = 13 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.92 (P = 0.003)

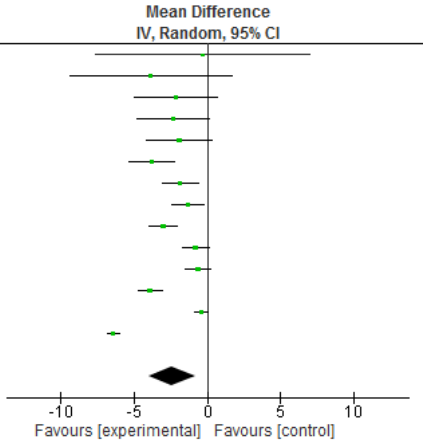


Figure 5b: Weight loss >28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
IDEA 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]
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]
NEW 2012	-8	12	235	-1.45	12.4	204	6.0%	-6.55 [-8.84, -4.26]
ACHIEVE 2013	-2.8	7.96	137	-0.4	9.28	142	6.2%	-2.40 [-4.43, -0.37]
ORBIT 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]
Villareal 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]
LISA 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]
TONE 1998	-4.4	4.8	259	-0.8	3.7	245	6.9%	-3.60 [-4.35, -2.85]
Look 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]
Total (95% CI)			**6079**			**5875**	**100.0%**	**-4.50 [-5.97, -3.03]**

Heterogeneity: Tau² = 7.96; Chi² = 404.88, df = 15 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.00 (P < 0.00001)

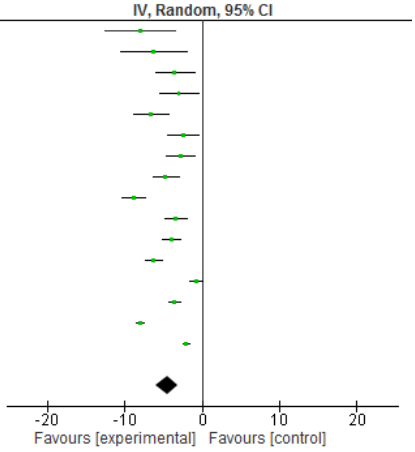


Figure 6a: Total mortality

Study or Subgroup	Lifestyle intervention Events	Total	Control Events	Total	Weight	Odds Ratio 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 I 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 II 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: Chi² = 15.54, df = 23 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

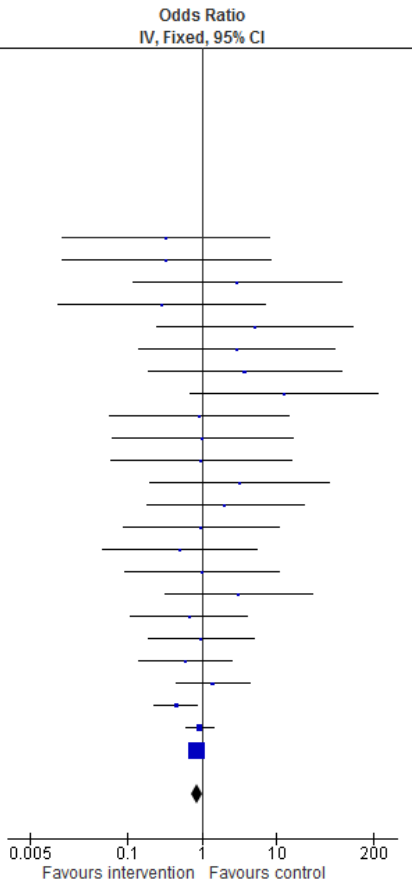


Figure 6a: Total mortality- funnel plots

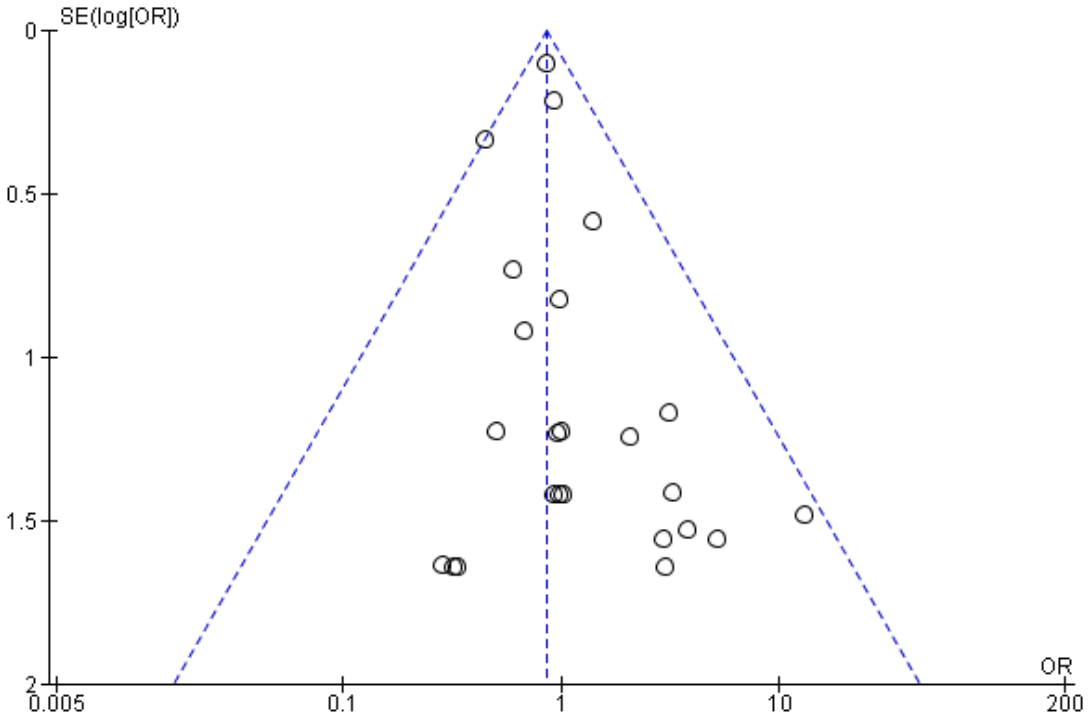


Figure 7a: Mortality ≤ 28 – interventions per year

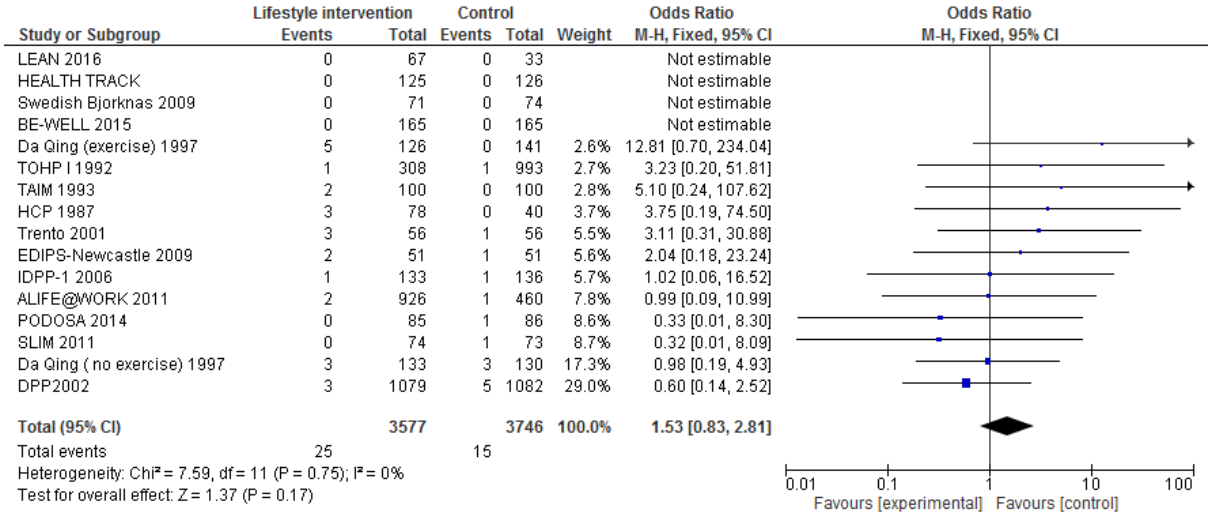
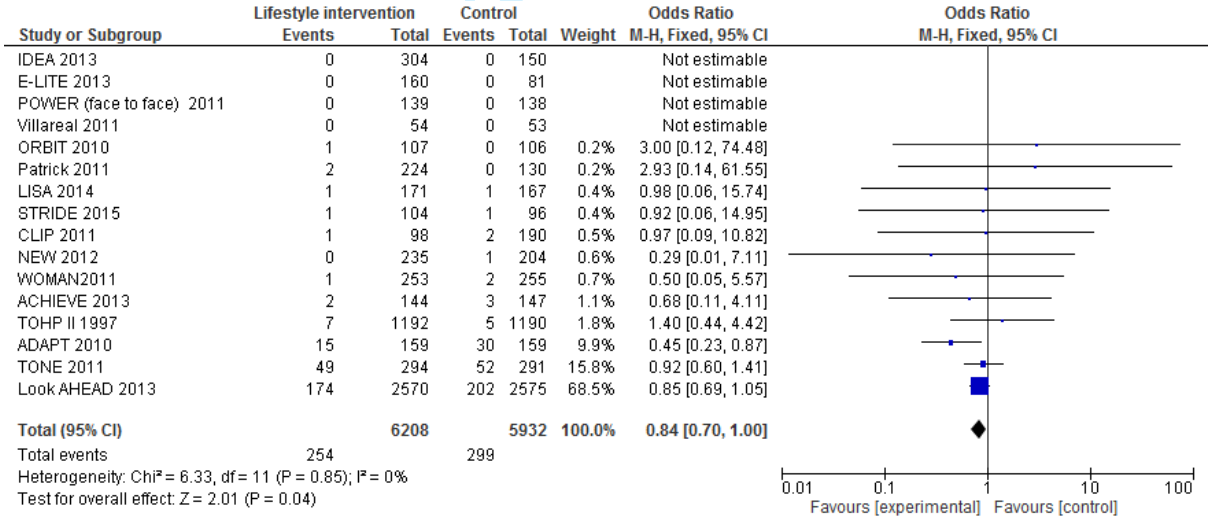


Figure 7b: Mortality >28 – interventions per year



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 (e.g., risk ratio, difference in means).	7

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

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.	Supplementary 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

PRISMA 2009 Checklist

FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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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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

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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All authors contributed to this work and have no competing interests.

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Total word count: 6551 words

Abstract

Objectives

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

Design

Meta-analysis of randomised trials using PRISMA guidelines and RevMan software version 5·2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Data sources

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

Eligibility Criteria

Randomised studies 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.

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

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 studies with > 28 compared to ≤ 28 interventions per year (4.50 kg, 95%CI 3.03, 5.97 vs 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% CI 0.73, 1.02), p=0.09.

Conclusion

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

Strengths and Limitations of study

- Previous meta-analyses of randomised trials of lifestyle interventions have not considered the level of intervention needed to achieve clinically meaningful (>5%) weight loss. There was wide variation in the type of lifestyle advice, but it was not possible to assess which type of lifestyle advice is most effective.
- Most evidence is in middle aged people (age 50 -60) with cardiometabolic risk factors. There is limited data on effects of lifestyle interventions for weight loss in older patients and those with cardiovascular disease or cancer.
- Lifestyle interventions for weight loss may reduce mortality if sustained. However in most studies the duration of the intervention and follow-up were too short and mortality too low to allow a reliable assessment.

Introduction

It has been estimated that nearly a third of the world's population are either obese (BMI≥30 kg/m^2) or overweight (25≤BMI<30 kg/m^2).(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.

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.

There was no patient or public Involvement in this study

Study Search and inclusion criteria

The full strategy is described in Supplementary document 1, the protocol. 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 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 ≥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 ≥ 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 queries 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 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).

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)

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.

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 I^2 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 (I^2≥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 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 ≥ 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 ≥60) and number of interventions per year (≤ 6, 7-12, 13-24, and ≥25).

Sensitivity analysis was undertaken to assess effects of studies that deviated significantly from the standard error of the total study result or studies where baseline values differed significantly from the mean baseline. Funnel plots were used to assess for publication bias.

The statistical analyses were performed using RevMan software version 5·2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Subgroup analysis followed guidelines suggested by Wang. (27)

A regression analysis evaluated the relationship between the number of interventions/study and weight loss using Statistical Analysis Software (SAS). Intervention doses more than 3 standard deviations above the mean were considered outliers, and were removed from the analysis. (28)

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.

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)

interventions. 14 studies reported 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.

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 2.58,4.67 at 1 year. This difference decreased over time and at year 3 was 2.45kg (95%CI 1.17, 3.73). 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 3.03, 5.97), and ≤28 interventions/year was 2.38 kg (95%CI 0.78, 3.98), 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

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%CI 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).

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,

lifestyle interventions 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 bariatric surgery is associated with lower all-cause, cardiovascular and cancer-related

mortality.(37) However, compared to lifestyle interventions bariatric surgery results in much 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.

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

progression of diabetes and to be cost effective.(40) The current meta-analysis did not assess other potential health benefits of weight loss such as reducing progression to diabetes.

Conclusion

Lifestyle programs with frequent patient interactions sustained over a year or more can achieve clinically meaningful weight loss, and this may lower mortality during long term follow-up. However the benefits of less frequent interventions over shorter durations in body weight are more modest and long term benefits to mortality risk are uncertain. Because there is limited data from randomised trials, it is uncertain whether lifestyle interventions for obesity decrease mortality in persons with cancer, heart failure or ischaemic heart disease.

Figure 1: Study flow chart

Figure 2: Effects of lifestyle intervention on weight loss at 1 year.

Figure 3: Effects of weight loss on mortality during a weighted average follow-up of 9.2 years. There is no heterogeneity for all (I^2=0).

Supplementary document 1: Protocol (includes search strategy)

Supplementary document 2: Supplementary figures.

Patient consent: Not required.

Contributor statement:

NS, RS and JB: conception of study, adjudication inclusion of studies, draft version manuscript. NS and JB: electronic database searches, data extraction, performed the analysis. RS and JB wrote the subsequent and final versions of manuscript in consultation

with NS, JB: regression model, designed the figures and tables. All authors discussed the results and commented on the manuscript.

Competing interests: nil

Funding: Nil

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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524 **Table 1: Baseline characteristic of 31 studies included in mortality meta-analysis.**
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Name of Study	Target population	Sample size N	Women number (%)	Mean BMI (kg/m²)	Mean initial weight (kg)	Mean age (years)	Intervention duration (years)	Follow-up duration (years)	Deaths
Summary statistic weighted mean		**615**	**346 (56)**	**32.5**	**87.2**	**53.8**	**2.39**	**2.49**	**19**
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 osteoarthritic older persons	318	229 (72)	34.3	93.8	68.5	1.5	1.5 (8 for mortality)	45
ALIFE@WORK (20)	Overweight/obese	1386	457 (33)	29.6	92.1	43	0.5	2	3

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

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

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

	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 pressure	564	180(32)	29.5	89.8	42.8	1.5	1.5	2
TOHP II (57)	Overweight/obese persons that are normo- or hypertensive	2382	810 (34)	30.9	93.6	43.6	3	3	12
TONE (30)	Overweight/obese elderly hypertensive persons	585	304 (52)	31.2	87.8	65.5	2.5	2.5 (12 mortality)	101
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

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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 contact outlines whether participants received interventions remotely by internet, email or over the phone (R) or face to face (F).

Study name Year Published	Type of contact	Mode of contact	Number of dietary interventions in year 1	Number of dietary interventions in year 2	Proportion of first year interventions in first 6 months (%)
All studies	***Individual= 7*** ***Group only = 5*** ***Group + individual=19***	***Face to face =11*** ***Remote = 3*** ***Face to face + remote= 17***	***27.5***	***3.96***	***66***
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

DPP (31)	G, I	F,R	22	12	73
EDIPS-Newcastle (44)	G,I	F	8	x	75
E-LITE (45)	G,I	F,R	38	x	61
HEALTH TRACK (32)	I	F,R	6	6	50
HCP (22)	I	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

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

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

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

Cancer	2	6%	2.70 [1.57, 3.83]	2	6%	2/438 (0.5%)	0.98 [0.06, 15.74]
Age							
40-49	12	47%	2.29 [0.97, 3.61]	14	9%	50/9868 (0.5%)	1.28 [0.71, 2.30]
50-59	12	39%	3.27 [2.38, 4.15]	12	69%	396/9691 (3.8%)	0.84 [0.69, 1.04]
>60	7	14%	4.50 [2.76, 6.25]	7	22%	155/2202 (7.0%)	0.78 [0.55, 1.10]
Look AHEAD	1	4%	3.40 [3.30, 3.50]	1	65%	376/5145 (7.3%)	0.85 [0.69, 1.05]
All other studies	29	96%	3.01 [2.23, 3.79]	32	35%	207/14455 (1.4%)	0.88 [0.66, 1.17]
Total	**30**	**100%**	**2.95 [2.35, 3.55]**	**32**	**100%**	**593/19463 (3.1%)**	**0.86 [0.73, 1.02]**

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*TAIM and HCP excluded for BMI

Da Quing excluded for all weight loss

+ P<0.0001 for all

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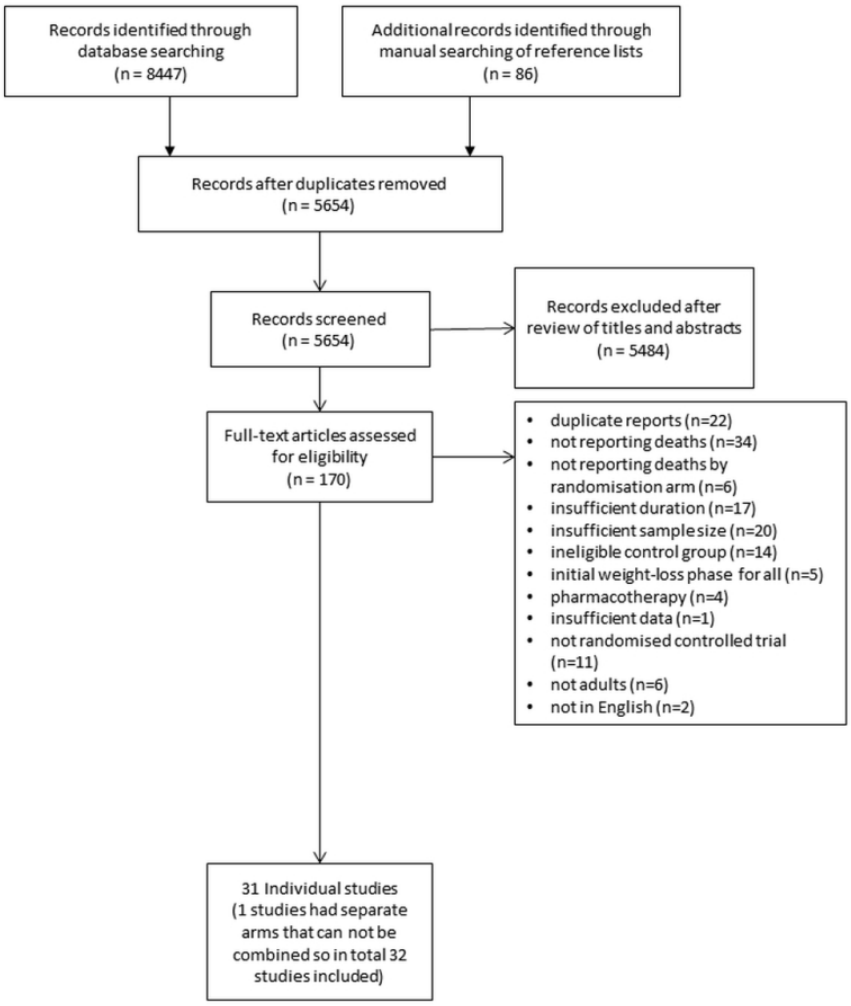
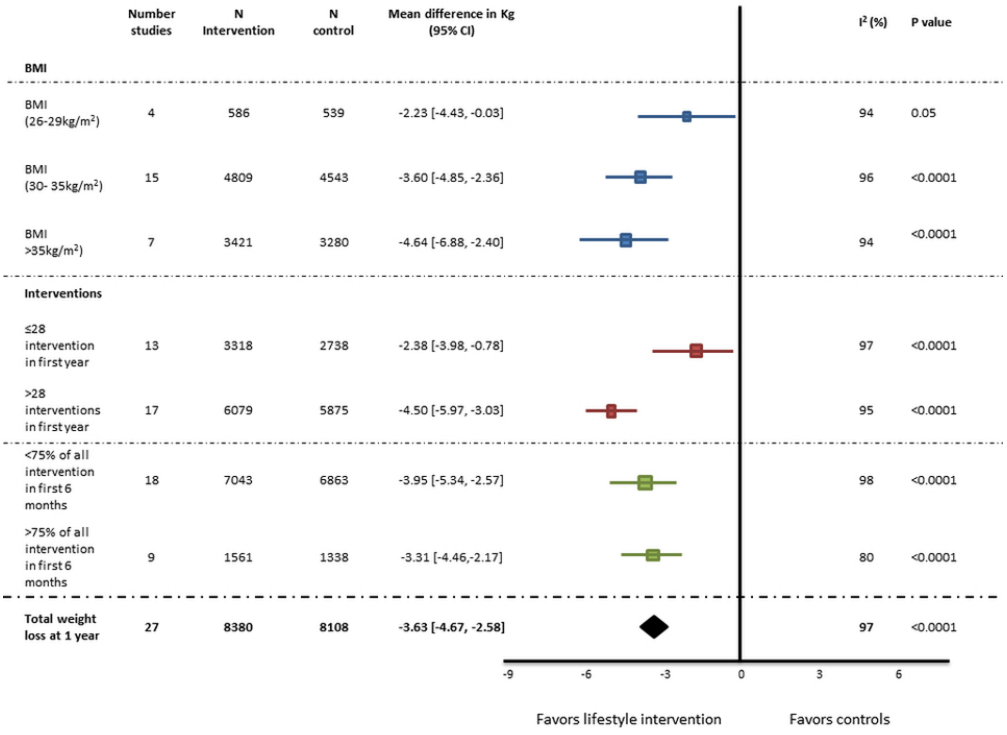


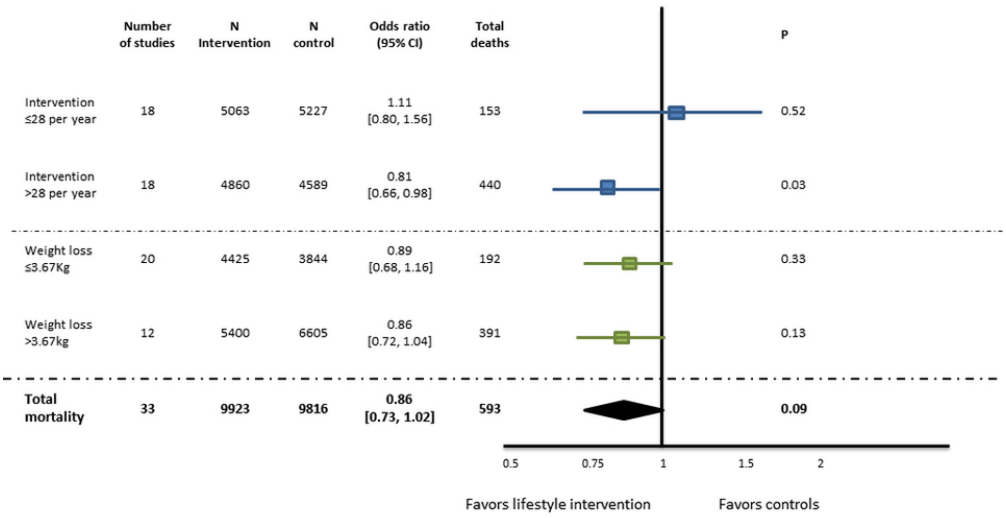
Study flow chart

67x90mm (300 x 300 DPI)



Effects of lifestyle intervention on weight loss at 1 year.

81x60mm (300 x 300 DPI)



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)

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

Study Protocol

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Background and Aim

Obesity has become a major public health issue with rates tripling between 1975 and 2016. In 2016 more than 2.1 billion people – nearly 30% of the world's population – were either obese (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. [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 guidelines[15] to prevent disease. These recommendations are predicated on the assumption that lifestyle advice achieves meaningful and sustained weight loss; and that this in turn is associated with reduced morbidity and mortality. Most guidelines do not stipulate precisely on how intensive lifestyle interventions have to be to be effective.

A previous meta-analysis[16] 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≥25kg/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 1and 2 broadly aimed to identify relevant studies in general populations, and search 3 broadly aimed to elicit appropriate studies in coronary heart disease populations. Duplicates between the three searches were removed.

The search details are as follows:

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

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

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

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

Statistical Analyses

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

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

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

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

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

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

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

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

1. Organisation WH. Obesity and overweight. February 2018 2018. http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 27 March 2018).
2. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifetsyle intervention or metformin. *New Eng J Med* 2002; **346**(6): 393-403.
3. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *The New England journal of medicine* 1997; **336**(16): 1117-24.
4. Casagrande DS, Rosa DD, Umpierre D, Sarmento RA, Rodrigues CG, Schaan BD. Incidence of cancer following bariatric surgery: systematic review and meta-analysis. *Obesity surgery* 2014; **24**(9): 1499-509.
5. Luo J, Chlebowski RT, Hendryx M, et al. Intentional Weight Loss and Endometrial Cancer Risk. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017; **35**(11): 1189-93.
6. Tee MC, Cao Y, Warnock GL, Hu FB, Chavarro JE. Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. *Surgical endoscopy* 2013; **27**(12): 4449-56.
7. Sundström J, Bruze G, Ottosson J, Marcus C, Näslund I, Neovius M. Weight Loss and Heart Failure: A Nationwide Study of Gastric Bypass Surgery Versus Intensive Lifestyle Treatment. *Circulation* 2017.
8. Adams TD, Davidson LE, Litwin SE, Hunt SC. Gastrointestinal surgery: cardiovascular risk reduction and improved long-term survival in patients with obesity and diabetes. *Current atherosclerosis reports* 2012; **14**(6): 606-15.
9. Lee GK, Cha YM. Cardiovascular benefits of bariatric surgery. *Trends in cardiovascular medicine* 2016; **26**(3): 280-9.
10. Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *European journal of preventive cardiology* 2014; **21**(6): 664-81.
11. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **130**(25): 2354-94.
12. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European heart journal* 2013; **34**(38): 2949-3003.

13. Standards of Medical Care in Diabetes-2017: Summary of Revisions. *Diabetes care* 2017; **40**(Suppl 1): S4-S5.
14. Federation ID. http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.
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-activity-cancer-prevention/guidelines.html (accessed 12 April 2018).
16. Kritchevsky SB, Beavers KM, Miller ME, et al. Intentional Weight Loss and All-Cause Mortality: A Meta-Analysis of Randomized Clinical Trials. *PloS one* 2015; **10**(3): e0121993.

Supplementary document 2

Supplementary figures

Figure 1a: Weight loss at 1 year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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	23.4	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]
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]
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]
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]
ADAPT 2010	-4.8	7.5	159	-1.4	5.1	159	3.9%	-3.40 [-4.81, -1.99]
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]
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 I 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]**

Heterogeneity: Tau² = 6.78; Chi² = 797.51, df = 26 (P < 0.00001); I² = 97%
Test for overall effect: Z = 6.81 (P < 0.00001)

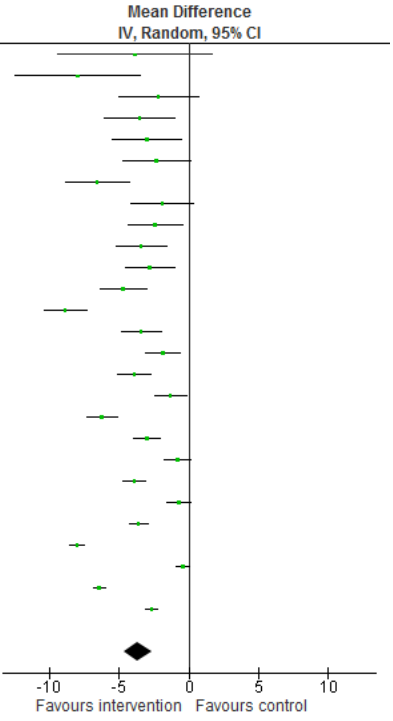


Figure 1b : Weight loss at 1 year- funnel plot

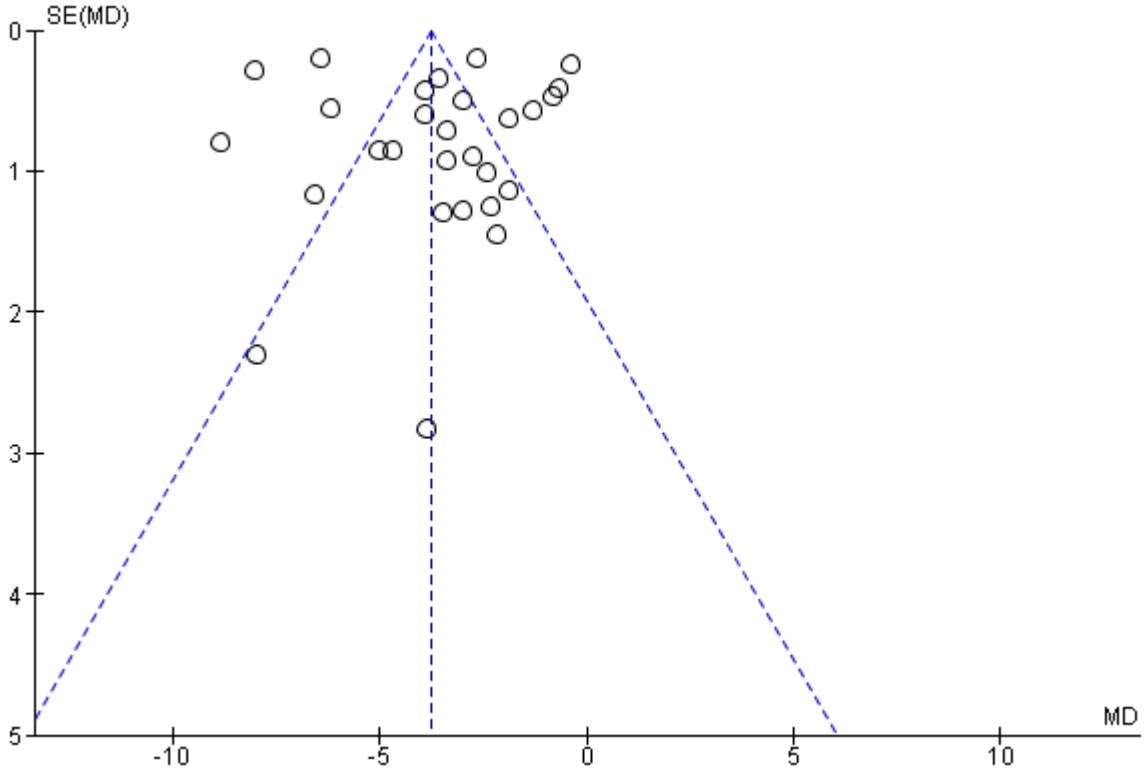


Figure 2a: Weight loss at 2 years

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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: Tau² = 6.07; Chi² = 419.82, df = 11 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.28 (P = 0.001)

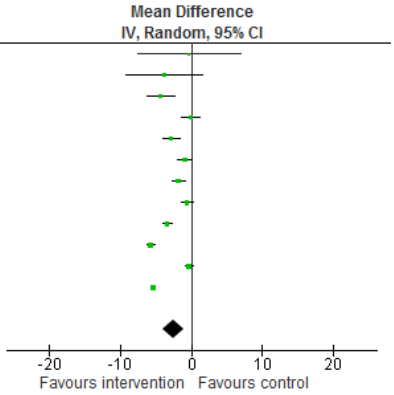


Figure 2b: Weight loss at 2 years- funnel plot

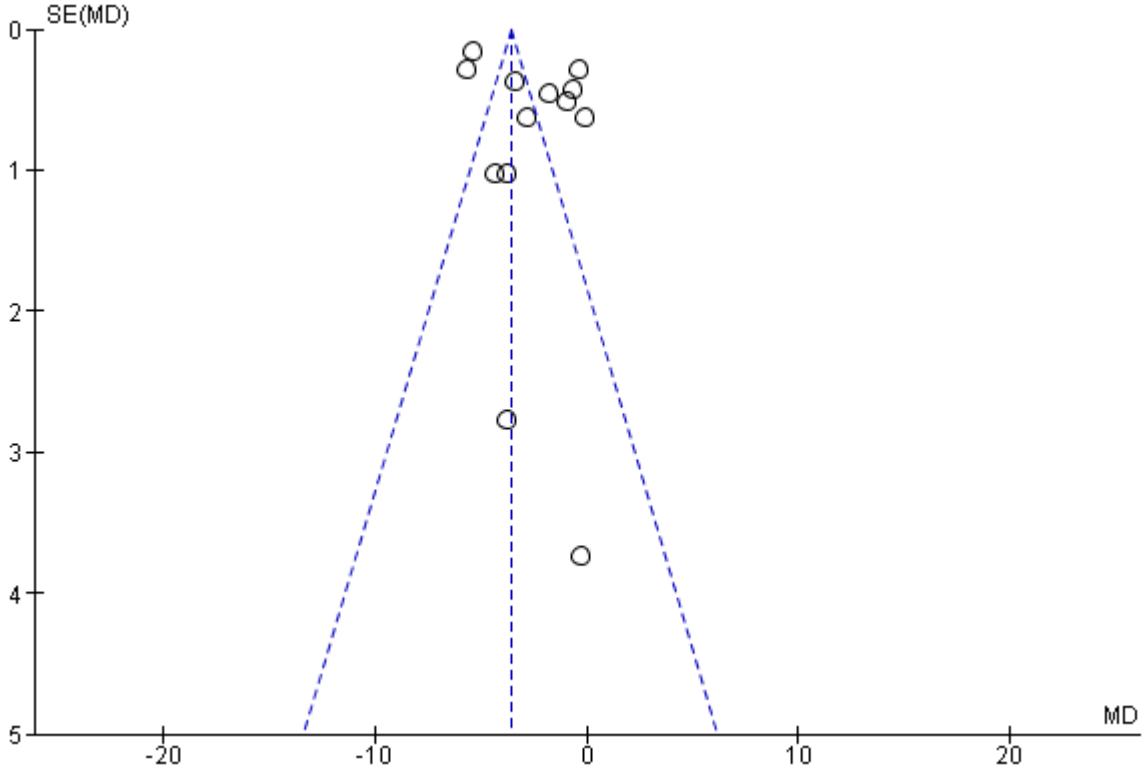


Figure 3a: Weight loss at 3 years

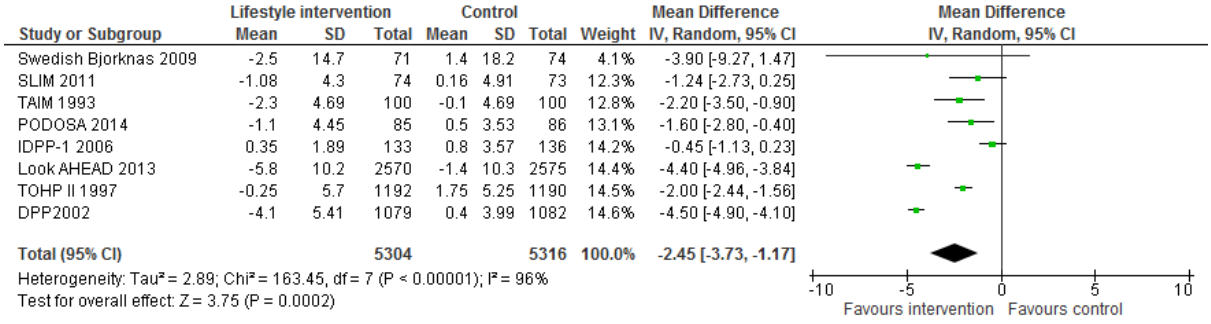


Figure 3b: Weight loss at 3 years- funnel plot

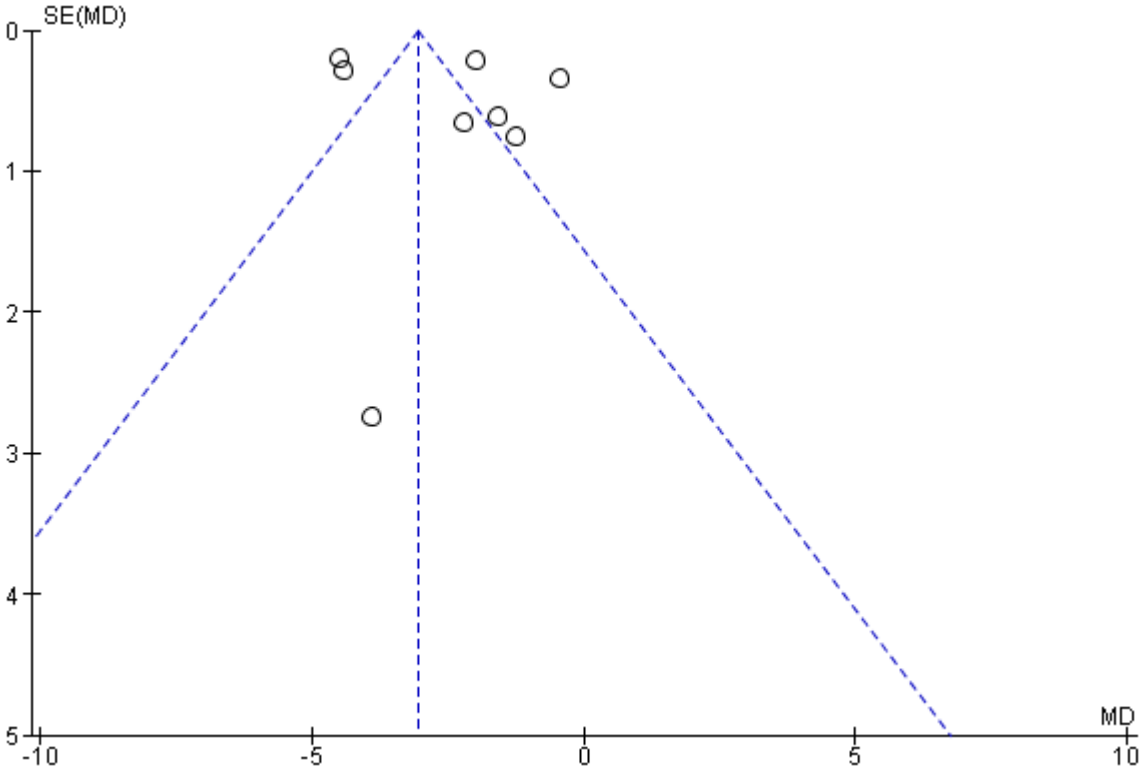
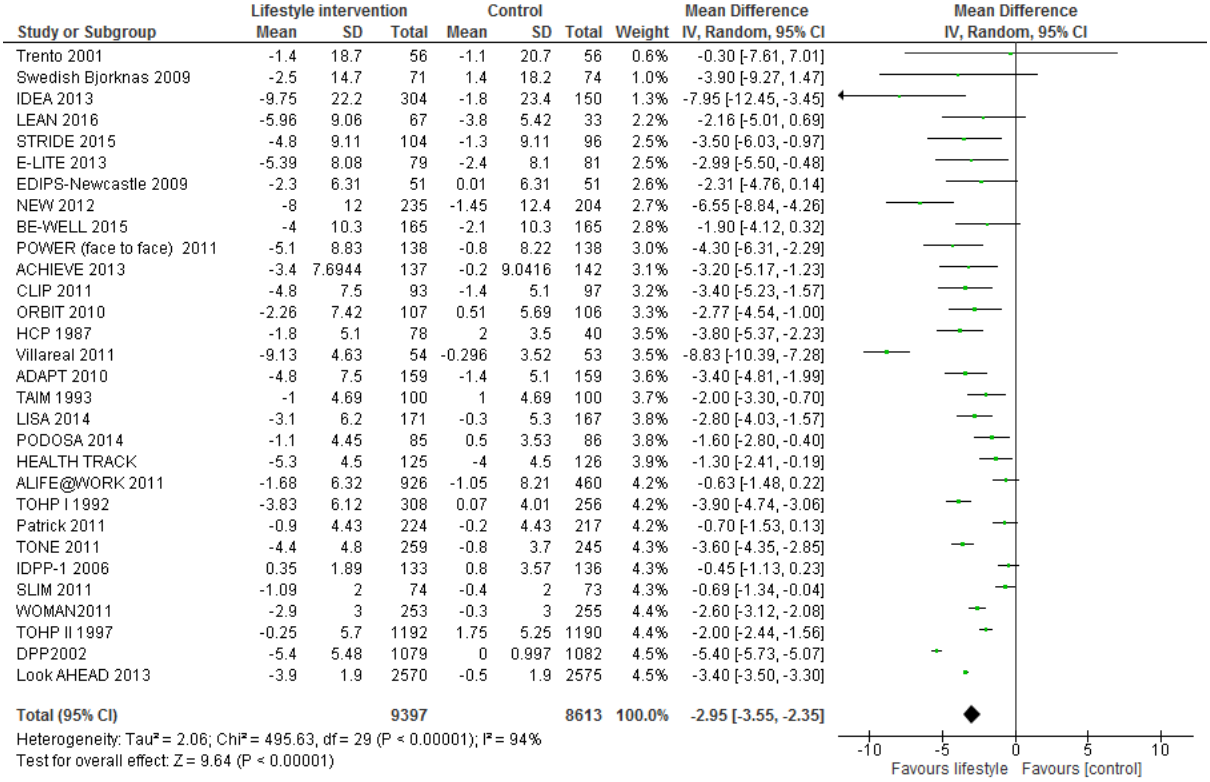


Figure 4a: Weight loss achieved by end of study



Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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 I 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	5.25	1190	4.4%	-2.00 [-2.44, -1.56]
DPP2002	-5.4	5.48	1079	0	0.997	1082	4.5%	-5.40 [-5.73, -5.07]
Look AHEAD 2013	-3.9	1.9	2570	-0.5	1.9	2575	4.5%	-3.40 [-3.50, -3.30]
Total (95% CI)			9397			8613	100.0%	-2.95 [-3.55, -2.35]

Heterogeneity: Tau² = 2.06; Chi² = 495.63, df = 29 (P < 0.00001); I² = 94%
Test for overall effect: Z = 9.64 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
Favours lifestyle Favours [control]

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

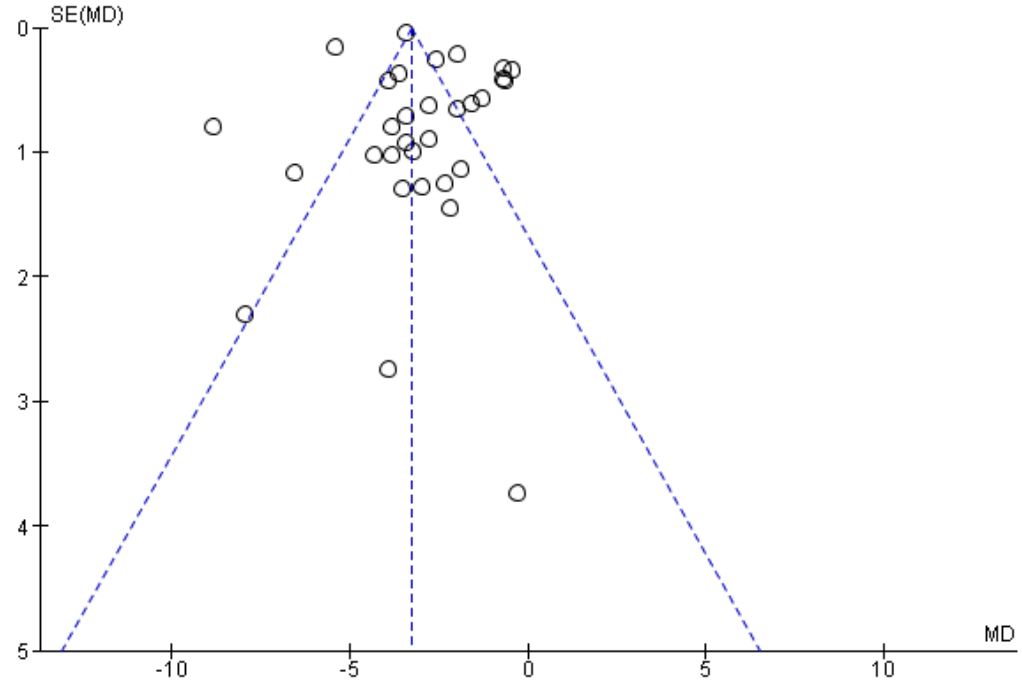


Figure 5a: Weight loss ≤28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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]
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 I 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: Tau² = 8.01; Chi² = 450.59, df = 13 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.92 (P = 0.003)

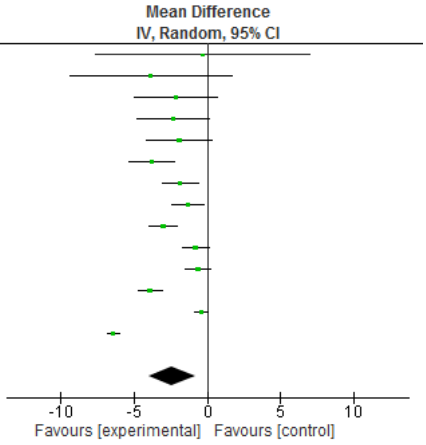


Figure 5b: Weight loss >28 interventions/year

Study or Subgroup	Lifestyle intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
IDEA 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]
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]
NEW 2012	-8	12	235	-1.45	12.4	204	6.0%	-6.55 [-8.84, -4.26]
ACHIEVE 2013	-2.8	7.96	137	-0.4	9.28	142	6.2%	-2.40 [-4.43, -0.37]
ORBIT 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]
Villareal 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]
LISA 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]
TONE 1998	-4.4	4.8	259	-0.8	3.7	245	6.9%	-3.60 [-4.35, -2.85]
Look 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]
Total (95% CI)			**6079**			**5875**	**100.0%**	**-4.50 [-5.97, -3.03]**

Heterogeneity: Tau² = 7.96; Chi² = 404.88, df = 15 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.00 (P < 0.00001)

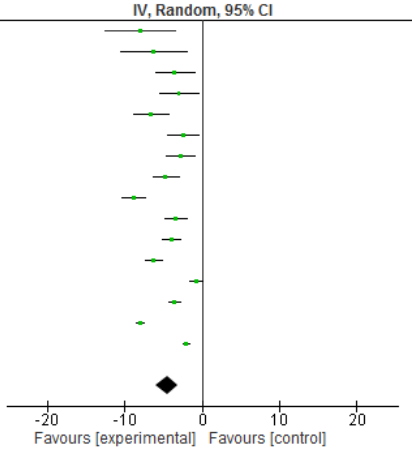


Figure 6a: Total mortality

Study or Subgroup	Lifestyle intervention Events	Total	Control Events	Total	Weight	Odds Ratio 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 I 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 II 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: Chi² = 15.54, df = 23 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

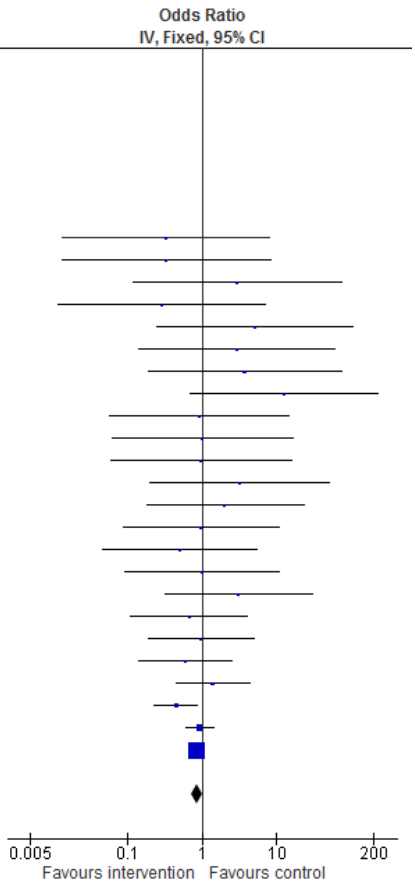


Figure 6a: Total mortality- funnel plots

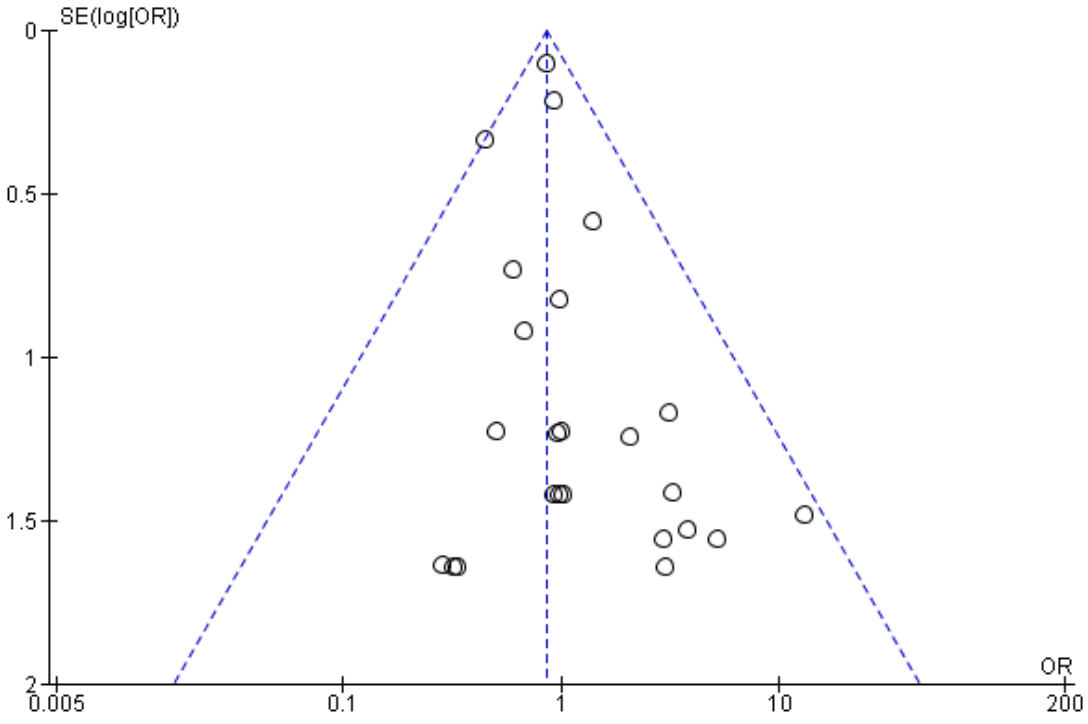


Figure 7a: Mortality ≤ 28 – interventions per year

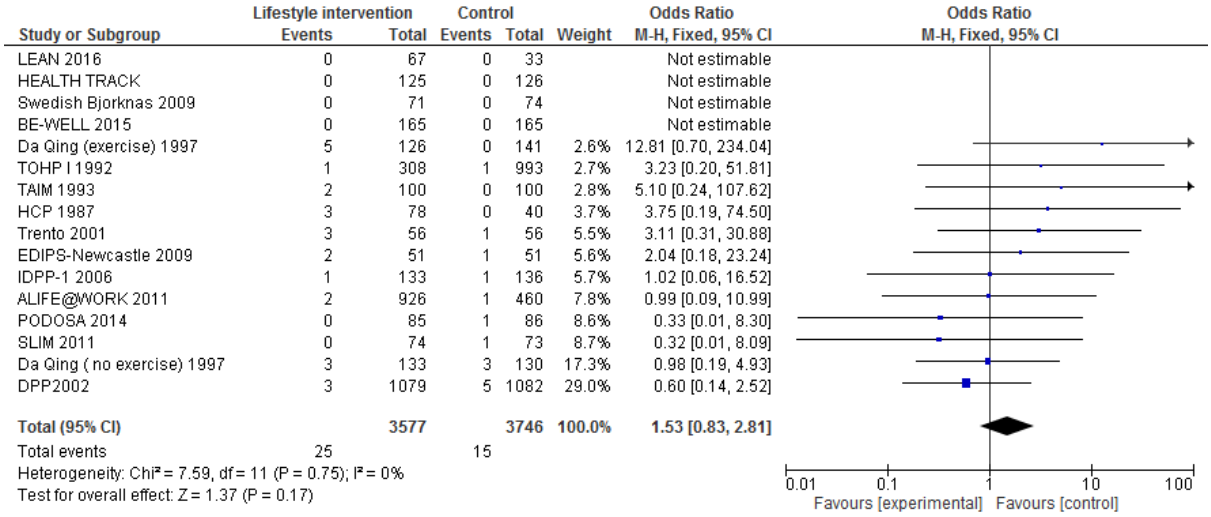
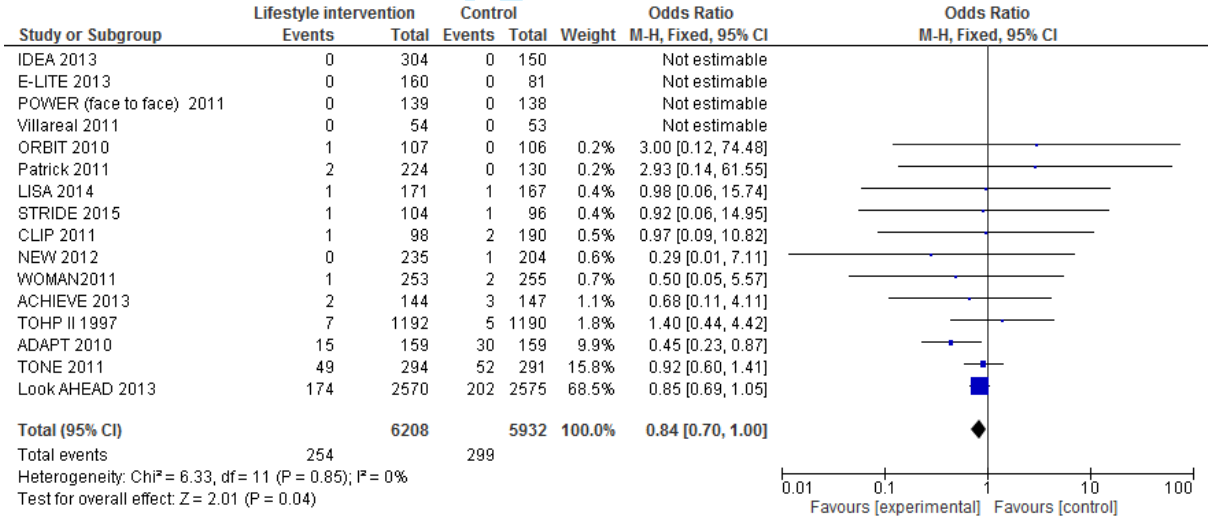


Figure 7b: Mortality >28 – interventions per year



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 (e.g., risk ratio, difference in means).	7

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

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.	Supplementary 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

PRISMA 2009 Checklist

FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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