Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis

Chenhan Ma,[1] Alison Avenell,[1] Mark Bolland,[2] Jemma Hudson,[1] Fiona Stewart,[1] Clare Robertson,[1] Pawana Sharma,[1] Cynthia Fraser,[1] Graeme MacLennan[3]

[1]Health Services Research Unit, University of Aberdeen, Health Sciences Building, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK

[2]Bone and Joint Research Group, Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand

[3]Centre for Healthcare Randomised Trials, University of Aberdeen, Health Sciences Building, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK

Correspondence to: A Avenell
a.avenell@abdn.ac.uk

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ABSTRACT

OBJECTIVE

To assess whether weight loss interventions for adults with obesity affect all cause, cardiovascular, and cancer mortality, cardiovascular disease, cancer, and body weight.

DESIGN

Systematic review and meta-analysis of randomised controlled trials (RCTs) using random effects, estimating risk ratios, and mean differences. Heterogeneity investigated using Cochran's Q and I^2 statistics. Quality of evidence assessed by GRADE criteria.

DATA SOURCES

Medline, Embase, the Cochrane Central Register of Controlled Trials, and full texts in our trials' registry for data not evident in databases. Authors were contacted for unpublished data.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

RCTs of dietary interventions targeting weight loss, with or without exercise advice or programmes, for adults with obesity and follow-up ≥1 year.

RESULTS

54 RCTs with 30 206 participants were identified. All but one trial evaluated low fat, weight reducing diets. For the primary outcome, high quality evidence showed that weight loss interventions decrease all cause mortality (34 trials, 685 events; risk ratio 0.82, 95% confidence interval 0.71 to 0.95), with six fewer deaths per 1000 participants (95% confidence interval two to 10). For other primary outcomes moderate quality evidence showed an effect on cardiovascular mortality (eight trials, 134 events; risk ratio 0.93, 95% confidence interval 0.67 to 1.31), and very low quality evidence showed an effect on cancer mortality (eight trials, 34 events; risk ratio 0.58, 95% confidence interval 0.30 to 1.11). Twenty four trials (15 176 participants) reported high quality evidence on participants developing new cardiovascular events (1043 events; risk ratio 0.93, 95% confidence interval 0.83 to 1.04). Nineteen trials (6330 participants) provided very low quality evidence on participants developing new cancers (103 events; risk ratio 0.92, 95% confidence interval 0.63 to 1.36).

CONCLUSIONS

Weight reducing diets, usually low in fat and saturated fat, with or without exercise advice or programmes, may reduce premature all cause mortality in adults with obesity.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42016033217.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

Whether recommendations to follow weight reducing diets can reduce premature mortality, cardiovascular disease, and cancer for adults who are obese is unclear

WHAT THIS STUDY ADDS

Weight reducing diets, usually low in fat and saturated fat, with or without exercise advice or programmes, may reduce premature all cause mortality in adults who are obese

Our data provide supporting evidence for public health measures to prevent weight gain and facilitate weight loss using diets low in fat and saturated fat

Introduction

Adults with obesity have an increased risk of premature mortality, cardiovascular disease, some cancers, type 2 diabetes, and many other diseases.[1 2] These associations inform the need for programmes to prevent obesity, but, apart from prevention of type 2 diabetes,[3 4] limited evidence from randomised controlled trials (RCTs) shows that weight loss interventions can prevent serious harm for people with obesity. Evidence from cohort studies has led to debate that deliberate weight loss for people who are overweight or obese, with body mass index (BMI) ≤35 kg/m^2, might actually be harmful.[5] Studies show that older people,[6] and those with cardiovascular disease[7] who are less markedly obese, might experience adverse consequences from deliberate weight loss. Recent analyses by the Global BMI Mortality Collaboration, however, tried to limit confounding and corrected for reverse causality, finding that the risk of premature mortality was lowest at BMIs of 20-25.[8]

Association studies cannot tell us if deliberate weight loss in adults with obesity can reduce their risk of premature mortality, cardiovascular disease, or cancer. Only one systematic review and meta-analysis of RCTs of intentional weight loss in adults with obesity has examined this question.[9] That review included 15 trials, reporting a 15% relative reduction in premature mortality (risk ratio 0.85, 95% confidence interval 0.73 to 1.00), but did not evaluate causes of death or cardiovascular and cancer outcomes.[9] We knew of many other weight loss RCTs with mortality data, as well as cancer and cardiovascular outcomes, from our database of long term RCTs of weight loss interventions for adult obesity, which was developed for health technology assessments[10 11] and is continually updated. We systematically reviewed long term (≥1 year) RCTs of weight loss interventions for adults with obesity to examine the effects of any type of weight loss

diet on all cause, cardiovascular, and cancer mortality, cardiovascular disease, cancer, and body weight.

Methods

We adhered to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for systematic reviews of interventions.[12] We used a prespecified protocol, registered with PROSPERO (CRD42016033217).[13]

Search strategy and selection criteria

We included RCTs with adults (mean or median age ≥18 years) and a minimum follow-up of one year. Participants had a mean BMI ≥30 at baseline. Included trials had to be focused clearly on weight loss with a weight reducing diet, with or without advice for increasing physical activity and/or provision of a physical activity programme to attend, compared with a control intervention. We didn't include trials in pregnant or postpartum women.

We sought summary data for three primary outcomes: all cause mortality, cardiovascular mortality, and cancer mortality. Secondary outcomes were participants with a new cardiovascular event, participants with a new cancer, and weight change. In our main analysis we used cardiovascular mortality and events as defined by the investigators but did not include the development of hypertension. We undertook post hoc analyses of cardiovascular mortality and cardiovascular events as defined in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[14]

We identified RCTs by searching the full texts of trial reports in our database of all long term (≥1 year) RCTs of weight loss interventions for adults with obesity used in our previous systematic reviews and health technology assessments. Our database is derived from previous search strategies compiled from Medline, Embase, and the Cochrane Central Register of Controlled Trials, from 1966 to December 2015.[10 11] We performed an updated search from August 2015 to December 2016. We didn't apply any language exclusions. In 2016-17 we contacted the authors of 48 RCTs to clarify data or request unpublished outcome data, where trial reports implied that relevant data might be available; for example, when the trial reported hospital admissions or adverse events without giving further details.

Data analysis

AA and CM independently confirmed study eligibility. CM, FS, CR, and PS extracted data, which were then checked by a second author (AA, CM). Cancer outcome and cardiovascular outcome data (including coding outcomes defined by the ACC/AHA guideline[14]) were further adjudicated by MB, with differences resolved by Andrew Grey (associate professor in the Department of Medicine, University of Auckland). Two authors (AA, CM, FS, CR, PS) independently assessed quality using the Cochrane risk of bias tool.[15] All differences were resolved by discussion.

We used random effects meta-analysis to analyse pooled outcome data. For binary outcomes, we estimated risk ratios and 95% confidence intervals, using all participants randomised for the denominators. We estimated weighted mean differences and 95% confidence intervals for continuous outcomes, giving preference to intention to treat data and data taking account of dropouts (preferentially baseline observation carried forward) if these were provided. We included outcome data from two cluster RCTs[16 17] using the correction method described in the Cochrane Handbook[18] and the intraclass correlation coefficients reported in the original trial publications. We assessed heterogeneity between studies using Cochran's Q statistic and the I^2 test. We originally planned meta-regression to investigate heterogeneity in disease outcomes, but I^2 tests for disease outcomes were 0%, so it was not appropriate. We carried out a sensitivity analysis with a random effects bayesian logistic regression model (with non-informative priors) using WinBUGS 1.4.3[19] because some trials reported few events, which may cause sparse data bias. We performed all other analyses using Stata Release 14[20] and used funnel plots to examine small study bias.

For all outcomes we performed prespecified subgroup analyses for sex, age (<60 *v* ≥60), BMI (<40 *v* ≥40, later changed to <35 *v* ≥35 as we found no trial with BMI ≥40), glycaemic control (normal *v* impaired glucose tolerance or impaired fasting glucose *v* type 2 diabetes), ethnicity (defined if ≥80% of participants belonged to an ethnic group, otherwise defined as mixed), physical activity interventions (none *v* advice only *v* exercise programme provided).

In post hoc additional analyses we added trials in any Asian population group if the mean BMI was ≥25, as diseases associated with obesity are known to occur at lower BMI in Asian populations than other ethnic groups.[21] No single BMI cut-off has been agreed to define obesity in Asian populations. Although the World Health Organization recommends 27.5 as a BMI threshold for a high risk of comorbidities,[21] it also suggests that Asian countries develop their own specific BMI cut-offs for obesity. India and Japan have set ≥25 as the threshold for obesity,[22 23] and in China the risk of comorbidities has been found to increase for BMI over 28.[24]

For all outcomes we performed two prespecified sensitivity analyses for allocation concealment (low risk of bias vs other risk of bias) and follow-up (<80% vs ≥80%).

We used GRADE (grading of recommendations, assessment, development, and evaluations) to judge the quality of the evidence for mortality, cardiovascular, and cancer outcomes.[25]

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing this report. CM and AA had full access to all study data and had final responsibility for the decision to submit for publication.

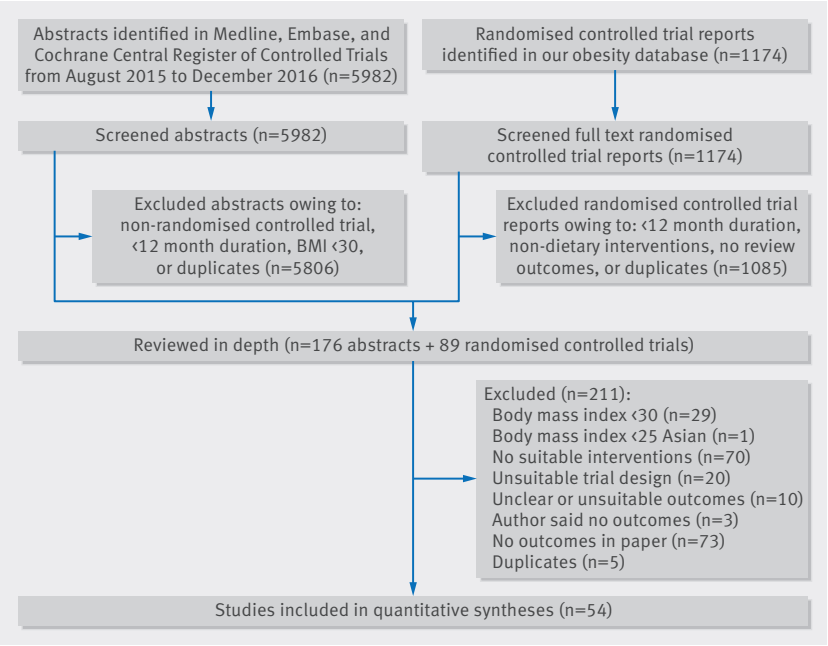

Fig 1 | Study selection

Patient involvement

No patients or members of the public were involved in the development of research questions, the design of the study, or the development of outcome measures. No patients were asked to advise on interpretation or writing up of results. There are plans to disseminate the results of the research to the relevant patient community.

Results

Trial characteristics

We screened 1174 full text trial reports and 5982 titles and abstracts (fig 1) and identified 54 RCTs for inclusion[3 4 16 17 26-96] in the final review.

Table 1 provides details of the included studies, involving 30 206 adults with obesity. Nine trials (16.7%) included women only,[2 6 44 45 50-52 77 88 94] and two (3.7%) men only.[58 72] Twelve trials (22.2%) recruited participants with no reported existing medical conditions or no reported increased risk of developing comorbidities related to obesity. Other trials recruited participants with increased risk of type 2 diabetes or hypertension or included participants that already had at least one of the following conditions: hypertension, type 2 diabetes, hyperlipidaemia, breast cancer, colorectal adenoma, psychiatric illnesses, cognitive impairment, osteoarthritis of the knee, coronary heart disease, or urinary incontinence.

Five trials (9.3%) were undertaken in Asian populations,[16 17 59 75 80] but only one with BMI ≥30,[2 16] one trial (1.9%) was in a population of black people in the USA,[50] 31 (57.4%) in populations of white people, and 17 (31.5%) in mixed population groups. Thirty one (57.4%) trials took place in North America, 16 (29.6%) in Europe, two (3.7%) in Australia, and one (1.9%) in Brazil. The four trials in Asian populations outside the UK had mean BMIs between 25 and 30.[17 59 75 80] Thirty six (66.7%) trials had participants with a mean or median BMI <35, and 14 (25.9%) had BMIs ≥35 (table 1).

Most trials recruited predominantly middle aged adults. Fourteen (25.9%) had a mean or median age at baseline of 60 years or more, none had a mean or median age of under 40 years. Thirty one (57.4%) trials followed participants for two years or longer, and seven (13.0%) trials (9,937 participants) followed participants for five years or longer. In 39 trials (72.2%) the drop-out rate was <20% at trial completion.

Detailed descriptions of the weight loss diets were not always clearly provided in the trials. All but one of the trials described at least one of their interventions as being a low fat weight reduction diet (usually ≤30% of energy as fat, although this was not always specified) or had sufficient information to establish that a reduction in fat intake was prescribed. Most trials also described the prescription of a reduction in saturated fat. One trial described using a balanced Mediterranean diet.[79] One trial included the option to undertake a diet with ≤50 g/day of carbohydrate.[96] Two weight loss trials specifically described diets to reduce low glycaemic index as part of their intervention,[26 30] whereas other trials generally described diets that would be compatible with lowering glycaemic indices by increasing intake of complex carbohydrates and dietary fibre. Four trials (7.4%) were based on the DASH (dietary approaches to stop hypertension) diet.[31 39 40 54] Eight (14.8%) trials based their diets on those of the US Diabetes Prevention Program,[4 26 52 60 67 74 93 94] and four trials (7.4%) described basing their content in part on different editions of the Dietary Guidelines for Americans.[64 69 72 76]

Only three trials (5.6%) did not report providing exercise advice or an exercise programme.[45 55 68] Twenty two trials (40.7%) provided an exercise programme for participants to attend, and 29 trials (53.7%) described providing advice to increase exercise only, without an exercise programme.

Supplementary figure 1 provides our risk of bias assessments for individual studies. Only 15 trials (27.8%) reported methods of randomisation and allocation concealment judged to be at low risk of bias. Blinding of participants and study personnel was rarely possible, but we judged that lack of blinding of outcome assessment would rarely have been a source of bias except for weight outcomes. Only 10 (18.5%) trials were judged to be at low risk for attrition bias, and 12 (22.2%) at low risk for reporting bias. Seven (13.0%) trials were judged to be at high risk of bias as a result of premature trial termination,[52 65 75] change in the primary outcome,[16] influence of a drug placebo in the control group,[4] or trial investigators reporting that they were sponsored by grants from a commercial weight loss programme[71] or that they were co-owners of a company developing products related to the research.[72]

Table 1 | Characteristics of randomised controlled trials

Trial	n	Dropout (%)	Follow-up (months)	Comorbidities and drugs	Mean age (SD)	Female (%)	Smoke (%)	Ethnicity	Mean BMI, kg/m2 (SD)	Main weight loss interventions	Comparisons
Abbenhardt, 2013, USA[26 27]	439	9.1	12	NR	58.0 (5.0)	100	0	White	30.9 (4.0)	Group 1—Diet based on DPP and Look AHEAD (1200-2000 kcal/d, <30% calories from fat, <10% from saturated fat, for 10% weight loss) Group 2—Diet as above plus exercise programme	Group 3—Control Group 4—Exercise programme
Abed, 2013, Australia[28]	150	46.0	15	Atrial fibrillation	60.1 (9.9)	33	5	White	33.3 (3.8)	Group 1—Diet (800-1200 kcal/d for 8 weeks as 2 VLCD sachets and 1 low GI meal; weight maintenance low GI and low fat diet) and exercise advice	Group 2—Control
Ackerman, 2015, USA[29]	509	15.5	12	Impaired glucose tolerance or impaired fasting glucose	51.0 (12.1)	70.7	NR	Mixed	36.8 (8.5)	Group 1—Diet based on DPP (low calorie, <25% calories from fat, low saturated fat, for 5-7% weight loss) and exercise advice	Group 2—Control
Andrews, 2011, UK[30]	593	2.4	12	Type 2 diabetes	60.0 (10.1)	35	8	White	31.7 (5.7)	Group 1—Diet based on Diabetes UK and Food Standards Agency (<35% calories from fat, <10% from saturated fat, low GI, for 5-10% weight loss) Group 2—Diet as above and exercise advice	Group 3—Control
Appel, 2003, USA (PREMIER)[31-33]	810	11.4	18	Above normal blood pressure	50.3 (8.9)	62	5	Mixed	33.1 (5.8)	Group 1—Diet (≤30% calories from fat, ≤10% from saturated fat, ≥6.8 kg weight loss) and exercise programme Group 2—Diet based on DASH (≤25% calories from fat, ≤7% from saturated fat, ≥6.8 kg weight loss) and exercise programme	Group 3—Control
Ard, 2016, USA[34]	167	11.4	12	Drugs for diabetes, lipids, or blood pressure	70.3 (4.7)	62.2	NR	Mixed	33.7 (2.95)	Group 1—Diet (28% calories from fat and 500 kcal/d deficit) and exercise programme Group 2—Diet (28% fat for weight maintenance) and exercise programme	Group 3—Exercise programme
Aveyard, 2016, UK[35]	1882	24.6	12	NR	56.0 (16.1)	57.2	NR	White	34.9 (4.8)	Group 1—Diet mainly Slimming World (low fat and low saturated fat) and exercise advice	Group 2—Control
Bennett, 2012, USA[36]	365	14.0	24	Drugs for blood pressure	54.6 (10.9)	69	18	Mixed	37.0 (5.1)	Group 1—Diet (low fat and low saturated fat, weight reducing diet) and exercise advice	Group 2—Control
Anderson, 2014, UK (BeWEL)[37]	329	7.3	12	Colorectal adenoma removal	63.6 (6.8)	26	NR	White	30.7 (4.2)	Group 1—Diet based on British Heart Foundation (600 kcal/d deficit, low fat, low saturated fat, for 7% weight loss) and exercise advice	Group 2—Control
Bhopal, 2014, UK[16]	171	2.3	36	Impaired glucose tolerance or impaired fasting glucose	52.5 (10.3)	54	6	Asian	30.6 (4.8)	Group 1—Diet based on the Counterweight programme (500-600 kcal/d deficit, 30% calories from fat, for 5-10% weight loss) and exercise advice	Group 2—Control
Blonk, 1994, Netherlands[38]	60	11.7	24	Type 2 diabetes	58.8*	57	NR	White	32.0*	Group 1—Diet (500 kcal/d deficit, 30% calories from fat, low saturated fat) and exercise programme	Group 2—Control
Burke, 2008, Australia[39]	241	41.9	40	Drugs for blood pressure	56.2 (7.4)	56	3	White	30.1 (2.7)	Group 1—Diet based on DASH (<30% calories from fat, low sat fat, for 5-10% weight loss) and exercise advice	Group 2—Control
Daumit, 2013, USA[40]	291	4.1	18	Psychiatric illness rehabilitation	45.3 (11.3)	50	NR	Mixed	36.3 (7.3)	Group 1—Diet based on DASH (low fat, low saturated fat, for 4.5 kg weight loss) and exercise programme	Group 2—Control

(Continued)

Table 1 | Characteristics of randomised controlled trials (Continued)

Trial	n	Dropout (%)	Follow-up (months)	Comorbidities and drugs	Mean age (SD)	Female (%)	Smoke (%)	Ethnicity	Mean BMI, kg/m2 (SD)	Main weight loss interventions	Comparisons
Davis, 1993, USA (TAIM)[41]	587	31.0	30	Mild hypertension	47.9 (NR)	46	16	Mixed	30.2 (NR)	Group 1—Diet (low fat, for 4.5kg or 10% weight loss) and exercise advice	Group 2—Control
de Vos, 2014, Netherlands[42-44]	407	39.3	80	Free of knee osteoarthritis or rheumatic diseases	55.7 (3.2)	100	17.9	White	32.4 (4.3)	Group 1—Diet (tailored low fat or low calorie reducing diet) and exercise programme	Group 2—Control
de Waard, 1993, Netherlands, Poland[45]	107	28.6	36 Netherlands, 12 Poland	Breast cancer	50-69†	100	NR	White	30.2 (NR)	Group 1—Diet (1000-1500 kcal/d balanced diet)	Group 2—Control
DPP, 2002, USA[4 46 47]	3234	9.9	34	Impaired glucose tolerance	50.6 (10.7)	67	7	Mixed	34.0 (6.7)	Group 1—Diet (low calorie, <25% calories from fat, low saturated fat, for 7% weight loss) and exercise programme	Group 2—Control and metformin placebo
Finnish DPS, 2009, Finland[3 48 49]	523	16.4	138	Impaired glucose tolerance	55.2 (7.2)	67	7	White	31.3 (4.5)	Group 1—Diet (<30% calories from fat, <10% from saturated fat, for ≥5% weight loss) and exercise programme	Group 2—Control
Fitzgibbon, 2010, USA[50]	213	10.8	18	NR	46.0 (8.4)	100	NR	Black	39.2 (5.7)	Group 1—Diet (low calorie, low fat, for 7% weight loss) and exercise programme	Group 2—Control
Gabriel, 2011, USA[51]	508	10.2	48	Postmenopausal, some on hormone replacement therapy	57.0 (2.9)	100	6	White	30.8 (3.8)	Group 1—Diet (<17% calories from fat, <4% from saturated fat, 1300-1500 kcal/d) and exercise advice	Group 2—Control
Goodwin, 2014, Canada, USA[52]	338	12.7	24	Breast cancer, letrozole therapy	61.0 (7.2)	100	7	White	31.3 (5.2)	Group 1—Diet based on DPP (20% calories from fat, 500-1000 kcal/d deficit) and exercise advice	Group 2—Control
Greaves, 2015, UK[53]	108	11.1	12	High cardiovascular risk	65.1 (7.0)	30.6	NR	White	32.7 (3.1)	Group 1—Diet (low fat, low sat fat diet, for ≥5% weight loss) and exercise advice	Group 2—Control
Green, 2015, USA[54]	200	18.0	24	Antipsychotic drugs	47.2 (10.6)	72	33	White	38.3 (8.3)	Group 1—Diet based on DASH (≤30% calories from fat, ≤10% from saturated fat, for 4.5-6.8 kg weight loss) and exercise programme	Group 2—Control
Heller, 1988, UK[55]	87	13.8	12	Diabetes	56.5 (7.7)	52	NR	White	31.6 (3.3)	Group 1—Diet (low sugar, high fibre for weight loss)	Group 2—Control
Heshka, 2003, USA[56]	423	27.0	24	NR	44.5 (10.0)	85	9	White	33.7 (3.6)	Group 1—Diet (Weight Watchers for weight loss of 0.9 kg/w) and exercise advice	Group 2—Control
Horie, 2016, Brazil[57]	80	6.3	12	Mild cognitive impairment	68.1 (4.9)	83.8	1.3	Mixed	35.5 (4.4)	Group 1—Diet (<30% calories from fat, 500 kcal/d deficit) and exercise advice	Group 2—Control
Hunt, 2014, UK (FFIT)[58]	748	17.7	12	NR	47.1 (8.0)	0	NR	White	35.3 (4.9)	Group 1—Diet (low fat, 600 kcal/d deficit, healthy eating) and exercise programme	Group 2—Control
Hydrie, 2012, Pakistan[59]	317	13.6	18	Impaired glucose tolerance	43.6 (9.9)	25	NR	Asian	27.0 (5.0)	Group 1—Diet (<30% calories from fat, for ≥5% weight loss) and exercise programme	Group 2—Control
Katula, 2013, USA[60]	301	13.3	24	Impaired fasting glucose	57.9 (9.5)	58	5	Mixed	32.7 (4.0)	Group 1—Diet based on DPP (low calorie, 25-30% fat, 7% saturated fat, 1200-1800 kcal/d, for 5-7% weight loss) and exercise advice	Group 2—Control
Li Da Qing, 2014, China[17 61-63]	577 (33 clinics)	8.1	72	Impaired glucose tolerance	45.0 (9.1)	47	41	Asian	25.8 (3.8)	Group 1—Diet (BMI <25, 25-30 kcal/kg, 25-30% calories from fat; BMI ≥25 reduce calories to lose 0.5-1 kg/month, until BMI=23). Group 2—Diet as above and exercise advice	Group 3—Control Group 4—Exercise advice
Logue, 2005, USA[64]	665	34.6	24	NR	52.3 (NR)	69	NR	Mixed	34.2 (NR)	Group 1—Diet based on DGA (low calorie, low fat, low saturated fat, portion control) and exercise advice	Group 2—Control

(Continued)

Table 1 | Characteristics of randomised controlled trials (Continued)

Trial	n	Dropout (%)	Follow-up (months)	Comorbidities and drugs	Mean age (SD)	Female (%)	Smoke (%)	Ethnicity	Mean BMI, kg/m2 (SD)	Main weight loss interventions	Comparisons
Look AHEAD, 2013, USA[65 66]	5145	3.7	115	Type 2 diabetes	58.8 (6.9)	60	4	Mixed	36.0 (5.9)	Group 1—Diet (1200-1800 kcal/d, <30% calories from fat, <10% from saturated fat, for 7% weight loss, meal replacements) and exercise programme	Group 2—Control
Ma, 2013, USA[67]	241	34.4	24	Impaired fasting glucose or metabolic syndrome	52.9 (10.6)	47	NR	White	32.0 (5.4)	Group 1—Diet based on DPP (500-1000 kcal/d deficit, 25% calories from fat, for 7% weight loss) and exercise programme Group 2—Self directed diet and exercise as above	Group 3—Control
Mengham, 1999, UK[68]	75	1.3	12	Diabetes	60.6 (12.5)	45	NR	White	31.6 (4.6)	Group 1—Diet based on British Dietetic Association recommendations (low fat)	Group 2—Control
Messier, 2013, USA[69]	454	12.1	18	Knee osteoarthritis	66 (NR)6	72	NR	White	33.6 (3.7)	Group 1—Diet based on DGA (800-1000 kcal/d deficit, meal replacements ≤2/day, <30% alories from fat) Group 2—Diet as above and exercise programme	Group 3—Exercise programme
Oldroyd, 2006, UK[70]	78	30.8	24	Impaired glucose tolerance	57.9 (NR)	44	NR	White	30.2 (5.3)	Group 1—Diet (aim for BMI <25, ≤30% calories from fat, PUFA/SFA ratio ≥1.0) and exercise programme	Group 2—Control
O'Neil, 2016, USA[71]	563	14.0	12	Type 2 diabetes	55.1 (19.1)	71.0	NR	Mixed	37.1 (5.7)	Group 1—Diet (Weight Watchers, hypoenergetic healthy eating) and exercise advice	Group 2—Control
Patrick, 2011, USA[72]	441	29.9	12	NR	43.9 (8.0)	0	NR	White	34.3 (4.1)	Group 1—Diet based on DGA (saturated fat ≤20 g/day) and exercise advice	Group 2—Control
Penn, 2009, UK[73]	102	48.0	37	Impaired glucose tolerance	57.1 (NR)	60	NR	White	33.8 (5.1)	Group 1—Diet (reduced saturated fat and <30% calories from fat until BMI <25) and exercise advice	Group 2—Control
Perri, 2014, USA[74]	612	19.6	24	NR	52.3 (11.5)	78	NR	White	36.3 (4.0)	Groups 1-3—Diet based on DPP (1200-1800 kcal/d, low fat) and exercise advice. Three groups received different intensities of both diet and exercise interventions	Group 4—Control
Ramachandran, 2006, India[75]	531	5.5	30	Impaired glucose tolerance	45.9 (5.7)	21	22	Asian	25.8 (3.5)	Group 1—Diet (low calorie, low fat) and exercise advice Group 2—Diet as above and exercise advice and metformin	Group 3—Control Group 4—Metformin
Rejeski, 2011, USA (CLIP)[76]	288	13.5	18	Recent cardiovascular disease, metabolic syndrome, or mobility limitation	67.1 (4.8)	67	NR	White	32.8 (3.8)	Group 1—Diet based on DGA (1200-1800 kcal/d, low fat, for 7-10% weight loss) and exercise programme	Group 2—Control Group 3—Exercise programme
Rock, 2015, USA[77 78]	698	15.9	24	Breast cancer	56 (NR)9	100	3.45	White	31.5 (4.7)	Group 1—Diet (500-1000 kcal/d deficit, low energy density, for 7% weight loss) and exercise advice	Group 2—Control
Ross, 2012, Canada (PROACTIVE)[79]	490	19.2	24	NR	51.8 (11.4)	70	NR	White	32.3 (4.2)	Group 1—Diet (balanced Mediterranean type diet for weight loss, 5-10% reduction in waist circumference) and exercise advice	Group 2—Control
Saito, 2011, Japan[80]	641	9.2	36	Impaired fasting glucose	49.0*	29	27	Asian	27.0 (2.6)	Group 1—Diet (low calorie, 20-25% calories from fat, for 5% weight loss) and exercise advice	Group 2—Control

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Table 1 | Characteristics of randomised controlled trials (Continued)

Trial	n	Dropout (%)	Follow-up (months)	Comorbidities and drugs	Mean age (SD)	Female (%)	Smoke (%)	Ethnicity	Mean BMI, kg/m2 (SD)	Main weight loss interventions	Comparisons
Shea, 2010, USA (ADAPT)[81 82]	318	20.8	96	Knee osteoarthritis	68.7 (5.4)	72	NR	Mixed	34.2 (5.5)	Group 1—Diet based on TONE based (500 kcal/d deficit, fat and portion control, for 5% weight loss) Group 2—Diet as above and exercise programme	Group 3—Control Group 4—Exercise programme
Shea, 2011, USA (TONE) [83-85]	585	<20	152	Drugs for blood pressure	66.0 (4.3)	53	5	Mixed	31.2 (2.3)	Group 1—Diet (low calorie, low fat, for ≥4.5 kg weight loss) and exercise programme Group 2—Diet (low calorie, low fat, for ≥4.5 kg weight loss), exercise programme, and sodium restriction	Group 3—Control Group 4—Sodium restriction
TOHP II, 2007, USA[86 87]	2382	23.0	144	High normal diastolic blood pressure	43.6 (6.1)	34	9	Mixed	30.9 (3.1)	Group 1—Diet (low calorie, low fat, for ≥4.5 kg weight loss) and exercise programme Group 2—Diet (low calorie, low fat, for ≥4.5 kg weight loss), exercise programme, for sodium restriction	Group 3—Control Group 4—Sodium restriction
Toobert, 2000, USA[88]	28	10.7	24	Coronary heart disease	63.6 (10.4)	100	7	White	32.0 (4.8)	Group 1—Diet based on Ornish (vegetarian diet, <10% calories from fat) and exercise programme	Group 2—Control
Uusitupa, 1993, Finland[89-91]	90	8.9	24	Type 2 diabetes	53.2 (6.6)	43	17	White	33.5 (5.1)	Group 1—Diet (≤30% calories from fat, ≤10% from saturated fat) and exercise advice	Group 2—Control
Villareal, 2011, USA[92]	107	13.1	12	Frailty	69.7 (4.0)	63	NR	White	37.2 (5.0)	Group 1—Diet (balanced diet, 500-750 kcal/d deficit, for 10% weight loss) Group 2—Diet as above and exercise programme	Group 3—Control Group 4—Exercise programme
Wadden, 2011, USA[93]	390	13.8	24	Metabolic syndrome	51.5 (11.5)	80	NR	Mixed	38.5 (4.7)	Group 1—Diet based on DPP (1200-1800 kcal/d, 20-35% calories from fat) and exercise advice (brief counselling) Group 2—Diet based on DPP (1200-1800 kcal/d, 20-35% calories from fat; meal replacements, orlistat or sibutramine if required) and exercise advice (enhanced counselling)	Group 3—Control
Wing, 2010, USA (PRIDE)[94 95]	338	14.5	18	Urinary incontinence	52.7 (10.3)	100	5	Mixed	36.3 (5.3)	Group 1—Diet based on DPP and Look AHEAD (1200-1800 kcal/d, <30% calories from fat, for 7-9% weight loss, SlimFast vouchers) and exercise advice	Group 2—Control
Yardley, 2014, UK[96]	179	31.3	12	NR	51.2 (13.1)	64	NR	White	35.7 (5.5)	Group 1—Diet (self selected from: 600k cal/d deficit by reducing portions; or traffic light system; or low carbohydrate diet ≤50 g/d with traffic light system) and exercise advice (web based) Group 2—Diet as above and exercise advice (basic nurse support) Group 3—Diet as above and exercise advice (regular nurse support)	Group 4—Control

Group 4—Control
1 kcal=4.18 kJ
*Median
†Range
ADAPT=arthritis, diet, and activity promotion trial; CLIP=community level interventions for pre-eclampsia; DASH=dietary approaches to stop hypertension; DGA=dietary guidelines for Americans; DPP=diabetes prevention program; DPS=diabetes prevention study; FFIT=football fans in training; GI=glycaemic index; Look AHEAD=look action for health in diabetes; NR=not reported; PRIDE=program to reduce incontinence by diet and exercise; PUFA/SFA=polyunsaturated fatty acids/saturated fatty acids; SD=standard deviation; TAIM=trial of antihypertensive interventions and management; TONE=trial of nonpharmacologic intervention in the elderly; TOHP=trials of hypertension prevention; VLCD=very low calorie diet.

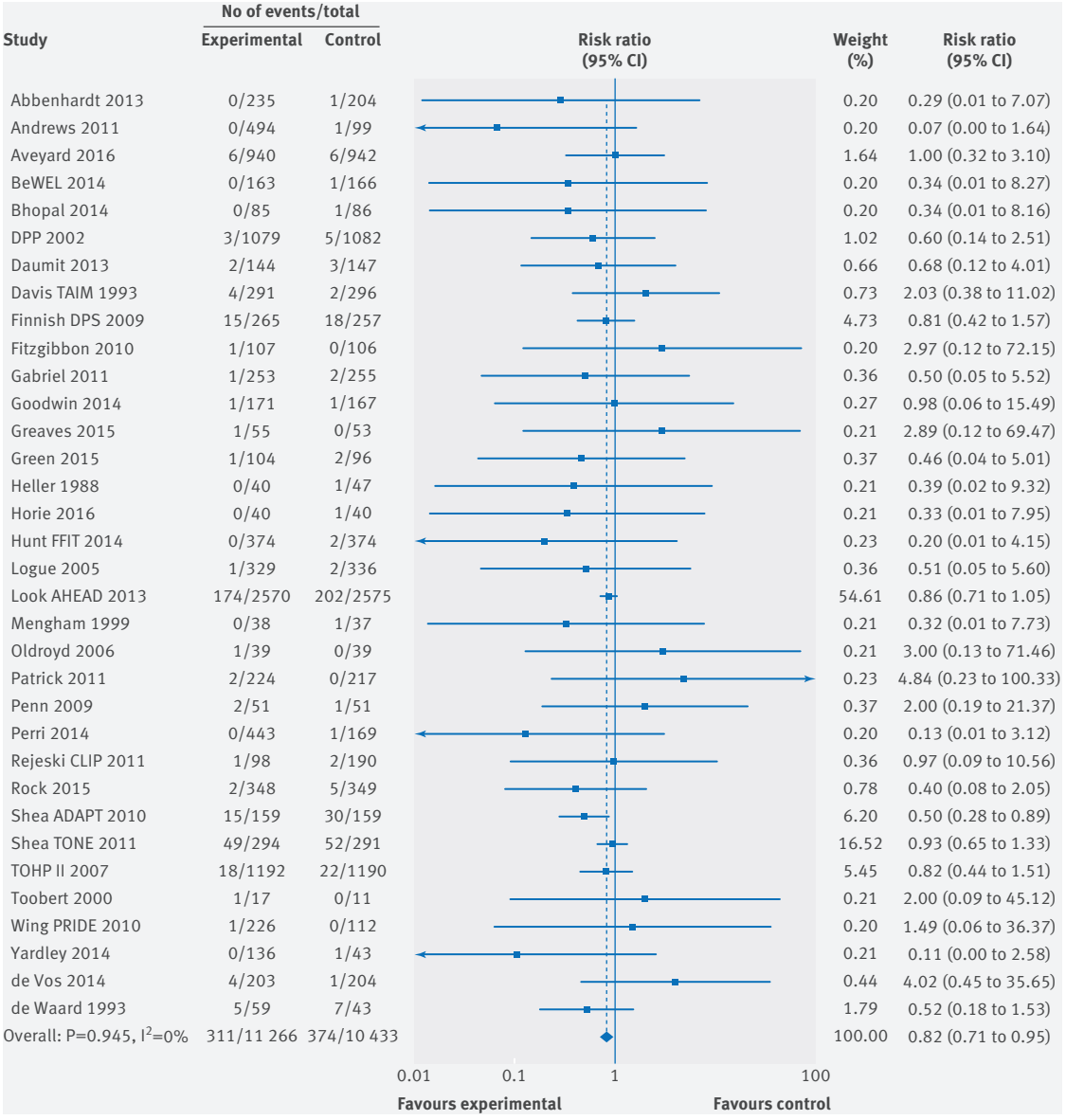

Fig 2 | Random effects meta-analysis of the effects of weight loss interventions on all cause mortality. ADAPT=arthritis, diet, and activity promotion trial; CLIP=community level interventions for pre-eclampsia; DPP=diabetes prevention program; DPS=diabetes prevention study; FFIT=football fans in training; Look AHEAD=look action for health in diabetes; PRIDE=program to reduce incontinence by diet and exercise; TAIM=trial of antihypertensive interventions and management; TOHP=trials of hypertension prevention; TONE=trial of nonpharmacologic intervention in the elderly.

Meta-analyses

Details of our adjudication processes for cardiovascular and cancer outcomes are provided in supplementary tables 1-3. Supplementary table 1 compares all cause mortality, cardiovascular mortality, and cancer mortality across all trials, showing that we were not always able to obtain causes of death from authors.

Based on the GRADE approach for judging quality of the evidence (supplementary table 4) we found high quality evidence from 34 trials (21 699 participants) providing data on all cause mortality (fig 2), which showed a decrease in premature mortality with weight loss interventions (n=34 trials, 685 events; risk ratio 0.82, 95% confidence interval 0.71 to 0.95; I^2=0%). The Look AHEAD trial had 54.6% of the weighting in the meta-analysis.[65 66] Without this trial weight loss interventions were still associated with decreased all cause mortality (n=33 trials, 309 events; risk ratio 0.78, 95% confidence interval 0.63 to 0.96; I^2=0%). The funnel plot showed no evidence of small study bias (Egger's test P=0.269, supplementary figure 2).

Fewer trials reported data for cardiovascular mortality and cancer mortality, resulting in considerable uncertainty in the estimates of effects of weight loss interventions on these outcomes. We found moderate quality evidence for an effect on cardiovascular mortality (n=8 trials, 134 events; risk ratio 0.93, 95% confidence interval 0.67 to 1.31;

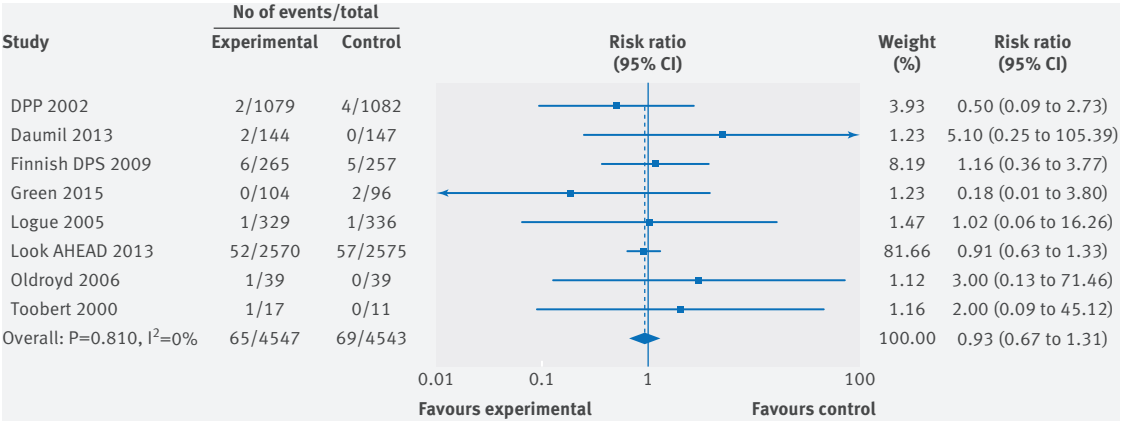

Fig 3 | Random effects meta-analysis of the effects of weight loss interventions on cardiovascular mortality. DPP=diabetes prevention program; DPS=diabetes prevention study.

I^2=0%) and very low quality evidence for an effect on cancer mortality (n=8 trials, 34 events; risk ratio 0.58, 95% confidence interval 0.30 to 1.11; I^2=0%) (figs 3 and 4). Limiting cardiovascular mortality to ACC/AHA defined events did not influence this result, as the data were identical (n=8 trials, 134 events; risk ratio 0.93, 95% confidence interval 0.67 to 1.31; I^2=0%).

Twenty four trials (15 176 participants) reported high quality evidence on participants developing new cardiovascular events (n=24, 1043 events; risk ratio 0.93, 95% confidence interval 0.83 to 1.04; I^2=0%). Using events classified according to ACC/AHA definitions, results were very similar (fig 5, supplementary figure 3). Nineteen trials (6330 participants) provided very low quality evidence on participants developing new cancers (n=19, 103 events; risk ratio 0.92, 95% confidence interval 0.63 to 1.36; I^2=0%) (fig 6). Bayesian meta-analyses for all of the above outcomes provided similar results (supplementary table 5).

Interventions had a beneficial effect on weight change after one year (n=44, mean difference −3.42 kg; 95% confidence interval −4.09 to −2.75 kg; I^2=92%), after two years (n=20, mean difference −2.51 kg; 95% confidence interval −3.42 to −1.60 kg; I^2=89%) and after three or more years (n=8, mean difference −2.56 kg; 95% confidence interval −3.50 to −1.62 kg; I^2=87%) (supplementary figures 4 to 6). Heterogeneity for each of these meta-analyses was very high (I^2=87% to 92%), reflecting the wide diversity of weight loss interventions and their effects on weight.

Sensitivity analyses

Sensitivity analyses for allocation concealment (low risk of bias versus other risk of bias) and completion of follow-up (<80% *v* ≥80% of participants completed) did not show any statistically significant heterogeneity for mortality, cardiovascular outcomes, or cancer outcomes (supplementary table 6).

Weight change at final follow-up was lower in trials with low risk of bias for allocation concealment (n=17, mean difference −2.33 kg; 95% confidence interval −2.87 to −1.79 kg) than for trials with high or unclear risk of bias for allocation concealment (n=31, mean difference −3.24 kg; 95% confidence interval −4.00 to −2.49 kg).

Weight change at final follow-up was lower in trials with completed follow-up of less than 80% (n=15, MD −2.09 kg; 95% CI: −2.80 to −1.37 kg) than for trials with follow-up of 80% or more (n=33, MD −3.13 kg; 95% CI: −3.71 to −2.55 kg).

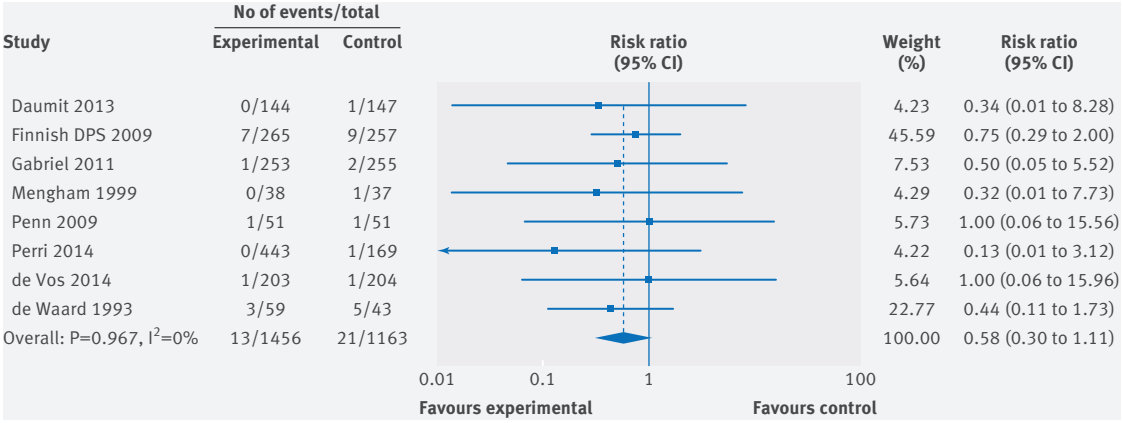

Fig 4 | Random effects meta-analysis of the effects of weight loss interventions on cancer mortality. DPS=diabetes prevention study.

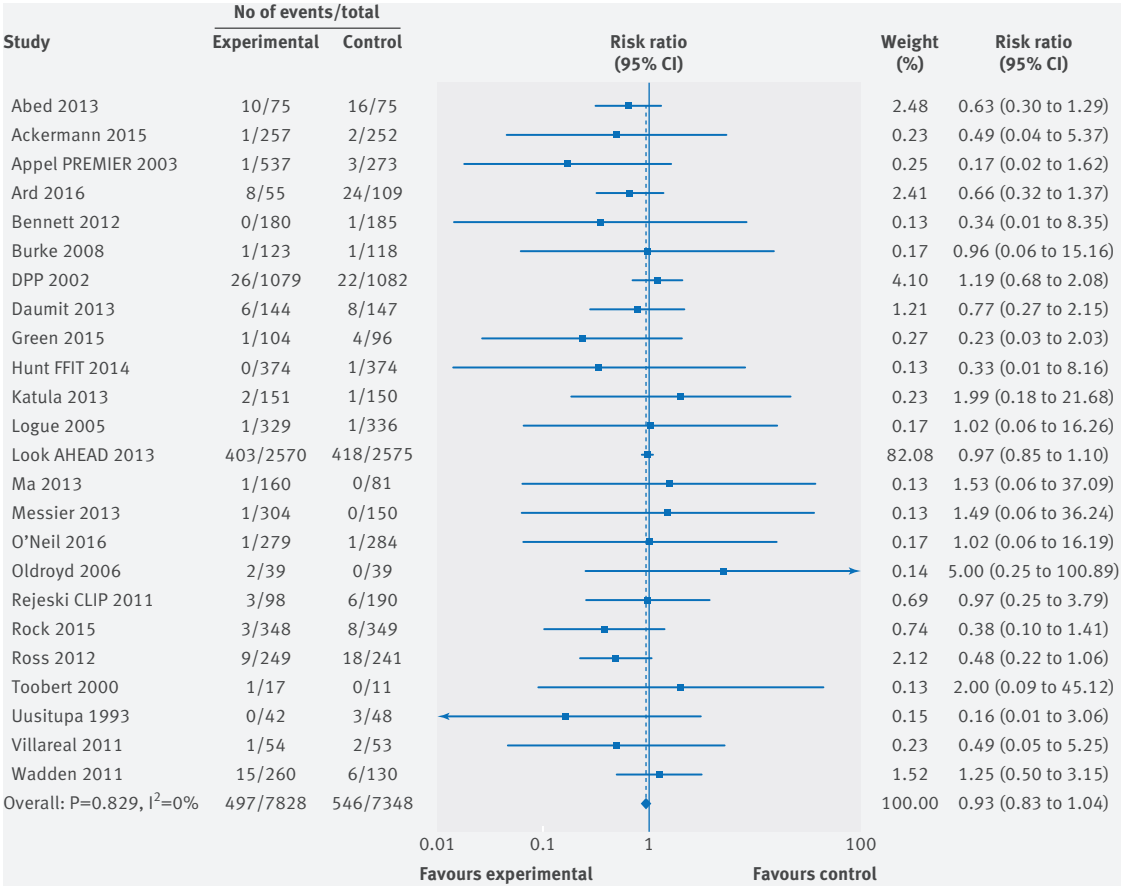

Fig 5 | Random effects meta-analysis of the effects of weight loss interventions on participants with a cardiovascular event. CLIP=community level interventions for pre-eclampsia; DPP=diabetes prevention program; FFIT=football fans in training.

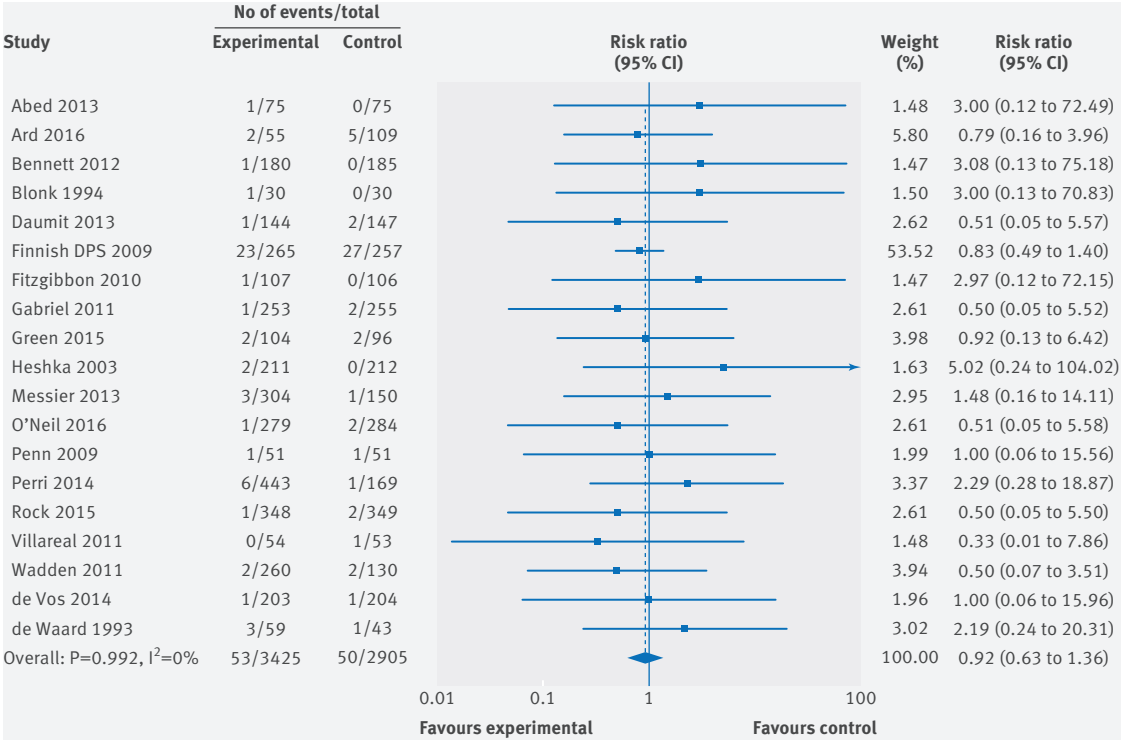

Fig 6 | Random effects meta-analysis of the effects of weight loss interventions on participants developing cancer. DPS=diabetes prevention study.

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Subgroup analyses

We undertook many subgroup analyses, including post hoc analyses with the addition of trials in Asian populations with BMI ≥25 (supplementary table 6, supplementary figures 7-9). Tests for subgroup differences for mortality, cardiovascular outcomes, and cancer outcomes provided weak evidence that participants without type 2 diabetes might be at lower risk of a new cardiovascular event than participants with type 2 diabetes or those with impaired glucose tolerance or impaired fasting glycaemia. Similarly, we found weak evidence that groups of white participants may be at lower risk of a new cardiovascular event than black, mixed, or Asian population groups when following weight loss interventions.

Subgroup analyses for weight change at final follow-up provided weak evidence that participants aged 60 or over lost more weight than younger participants and that participants in trials in Asian populations lost less weight than those in trials with other population groups. Similarly, we found weak evidence of better long term weight loss with trials that provided a physical activity programme, compared with trials that gave only physical activity advice or did not report providing physical activity advice.

Discussion

We found high quality evidence that weight reducing diets for adults with obesity, usually low in fat and low in saturated fat, were associated with a 18% relative reduction in premature mortality over a median trial duration of two years, corresponding to six fewer deaths per 1000 participants (95% confidence interval two to 10). This evidence provides a further reason for weight reducing diets to be offered alongside their already proven benefits, such as type 2 diabetes prevention. We were unable to show effects on cardiovascular and cancer mortality, or participants developing cardiovascular events or new cancers, although fewer trials reported events for these outcomes, resulting in much uncertainty around their effect estimates.

We identified 34 trials reporting mortality data compared with 15 in the previous systematic review by Kritchevsky and colleagues,[9] which included weight loss interventions irrespective of baseline BMI, and we made very considerable efforts to clarify data and retrieve unpublished data from 48 trialists. We used a comprehensive search strategy with full text searching of trials in our obesity database. The trials we included were not necessarily designed to collect data on mortality, cardiovascular, and cancer outcomes, although larger trials generally were.[65 66 81-87] We might have failed to identify all trials with outcome data, if trialists did not present these outcomes or presented them as unspecified adverse events. This may have biased results, although we could not see obvious funnel plot asymmetry for all cause mortality. Trials generally excluded participants with a recent diagnosis of cancer, but this was not always clear, so some participants may have had a recurrence of cancer, rather than a new event. Many of the trials had quite intensive control group interventions, and the unblinded nature of the interventions could have led to more medical treatment in control groups, tending to reduce differences between groups.[65] Using GRADE to assess the quality of the evidence aids interpretation of the limitations of the evidence. We undertook sensitivity and subgroup analyses, including post hoc analyses, which should be regarded with caution. Individual patient data meta-analyses are required for further exploration of these subgroup findings.

In systematic reviews of controlled cohort studies, bariatric surgery has been associated with significant reductions in mortality, cardiovascular events, myocardial infarction, stroke, and risk of cancer.[97 98] A systematic review and meta-analysis of population prospective cohort studies by Flegal and colleagues found that BMIs of 30 to <35 were not associated with higher mortality, compared with BMIs of 18.5 to <25.[5] By contrast, the Global BMI Mortality Collaboration found that obesity (BMI 30 to <35) was associated with higher mortality; the investigators reduced reverse causality by examining data in non-smokers and excluding the first five years of follow-up.[8] Their findings were consistent for men and women, up to 89 years, and in the four continents examined. Similar findings were seen for deaths due to coronary heart disease, stroke, cancer, and respiratory disease. Our findings for BMI from RCT evidence are consistent with data from the Global BMI Mortality Collaboration.[8] Epidemiological studies can demonstrate the risks of higher BMIs and, therefore, the necessity for preventing obesity, but epidemiological associations between changes in body weight and changes in disease and mortality are often limited by the lack of information on the intentionality of that weight loss. Furthermore, treatment effects found in RCTs might differ from those expected in epidemiological studies, whereby epidemiological studies might overestimate benefits.[99]

Evidence from systematic reviews indicates that physical activity as an adjunct to weight reducing diets might be more effective than diets alone, in terms of weight loss and improvements in blood lipids and blood pressure.[100] We were unable to show differences for mortality, cardiovascular disease, and cancer between weight reducing diets alone, diets plus advice on exercise, and diets plus an exercise programme for people to attend, for which we had limited statistical power. The majority of RCTs of weight loss interventions for obesity in adults have used low fat, weight reducing diets. But a recent systematic review by Tobias and colleagues[101] found that low carbohydrate weight reducing diets were more effective for weight loss than low fat, weight reducing diets, but found no difference between low fat, weight reducing diets (defined as <30% fat) and higher fat, weight reducing diets on weight loss. Recent US guidelines[102] have been criticised for the lack of evidence from RCTs to support guidance.[103] Thus, we must consider whether the type of weight loss diet, particularly low fat, weight reducing diets, usually with <10% of energy

as saturated fat, affects important health outcomes beyond cardiovascular risk factors or weight.[100] That all except one of the interventions included here used a low fat, weight reducing diet provides important evidence on all cause mortality for weight reduction with this type of diet. We do not have the evidence to establish whether other forms of weight reducing diets have this effect, and we cannot dissociate the effects of weight loss from the use of low fat diets in our results.

We encourage investigators studying weight reducing diets to adhere to CONSORT guidance on reporting harms by always reporting clinically important outcomes and adverse events, irrespective of whether they think these events are related to the interventions.[104] Collecting and reporting major disease outcomes in weight reducing trials for obesity is important, particularly cardiovascular disease and cancer. We did not have sufficient data to examine whether other types of diet or physical activity influence outcomes or whether certain groups in the population are more or less likely to benefit.

In conclusion, weight reducing diets, usually low in fat and low in saturated fat, with or without an exercise component, may reduce premature all cause mortality in adults who are obese. By implication, our data support public health measures to prevent weight gain and facilitate weight loss using these types of diet.

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Contributors and sources: AA, CM, MJB, CF, and GM designed this study. CM, AA, and CF searched the literature. CM, AA, FS, CR, PS, and MJB extracted data. CM, AA, JH, MJB, and GM analysed data. CM and AA wrote the first draft of the manuscript. All authors contributed to revisions of the manuscript. AA is the guarantor.

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Data sharing: All data are included in the paper or supplementary appendix. No additional data are available.

Transparency: AA and CM affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix: Supplementary figures 1-11 and supplementary tables 1-6