

# What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions

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## Abstract

**Background** Evidence is needed for the effectiveness of interventions given with reducing diets for obese adults: drug therapy, exercise, or behaviour therapy.

**Methods** We systematically reviewed randomized controlled trials in any language. We searched 13 databases and handsearched journals. Trials lasted 1 year or more. One investigator extracted data and a second checked data extraction. Trial quality was assessed.

**Results** Adding orlistat to diet was associated with weight change for up to 24 months (−3.26 kg, 95% CI, −4.15 to −2.37 kg), and statistically significant beneficial changes were found for total and LDL cholesterol, blood pressure and glycaemic control. Adding sibutramine to diet was associated with a 12 month weight change of −4.18 kg (95% CI, −5.14 to −3.21 kg), and statistically significant beneficial effects on high density lipoprotein cholesterol (HDL) and triglycerides (TGs), but an increase in diastolic blood pressure. Adding exercise to diet, or to diet and behaviour therapy, was associated with improved weight loss for up to 36 months and improvements in HDL, TGs and blood pressure. Adding behaviour therapy to diet, or to diet and sibutramine together, was associated with improved weight loss for up to 18 months. Adding drugs, exercise or behaviour therapy to dietary advice was each associated with similar weight change.

**Conclusions** Adding orlistat, sibutramine, exercise, or behaviour modification to dietary advice can improve long-term weight loss.

## Introduction

Adult obesity, defined as a body mass index (BMI)  $\geq 30 \text{ kg m}^{-2}$  [weight in kg and height in  $\text{m}^2$ ] continues to increase in the United Kingdom (Department of Health, 2003) and worldwide (World Health Organization, 2000). Adults with a BMI  $\geq 40 \text{ kg m}^{-2}$ , in particular, are at increased risk of type 2 diabetes, hypertension, hypercholesterolaemia, asthma, arthritis and poor health (Mokdad *et al.*, 2003). It has been estimated that white men aged 20 years with BMIs  $> 45 \text{ kg m}^{-2}$  lose 13 years of life compared with people of the same age with BMIs of  $24 \text{ kg m}^{-2}$ , with a comparable figure of 8 years of life lost for women (Fontaine *et al.*, 2003). The direct cost of obesity to the National Health Service in England has been conservatively estimated at £480 million in 1998 (National Audit Office, 2001).

Drug therapy, the provision of an exercise programme, or behaviour therapy, each have important implications for health services organization in terms of staff expertise and costs. We sought to systematically review studies where these treatments were evaluated as additions to dietary advice in adults with obesity, in order to enhance long-term benefits on weight, cardiovascular risk factors and clinical outcomes. We presumed that dietary advice was essential (this is the subject of another review), and thus did not evaluate the effects of drugs, exercise, behaviour therapy or combinations of these interventions without dietary advice. We also did not compare combinations of these treatments and diet against no treatment. This review is part of a much larger report commissioned by the National Health Service Research and Development Health Technology Assessment Programme, due for publication in late spring 2004 (Avenell *et al.*, in press), which is a systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.

## Methods

The systematic review was undertaken using a prespecified protocol, devised using the methods of

the Cochrane Collaboration (Clarke & Oxman, 2002).

## Search strategy

We searched 13 electronic databases including MEDLINE, EMBASE, CAB abstracts, The Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO, (earliest date 1966 to May 2001) for randomized controlled trials (RCTs) and systematic reviews of RCTs. We used weight loss, weight maintenance and obesity related terms and textwords, specific to each database, in addition to the search strategy for RCTs and systematic reviews, based on that by Dickersin *et al.* (1994) (details of search strategy and results available from the authors). We handsearched seven nutrition and obesity journals, including The International Journal of Obesity and Obesity Research (date of last search June 2001). We searched reference lists of included studies and contacted authors for further details of their trials. We accepted trials in any language, including unpublished trials and abstracts (if full details available).

## Study inclusion criteria

Weight loss, or prevention of weight gain had to be explicitly stated as an outcome of the study. Studies where participants were randomized to treatments after a period of weight loss of 3 months or longer were classified as weight maintenance RCTs, e.g. the STORM trial (James *et al.*, 2000) or the orlistat trial by Hill *et al.* (1999) and are not discussed here. Thus 'weight loss' studies discussed here had an initial period of weight loss followed by attempts at weight maintenance (the distinction between the two phases was rarely made by the investigators). Included RCTs had to have a mean or median duration of 52 weeks from randomization. This included the period of active intervention, however long, and period of follow-up. Where results were presented from the start of a non-randomized run-in period, we worked out differences from the time of randomization. The mean or median age for groups had to be  $\geq 18$  years with a minimum mean

or median BMI of 28 kg m<sup>-2</sup> (chosen as a result of UK drug licensing requirements). Where heights were not provided, we estimated BMI using the following imputed values:

- For US populations 1.768 m for males and 1.636 m for females based on NHANES data (National Health and Nutrition Examination Survey, 2001)
- For other populations 1.745 m for males and 1.617 m for females based on the UK National Diet and Nutrition Survey (Wiseman *et al.*, 1990)

We categorized diets as:

- Low fat diet (LFD): advice given to reduce the fat content of the diet with clear intention to also reduce energy intake, but energy intake >6.7 MJ day<sup>-1</sup>
- Low calorie diet (LCD): 4.2–6.7 MJ day<sup>-1</sup>
- Very low calorie diet (VLCD): <4.2 MJ day<sup>-1</sup>
- Protein sparing modified fast (PSMF): where carbohydrate content was ≤40 g day<sup>-1</sup>, irrespective of energy content. This category also included the low carbohydrate Optifast and Modifast slimming products.

If an intervention included more than two diets, e.g. VLCD followed by a LCD, we used the most stringent energy restriction to classify the diet, irrespective of the time for which it was given. In the case of the more stringent diets, these were often given for short periods only during the year, and details are provided in Tables 1–3. If the information provided on diets was insufficient to categorize the diet it was categorized as LFD. Multifaceted interventions, incorporating clear efforts at smoking cessation or salt reduction in addition to diet, were not included because smoking cessation or salt restriction may also cause changes in weight and risk factors, and hence the effect of the weight loss interventions alone could not be isolated.

Amongst drug trials, we only included trials of orlistat 120 mg three times daily and sibutramine 10–15 mg daily. We did not evaluate trials where drugs were given for varying lengths of time in the same trial.

For exercise or behaviour therapy interventions, study investigators had to give a detailed description of an intervention programme (and details of the theories and components in the case of

behaviour therapy). If, for example, the study only reported that participants were advised to increase their level of exercise with no further details, this was not categorized as an exercise intervention.

### Types of outcomes

We sought information on the following outcomes: mortality; morbidity; quality of life; economic outcomes; weight changes; cardiovascular risk factors: total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TGs), systolic and diastolic blood pressure (SBP and DBP), fasting glucose, glycosylated haemoglobin (HbA1c); drop-outs; and adverse events.

### Data abstraction and quality assessment of studies

For each study, the data were abstracted by a single researcher, and then checked by a second researcher. Most differences of opinion were resolved by discussion, with reference to a third researcher if no agreement could be reached. We assessed trial quality, including the quality of random allocation concealment, whether the analysis was undertaken on an intention to treat basis, and blinding of outcome assessors.

### Data analysis

Where results from studies could be quantitatively combined, a statistical meta-analysis of the data was undertaken to estimate the typical effect size of the intervention. For continuous data a weighted mean difference was calculated (weighted by the inverse of the variance) (Clarke & Oxman, 2002). For dichotomous data a 'typical' odds ratio was derived using Peto's method (Clarke & Oxman, 2002). Analyses for both dichotomous data, such as mortality, and continuous data, such as weight change, adopted a fixed effects approach (Clarke & Oxman, 2002).

Evidence of heterogeneity across studies was explored using the Chi-squared test for heterogeneity; if evidence of significant heterogeneity was identified, potential sources of heterogeneity

Table 1 Included trials of orlistat

Study ID	Participants	Interventions	Outcomes
Broom 2001 (Broom, 2001; Wilding, 2001; Broom et al., 2002)	Location: 54 general practices and 12 hospital clinics, UK. Comorbidity: at least one of impaired glucose tolerance, hypercholesterolaemia, hypertension. Sex: 409 female, 113 male. Age: mean(SD) years: (a) 46.7(11.4), (b) 45.3(11.5). BMI: mean(SD) kg m <sup>-2</sup> : (a) 37.1(6.4), (b) 37.0(6.2).	(a) + (b) 2 weeks pre-treatment phase of single blind placebo and 2.5 MJ day <sup>-1</sup> deficit (minimum: 5.0 MJ day <sup>-1</sup> ) LFD, diet continued post-randomization to month 6, then reduced further 1.3 MJ day <sup>-1</sup> . (a) 120 mg orlistat 3 times daily for 12 months. (b) placebo three times daily for 12 months. Allocated: (a) 265; (b) 266. % Dropout: (a) 30%; (b) 40% at 12 months.	Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, glucose, adverse events, compliance, deaths.
Davidson 1999 (Foreyt, 1997; Davidson et al., 1999)	Location: 18 research centers, USA. Sex: 741 female, 139 male. Age mean(SD) years: (a) 43.3(0.6), (b) 44.0(0.7). BMI mean(SD) kg m <sup>-2</sup> : (a) 36.5(0.9), (b) 36.2(0.1).	(a) + (b) 4 weeks pre-treatment phase of single-blind placebo and 2.1–3.3 MJ day <sup>-1</sup> deficit LFD continued for 24 months, if losing weight in last 3 months of year 1 energy increased 0.8–1.3 MJ day <sup>-1</sup> . (a) 120 mg orlistat three times daily for 12 months. (b) placebo three times daily for 24 months. (a) rerandomized at week 52 to: (c) placebo three times daily year 2 (d) orlistat 120 mg three times daily for year 2. (e) orlistat 60 mg three times daily for year 2 (not used here). Allocated: (a) 668, (b) 224. % Dropout: (a) 31%, (b) 41% at 12 months; (b) 57%, (c) 31%, (d) 29% at 24 months.	Follow-up: 24 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, glucose, adverse events, compliance, deaths, cancers.
Finer 2000 (James et al., 1997; Finer et al., 2000)	Location: Five centres, UK. Sex: 193 female, 25 male. Age mean(SD) years: (a) 41.5(10.5), (b) 41.4(10.0). BMI mean(SD) kg m <sup>-2</sup> : (a) 36.8(3.6), (b) 36.8(3.7).	(a) + (b) 4 weeks pre-treatment phase of single-blind placebo and 2.5 MJ day <sup>-1</sup> deficit LFD (minimum: 4.0 MJ day <sup>-1</sup> ), reduced further 1.3 MJ day <sup>-1</sup> at week 24 (or reduced to 4.2 MJ day <sup>-1</sup> if already at 5.0 MJ day <sup>-1</sup> ). (a) 120 mg orlistat three times daily for 12 months. (b) placebo three times daily for 12 months. Allocated: (a) 114, (b) 114. % Dropout: (a) 36%; (b) 42% at 12 months.	Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, adverse events.
Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000)	Location: 17 primary care centres, USA. Sex: 497 female, 138 male. Age mean(SD) years: (a) 42.6(11.7), (b) 43.2(10.1), (c) 41.6(10.2). BMI mean(SD) kg m <sup>-2</sup> : (a) 35.8(4.4), (b) 36.0(2.9), (c) 36.1(4.4) 4 weeks prior to randomization.	(a) + (b) + (c) 4 weeks pre-treatment phase of single-blind placebo and 5.0 MJ day <sup>-1</sup> LFD for participants <90 kg or 6.3 MJ day <sup>-1</sup> LFD for participants ≥90 kg. Diet increased after 12 months by 1.3 MJ day <sup>-1</sup> for participants still losing weight. (a) 60 mg orlistat three times daily for 24 months (not used here). (b) 120 mg orlistat three times daily for 24 months. (c) placebo three times daily for 24 months. Allocated: (a) 213, (b) 210, (c) 212. % Dropout: (a) 28%, (b) 28%, (c) 42% at 12 months.	Follow-up: 24 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, glucose, adverse events, compliance, deaths.

<p>Hollander 1998 (Kelley, 1997; Hollander <i>et al.</i>, 1998)</p>	<p>Location: 12 diabetic clinic centres, USA. Comorbidity: type 2 diabetes on sulphonylurea. Sex: 157 female, 164 male. Age mean(SD) years: (a) 55.4(8.8), (b) 54.7(9.7). BMI mean(SD) kg m<sup>-2</sup>: (a) 34.5(3.2), (b) 34.0(3.4).</p>	<p>(a) + (b) 5 weeks pre-treatment phase of single-blind placebo, and 2.1 MJ day<sup>-1</sup> deficit LFD to 12 months. (a) 120 mg orlistat three times daily. Allocated: (a) 162, (b) 159. % Dropout: (a) 15%, (b) 28% at 12 months.</p>	<p>Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, HbA1c, glucose, adverse events.</p>
<p>Lindgarde, 2000 (Lindgarde, 1999, 2000)</p>	<p>Location: 33 primary care centres, Sweden. Comorbidity: fasting serum glucose <math>\geq 6.7</math> mmol L<sup>-1</sup>, or confirmed type 2 diabetes (not on insulin); cholesterol <math>\geq 6.5</math> mmol L<sup>-1</sup> and/or LDL <math>\geq 4.2</math> mmol L<sup>-1</sup> on at least two occasions or prescribed lipid lowering medications; DBP <math>\geq 90</math> mmHg on at least two occasions or hypertensive treated with antihypertensive medication. Sex: 239 female, 137 male. Age mean(SD) years: (a) 53.7(9.4), (b) 53.2(9.9) 2 weeks before randomization. BMI mean(SD) kg m<sup>-2</sup>: (a) 33.2(3.0), (b) 33.2(3.1) 2 weeks before randomization.</p>	<p>(a) + (b) 2 weeks pre-treatment phase of single-blind placebo and 2.5 MJ day<sup>-1</sup> deficit LFD (minimum: 5.0 MJ day<sup>-1</sup>) at month 6 energy content reduced additional 1.3 MJ day<sup>-1</sup>. (a) 120 mg orlistat three times daily. (b) placebo three times daily. Allocated: (a) 190, (b) 186. % Dropout: (a) 16%, (b) 12% at 12 months.</p>	<p>Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, HbA1c, glucose, adverse events, compliance, deaths.</p>
<p>Rossner 2000 (Toornvliet <i>et al.</i>, 1997; Rossner <i>et al.</i>, 2000)</p>	<p>Location: 14 centres, Europe. Sex: 591 female, 127 male. Age mean(SD) years: (a) 44.7(10.7), (b) 43.6(11.4), (c) 44.3(10.8). BMI mean(SD) kg m<sup>-2</sup>: (a) 35.2(3.9), (b) 34.7(3.7), (c) 35.3(4.1).</p>	<p>(a) + (b) + (c) 4 weeks pre-treatment phase of single-blind placebo and 2.5 MJ day<sup>-1</sup> deficit LFD, at randomization diet continued. During year 2: those who had lost <math>\geq 3</math> kg 40–52 weeks energy intake at estimated energy intake minus 10%; those who lost &lt;3 kg no dietary adjustment. (a) 60 mg orlistat three times daily (not used here). (b) 120 mg orlistat three times daily. (c) placebo three times daily. Allocated: (b) 244, (c) 243. % Dropout: (b) 35%, (c) 44% at 24 months.</p>	<p>Follow-up: 24 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, DBP, SBP, glucose, adverse events, compliance, quality of life.</p>
<p>Sjostrom 1998 (Sjostrom <i>et al.</i>, 1998; Vidgren <i>et al.</i>, 1999; Fransson &amp; Rossner, 2000; Karhunen <i>et al.</i>, 2000; Rissanen <i>et al.</i>, 2001)</p>	<p>Location: 15 centres, Europe. Sex: 567 female, 116 male. Age mean(range) years: (a) 45.2(20–76), (b) 44.3(18–77). BMI mean kg m<sup>-2</sup>: (a) 36.1, (b) 36.2.</p>	<p>(a) + (b) 4 weeks pre-treatment of single-blind placebo daily 2.5 MJ day<sup>-1</sup> deficit LFD. First 24 weeks all participants continued 2.5 MJ day<sup>-1</sup> deficit (minimum: 5.0 MJ day<sup>-1</sup>) then until week 52 reduced additional 1.3 MJ day<sup>-1</sup> (minimum: 4.2 MJ day<sup>-1</sup>); year 2 all participants advised on weight maintenance diet. (a) orlistat 120 mg three times daily for 24 months. (b) placebo three times daily for 24 months. Both groups (a) and (b) rerandomized to placebo or orlistat 120 mg three times daily end week 52. Only data from groups on same treatment for 24 months used here. Allocated: (a) 345, (b) 343 at baseline, (a) 135, (b) 126 end week 52. % Dropout: (a) 18%, (b) 24% at 12 months, (a) 16%, (b) 19% at 24 months.</p>	<p>Follow-up: 24 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, glucose, adverse events.</p>

**Table 2** Included trials of sibutramine

Study ID	Participants	Interventions	Outcomes
Apfelbaum 1999 (Apfelbaum <i>et al.</i> , 1999)	Location: 12 medical centres, France. Sex: 127 female, 33 male. Age mean(SD) years: (a) 36.3(9.5), (b) 39.1(9.1). BMI mean(SD) kg m <sup>-2</sup> : (a) 35.9(6.6), (b) 35.1(5.8).	(a) + (b) 1 week run-in phase for screening tests then 4 week pretreatment phase of VLCD (0.9–3.3 MJ day <sup>-1</sup> ); after randomization reduced energy intake 20–30% compared with pre-VLCD intake for 12 months, with follow-up 3 months later. (a) 10 mg sibutramine daily for 12 months. (b) placebo daily for 12 months. Allocated (a) 82, (b) 78. % Dropout: (a) 39%, (b) 27% at 12 months.	Follow-up: 15 months. Outcomes: weight, LDL, HDL, TGs, adverse events, compliance.
Smith, 2001; Smith 2001a: 10 mg sibutramine; Smith 2001b: 15 mg sibutramine (Jones <i>et al.</i> , 1995; Smith, 1997, 2001)	Location: 12 general practices, UK. Sex: 390 female, 95 male. Age mean(SD) years: (a) 41.0(12.1), (b) 42.7(11.7), (c) 41.9(11.6). BMI mean(SD) kg m <sup>-2</sup> : (a) 32.9(4.1), (b) 32.7(3.3), (c) 32.4(3.5).	(a) + (b) + (c) 2 week single-blind placebo run-in period, tablets for 12 months, follow-up 1 month after completion, LFD. (a) 10 mg sibutramine daily for 12 months. (b) 15 mg sibutramine daily for 12 months. (c) placebo for 12 months. Allocated (a) 161, (b) 161, (c) 163. % Dropout: (a) 42%, (b) 49%, (c) 51% at 12 months.	Follow-up: 13 months. Outcomes: weight, cholesterol, TGs, SBP, DBP, glucose, adverse events.

were sought. If data could not be combined quantitatively they were assessed qualitatively. Results from cluster randomized trials are reported separately from other RCTs. In some studies the investigators undertook several analyses of weight loss data. Our primary approach was to use the analysis with the largest number of participants. In some cases the results presented included imputed values for weight, e.g. for people who dropped out the last recorded weight was carried forward to the end of the trial.

#### *Handling of missing data*

To fully utilize data for meta-analysis that required the mean and standard deviation of the change between two time points, we made several assumptions. Where weight or risk factors were presented as actual values rather than changes, differences were calculated by subtraction of the endpoint value from the value at time of randomization. Where mean changes were not avail-

able, median values were used. In the case of missing standard deviations (SDs) for changes in weight and risk factors, assumptions were made (irrespective of whether the changes were negative or positive). A linear regression was made of the SD of the mean change in weight on the absolute mean change for weight, for the studies which provided these data, and used to impute values for missing SDs:

- SD of weight change in kg = 5.915 + (0.283 × mean change in weight)

Similar linear regressions were attempted for risk factors. However, clear relationships were not found, so the means of reported SDs were used to impute values for missing SDs:

- SD for change in systolic blood pressure = 12.7 mmHg
- SD for change in diastolic blood pressure = 8.3 mmHg
- SD for change in cholesterol = 1.08 mmol L<sup>-1</sup>
- SD for change in LDL = 0.74 mmol L<sup>-1</sup>

**Table 3** Included trials of the addition of exercise and/or behaviour therapy

Study	Participants	Interventions	Outcomes
Blonk 1994 (Blonk <i>et al.</i> , 1994)	Location: University, The Netherlands. Comorbidity: type 2 diabetes(not on insulin). Sex: 40 female, 20 male. Age median(range) years: (a) 59(42–69), (b) 58.5(29–70). BMI median(range) kg m <sup>-2</sup> : (a) 31.3(27.2–44.3), (b) 32.8(27.9–45.8).	(a) + (b) all participants underwent 3 month run-in, post-randomization all participants received dietary counselling on 2.1 MJ day <sup>-1</sup> deficit LFD (minimum: 4.2 MJ day <sup>-1</sup> ) for 24 months. (a) behaviour modification programme for 20 months and exercise training for 18 months (maximum 60 min week <sup>-1</sup> ). Allocated: (a) 30, (b) 30. % Dropout: (a) 10%, (b) 13% at 24 months.	Follow-up: 24 months. Outcomes: weight, cholesterol, TGs, SBP, DBP, HbA1c, adverse events.
Foreyt 1993 (Foreyt <i>et al.</i> , 1993; Skender <i>et al.</i> , 1996)	Location: University, USA. Sex: 80 female, 85 male. Age: not given. Weight in kg: mean(SD): (a) 93.9(20.8), (b) 97.7(22.0), (c) 97.6(25.5).	(a) + (c) LFD and behaviour modification programme for 12 months. (a) advised to maintain sedentary lifestyle. (b) + (c) exercise programme increased to 3–5 sessions of 45 min week <sup>-1</sup> for 12 months. (b) advised to maintain current eating habits. Allocated: (a) 42, (b) 43, (c) 42. % Dropout: (a) 64%, (b) 40%, (c) 50% at 24 months.	Follow-up: 24 months. Outcome: weight.
Jones 1986 (Jones <i>et al.</i> , 1986)	Location: Outpatient clinic, UK. Sex: 160 female. Age mean(SD) years: 50.3(13.5) overall. BMI mean(SD) kg m <sup>-2</sup> : 35.1(9.2) overall.	(a)–(h) individualized dietary advice 4.2 MJ day <sup>-1</sup> below energy requirements but not less than 4.2 MJ day <sup>-1</sup> at first session; (treatment beyond 17 weeks if warranted). (a) 4 group treatment sessions for 16 weeks. (b) seen individually for 16 weeks. (c) received leaflet regarding cue avoidance and food management, seen in groups for 16 weeks. (d) received leaflet regarding cue avoidance and food management, seen individually for 16 weeks. (e) daily food diary, seen in groups for 16 weeks. (f) daily food diary, seen individually for 16 weeks. (g) received leaflet, daily food diaries, seen in groups for 16 weeks. (h) received leaflet, daily food diaries, seen individually for 16 weeks. Allocated: (a) 17, (b) 21, (c) 20, (d) 22, (e) 19, (f) 20, (g) 20, (h) 21. % Dropout: 64% overall at 69 weeks.	Follow-up: 69 weeks. Outcome: weight.
Kaplan 1987 (Kaplan <i>et al.</i> , 1987)	Location: Two Universities, USA. Comorbidity: type 2 diabetes. Sex: 45 female, 32 male (gender unknown for one participant). Age mean(SD) years: (a) 54.9(12.3), (b) 53.8(8.0), (c) 57.0(9.0), (d) 54.5(8.8). Weight mean(SD) kg: (a) 83.9(16.9), (b) 89.2(21.1), (c) 92.1 (20.4), (d) 92.2 (21.8).	(a)–(d) LCD of 5.0 MJ day <sup>-1</sup> , exercise advice for 10 weeks. (a) behaviour modification for 10 weeks. (b) up to 20 min stretching, 45–60 min walking and 5–10 min weekly, encouraged to perform these exercise sessions at least two more times weekly; and exercise focused behavioural programme; for 10 weeks. (c) shortened diet, exercise and behavioural modification programmes (not used here). Allocated: 78 in total. % Dropout 10% overall at 18 months.	Follow-up: 18 months. Outcomes: weight, HbA1c, deaths, quality of life.

Table 3 Continued

Study	Participants	Interventions	Outcomes
Long, 1983 (Long, 1983)	Location: outpatient clinic, UK. Sex: 36 female. Age mean(range) years: 36.8(18–56) overall. BMI mean(range) (kg m <sup>-2</sup> ): 33.5(28.9–49.4) overall.	(a) + (b) + (c) all participants received same advice on diet 4.2–5.0 MJ day <sup>-1</sup> high fibre diet and exercise over 16 weeks. (a) seen individually. (b) group sessions. (c) group sessions included behaviour modification programme. Allocated: (a) 12, (b) 12, (c) 12. % Dropout: (a) 42%, (b) 42%, (c) 25% at 68 weeks.	Follow-up: 68 weeks. Outcome: weight.
ODES 1995 (Urdal et al., 1993; Anderssen, 1995; Anderssen et al., 1995, 1996, 1998; Torjesen et al., 1997; Reseland et al., 2001)	Location: Hospital, Norway. Comorbidity: slightly increased blood pressure, TGs, cholesterol; and decreased HDL. Sex: 21 female, 198 male. Age mean(SD) years: 44.9 (2.5). BMI mean(SD) kg m <sup>-2</sup> : (a) 29.5(3.9), (b) 28.6(3.2), (c) 28.6(3.5), (d) 28.3(3.2).	(a) counselling on LFD for 12 months. (b) 12 month exercise intervention (group not used here). (c) 12 month counselling on LFD and exercise intervention (d) asked not to change lifestyle (group not used here). Allocated: (a) 55, (b) 54, (c) 67, (d) 43. % Dropout: (a) 5%, (b) 9%, (c) 3%, (d) 0%.	Follow-up: 12 months. Outcomes: weight cholesterol, LDL, HDL, TGs, SBP, DBP, glucose, cancer, deaths.
Pavlou 1989: 2 Pilot study (Pavlou et al., 1989)	Location: University, USA. Sex: 24 male. Age mean(SD) years: (a) 49.2(6.5), (b) 44.8(7.8), (c) 46.1(5.1), (d) 48.1(4.7) (completers). BMI mean kg m <sup>-2</sup> : (a) 31.8, (b) 31.9, (c) 31.1, (d) 30.4 (completers).	(a) + (b) 12 week LCD of 4.2 MJ day <sup>-1</sup> . (c) + (d) PSMF of 4.2 MJ day <sup>-1</sup> for 12 weeks. (a) + (c) exercise programme. (b) + (d) no exercise program. % Dropout: 13% at 36 months post-treatment.	Follow-up: 168 weeks. Outcome: weight.
Pavlou 1989: 1 Main study (Pavlou et al., 1989)	Location: University, USA. Sex: 160 male. Age mean(SD) years: (a) 41.5(7.6), (b) 42.9(6.6), (c) 45.1(10.0), (d) 49.6(8.4), (e) 41.8(10.4), (f) 41.8(7.6), (g) 46.1(9.3), (h) 44.5(9.6) (completers). BMI mean kg m <sup>-2</sup> : (a) 32.5, (b) 32.4, (c) 32.1, (d) 31.5, (e) 30.1, (f) 34.8, (g) 31.9, (h) 33.8 (completers).	(a) + (b) 8 week LCD of 4.2 MJ day <sup>-1</sup> . (c) + (d) 8 week PSMF of 4.2 MJ day <sup>-1</sup> . (e) + (f) 8 week 1.8 MJ day <sup>-1</sup> (assumed PSMF). (g) + (h) 8 week VLCD 3.3 MJ day <sup>-1</sup> . (a) + (c) + (e) + (g) exercise programme. (b) + (d) + (f) + (h) no exercise programme. Allocated: 160 % Dropout: 31% at 18 months post-treatment	Follow-up: 86 weeks. Outcomes: weight, cholesterol, HDL, TGs, SBP, DBP.
Phenix, 1990 (Phenix, 1990)	Location: University, USA. Sex: 105 female. Age: not given. Weight mean(SD) kg: (a) 85.2(17.1), (b) 81.1(14.6), (c) 76.2(10.7), (d) 85.8(14.3), (e) 76.4(8.7), (f) 84.2(22.4), (g) 79.2(11.5), (h) 76.0(12.5).	(a)–(f) 4.2–5.0 MJ day <sup>-1</sup> as LFD for 8 weeks. (a) food tasting for 8 weeks (treated as control). (b) overt behaviour therapy for 8 weeks. (c) cognitive behaviour therapy for 8 weeks. (d) 20 min advised home aerobic exercise three times per week for 8 weeks. (e) exercise as group (d), overt behaviour therapy as group (b). (f) exercise as groups (d) and (e), cognitive behaviour therapy as group (c). (g) exercise as groups (d), (e) and (f); overt behaviour therapy as groups (b) and (e); cognitive behaviour therapy as groups (c) and (f). (h) waiting list control group (data not used here), 8 weeks only. Allocated: 105 in total. % Dropout: 18% at 12 months.	Follow-up: 12 months. Outcome: weight.



<p>Sikand 1988 (Sikand <i>et al.</i>, 1988)</p>	<p>Location: University, USA. Sex: 30 female. Age mean(SD) years: (a) 39.8(9.1), (b) 37.8(8.4). Weight mean(SD) kg: (a) 105.6(23.6), (b) 106.6 (15.2).</p>	<p>(a) + (b) VLCD (energy content not given) and behaviour modification programme for 4 months. a: exercise programme twice weekly for 4 months, encouraged to exercise other days. Allocated: (a) 15, (b) 15. % Dropout: (a) 53%, (b) 47% at 2 years.</p>	<p>Follow-up: 24 months. Outcome: weight.</p>
<p>Wadden 1989 (Wadden &amp; Stunkard, 1986; Wadden <i>et al.</i>, 1987, 1988, 1989)</p>	<p>Location: University, USA. Sex: 76 female (completers only, males excluded from analyses due to small numbers). Age mean(SEM) years: 42.1(1.1) female completers. BMI mean(SEM) kg m<sup>-2</sup>: 39.4(0.8) female completers.</p>	<p>(a) LCD 4.2–5.0 MJ day<sup>-1</sup> diet for 25 weeks. (b) + (c) LCD 4.2–5.0 MJ day<sup>-1</sup> for month 1, months 2 + 3 PSMF 1.7–2.1 MJ day<sup>-1</sup>, month 4 refeeding to conventional foods. (c) in addition months 5 + 6 prescribed 4.2–5.0 MJ day<sup>-1</sup>. (a) + (c) behaviour therapy. Allocated: unclear % Dropout: unclear</p>	<p>Follow-up: 64–66 months. Outcomes: weight, depression scores, medication use.</p>
<p>Wadden 1998 (Ashutosh <i>et al.</i>, 1997; Gladis <i>et al.</i>, 1998; Wadden <i>et al.</i>, 1998, 1999; Weinstock <i>et al.</i>, 1998)</p>	<p>Location: Two Universities, USA. Sex: 128 female. Age mean(SD) years: 40.9(8.6). BMI mean(SD) kg m<sup>-2</sup>: a 36.3(5.3).</p>	<p>(a)–(d) 3.9 MJ day<sup>-1</sup> weeks 0–16 then 5.0–6.3 MJ day<sup>-1</sup> to week 48; behavioural therapy for 48 weeks. (a) advised not to increase exercise. (b) + (c) + (d) 3 × 1 hour exercise training per week for 28 weeks, two sessions per week during weeks 29–48 and one home exercise session per week. (b) step aerobics. (c) strength exercises. (d) step aerobics and strength exercises. Allocated: not clear. % Dropout: 40% overall at 100 weeks.</p>	<p>Follow-up: 100 weeks. Outcome: weight.</p>
<p>Wadden 2001 (Wadden <i>et al.</i>, 2001)</p>	<p>Location: University, USA. Sex: female only. Age mean(SD): 47.2(9.8). BMI mean(SD) kg m<sup>-2</sup>: 37.7(3.6).</p>	<p>(a) + (b) + (c) 10 mg sibutramine increased to 15 mg at week 8 if tolerated, and exercise prescription for 12 months. (a) + (b) 5.0–6.3 MJ day<sup>-1</sup> LFD for 12 months. (b) + (c) behaviour modification programme. (c) 4.2 MJ day<sup>-1</sup> LCD for 16 weeks (four servings per day of OPTIFAST) and meal, by week 20 5.0–6.3 MJ day<sup>-1</sup> LCD as meals until 12 months. Allocated: (a) 20, (b) 18, (c) 17. % Dropout: (a) 35%, (b) 28%, (c) 0% at 12 months.</p>	<p>Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, TGs, SBP, DBP, adverse events, compliance.</p>
<p>Wing 1988a (Wing <i>et al.</i>, 1988)</p>	<p>Location: University, USA. Comorbidity: type 2 diabetes (not on insulin). Sex: 21 female, 4 male. Age mean(SD) years: (a) 56.2(7.5), (b) 52.5(8.9). BMI mean(SD) kg m<sup>-2</sup>: (a) 38.1(6.4), (b) 37.5(6.2).</p>	<p>(a) + (b) 6.7 MJ day<sup>-1</sup> LFD and behaviour modification programme for 36 weeks. (a) walking exercise increased until participants were walking 3 miles within the hour session, twice per week as a group and once per week on own for 36 weeks. (b) low intensity exercise designed as placebo, twice per week as a group and once per week on own for 36 weeks. Allocated: (a) 12, (b) 13. % Dropout: (a) 33%, (b) 15% at 62 weeks.</p>	<p>Follow-up: 62 weeks. Outcome: weight.</p>

Table 3 Continued

Study	Participants	Interventions	Outcomes
Wing 1988b (Wing <i>et al.</i> , 1988)	Location: University, USA. Comorbidity: type 2 diabetes (not on insulin). Sex: 21 female, 9 male. Age: mean(SD) (a) 56.1 (6.4), (b) 55.1 (7.2) BMI: ( $\text{kg m}^{-2}$ ) mean (SD) (a) 38.2 (6.6), (b) 37.9 (6.5)	(a) + (b) 6.7 MJ $\text{day}^{-1}$ LFD and behaviour modification programme for 72 weeks. (a) walked 3 miles with therapist three times per week and asked to exercise once per week on their own. (b) asked not to change baseline level of activity. Allocated: (a) 15, (b) 15. % Dropout: (a) 13%, (b) 0% at 72 weeks.	Follow-up: 72 weeks. Outcomes: weight, cholesterol, HDL, TCs, HbA1c, glucose.
Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	Location: University, USA. Comorbidity: One or two parents with type 2 diabetes. Sex: 122 female, 32 male. Age mean(SD) years: (a) 45.0(4.7), (b) 46.4(4.5), (c) 46.3(3.8), (d) 45.3(4.9). BMI mean(SD) $\text{kg m}^{-2}$ : (a) 36.1(4.1), (b) 36.0(3.7), (c) 35.7(4.1), (d) 36.0(5.4).	(a) 3.3–4.2 MJ $\text{day}^{-1}$ weeks 1–8 then adjusted to 5.0–6.3 MJ $\text{day}^{-1}$ by week 16, and behavioural therapy, for 24 months. (b) 50–60 minutes weekly walk with therapist (second walk available for weeks 1–10), increased to e.g. 3 miles brisk walking 5 days/week, other activities, e.g. aerobics and line dancing, and behavioural therapy, for 24 months. (c) same diet as group a and same exercise as group (b) (half time for each), behavioural programme, for 24 months. (d) self-help manual on diet, exercise and behavioural strategies. Allocated: (a) 37, (b) 37, (c) 40, (d) 40. % Dropout: (a) 5%, (b) 16%, (c) 20%, (d) 23% at 2 years.	Follow-up: 24 months. Outcomes: weight, cholesterol, HDL, LDL, TCs, SBP, DBP, HbA1c, glucose, development of type 2 diabetes, compliance.
Wood 1991 (Wood <i>et al.</i> , 1989, 1991; Williams <i>et al.</i> , 1994; Kiernan <i>et al.</i> , 1998)	Location: University, USA. Sex: 132 female, 132 male. Age mean(SD) years: 39.1(6.4) female, 40.3(6.3) male. BMI mean(SD) $\text{kg m}^{-2}$ : 27.9(2.2) female, 30.7(2.2) male.	(a) 12 months counselling on LFD. (b) 12 months LFD and exercise intervention (group not used here). (c) usual care. Allocated: (a) 87, (b) 90, (c) 87. % Dropout: (a) 10%, (b) 18%, (c) 10% at 12 months.	Follow-up: 12 months. Outcomes: weight, cholesterol, LDL, HDL, TCs, SBP, DBP.

- SD for change in HDL = 0.29 mmol L<sup>-1</sup>
- SD for change in TGs = 0.96 mmol L<sup>-1</sup>

In the case of fasting plasma glucose and HbA1c, two levels of SDs were used, to allow for the greater variability of such measures evident from the studies with diabetic participants:

- If the initial fasting plasma glucose was <7 mmol L<sup>-1</sup>, the SD for change in fasting plasma glucose was 1.35 mmol L<sup>-1</sup>
- If the initial fasting plasma glucose was ≥7 mmol L<sup>-1</sup>, the SD for change in fasting plasma glucose was 3.77 mmol L<sup>-1</sup>
- If the initial HbA1c was <7%, the SD for change in HbA1c was 0.71%
- If the initial HbA1c was ≥7%, the SD for change in HbA1c was 2.58%

## Results

### Drug therapy

#### *Adding orlistat to diet alone*

Eight RCTs provided change in weight at 12 months or longer with 360 mg orlistat day<sup>-1</sup> (Table 1). Three studies continued for a second year (Farrell, 1997; Foreyt, 1997; Toornvliet *et al.*, 1997; Davidson *et al.*, 1999; Hauptman *et al.*, 1999; Hauptman *et al.*, 2000; Rossner *et al.*, 2000).

One study recruited people with type 2 diabetes (Kelley, 1997; Hollander *et al.*, 1998), two studies recruited people at cardiac risk (Lindgarde, 1999, 2000; Broom, 2001; Wilding, 2001; Broom *et al.*, 2002). Reported mean BMI ranged from 33.2 kg m<sup>-2</sup> (Lindgarde, 1999, 2000) to 37.1 kg m<sup>-2</sup> (Broom, 2001; Wilding, 2001; Broom *et al.*, 2002).

Four studies clearly reported a good attempt at concealment of randomization. No study clearly reported undertaking intention to treat analysis, although this was a possibility in two studies (Kelley, 1997; Hollander *et al.*, 1998; Lindgarde, 1999; Lindgarde, 2000). Six studies reported using 'last observation carried forward' for dropouts.

Most studies included a single blind pretreatment phase, which ranged from 2 weeks (Lindgarde, 1999, 2000; Broom, 2001; Wilding, 2001; Broom *et al.*, 2002) to 5 weeks (Kelley, 1997; Hollander *et al.*, 1998). All the studies included

low fat dietary advice. Two studies gave very brief details of a behavioural intervention, e.g. videos (Farrell, 1997; Foreyt, 1997; Davidson *et al.*, 1999; Hauptman *et al.*, 1999, 2000). Four studies reported giving advice to increase physical exercise, but no other details.

There was the possibility of unblinding of participants and health care providers due to the gastrointestinal adverse events associated with orlistat e.g. oily stools. Apart from one study (Lindgarde, 1999, 2000), dropout rates in the control groups were always higher than in the intervention groups.

**Weight reduction.** The addition of orlistat 360 mg day<sup>-1</sup> to diet was associated with a weight change at 12 months of -3.01 kg (95% CI, -3.48 to -2.54 kg) in the weight reduction studies.

Observed weight change after 2 years was -3.26 kg (95% CI, -4.15 to -2.37 kg) (Farrell, 1997; Toornvliet *et al.*, 1997; Hauptman *et al.*, 1999, 2000; Rossner *et al.*, 2000). Re-randomization at the end of year 1 in one study (Foreyt, 1997; Davidson *et al.*, 1999) led to uncertainty in denominators, so that this trial could not be included in the 2 year meta-analysis. For all participants treated with orlistat during the first year, this trial reported 3.2 kg weight regain in the group treated with orlistat during year 2, compared with 5.63 kg regain in the group treated with placebo in year 2.

**Risk factors.** All risk factors showed statistically significant beneficial changes at 1 year, except for HDL cholesterol and TGs (Tables 4 and 5). There was evidence of heterogeneity for HbA1c, fasting plasma glucose and TGs at 12 months. This may have related to the inclusion of people with diabetes in two studies (Kelley, 1997; Hollander *et al.*, 1998; Lindgarde, 1999, 2000). After 12 months of orlistat in people with diabetes a change in HbA1c of -0.27% (95% CI, -0.38% to -0.15%) compared with the control group was observed, and -0.11% (95% CI, -0.20% to -0.02%) for non-diabetics compared with controls. Similarly, for fasting glucose the observed change was -0.58 mmol L<sup>-1</sup> (95% CI, -0.80 to -0.36 mmol L<sup>-1</sup>) for diabetics and -0.16 mmol L<sup>-1</sup> (95% CI, -0.27 to -0.05 mmol L<sup>-1</sup>) for non-diabetics. However, for TGs observed changes were less marked between

**Table 4** Changes in lipids in included studies, with details of studies providing data

Time interval	Cholesterol (mmol L <sup>-1</sup> )	HDL cholesterol (mmol L <sup>-1</sup> )	LDL cholesterol (mmol L <sup>-1</sup> )	Triglycerides (mmol L <sup>-1</sup> )
<b>Drugs</b>				
<b>Adding orlistat to diet alone</b>				
12 months	-0.34 (-0.41 to -0.27) Broom 2001 (Broom, 2001); Wilding, 2001; Broom <i>et al.</i> , 2002), Finer 2000 (James <i>et al.</i> , 1997; Finer <i>et al.</i> , 2000), Finer <i>et al.</i> , 2000), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander <i>et al.</i> , 1998), Hollander <i>et al.</i> , 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000), Sjostrom 1998 (Sjostrom <i>et al.</i> , 1998; Vidgren <i>et al.</i> , 1999; Franson & Rossner, 2000; Karhunen <i>et al.</i> , 2000; Rissanen <i>et al.</i> , 2001)	-0.03 (-0.01 to -0.05) Finer 2000 (James <i>et al.</i> , 1997; Finer <i>et al.</i> , 2000), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander <i>et al.</i> , 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000), Sjostrom 1998 (Sjostrom <i>et al.</i> , 1998; Vidgren <i>et al.</i> , 1999; Franson & Rossner, 2000; Karhunen <i>et al.</i> , 2000; Rissanen <i>et al.</i> , 2001)	-0.29 (-0.34 to -0.24) Broom 2001 (Broom, 2001); Wilding, 2001; Broom <i>et al.</i> , 2002), Finer 2000 (James <i>et al.</i> , 1997; Finer <i>et al.</i> , 2000), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander <i>et al.</i> , 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000), Sjostrom 1998 (Sjostrom <i>et al.</i> , 1998; Vidgren <i>et al.</i> , 1999; Franson & Rossner, 2000; Karhunen <i>et al.</i> , 2000; Rissanen <i>et al.</i> , 2001)	0.03 (-0.04 to 0.10) Broom 2001 (Broom, 2001); Wilding, 2001; Broom <i>et al.</i> , 2002), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander <i>et al.</i> , 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000), Sjostrom 1998 (Sjostrom <i>et al.</i> , 1998; Vidgren <i>et al.</i> , 1999; Franson & Rossner, 2000; Karhunen <i>et al.</i> , 2000; Rissanen <i>et al.</i> , 2001)
24 months	-0.21 (-0.34 to -0.09) Davidson 1999 (Foreyt, 1997; Davidson <i>et al.</i> , 1999), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000)	-0.03 (0 to -0.07) Davidson 1999 (Foreyt, 1997; Davidson <i>et al.</i> , 1999), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000)	-0.22 (-0.31 to -0.13) Davidson 1999 (Foreyt, 1997; Davidson <i>et al.</i> , 1999), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000)	0.04 (-0.07 to 0.15) Davidson 1999 (Foreyt, 1997; Davidson <i>et al.</i> , 1999), Hauptman 2000 (Farrell, 1997; Hauptman <i>et al.</i> , 1999, 2000), Rossner 2000 (Toornvliet <i>et al.</i> , 1997; Rossner <i>et al.</i> , 2000)
<b>Adding sibutramine to diet alone</b>				
12 months	0.01 (-0.19 to 0.20) Smith 2001 (Jones <i>et al.</i> , 1995; Smith, 1997, 2001)	0.11 (0.18 to 0.04) Apfelbaum 1999 (Apfelbaum <i>et al.</i> , 1999)	-0.16 (-0.36 to 0.04) Apfelbaum 1999 (Apfelbaum <i>et al.</i> , 1999)	-0.15 (-0.27 to -0.04) Apfelbaum 1999 (Apfelbaum <i>et al.</i> , 1999), Smith 2001 (Jones <i>et al.</i> , 1995; Smith, 1997, 2001)

**Exercise****Adding exercise to diet alone**

12 months  
 -0.03 (-0.20 to 0.13)  
 ODES 1995 (Urdal *et al.*, 1993);  
 Anderssen, 1995;  
 Anderssen *et al.*, 1995, 1996,  
 1998; Torjesen *et al.*, 1997;  
 Reseland *et al.*, 2001),  
 Wood 1991 (Wood *et al.*,  
 1989, 1991; Williams *et al.*, 1994;  
 Kiernan *et al.*, 1998)

0.10 (0.14 to 0.06)  
 ODES 1995 (Urdal *et al.*, 1993);  
 Anderssen, 1995; Anderssen *et al.*, 1995,  
 1996, 1998; Torjesen *et al.*, 1997;  
 Reseland *et al.*, 2001),  
 Wood 1991 (Wood *et al.*, 1989, 1991;  
 Williams *et al.*, 1994; Kiernan *et al.*, 1998)

-0.03 (-0.19 to 0.13)  
 ODES 1995 (Urdal *et al.*, 1993);  
 Anderssen, 1995;  
 Anderssen *et al.*, 1995,  
 1996, 1998; Torjesen *et al.*,  
 1997; Reseland *et al.*, 2001),  
 Wood 1991 (Wood *et al.*,  
 1989, 1991;  
 Williams *et al.*, 1994;  
 Kiernan *et al.*, 1998)

-0.18 (-0.31 to -0.06)  
 ODES 1995 (Urdal *et al.*, 1993);  
 Anderssen, 1995; Anderssen *et al.*,  
 1995, 1996, 1998; Torjesen *et al.*,  
 1997; Reseland *et al.*, 2001),  
 Wood 1991 (Wood *et al.*, 1989,  
 1991; Williams *et al.*, 1994;  
 Kiernan *et al.*, 1998)

**Adding exercise to diet and behaviour therapy**

12 months  
 0.05 (-0.27 to 0.37)  
 \*Wing 1988b (Wing *et al.*, 1988),  
 Wing 1998 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

0.01 (0.09 to -0.07)  
 \*Wing 1988b  
 (Wing *et al.*, 1988), Wing 1998  
 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

0.01 (-0.30 to 0.34)  
 Wing 1998 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

-0.58 (-1.22 to 0.06)  
 \*Wing 1988b (Wing *et al.*, 1988),  
 Wing 1998 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

24 months  
 0.21 (-0.10 to 0.52)  
 Wing 1998 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

0 (-0.10 to 0.10)  
 Wing 1998  
 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

0.28 (0 to 0.56)  
 Wing 1998 (Polley *et al.*, 1997;  
 Wing *et al.*, 1998)

-0.47 (-1.39 to 0.45)  
 Wing 1998 (Polley *et al.*,  
 1997; Wing *et al.*, 1998)

**Combined interventions****Adding exercise and behaviour therapy to diet**

12 months  
 -0.30 (-3.51 to 2.91)  
 \*Blonk 1994 (Blonk *et al.*, 1994)

Values in table are change in risk factor measurement (95% confidence interval).  
 \*All participants had type 2 diabetes.

Table 5 Changes in blood pressure, fasting glucose and HbA1c in included studies, with details of studies providing data

Time interval	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Fasting plasma glucose (mmol L <sup>-1</sup> )	HbA1c (%)
<b>Drugs</b>				
<b>Adding orlistat to diet alone</b>				
12 months	-2.02 (-2.87 to -1.17) Broom 2001 (Broom, 2001); Wilding, 2001; Broom et al., 2002), Davidson 1999 (Foreyt, 1997; Davidson et al., 1999), Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander et al., 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000), Sjostrom 1998 (Sjostrom et al., 1998; Vidgren et al., 1999; Franson & Rossner, 2000; Karhunen et al., 2000; Rissanen et al., 2001)	-1.64 (-2.20 to -1.09) Broom 2001 (Broom, 2001); Wilding, 2001; Broom et al., 2002), Davidson 1999 (Foreyt, 1997; Davidson et al., 1999), Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000), *Hollander 1998 (Kelley, 1997; Hollander et al., 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000), Sjostrom 1998 (Sjostrom et al., 1998; Vidgren et al., 1999; Franson & Rossner, 2000; Karhunen et al., 2000; Rissanen et al., 2001)	-0.24 (-0.34 to -0.14) Broom 2001 (Broom, 2001); Wilding, 2001; Broom et al., 2002), *Hollander 1998 (Kelley, 1997; Hollander et al., 1998), Lindgarde 2000 (Lindgarde, 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000), Sjostrom 1998 (Sjostrom et al., 1998; Vidgren et al., 1999; Franson & Rossner, 2000; Karhunen et al., 2000; Rissanen et al., 2001)	-0.17 (-0.24 to -0.10) Broom 2001 (Broom, 2001); Wilding, 2001; Broom et al., 2002), *Hollander 1998 (Kelley, 1997; Hollander et al., 1998), Lindgarde 2000 (Lindgarde, 1999, 2000)
24 months	-1.42 (-3.08 to 0.24) Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000)	-1.20 (-2.28 to -0.11) Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000)	-0.15 (-0.24 to -0.07) Davidson 1999 (Foreyt, 1997; Davidson et al., 1999), Hauptman 2000 (Farrell, 1997; Hauptman et al., 1999, 2000), Rossner 2000 (Toornvliet et al., 1997; Rossner et al., 2000)	
<b>Adding sibutramine to diet alone</b>				
12 months	1.15 (-0.86 to 3.17) Smith 2001 (Jones et al., 1995; Smith, 1997, 2001)	1.66 (0.34 to 2.98) Smith 2001 (Jones et al., 1995; Smith, 1997, 2001)	-0.04 (-0.28 to 0.20) Smith 2001 (Jones et al., 1995; Smith, 1997, 2001)	
<b>Exercise</b>				
<b>Adding exercise to diet alone</b>				
12 months	-0.03 (-1.99 to 1.93) ODES 1995 (Urdal et al., 1993; Anderssen, 1995; Anderssen et al., 1995, 1996, 1998; Torjesen et al., 1997; Reseland et al., 2001), Wood 1991 (Wood et al., 1989, 1991; Williams et al., 1994; Kiernan et al., 1998)	-1.14 (-2.56 to 0.29) ODES 1995 (Urdal et al., 1993; Anderssen, 1995; Anderssen et al., 1995, 1996, 1998; Torjesen et al., 1997; Reseland et al., 2001), Wood 1991 (Wood et al., 1989, 1991; Williams et al., 1994; Kiernan et al., 1998)	-0.05 (-0.26 to 0.16) ODES 1995 (Urdal et al., 1993; Anderssen, 1995; Anderssen et al., 1995, 1996, 1998; Torjesen et al., 1997; Reseland et al., 2001)	

18 months	-8.90 (-13.65 to -4.15) Pavlou 1989; 1 Main study (Pavlou <i>et al.</i> , 1989)	-12.10 (-15.20 to -9.00) Pavlou 1989; 1 Main study (Pavlou <i>et al.</i> , 1989)		
<b>Adding exercise to diet and behaviour therapy</b>				
12 months	-4.20 (-10.02 to 1.62) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	-4.40 (-8.98 to 0.18) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	-0.21 (-0.53 to 0.11) *Wing 1988b (Wing <i>et al.</i> , 1988), Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	-0.60 (-2.52 to 1.32) *Wing 1988b (Wing <i>et al.</i> , 1988)
24 months	-4.00 (-10.06 to 2.06) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	-3.20 (-7.66 to 1.26) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	0.20 (-0.36 to 0.76) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)	0.14 (-0.27 to 0.55) Wing 1998 (Polley <i>et al.</i> , 1997; Wing <i>et al.</i> , 1998)
<b>Combined interventions</b>				
<b>Adding exercise and behaviour therapy to diet</b>				
12 months				
18 months				-0.38 (-1.77 to 1.01) *Blonk 1994 (Blonk <i>et al.</i> , 1994)
24 months				-0.20 (-1.59 to 1.19) *Blonk 1994 (Blonk <i>et al.</i> , 1994) -0.41 (-1.80 to 0.98) *Blonk 1994 (Blonk <i>et al.</i> , 1994)

Values in table are change in risk factor measurement (95% confidence interval)

\*All participants had type 2 diabetes

diabetics [ $-0.05 \text{ mmol L}^{-1}$  (95% CI,  $-0.19$  to  $0.09 \text{ mmol L}^{-1}$ )] and non-diabetics [ $0.05 \text{ mmol L}^{-1}$  (95% CI,  $-0.03$  to  $0.14 \text{ mmol L}^{-1}$ )].

By 24 months the beneficial effects of orlistat on risk factors were still apparent, with the exception of TGs, HDL and systolic blood pressure (Tables 4 and 5).

**Clinical outcomes and quality of life.** Hollander and colleagues (Kelley, 1997; Hollander *et al.*, 1998) reported that the average dose of oral sulphonylureas decreased more in the orlistat than the placebo group ( $-23\%$  versus  $-9\%$  respectively,  $P = 0.002$ ). The study by Rossner and colleagues (Toornvliet *et al.*, 1997; Rossner *et al.*, 2000) evaluated overweight distress, which was observed to be statistically reduced in the orlistat group compared with the placebo group after 2 years ( $P < 0.05$ ). However, depression scores did not differ significantly between the treatment and placebo groups. In an abstract reporting on quality of life in five orlistat trials, overweight distress was also reported as being significantly decreased after 1 and 2 years compared with placebo, but depression scores were significantly improved at 1 year, but not 2 years (Mathias *et al.*, 1997).

**Adverse events.** From the 2198 participants randomized to orlistat, one participant was reported to have died of cancer, one from myocardial infarction, and one from a brain stem infarct. One participant was reported to have cholelithiasis, one diverticulitis, six breast cancer (three of whom had mammographic evidence of cancer before randomization). From the 1747 participants allocated to placebo, one was reported to have developed gastrointestinal cancer and two breast cancer (one of whom had mammographic evidence before randomization).

All the orlistat studies reported gastrointestinal adverse events, such as oily stools and faecal incontinence, to be more common in groups on orlistat groups than on placebo. Where required *per protocol*, vitamin supplementation was always more common in the orlistat groups than placebo groups.

#### *Adding sibutramine to diet alone*

Two RCTs provided change in weight from adding sibutramine to diet (Table 2) (Jones *et al.*, 1995;

Smith, 1997; Apfelbaum *et al.*, 1999; Smith, 2001). Apfelbaum *et al.* (1999) also evaluated weight change 3 months after treatment cessation. Smith and colleagues (Jones *et al.*, 1995; Smith, 1997, 2001) evaluated 10 and 15 mg doses of sibutramine.

Neither of the included studies reported assessor blinding or intention to treat analysis. Although reported as randomized, no further description was given. Both of the studies reported carrying data at the last visit forward to the end of the trial for those people who dropped out. Smith and colleagues (Jones *et al.*, 1995; Smith, 1997, 2001) included a single-blind placebo run in period, which ranged from 2–10 weeks duration. The study by Apfelbaum *et al.* (1999) included 4 weeks pre-treatment phase of VLCD with entry to randomization dependent upon a  $\geq 6$  kg weight loss. The study by Apfelbaum *et al.* (1999) provided dietary counselling to reduce total energy intake by 20–30% and Smith and colleagues (Jones *et al.*, 1995; Smith, 1997, 2001) advised a low fat diet.

The study by Smith *et al.* (Jones *et al.*, 1995; Smith, 1997, 2001) included people with hypertension if stabilized on medication. Reported mean BMI ranged from  $32.4 \text{ kg m}^{-2}$  (Jones *et al.*, 1995; Smith, 1997, 2001) to  $35.9 \text{ kg m}^{-2}$  (Apfelbaum *et al.*, 1999).

**Weight changes.** Sibutramine and diet compared with diet was associated with a weight change at 12 months of  $-4.18 \text{ kg}$  (95% CI,  $-5.14$  to  $-3.21 \text{ kg}$ ). The weight reduction study by Apfelbaum *et al.* (1999) was associated with a weight change at 15 months of  $-3.70 \text{ kg}$  (95% CI,  $-5.71$  to  $-1.69 \text{ kg}$ ).

**Risk factor changes.** After 12 months of sibutramine statistically significant beneficial effects were observed on HDL and TGs (Table 4). At 12 months, diastolic blood pressure showed a statistically significant increase of  $1.66 \text{ mmHg}$  (95% CI,  $0.34$ – $2.98 \text{ mmHg}$ ) and systolic blood pressure a change of  $1.15 \text{ mmHg}$  (95% CI,  $-0.86$  to  $3.17 \text{ mmHg}$ ) (Table 5).

**Adverse events.** In 404 people randomized to sibutramine, one participant was reported to have required a cholecystectomy, one participant with a history of epilepsy withdrew due to drop attacks, and one participant withdrew due to ventricular

ectopics. In the 241 people allocated to placebo, one person was withdrawn due to the development of hypertension.

Constipation was more commonly reported on sibutramine in one study (Apfelbaum *et al.*, 1999) (Peto odds ratio 3.49, 95% CI, 1.34–9.07), and dry mouth was more frequently reported in both sibutramine groups than placebo (Peto odds ratio: 4.11, 95% CI, 2.10 to 8.02) in the other study (Jones *et al.*, 1995; Smith, 1997, 2001).

## Exercise

### *Adding exercise to diet alone*

Five studies assessed the addition of exercise to diet for up to 36 months (Table 3) (Pavlou *et al.*, 1989; Wood *et al.*, 1989; Phenix, 1990; Wood *et al.*, 1991; Urdal *et al.*, 1993; Williams *et al.*, 1994; Anderssen, 1995; Anderssen *et al.*, 1995, 1996, 1998; Torjesen *et al.*, 1997; Kiernan *et al.*, 1998; Reseland *et al.*, 2001). One of these five studies was a cluster RCT (Phenix, 1990). The Oslo Diet and Exercise Study (ODES) (Urdal *et al.*, 1993; Anderssen, 1995; Anderssen *et al.*, 1995, 1996, 1998; Torjesen *et al.*, 1997; Reseland *et al.*, 2001) was the only study which included people at increased cardiovascular risk. Mean BMI ranged from  $27.9$  to  $34.8 \text{ kg m}^{-2}$  in the studies.

One study reported a good attempt at concealment of allocation (Urdal *et al.*, 1993; Anderssen, 1995; Anderssen *et al.*, 1995, 1996, 1998; Torjesen *et al.*, 1997; Reseland *et al.*, 2001). No studies clearly used an intention to treat analysis or blinded outcome assessors.

**Weight reduction.** Diet and exercise compared with diet alone was associated with a weight change at 12 months of  $-1.95 \text{ kg}$  (95% CI,  $-3.22$  to  $-0.68 \text{ kg}$ ), after 18 months  $-7.63 \text{ kg}$  (95% CI,  $-10.33$  to  $-4.92 \text{ kg}$ ) and after 36 months  $-8.22 \text{ kg}$  (95% CI,  $-15.27$  to  $-1.16 \text{ kg}$ ). Data from 18 and 36 months came only from the studies by Pavlou *et al.* (1989). In the cluster RCT (Phenix, 1990) the addition of exercise to diet was associated with a weight change at 12 months of  $-5.32 \text{ kg}$  compared with  $-4.82 \text{ kg}$  in the diet only group.

**Risk factors.** In two studies adding exercise to diet was associated with beneficial effects at 12 months



for HDL cholesterol (change  $0.1 \text{ mmol L}^{-1}$ , 95% CI, 0.06 to  $0.14 \text{ mmol L}^{-1}$ ) and TGs (change  $-0.18 \text{ mmol L}^{-1}$ , 95% CI,  $-0.31$  to  $-0.06 \text{ mmol L}^{-1}$ ) (Tables 4 and 5). Added exercise was also associated with significantly decreased systolic and diastolic blood pressure after 18 months in one study (Pavlou *et al.*, 1989) (Table 5).

**Adverse events.** Two cases of cancer and one cardiac event were reported in the ODES (Urdal *et al.*, 1993; Anderssen, 1995; Anderssen *et al.*, 1995, 1996, 1998; Torjesen *et al.*, 1997; Reseland *et al.*, 2001) but treatment allocation was not stated.

#### *Adding exercise to diet and behaviour therapy*

Seven RCTs assessed the addition of exercise to diet and behaviour therapy and provided change in weight at 12 months or longer (Table 3) (Kaplan *et al.*, 1987; Sikand *et al.*, 1988; Wing *et al.*, 1988; Phenix, 1990; Foreyt *et al.*, 1993; Skender *et al.*, 1996; Ashutosh *et al.*, 1997; Polley *et al.*, 1997; Gladis *et al.*, 1998; Wadden *et al.*, 1998; Weinstock *et al.*, 1998; Wing *et al.*, 1998; Wadden *et al.*, 1999). Two of these were cluster RCTs (Kaplan *et al.*, 1987; Phenix, 1990). Wing and colleagues carried out three of the studies, which recruited type 2 diabetics (Wing *et al.*, 1988) or people with at least one parent with type 2 diabetes (Polley *et al.*, 1997; Wing *et al.*, 1998). The cluster RCT by Kaplan *et al.* (1987) also recruited people with type 2 diabetes. Reported mean group BMI ranged from  $38.2 \text{ kg m}^{-2}$  (Wing *et al.*, 1988) to  $35.7 \text{ kg m}^{-2}$  (Polley *et al.*, 1997; Wing *et al.*, 1998).

Three studies assessed data using an intention to treat approach (Sikand *et al.*, 1988; Phenix, 1990; Polley *et al.*, 1997; Wing *et al.*, 1998). No study clearly reported concealed randomization, and only one study reported blinding of outcome assessors (Wing *et al.*, 1998).

**Weight reduction.** The addition of exercise to diet and behaviour therapy was associated with a weight change at 12 months of  $-3.02 \text{ kg}$  (95% CI,  $-4.94$  to  $-1.11 \text{ kg}$ ) and  $-2.16 \text{ kg}$  (95% CI,  $-4.20$  to  $-0.12 \text{ kg}$ ) at 24 months. In the cluster RCT by Phenix (Phenix, 1990) exercise, diet and cognitive behaviour therapy was associated with a mean weight change at 12 months of  $-1.13 \text{ kg}$  compared with  $-6.68 \text{ kg}$  in the diet and cognitive behaviour

group. Exercise, diet and overt behaviour therapy, in the same trial, was associated with a mean weight change at 12 months of  $-5.19 \text{ kg}$  compared with  $-3.26 \text{ kg}$  in the diet and overt behaviour therapy group. In the cluster RCT by Kaplan *et al.* (1987) the authors reported that 'weight was essentially constant' at 18 months in participants in the diet and behaviour therapy plus exercise group, compared with a mean weight change of  $-1.68 \text{ kg}$  in the diet and behaviour group.

**Risk factors, clinical outcomes and quality of life.** Few studies presented changes for risk factors, with the only observed statistically significant result for the addition of exercise being a potentially detrimental increase for LDL at 24 months (weighted mean difference change  $0.28 \text{ mmol L}^{-1}$ , 95% CI,  $0$ – $0.56 \text{ mmol L}^{-1}$ ) (see Tables 4 and 5). Wing and colleagues reported that 15.6% of people developed diabetes in the added exercise group, compared with 30.3% in the no exercise group (denominators unclear) (Polley *et al.*, 1997; Wing *et al.*, 1998). In the study by Kaplan *et al.* (1987) at 18 months the addition of exercise to diet and behaviour therapy was associated with a decrease in HbA1c of  $-1.48\%$  compared with  $-0.46\%$  in the diet and behaviour therapy group.

The addition of exercise was associated with 0.06 units of improvement in well being at 18 months, compared with 0.03 units for the diet and behaviour therapy group (the Quality of Well-being scale rates 1.0 as optimum function and 0 as dead).

#### Behaviour therapy

##### *Adding behaviour therapy to diet alone*

Four RCTs assessed the addition of behaviour therapy to diet and provided change in weight for up to 60 months (Table 3) (Long, 1983; Jones *et al.*, 1986; Wadden & Stunkard, 1986; Wadden *et al.*, 1987, 1988, 1989; Phenix, 1990). None of these studies reported data describing changes in cardiovascular risk factors. Three of the four studies recruited women only (Long, 1983; Jones *et al.*, 1986; Phenix, 1990). Reported mean BMI ranged from  $33.5 \text{ kg m}^{-2}$  (Long, 1983) to  $39.4 \text{ kg m}^{-2}$  (Wadden & Stunkard, 1986; Wadden *et al.*, 1987, 1988, 1989).

Only one study used an intention to treat approach (Phenix, 1990). None of the studies clearly reported concealed randomization or blinding of outcome assessors.

**Weight reduction.** The addition of behavioural therapy to diet was associated with a weight change at 12 months of  $-7.67$  kg (95% CI,  $-11.97$  to  $-3.36$  kg), at 18 months of  $-4.18$  kg (95% CI,  $-8.32$  to  $-0.04$  kg), at 36 months of  $-2.91$  kg (95% CI,  $-8.60$  to  $2.78$  kg) and at 60 months of  $1.90$  kg (95% CI,  $-3.75$  to  $7.55$  kg).

In the cluster RCT by Phenix (1990), the addition of overt behaviour therapy to a low calorie diet was associated with a mean weight change at 12 months of  $-3.26$  kg compared with  $-4.82$  kg in the diet only group. The addition of cognitive behaviour therapy to a low calorie diet was associated with a weight change at 12 months of  $-6.68$  kg compared with  $-4.82$  kg in the diet only group.

#### *Adding behaviour therapy to diet and exercise*

One cluster RCT assessed the addition of two forms of behaviour therapy to diet and exercise (Table 3) (Phenix, 1990). Women had a mean body weight of  $76$ – $86$  kg. Results were analysed using an intention to treat approach and assessor blinding was not undertaken.

**Weight reduction.** The addition of overt behaviour therapy to diet and exercise was associated with a mean weight change after 12 months of  $-5.19$  kg compared with  $-5.32$  kg in the diet and exercise group. The added effect of cognitive behaviour therapy to diet and exercise was associated with a mean weight change after 12 months of  $-1.13$  kg compared with  $-5.32$  kg in the diet and exercise group.

#### *Adding behaviour therapy to sibutramine, exercise and diet*

Wadden *et al.* (2001) assessed the addition of behaviour therapy, where all participants received LCDs, exercise and  $10$ – $15$  mg sibutramine daily (Table 3). All participants were women and the overall BMI at baseline was  $37.7$  kg m<sup>-2</sup>. Random allocation was described without further description, and outcome assessors did not appear to be blinded.

**Weight reduction, quality of life, and adverse events.** Behavioural therapy was associated with a weight change at 12 months of  $-10.69$  kg (95% CI,  $-14.22$  to  $-7.16$  kg) and significantly greater satisfaction with weight, health and energy level, appearance and self-esteem (reported  $P < 0.05$ ). With a conventional and a more conservative intention to treat analysis, in which participants who discontinued treatment were assumed to gain  $0.3$  kg per month after leaving the study, similar results for weight were found with either method. One participant was withdrawn from the  $10$ – $15$  mg sibutramine plus conventional low calorie diet, exercise and behaviour therapy group due to an increase in blood pressure.

#### Combined interventions

##### *Adding exercise and behaviour therapy to diet*

Two studies assessed the addition of behaviour therapy and exercise to diet (Table 3) (Phenix, 1990; Blonk *et al.*, 1994). One of these studies was in people with type 2 diabetes (Blonk *et al.*, 1994) and one was a cluster RCT (Phenix, 1990). Median BMI ranged from  $31.3$  to  $32.8$  kg m<sup>-2</sup> (Blonk *et al.*, 1994). Both studies used an intention to treat analysis, but did not blind outcome assessors. Concealed randomization was not described by Blonk *et al.* (1994).

**Weight reduction, risk factors and adverse events.** In the study by Blonk *et al.* (1994) adding exercise and behaviour therapy to diet was associated with non-statistically significant weight changes of  $-0.67$  kg (95% CI,  $-4.22$  to  $2.88$  kg) at 12 months,  $-2.06$  kg (95% CI,  $-5.57$  to  $1.45$  kg) at 18 months and  $-1.40$  kg (95% CI,  $-5.01$  to  $2.21$  kg) at 24 months. Changes in HbA1c and cholesterol were also not found to be significant (Tables 4 and 5). One participant withdrew in the diet, behaviour therapy and exercise group due to mesothelioma (Blonk *et al.*, 1994).

In the cluster RCT (Phenix, 1990) the addition of exercise and overt behaviour therapy to diet was associated with a mean weight change at 12 months of  $-5.19$  kg compared with  $-4.82$  kg in the diet only group. The addition of exercise and

cognitive behaviour therapy to diet was associated with a mean weight change at 12 months of -1.13 kg compared with -4.82 kg in the diet only group. The addition of exercise and a combination of both behaviour therapies to diet was associated with a mean weight change at 12 months of -4.97 kg compared with -4.82 kg in the diet only group.

**Discussion**

Overall discussion

These data suggest that orlistat or sibutramine, a prescribed exercise regimen, or behaviour therapy contribute to improved weight loss in obese people on reducing diets, and are important in long-term weight maintenance. Orlistat use was also associated with improved diabetic control. There is less evidence to determine what combinations of these interventions should be added. As has been found here, RCTs of drug therapy rarely incorporate intensive exercise and behaviour therapy programmes (Poston *et al.*, 2001). There may be overlaps between exercise and behaviour therapy, in that both may increase counselling time and therapist contact, and behaviour therapy may seek to improve physical activity. Some of these trials also increased therapist contact when exercise or behaviour therapy were added, compared with that given to comparison groups.

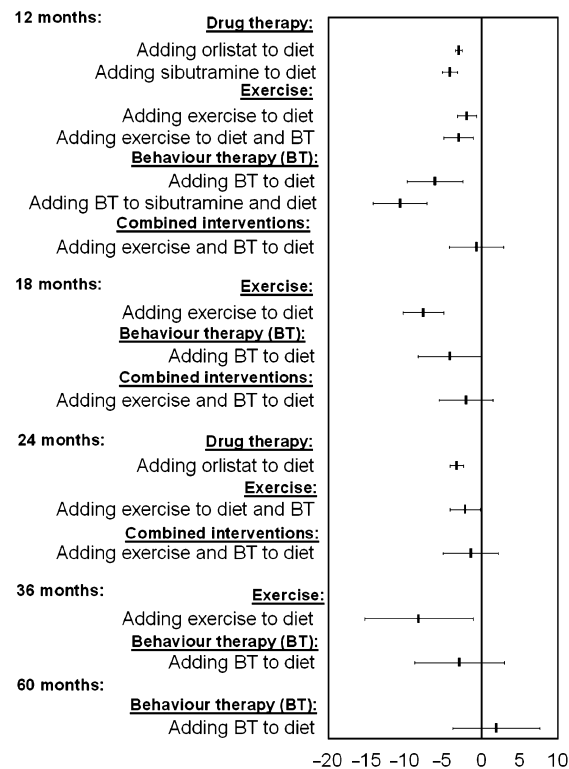
The additional exercise programmes provided in the studies described here were all supervised, with the exception of one study (Phenix, 1990). Activities included walking, jogging and cycling and were usually tailored to produce 60–80% of the maximum heart rate. The minimum period for the exercise programme was 20 min three times a week (Phenix, 1990), and the most 90 min three times a week (Pavlou *et al.*, 1989).

Behavioural therapy varied between trials, but usually included self-monitoring, slowing the rate of eating, reducing eating cues, responding to social pressures, pre-planning and relapse prevention techniques. More than half of the trials used trained psychologists to deliver these techniques.

Weight changes

After 12 months the greatest weight loss was associated with the addition of behaviour therapy to diet, or to sibutramine and diet, but confidence intervals were wide (Fig. 1). Adding exercise to diet or to diet and behaviour therapy, or adding orlistat or sibutramine to diet all led to improved weight loss at 12 months. Adding exercise to diet or diet and behaviour therapy together continued to lead to improved weight loss for up to 36 months. Orlistat was also associated with improved weight loss for up to 24 months.

Only one RCT assessed weight change after drug treatment was stopped, and found weight regain in sibutramine participants nearly twice that of the placebo group (Apfelbaum *et al.*, 1999). We also found in a previous systematic review (accompanying paper) that LFDs were associated with a weight change after 12 months of -5.31 kg. This contrasts with weight changes in the placebo



**Figure 1** Effect on weight in kilograms of adding drug therapy, exercise, behaviour therapy or combinations of interventions.

groups on orlistat, which also used LFDs, of  $-3.29$  kg, suggesting that participants in drug trials are responding differently to LFD dietary advice, and may rely more on drug therapy for support. Similarly, in the sibutramine study, which used a LFD, weight change in the placebo group was  $-1.60$  kg.

#### Risk factor changes

Orlistat and sibutramine appeared to have different effects on lipids and blood pressure. Weight reduction with sibutramine was associated with a significant beneficial effect on HDL and TGs at 12 months but not on any other risk factors. However, in the orlistat weight reduction studies, TGs were the only risk factor which orlistat did not appear to affect, and HDL was decreased.

In the sibutramine weight reduction studies, an increase in diastolic blood pressure was observed at 12 months, as compared with a fall in diastolic and systolic blood pressure with orlistat. The apparent beneficial effect of sibutramine on weight and risk factors needs to be balanced against the potential increase in blood pressure. Whether this reduces possible long-term benefits on cardiovascular disease remains unclear from present evidence.

In general, few risk factors were evaluated in the non-drug trials, and trials which examined risk factors were usually small and therefore had insufficient power to detect clinically important differences. However, the addition of exercise was associated with statistically significant beneficial changes to HDL and TGs after 12 months, risk factors which were not affected by orlistat. Blood pressure also appeared to fall with the addition of exercise in one small study (Pavlou *et al.*, 1989).

#### Clinical outcomes, quality of life and adverse events

The use of orlistat was associated with reduced need for oral hypoglycaemics in one study (Kelley, 1997; Hollander *et al.*, 1998). The XENDOS study, published after the time frame of this review,

found an association between adding orlistat and reduced incidence of type 2 diabetes in participants with impaired glucose tolerance (Torgerson *et al.*, 2004). Two other studies published after completing our review have also shown an association between orlistat and reduced need for medication in people with type 2 diabetes (Kelley *et al.*, 2002; Miles *et al.*, 2002). There was a suggestion of decreased development of type 2 diabetes as a result of adding exercise in one study (Polley *et al.*, 1997; Wing *et al.*, 1998).

Improved well being was associated with the use of orlistat and sibutramine. However, effects on quality of life were insufficiently reported in the studies reviewed here.

Adverse events were very rarely reported in the studies of lifestyle interventions. However, the use of orlistat was consistently associated with gastrointestinal adverse events related to the action of the drug, and a greater need for vitamin supplementation. Apart from the effects noted above on blood pressure, sibutramine was also associated with more constipation.

#### Recommendations for further research

None of the studies had participant groups with mean or median BMIs  $\geq 40$  kg m<sup>-2</sup>. More studies are needed in high-risk populations, whether defined by BMI, ethnic group, older age, cardiovascular risk factors or co-morbidities. Drug trials were especially noted for their narrow inclusion criteria. We also need to review the most effective type of exercise or behaviour therapy. As the prescription of drugs for the management of obesity is presently limited by time, drug trials should follow-up participants after cessation of the drug trial.

The evaluation of changes in cardiovascular risk factors, obesity-related comorbidities, quality of life and economic outcomes was seldom undertaken in these studies, particularly non-drug trials. Considering the scale and importance of obesity to long-term health, the lack of adequately powered long-term life-style studies examining best approaches to added treatments and improving adherence to such treatments is especially noticeable.

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