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Abstract

Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement

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Objectives: To undertake a systematic review of the long-term effects of obesity treatments on body weight, risk factors for disease, and disease.
Methods: The study encompassed three systematic reviews that examined different aspects of obesity treatments. (1) A systematic review of obesity treatments in adults where the methods of the Cochrane Collaboration were applied and randomised controlled trials (RCTs) with a follow-up of at least 1 year were evaluated. (2) A systematic epidemiological review, where studies were sought on long-term effects of weight loss on morbidity and/or mortality, and examined through epidemiological modelling. (3) A systematic economic review that sought reports with both costs and outcomes of treatment, including recent reports that assessed the cost-effectiveness of pharmaceutical and surgical interventions. A Markov model was also adopted to examine the cost-effectiveness of a low-fat diet and exercise intervention in adults with obesity and impaired glucose tolerance.
Results: The addition of the drugs orlistat or sibutramine was associated with weight loss and generally improved risk factors, apart from diastolic blood pressure for sibutramine. Metformin was associated with decreased mortality after 10 years in obese people with type 2 diabetes. Low-fat diets were associated with continuing weight loss for 3 years and improvements in risk factors, as well as prevention of type 2 diabetes and improved control of hypertension. Insufficient evidence was available to demonstrate the benefits of low calorie or very low calorie diets. The addition of an exercise or behaviour programme to diet was associated with improved weight loss and risk factors for at least 1 year. Studies combining low-fat diets, exercise and behaviour therapy suggested improved hypertension and cardiovascular disease. Family therapy was associated with improved weight loss for 2 years compared to individual therapy. There was insufficient evidence to conclude that individual therapy was more beneficial than group therapy. Weight lost more quickly (within 1 year), from the epidemiology review, may be more beneficial with respect to the risk of mortality. The effects of intentional weight loss need further investigation. Weight loss from surgical and non-surgical interventions for people suffering from obesity was associated with decreased risk of development of diabetes, and a reduction in low-density lipoprotein cholesterol, total cholesterol and blood pressure, in the long term. Targeting high-risk individuals with

drugs or surgery was likely to result in a cost per additional life-year or quality-adjusted life-year (QALY) of no more than £13,000. There was also suggestive evidence of cost saving from treatment of people with type 2 diabetes with metformin. Targeting surgery on people with severe obesity and impaired glucose tolerance was likely to be more cost-effective at £2329 per additional life-year. Economic modelling over 6 years for diet and exercise for people with impaired glucose tolerance was associated with a high initial cost per additional QALY, but by the sixth year the cost per QALY was £13,389. Results did not include cost savings from diseases other than diabetes, and therefore may be conservative.

Conclusions: The drugs orlistat and sibutramine appear beneficial for the treatment of adults with obesity, and metformin for obese patients with type 2 diabetes. Exercise and/or behaviour therapy appear to improve weight loss when added to diet. Low-fat diets with exercise, or with exercise and behaviour therapy are associated with the prevention of type 2 diabetes and hypertension. Long-term weight loss in epidemiological studies was associated with reduced risk of type 2 diabetes, and may be beneficial for cardiovascular disease. Low-fat diets and exercise interventions in individuals at risk of obesity-related illness are of comparable cost to drug treatments. Long-term pragmatic RCTs of obesity treatments in populations with obesity-related illness or at high risk of developing such illness are needed (to include an evaluation of risk factors, morbidity, quality of life and economic evaluations). Drug trials that include dietary advice, plus exercise and/or behaviour therapy are also needed. Research exploring effective types of exercise, diet or behaviour and also interventions to prevent obesity in adults is required.

Contents

List of abbreviations

AHI	apnoea–hypopnoea index
AHT	arterial hypertension
AI	apnoea index
AMED	Allied and Complementary Medicine Database
ANOVA	analysis of variance
ASSIA	Applied Social Science Index and Abstracts
BAROS	Bariatric Analysis and Reporting Outcome System
BCDD	balanced calorie deficit diet
BIGPRO	Biguanides in the Prevention of the Risk of Obesity
BMI	body mass index
BP	blood pressure
BPD	biliopancreatic diversion
BT	behaviour therapy
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CODE 2	Cost of Diabetes in Europe – Type 2
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CVD	cardiovascular disease
DARE	Database of Abstracts of Reviews of Effectiveness
DBP	diastolic blood pressure
DISH	Dietary Intervention Study of Hypertension
DM	diabetes mellitus
ECG	electrocardiogram
EWL	excess weight loss
Ex	exercise
F	female
FDPS	Finnish Diabetes Prevention Study
GIT	Groninger Intelligence Test
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
HMIC	Health Management Information Consortium
HOT	Hypertension Optimal Treatment
HPT	Hypertension Prevention Trial
HR	hazard ratio
HRT	hormone replacement therapy
HT	hypertension
IBW	ideal body weight
ICD	intensive conventional diet
ICER	incremental cost-effectiveness ratio
IGT	impaired glucose tolerance
IHQL	Index of Health Related Quality of Life
IQR	interquartile range
ITT	intention to treat
LCD	low-calorie diet
LDL	low-density lipoprotein
LOCF	last observation carried forward
M	male
MAOI	monoamine oxidase inhibitor
MI	myocardial infarction
NA	not applicable
NASH	non-alcoholic steatohepatitis
NCEP	National Cholesterol Education Program

continued

List of abbreviations *continued*

NDNS	National Diet and Nutrition Survey
NGT	normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NPV	Dutch Personality Inventory
NVM	Dutch Shortened Minnesota Multiphasic Personality Inventory
ODES	Oslo Diet and Exercise Study
OGTT	oral glucose tolerance test
OR	odds ratio
PSMF	protein-sparing modified fast
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
Rx	treatment
SA	sleep apnoea
SAS	sleep apnoea syndrome
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-36	Short Form 36
SIG	Scale for Interpersonal Behaviour
SOS	Swedish Obesity Subjects
SSRI	selective serotonin reuptake inhibitor
STORM	Sibutramine Trial of Obesity Reduction and Maintenance
Sx	surgery
TAIM	Trial of Antihypertensive Interventions and Management
TG	triglyceride
TOHP	Trials of Hypertension Prevention
TONE	Trial of Non-pharmacologic Interventions in the Elderly
UKNRR	UK National Research Register
UKPDS	United Kingdom Prospective Diabetes Study
VBG	vertical banded gastroplasty
VLCD	very low-calorie diet
WHO	World Health Organization
WMD	weighted mean difference

1 kcal = 4.18 kJ 1 kJ = 0.239 kcal

1 kg = 2.21 lb 1 lb = 0.454 kg

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Obesity is increasing in adults in the UK. In 1980 6% of men and 8% of women in England were obese, by 2000 these figures were 21% for both men and women. Obesity is associated with increased risk of cardiovascular disease (CVD), type 2 diabetes mellitus, hypertension, cancer and osteoarthritis. In 1998 the UK National Audit Office estimated that obesity cost the NHS in England £480 million.

This is a systematic review of the long-term effects of obesity treatments, not only on body weight, but also on risk factors for disease, and most importantly health.

Objectives

1. To review systematically obesity treatments in adults to identify therapies that impact by achieving weight reduction, risk factor modification or improved clinical outcomes.
2. Based on a systematic review of epidemiological data, to model the impact of moderate weight reduction on reducing the burden of obesity-associated disease.
3. To review systematically health economic evaluations of obesity treatments and assess costs to the NHS of these treatments.
4. To integrate the findings from the above objectives.

Methods

For the systematic review of obesity treatments in adults, the methods of the Cochrane Collaboration were adopted, in which randomised controlled trials (RCTs) with a follow-up of at least 1 year were evaluated.

For the systematic epidemiological review, studies were sought on long-term (at least 2 years, or 5 years for surgery) effects of weight loss on morbidity and/or mortality, and examined through epidemiological modelling.

The systematic economic review sought reports with both costs and outcomes of treatment. Recent reports assess the cost-effectiveness of pharmaceutical and surgical interventions. A Markov model was adopted to examine the cost-effectiveness of a low-fat diet and exercise intervention in adults with obesity and impaired glucose tolerance.

Conclusions are presented by integrating the above three components.

Results

Limitations in the evidence available for the reviews, particularly inadequate sample size and reporting, lack of long-term follow-up and few quality of life data, mean that most results should be interpreted with caution.

First, regarding the addition of drugs to the diet, orlistat was associated with a weight change of –3.26 kg [95% confidence interval (CI) –4.15 to –2.37 kg] after 2 years, and beneficial changes in risk factors. Sibutramine was associated with a weight change of –3.40 kg (95% CI –4.45 to –2.35 kg) after 18 months for people on a weight maintenance diet and beneficial changes in risk factors apart from diastolic blood pressure. Metformin was associated with decreased mortality and myocardial infarction-related mortality in the UK Prospective Diabetes Study after 10 years.

Low-fat diets (which included 600 kcal/day deficit diets) were associated with the prevention of type 2 diabetes, and improved control of hypertension. These diets were associated with a weight loss after 12 months of –5.31 kg (95% CI –5.86 to –4.77 kg) and improvements in risk factors, with weight loss continuing for 3 years. Insufficient evidence was available to assess putative benefits of low-calorie or very low-calorie diets.

Studies combining low-fat diets and exercise, with or without behaviour therapy, suggested improved control of hypertension and type 2 diabetes. The addition of an exercise programme to diet was associated with improved weight loss and risk factors for at least 1 year. The addition of a behaviour therapy programme to diet was also associated with improved weight loss for at least

1 year. It was unclear whether both exercise and behaviour therapy together further enhanced the effect of diet. Family therapy was associated with improved weight loss for up to 2 years compared with individual therapy. However, there was insufficient evidence to conclude that individual therapy was more beneficial than group therapy.

Second, women with obesity-related illnesses, who had intentional weight loss, irrespective of the amount of weight lost, had an associated reduced risk of death, CVD death, cancer and diabetes-related death. Weight loss appeared more beneficial if achieved within 1 year. Men with general illness who lost weight intentionally appeared to have a reduced risk of diabetes-related death, but there was no demonstrable effect on CVD mortality, and cancer mortality appeared increased.

Long-term weight loss was associated with reduced risk of developing type 2 diabetes and improved glucose tolerance in men and women, especially after surgery for obesity.

A weight loss of 10 kg was associated with a fall in total cholesterol of 0.25 mmol/l and a fall in diastolic blood pressure of 3.6 mmHg. A weight loss of 10% was associated with a fall in systolic blood pressure of 6.1 mmHg.

Third, targeting high-risk individuals with drugs or surgery was likely to result in a cost per additional life-year or quality-adjusted life-year (QALY) of no more than £13,000. There was also suggestive evidence of cost-saving from treatment of people with type 2 diabetes with metformin. Targeting surgery at people with severe obesity and impaired glucose tolerance was likely to be more cost-effective, at £2329 per additional life-year.

Economic modelling of diet and exercise over 6 years for people with impaired glucose tolerance was associated with a high initial cost per additional QALY, but by the sixth year the cost per QALY was £13,389. Results were sensitive to the quality of life weights, for which there were very limited data. Results did not include cost savings from diseases other than diabetes, and therefore may be conservative.

The cost of diet and exercise together appear comparable to treatments, for example drugs, in obese individuals with risk factors, such as impaired glucose tolerance.

Conclusions

Implications for healthcare

Orlistat, sibutramine and metformin appear beneficial for the treatment of adults with obesity. Exercise and/or behaviour therapy appear to improve weight loss when added to diet. Low-fat diets with exercise, with or without behaviour therapy, are associated with the prevention of type 2 diabetes and hypertension.

Long-term weight loss in epidemiological studies was also associated with reduced risk of developing diabetes, and may be beneficial for cardiovascular disease.

Low-fat diet and exercise interventions in individuals at risk of obesity-related illness, such as diabetes, are of comparable cost to drug treatments.

Recommendations for research

- RCTs and epidemiological studies are needed in high-risk populations, particularly people with co-morbidities, cardiovascular risk factors or body mass index $> 40\,kg/m^2$.
- RCTs are needed in primary care in high-risk groups.
- Drug trials should include lifestyle interventions, in addition to dietary advice.
- Exercise or behaviour therapy alone for obesity management should be reviewed.
- Further exploration of treatments for obesity should examine which type of exercise or behaviour therapy is best.
- A systematic review of treatments to prevent obesity should be undertaken.
- Research is needed to provide a clearer understanding of the incremental cost-effectiveness of different treatments for subgroups of high-risk individuals.
- Future RCTs should be adequately powered and adhere to the CONSORT statement for reporting. Guidelines are also required for the conduct and reporting of epidemiological studies.
- Research and funding bodies should be committed to structured long-term follow-up strategies so that the long-term effects of short-term interventions can be assessed accurately.

Chapter 1
Introduction

Prevalence

Obesity, defined as a body mass index [BMI = weight in kilograms/(height in metres)^2] of 30 kg/m^2 or more, is a chronic, progressive, relapsing disease,[1] the prevalence of which is increasing exponentially and has reached epidemic proportions.[2] It poses the most significant public health problem facing the UK in the twenty-first century. In 1980 the prevalence of obesity in England was 6% in men and 8% in women, by 1998 this had risen to 17% in men and 21% in women.[3] In 2000 21% of men and 21% of women in England were classified as obese.[3] The problem, however, is not only confined to the UK but is a pandemic affecting both developed and developing countries.[1] Similar trends are seen for the classification of overweight (BMI $\geqslant$ 25 to $<$ 30 kg/m^2), with the most recent survey indicating that 45% of men and 34% of women were overweight.[3] Thus, 66% of men and 55% of women in England are either overweight or obese. Predicted trends in obesity amongst men and women in England extrapolated to 2010 indicate that 26% of men and 28% of women will be clinically obese, imposing a huge burden on healthcare.[2] Within Europe the International Obesity Taskforce estimates that the prevalence of obesity increased between 10% and 40% from the late 1980s to the late 1990s, although during the same period the prevalence in England doubled.[1] This indicates a shift in position from being at the lower end of the range for obesity in Europe in the 1980s to the top of the range currently.

Who is at risk of obesity?

Sectors of the population are at considerably higher risk of developing obesity, with a concomitant increase in the incidence and prevalence of obesity-related co-morbidities.[4] Those individuals considered to be at high risk of developing obesity include:

- children, for genetic and/or environmental reasons, from families where at least one parent is obese[5–7]
- individuals of Asian origin,[8] where the definition of obesity may need to be altered for that specific population[1]
- people who stop smoking[9]
- people from lower social classes (defined as head of household social class): 14% of women in social class I are obese compared with 28% in social class V[10]
- older people: increasing age is associated with increasing prevalence of obesity up to the age of 64 years, then a decline in the prevalence begins.[3]

In addition, there appear to be certain time-points in life when the risks of developing obesity increase: in men in their late thirties, in women entering long-term partnerships, during pregnancy, at the menopause and on retirement.

Aetiology

Major genetic, environmental and socio-cultural (or behavioural) factors play roles in the development of obesity.[1] Abdominal obesity is more common in men and in women with higher androgen levels, for example in the polycystic ovarian syndrome. This suggests that abdominal fat deposition may have a hormonal basis.

Adoption studies[11–13] have demonstrated that the weight of children is related to their natural parents. Genes also appear to play a role in the distribution of body fat. Single gene defects identified with the obese phenotype are relatively few but increasing with time. The most common defect is that of the melanocortin-4 receptor, contributing to about 5% of obesity.[14] Overall the genetic influence has been estimated to contribute 25–40% to the aetiology of obesity.[13]

Many genetic polymorphisms have been associated with the propensity to gain excess weight. The mechanism by which genes cause obesity is not known despite searches for alterations in metabolic rate and altered energy substrate metabolism.

However, genetic factors do not impinge dramatically on the increasing prevalence of disease. Most human obesity results from the sum of effects of the environment on several different susceptibility genes causing excess adiposity.[15]

Clearly, with the rapid evolution of the obese phenotype there has not been time to alter the gene pool. Consequently, changes in the environment and lifestyle since the 1970s have played the dominant role in provoking the current epidemic of obesity. Although there is an appreciable genetic predisposition to obesity, the disease does not occur without an alteration in the individual's energy balance, that is, inappropriate food intake and/or change in the physical activity level. Both of these are affected by the macroenvironment (e.g. food availability in supermarkets and safety to walk or play) and the microenvironment (i.e. the home).

Changes in eating behaviour over the years have certainly affected the prevalence of obesity. Evidence suggests that the percentage of fat in the diet has been increasing with time and that this predisposes to increased deposition of fat.[16] Thus, population approaches to dealing with the obesity problem have centred on reducing fat intake in association with increased activity.

Levels of activity within the population have also reduced dramatically since the 1980s, with a marked increase in sedentary habits, such as watching television and playing computer games. Thus, both the reduction in activity and increase in sedentary pursuits are associated with decreased energy expenditure and provide a major contribution to obesity in the population. Diet and lifestyle changes have thus provided the cornerstone for obesity treatment over the years.[17–19]

Obesity co-morbidities

Obesity is the primary aetiological factor in a number of disease processes. A BMI greater than 30 kg/m^2 is associated with an increase in all-cause mortality.[20] It is not just the amount of fat in the body, but also its distribution that determines the risks of diseases associated with obesity. Abdominal or visceral fat (android obesity) is the type particularly associated with impaired glucose tolerance or type 2 diabetes, hypertension and dyslipidaemia, which contribute markedly to the risk of cardiovascular disease (CVD) and the health costs of obesity. Impaired glucose tolerance and diabetes are associated with higher plasma glucose and glycosylated haemoglobin (a long-term measure of plasma glucose control, HbA_{1c}).

High levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TGs) increase the risk of CVD, as do higher levels of systolic and diastolic blood pressure (SBP and DBP). Conversely, low levels of high-density lipoprotein (HDL) cholesterol increase the risk of CVD, such that it may be beneficial to increase the levels of HDL. In general, the greater the degree of obesity, the greater the associated risk factors.

Obesity-associated diseases can be classified into five major areas:

- chronic disease
- CVD/stroke
- cancer
- metabolic/endocrine disease
- psychosocial disease.

Chronic diseases include osteoarthritis (primarily of knees and hips), chronic back pain, obstructive lung disease, sleep apnoea and cholelithiasis.

Data from the Framingham Heart Study[21] clearly demonstrate a positive correlation between obesity and the incidence of CVD. Obesity is implicated in the causation of

- coronary heart disease (CHD)
- congestive cardiac failure
- cerebrovascular disease (haemorrhagic and non-haemorrhagic).

A direct relationship between obesity and cerebrovascular disease is not clear but is more likely to be implicated through effects on blood pressure and metabolic parameters, such as plasma lipids.

Several cancers are more prevalent in obese individuals than the non-obese. These can be classified into hormone dependent and hormone independent. Associated metabolic changes, specifically in sex hormone production, in people with obesity, may be the underlying aetiological factors in the development of cancer in the breast, ovary, uterus and prostate.[1] There is also an increased risk of development of hormone-independent tumours in obesity, such as colorectal cancer.[1]

Perhaps the most common obesity-related co-morbidity, and that which is likely to cause the greatest health burden, is type 2 (non-insulin-dependent) diabetes mellitus (NIDDM). Around 70% of type 2 diabetes appears to be related to having a BMI > 25 kg/m^2.[1] With increasing weight, the risk of developing type 2 diabetes increases exponentially.[22] Obesity is a triggering factor in abnormal glucose metabolism resulting in an

insulin-resistant state. This is also associated with abnormalities in lipid metabolism.

Obesity is thus a primary aetiological factor in the development of the disease burden affecting the UK population, but few resources are allocated to its prevention or treatment. Resources are primarily allocated to the treatment of the associated co-morbidities with major costs to society.

Costs of obesity

The recent National Audit Office Report[2] highlighted the direct and indirect costs of the obesity burden in the UK relative to treatment costs of the co-morbidity burden. This report was unable to evaluate the costs of obesity-related back pain and several other conditions and therefore the true costs may exceed the estimates. Obesity accounted for 18 million lost working days due to associated illness and 30,000 deaths in 1998 for England. The direct cost of treatment of obesity and associated co-morbidities was conservatively estimated at £480 million (1.5% of the total NHS expenditure in England). Indirect costs due to lost earnings were estimated for England in 1998 at £2150 million.

Strategies for obesity

With the increasing prevalence of obesity it is thus essential to assess and develop suitable treatment strategies that will result in long-term weight reduction and maintenance of weight loss. It is, therefore, of paramount importance to evaluate those treatments, either singly or in combination, that are likely to produce the best results. Treatments to evaluate include all aspects of diet and lifestyle alteration, with or without pharmacotherapy, and in some cases surgery.

Orlistat (Xenical®, manufactured by Roche) and sibutramine (Reductil® and Meridia®, manufactured by Abbott) are two drugs which currently have product licences in the UK for the treatment of obesity. Both have been reviewed for and evaluated by the National Institute for Clinical Excellence (NICE).[23–26] Other drugs that are sometimes used to aid weight loss are metformin (Glucophage®, Lipha; Glucamet®, Opus), acarbose (Glucobay®, Bayer), and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine (Prozac®, Dista; Felicium®, Opus) and sertraline (Lustral®, Pfizer).

Orlistat inhibits all gastrointestinal lipases, which are needed to absorb dietary fat. By reducing fat absorption caloric intake is decreased, and it is essential to follow a low-fat diet if the gastrointestinal side-effects of fat malabsorption are to be avoided. Present UK guidelines[23] recommend that orlistat is prescribed only after a weight loss of 2.5 kg over the preceding month, in people with a BMI ≥ 28 kg/m^2 with significant co-morbidities (e.g. type 2 diabetes, high blood pressure and/or high total cholesterol) or BMI ≥ 30 kg/m^2 with no associated co-morbidities. It is recommended that orlistat only be continued if weight loss is over 5% in the first 3 months, and 10% in the first 6 months. Treatment is not usually continued beyond 1 year and never beyond 2 years.[23]

Sibutramine is a reuptake inhibitor of noradrenaline, serotonin and to a lesser extent dopamine in the brain. It reduces food intake by producing a feeling of satiety. Present UK guidelines[24] recommend use only for people with a BMI ≥ 27 kg/m^2 with significant co-morbidities, or ≥ 30 kg/m^2 without associated co-morbidities. Sibutramine is associated with an increase in blood pressure in some people, thus regular review of blood pressure is recommended. It is advised[24] that treatment continuation requires a 2 kg weight loss in the first 4 weeks and a 5% weight loss from the start of treatment in the first 3 months. Sibutramine treatment is not recommended beyond 12 months.

Acarbose inhibits the digestion of starch and sucrose in the gut and is used to improve blood glucose control in people with diabetes.

Metformin decreases the release of glucose into the circulation and increases glucose uptake into the tissues, thus also improving blood glucose control in people with diabetes. Metformin is being used increasingly to decrease resistance to the action of insulin in people who are obese and have polycystic ovary syndrome.

The SSRIs, which are primarily used to treat depression, inhibit the uptake of serotonin by the brain and are known to also inhibit appetite.

Surgery for people with obesity (BMI ≥ 40 kg/m^2, or BMI ≥ 35 kg/m^2 with significant co-morbidities) has recently been reviewed for, and evaluated by, NICE.[27,28] When compared with conventional treatment, surgery was associated with greater weight loss (23–37 kg at 2 years), which was maintained at 8 years, and improved quality of life

and co-morbid conditions. Gastric bypass was associated with more weight loss, and/or improvements in co-morbidities and complications, than gastroplasty or jejunoileal bypass.

Previous systematic reviews of randomised controlled trials (RCTs) of obesity treatments in adults include those undertaken by the NHS Centre for Reviews and Dissemination (CRD) in York, UK,[29] and for the United States National Institutes of Health.[19] There is a need to update these reviews, in view of the rapidly increasing number of RCTs.

RCTs of interventions for the treatment of adult obesity have generally been short-term, only reporting changes in weight and cardiovascular risk factors. There is a need to evaluate longer term epidemiological evidence to see how changes in weight and risk factors could translate into changes in morbidity and mortality.

The projected impact of weight loss on obesity-associated disease can be modelled and the overall impact on resource utilisation for treatment strategies can then be evaluated.

Aims of this report

The aims of this report are thus four-fold:

1. To carry out a systematic review of obesity treatments in adults to identify those therapies that will impact by achieving weight reduction, risk factor modification or improved clinical outcomes (reported in Chapter 2).
2. Based on epidemiological data, and systematic review of such data, to model the impact of moderate weight reduction on reducing the burden of obesity-associated disease (reported in Chapter 3).
3. To review systematically health economic evaluations of obesity treatments and to assess the impact of treatments on the costs to the NHS by the application of modelling techniques in specific disease areas (reported in Chapters 4 and 5).
4. To integrate the findings from the above objectives (reported in Chapter 6).

Chapter 2

Systematic review of RCTs

Introduction

The methods of the systematic review of RCTs were based on those used by the Cochrane Collaboration.[30] For the synthesis and presentation of the data on clinical effectiveness, the format of the Cochrane Collaboration was chosen. The principal reason for this decision was that the reviews were based on RCTs, and customised software (Review Manager version 4.2.2) was available for the preparation and analysis of systematic reviews, which incorporated statistical programmes for meta-analysis, when appropriate.

Methods

Development of protocol

A review protocol (for full details please see Appendix 1) was formulated using the structure recommended by the Cochrane Collaboration.[30] The protocol explicitly described:

- the objectives of the review
- the types of studies, participants and interventions required of studies for inclusion
- the outcome measures of importance
- the search strategy to be used for identification of trials
- the methods of quality assessment
- the methods of data abstraction and qualitative and quantitative synthesis of results.

Study inclusion criteria

This systematic review was limited to assessing RCTs. It is widely acknowledged that the RCT is the 'gold standard' design for the evaluation of healthcare interventions as it ensures that the potential for bias in results is minimised. Subsequent to the development of the protocol, it was necessary to provide additional clarification on inclusion criteria. RCTs were only included if a full study report, published or unpublished, could be obtained. Information published as abstracts only was not included.

Adults

Included RCTs had to have a mean or median age for all groups of 18 years or over.

BMI cut-off

As a result of the recommendations by NICE (see NICE website)[23,24] for cut-offs in BMI for prescribing drugs for the treatment of obesity in adults, the review was limited to RCTs with a mean or median BMI of 28 kg/m^2 or over for all groups combined. Where heights were not provided, BMI was estimated using the following imputed values:

- for US populations 1.768 m for males and 1.636 m for females, based on National Health and Nutrition Examination Survey (NHANES) III data[31]
- for other populations 1.745 m for males and 1.617 m for females, based on the UK National Diet and Nutrition Survey (NDNS).[32]

Assumed heights were still used in the calculation of BMI, even if the percentage of overweight participants was given.

Duration

Included RCTs had to have a mean or median duration of 52 weeks or over for all groups. The length of the RCT was counted from randomisation. The period included the period of active intervention, however long, and period of follow-up. Where results were presented from the start of a non-randomised run-in period, changes in outcomes were calculated by working out differences from the time of randomisation.

Types of interventions

Interventions took the form of drugs, diets, exercise, behaviour therapy, surgery and complementary therapies specifically aimed to reduce weight or prevent weight gain. Prespecified diet categories were:

- healthy eating advice
- 600 kcal/day deficit or low-fat diet
- low-calorie diet (LCD): 1000 – 1600 kcal/day
- very low-calorie diet (VLCD): <1000 kcal/day
- protein-sparing modified fast (PSMF), where the carbohydrate content was ≤ 40 g/day, irrespective of calorie content. This category also included the low-carbohydrate Optifast and Modifast slimming products
- low-carbohydrate, high-monounsaturated fat diet

- salt restriction (where compared with weight loss).

Information provided on diets was often insufficient to distinguish clearly among the categories given above. Although healthy eating advice and the 600 kcal/day deficit or low-fat diet were specified in the protocol as separate categories, no distinction could be made between these groups and thus they were combined under the heading 600 kcal/day deficit or low-fat diet. Where the calorie content of a diet as a result of fat or calorie restriction was not clearly stated, or could not be estimated, it was placed in the category 600 kcal/day deficit or low-fat diet. If an intervention included two or more diets, e.g. VLCD followed by an LCD, the most stringent calorie restriction was used to classify the diet, irrespective of the time for which it was given.

Multifaceted interventions, incorporating clear efforts at smoking cessation or salt reduction in addition to weight loss for reduction of cardiovascular risk, were not included. This was because smoking cessation or salt reduction may also cause changes in weight and risk factors, and hence the effect of the weight loss intervention alone could not be identified.

For exercise or behaviour therapy interventions, study investigators had to give a detailed description of the components of the intervention (and details of the theories and components in the case of behaviour therapy). If, for example, the study only reported that participants were asked to increase their level of exercise with no further details, this was not categorised as an exercise intervention.

In some cases participants entered the randomised phase of the study after a non-randomised weight loss phase. If the weight loss phase before randomisation was over 3 months, the randomised phase was called 'weight maintenance', rather than 'weight reduction'. For drug trials the second year of two year studies was also examined separately as a period of weight maintenance.

Types of outcomes

Weight loss, or prevention of weight gain had to be explicitly stated as a main outcome of the study. The protocol prespecified that weight change and changes in waist circumference would be examined, however defined. Eventually a decision was made to examine weight change in kilograms only, because this was provided by more studies than any other measure. Waist circumference was not examined owing to the time constraints of the review. In many cases the percentage changes in weight could not be calculated, as no starting weight was given.

Search strategy for the identification of studies for inclusion in the systematic review

The systematic search for studies of effectiveness was limited to finding RCTs. A broad search strategy was adopted to identify as many RCTs as possible relevant to the management of adult patients with a BMI ≥ 28 kg/m^2. This allowed the establishment of a register of RCTs relevant to the management of obesity, which can be used in future systematic reviews in this area (including Cochrane Reviews).

Systematic electronic bibliographic database searching

Thirteen electronic databases were searched systematically:

- MEDLINE (National Library of Medicine, USA: the electronic version of *Index Medicus*) using the search software Ovid
- EMBASE (Elsevier Science Publishers, The Netherlands: the electronic version of *Excerpta Medica*) using the search software Ovid
- BIOSIS (Biological Abstracts, USA: the electronic version of *Biological Abstracts*) using the search software BASIS
- CAB Nutrition Abstracts and Reviews (Commonwealth Agricultural Bureau International Publishing, UK) using the search software Ovid
- The Cochrane Controlled Trials Register (Cochrane Collaboration, UK: Update Software, 2001; Issue 1, CD-ROM version)
- PsycINFO (American Psychological Association, USA) using the search software SilverPlatter
- Science Citation Index (ISI Web of Science, Thomson Scientific, USA), accessed via http://wos.mimas.ac.uk
- British Library Inside, accessed via http://www.bl.uk.inside
- CINAHL (CINAHL Information Systems, USA: Cumulative Index of the Nursing and Allied Health Literature) using the search software Ovid
- HealthSTAR (Health Services, Technology, Administration and Research, National Library of Medicine; and American Hospital Association, Chicago, USA) using the search software Ovid
- AMED (Allied and Complementary Medicine Database produced by the Health Care

Information Service of the British Library) using the search software Ovid
- SPORTDiscus (Sport Information Resource Centre, Canada) using the search software Ovid
- UK National Research Register (ongoing and recently completed research projects funded by, or of interest to the UK NHS), accessed via http://update-software.com/National/

For full details of the search strategies, including the periods searched, see Appendix 2.

Handsearching of specific journals

Nutrition journals, particularly in the field of obesity, were handsearched to locate RCTs, particularly those mentioned in conference abstracts and supplements. Handsearching was undertaken by one researcher.

The following journals were handsearched (including all supplements):

- *International Journal of Obesity* (Volume 1, part 1, 1977 to Volume 24, part 12, 2000)
- *Obesity Research* (Volume 1, part 1, 1993 to Volume 9, part 2, 2001)
- *Obesity Surgery* (Volume 1, part 1, 1991 to Volume 11, part 2, 2001)
- *American Journal of Clinical Nutrition* (Volume 18, part 5–6, 1966 to Volume 72, part 6, 2000)
- *Proceedings of the Nutrition Society* (Volume 19, part 1, 1960 to Volume 59, part 4, 2000)
- *Journal of Human Nutrition and Dietetics* (Volume 1, part 1, 1988 to Volume 14, part 1, 2001)
- *Journal of the American Dietetic Association* (Volume 77, part 1, 1980 to Volume 90, part 12, 1990).

Electronic searching for references finished at the end of April 2001. However, the following journals were handsearched from January 2001 to the end of June 2001, to locate references that might not have been indexed by the above databases:

- *American Journal of Clinical Nutrition*
- *Annals of Internal Medicine*
- *Archives of Internal Medicine*
- *British Medical Journal*
- *International Journal of Obesity*
- *Journal of Consulting and Clinical Psychology*
- *Journal of Human Nutrition and Dietetics*
- *Journal of the American Medical Association*
- *Lancet*
- *New England Journal of Medicine*
- *Obesity Research*
- *Obesity Surgery*
- *Proceedings of the Nutrition Society*.

Other methods of ascertainment of RCTs

Reference lists of selected articles

The reference lists of other reviews (both narrative and systematic) and identified RCTs were checked for possible RCTs. For a list of the reviews that were checked see Appendix 3.

Abstracts and UK National Research Register (UKNRR)

Authors of abstracts, including those in the UKNRR, which appeared to report eligible RCTs were contacted in order to obtain full reports, published or unpublished, for this review.

Triallists and biomedical companies

Known triallists in the field were contacted for further details of their trials, as well as pharmaceutical companies if the triallists were unable to provide information. Roche Products Ltd provided further details for three studies.[33–38]

Other experts in the field

Owing to the tight timescale of the report, triallists were not contacted for details of any other relevant RCTs.

Identification of possible RCTs

All possible RCTs were electronically imported or manually entered into the reference managing software package, Reference Manager (version 9.0, Research Information Systems, Carlsbad, CA, USA). Subject keywords, notes and sources of the articles were added.

Register of possible RCTs

All electronically derived abstracts and study titles were assessed for inclusion by one researcher using a standard form (see Appendix 4). In cases of uncertainty a second researcher also assessed abstracts and study titles. Those studies identified as relevant or possibly relevant were then obtained as full reports.

Change in scope of the review

The time constraints placed on the report, the very large number of RCTs identified and the concurrent HTA review of surgery for obesity undertaken for NICE[27] meant not all of the interventions specified in the original protocol could be examined. This review did not examine comparisons between low-fat and low-calorie diets, where the intention was to provide a comparison of two types of reducing diet with the same calorie value, as this is the subject of a Cochrane review, which found no evidence to suggest that fat-restricted diets were better than calorie-restricted diets in achieving weight loss.[39] The review did

not compare two kinds of diet from the same category, for example a VLCD supplied from the diet compared with a VLCD from diet and liquid supplements, and did not examine comparisons between low-sodium and weight-loss diets.

Reports of RCTs of obesity surgery were passed to researchers undertaking the HTA review of obesity surgery for NICE.[27] The present authors did not duplicate this review, but refer to it in this report. Complementary medicines were not reviewed. Exercise and/or behaviour therapies were examined only where they were provided in conjunction with dietary advice, that is, examining the added effect of behaviour therapy and/or exercise over and above diet. Thus, no comparison was made of dietary advice alone with exercise alone for weight management. There was insufficient time to subcategorise exercise and behaviour interventions to examine how the type of exercise or behaviour therapy influenced outcomes.

The number of drugs examined in this review was reduced from that in the original protocol. The drugs examined were orlistat, sibutramine, metformin, acarbose and SSRIs (e.g. fluoxetine). The authors chose to re-examine orlistat and sibutramine, despite the HTA reviews for NICE,[25,26] because new studies were available subsequent to these reviews and because further data analysis was undertaken beyond the scope of these reviews.

Quality assessment of studies

Full copies of studies were assessed by one researcher for methodological quality using a standard form (see Appendix 5). A second researcher checked the quality assessment scoring. The assessors were not blinded to author, institution or journal. Any differences of opinion were resolved by discussion, with reference to a third researcher if no agreement could be reached. Where studies were reported as 'double-blind' it was assumed that both participants and healthcare providers were blinded, unless otherwise stated. It was also assumed that weight was always measured by the healthcare provider, unless otherwise stated.

Data abstraction

A data abstraction form was generated for the review before the actual abstraction of the data from each paper (see Appendix 6; see Appendix 7 for a list of studies). Only comparisons and outcomes that had been identified a priori in the protocol were included. For each study, the data were abstracted by a single researcher, and then checked by a second researcher, before being entered into Review Manager. Any differences of opinion were resolved by discussion, with reference to a third researcher if no agreement could be reached. A second researcher also checked data entry into Review Manager. Where only graphical data were available, images were scanned onto computer and analysed.

Data analysis

Where results from studies could be quantitatively combined, a statistical meta-analysis of the data was undertaken to determine the typical effect size of the intervention. For continuous data a weighted mean difference (WMD) was calculated (weighted by the inverse of the variance). For dichotomous data a 'typical' odds ratio (OR) was derived. Analyses for both dichotomous data, such as mortality, and continuous data adopted a fixed effects approach.

All comparisons were framed in terms of unfavourable events, rather than freedom from adverse symptoms. An OR of less than 1 would favour the experimental treatment, and an OR greater than 1 would favour the control treatment. Ninety-five per cent confidence intervals (CIs) were derived for all comparisons. Meta-analysis graphs have been presented where possible. An annotated example of such a graph is shown in *Figure 1*.

Meta-analyses of risk factors demonstrate whether treatment or control is favoured. For some continuous outcomes a higher value indicated a better outcome; for example, a higher HDL is better. Labelling of the horizontal axis has been changed in such cases.

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 were sought. If data could not be combined quantitatively they were assessed qualitatively.

Results from cluster randomised trials are reported separately from other RCTs. In the case of cross-over studies, results are presented for data from the first period only if this lasted for at least 52 weeks.

In some studies several analyses of weight loss data were undertaken. The analysis with the

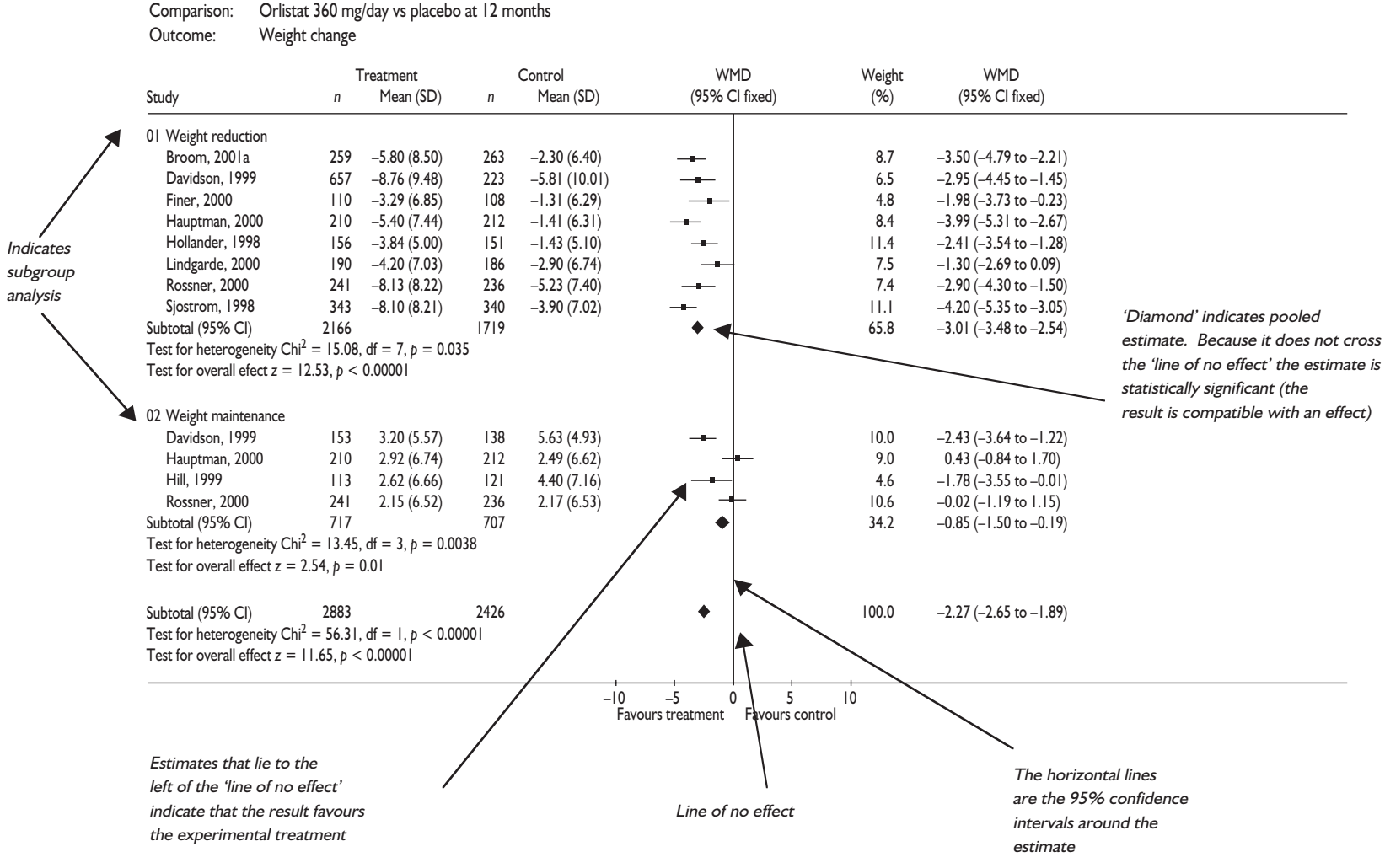


FIGURE 1 *How to interpret a meta-analysis plot*

largest number of participants was always used; this was an intention-to-treat (ITT) analysis, if available. In some cases the results presented included the last recorded weight of people who dropped out, carried forward to the end of the trial [last observation carried forward (LOCF)]. Notes on data handling are provided in the Table of included studies (Appendix 8).

In studies where there were multiple comparisons against the same control group the control group was split for dichotomous data. However, the same control group was used on more than one occasion, where indicated, in a meta-analysis of continuous data.

Purported serious adverse events in the RCTs were scarce and are generally not presented in the meta-analysis plots, but are reported in the text of the results.

Handling of missing data

To utilise fully data for meta-analysis that required the mean and standard deviation (SD) of the change between two time-points, several assumptions were made. Where weight or risk factors were presented as actual values rather than changes, differences were calculated by subtraction of the end-point value from the value at time of randomisation. Changes expressed as medians and interquartile ranges (IQRs) were assumed to be mean changes and 50% CIs. In the case of missing 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 (see Appendix 13):

- SD of weight change in kg = 5.915 + (0.283 × mean change in weight, whether negative or positive).

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 (see Appendix 14):

- SD for change in SBP = 12.7 mmHg
- SD for change in DBP = 8.3 mmHg
- SD for change in cholesterol = 1.08 mmol/l
- SD for change in LDL cholesterol = 0.74 mmol/l
- SD for change in HDL cholesterol = 0.29 mmol/l
- SD for change in triglycerides = 0.96 mmol/l.

In the case of fasting plasma glucose and HbA_{1c}, two levels of SDs were used, to allow for the greater variability of such measures evident from the studies.

- If the initial fasting plasma glucose was < 7 mmol/l, the SD for change in fasting plasma glucose was 1.35 mmol/l.
- If the initial fasting plasma glucose was ≥ 7 mmol/l, the SD for change in fasting plasma glucose was 3.77 mmol/l.
- If the initial HbA_{1c} was < 7%, the SD for change in HbA_{1c} was 0.71%.
- If the initial HbA_{1c} was ≥ 7%, the SD for change in HbA_{1c} was 2.58%.

Where continuous data were provided with one figure after the decimal point, Review Manager inputs a zero in the second place after the decimal point as a default mechanism. This implies a degree of precision that was not provided in the data.

Reporting

The review is reported in a modified form of the standard format of the Cochrane Collaboration.

Results

Results of literature search

The flow chart (*Figure 2*) indicates the filtering process for RCTs:

The CRD report from York[29] was searched initially and provided 23 out of 84 primary reports of RCTs included in this review. This represented only 23 out of the 99 studies covered by the York review. This was due to the different focus of the review here, which did not include RCTs of dexfenfluramine, surgical treatments, behaviour and exercise treatments (unless as an adjunct to diet), or studies in children.

Of the electronic databases, the MEDLINE search strategy was designed and executed first. *Table 1* displays the databases in the order that they were searched. The last column indicates how many additional RCTs were identified as each database was searched, for example, the five EMBASE RCTs were not found on MEDLINE. Forty out of 84 primary reports of RCTs included in the review were initially located in MEDLINE. Thirty-two of the RCTs included in the review were found by handsearching (23 from the York review and seven from other sources).

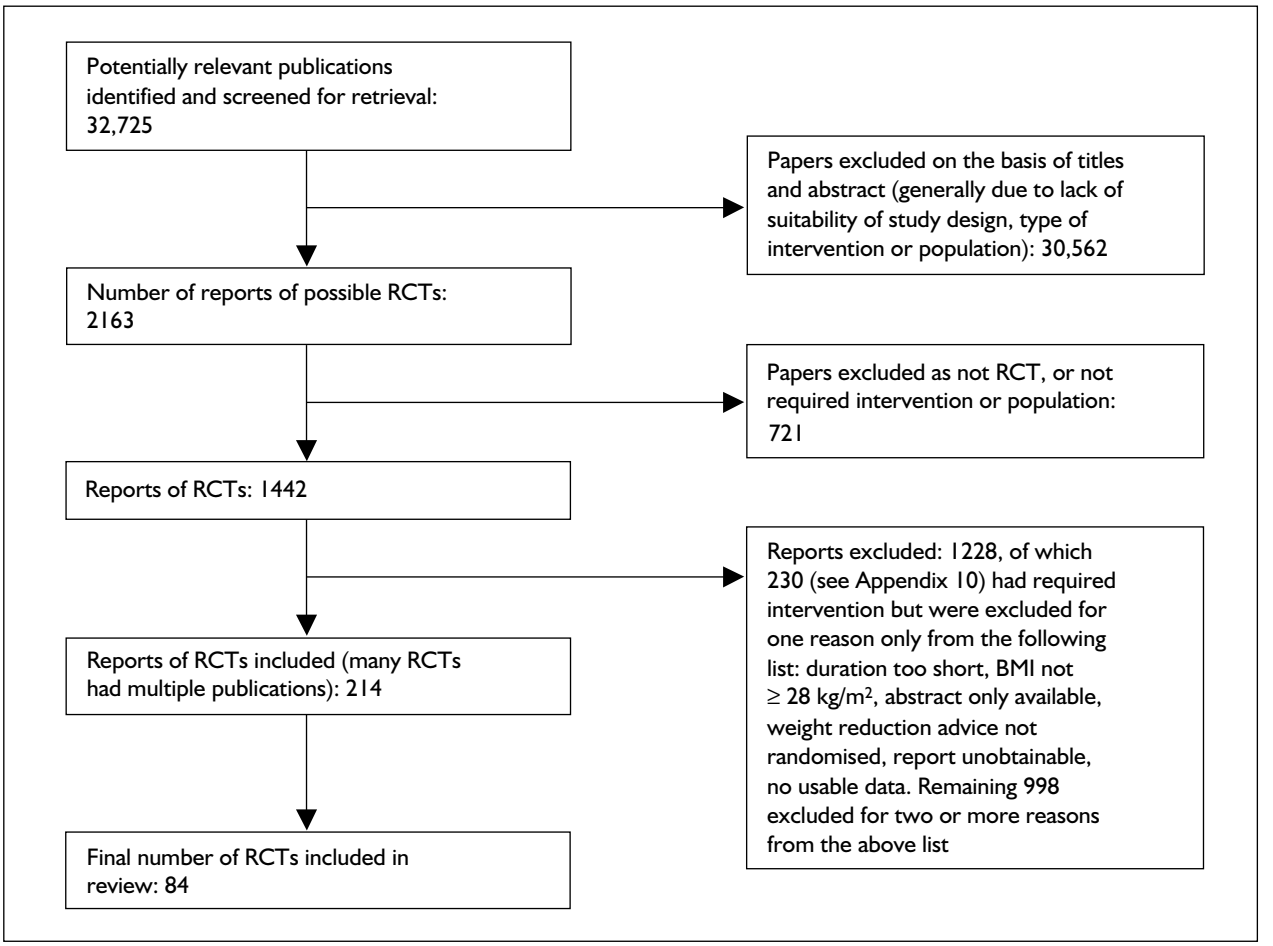


FIGURE 2 *Flow diagram for locating RCTs for systematic review*

The remaining 12 primary reports of RCTs were found (in descending order of numbers found) in EMBASE, the Cochrane Controlled Trials Register, CAB Nutrition Abstracts and Reviews, HealthSTAR and PsycINFO.

Seven other databases did not provide any additional primary reports of RCTs included in the review. These databases were BIOSIS, CINAHL, AMED, SPORTDiscus, the UK National Research Register, British Library Inside and the Science Citation Index.

Excluded RCTs are detailed in Appendix 10.

Effects of orlistat 360 mg/day and diet versus placebo and diet

Description of studies

Nine RCTs provided change in weight at 12 months or longer.[33–38,40–56] Eight of these interventions aimed to produce weight reduction in the first year.[33–38,40–47,50–56] Three of these eight studies aimed to produce weight maintenance in the second year.[37,38,41,42,45–47] One study aimed to produce weight maintenance during a 1-year intervention following a 6-month run-in weight reduction phase.[48,49] The meta-analyses for these data are therefore split into weight reduction and weight maintenance subgroups where the second years of the 2-year studies are categorised as weight maintenance. The overall changes for 2-year studies are also presented in meta-analyses.

One study recruited people with type 2 diabetes[33,34] and two studies recruited people at high cardiac risk.[35,36,40,50,51] Data were provided for blood pressure, lipids, fasting plasma glucose and HbA_{1c} at 12 months and all except for HbA_{1c} at 24 months. All the studies reported using ITT analysis, but it was unclear whether this was carried out as participants were excluded after randomisation for protocol violations. Reported mean BMI ranged from 32.6 kg/m^2 [48,49] to 37.1 kg/m^2.[35,36,40]

All the studies included a single-blind pretreatment run-in phase, which ranged from 2 weeks[35,36,40,50,51] to 5 weeks[33,34] for the weight reduction studies

TABLE 1 *Results of literature search*

Source	Total no. of reports identified	No. of reports of possible RCTs	Source of primary report of RCTs included in review
Handsearch			
CRD Report York			23
Databases			
MEDLINE	6,163	1,078	40
EMBASE	10,588	380	5
CAB Nutrition Abstracts and Reviews	2,664	48	2
BIOSIS	2,695	58	0
HealthSTAR	47	3	1
CINAHL	1,557	48	0
AMED	59	5	0
SPORTDiscus	415	24	0
UK National Research Register	452	38	0
Cochrane Controlled Trials Register	4,340	226	3
British Library Inside	251	21	0
Science Citation Index	548	39	0
PsycINFO	2,946	195	1
Other handsearching			
Sources other than CRD Report York			7
Triallists			2
Totals	32,725	2,163	84

Sources of RCTs are listed in order of searching, together with the number of additional RCTs found in that source.

and 6 months for the 1-year weight maintenance study.[48,49] All the studies included dietary advice for all participants, and the study by Hauptman and colleagues[45–47] included an exercise prescription for all participants.

There was the possibility of unblinding of both participants and healthcare providers owing to the gastrointestinal adverse events associated with orlistat, such as oily stools. With the exception of the study by Lindgarde and colleagues,[50,51] dropout rates in the control groups (24–42%) were always higher than in the intervention groups (15–36%).

Review results

The added effect of orlistat 360 mg/day on weight reduction produced an overall WMD weight change at 12 months of –3.01 kg (95% CI –3.48 to –2.54 kg) (*Figure 3*). The added effect of orlistat 360 mg/day on weight maintenance produced an overall WMD weight change after 12 months of –0.85 kg (95% CI –1.50 to –0.19 kg) with evidence of heterogeneity in these four studies (*Figure 3*). There is no readily apparent cause for this heterogeneity. In three of these four studies energy intake was increased over this period,[41,42,45–49] but this appears unrelated to the weight change.

All the risk factors for the 1-year weight reduction phase showed beneficial changes, except for HDL cholesterol, which showed a small decrease, and TGs (*Figures 4–11*). There was evidence of heterogeneity for HbA_{1c}, fasting plasma glucose and triglycerides for this 12-month weight reduction phase. This may have related to the inclusion of people with diabetes in two studies.[33,34,50,51] After 12 months of orlistat in people with diabetes a change in HbA_{1c} 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 (95% CI –0.80 to –0.36 mmol/l) for diabetics compared with controls and –0.16 mmol/l (95% CI –0.27 to –0.05 mmol/l) for non-diabetics. However, for TGs observed changes were less marked between diabetics compared with controls (–0.05 mmol/l, 95% CI –0.19 to 0.09 mmol/l) and non-diabetics (0.05 mmol/l, 95% CI –0.03 to 0.14 mmol/l). For the 12-month weight maintenance phase there were no added benefits on risk factors.

Two weight reduction studies produced an overall WMD weight change at 24 months of –3.26 kg (95% CI –4.15 to –2.37 kg) (*Figure 12*).[37,38,45–47] By 24 months the beneficial effects of orlistat on risk factors were still seen, with the exception of triglycerides and SBP (*Figures 13–19*).

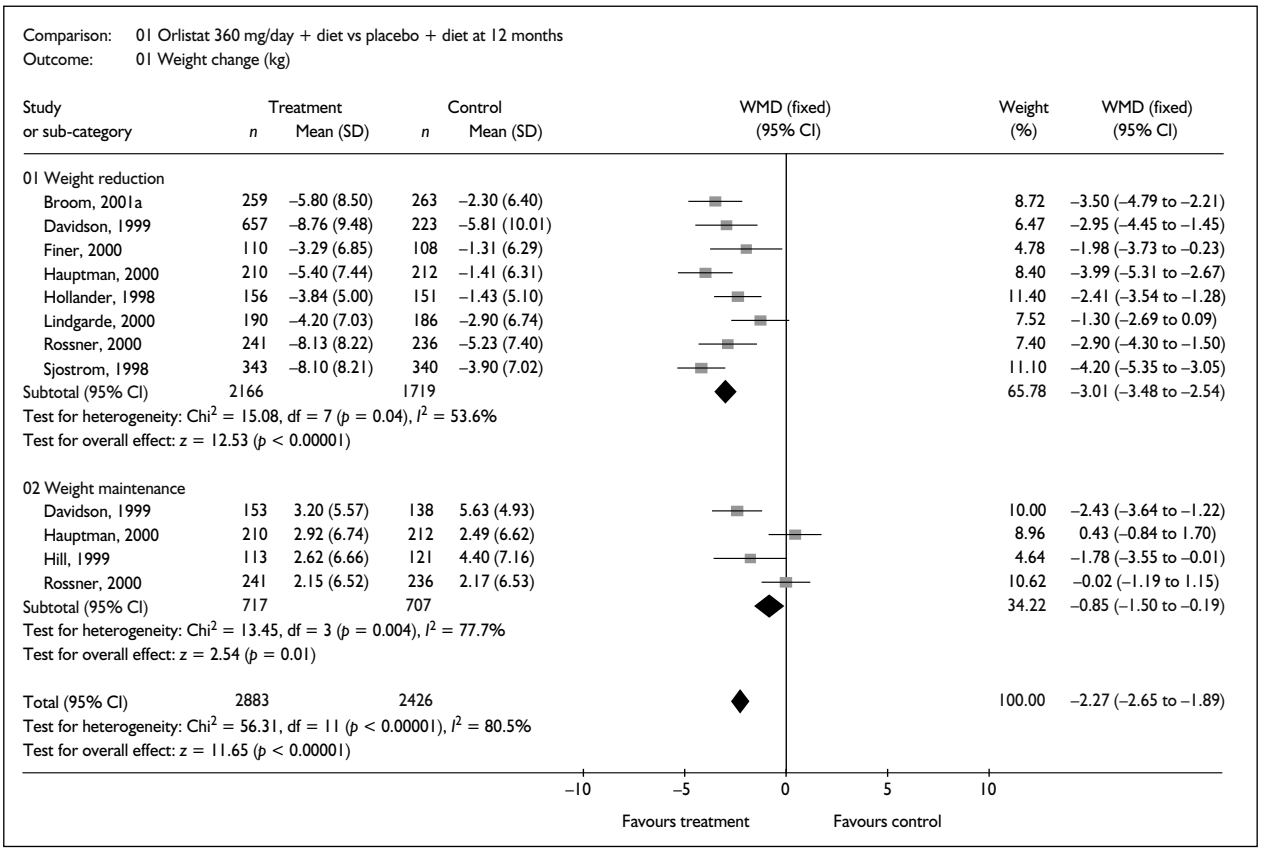


FIGURE 3

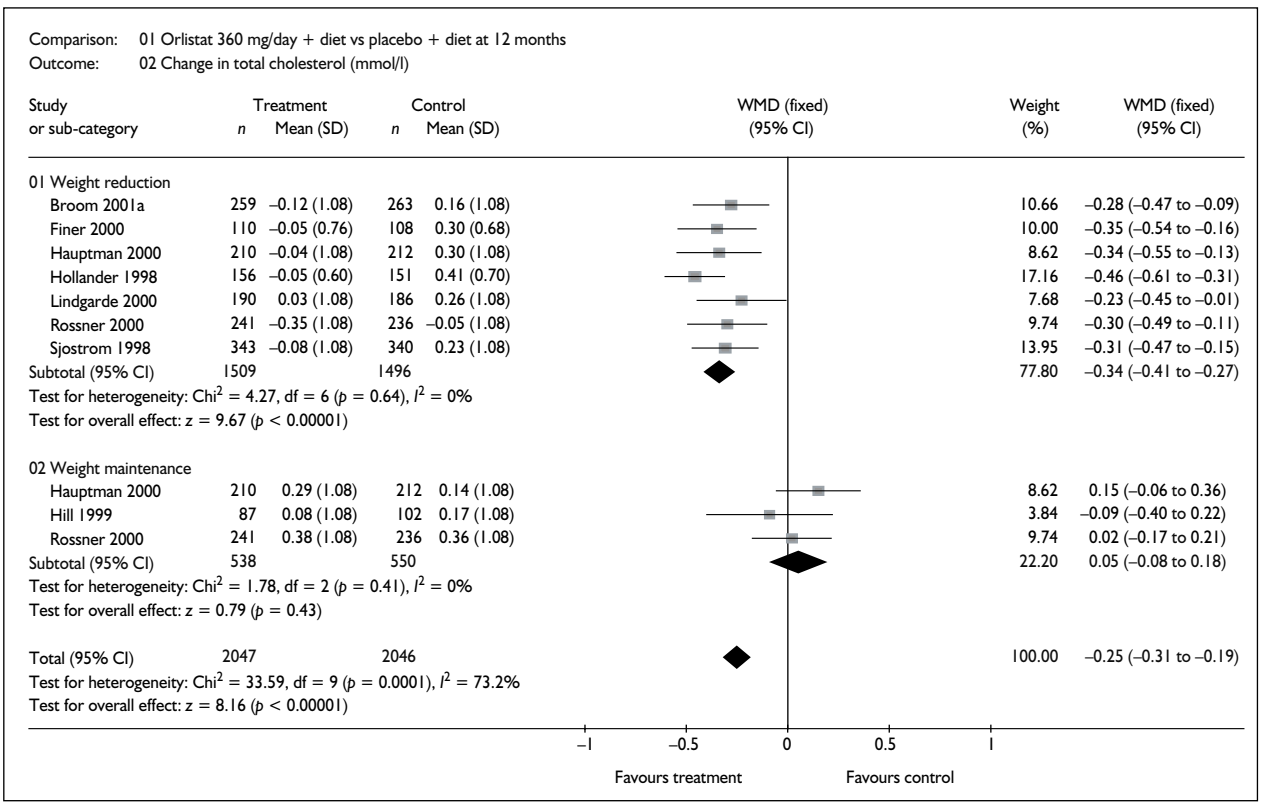


FIGURE 4

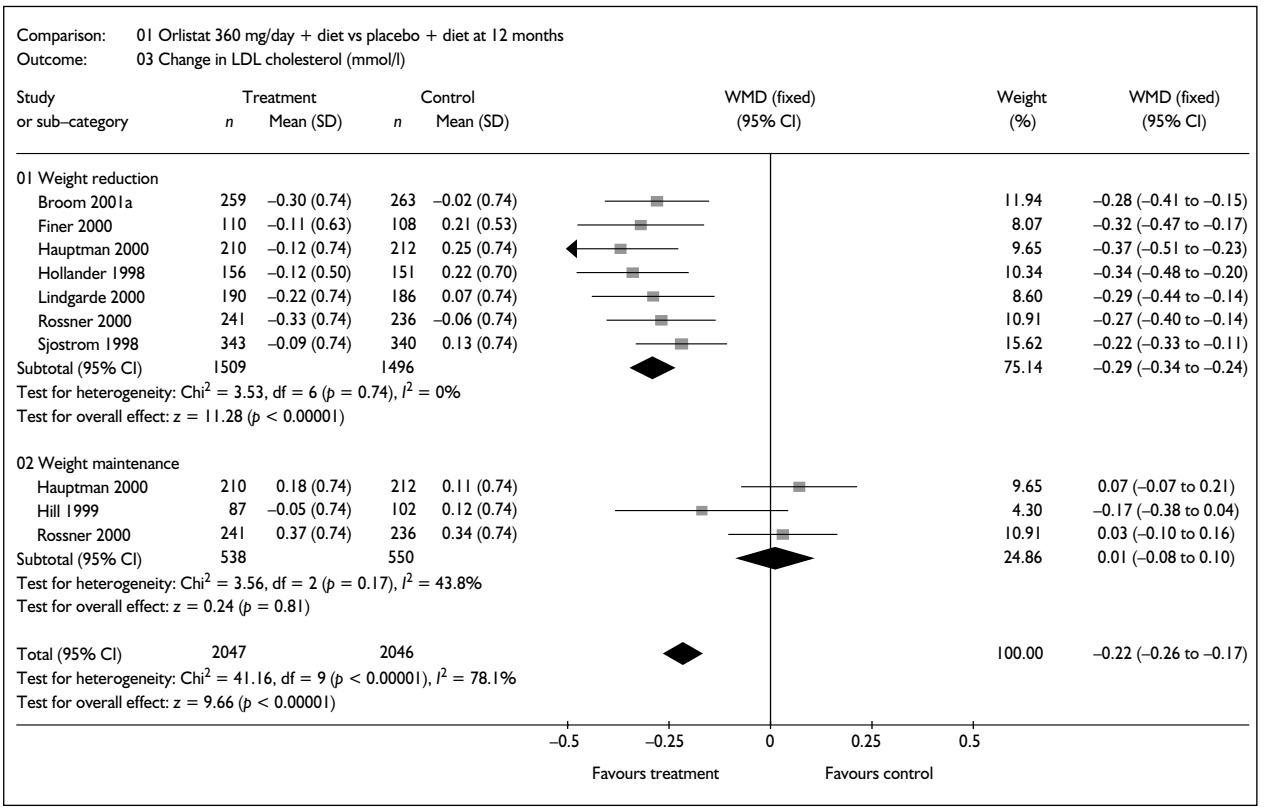


FIGURE 5

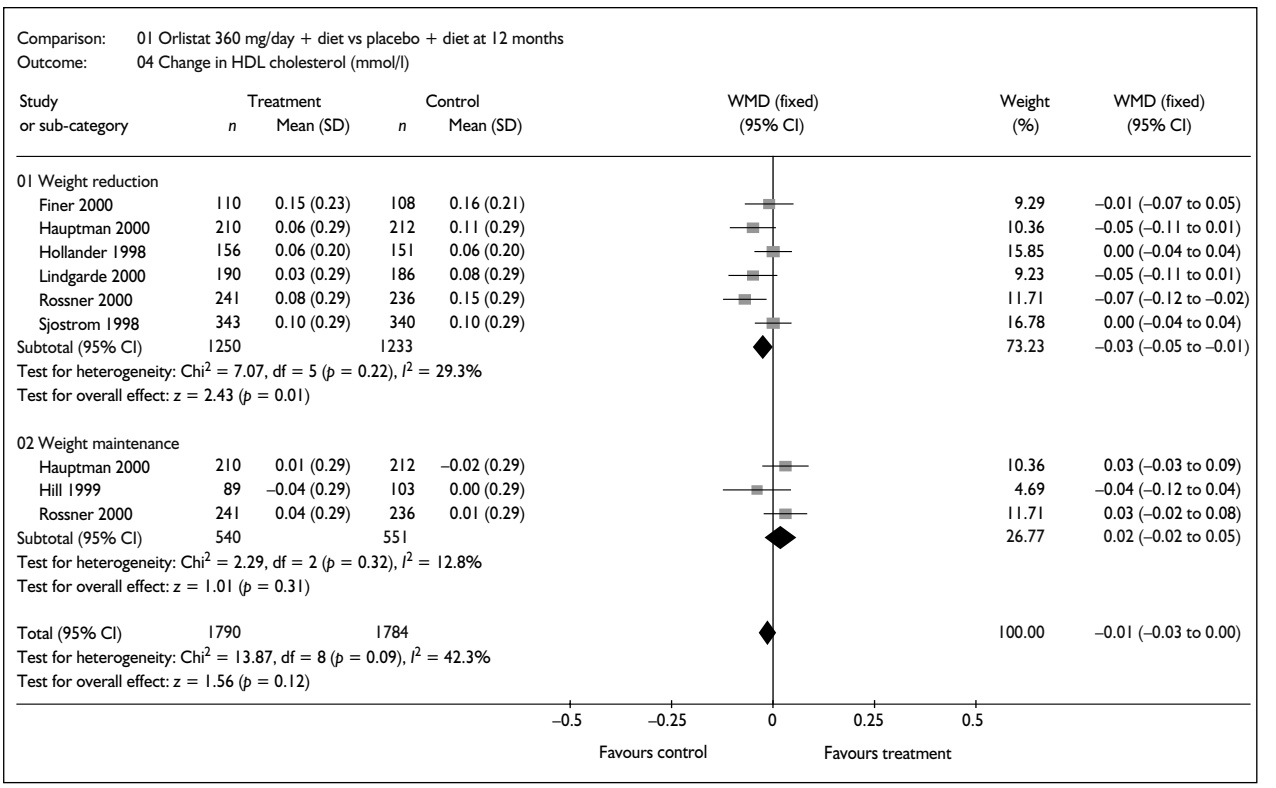


FIGURE 6

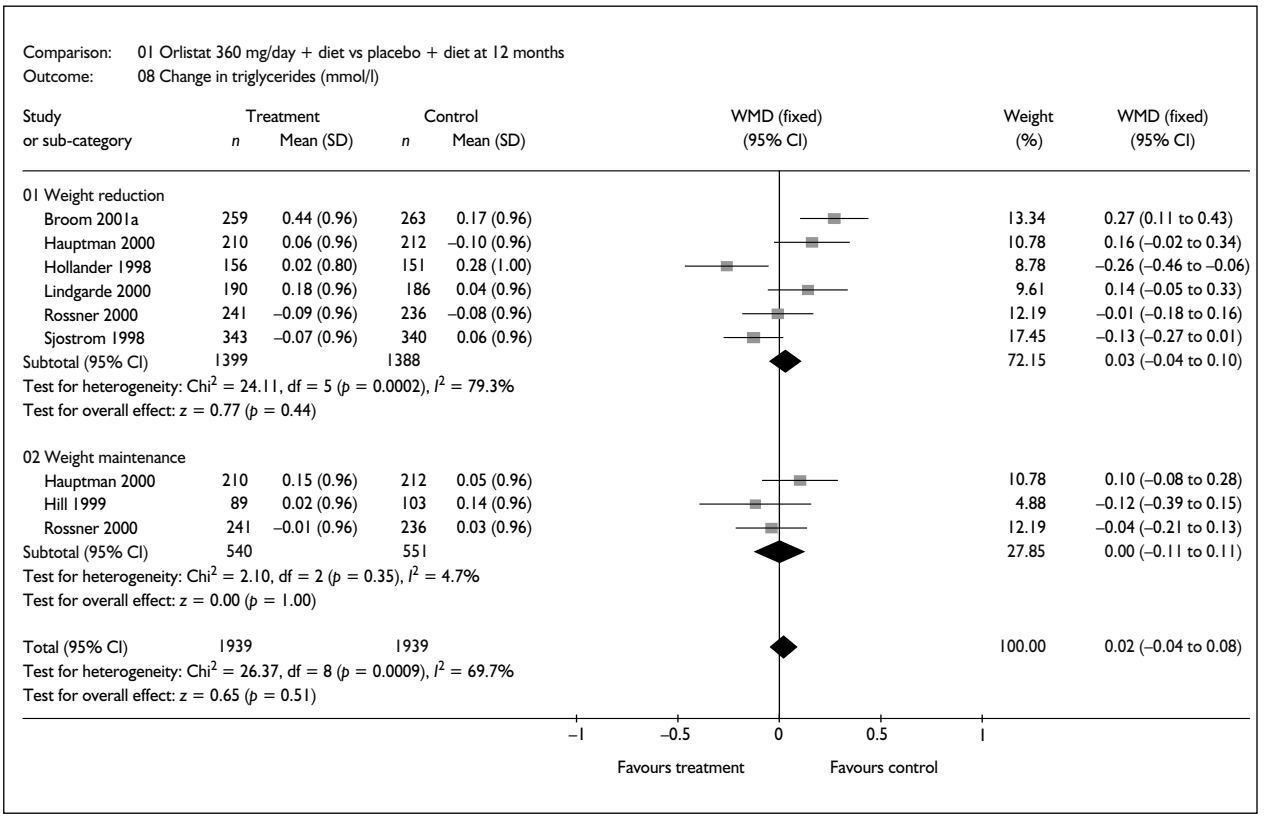


FIGURE 7

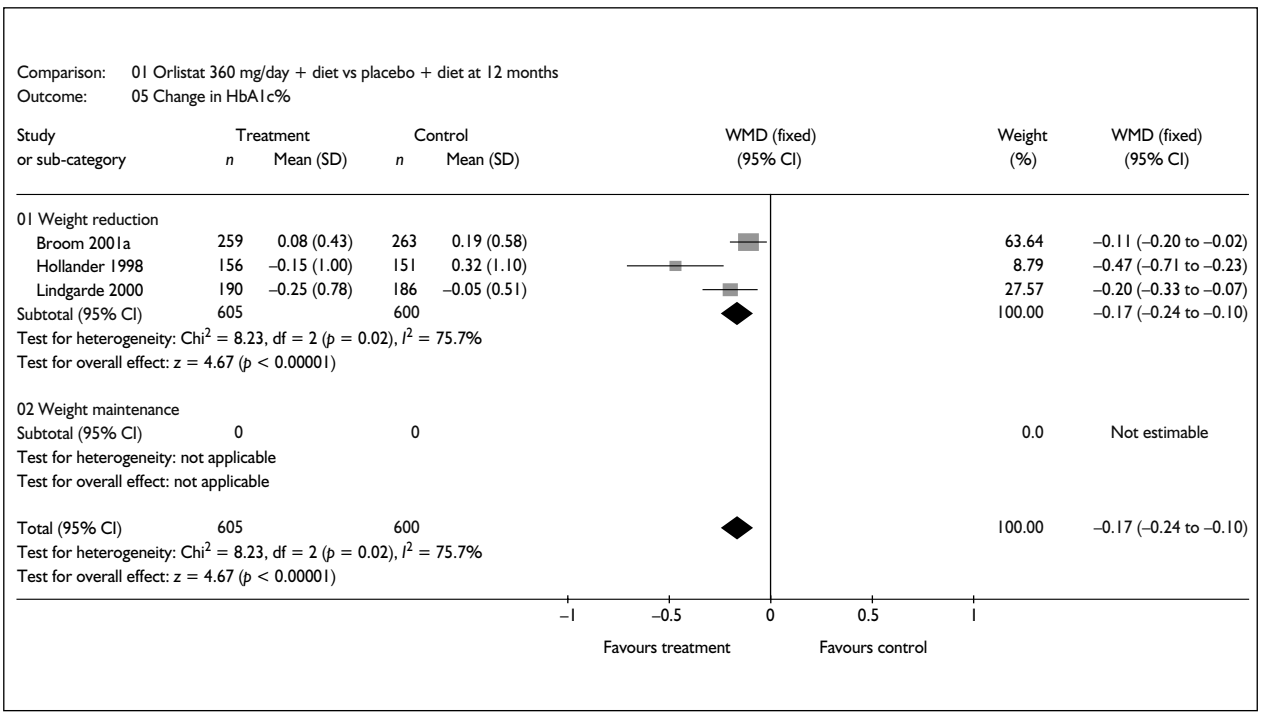


FIGURE 8

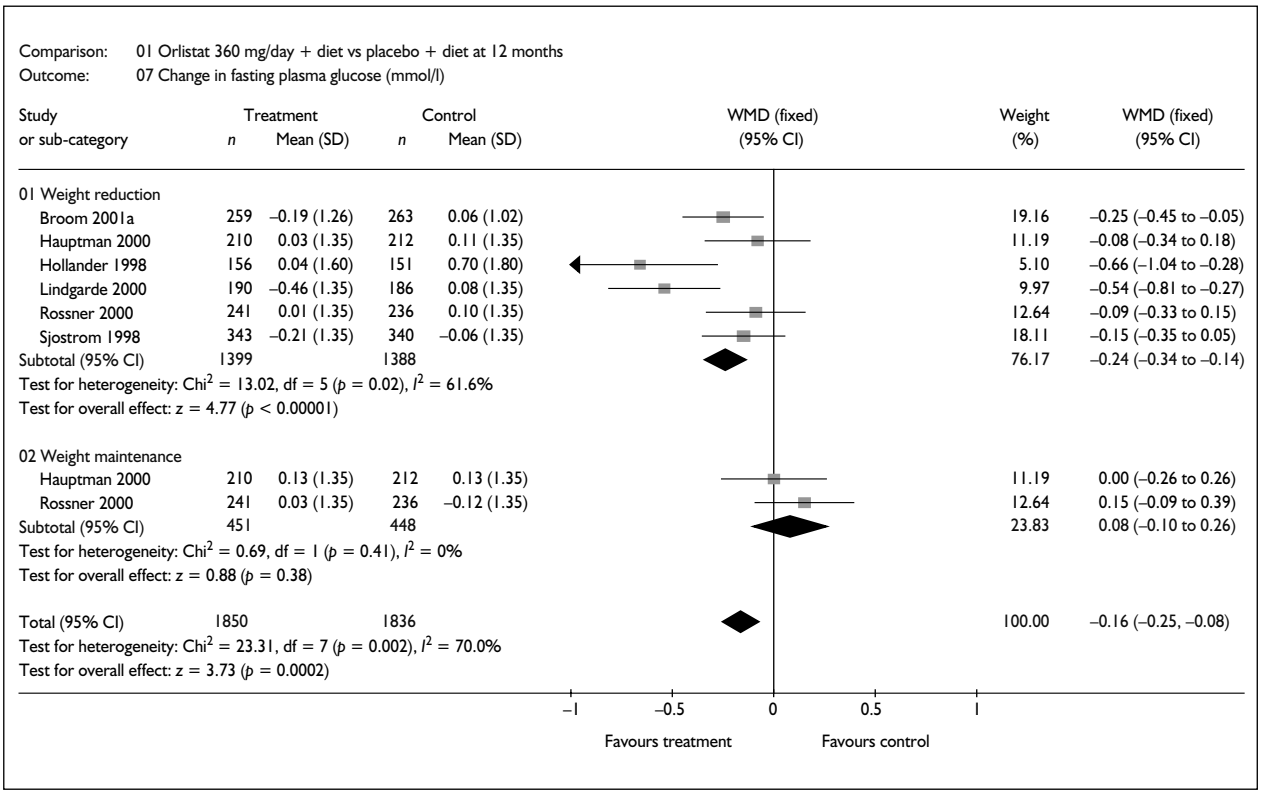


FIGURE 9

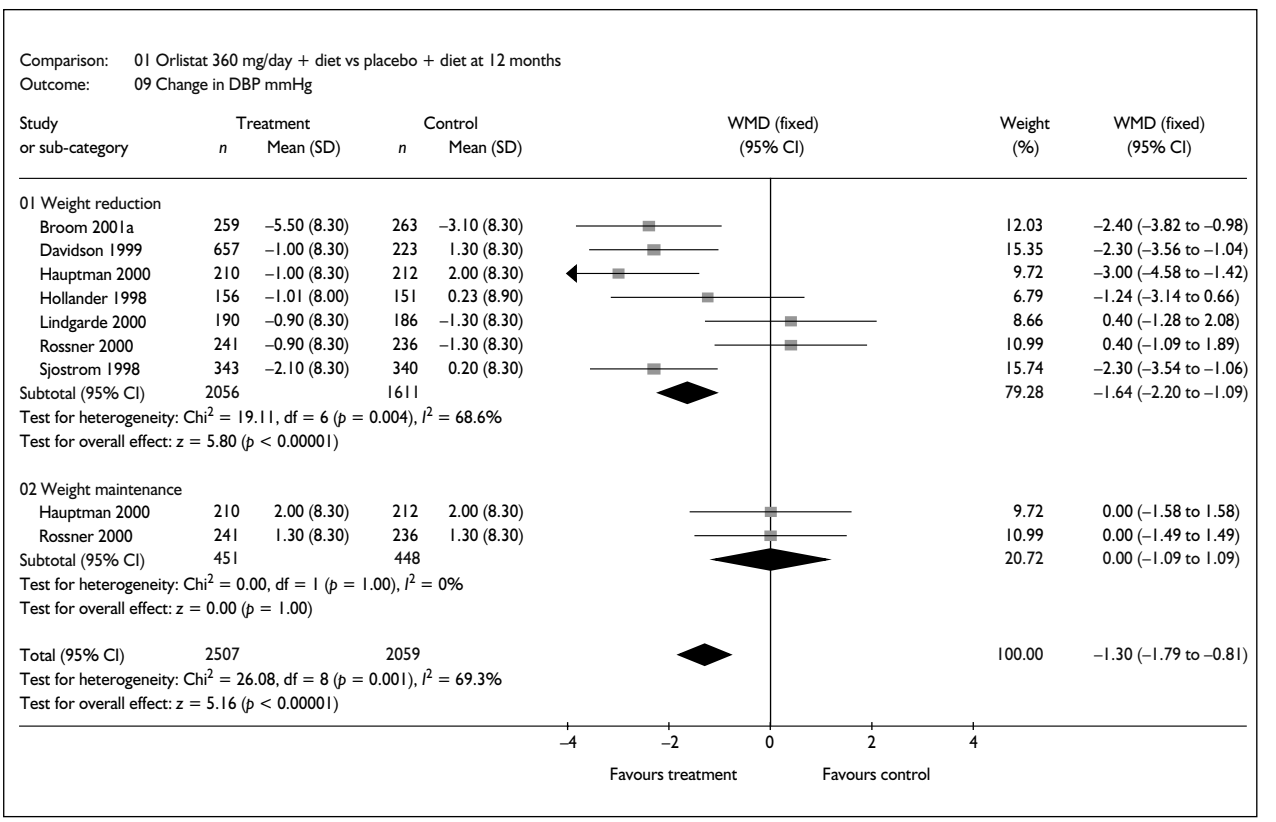


FIGURE 10

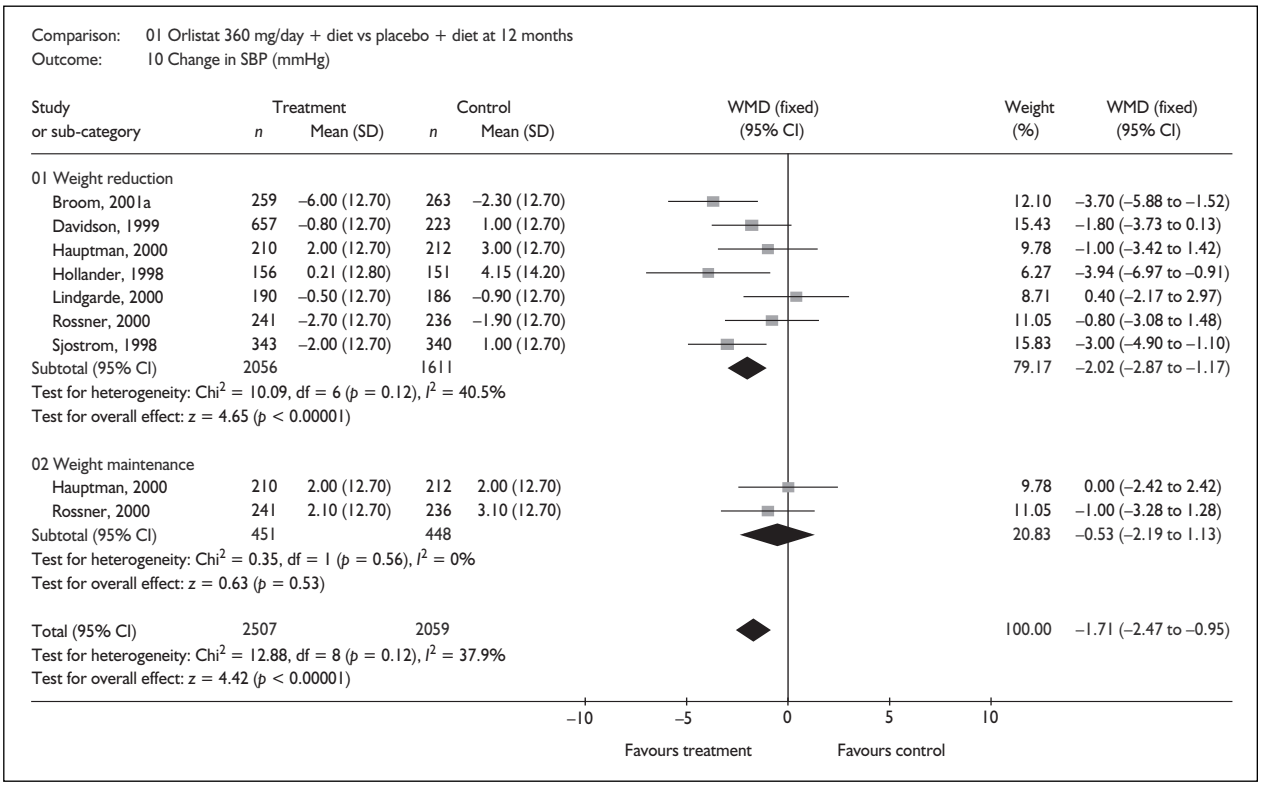


FIGURE 11

One death occurred in the orlistat arm of the study by Broom and colleagues[35,36,40] from cancer and one death in the orlistat arm of the study by Hauptman and colleagues[45–47] from acute myocardial infarction (MI). One death from brainstem infarction occurred in the orlistat arm of the study by Lindgarde and colleagues.[50,51]

Davidson and colleagues[41,42] reported four cases of breast cancer in year 1, three of these cases in participants treated with orlistat and one case in a participant treated with placebo (one in each group had evidence of breast cancer on mammograms before study entry). Rossner and colleagues[37,38] reported one participant with cholelithiasis. Rossner also reported one participant with breast cancer in the placebo group and three participants with breast cancer in the 120-mg orlistat group (of whom two had mammogram evidence of cancer before recruitment). Sjostrom and colleagues[52–56] reported one participant with gastrointestinal cancer in the placebo/placebo group during the 2 years of the study. (See *Figures 20 and 21* for cancer data.)

All the orlistat studies reported gastrointestinal adverse events, such as oily stools and faecal incontinence, to be more common in the orlistat groups than in the placebo groups.

In two studies vitamin supplementation was routinely given to all participants.[41,42,48,49] Where reported, vitamin supplementation *per protocol* was always required more commonly in the orlistat groups than in the placebo groups.[33,34,37,38,41–47,52–56]

Hollander and colleagues[33,34] reported that the average dose of oral sulfonylureas decreased more in the orlistat than in the placebo group (–23% versus –9%, respectively, $p = 0.0019$).

Effects of orlistat 360 mg/day for 52 weeks and diet versus placebo for 24 weeks and diet then orlistat 360 mg/day for 28 weeks and diet

Description of study

One RCT assessed the effects of 52 weeks of orlistat 360 mg/day compared with 24 weeks of placebo followed by 28 weeks of orlistat 360 mg/day in an obese population with hyperlipidaemia.[57] Throughout the study all participants were advised regarding a 600 kcal/day deficit diet. Thirty per cent of participants in the 52-weeks orlistat group and 20% of participants in

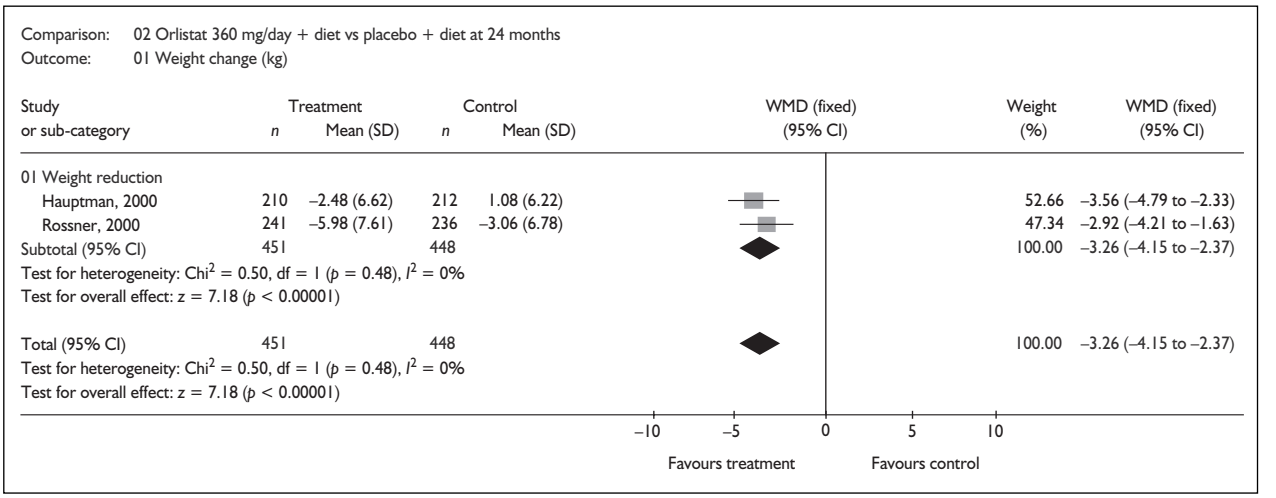


FIGURE 12

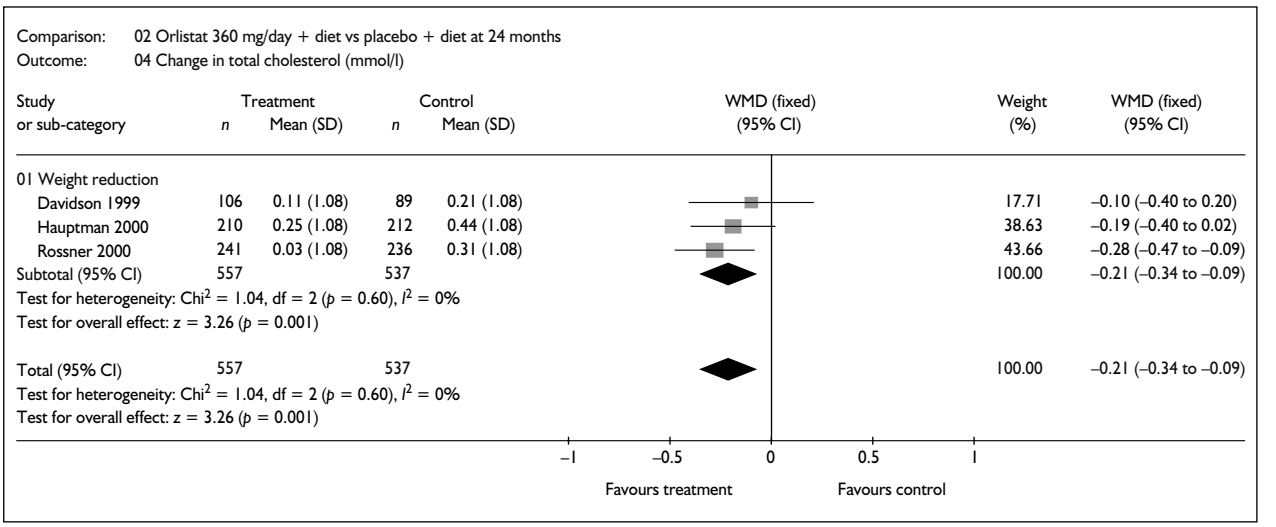


FIGURE 13

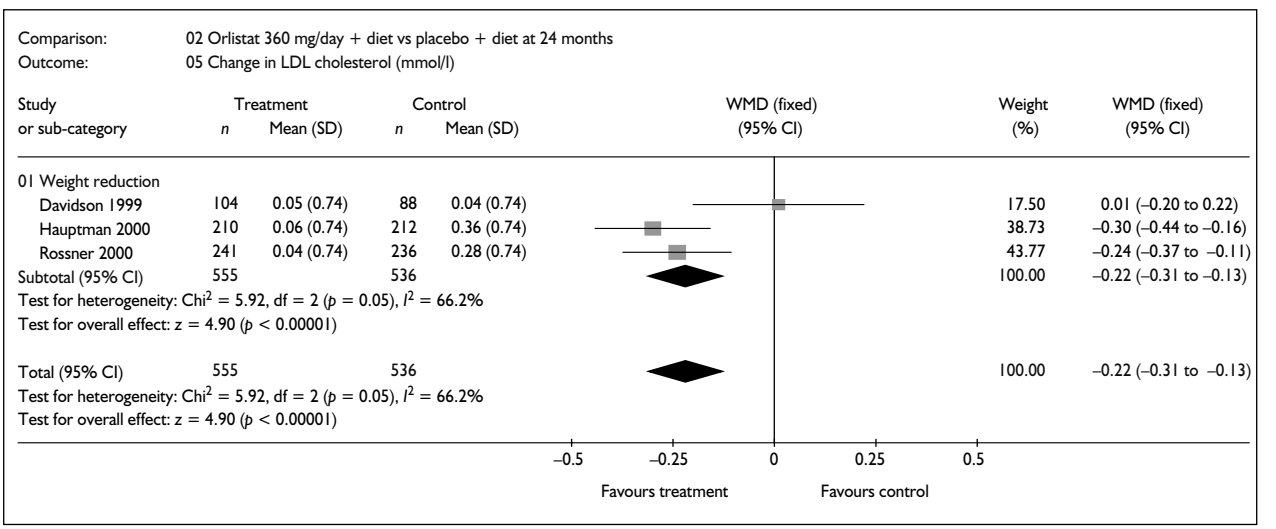


FIGURE 14

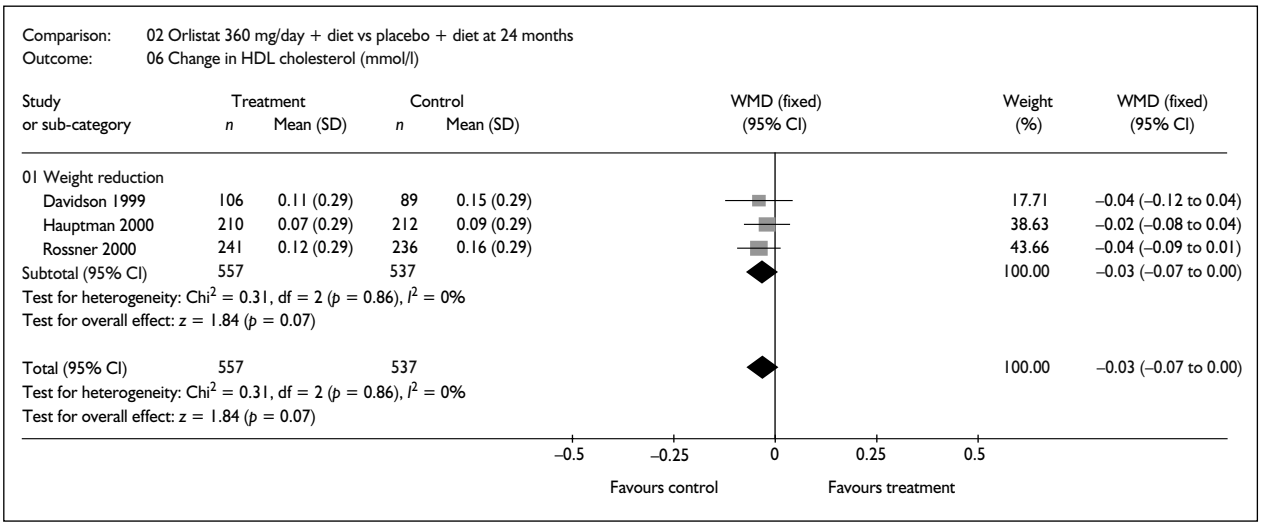


FIGURE 15

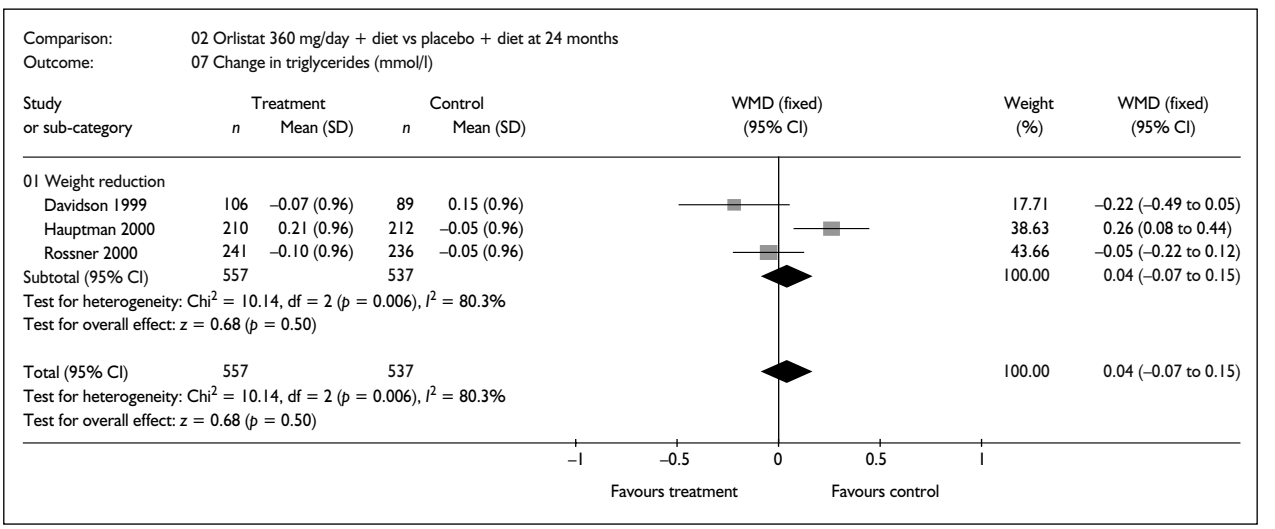


FIGURE 16

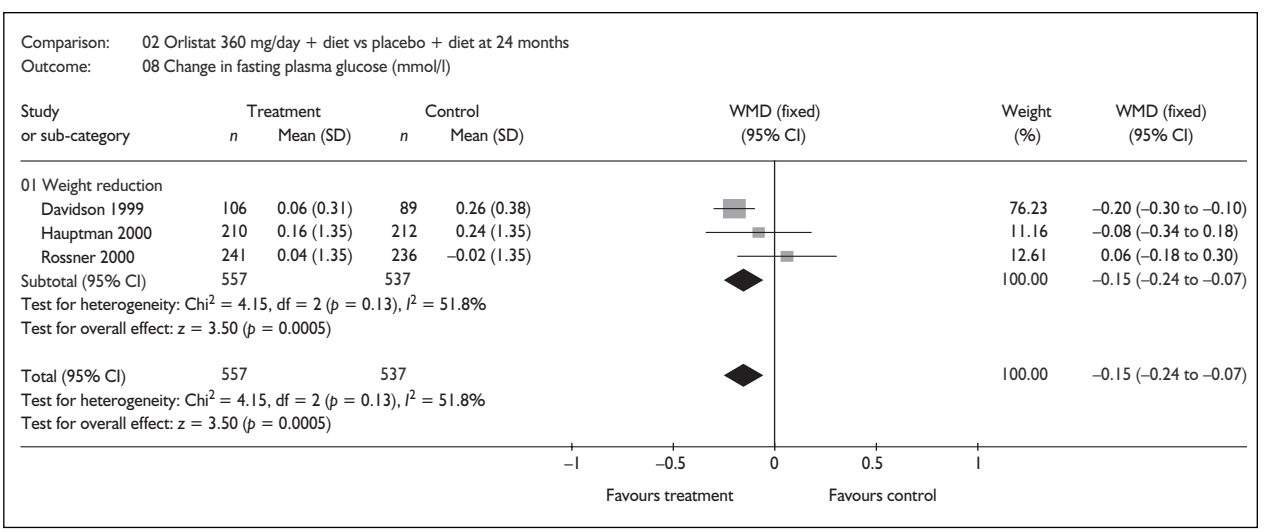


FIGURE 17

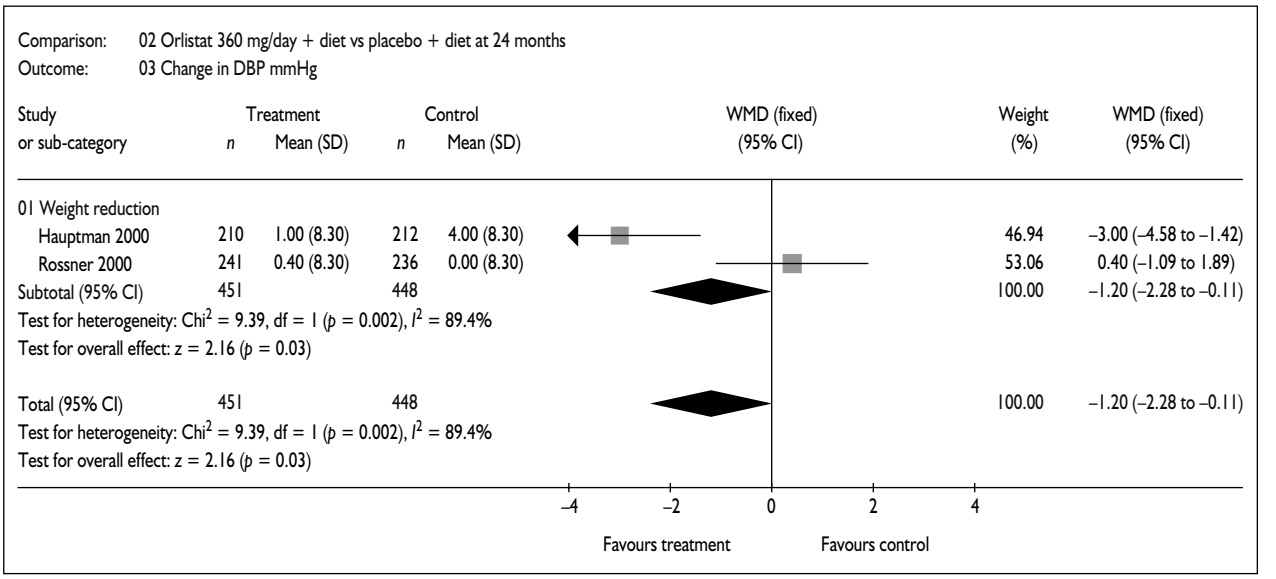


FIGURE 18

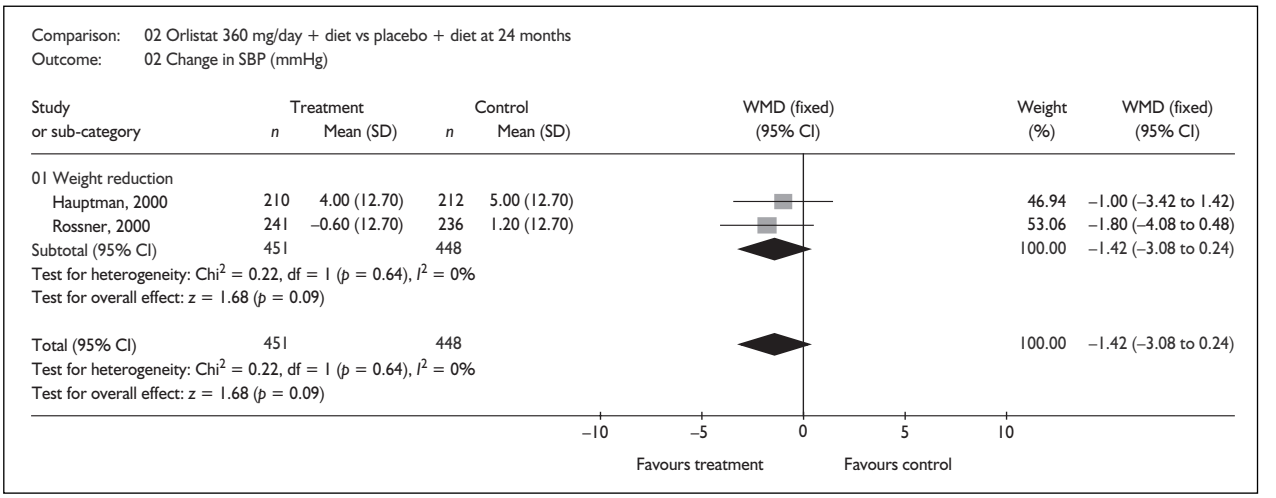


FIGURE 19

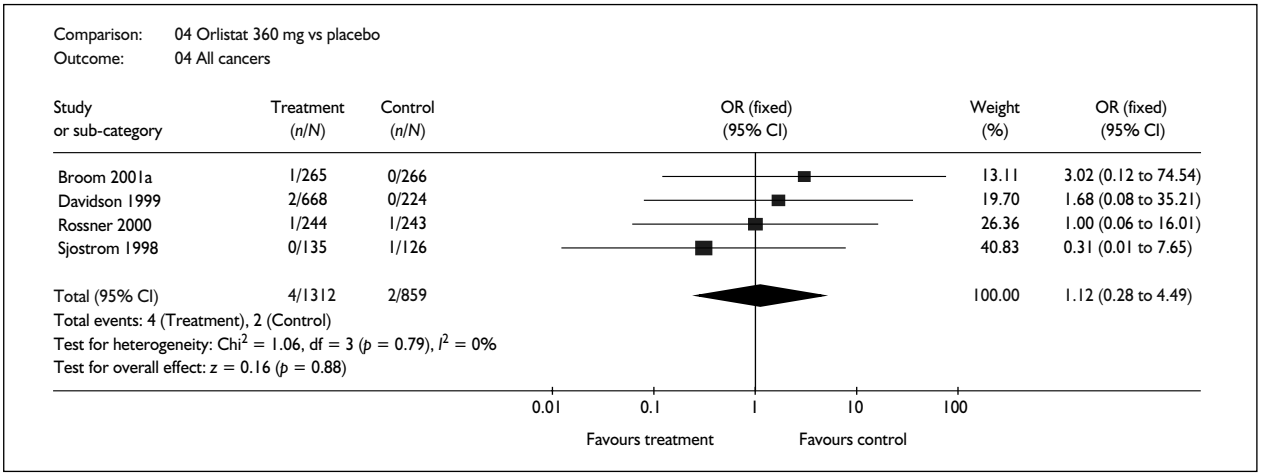


FIGURE 20

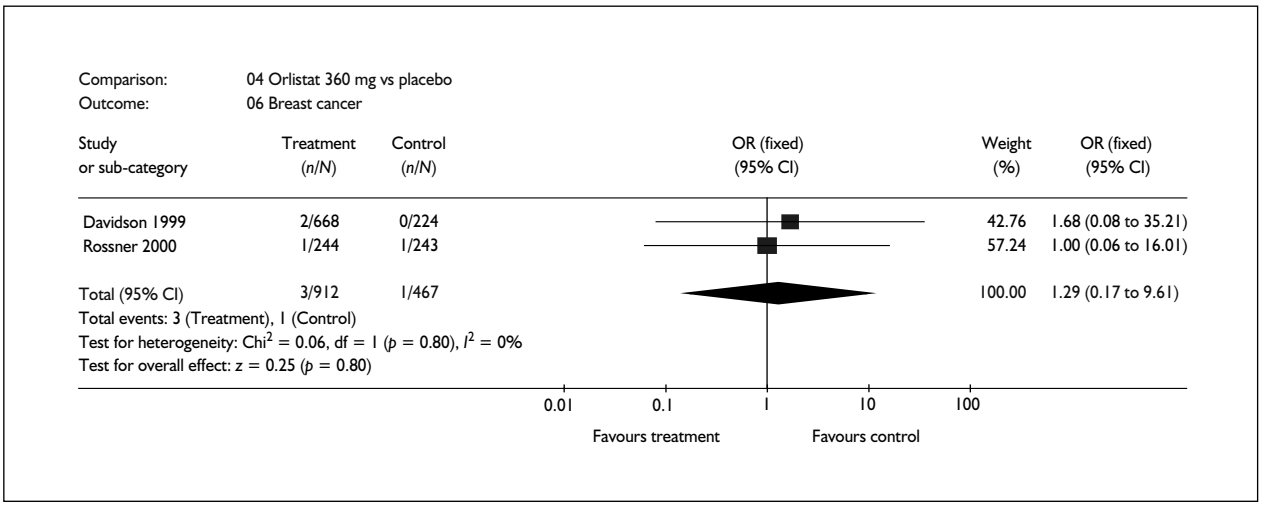


FIGURE 21

the 28-weeks orlistat group were type 2 diabetics. Data were provided on change in weight, total cholesterol, LDL cholesterol and fasting plasma glucose at 12 months.

Change in weight and risk factors was assessed using an LOCF basis, with five participants in total excluded (either did not receive study medication or did not return for follow-up visit). Dropout rates were 52% for the orlistat group at 52 weeks and 39% for the placebo/orlistat group. Mean overall BMI at baseline was 37 kg/m^2. All participants received an identical number of appointments.

Review results

At 12 months 52 weeks of orlistat 360 mg/day was associated with a WMD weight change of –0.69 kg (95% CI –2.85 to 1.47 kg) compared with the placebo/orlistat group (*Figure 22*). Compared with the placebo/orlistat group, the orlistat group had changes at 12 months in total cholesterol of –0.29 mmol/l (95% CI –0.65 to 0.07 mmol/l) (*Figure 23*), LDL cholesterol of –0.51 mmol/l (95% CI –0.76 to –0.26 mmol/l) (*Figure 24*) and fasting plasma glucose –0.30 mmol/l (95% CI –0.75 to 0.15 mmol/l) (*Figure 25*). However, all these results are from only one study.

During the double-blind phase of 24 weeks 86.6% of participants on orlistat and 42.3% of participants on placebo experienced gastrointestinal side-effects. One participant required a cholecystectomy in the placebo/orlistat group and one participant developed a stroke in the 52-weeks orlistat 360 mg/day group.

Effects of sibutramine and diet versus placebo and diet

Description of studies

Four RCTs provided change in weight at 12 months or longer.[58–70] One of these studies aimed to assess the ability of sibutramine to maintain weight loss over 18 months following a 6-month weight reduction phase.[64–70] Three weight reduction studies provided change in weight at 12 months.[58–63] Apfelbaum and colleagues[58] also evaluated weight change at 15 months (3 months after treatment cessation). The Sibutramine Trial in Obesity Reduction and Maintenance (STORM)[64–70] study assessed weight change at 18 months.

Data were provided for lipids, blood pressure, fasting plasma glucose and HbA_{1c} at 12 months and at 18 months, with the exception of blood pressure. One study[64–70] clearly reported assessing change in weight using an ITT approach.

The studies used a variety of diets. The study by Apfelbaum and colleagues[58] provided dietary counselling to reduce total calorie intake by 20–30%. McMahon and colleagues[59,60] gave brief general dietary counselling for weight reduction at the initial run-in visit only. Smith and colleagues[61–63] advised a low-fat diet and the STORM trial[64–70] advised a 600 kcal/day deficit diet.

McMahon[59,60] and Smith[61–63] included single-blind placebo run-in periods, which ranged from 2 to 10 weeks' duration. The study by Apfelbaum and colleagues[58] included a 4-week pretreatment phase of VLCD with entry to randomisation dependent

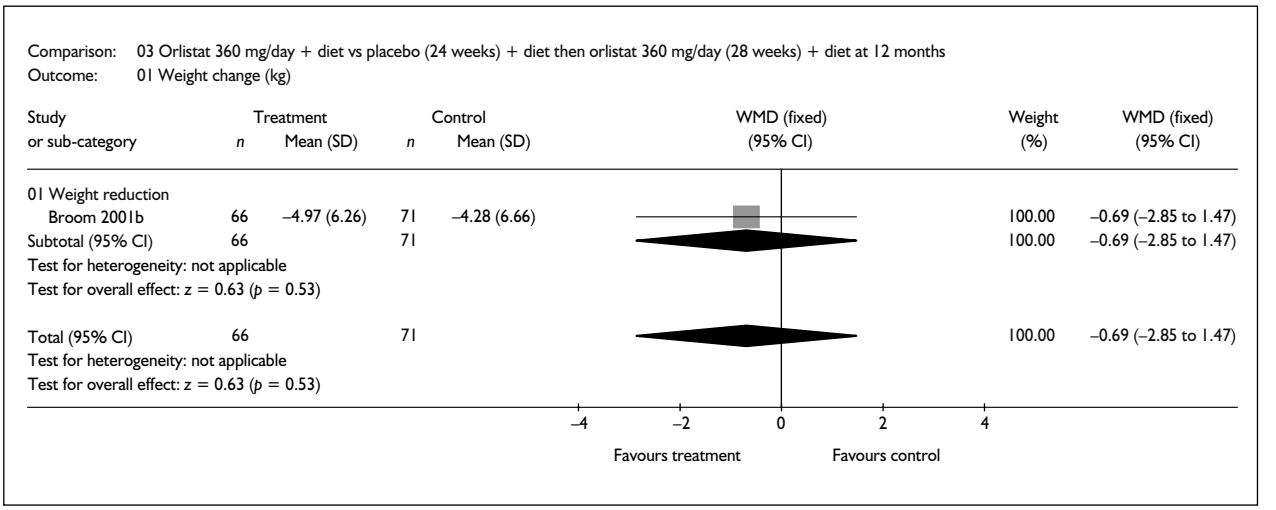


FIGURE 22

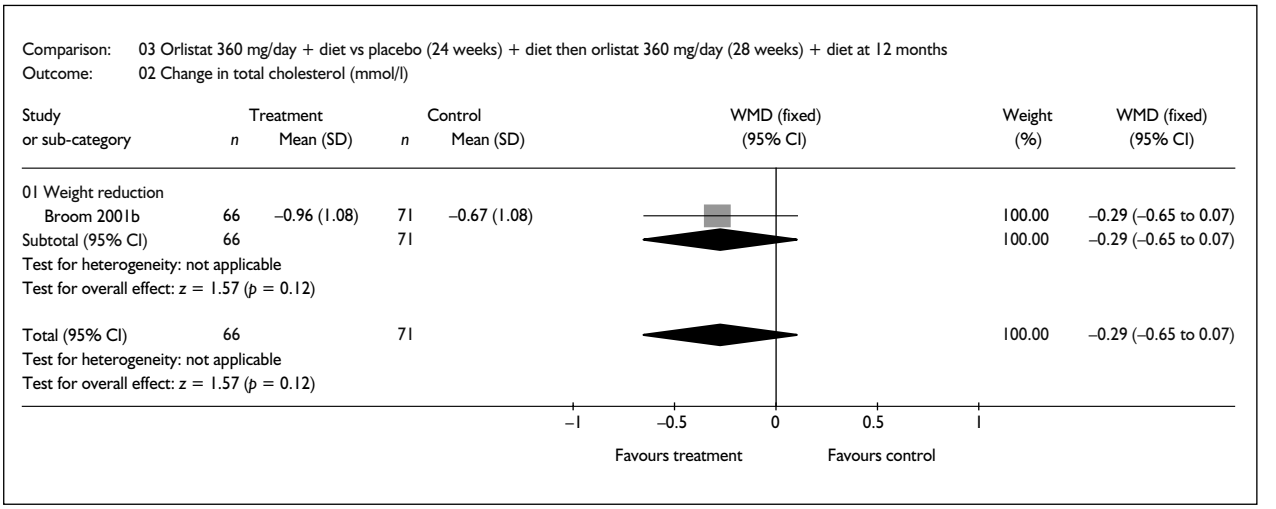


FIGURE 23

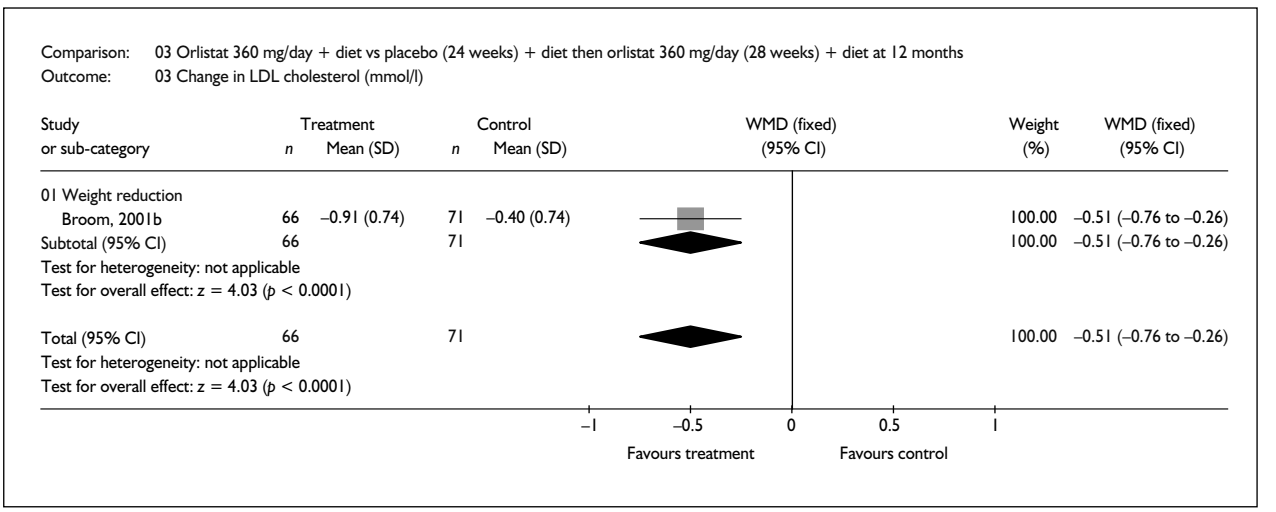


FIGURE 24

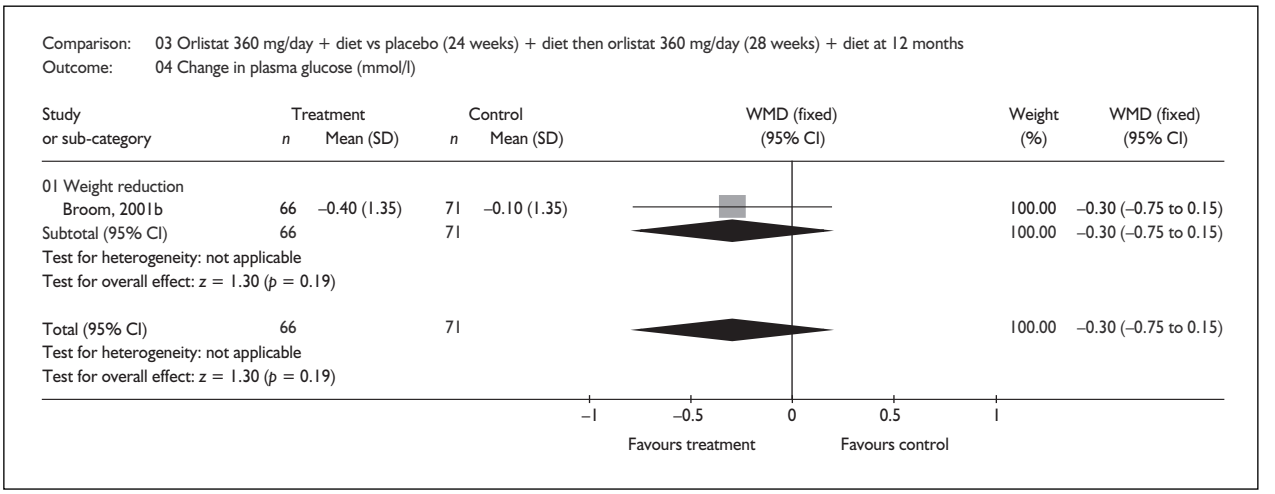


FIGURE 25

upon a weight loss of 6 kg or more during this phase. STORM[64–70] included a 6-month open pretreatment phase of 10 mg sibutramine daily plus 600 kcal/day deficit diet plus advice on behaviour modification and advice to walk 30 minutes extra per day.

McMahon[59,60] recruited people with hypertension and the studies by Smith[61–63] and STORM[64–70] included people with hypertension if stabilised on medication. Reported mean BMI ranged from 32.4 kg/m^2 [61–63] to 36.6 kg/m^2.[64–70]

Dropout rates at 12 months ranged from 27%[58] to 59%.[64–70] In three of the studies dropout rates were lower in the placebo group.[58–60,64–70]

Review results

Sibutramine and diet compared with diet in the three weight reduction studies was associated with an overall WMD weight change at 12 months of –4.12 kg (95% CI –4.97 to –3.26 kg) (*Figure 26*).[58–63] The weight reduction study by Apfelbaum and colleagues[58] was associated with a weight change at 15 months of –3.70 kg (95% CI –5.71 to –1.69 kg) (*Figure 27*). The STORM[64–70] weight maintenance study was associated with a weight change at 18 months of –3.40 kg (95% CI –4.45 to –2.35 kg) (*Figure 28*).

At 12 months sibutramine in the weight reduction studies showed beneficial effects on HDL cholesterol and triglycerides, as did the sibutramine group in the STORM[64–70] weight maintenance study (*Figures 29–34*). At 18 months in the STORM study HDL and triglycerides were still significantly improved (*Figures 35–40*).

At 12 months, SBP showed a WMD change of 1.16 mmHg (95% CI –0.60 to 2.93 mmHg) in two weight reduction studies (*Figure 41*).[59–63] Diastolic blood pressure showed a WMD change of 2.04 mmHg (95% CI 0.89 to 3.20 mmHg) (*Figure 42*). Results for the sibutramine study for people with hypertension are shown in *Table 2*.

One person required a cholecystectomy in the sibutramine group of the study by Apfelbaum and colleagues.[58] One person was also withdrawn from the placebo group in this study because of the development of hypertension. Adverse events did not appear to differ between the treatment arms for this study, with the exception of constipation, which was more common with sibutramine (OR 4.14, 95% CI 1.31 to 13.10), although the confidence interval was wide.

In the study by Smith and colleagues[61–63] one participant withdrew from the 10-mg sibutramine group owing to four drop attacks within 2 weeks of the start (history of epilepsy) and one participant withdrew from the 15-mg sibutramine group owing to palpitations due to frequent ventricular ectopic beats. Dry mouth was also significantly more frequent in both sibutramine groups than in participants on placebo (OR 11.42, 95% CI 2.72 to 47.87).

In the study by McMahon[59,60] dry mouth and constipation were also the adverse events reported as being significantly more frequent in the group on sibutramine ($p < 0.05$). Eight out of 150 participants discontinued sibutramine as a result of hypertension, compared with one out of 74 participants on placebo (OR 4.11, 95% CI 0.50 to 33.52).

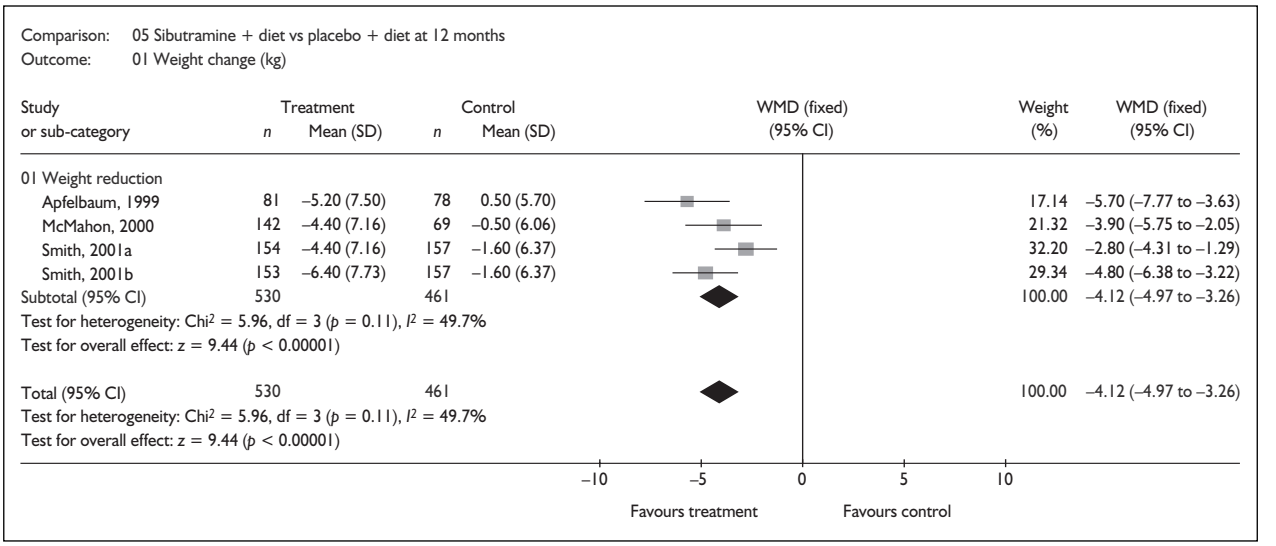


FIGURE 26

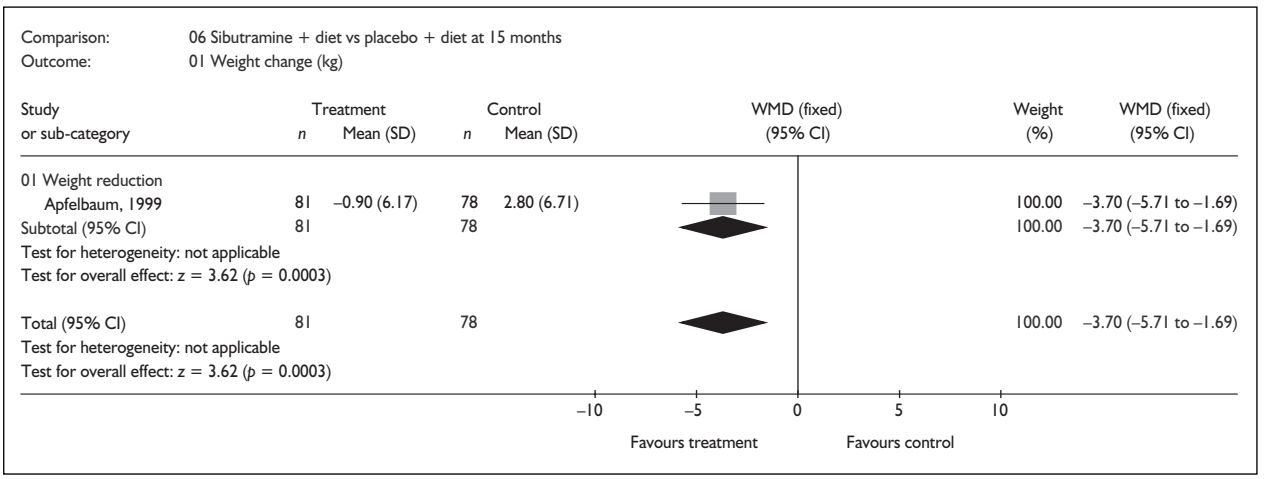


FIGURE 27

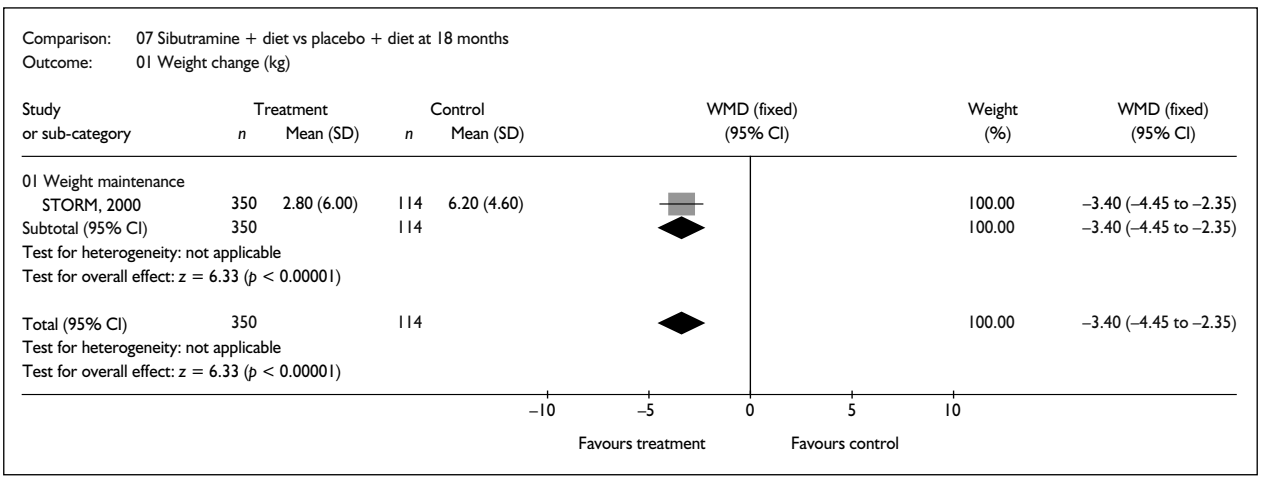


FIGURE 28

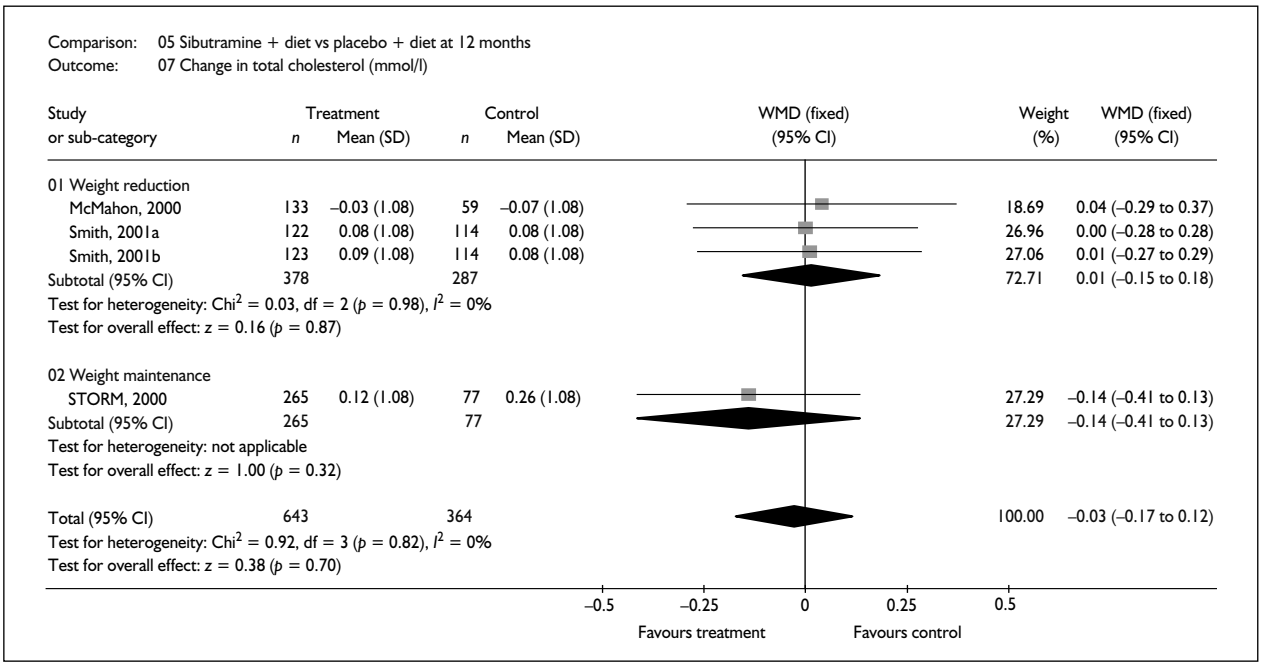


FIGURE 29

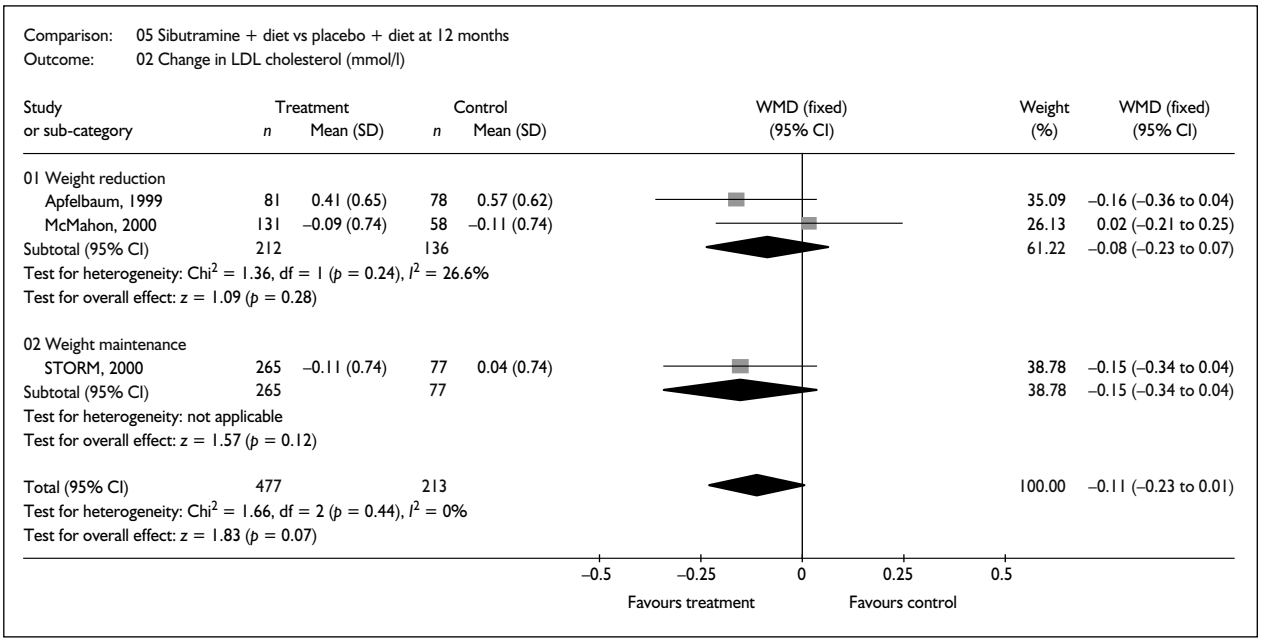


FIGURE 30

The STORM study[64–70] found dry mouth, constipation, increased blood pressure, insomnia and nausea to be more than twice as frequent in the sibutramine participants. One participant in each of the sibutramine and placebo groups was withdrawn as a result of hypertension. Of the participants with hypertension taking sibutramine, two needed an increase in therapy and two a decrease.

Effects of SSRIs and diet versus placebo and diet

Description of studies

Five RCTs provided change in weight at 12 months.[71–79] Four of these interventions aimed to produce weight reduction[71–77] and one study aimed to produce weight maintenance after a 26-week pretreatment phase.[78,79] The meta-analyses

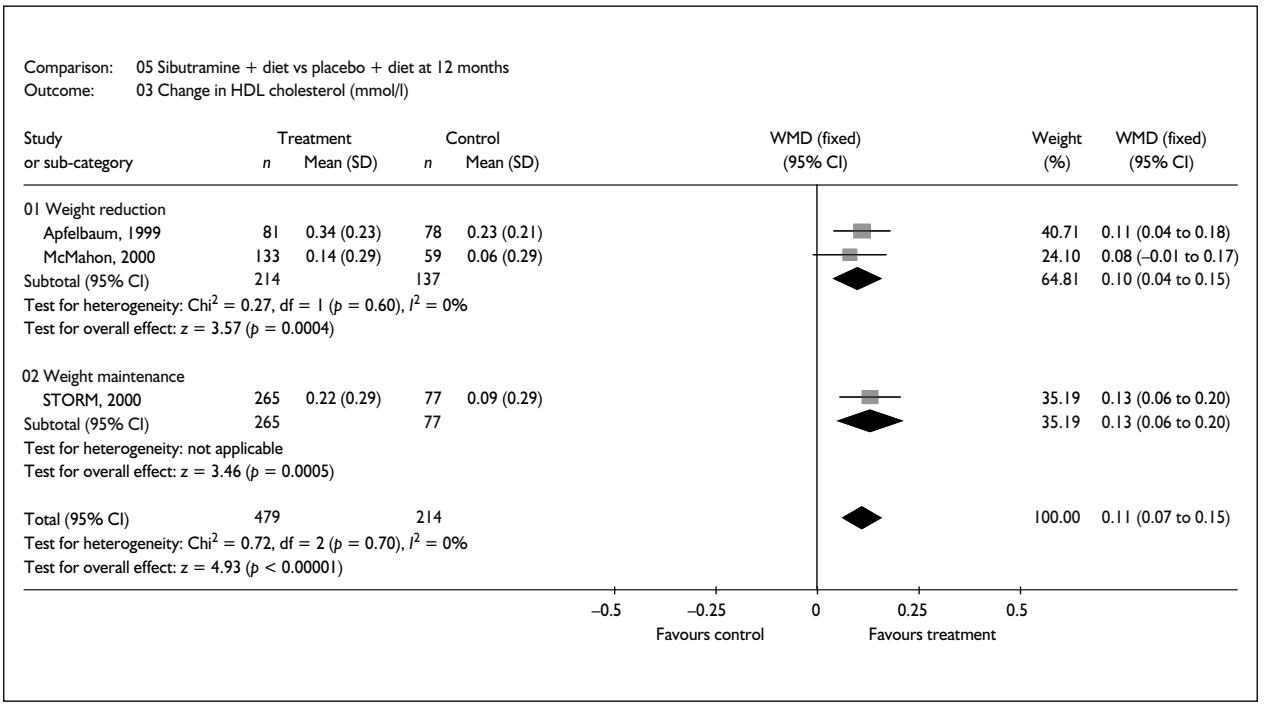


FIGURE 31

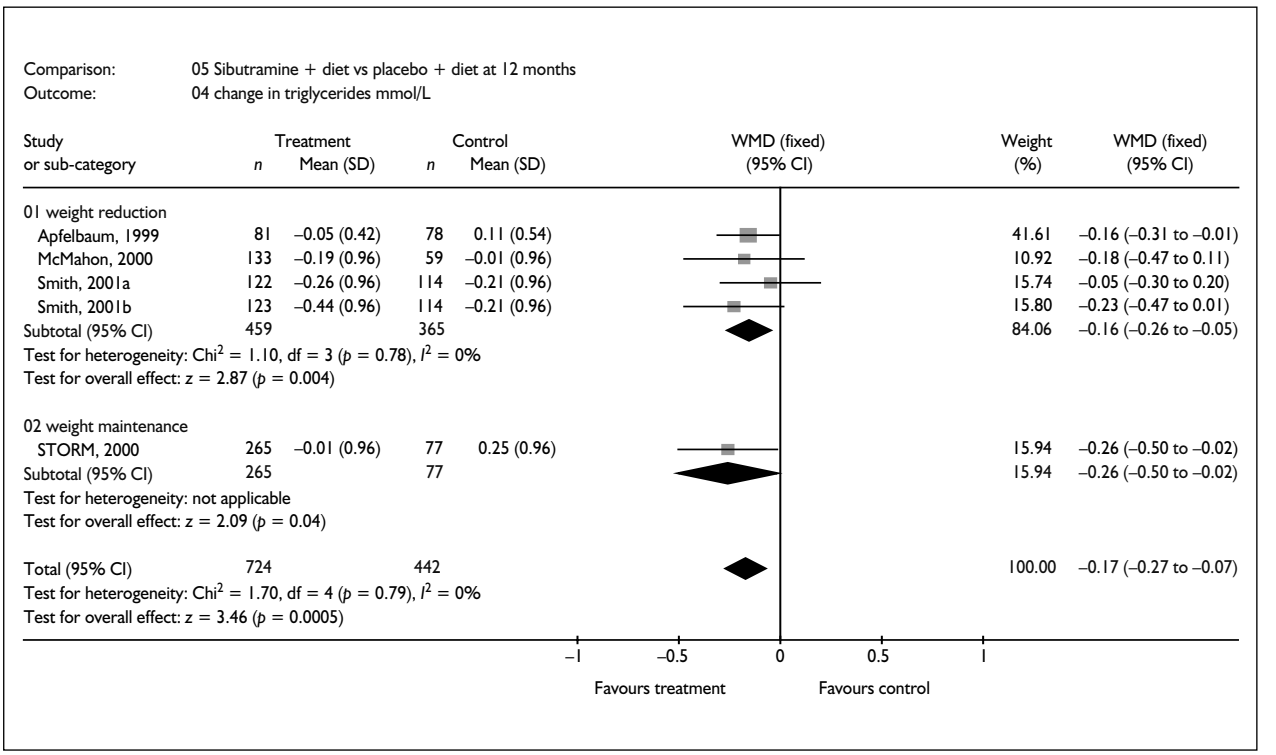


FIGURE 32

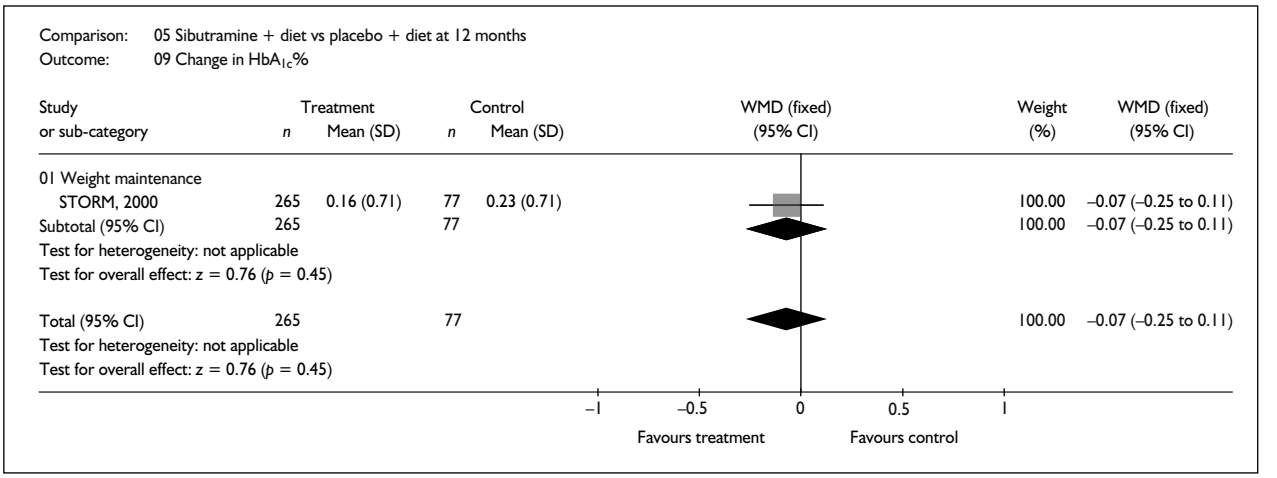


FIGURE 33

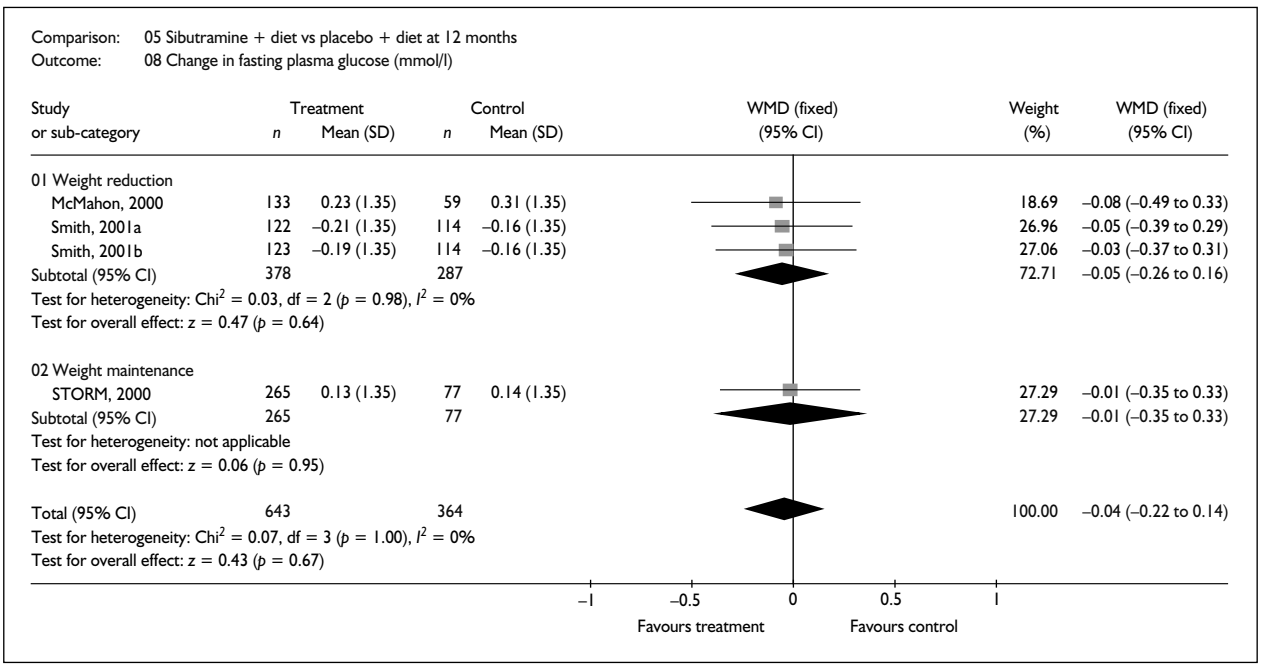


FIGURE 34

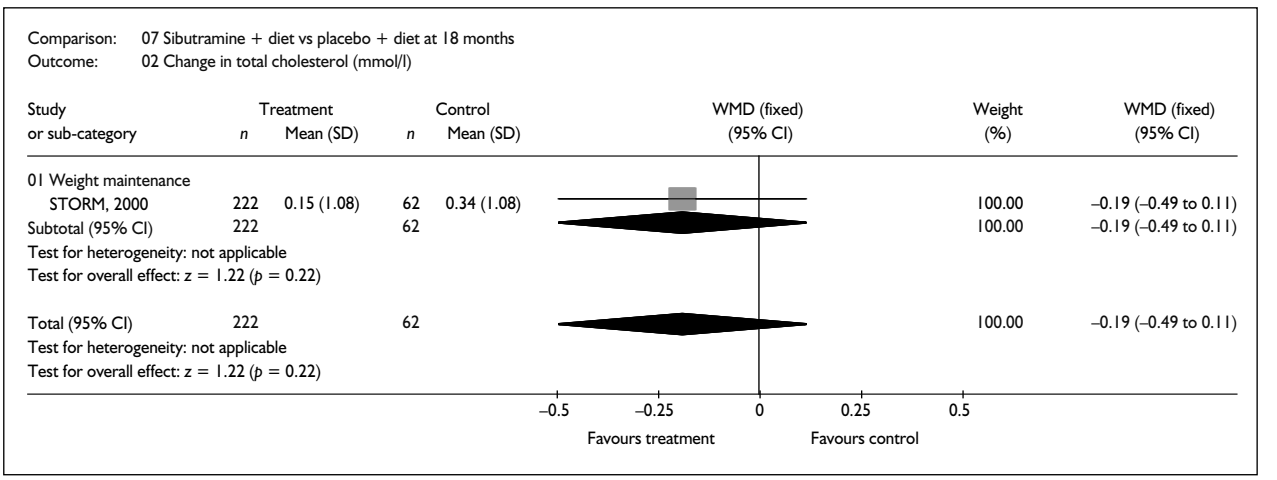


FIGURE 35

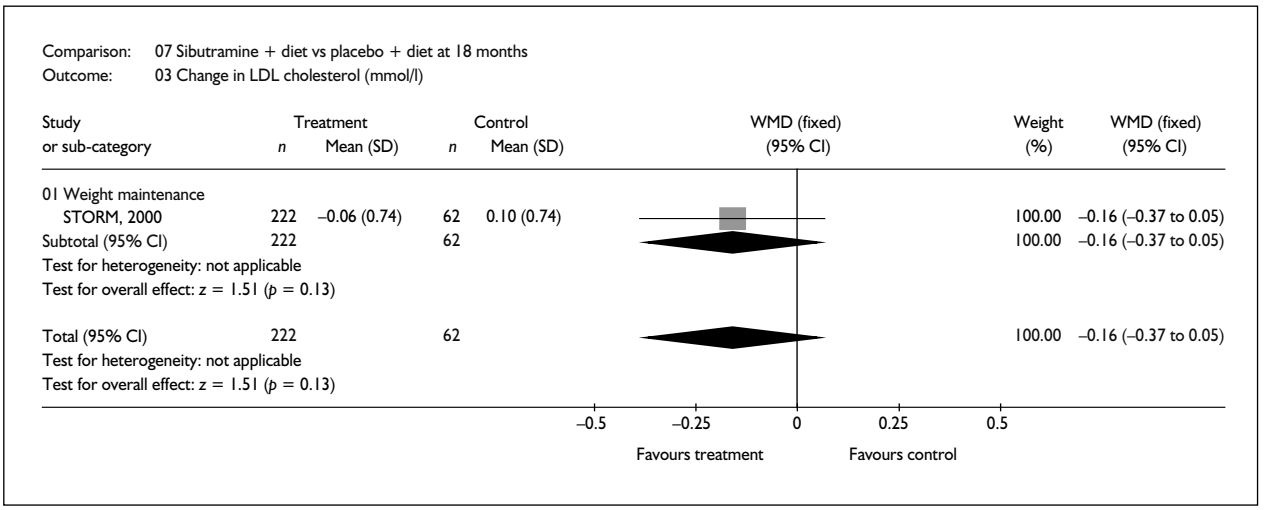


FIGURE 36

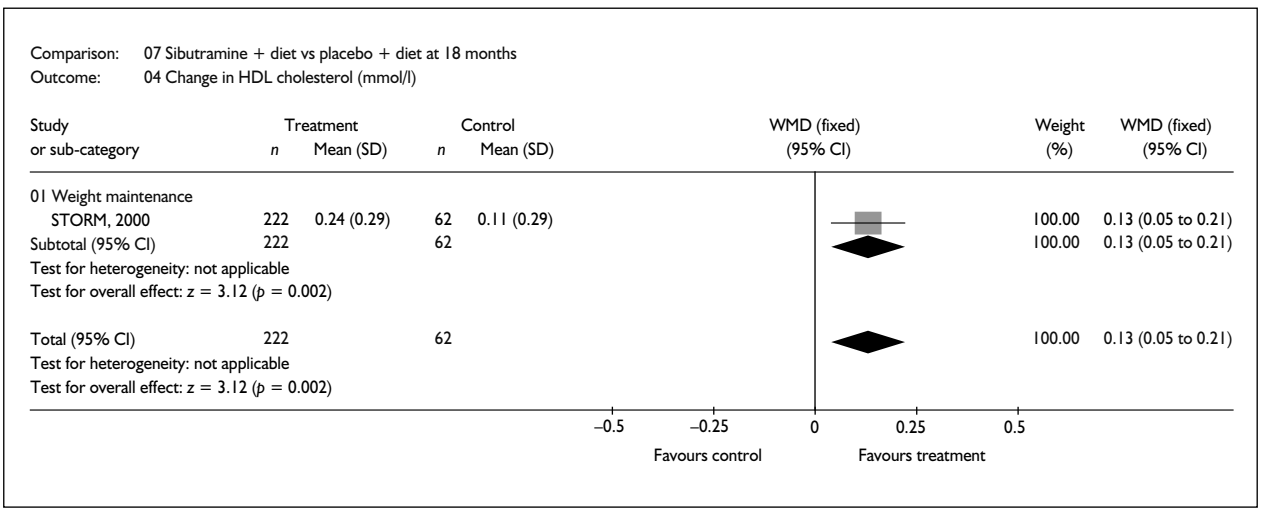


FIGURE 37

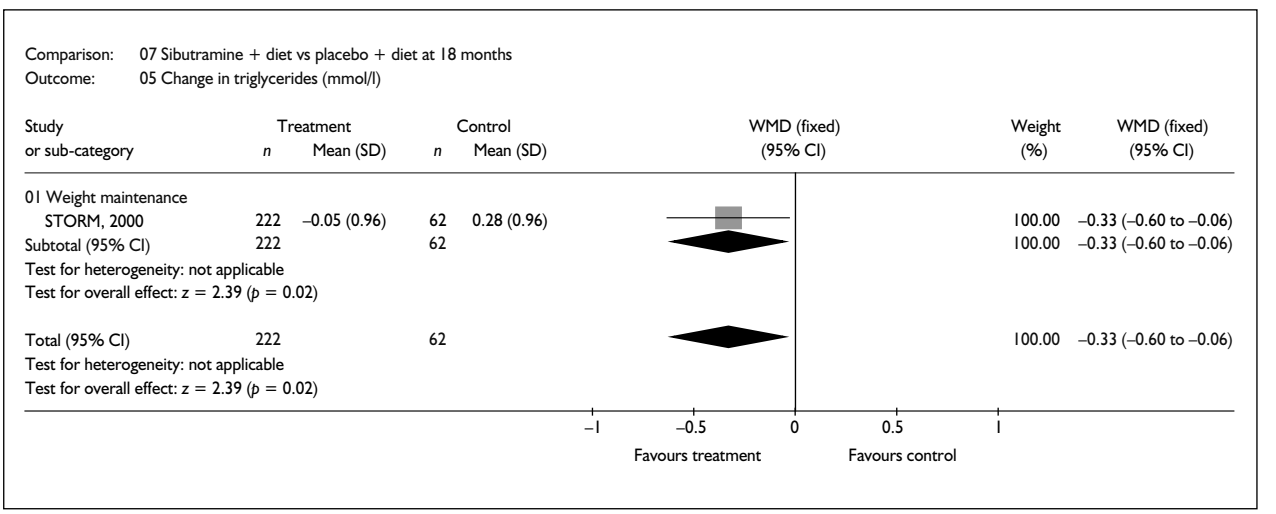


FIGURE 38

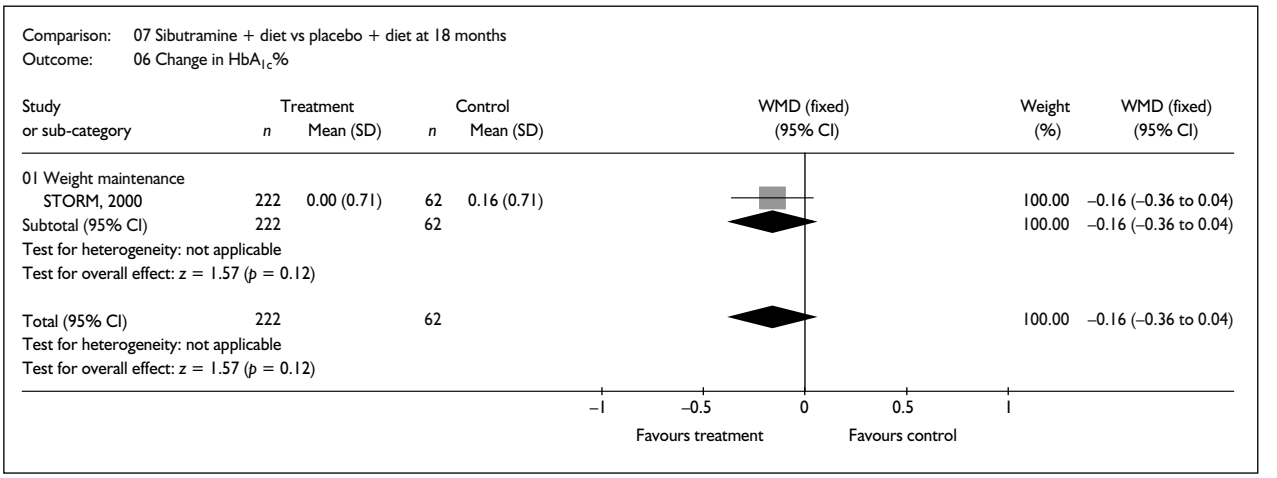


FIGURE 39

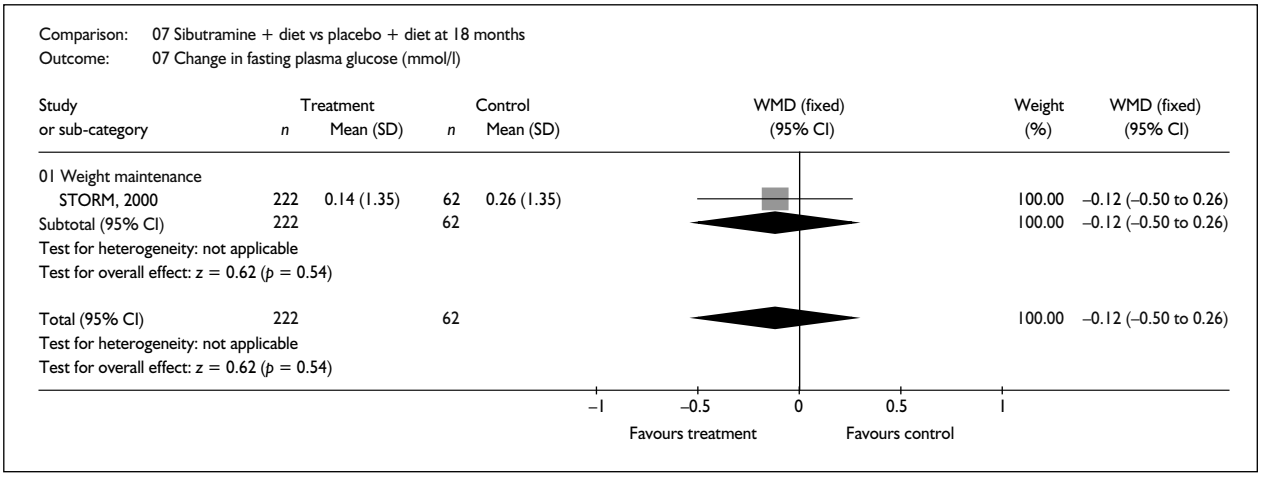


FIGURE 40

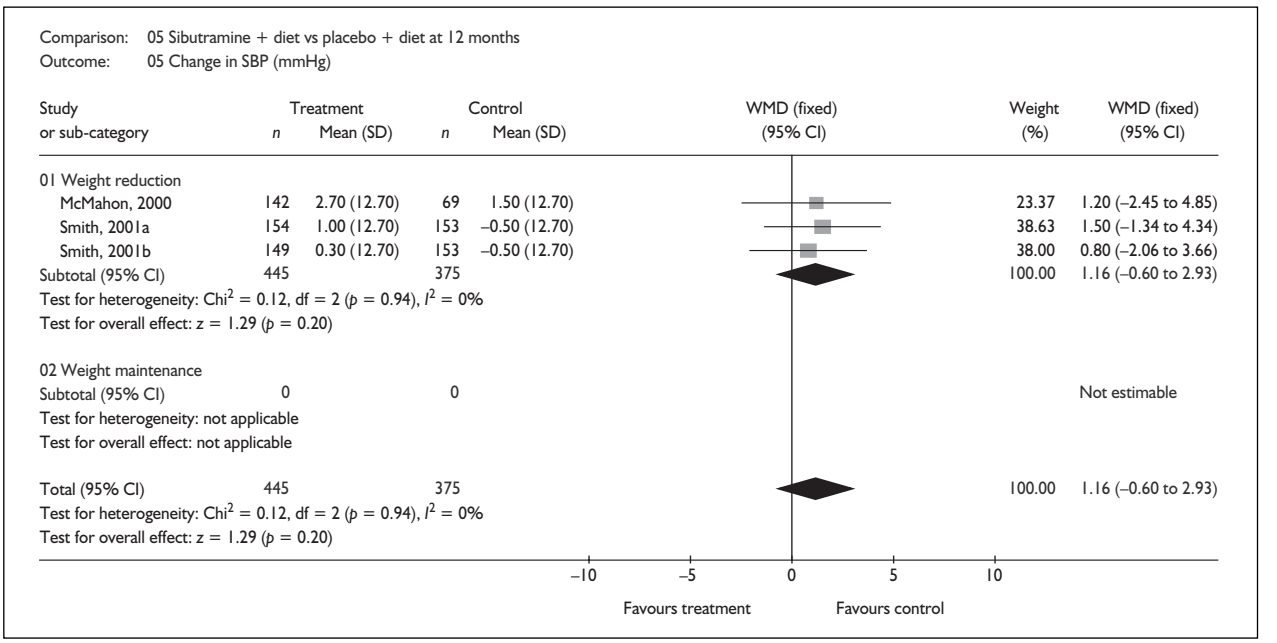


FIGURE 41

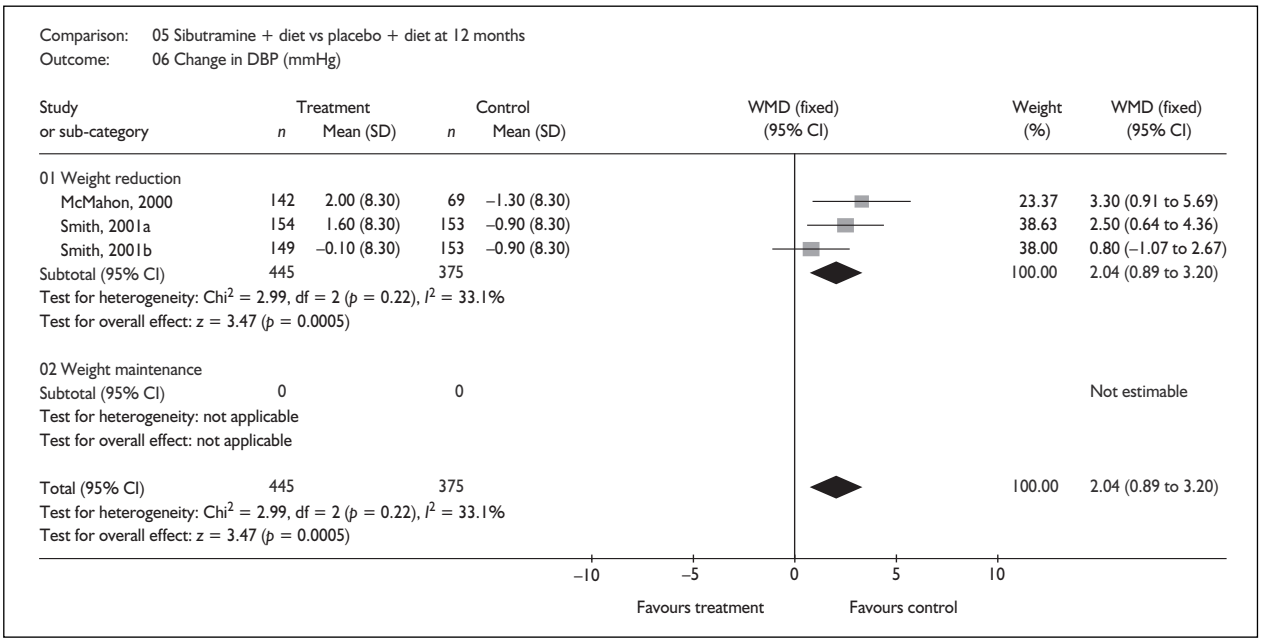


FIGURE 42

for these data are therefore divided into weight reduction and weight maintenance subgroups. The study by Bitsch and Skrumsager[71] did not report the numbers of participants assessed in each group for change in weight at 1 year. The results for this study are therefore discussed separately.

Two studies reported using an ITT analysis.[71,78,79] The numbers of participants allocated to each group in the studies varied from 10[77] to 230.[73–76] Dropout rates were reported of 50% or greater in each arm of two studies.[73–76,78,79] The overall dropout rate for the study by Bitsch and Skrumsager[71] was 53% at 1 year. One study examined people with type 2 diabetes[77] and one study examined people with either type 2 diabetes or impaired glucose tolerance.[72] See results in *Table 3* for people with type 2 diabetes. Reported mean BMI ranged from 29.2 kg/m^2 [78,79] to 39.5 kg/m^2.[72] The study by Bitsch and Skrumsager[71] did not report body weight or BMI at baseline but recruited participants at 20% or above ideal body weight (IBW). The study by Wadden and colleagues[78,79] recruited females only.

All participants in each group in each of the studies received equal numbers of contact visits. These were similar across studies, ranging from ten to 16 visits, except for the study by Wadden and colleagues[78,79] where participants were seen 29 times during 12 months. All participants in each arm of the studies received identical treatment, except for receiving either SSRI or placebo. The content of the non-drug interventions varied across the studies. Bitsch and Skrumsager[71] advised participants to consume an LCD, whereas Breum and colleagues[72] advised participants to follow an LCD and provided behaviour therapy. Goldstein and colleagues[73–76] advised a diet aimed to produce weight loss of 0.45 kg per week with behaviour therapy (which varied between trial sites). Participants in the study by O'Kane and colleagues[77] were advised to continue their usual diet and exercise patterns. Participants in the study by Wadden and colleagues[78,79] were required to have lost at least 10% of their initial weight during a 26-week pretreatment phase of VLCDs plus behaviour therapy. The VLCDs were 420, 660 or 800 kcal/day. Participants were then randomised to sertraline up to 200 mg/day or placebo and given advice on a 1500–1800 kcal/day diet with behaviour therapy and exercise. The study by Bitsch and Skrumsager[71] randomised participants to up to 600 mg femoxetine daily or placebo and the three other studies used 60 mg fluoxetine daily or placebo.[72–77]

Review results

SSRIs had no apparent added effect on weight loss or maintenance or any of the reported risk factors (*Figures 43–50*). At 12 months the added effect of SSRIs on weight reduction was associated with an overall WMD weight change of –0.33 kg (95% CI –1.49 to 0.82 kg). This was primarily influenced by the study of Goldstein and colleagues.[73–76]

TABLE 2 *Effects of sibutramine and diet versus diet on weight and risk factors in weight reduction studies in people with hypertension*

	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)	Fasting plasma glucose (mmol/l)
12 months	–3.90	0.04	0.08	0.02	–0.18	1.20	3.30	–0.08
WMD (95% CI)	(–5.75 to –2.05)	(–0.29 to 0.37)	(–0.01 to 0.17)	(–0.21 to 0.25)	(–0.47 to 0.11)	(–2.45 to 4.85)	(0.91 to 5.69)	(–0.49 to 0.33)
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1

TABLE 3 *Effects of SSRI and diet versus placebo and diet in people with type 2 diabetes*

	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)	Fasting plasma glucose (mmol/l)	HbA_{1c}%
12 months	–3.27	0.50	–0.08	–0.08	5.60	–0.30	–1.13	–0.84
WMD (95% CI)	(–8.83 to 2.29)	(–0.17 to 1.17)	(–0.29 to 0.13)	(–0.67 to 0.50)	(–3.65 to 14.85)	(–6.35 to 5.75)	(–2.68 to 0.43)	(–2.46 to 0.77)
No. of studies	*n* = 2	*n* = 2	*n* = 1	*n* = 2	*n* = 1	*n* = 1	*n* = 2	*n* = 2

The study by Bitsch and Skrumsager[71] assessed weight at 12 months in 37 participants and reported a median change in weight of –6.6 kg for the femoxetine group and –8.8 kg for the placebo group.

O'Kane and colleagues[77] reported one serious adverse event of colonic malignancy in the placebo group. Wadden and colleagues[78,79] reported no difference in depression scores between participants on sertraline and placebo; other studies did not report on mood. Goldstein and colleagues,[73–76] Wadden and colleagues[78,79] and Bitsch and Skrumsager[71] reported significantly more adverse events in the SSRI groups, which were expected side-effects of the drugs.

Effects of metformin and diet versus placebo and diet

Description of studies

Three RCTs provided change in weight at 12 months or longer.[80–93] Two studies provided change in weight at 12 months[84–93] and one of these studies also provided change in weight at 2 years.[84] One of these studies was a subgroup of the UK Prospective Diabetes Study (UKPDS), which investigated the management of people with newly diagnosed type 2 diabetes, in which

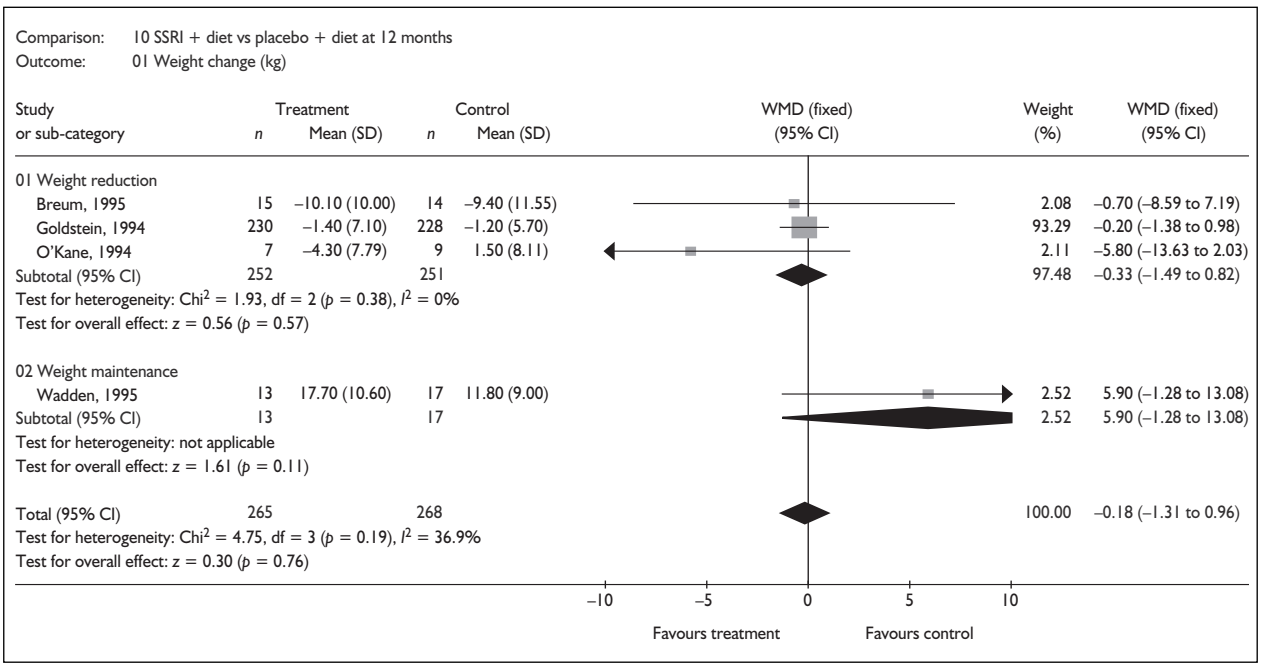


FIGURE 43

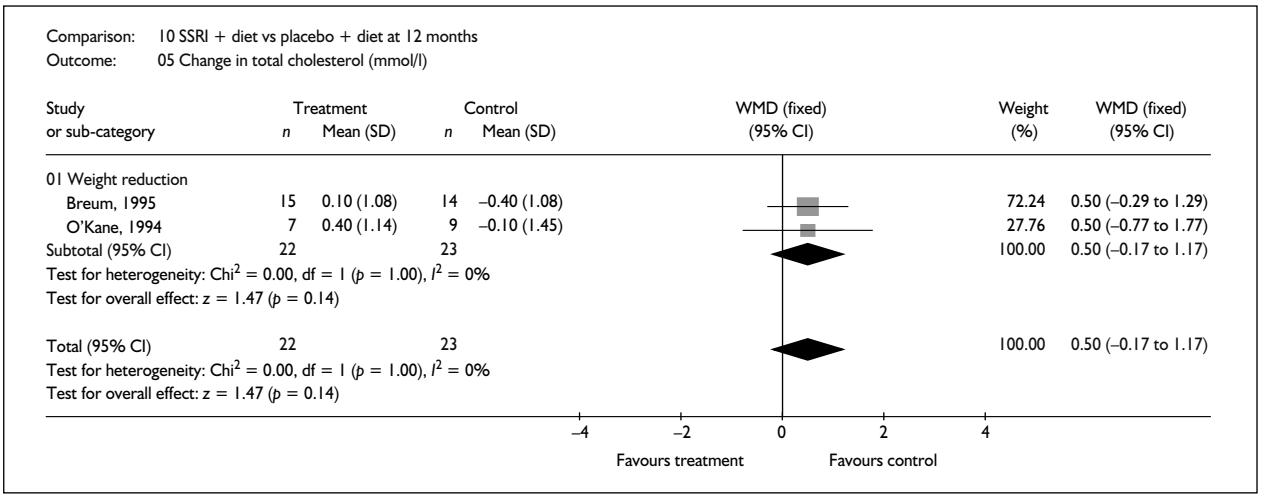


FIGURE 44

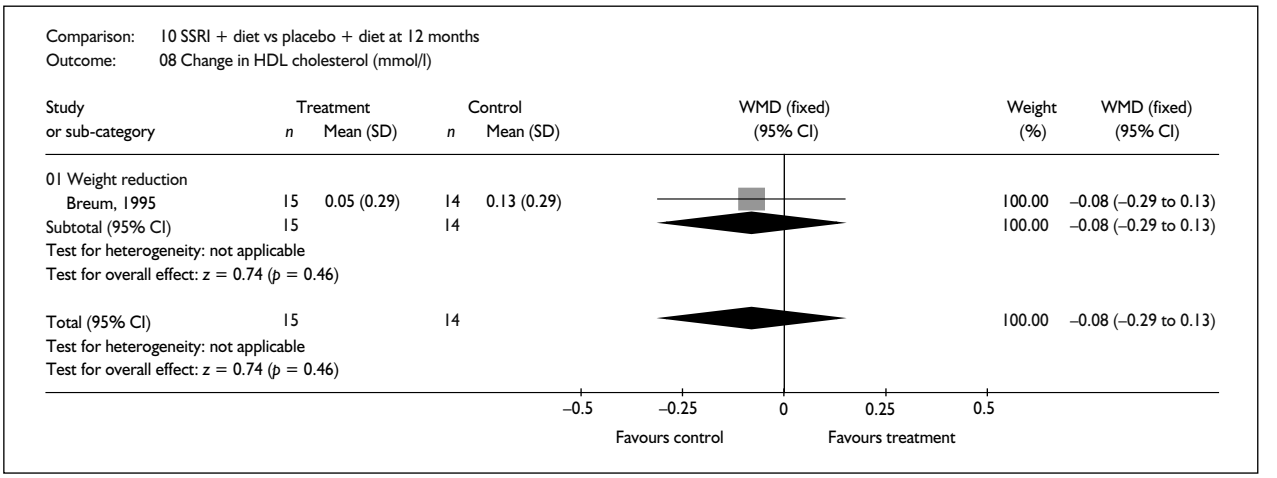


FIGURE 45

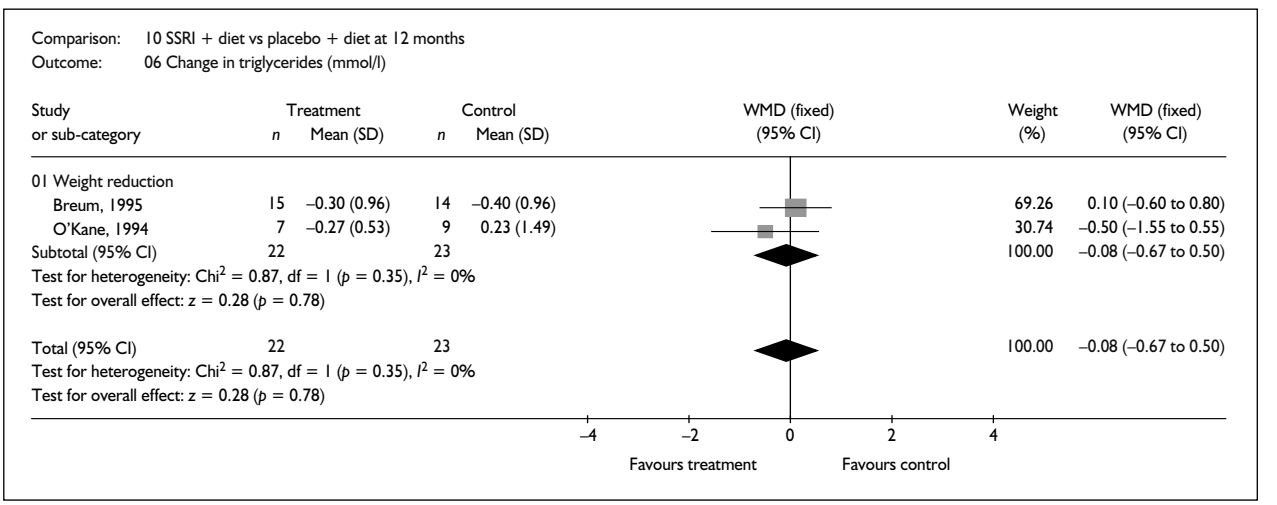


FIGURE 46

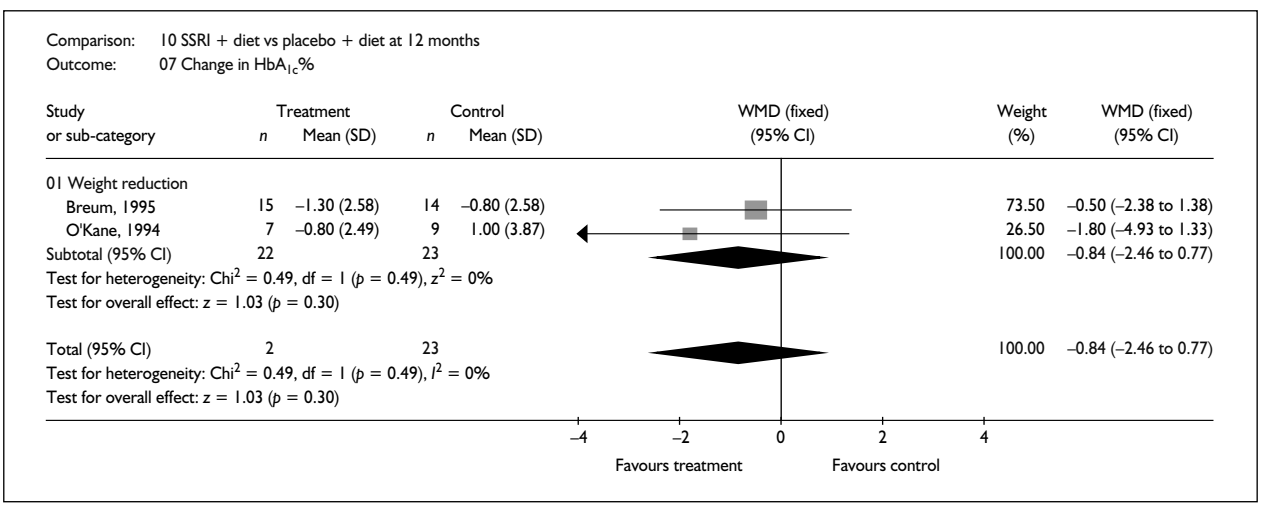


FIGURE 47

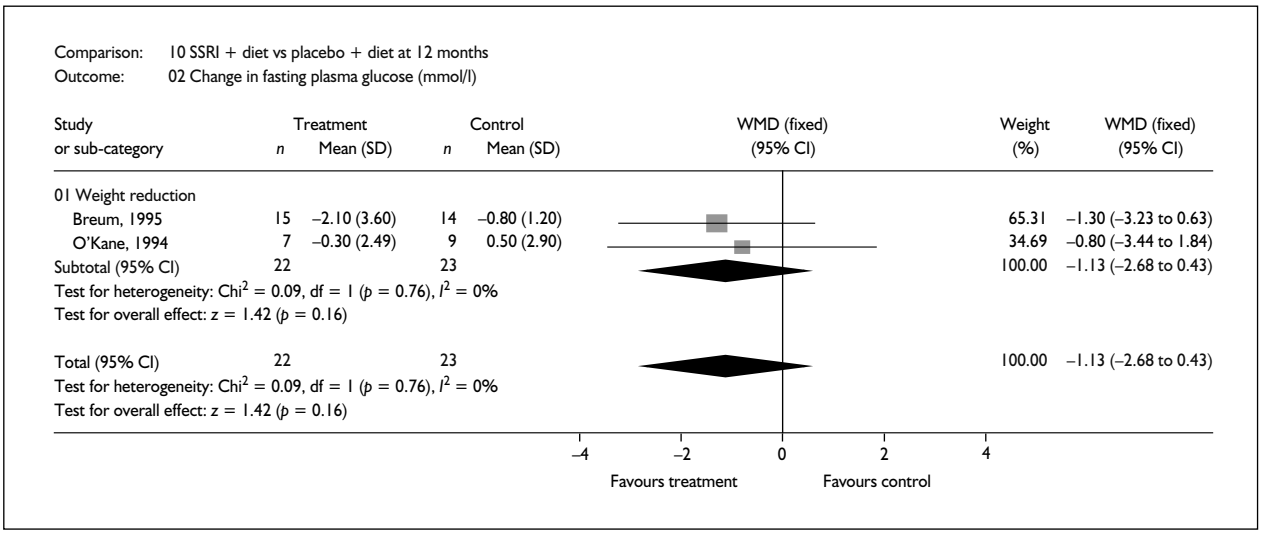


FIGURE 48

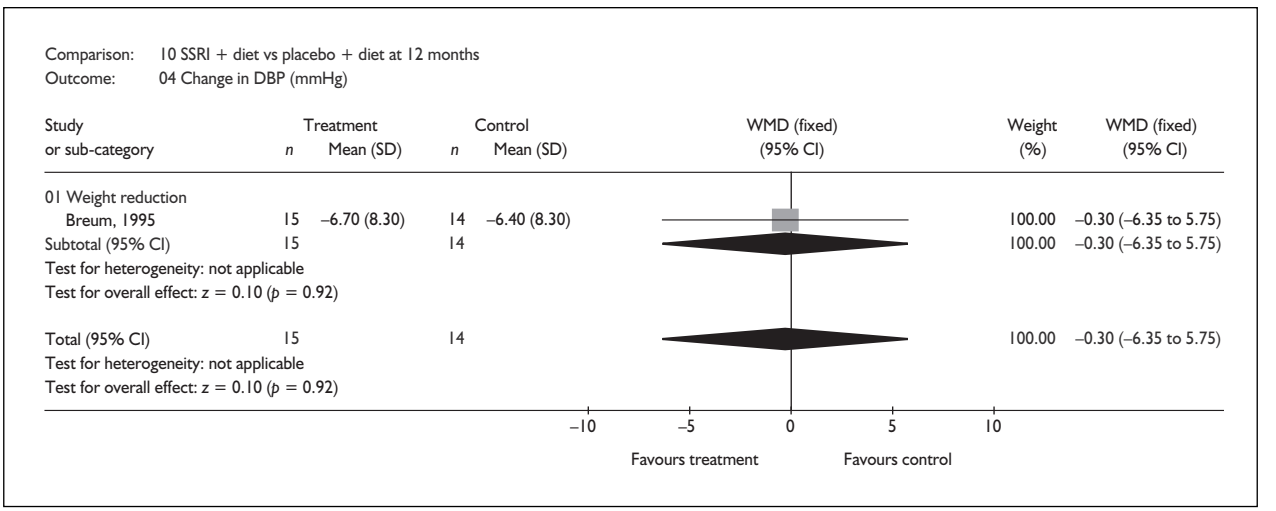


FIGURE 49

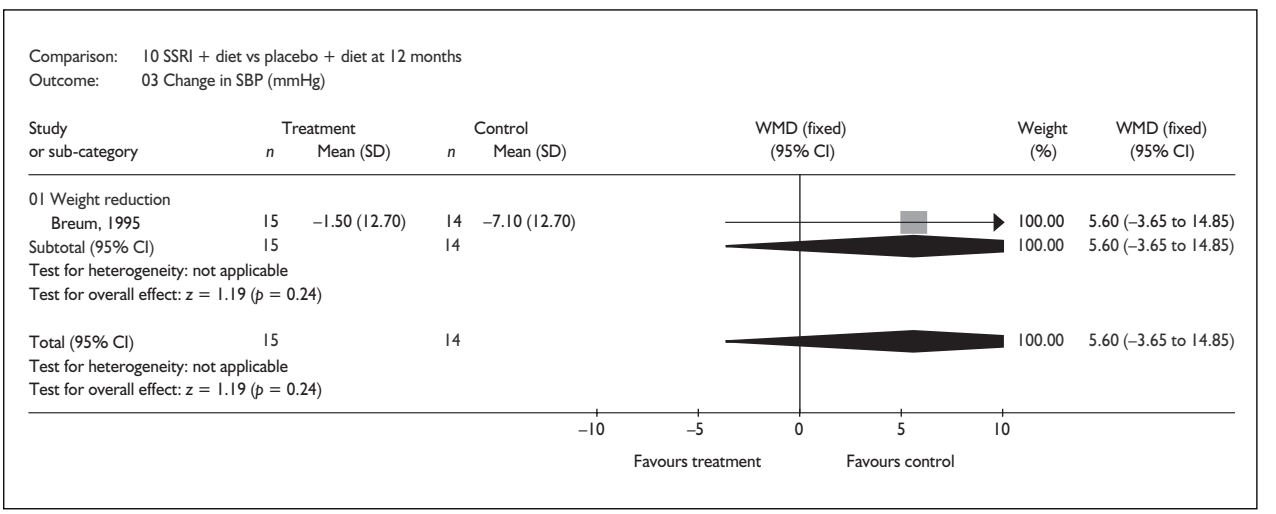


FIGURE 50

411 participants were randomised to receive dietary treatment and 343 metformin in addition. The UKPDS[85–93] provided change in weight at median follow-up periods of 5, 10 and 15 years. Data were provided for lipids, blood pressure, fasting plasma glucose and HbA_{1c} at 12 months and for total cholesterol, triglycerides, blood pressure and HbA_{1c} at 24 months. The UKPDS[85–93] provided data for fasting plasma glucose and HbA_{1c} at median follow-up periods of 5, 10 and 15 years.

The Biguanides and the Prevention of the Risk of Obesity (BIGPRO 1)[80–83] study recruited people with a high waist-to-hip ratio and the studies by Teupe and Bergis[84] and UKPDS[85–93] recruited people with type 2 diabetes. One study assessed participants using an ITT approach.[80–83] It was unclear whether an ITT approach had been used in the UKPDS.[85–93] The UKPDS included a 3-month dietary run-in period before randomisation. Dropouts in the study by Teupe and Bergis[84] were 46% at 2 years, and 29% in BIGPRO 1.[80–83] Data were only available for 5% of the control group and 6% of the metformin group at the median follow-up period of 15 years in UKPDS.[85–93]

The second year of the study by Teupe and Bergis[84] was categorised as a weight maintenance phase. Reported mean BMI in studies ranged from 30.5 kg/m^2 [84] to 33.3 kg/m^2.[80–83] All participants in each study received an equal number of appointments and participants in the active treatment groups received a maximum of 1700 mg metformin daily.

Review results

Metformin for weight reduction was associated with a WMD effect on weight at 12 months of –1.09 kg (95% CI –2.29 to 0.11 kg) and at 24 months of –0.50 kg (95% CI –4.02 to 3.02 kg) (*Figures 51 and 52*, 12.01). At a median of 5 years metformin was associated with a WMD weight change of –0.12 kg (95% CI –1.13 to 0.89 kg), at 10 years of –0.37 kg (95% CI –1.67 to 0.93 kg) and at 15 years of –2.71 kg (95% CI –6.98 to 1.56 kg) (*Figures 53–55*). The longer term data were only available for the UKPDS study.

Metformin had a beneficial effect on total cholesterol at 12 and 24 months (*Figures 56–61*) and on fasting plasma glucose at 12 months (*Figure 62*). At a median of 5 years metformin was associated with a WMD in fasting plasma glucose of –1.30 mmol/l (95% CI –1.91 to –0.69 mmol/l), 10 years of –0.34 mmol/l (95% CI –1.10 to 0.42 mmol/l) and 15 years of –1.51 mmol/l (95% CI –3.76 to 0.74 mmol/l) (*Figures 63–65*). The UKPDS[85–93] was associated with a WMD in HbA_{1c} at a median of 5 years of –1.08% (95% CI –1.50 to –0.66%), 10 years of –0.46% (95% CI –0.98 to 0.06%) and 15 years of –2.31% (95% CI –3.85 to –0.77%) (*Figures 66–70*).

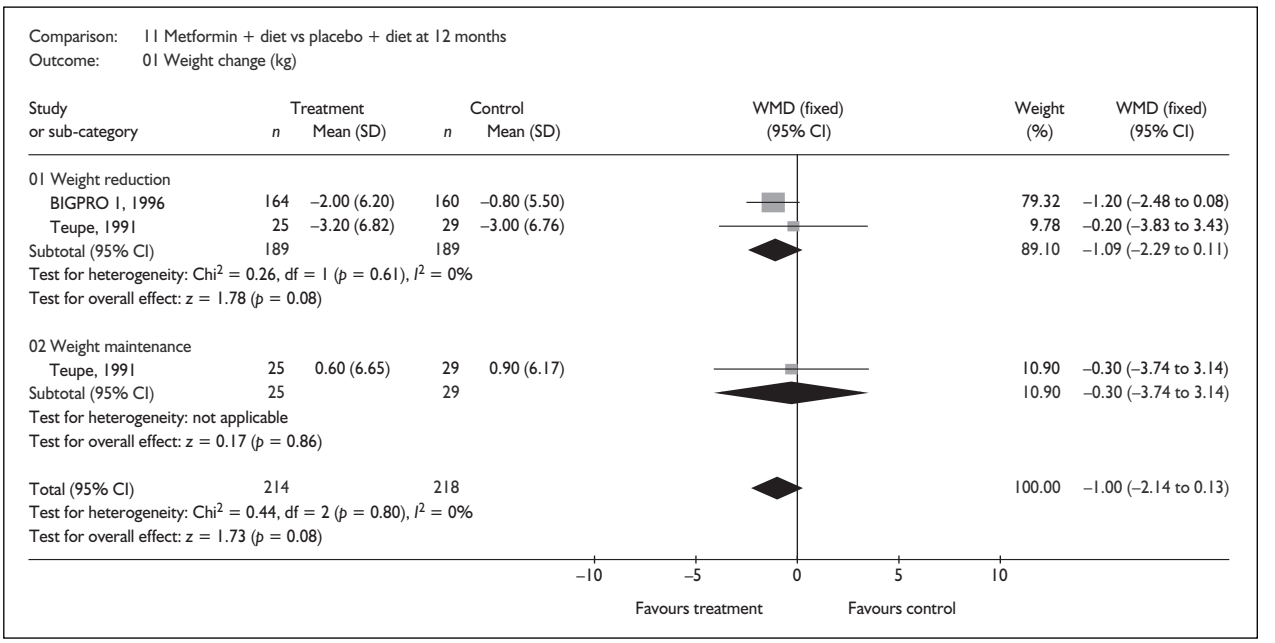


FIGURE 51

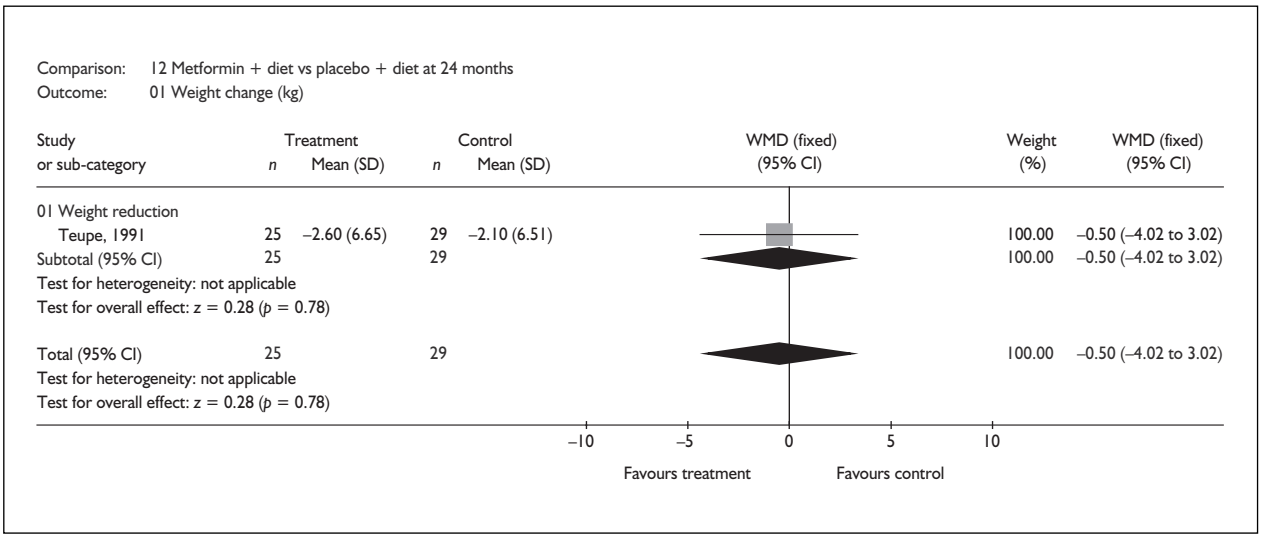


FIGURE 52

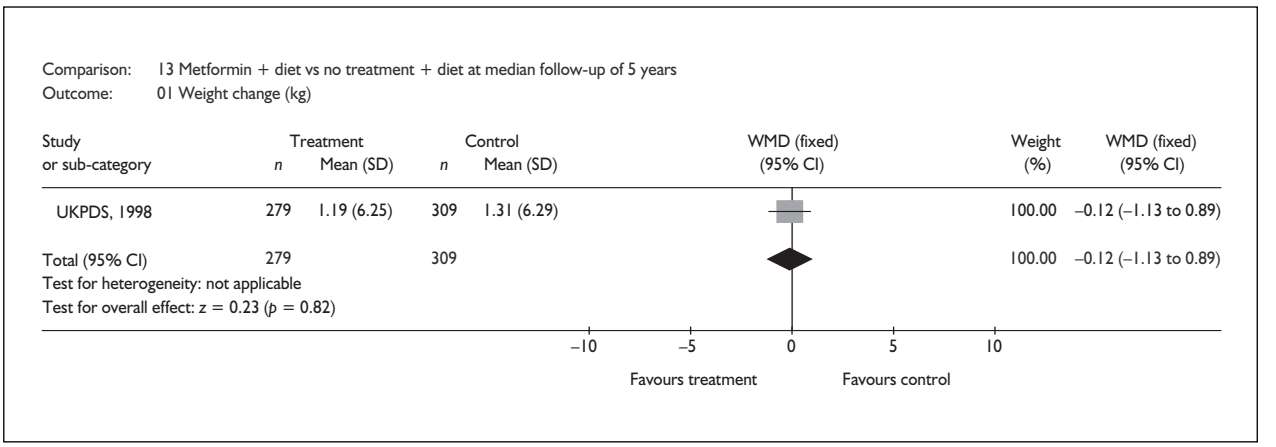


FIGURE 53

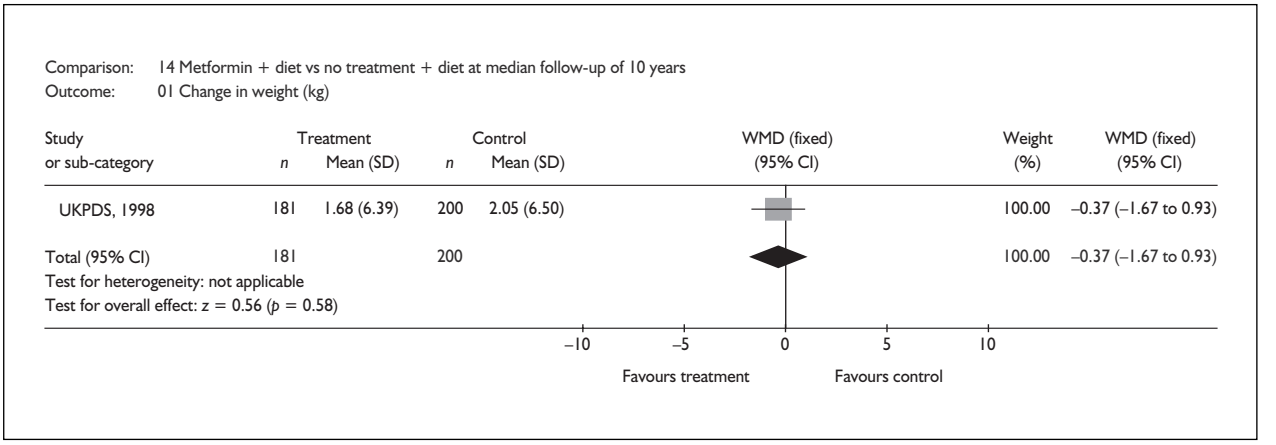


FIGURE 54

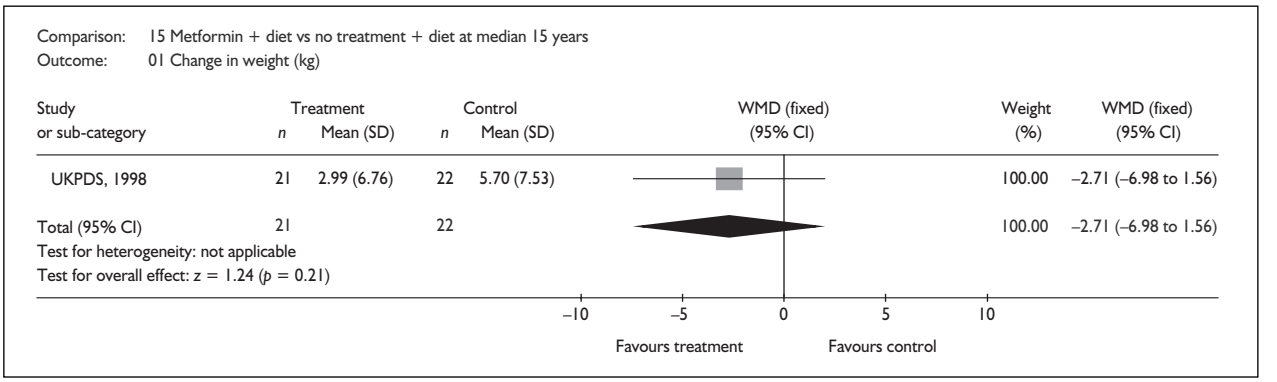


FIGURE 55

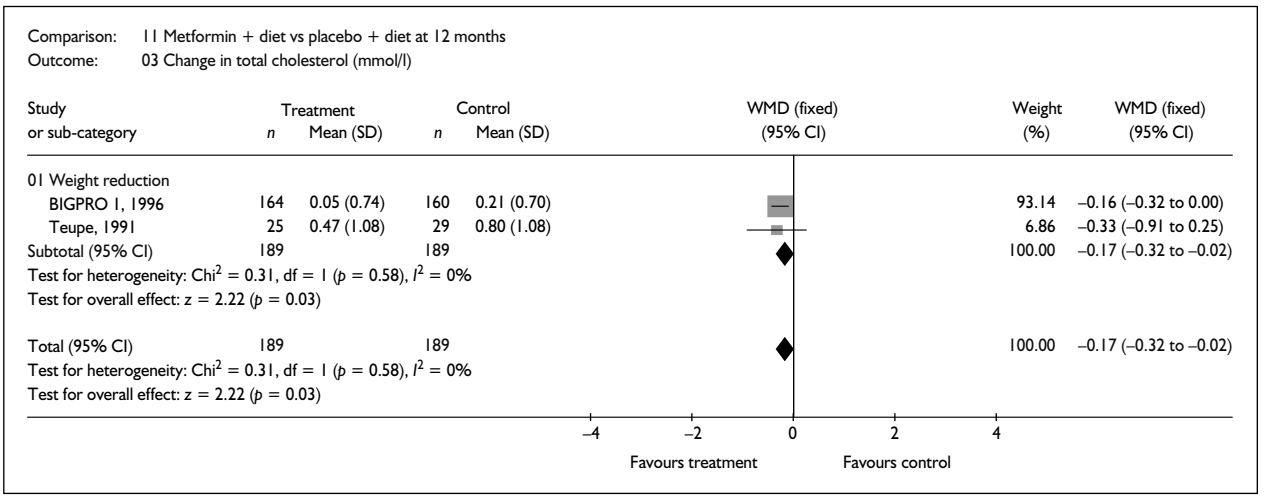


FIGURE 56

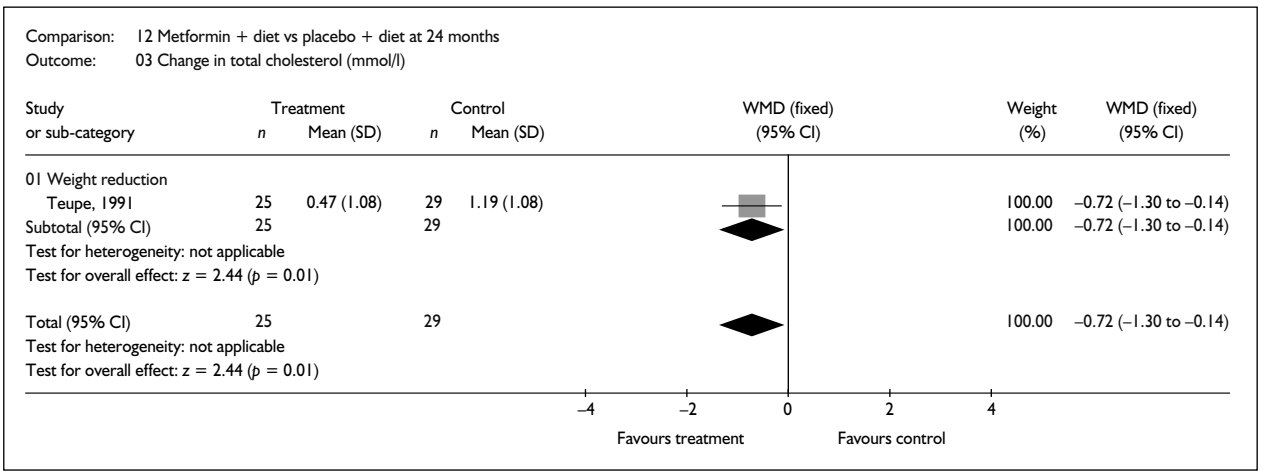


FIGURE 57

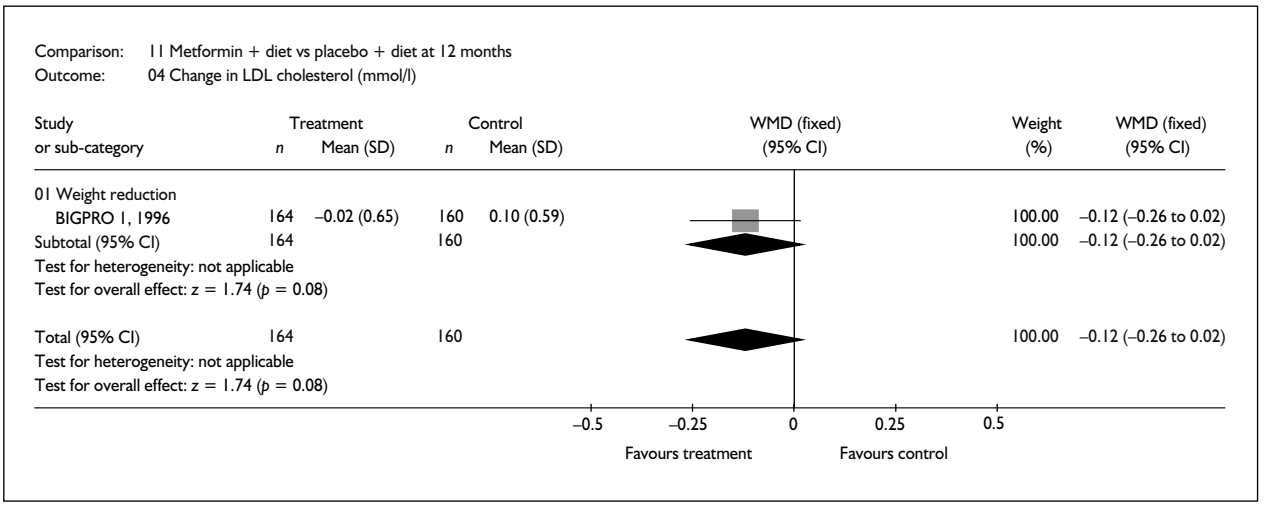


FIGURE 58

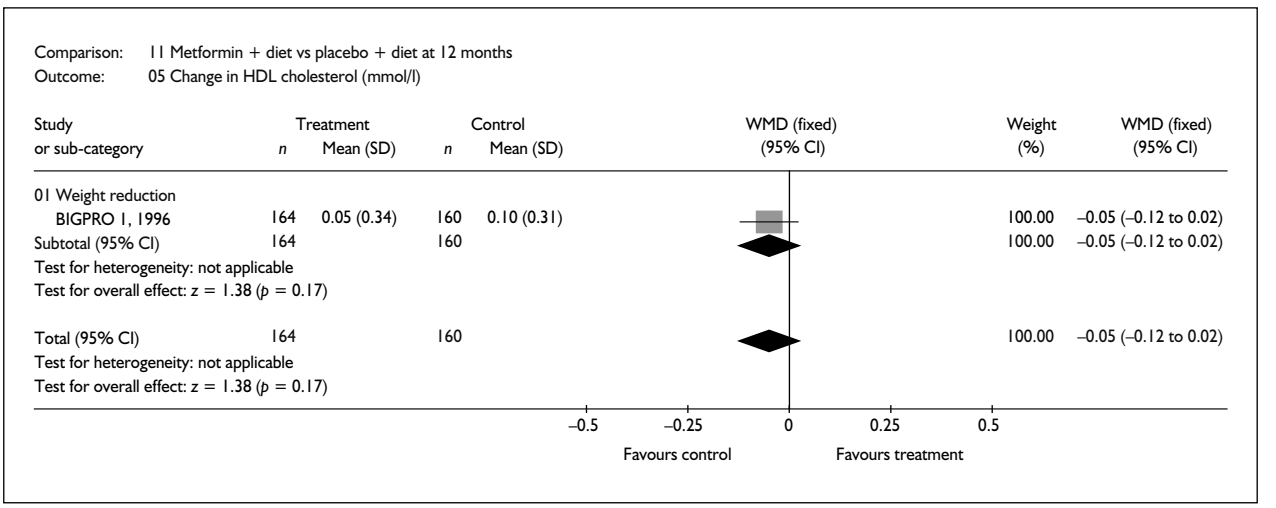


FIGURE 59

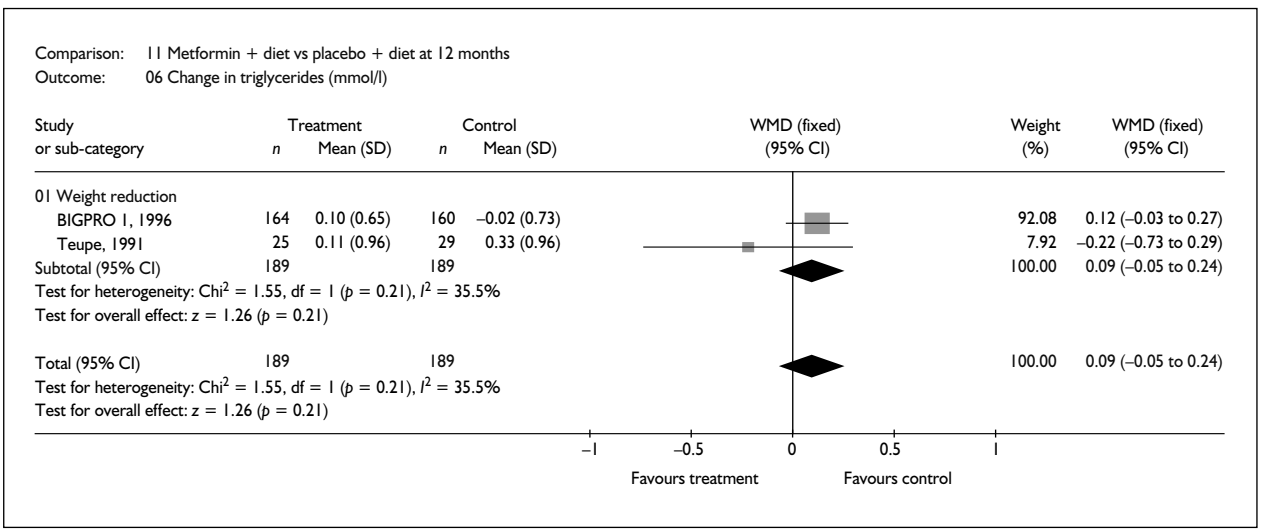


FIGURE 60

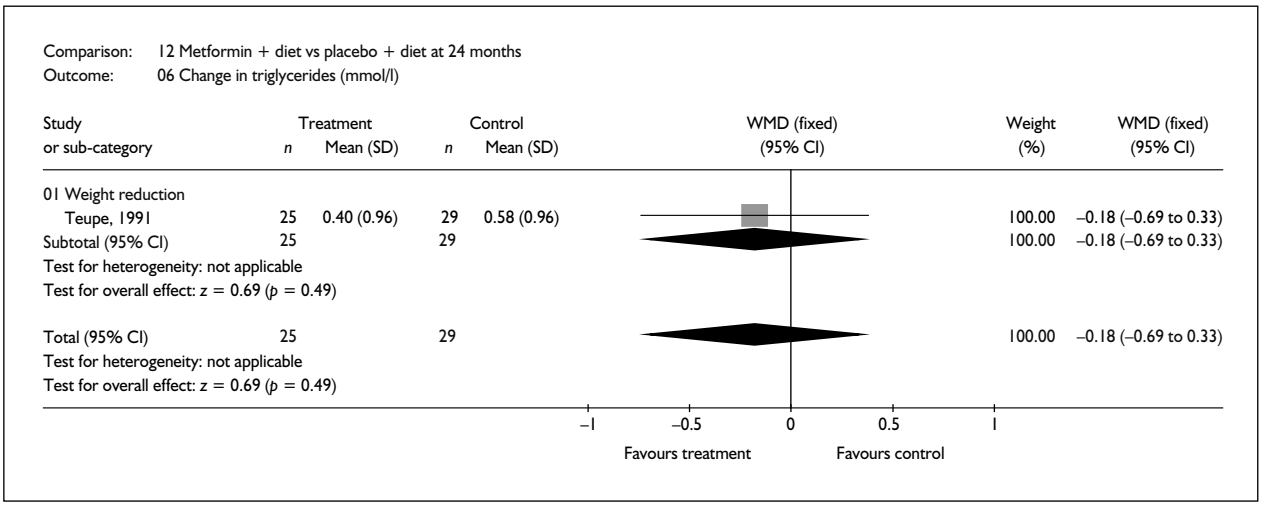


FIGURE 61

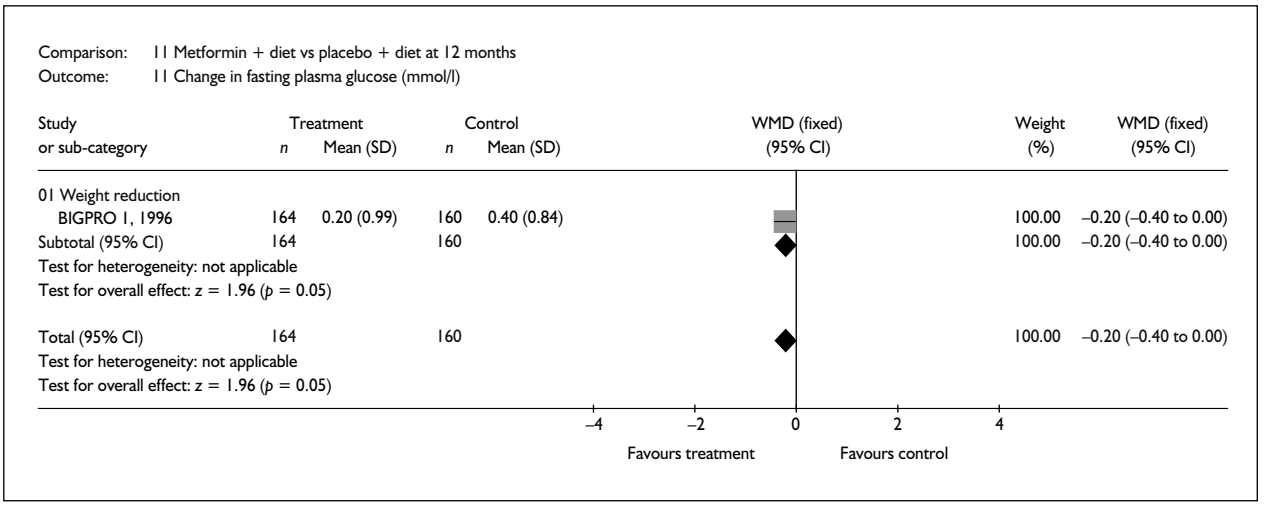


FIGURE 62

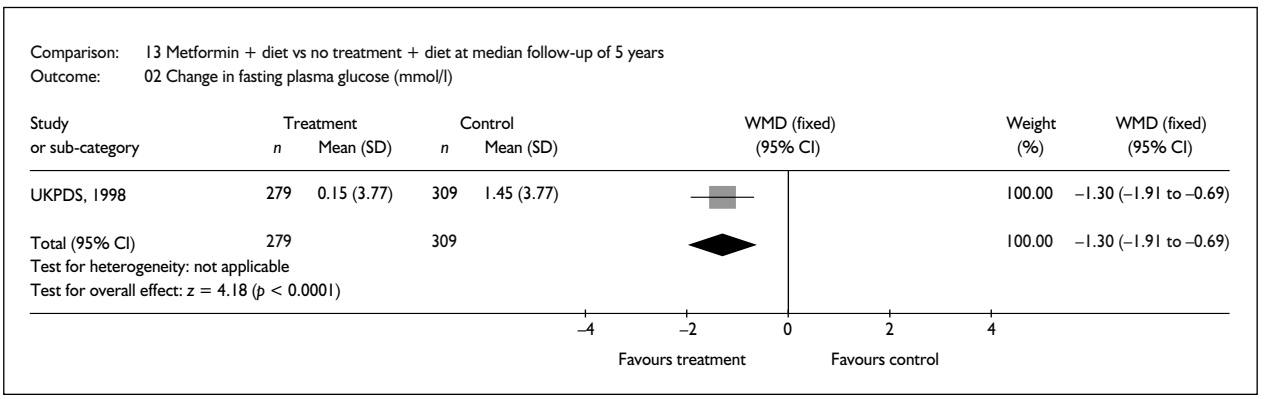


FIGURE 63

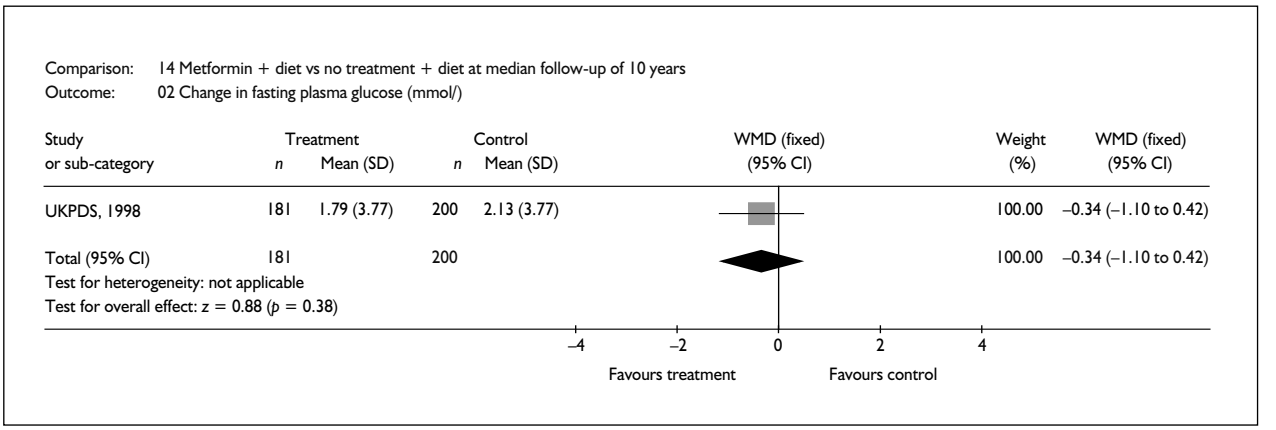


FIGURE 64

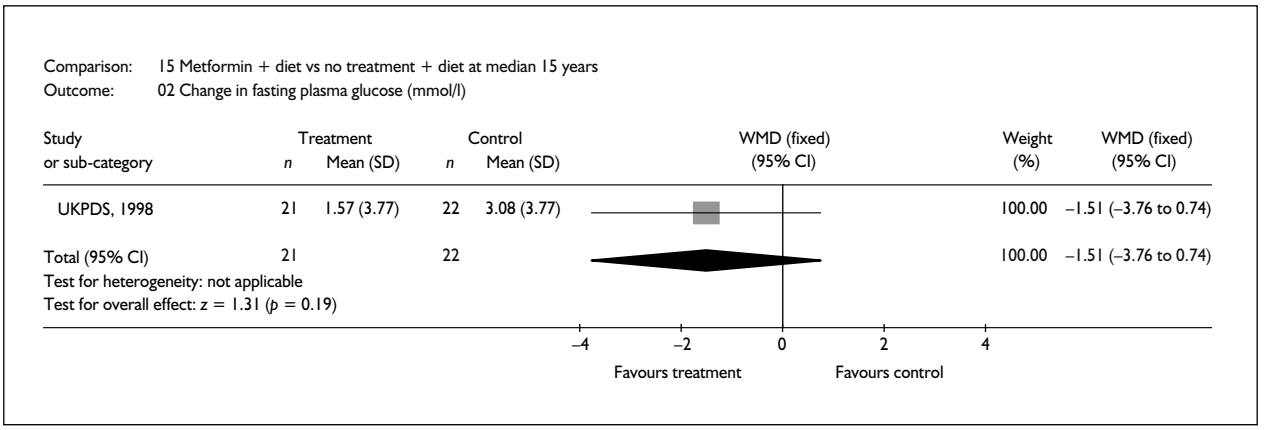


FIGURE 65

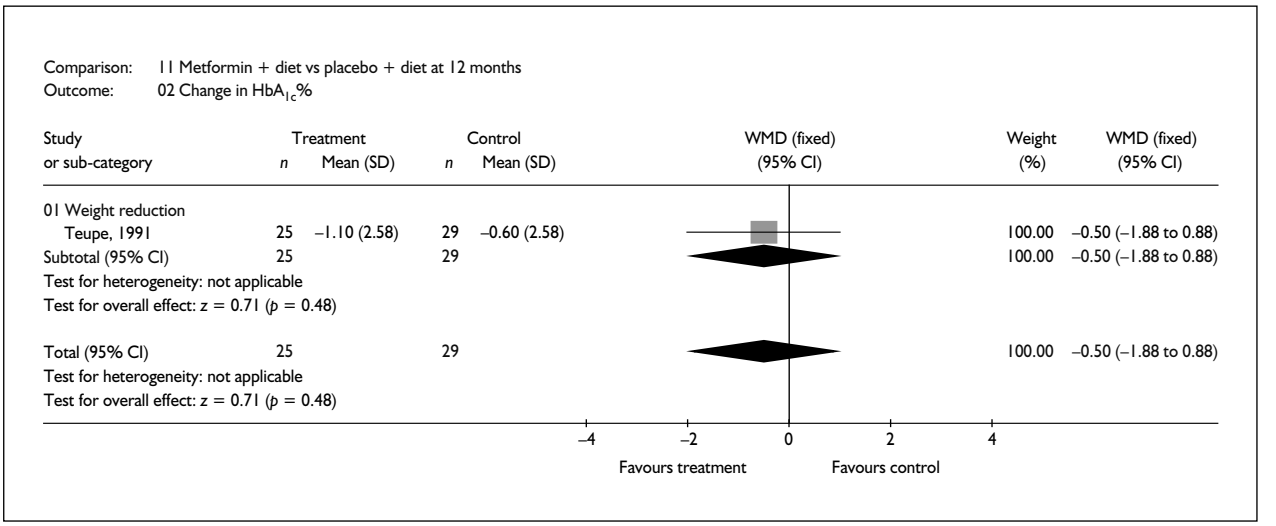


FIGURE 66

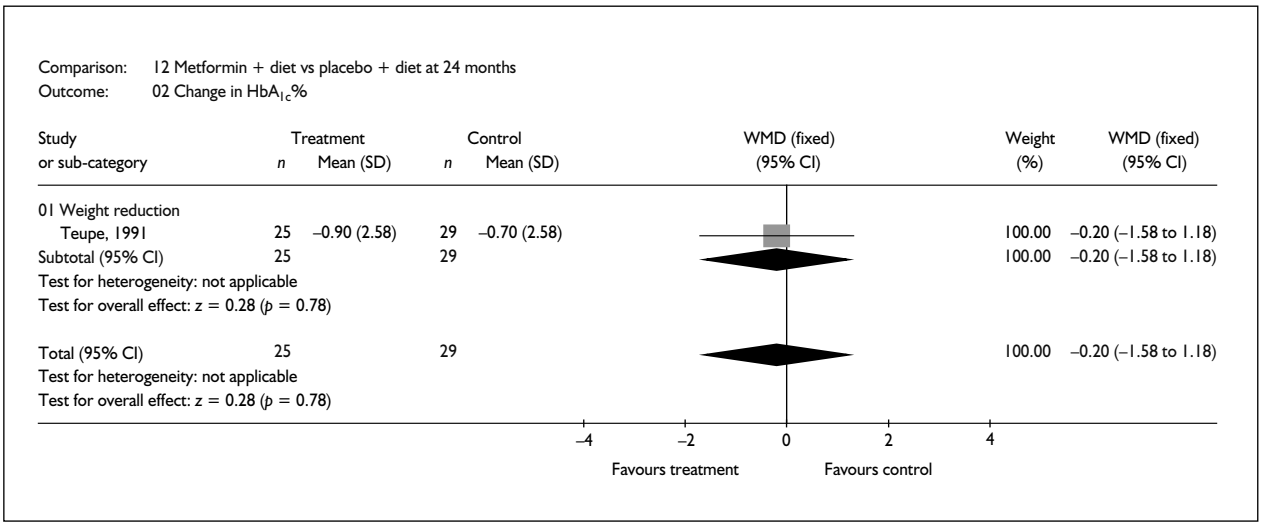


FIGURE 67

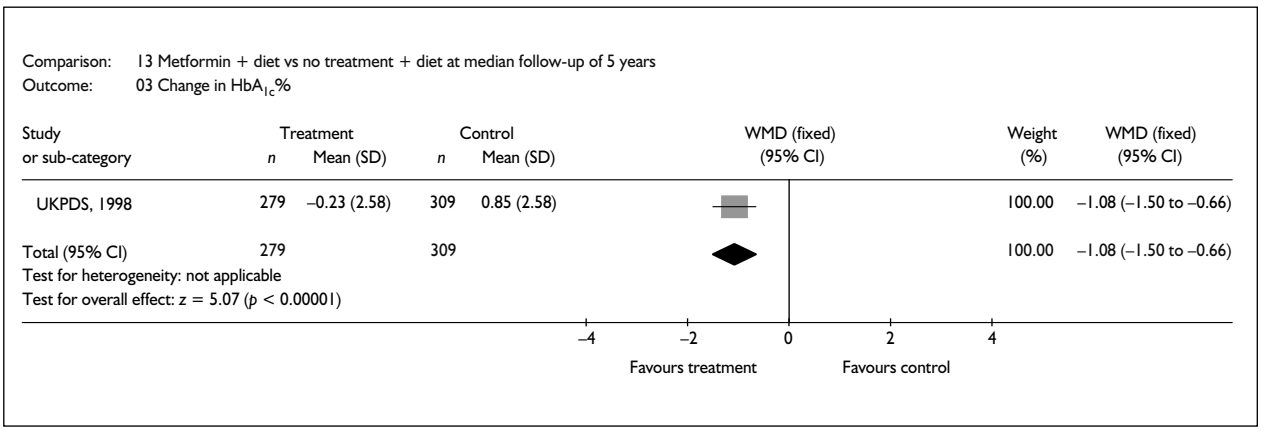


FIGURE 68

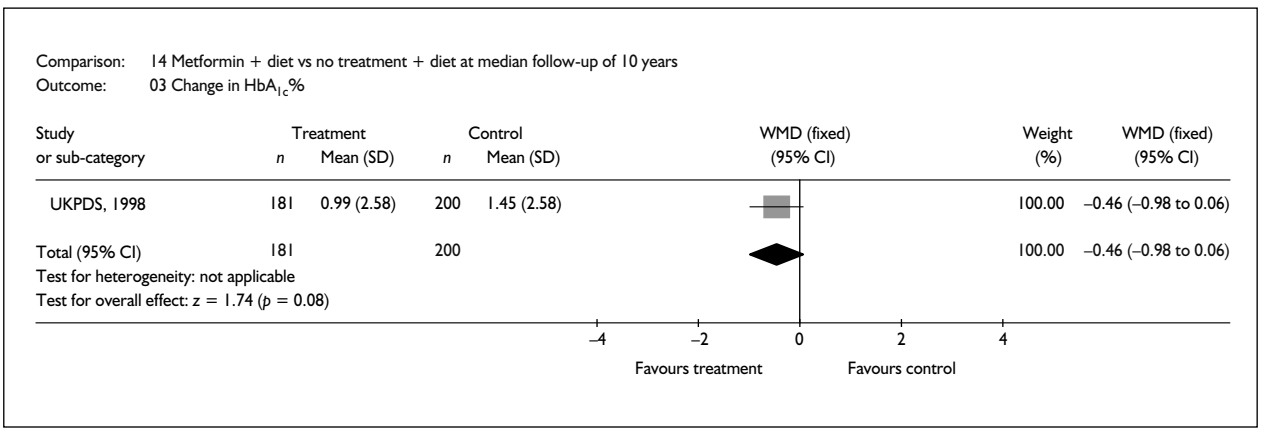


FIGURE 69

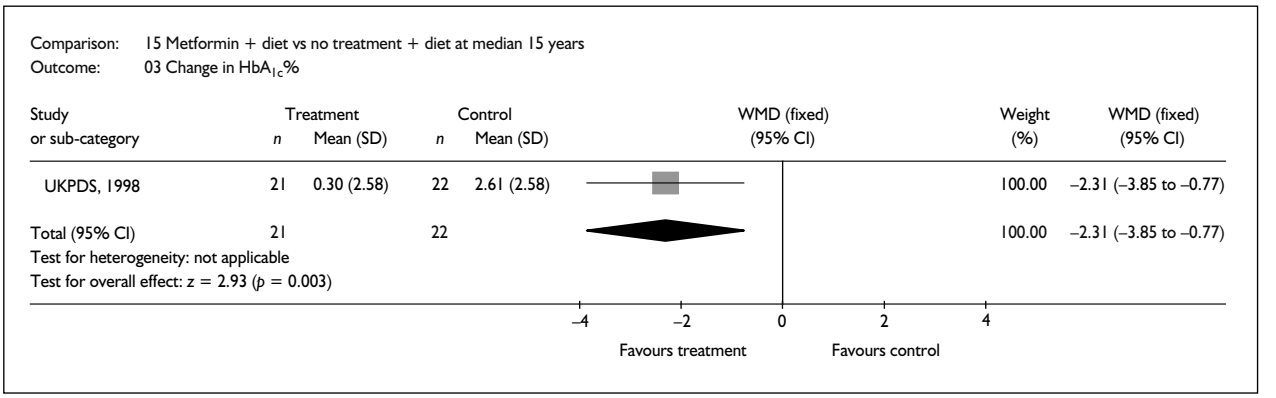


FIGURE 70

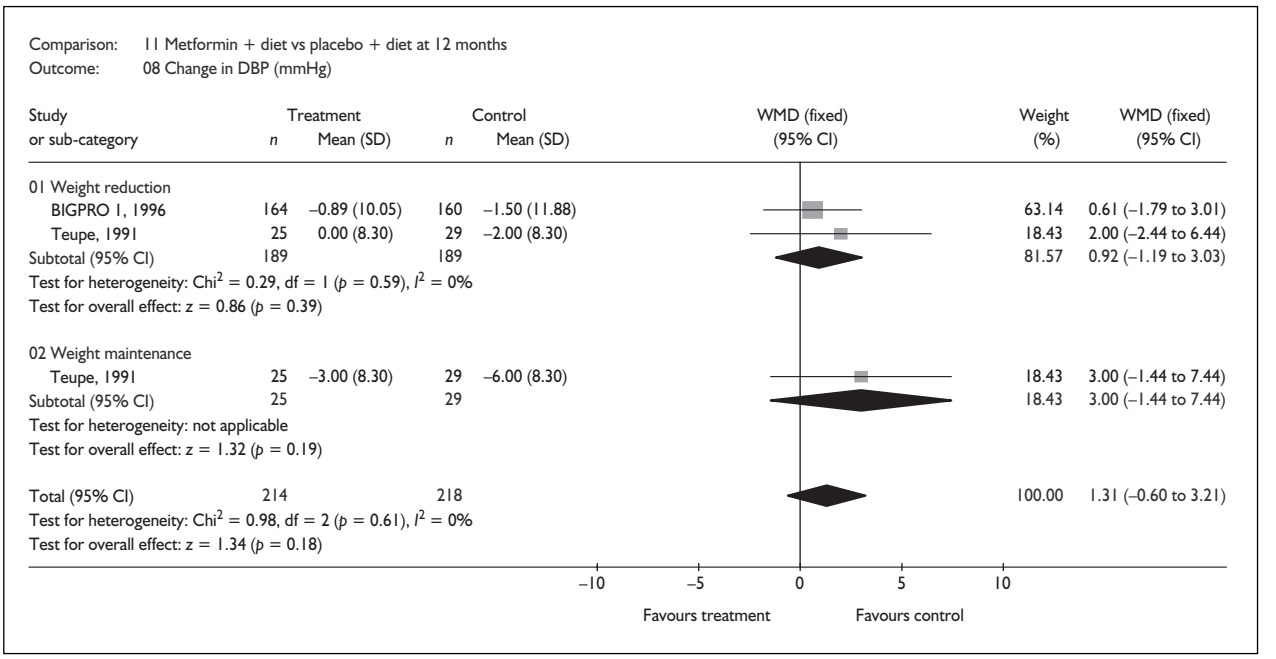


FIGURE 71

At 12 months the control arms were associated with greater reduction in SBP and DBP than the metformin arms and at 24 months this was statistically significant (*Figures 71–74*). The WMD effect on SBP at 24 months was 10.00 mmHg (95% CI 3.21 to 16.79 mmHg) and on DBP at 24 months was 5.00 mmHg (95% CI 0.56 to 9.44 mmHg). It should be noted these data at 24 months were derived from one study with small numbers of participants[84] and that the confidence intervals are wide.

Results for risk factor and weight changes for studies with diabetic participants only are shown in *Table 4*.

One death and no new cases of diabetes were reported in the metformin group of the BIGPRO 1 study[80–83] and five new cases of diabetes occurred in the placebo group (OR for developing diabetes 0.09, 95% CI 0.00 to 1.64) (*Figures 75 and 76*). Teupe and Bergis[84] reported one MI in the treatment group at 1 year (*Figure 77*). Diarrhoea was more commonly reported for participants on metformin in BIGPRO 1[80–83] and the study by Teupe and Bergis.[84]

The UKPDS[85–93] reported outcomes of total mortality, and deaths from MI, stroke and all-cause cancers at a median period of 10 years (*Figures 78–81*). For all-cause mortality the OR was 0.62 (95% CI 0.42 to 0.91) in favour of metformin,

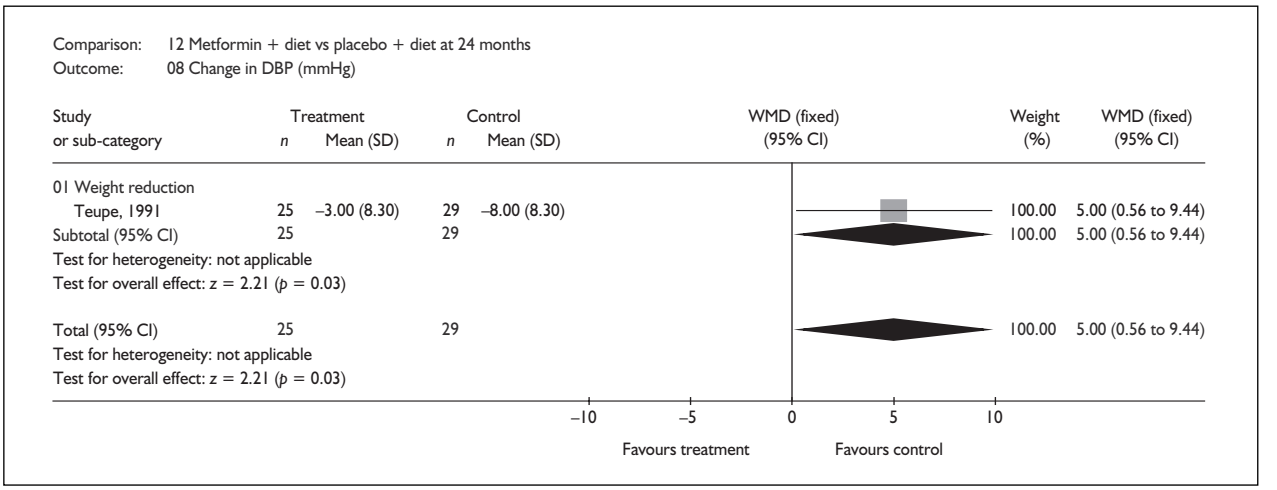


FIGURE 72

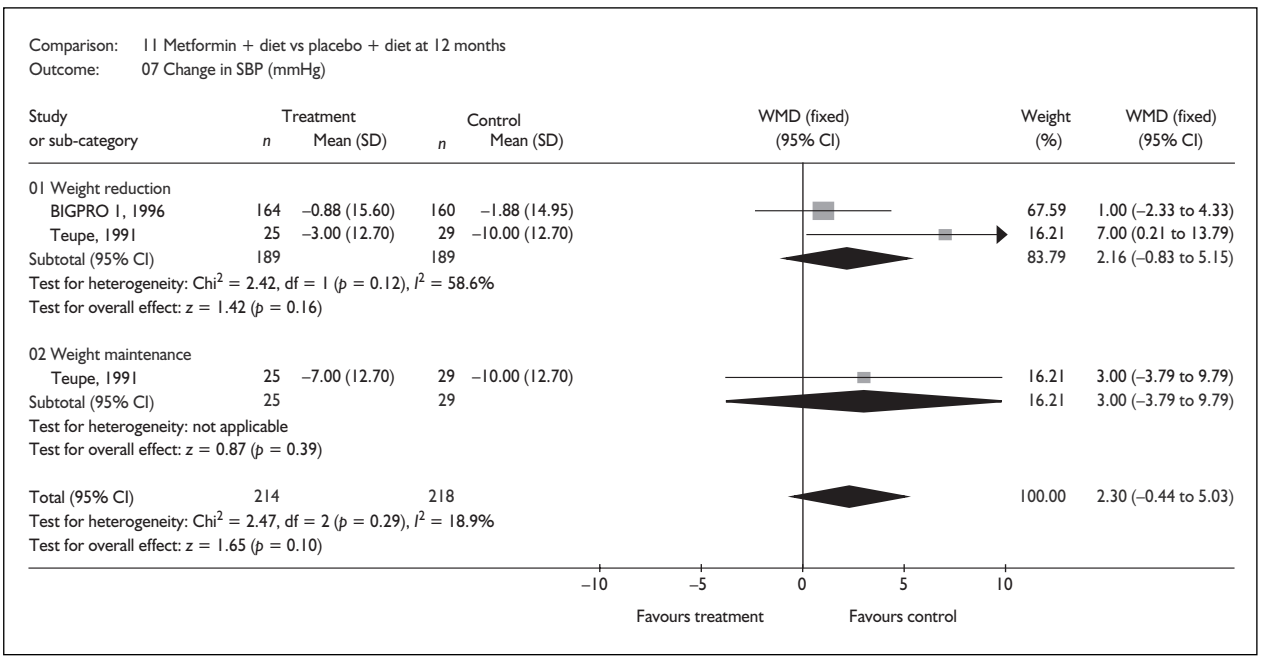


FIGURE 73

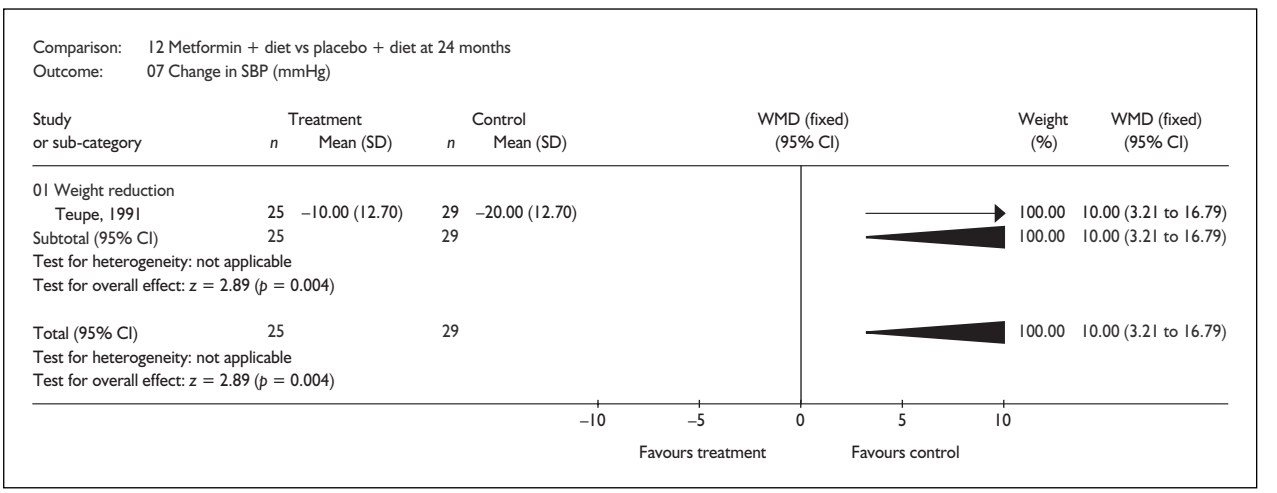


FIGURE 74

TABLE 4 *Effects of metformin and diet versus no treatment and diet on weight and risk factors in people with type 2 diabetes*

	Weight (kg)	Total cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)	Fasting plasma glucose (mmol/l)	HbA_{1c}%
12 months	–0.20	–0.33	–0.22	7.00	2.00		–0.50
WMD (95% CI)	(–3.83 to 3.43)	(–0.91 to 0.25)	(–0.73 to 0.29)	(0.21 to 13.79)	(–2.44 to 6.44)		(–1.88 to 0.88)
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1		*n* = 1
24 months	–0.50	–0.72	–0.18	10.00	5.00		–0.20
WMD (95% CI)	(–4.02 to 3.02)	(–1.30 to –0.14)	(–0.69 to 0.33)	(3.21 to 16.79)	(0.56 to 9.44)		(–1.58 to 1.18)
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1		*n* = 1
60 months	–0.12					–1.30	–1.08
WMD (95% CI)	(–1.13 to 0.89)					(–1.91 to –0.69)	(–1.50 to –0.66)
No. of studies	*n* = 1					*n* = 1	*n* = 1
120 months	–0.37					–0.34	–0.46
WMD (95% CI)	(–1.67 to 0.93)					(–1.10 to 0.42)	(–0.98 to 0.06)
No. of studies	*n* = 1					*n* = 1	*n* = 1
180 months	–2.71					–1.51	–2.31
WMD (95% CI)	(–6.98 to 1.56)					(–3.76 to 0.74)	(–3.85 to –0.77)
No. of studies	*n* = 1					*n* = 1	*n* = 1

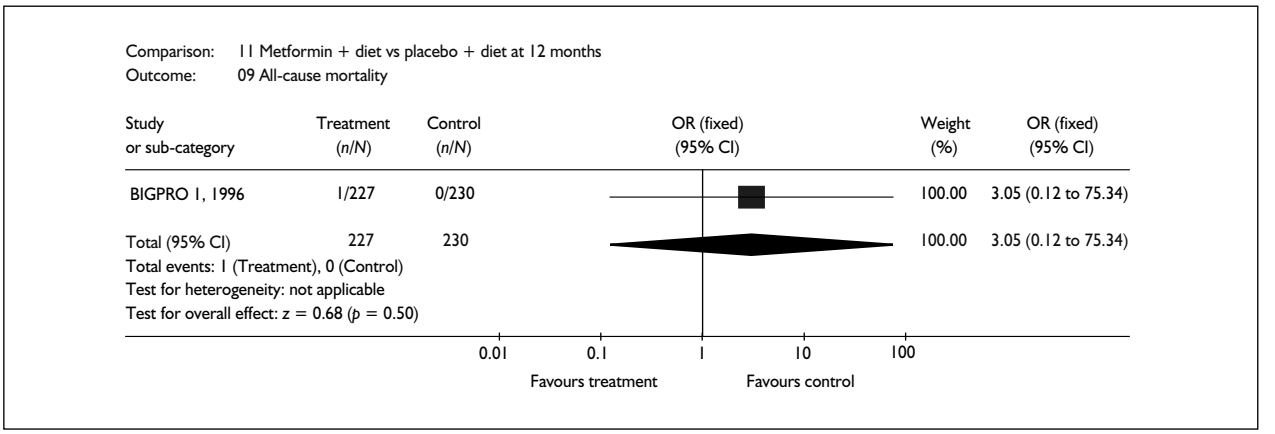


FIGURE 75

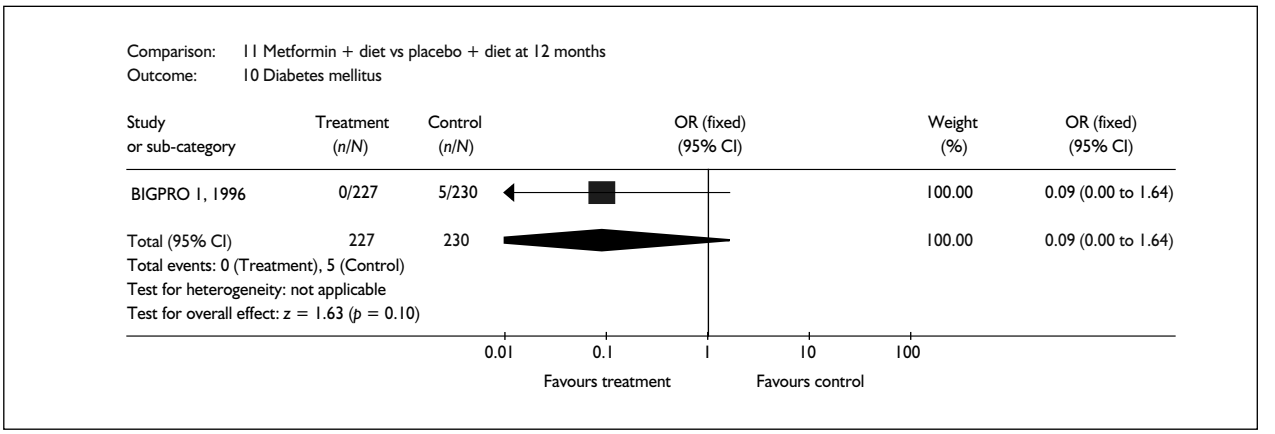


FIGURE 76

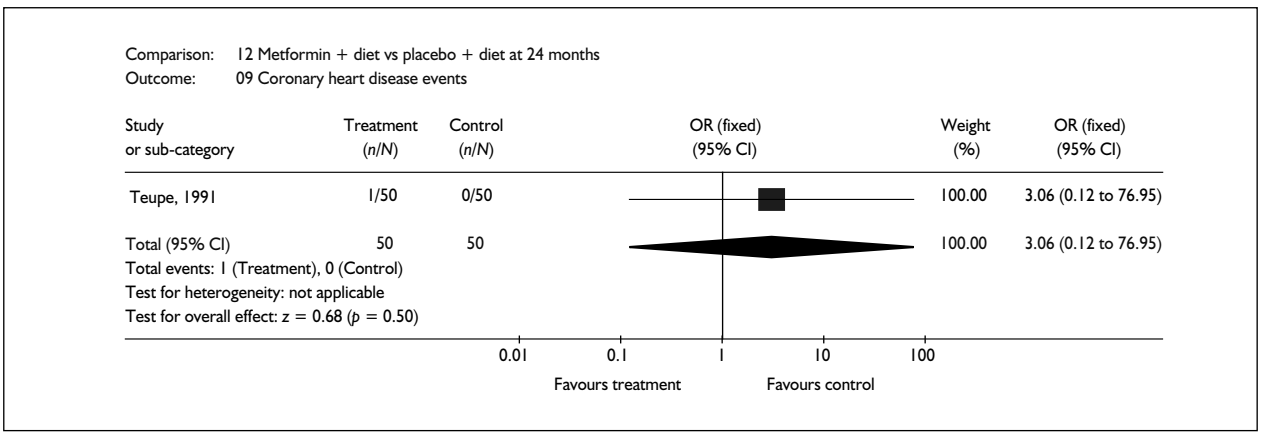


FIGURE 77

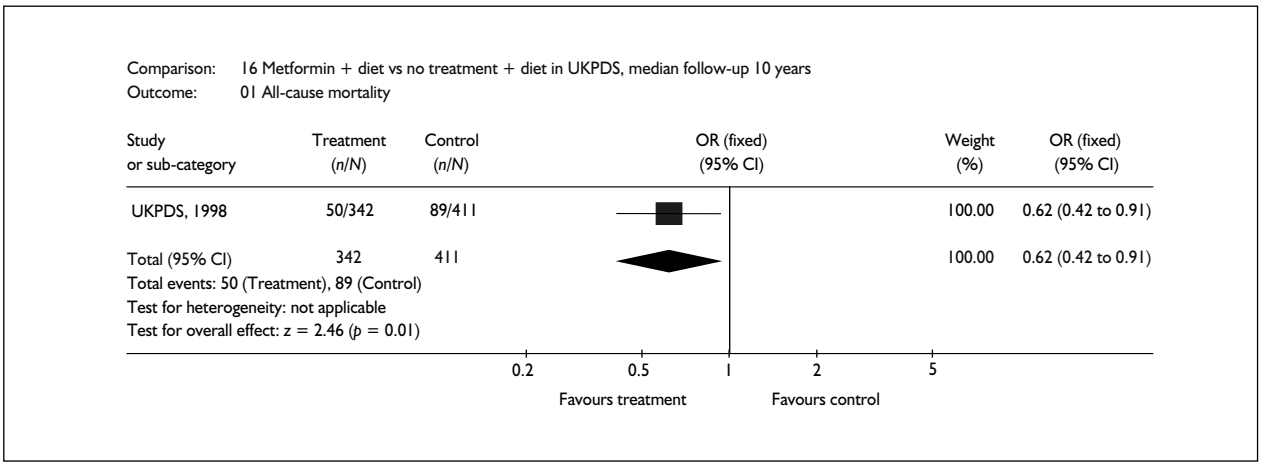


FIGURE 78

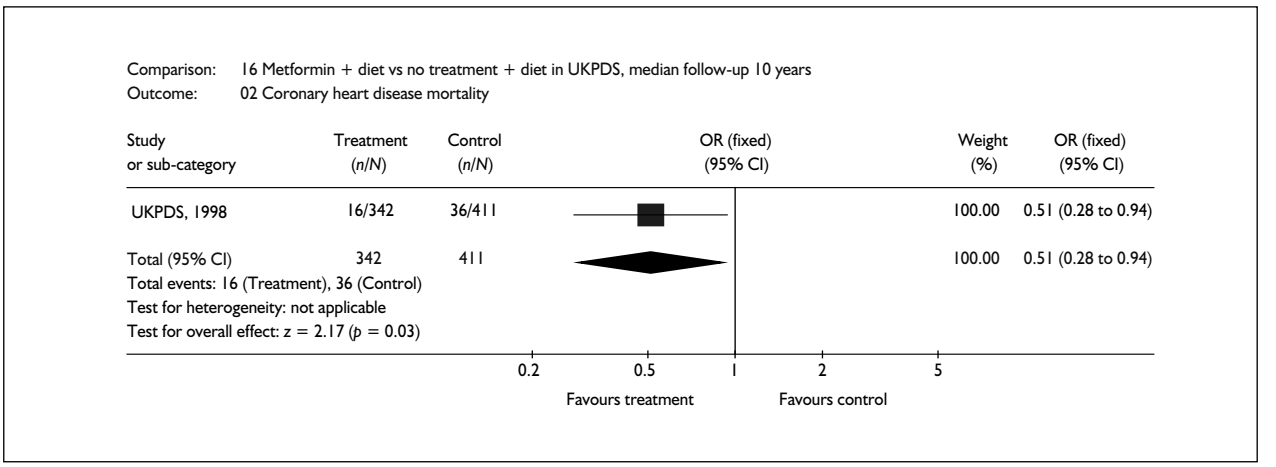


FIGURE 79

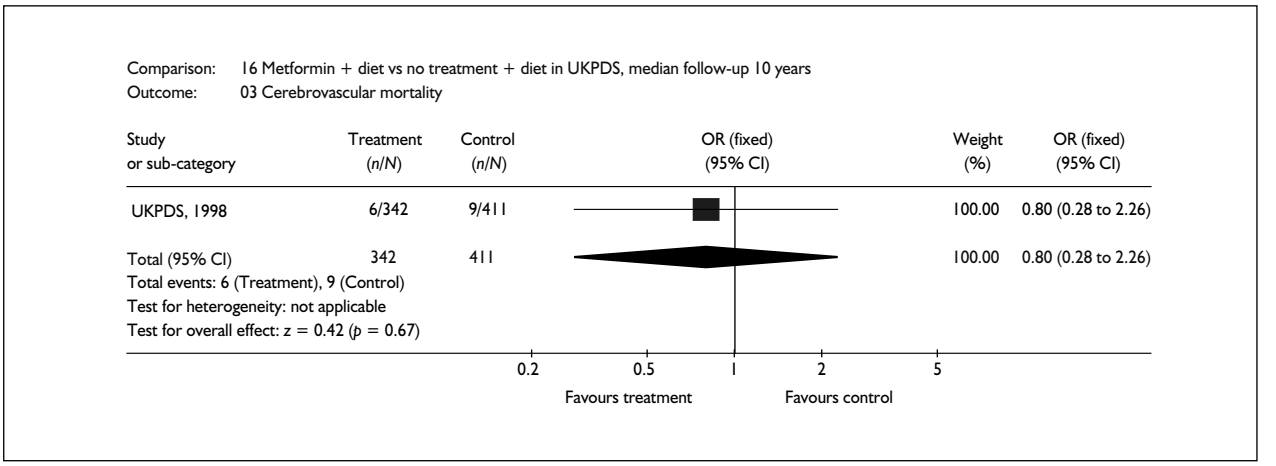


FIGURE 80

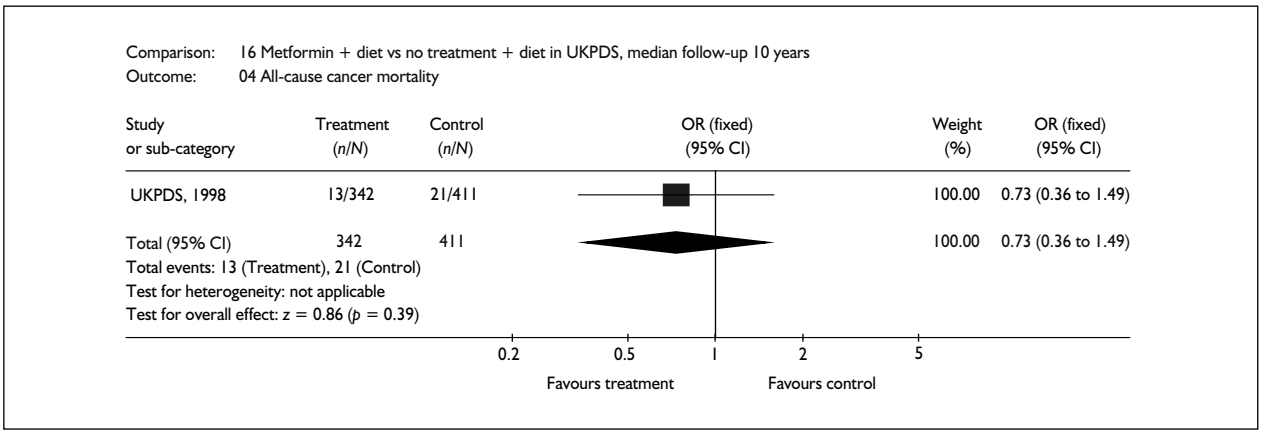


FIGURE 81

for MI mortality the OR was 0.51 (95% CI 0.28 to 0.94). For cerebrovascular mortality the OR was 0.80 (95% CI 0.28 to 2.26) and for all-cause cancer mortality it was 0.73 (95% CI 0.36 to 1.49).

Effects of acarbose and diet versus placebo and diet in an obese population with type 2 diabetes

Description of study

One RCT provided change in weight, HbA_{1c} and fasting plasma glucose at 12 months[94–98] for acarbose up to 600 mg/day versus placebo. The study was conducted in an obese population with type 2 diabetes. Mean body weight was 84.5 kg in the acarbose group and 81.1 kg in the placebo group. All participants received the same number of contact visits. Data for the risk factors, but not weight, were presented as a mean of 6, 9 and 12 months and for subgroups only of participants receiving either diet alone, metformin, sulfonylurea or insulin treatment for diabetes.

Review results

Over 12 months acarbose was associated with a WMD weight change of –0.79 kg (95% CI –1.53 to –0.05 kg) (*Figure 82*). Over 12 months acarbose was associated with a WMD change in HbA_{1c} of –0.76% (95% CI –1.05 to –0.47%) and in fasting plasma glucose of –1.36 mmol/l (95% CI –1.96 to –0.75 mmol/l) (*Figures 83 and 84*). The authors reported that lipids did not change in participants who received acarbose, but the data were not provided.

Acarbose led to significant decreases in the doses of metformin, sulfonylurea and insulin prescribed. Acarbose was more frequently associated with gastrointestinal adverse effects, classified as mild. Four participants on insulin (one receiving acarbose and three receiving insulin) required correction of severe hypoglycaemia.

Effects of 600 kcal/day deficit or low-fat diet versus control

Description of studies

Twelve RCTs, where individuals were individually randomised, provided change in weight at 12 months or longer.[99–145] One cluster RCT, with randomisation according to treating physician, provided change in weight at 12 months.[146] Two studies provided change in weight at 18 months,[107,130–135] three studies at 24 months,[107,128–135] one study at 30 months,[107] two studies at 36 months[108–114,128,129] and one study at 60 months.[128,129]

Only two studies assessed participants using an ITT approach.[108–114,122–126] The study by Swinburn[128,129] included one worksite, where all six participants were assigned to the active treatment.

Data were provided for lipids, blood pressure, HbA_{1c} and fasting plasma glucose at 12 months, for fasting plasma glucose at 24, 36 and 60 months,[128,129] and for blood pressure at 36 months.[108–114]

Five studies recruited people with hypertension.[99–103,107,127,130–135,146] One study recruited people with 'high normal' blood pressure,[108–114] one study recruited people with glucose intolerance, which included some people with diabetes,[128,129] and one study recruited people with type 2 diabetes.[127] Hankey and colleagues[105,106] evaluated the diet in people after MI, who all received 12 exercise sessions. Both arms of the Trial of Antihypertensive Interventions and Management (TAIM) study[130–135] received placebo antihypertensive medication.

Three studies recruited men only.[104,122–126,136–141] Reported mean BMI ranged from 27.9 kg/m^2 [142–145]

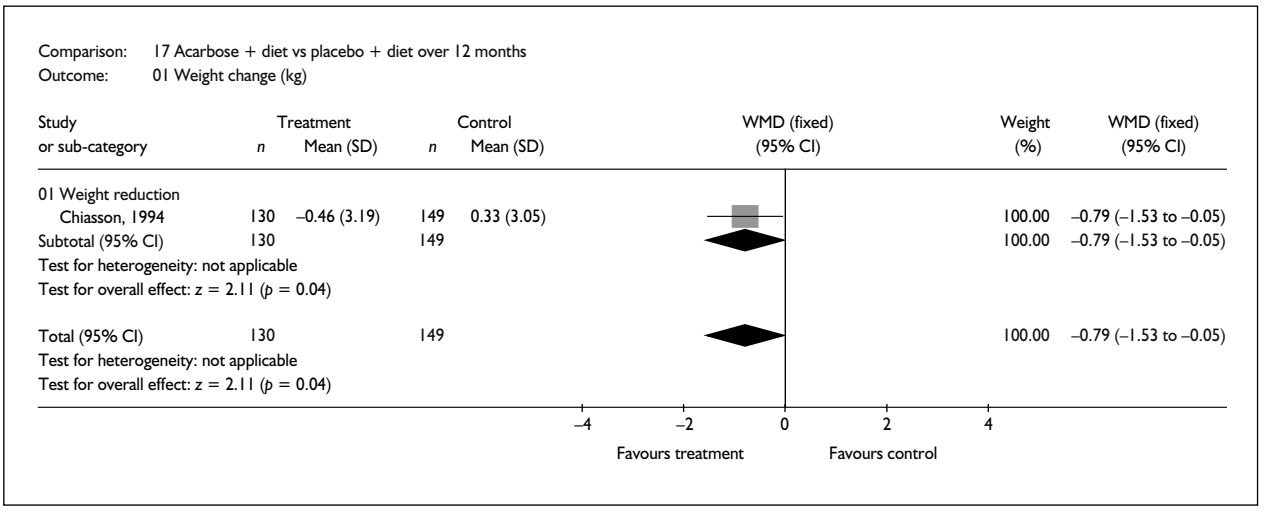


FIGURE 82

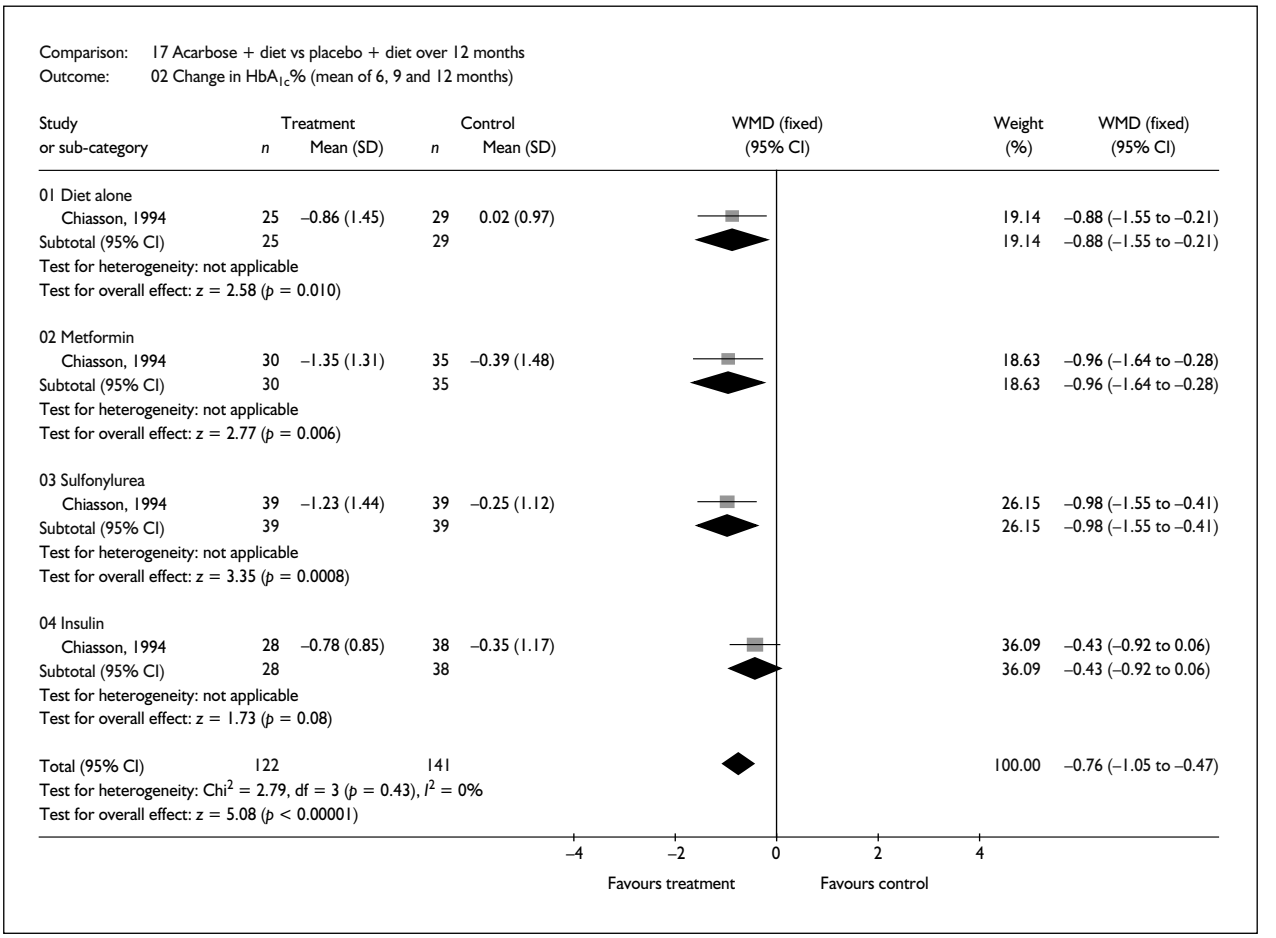


FIGURE 83

to 34.0 kg/m^2.[107,146] Reported mean body weight ranged from 85.5 kg[127] to 95.4 kg.[136–141] Dropouts at 1 year ranged from none[146] to 45% in one group.[128,129]

Review results

The 600 kcal/day deficit or low-fat diets were associated with an overall WMD weight change at 12 months of –5.31 kg (95% CI –5.86 to –4.77 kg) (*Figure 85*). There was evidence of statistical

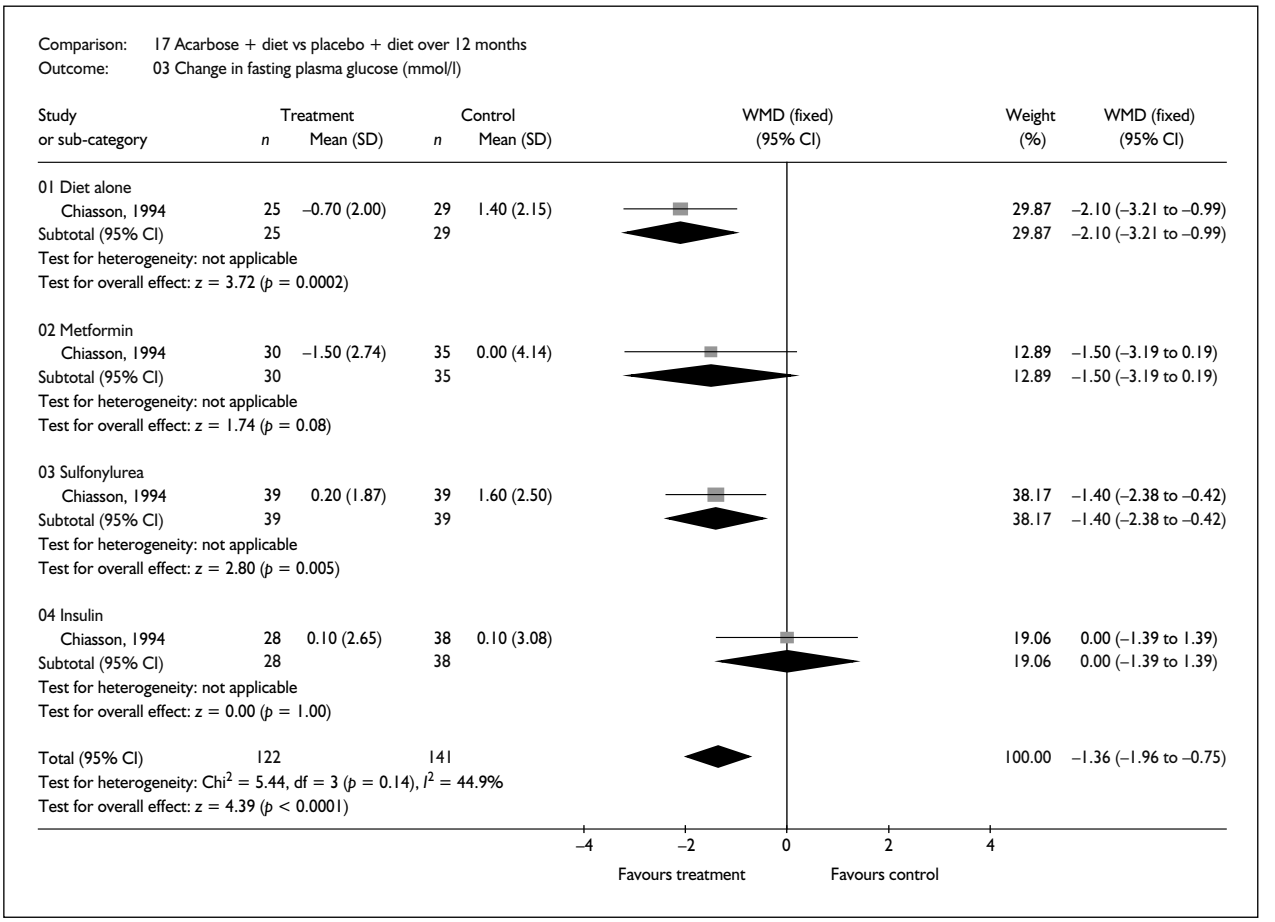


FIGURE 84

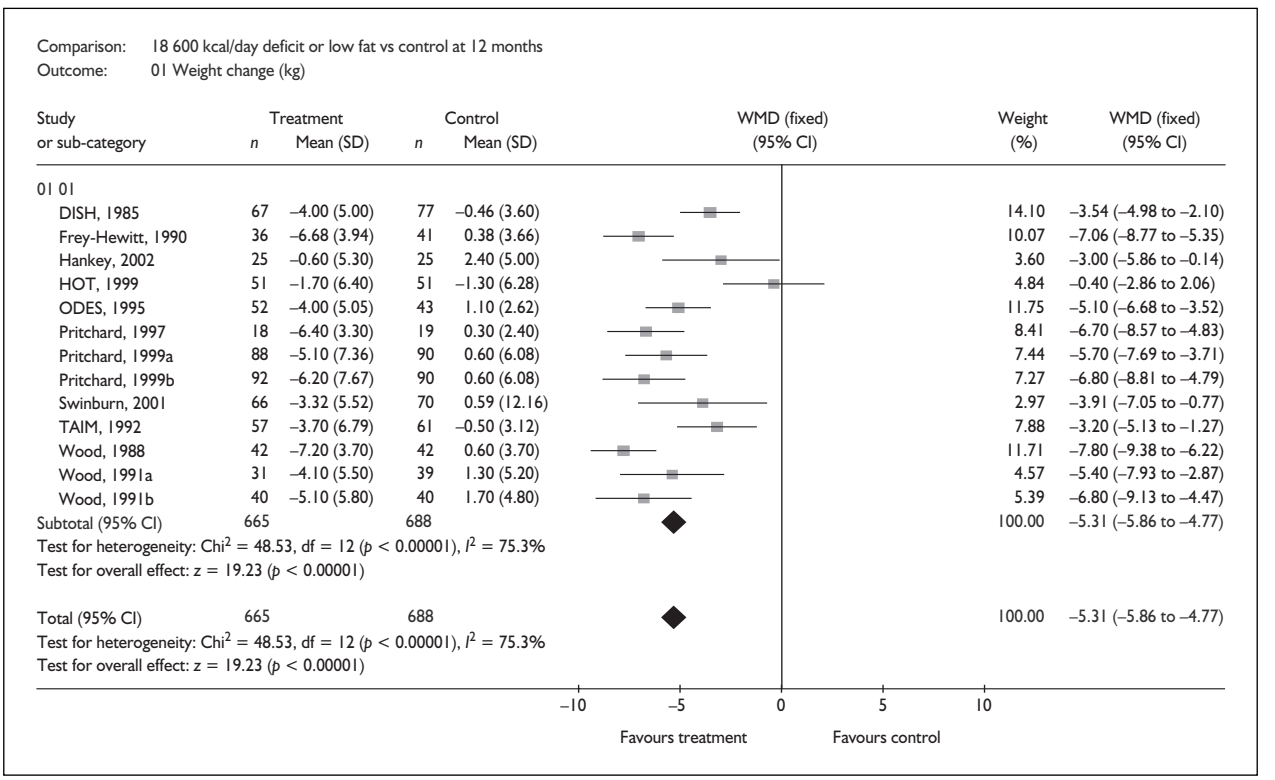


FIGURE 85

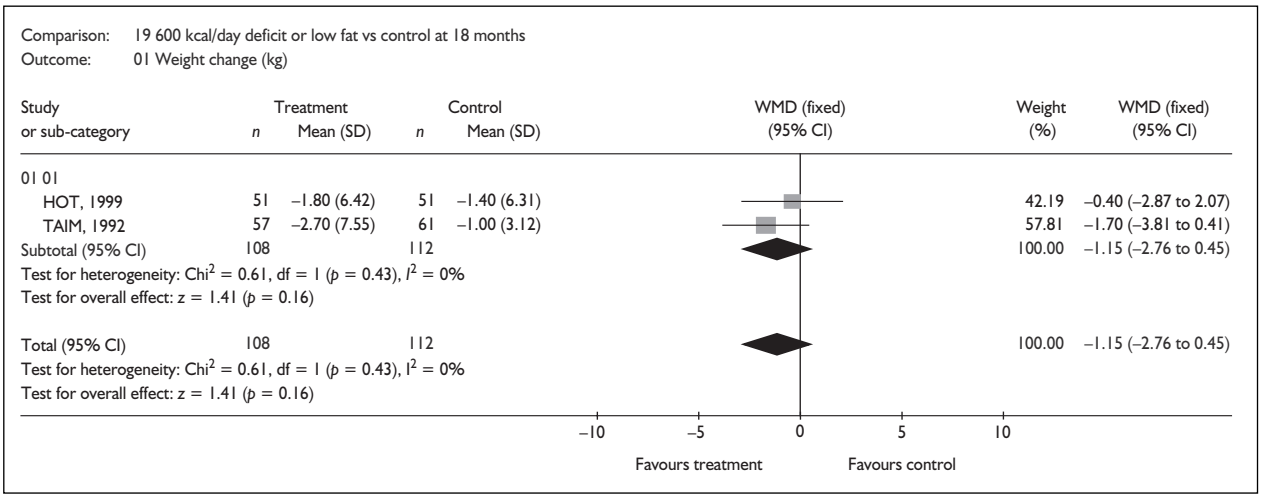


FIGURE 86

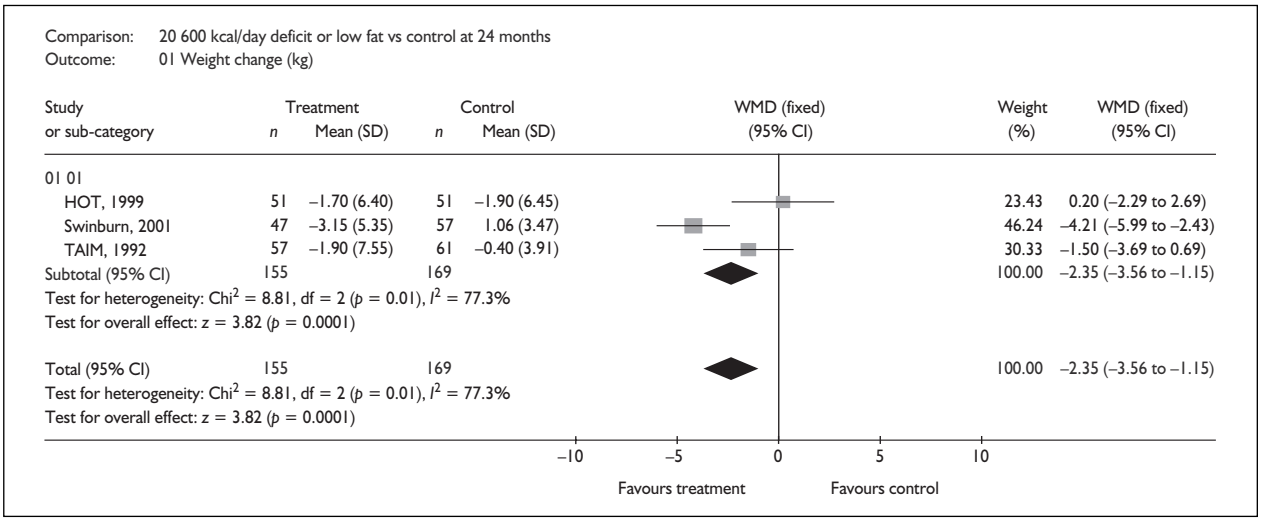


FIGURE 87

heterogeneity, although the direction of effect was consistent across all studies. When 12-month weight changes from studies with imputed values were compared with studies with no assumed values, the weight changes were –4.52 kg (95% CI –5.67 to –3.36 kg) compared with –5.55 kg (95% CI –6.17 to –4.94 kg). When 12-month weight loss from RCTs with participants with cardiovascular risk factors was compared with RCTs with participants with no reported risk factors, a clearer difference between studies emerged (–4.19 kg, 95% CI –4.90 to –3.48 kg; compared with –6.98 kg, 95% CI –7.83 to –6.12 kg, respectively).

At 18 months weight change was –1.15 kg (95% CI –2.76 to 0.45 kg), 24 months –2.35 kg (–3.56 to –1.15 kg), 30 months 0.70 kg (95% CI –1.78 to 3.18 kg), 36 months –3.55 kg (95% CI –4.54 to –2.55 kg) and at 60 months –0.20 kg (95% CI –2.03 to 1.63 kg) (*Figures 86–90*). After 12 months only a maximum of three studies provided data towards any one comparison.

At 12 months DBP and SBP, lipids and fasting plasma glucose were all significantly improved compared with the control group (*Figures 91–102*). However, the limited data after 12 months no longer show statistically significant risk factor changes. Results for changes in risk factors for people with hypertension and diabetes are presented in *Tables 5* and *6*.

In the cluster RCT[146] the weight change at 12 months was –0.88 kg (SD 4.0 kg) for the diet group and 1.3 kg (SD 3.0 kg) for the control group, which was not found to be a statistically significant difference.

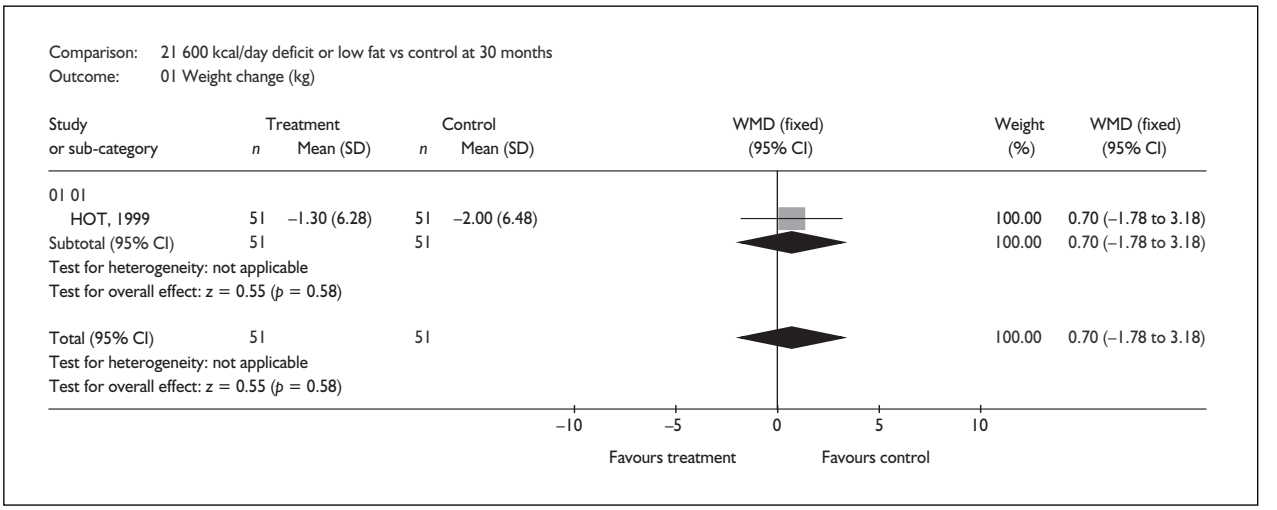


FIGURE 88

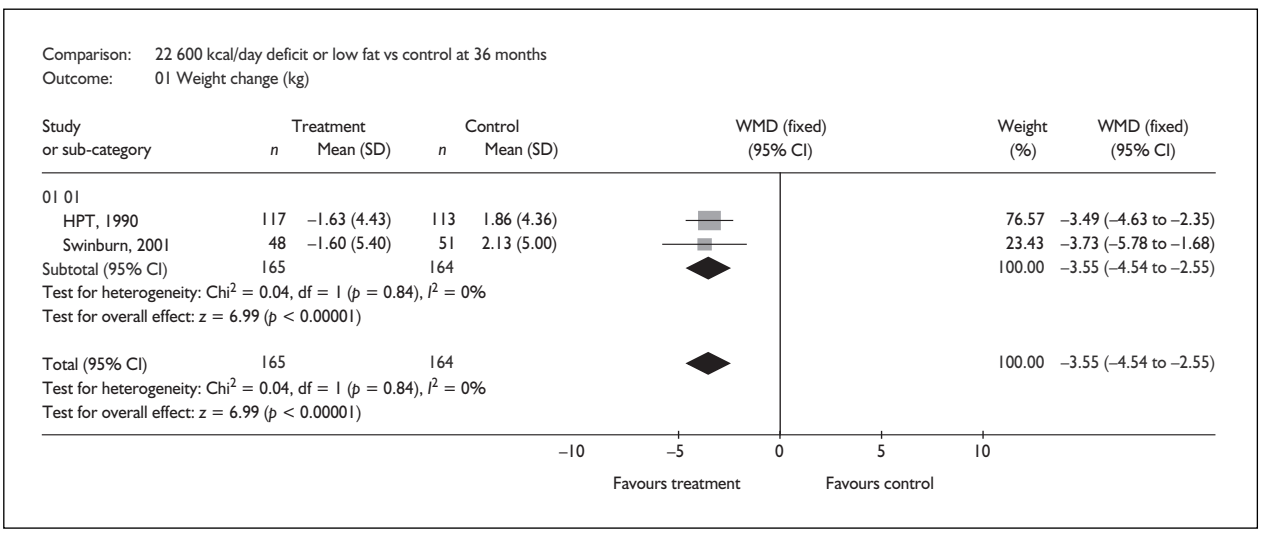


FIGURE 89

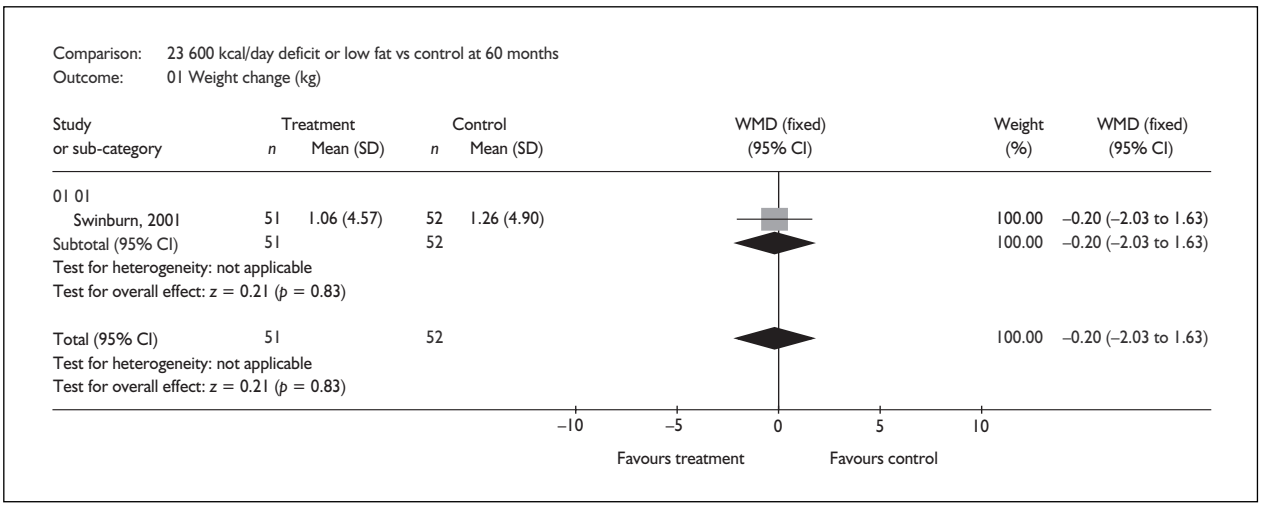


FIGURE 90

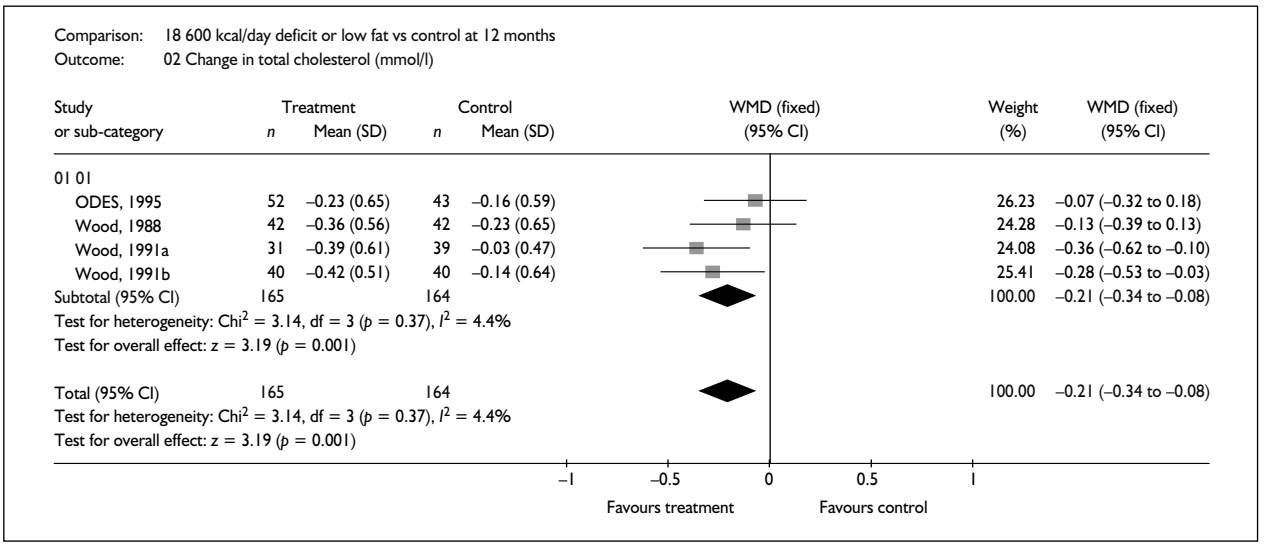


FIGURE 91

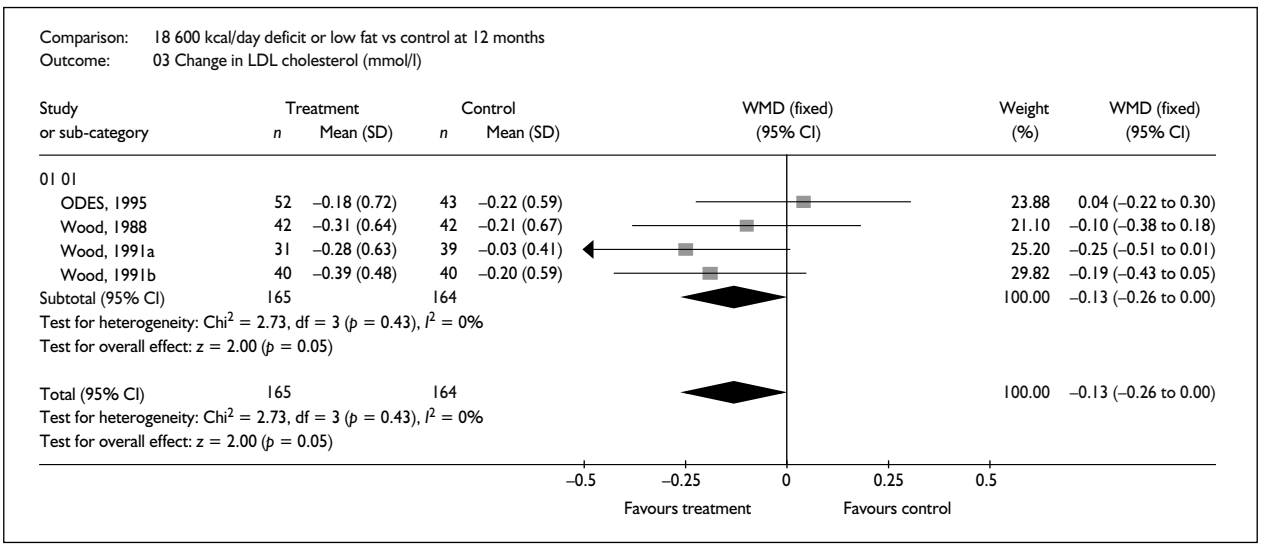


FIGURE 92

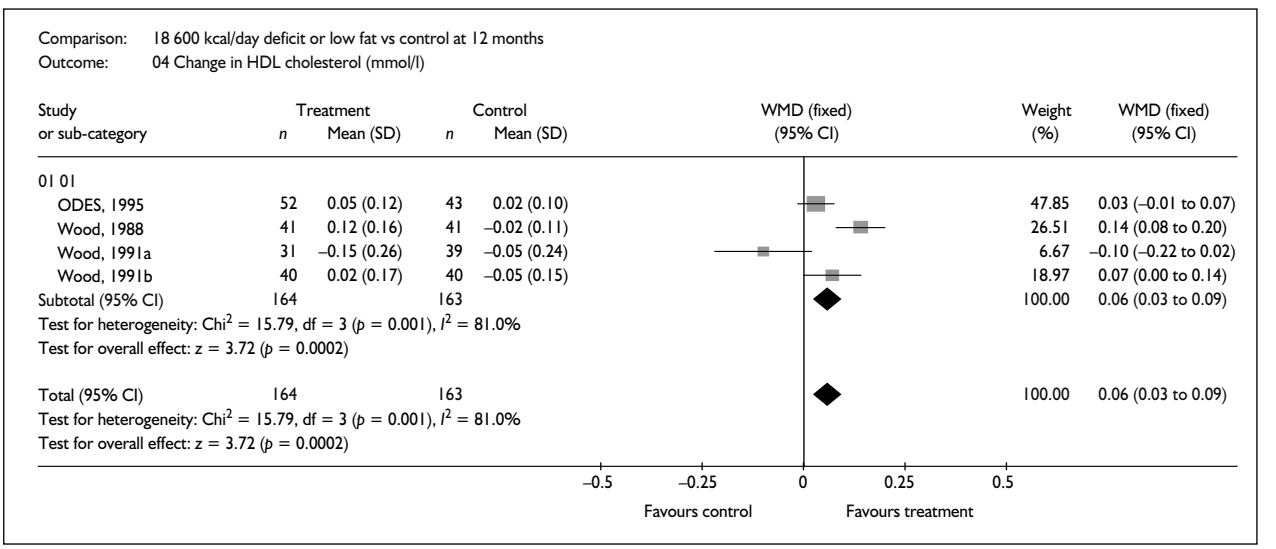


FIGURE 93

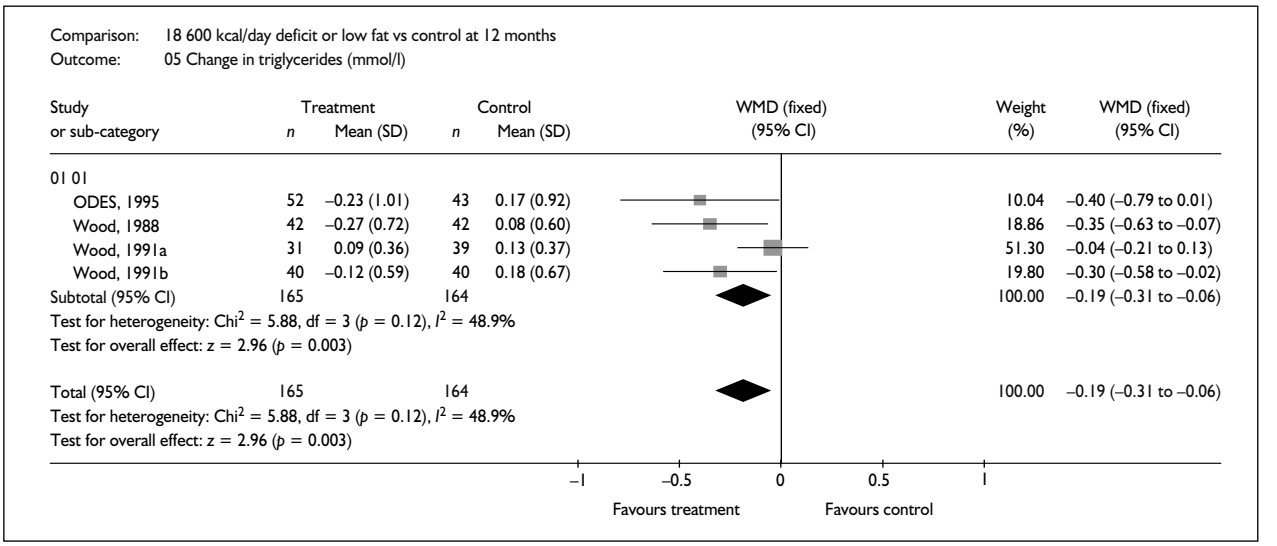


FIGURE 94

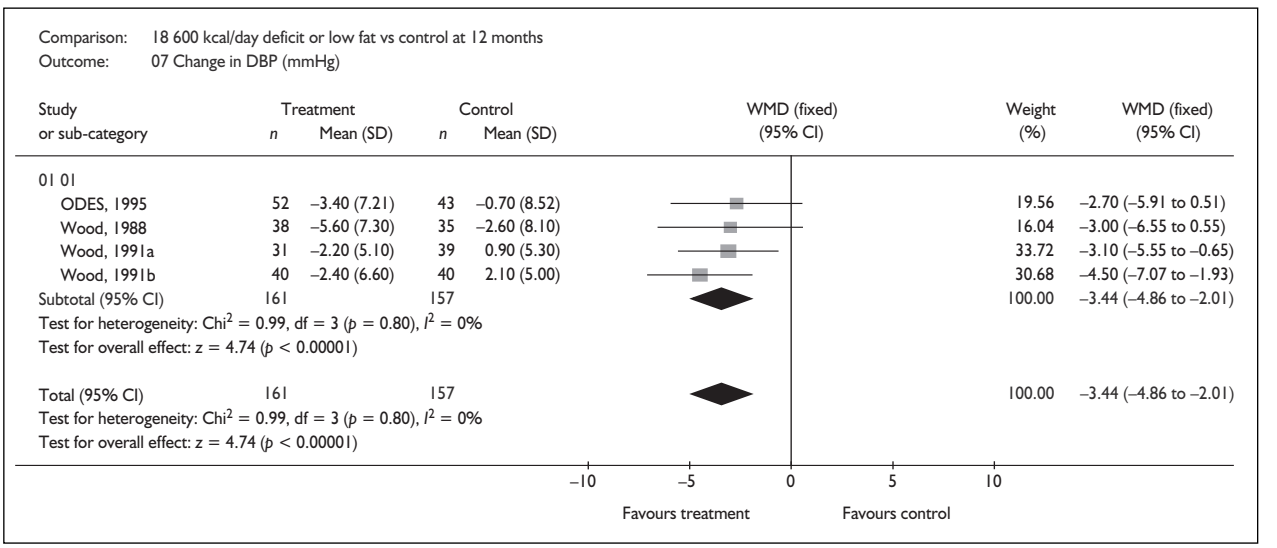


FIGURE 95

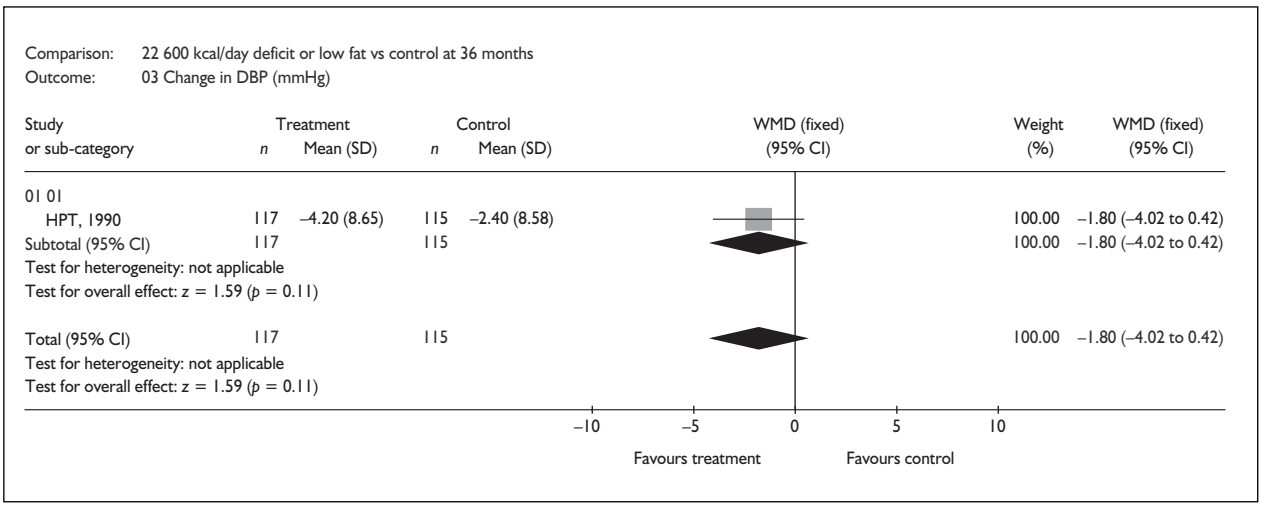


FIGURE 96

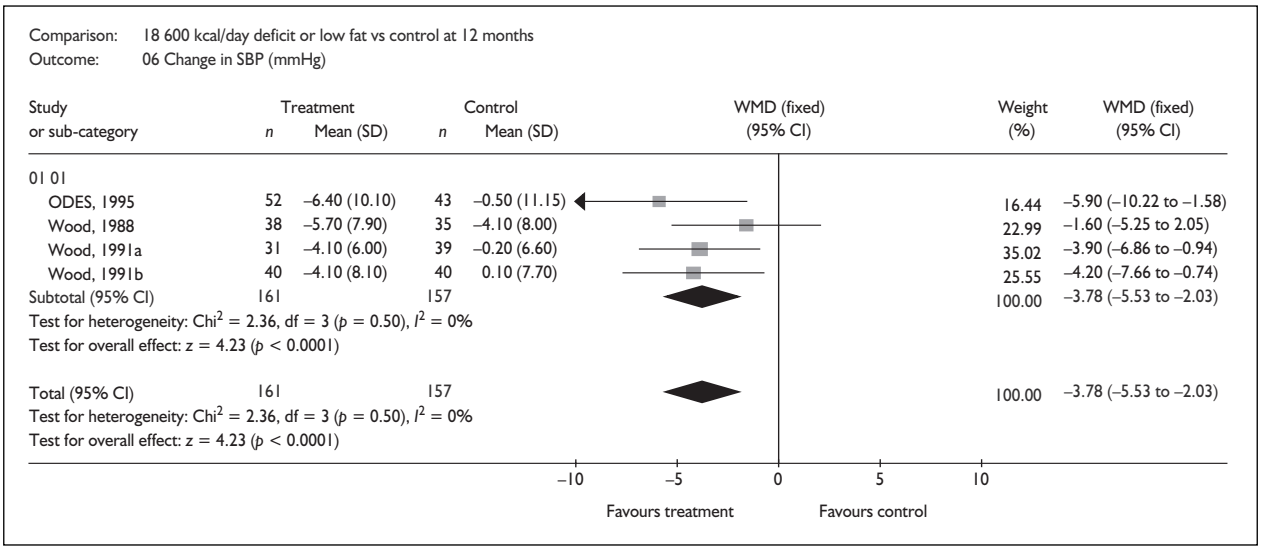


FIGURE 97

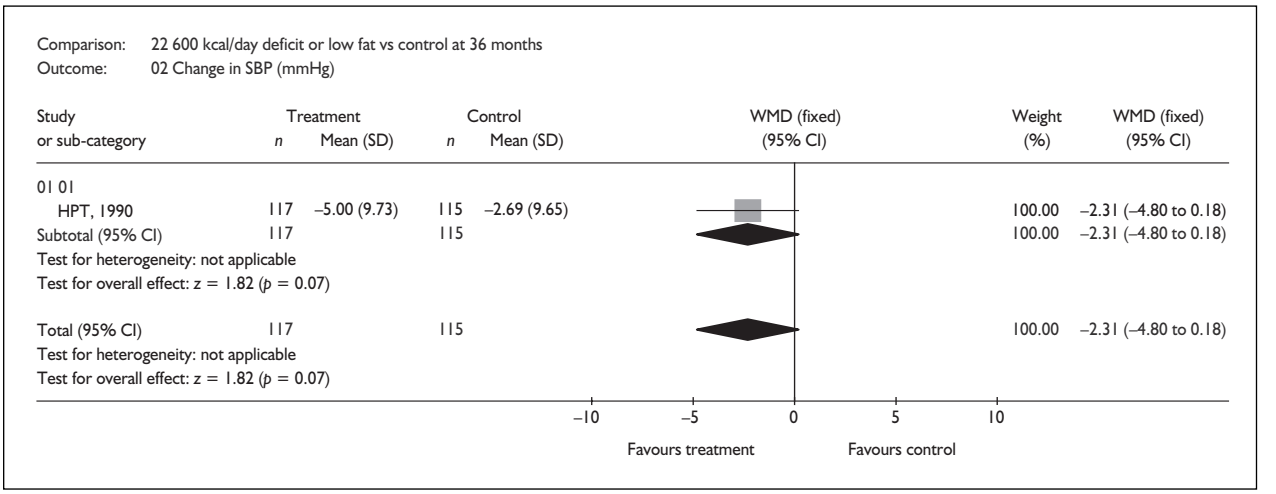


FIGURE 98

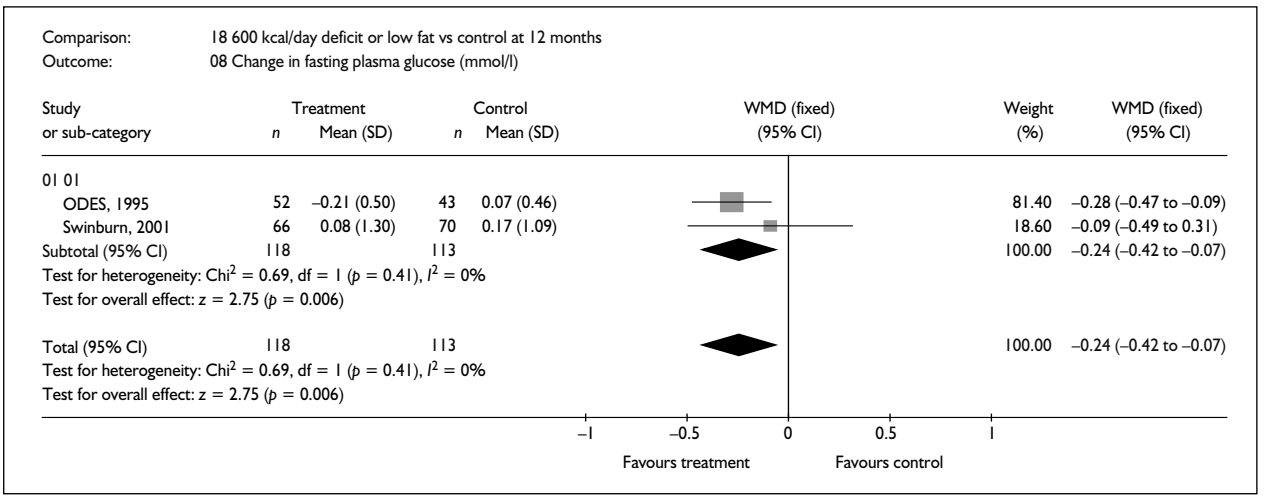


FIGURE 99

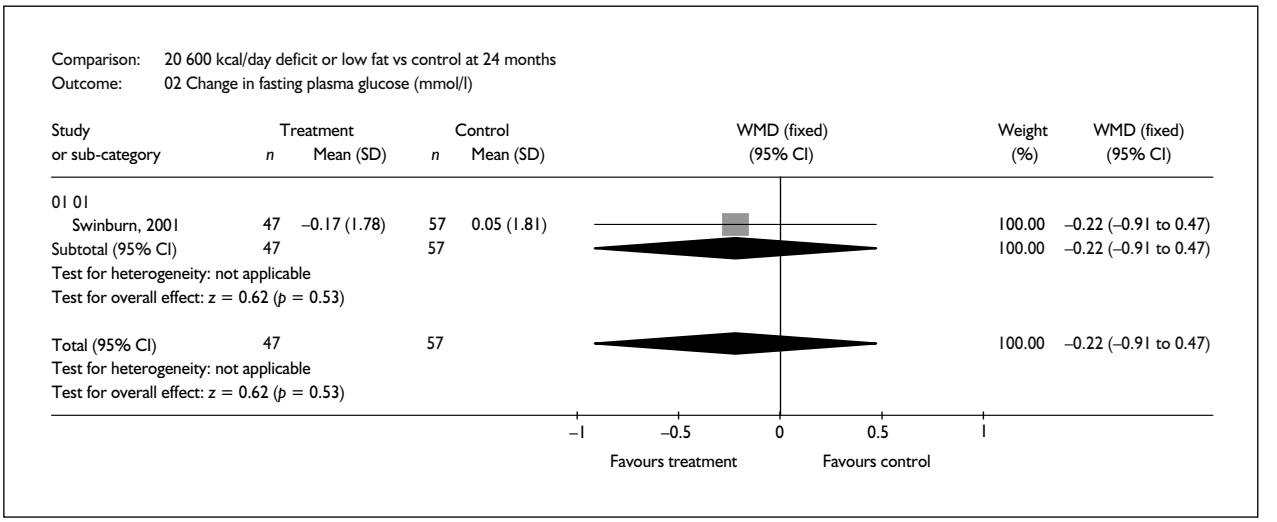


FIGURE 100

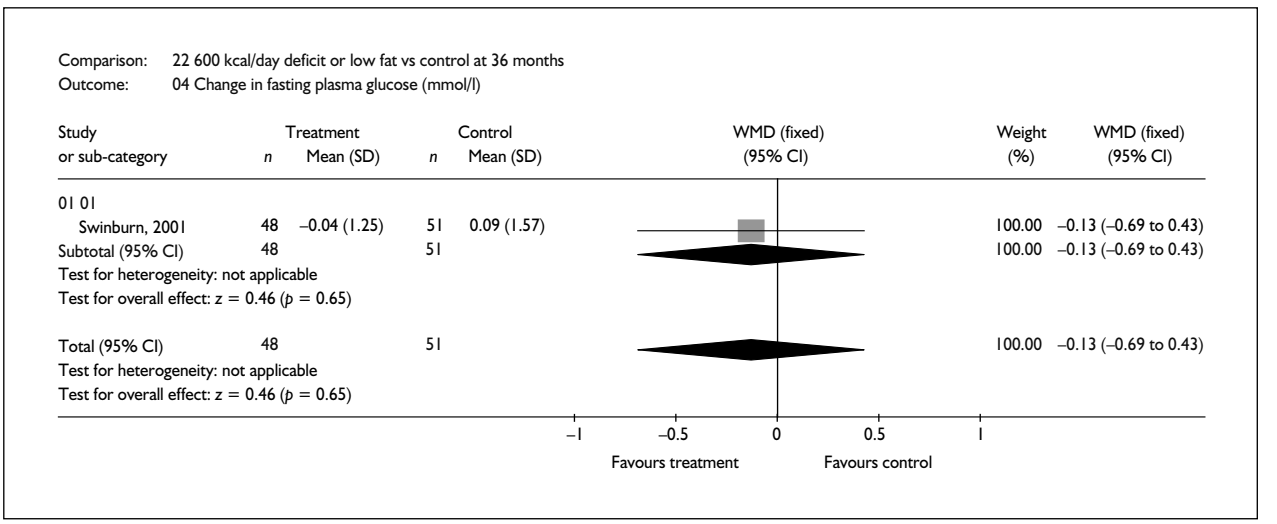


FIGURE 101

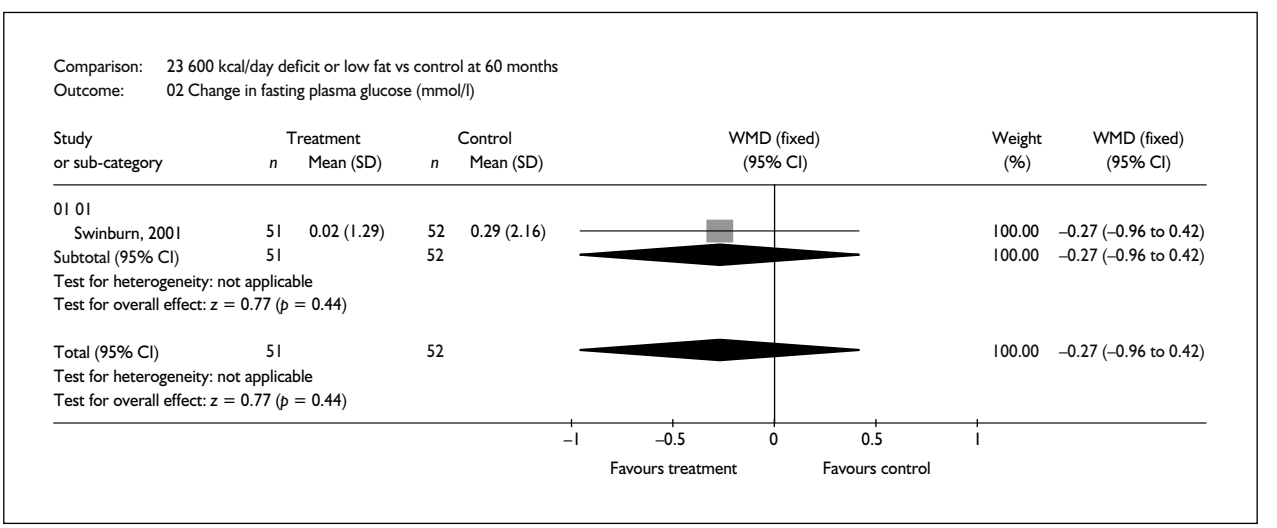


FIGURE 102

TABLE 5 *Effects of 600 kcal/day deficit or low-fat diet versus control on weight and risk factors in obese populations with hypertension*

	12 months	18 months	24 months	30 months	36 months
Weight (kg) WMD (95% CI) No. of studies	–4.07 (–4.91 to –3.23) *n* = 4	–1.15 (–2.76 to 0.45) *n* = 2	–0.76 (–2.41 to 0.89) *n* = 2	0.70 (–1.78 to 3.18) *n* = 1	–3.49 (–4.63 to –2.35) *n* = 1
SBP WMD (95% CI) No. of studies					–2.31 (–4.80 to 0.18) *n* = 1
DBP WMD (95% CI) No. of studies					–1.80 (–4.02 to 0.42) *n* = 1

TABLE 6 *Effects of 600 kcal/day deficit or low-fat diet versus control on weight and risk factors in obese populations with type 2 diabetes*

	12 months	24 months	36 months	60 months
Weight (kg) WMD (95% CI) No. of studies	–5.85 (7.14 to –4.56) *n* = 2	–4.21 (–5.99 to –2.43) *n* = 1	–3.73 (–5.78 to –1.68) *n* = 1	–0.20 (–2.03 to 1.63) *n* = 1
Fasting plasma glucose (mmol/l) WMD (95% CI) No. of studies	–0.09 (–0.49 to 0.31) *n* = 1	–0.22 (–0.91 to 0.47) *n* = 1	–0.13 (–0.69 to 0.43) *n* = 1	–0.27 (–0.96 to 0.42) *n* = 1

The two studies that were associated with the least mean difference in weight change also had populations with the largest mean BMI of 34.0 kg/m^2.[107,146]

One death occurred in the control arm of the Hypertension Prevention Trial (HPT) study[108–114] and two deaths in the intervention arm of the TAIM Phase I study.[130–135] Two deaths in the intervention group and one in the control group occurred in the study by Hankey and colleagues,[105,106] three deaths in the Hypertension Optimal Treatment (HOT) study[107] and four deaths in the first year of the study by Swinburn and colleagues (group allocation not known).[128,129] One diagnosis of cancer occurred in year 2 of the study by Wood and colleagues,[136–141] and two cancers and one cardiac event in the Oslo Diet and Exercise Study (ODES) (allocation unknown).[115–121]

Swinburn and colleagues[128,129] found that 47% of participants developed diabetes or impaired glucose tolerance, compared with 67% in the control group. After 1 year the investigators for the Dietary Intervention Study of Hypertension (DISH)[99–103] reported that 59.5% of participants allocated to diet remained off medications, compared with 35.3% of controls (reported $p = 0.0015$). The investigators for the HOT study[107] also reported that people in the diet intervention arm required fewer medications between 1 year and 30 months, a difference that was consistently statistically significant. In the HPT[108–114] 9% of intervention and control groups required drug treatment for hypertension during the 3 years of the study.

One study reported no effect of diet counselling by doctor and dietitian or dietitian alone on subsequent use of medication.[127] The same study reported that the cost of an extra kilogram weight loss was Aus$9.76 for the doctor/dietitian group and Aus$7.30 for the dietitian group.

Effects of low-calorie diet versus control

Description of study

One RCT provided change in weight at 12 months, 24 months and 36 months for an LCD versus control.[147] This was a feasibility study to examine the effect of an LCD as an adjunct to treatment for postmenopausal breast cancer. Data were not provided for any changes in risk factors.

The study took place in three hospitals in The Netherlands and two hospitals caring for cancer

patients in Poland. The trial lasted for 1 year in Poland and 3 years in The Netherlands. Mean BMI ranged from 29.3 kg/m^2 in participants from The Netherlands, who received active treatment, to 32.2 kg/m^2 in control participants in Poland.

The study participants were obese postmenopausal women who had undergone primary treatment for breast cancer with no signs of distant metastases. Weight data were provided separately for countries.

Review results

Compared with the control group, the LCD was associated with a WMD weight change at 12 months of –6.25 kg (95% CI –9.05 to –3.45 kg), at 24 months of –7.00 kg (95% CI –10.99 to –3.01 kg) and at 36 months of –6.10 kg (95% CI –10.71 to –1.49 kg) (*Figures 103–105*). However, the study was small, reflected in the wide confidence intervals.

Three breast cancers occurred in the intervention group and one in the control group. Three people died from breast cancer in the intervention group and five people in the control group. There were two deaths from other causes in each of the two groups.

Effects of very low-calorie diet versus control in an obese population with asthma

Description of study

One RCT provided change in weight at 12 months in an obese population with asthma.[148] The study, with 38 participants, used an ITT analysis and there were no dropouts at 12 months. Data were not provided for any risk factor changes, but were provided for outcomes related to asthma. The VLCD group had an initial 14-week weight reduction programme that included 8 weeks of 420 kcal/day. Two participants in the VLCD group found the meal replacements (Nutrilett) intolerable and followed a low-energy diet instead.

Mean baseline BMI was 35.8 kg/m^2 in the VLCD group and 36.7 kg/m^2 in the control group. All participants received a 2–3-week pretreatment phase for tests to fulfil inclusion criteria and 2 weeks of baseline measurements. All participants had the same number of visits and all received education about asthma and allergy.

Review results

At 12 months VLCD compared with control was associated with a WMD weight change of –13.40 kg (95% CI –18.43 to –8.37 kg) (*Figure 106*). After 1 year the difference in forced expiratory volume in 1 second between VLCD and control groups was 7.6% (95% CI 1.5 to 13.8%), forced vital capacity 7.6% (95% CI 3.5 to 11.8%) and peak expiratory flow 6.2% (95% CI –1.4 to 13.7%). The small size of the study, 38 participants, is reflected in the wide confidence intervals.

During the year of follow-up 18 out of 19 participants in the control group and 16 out of 19 participants in the VLCD group had at least one exacerbation of asthma. The median number of exacerbations was 1 (range 0–7) in the control group and 1 (range 0–4) in the VLCD group (reported $p = 0.001$). Overall reduction in rescue medication was 0.5 doses in the VLCD group and zero doses in the control group. Thirteen out of 19 participants in the control group needed a course of oral steroids during the year and ten out of 19 participants in the VLCD group.

Effects of low-calorie diet versus 600 kcal/day deficit or low-fat diet

Description of study

One study assessed the effects of an LCD compared with a low-fat diet in women at 12 months.[149] Change in weight was assessed in participants who provided complete data. Numbers of participants allocated to each group were not reported. Dropout rate was 39% overall at 12 months. Mean body weight at baseline was 80 kg. Active treatment was for 26 weeks and participants in each group had the same number of appointments. All participants received identical behaviour therapy and exercise and only differed with regard to dietary advice.

Review results

At 12 months an LCD compared with a low-fat diet was associated with a WMD weight change of 1.63 kg (95% CI –1.26 to 4.52 kg) (*Figure 107*).

Effects of very low-calorie diet versus 600 kcal/day deficit or low-fat diet in a population with type 2 diabetes

Description of study

One RCT comparing a VLCD to a low-fat diet provided change in weight at 24 months in a population with type 2 diabetes.[150] The study had only 16 participants and no dropouts at 24 months.

Overall mean initial BMI was 32 kg/m^2. All participants received a 6-week pretreatment phase where they were advised to consume an *ad libitum* diet and from month 4 to month 24 received individually tailored diets to provide a daily energy balance of zero.

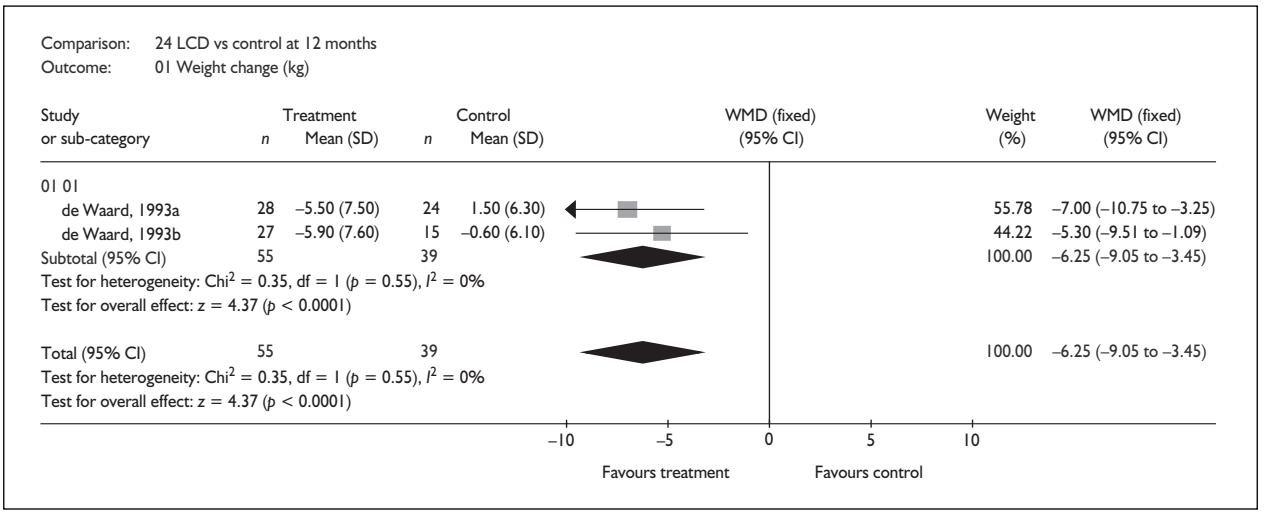


FIGURE 103

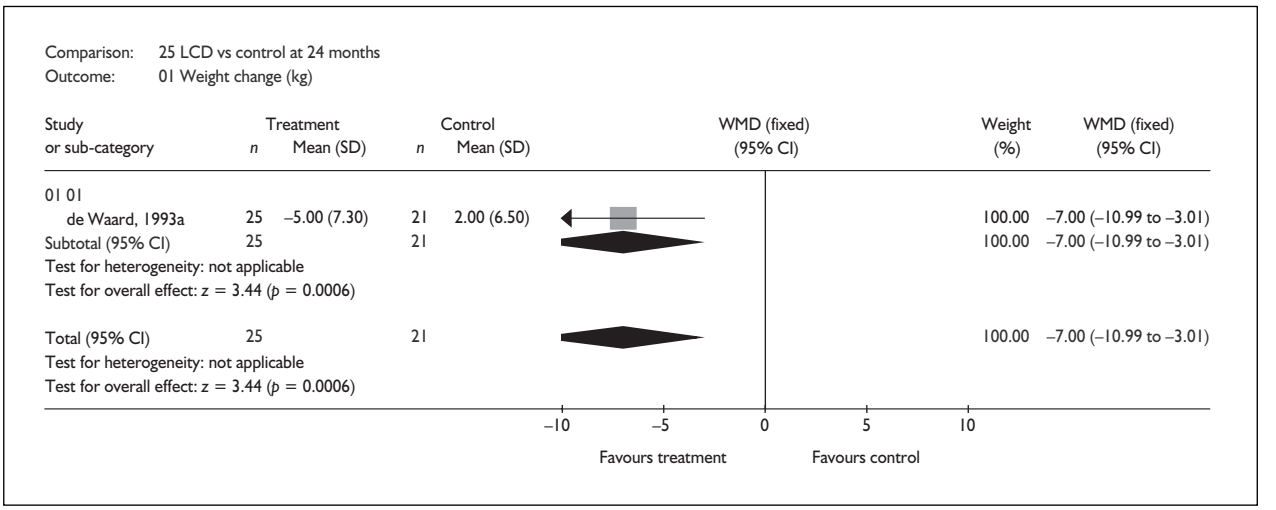


FIGURE 104

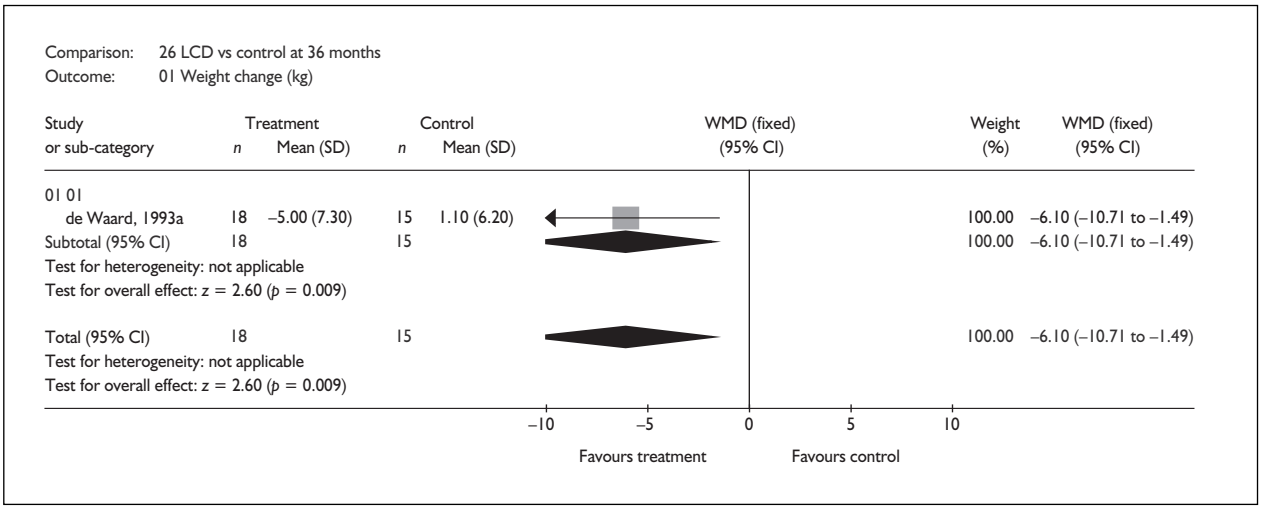


FIGURE 105

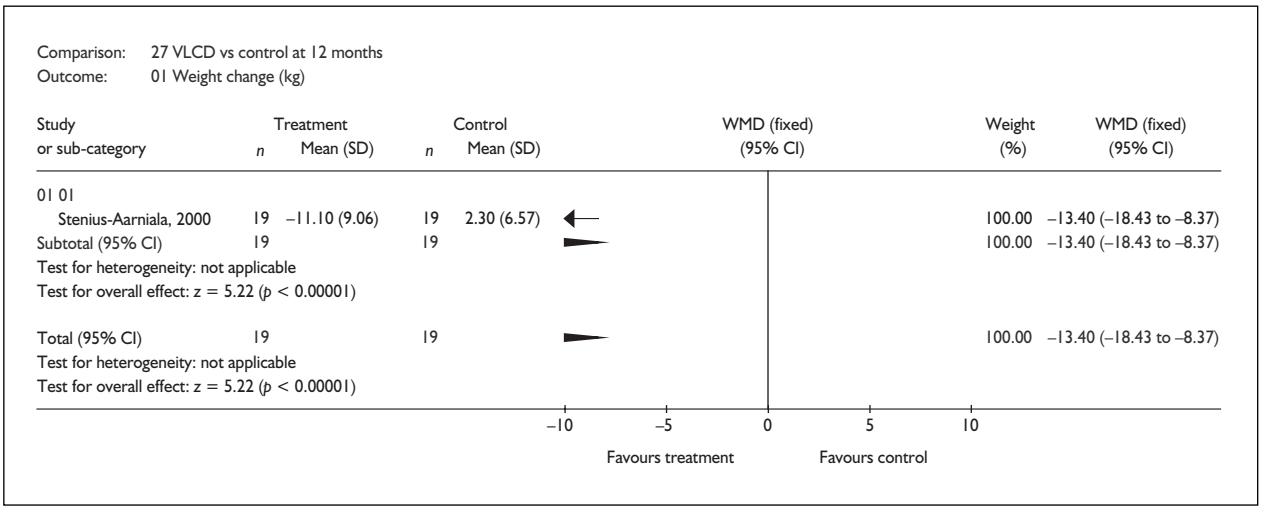


FIGURE 106

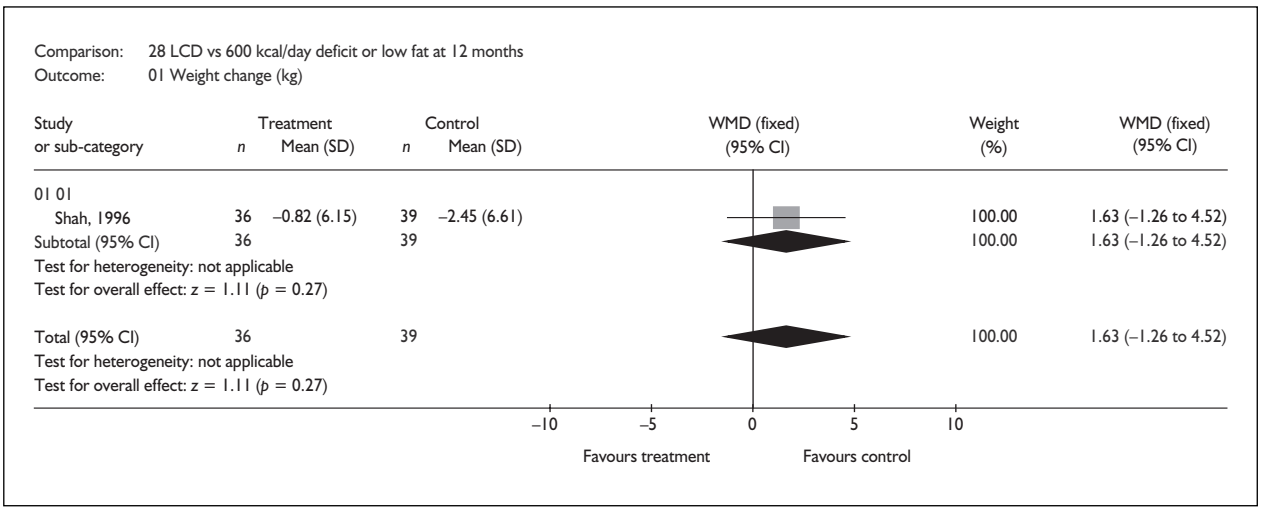


FIGURE 107

There were clear differences between groups at baseline. Eight of the ten participants in the VLCD group and two of the six participants in the low-fat group were treated for their diabetes by diet only before the trial commenced. There were also marked differences between the groups at baseline for HbA_{1c}: VLCD group mean 6.3% (SD 1.2%), low-fat group mean 8.5% (SD 0.9%) (reported $p = 3 \times 10^{-5}$). For this reason only changes in weight outcome data were evaluated in this review.

Active treatment was for 3 months from randomisation: one group received a low-fat diet and the other a 300 kcal/day meal replacement diet (Cambridge diet).

Review results

At 24 months the VLCD compared with low-fat diet produced a WMD weight change of –4.70 kg (95% CI –11.79 to 2.39 kg) (*Figure 108*). However, given the small size of the trial and the imbalances at baseline, the results should be interpreted with caution.

Effects of very low-calorie diet versus low-calorie diet

Description of studies

Three RCTs provided change in weight at 12 months or longer,[151,152] with one providing data at 18 months.[153] One study reported using an ITT analysis.[152] This was unclear in another of the studies.[153]

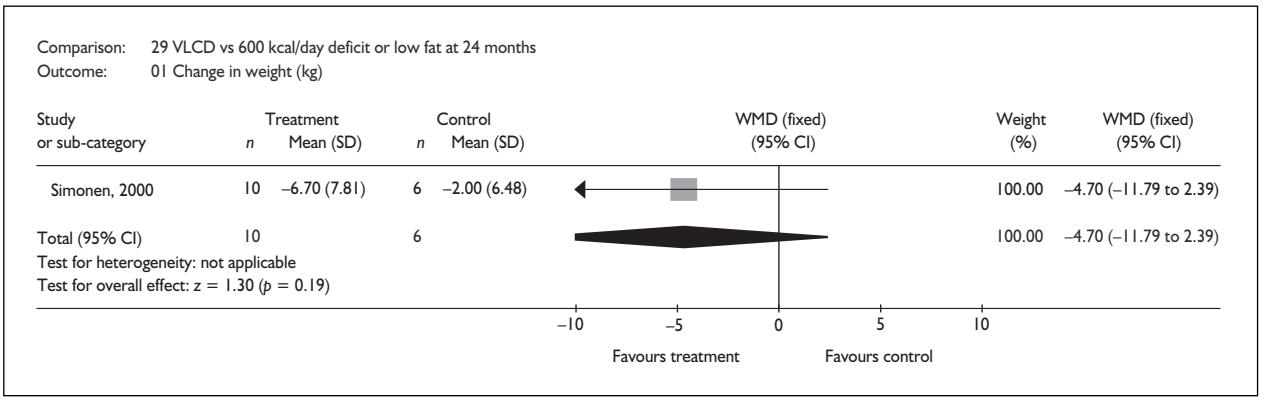


FIGURE 108

Pavlou and colleagues[153] recruited men only, whereas Viegener and colleagues[151] recruited women only. Reported mean BMI ranged from 30.1 kg/m^2 [153] to 36.5 kg/m^2.[152] Reported mean body weight was 94.6 kg in the VLCD group and 98.6 kg in the LCD group of the study by Viegener and colleagues.[151]

Active treatment ranged from 8 weeks[153] to 1 year[151] and contact visits ranged from ten times in the first year[153] to 39 times in the initial year.[151] Participants in both the VLCD and LCD groups in each study received similar contact visits and identical treatment except for the diet. Dropouts at 12 months ranged from 8% overall[152] to 30% in one group in the study by Viegener and colleagues.[151]

The VLCDs ranged from < 750 to 800 kcal/day and from 8 weeks[153] to 26 weeks.[151]

The study by Pavlou and colleagues[153] included four diet arms and either exercise or no exercise. The study by Wing and colleagues[152] included massed or spaced behaviour therapy maintenance sessions with both VLCD and LCD.

Review results

Compared with LCD, VLCD was associated with an overall WMD weight change at 12 months of –0.15 kg (95% CI –2.73 to 2.43 kg) and at 18 months of –1.13 kg (95% CI –5.32 to 3.06 kg) (*Figures 109–110*). Thus, there was no evidence to suggest that VLCD was associated with a significantly greater weight loss than LCD at any of the time-points.

Effects of protein-sparing modified fast versus low-calorie diet

Description of studies

Seven RCTs provided change in weight at 12 months or longer,[153–166] with the longest follow-up being 60 months.[159–162] Two studies clearly reported using an ITT analysis.[163–166] Two studies provided changes in risk factors,[154–158] and both these studies had participants with type 2 diabetes. Two studies recruited men only,[153] and one study recruited women only.[163,164] BMI ranged from 30.4 kg/m^2 [153] to 40.5 kg/m^2.[165,166] Dropouts at 12 months ranged from 0%[154,155] to 25%.[163,164]

Participants in all arms of each study had an equal number of contact visits, except for the study by Torgerson and colleagues.[165,166] Only the study by Wadden and colleagues[159–162] contained no exercise or behaviour therapy. Two studies gave the option of using optifast 70 (Sandoz Nutrition) for the PSMF,[154–158] and one used modifast (Novartis Nutrition).[165,166]

Review results

At 12 months the PSMF compared with LCD was associated with an overall WMD weight change of –3.57 kg (95% CI –7.36 to 0.22 kg), at 18 months 0.69 kg (95% CI –1.58 to 2.96 kg), at 24 months of –2.17 kg (95% CI –4.88 to 0.54 kg), at 36 months of –1.51 kg (95% CI –5.43 to 2.41 kg) and at 60 months of 0.20 kg (95% CI –5.68 to 6.08 kg) (*Figures 111–115*). There were no statistically significant changes in lipids at 18 months in one study in diabetics,[154,155] although the same study found an association between the PSMF diet and reduced HbA_{1c} of –2.60% (95% CI –4.36 to –0.84%) and fasting plasma glucose of –4.5 mmol/l (95% CI –7.07 to –1.93 mmol/l) at 18 months (*Figures 116–122*).

Effects of protein-sparing modified fast versus very low-calorie diet

Description of study

One study provided change in weight at 18 months.[153] Data were not provided for any risk

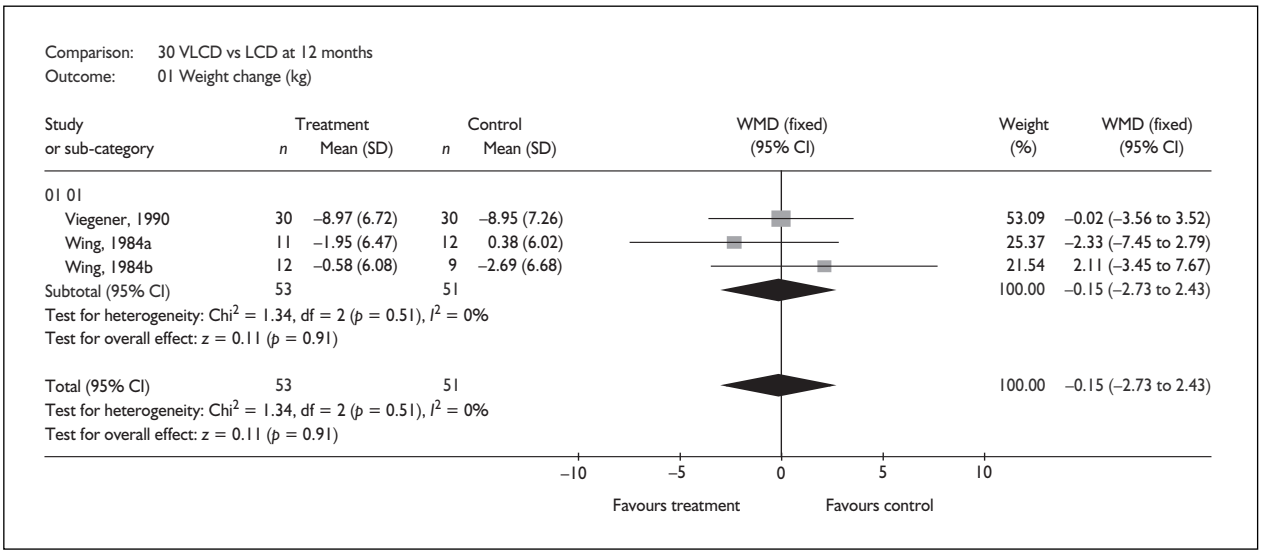


FIGURE 109

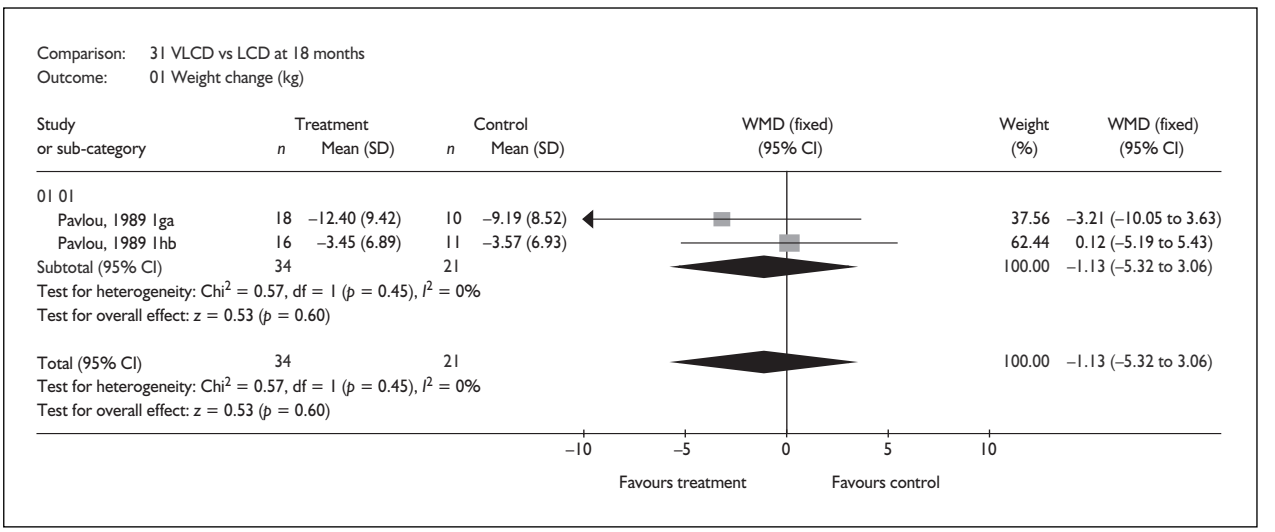


FIGURE 110

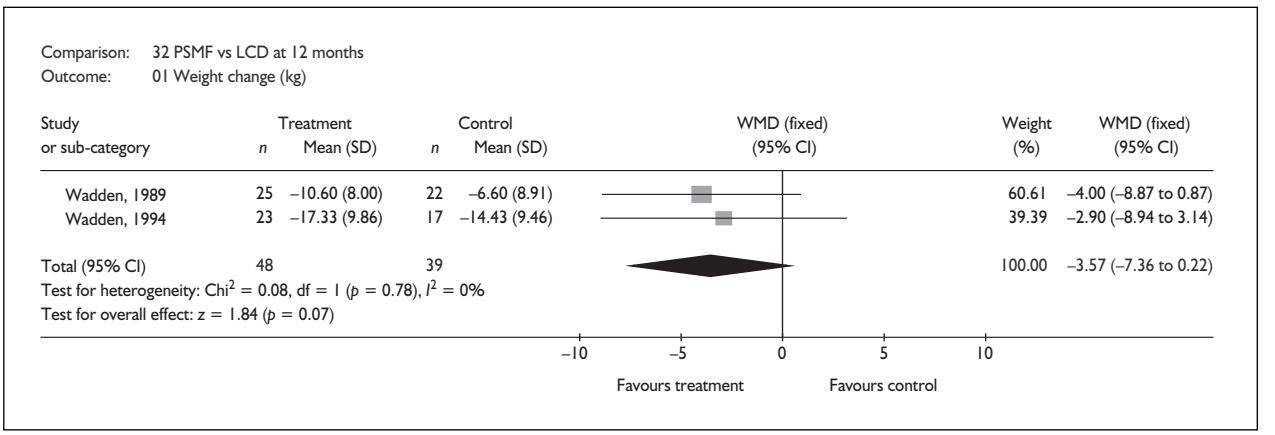


FIGURE 111

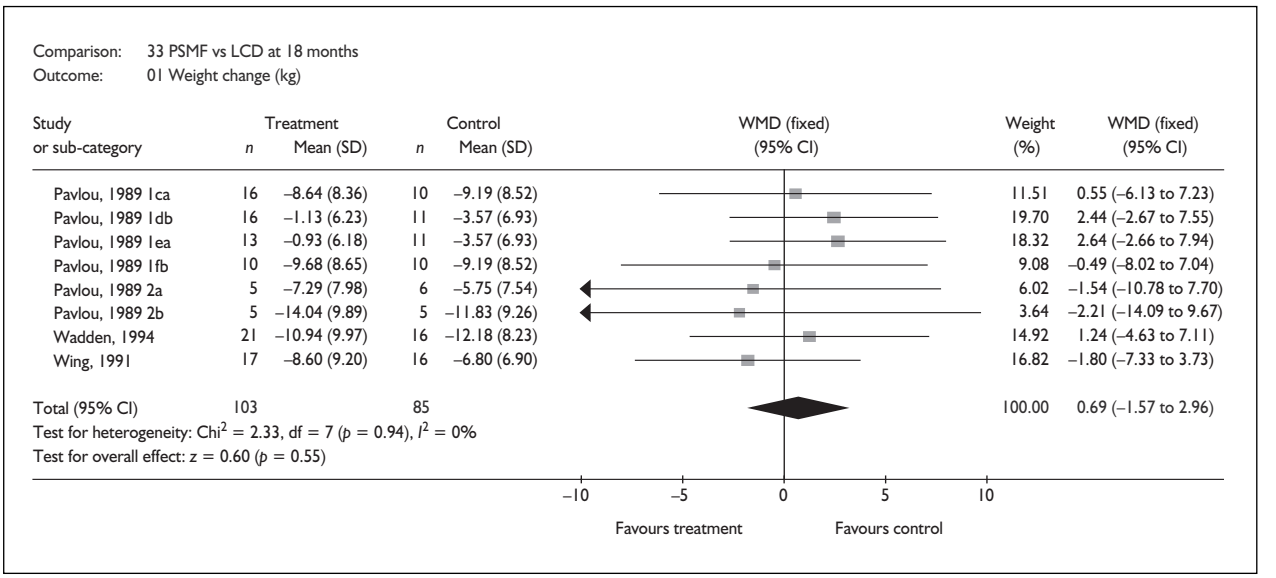


FIGURE 112

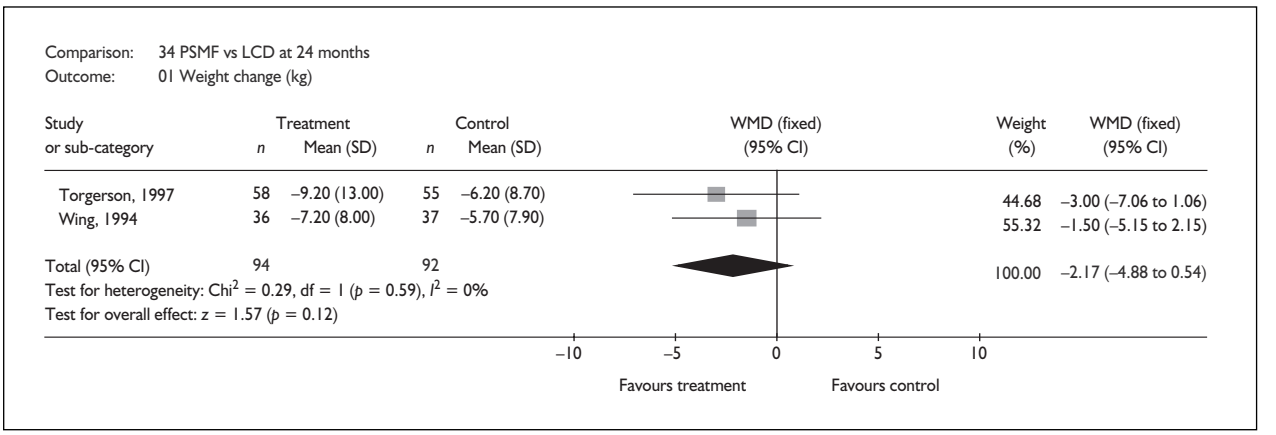


FIGURE 113

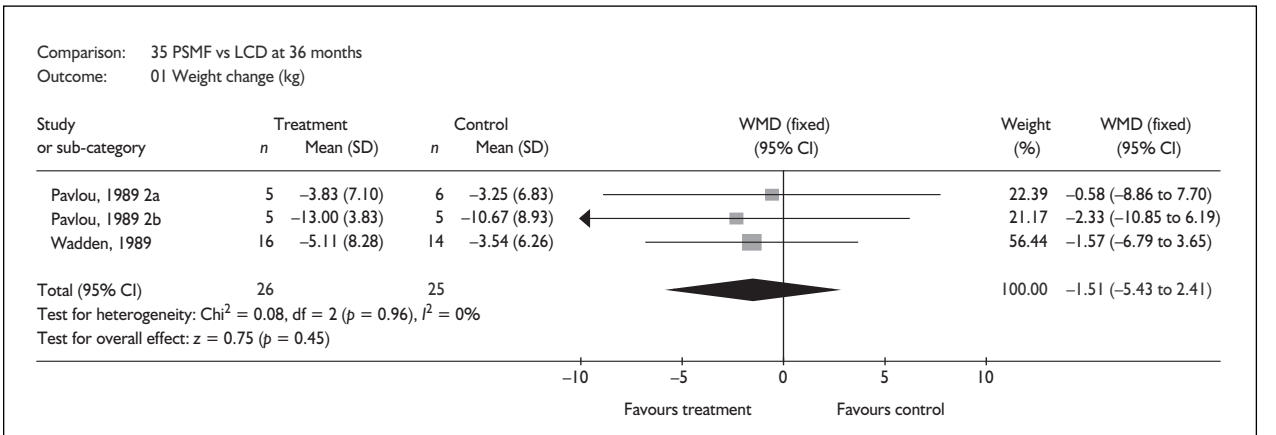


FIGURE 114

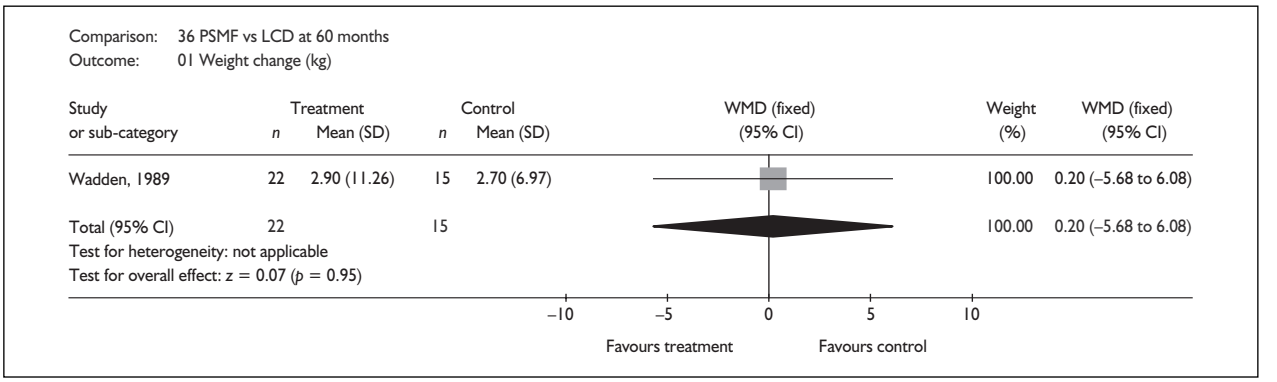


FIGURE 115

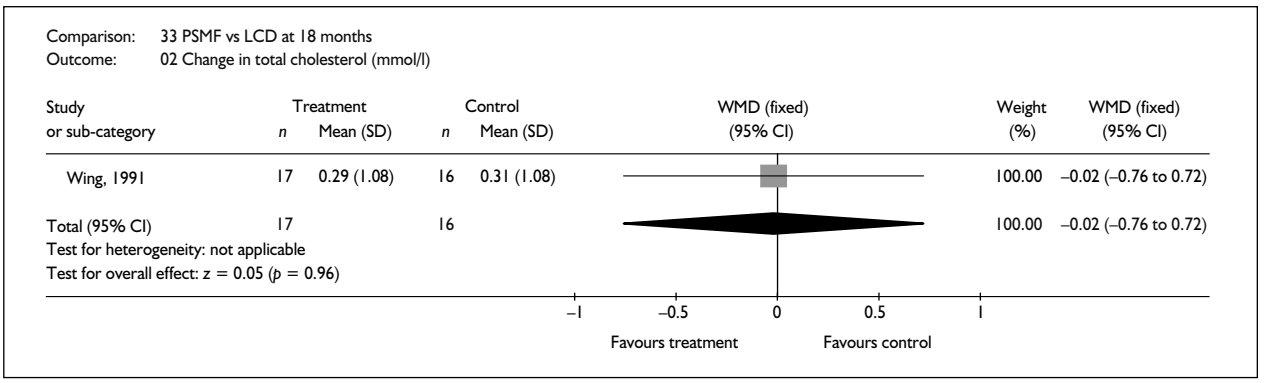


FIGURE 116

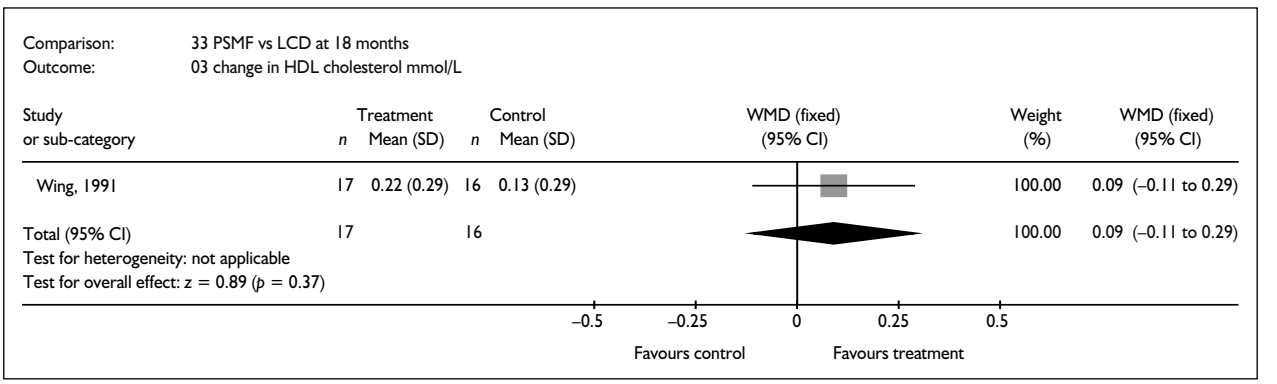


FIGURE 117

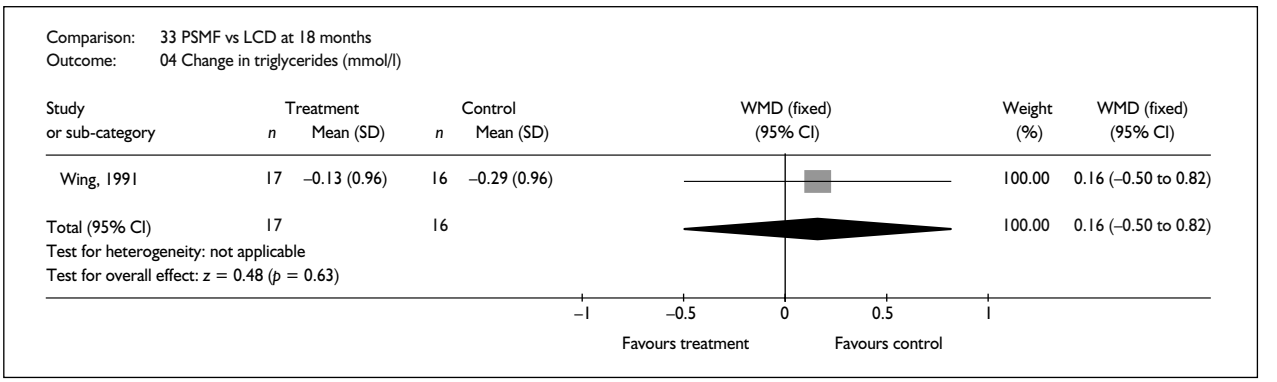
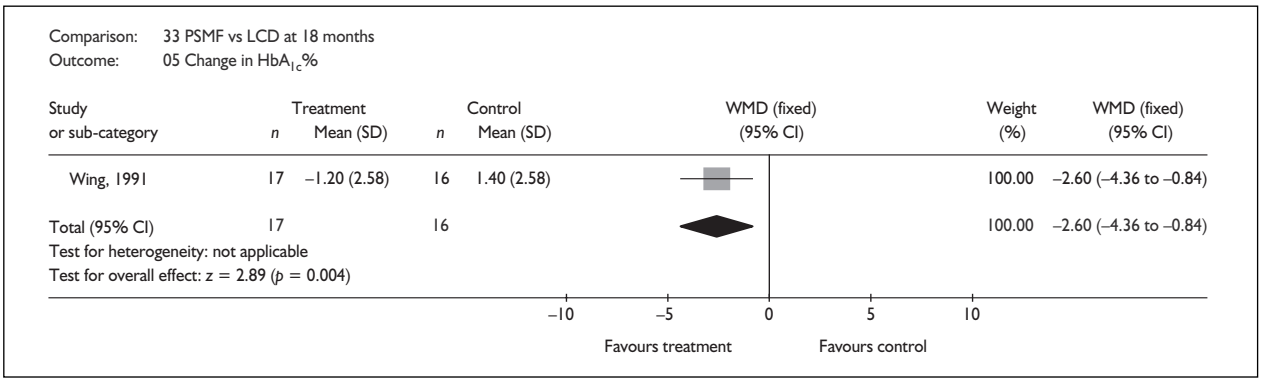


FIGURE 118



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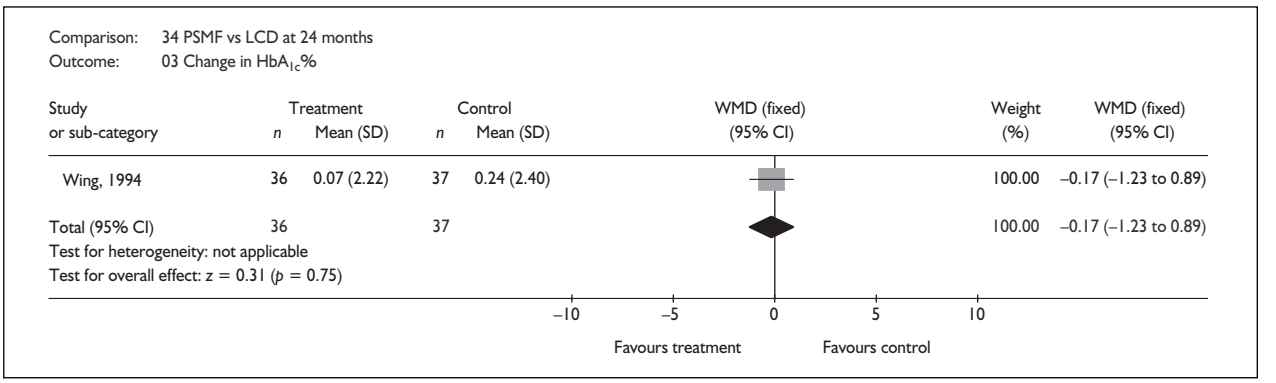


FIGURE 120

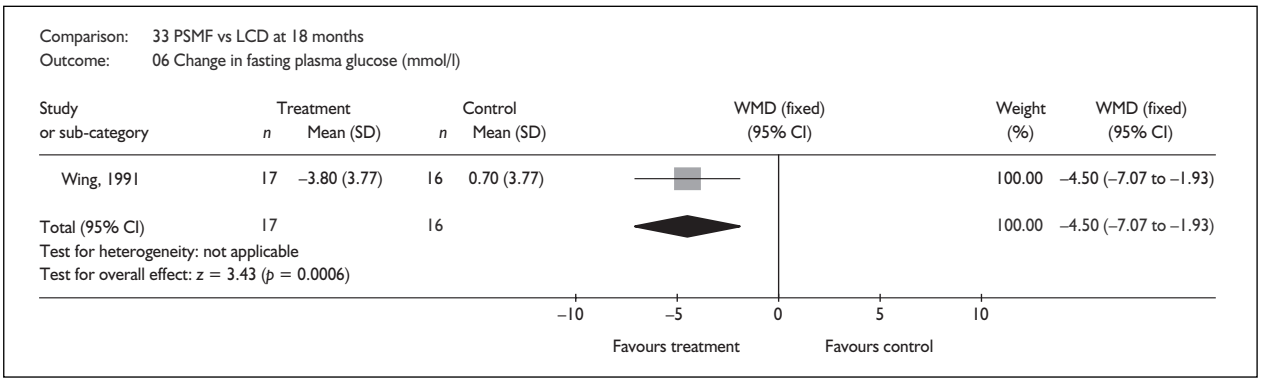


FIGURE 121

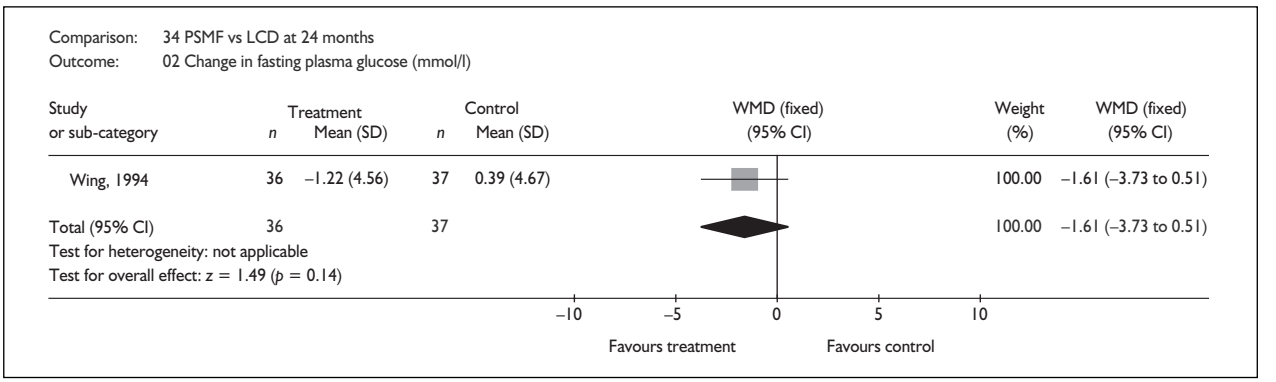


FIGURE 122

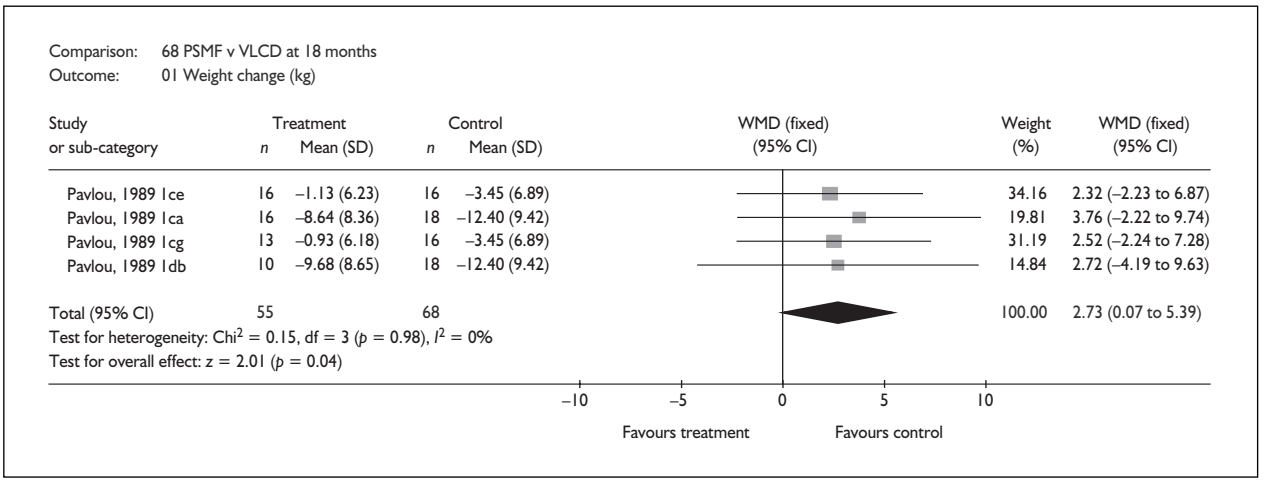


FIGURE 123

factor changes. It was unclear whether an ITT analysis had been used. The study recruited 160 men and had an overall dropout of 31% at 18 months. All participants received an equal number of contacts and received behaviour therapy as part of the intervention. The study compared two PSMF diets to a VLCD, incorporated in a factorial design with exercise.

Review results

At 18 months PSMF compared with VLCD was associated with a WMD weight change of 2.73 kg (95% CI 0.07 to 5.39 kg) (*Figure 123*). Again, however, the number of participants contributing to this comparison was small.

Effects of diet and exercise versus control

(See Appendix 12; meta-analyses 38.01–08, 39.01–02.)

Description of studies

Three studies provided change in weight at 12 months[115–121,142–145,167–171] and one of these also provided change in weight at 24 months.[167–171] Data were provided for changes in lipids, blood pressure and fasting plasma glucose at 12 months, and for fasting plasma glucose at 24 months.

None of the studies reported using an ITT analysis. All studies demonstrated some statistically significant differences for risk factors, but not weight or BMI, between groups at baseline. One study initially used less strict recruitment criteria.[167–171] One study recruited participants with impaired glucose tolerance.[167–171] Reported mean BMI ranged from 27.9 kg/m^2 for females in the study by Wood and colleagues[142–145] to 31.3 kg/m^2.[167–171] Outcome data were presented by gender in the study by Wood and colleagues.[142–145]

All studies used a 600 kcal/day deficit or low-fat diet. In the Finnish Diabetes Prevention Study (FDPS)[167–171] 22 participants had VLCD in year 1 and 25 in year 2 of 3–8 weeks' duration due to no weight loss in the first 6–12 months. The FDPS also invited the person in the participant's family responsible for preparing meals to attend sessions if this person was not the participant.

The exercise prescription was similar for two studies,[115–121,142–145] with up to three supervised exercise sessions of 45–60 minutes weekly. In the FDPS[167–171] the endurance programme differed between study centres, with supervised circuit type training twice weekly where possible. Participants in this study were also advised to perform 30 minutes of daily moderate exercise.

Review results

Diet plus exercise versus no treatment was associated with an overall WMD weight change at 12 months of –4.78 kg (95% CI –5.41 to –4.16 kg) (*Figure 124*). Weight loss at 24 months was still evident, with diet plus exercise associated with a WMD weight change of –2.70 kg (95% CI –3.60 to –1.80 kg) (*Figure 125*).

Diet plus exercise compared with controls demonstrated a statistically significant effect on lipids, blood pressure and fasting plasma glucose at 12 months, and fasting plasma glucose at 24 months (*Figures 126–133*).

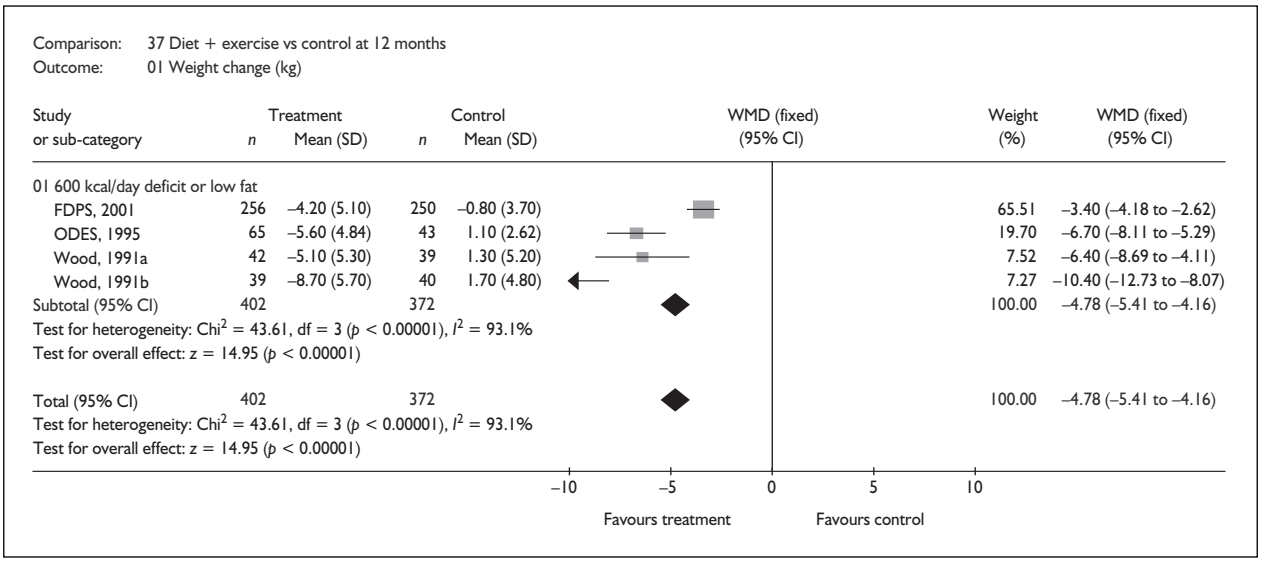


FIGURE 124

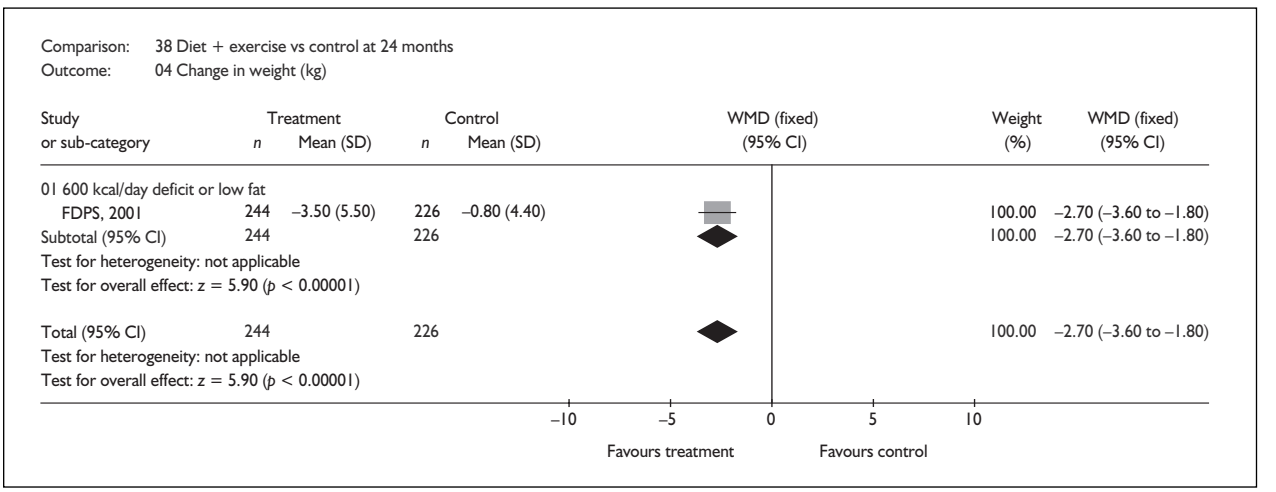


FIGURE 125

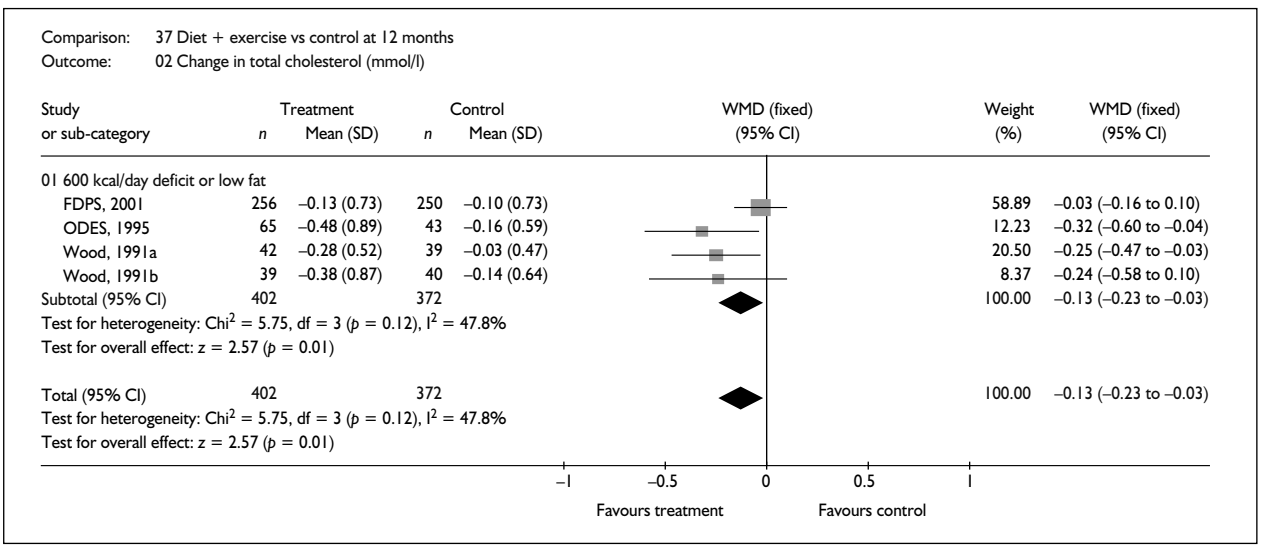


FIGURE 126

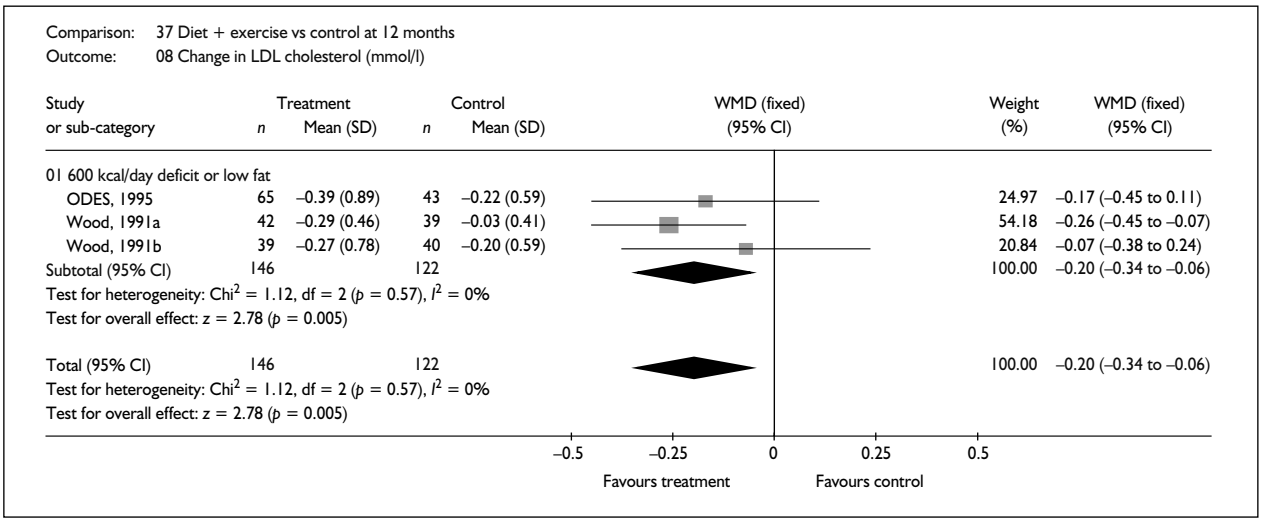


FIGURE 127

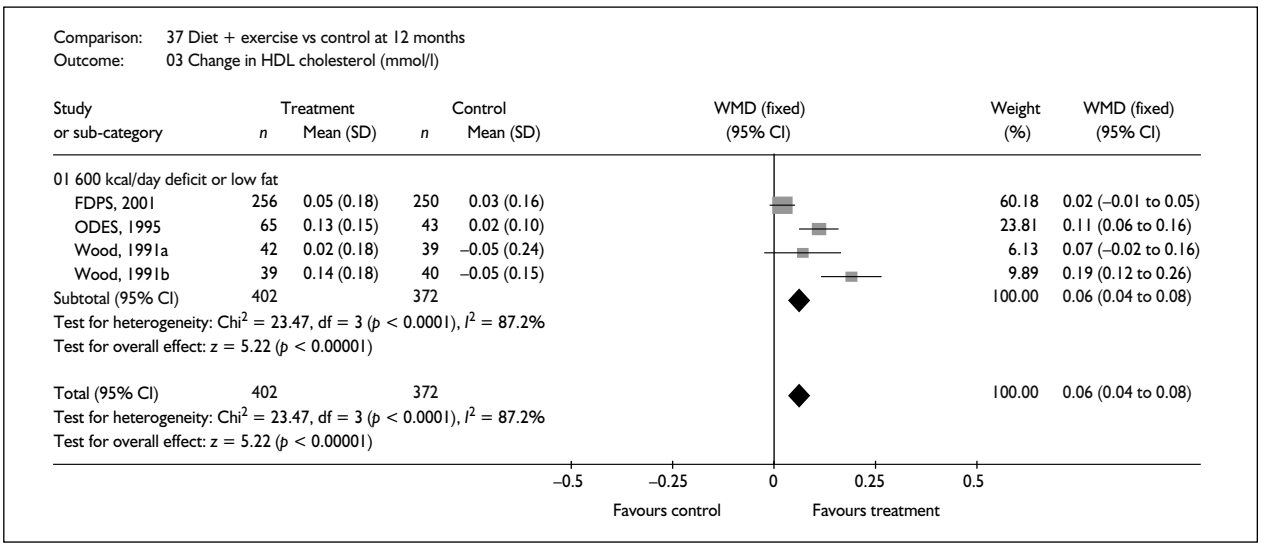


FIGURE 128

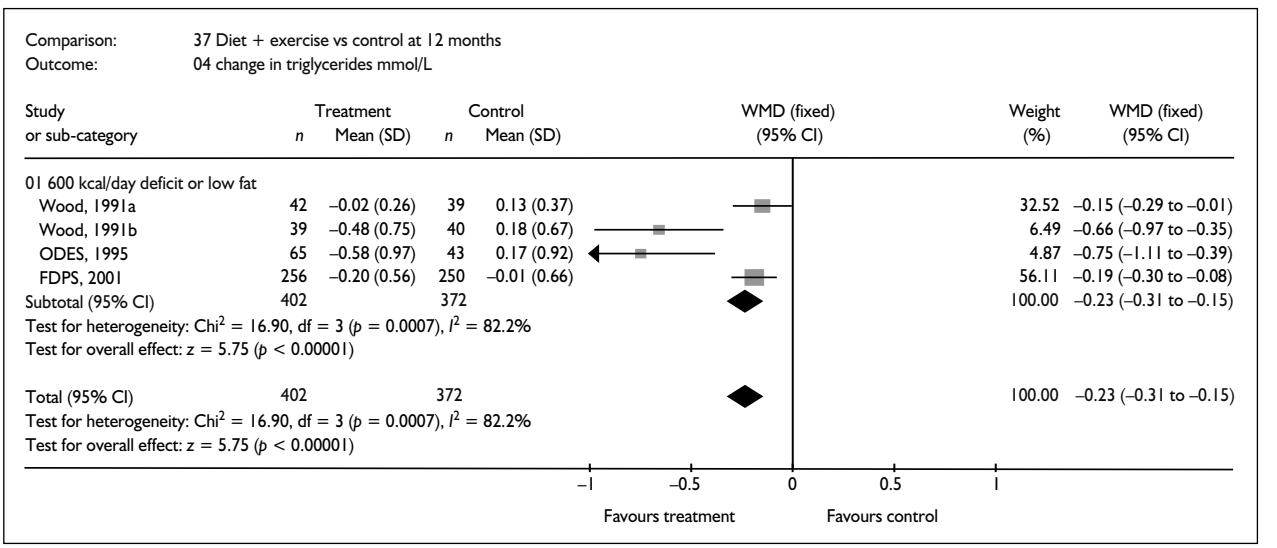


FIGURE 129

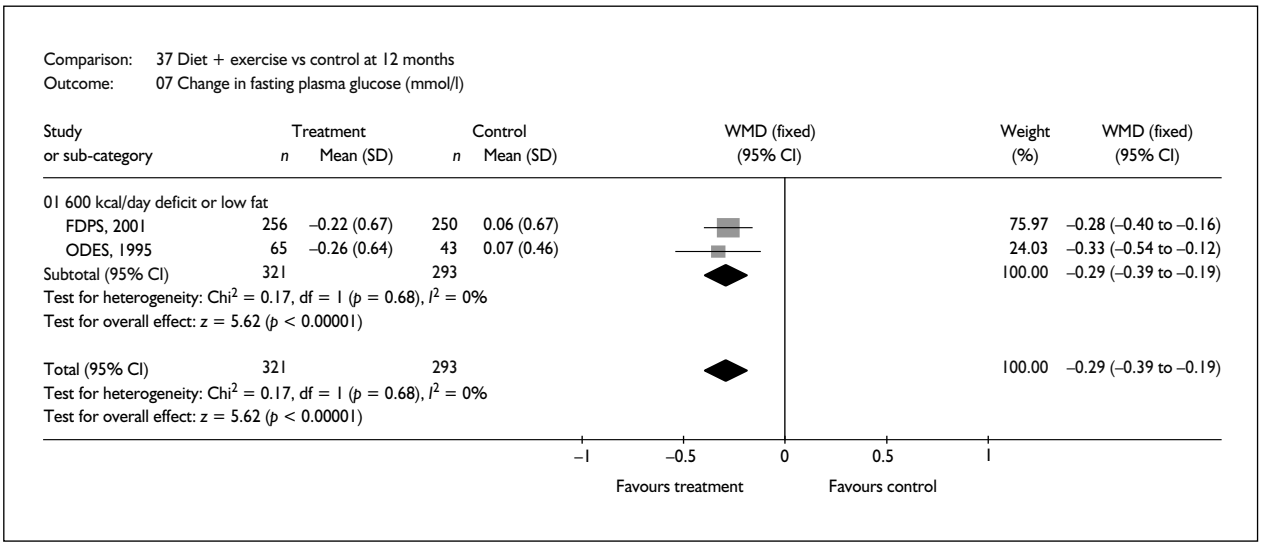


FIGURE 130

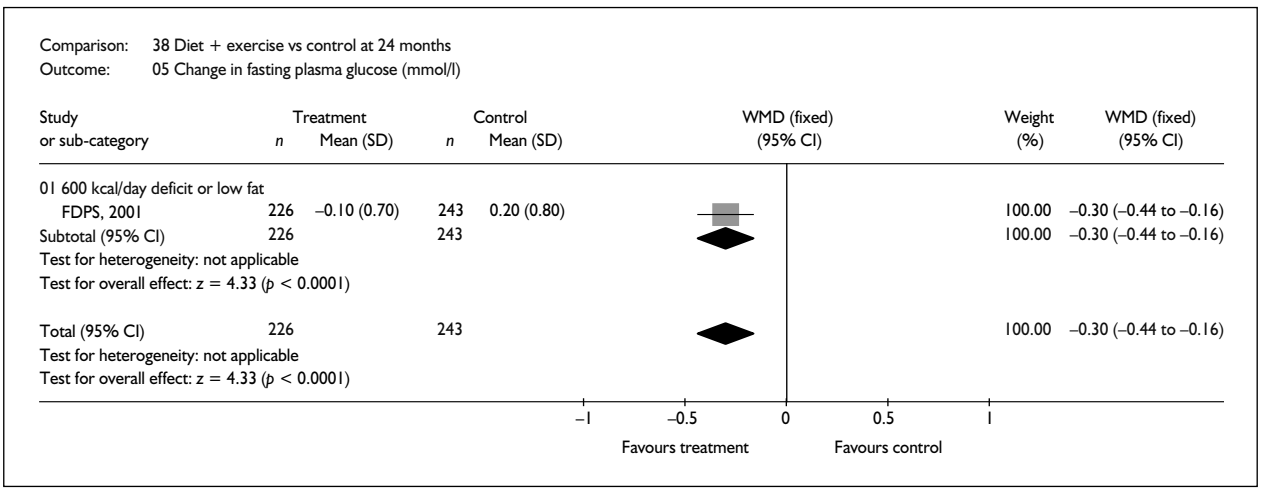


FIGURE 131

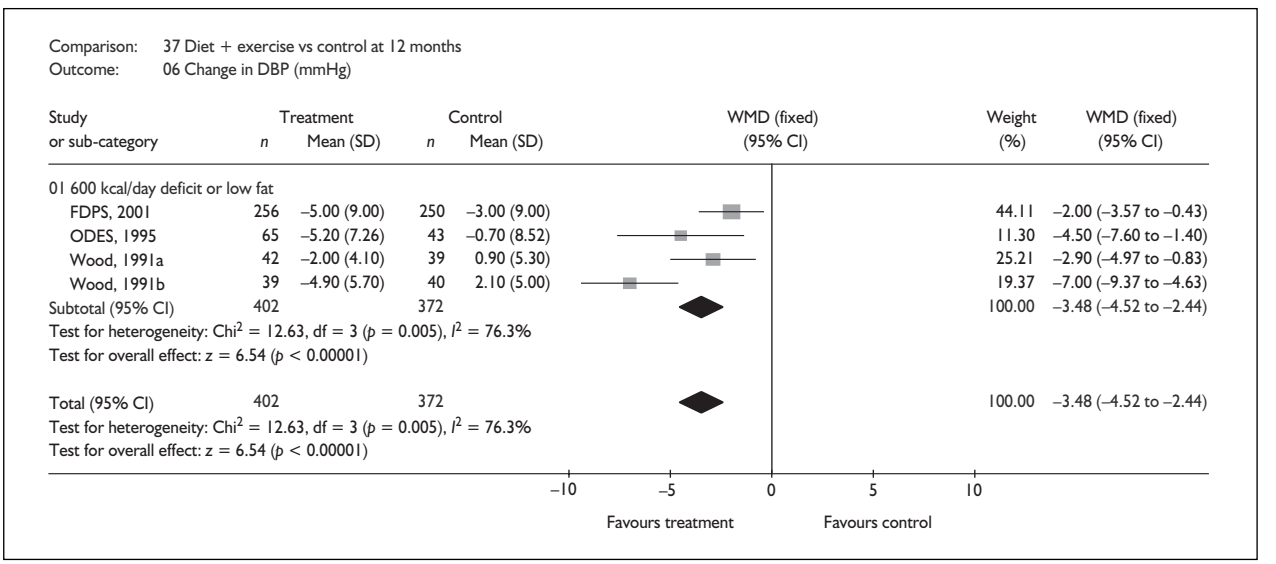


FIGURE 132

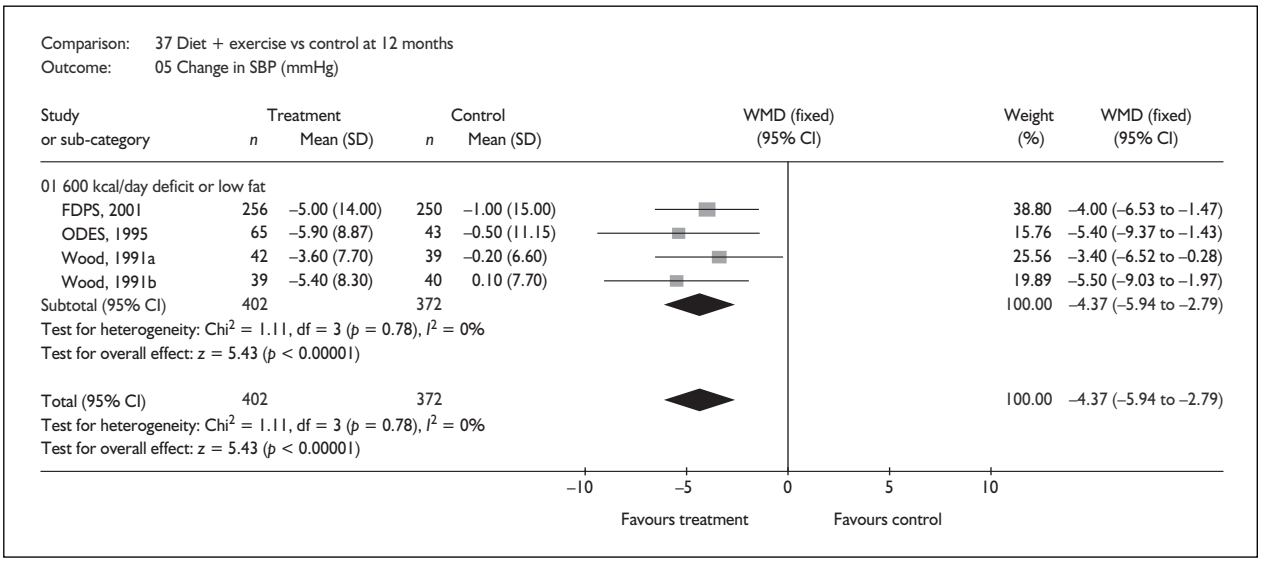


FIGURE 133

In the FDPS[167–171] the cumulative incidence of diabetes for both men and women was 58% lower in the intervention group than in the control group, hazard ratio 0.4 (95% CI 0.3 to 0.7). The FDPS reported one death and two people with breast cancer in the active treatment group, and one participant developed cancer of the large intestine in the control group. Two cases of cancer and one cardiac event were reported in the ODES,[115–121] but the treatment status was not stated.

Effects of diet and behaviour therapy versus control

Description of studies

Three RCTs provided change in weight at 12 months[172–177] and one of these studies also provided weight change at 24 months.[176,177] Data were provided for lipids, blood pressure and fasting plasma glucose at 12 months and, in addition, HbA_{1c} at 24 months. One cluster RCT[178] also reported change in weight and HbA_{1c} at 18 months for the diet and behaviour therapy group but not for the control.

One study used an ITT approach[176,177] and it was unclear whether this was the case for the other three studies.[172–175,178] Two of the studies were performed by the same authors at the Rehabilitation Research Centre of the Social Insurance Institution in Turku, Finland.[172–175] One study recruited people with one or two biological parents with type 2 diabetes.[176,177] The cluster RCT by Kaplan and colleagues, where groups were randomised,[178] recruited people with type 2 diabetes.

Reported mean was BMI 34 kg/m^2 in two studies[172–175] and 36 kg/m^2 in the study by Wing and colleagues.[176,177] Participants in the control groups of these three studies received minimal treatment. Contact visits for participants in the diet plus behaviour therapy groups were much more frequent in the study by Wing and colleagues,[176,177] where participants were contacted 40 times in the initial year compared with 13 times in the study by Karvetti and colleagues.[175]

Two studies used an LCD throughout[172–175] and one study used a VLCD for the initial 8 weeks, which was adjusted to provide an LCD by week 16.[176,177] The cluster RCT by Kaplan and colleagues[178] evaluated an LCD and behaviour therapy.

Review results

The meta-analysis of diet and behaviour therapy compared with no treatment showed a WMD weight change at 12 months of –7.21 kg (95% CI –8.68 to –5.75 kg) and at 24 months of –1.80 kg (95% CI –4.77 to 1.17 kg) (*Figures 134* and *135*).

At 12 months diet and behaviour therapy demonstrated beneficial effects on HDL cholesterol, with a weighted mean difference of 0.11 mmol/l (95% CI 0.06 to 0.17 mmol/l), triglycerides –0.58 mmol/l (95% CI –0.98 to –0.17 mmol/l), SBP –3.39 mmHg (95% CI –5.91 to –0.86 mmHg) and DBP –3.37 mmHg (95% CI –5.16 to –1.58 mmHg) (*Figures 136–150*). At 24 months the study by Wing and colleagues[176,177] showed significant beneficial

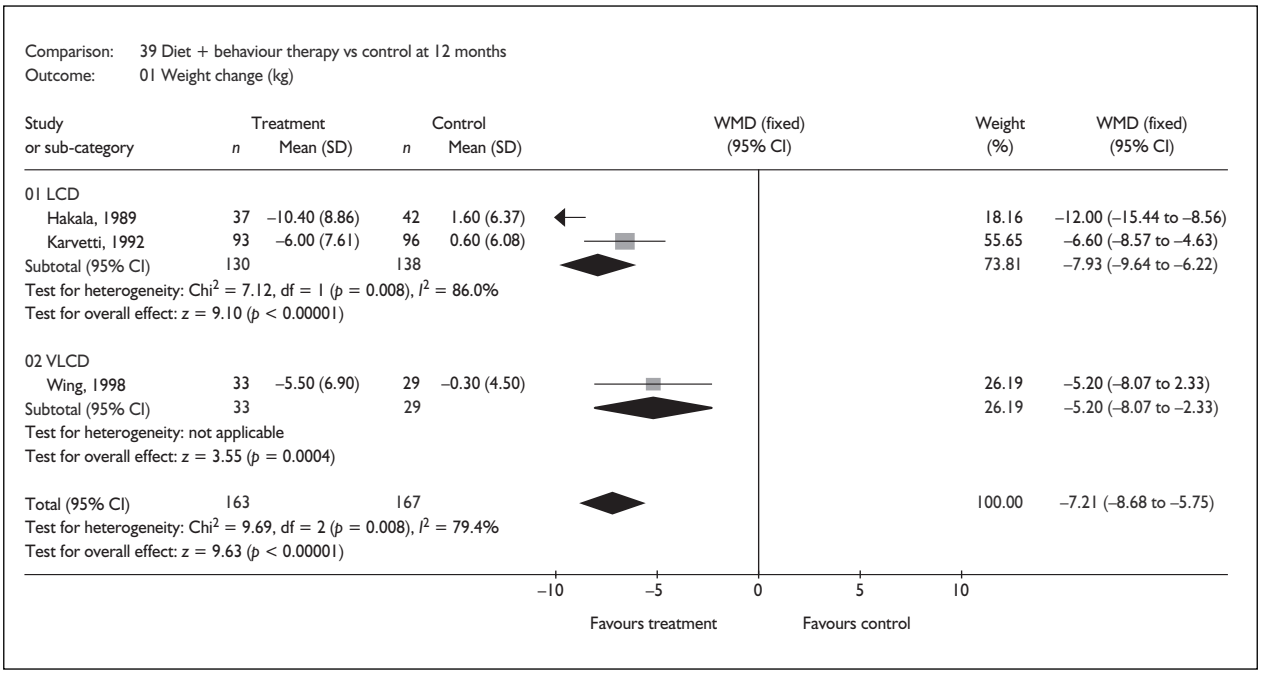


FIGURE 134

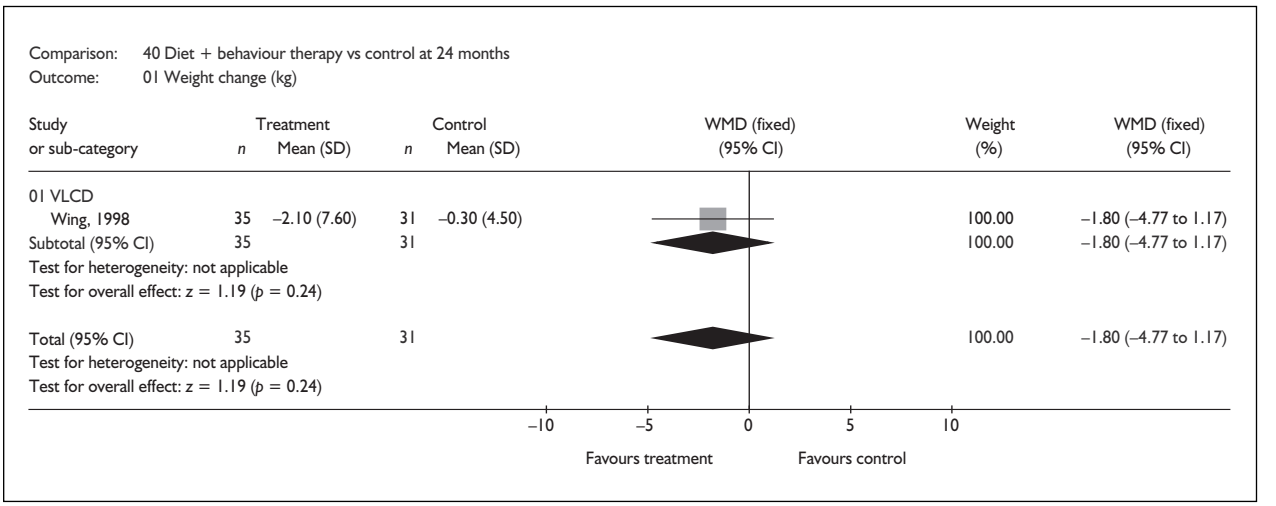


FIGURE 135

effects on total cholesterol only, WMD –0.30 mmol/l (95% CI –0.58 to –0.02 mmol/l), but the number of participants in this study was small.

In the cluster RCT by Kaplan and colleagues,[178] mean body weight in the groups ranged from 83.9 to 92.2 kg. All participants received an equal number of contacts and an active initial treatment period of 10 weeks. LCD plus behaviour therapy was associated with a mean weight change at 18 months of –1.68 kg, but weight change was not reported for the control group. At 18 months the diet and behaviour group was associated with a mean change in HbA_{1c} of –0.46% compared with 0.36% in the control group. Quality of well-being was also assessed, and was increased by 0.03 units in the diet and behaviour group and decreased by 0.04 units in the control group at 18 months.

No deaths or serious adverse events were reported in any of the studies. Wing and colleagues[176,177] reported that the risk of developing diabetes was 7% in the control group and 30.3% in the diet and behaviour therapy group.

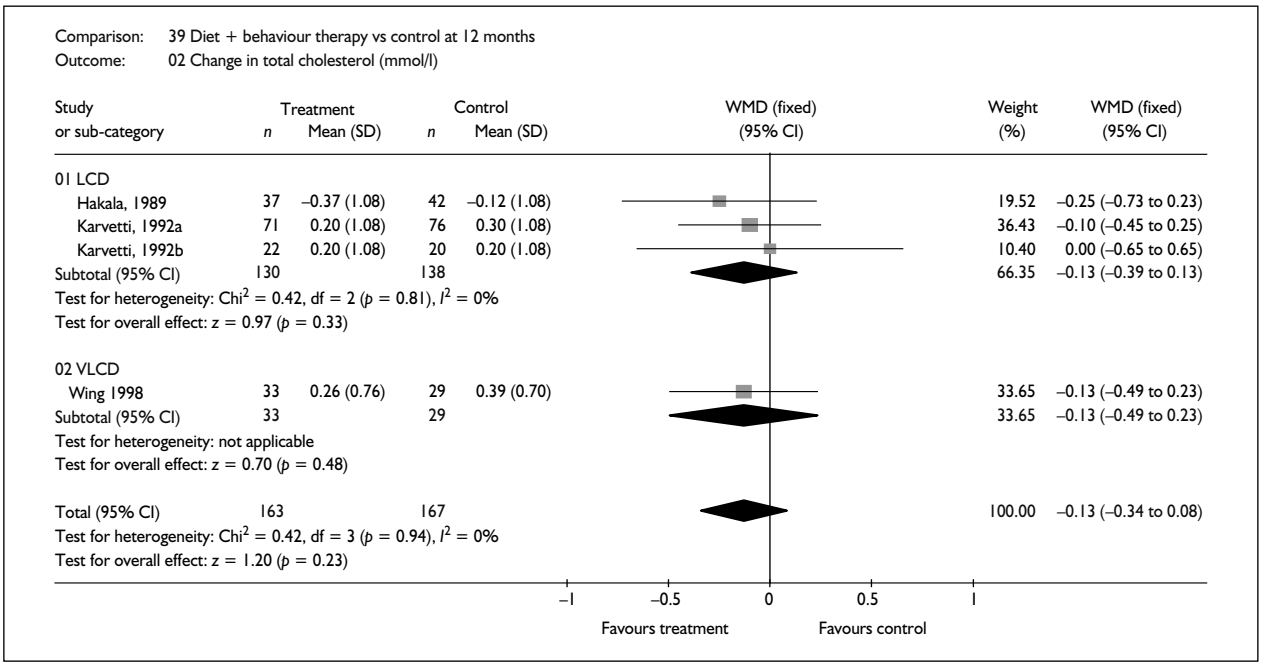


FIGURE 136

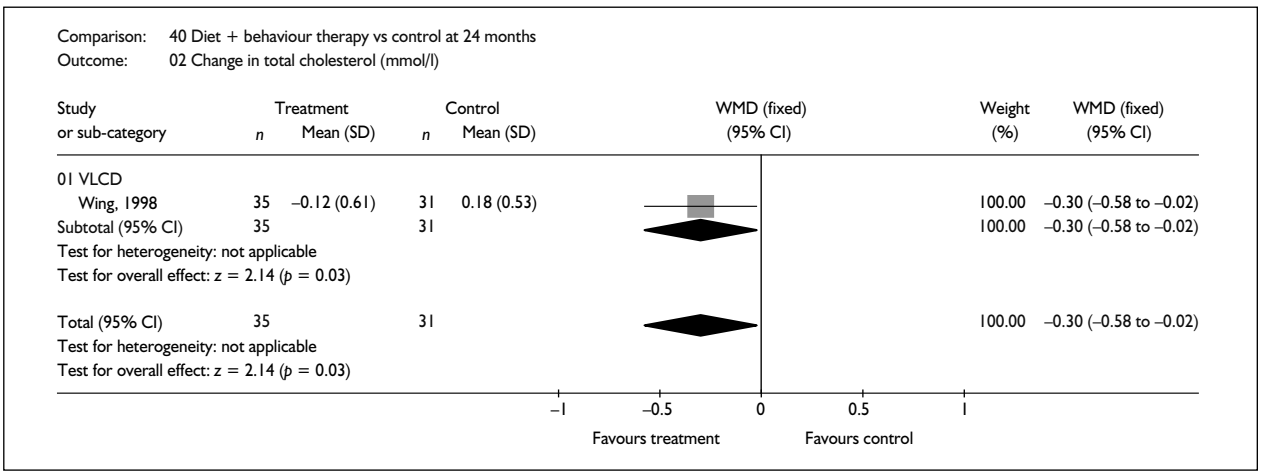


FIGURE 137

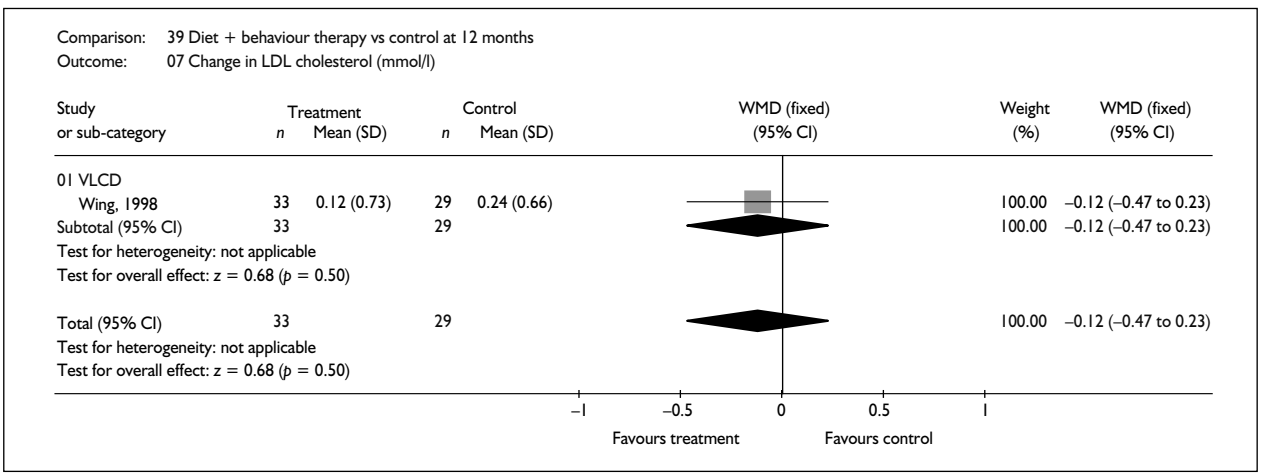


FIGURE 138

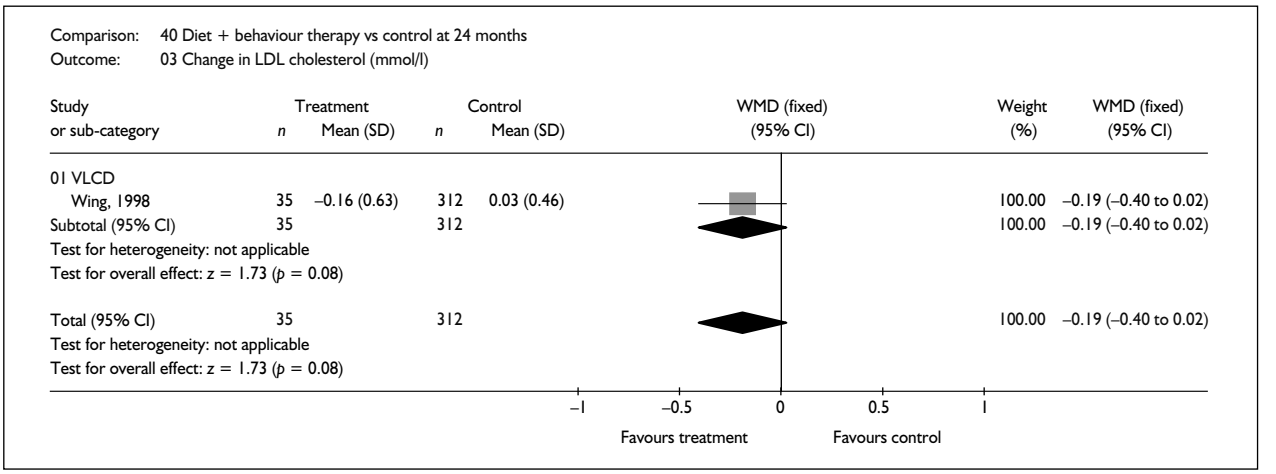


FIGURE 139

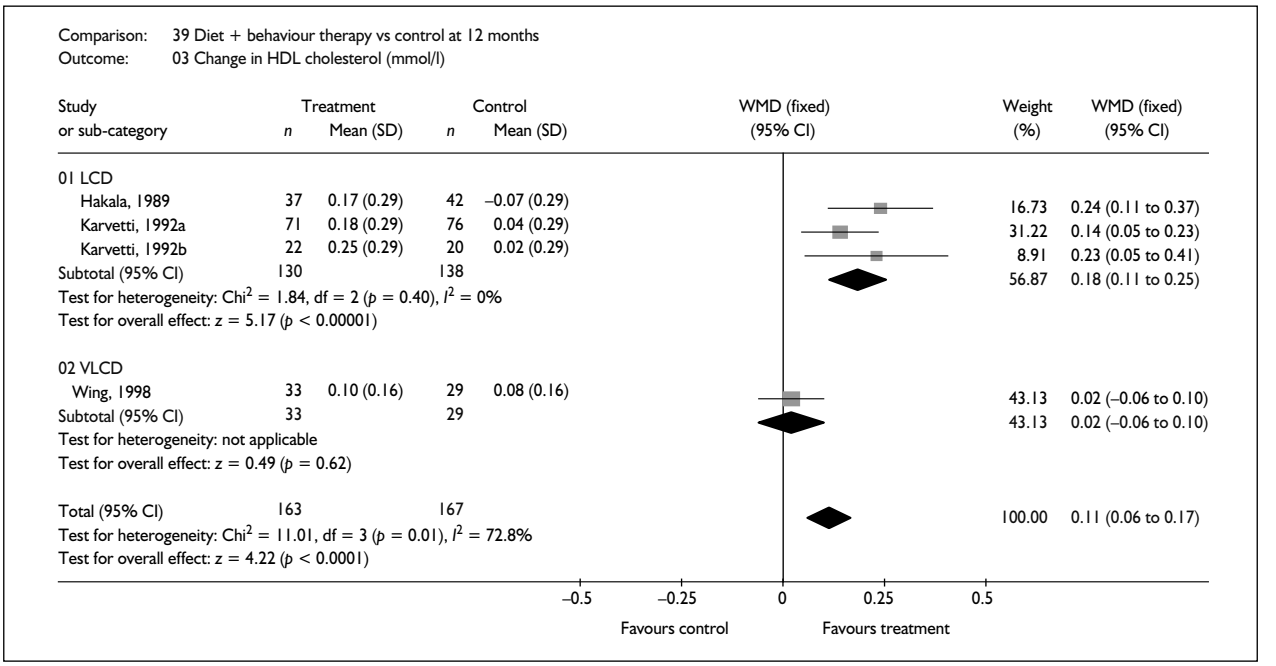


FIGURE 140

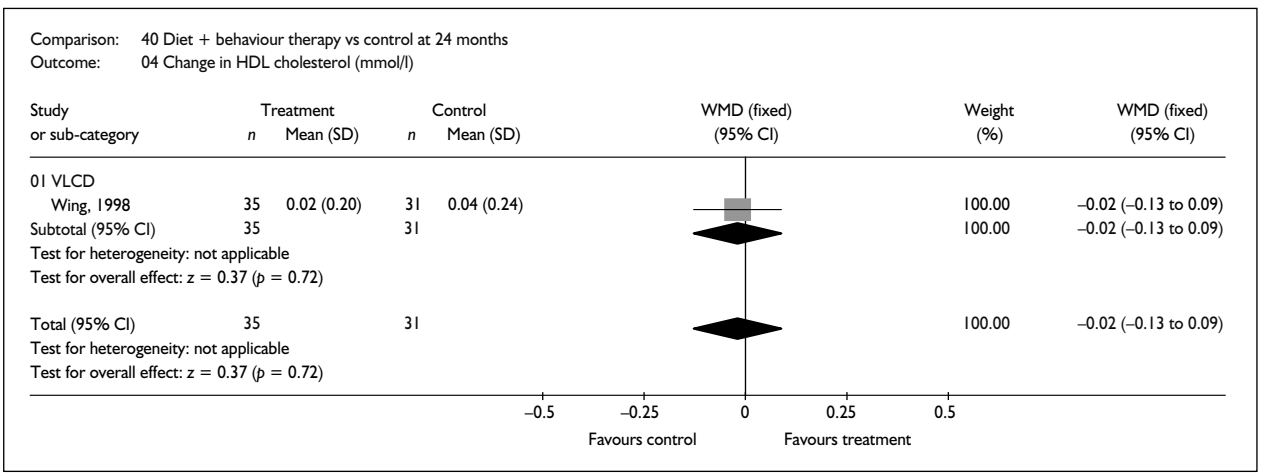


FIGURE 141

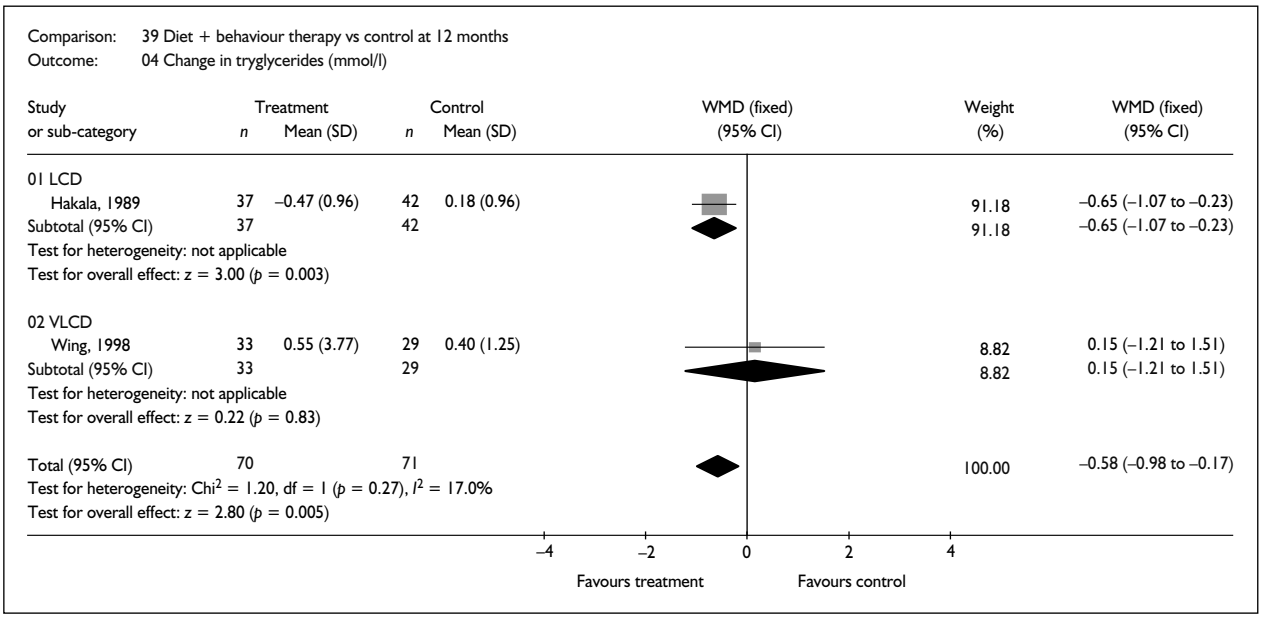
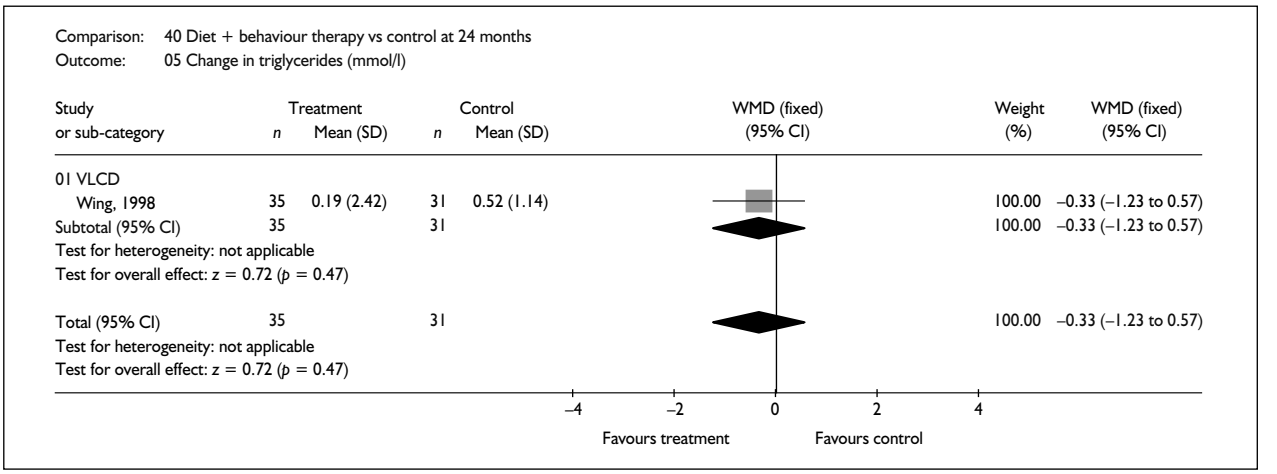


FIGURE 142



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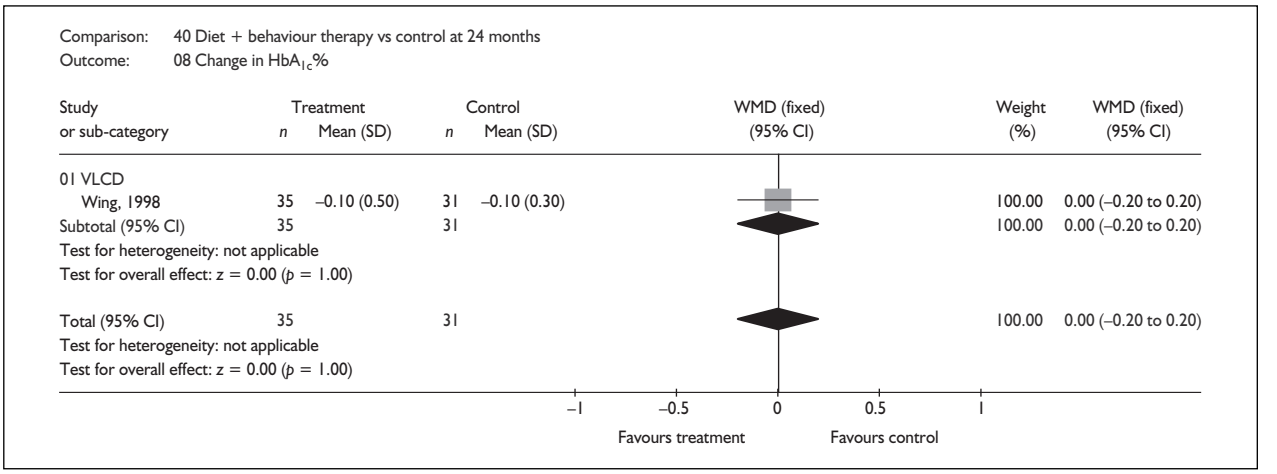

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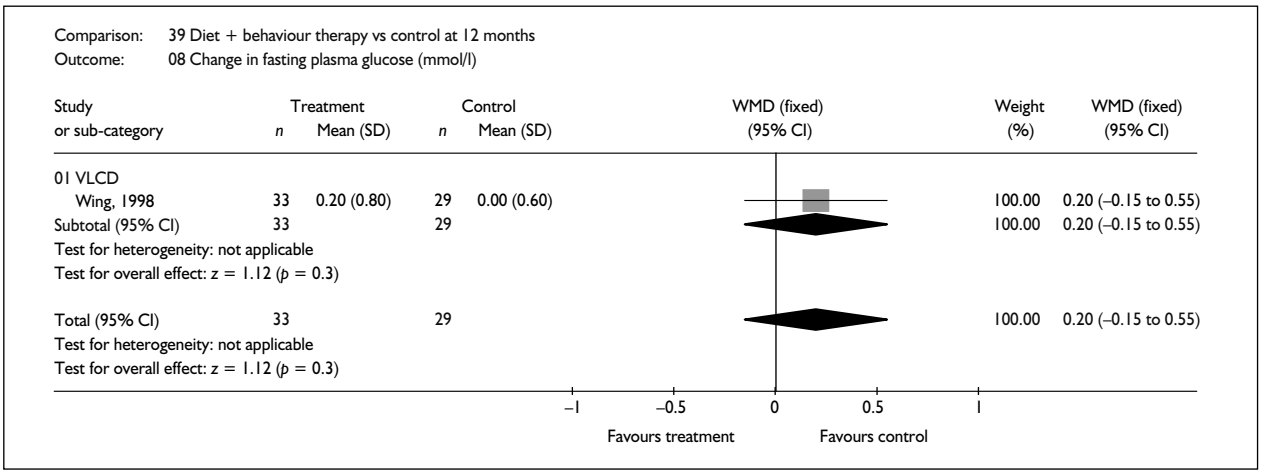

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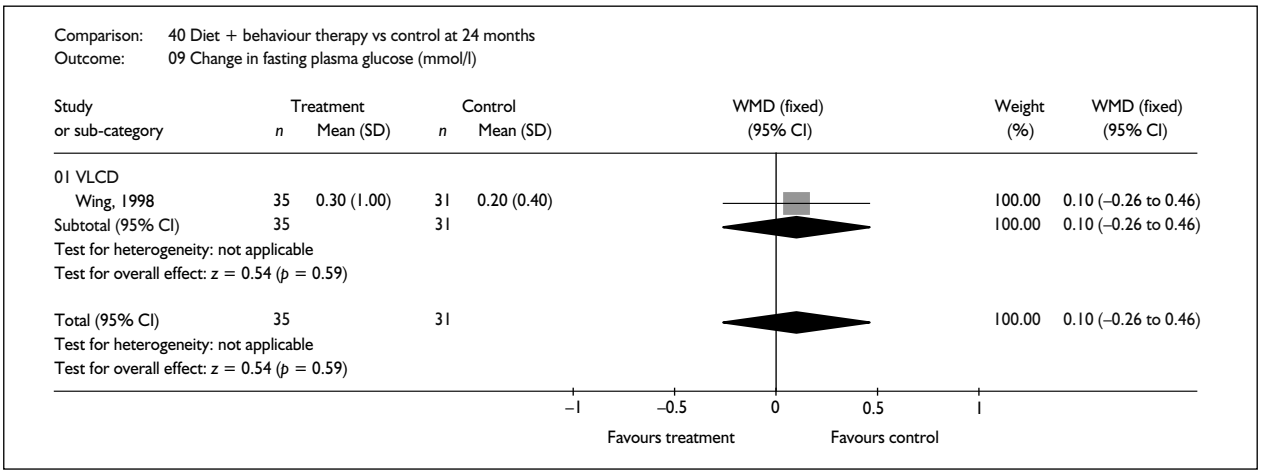

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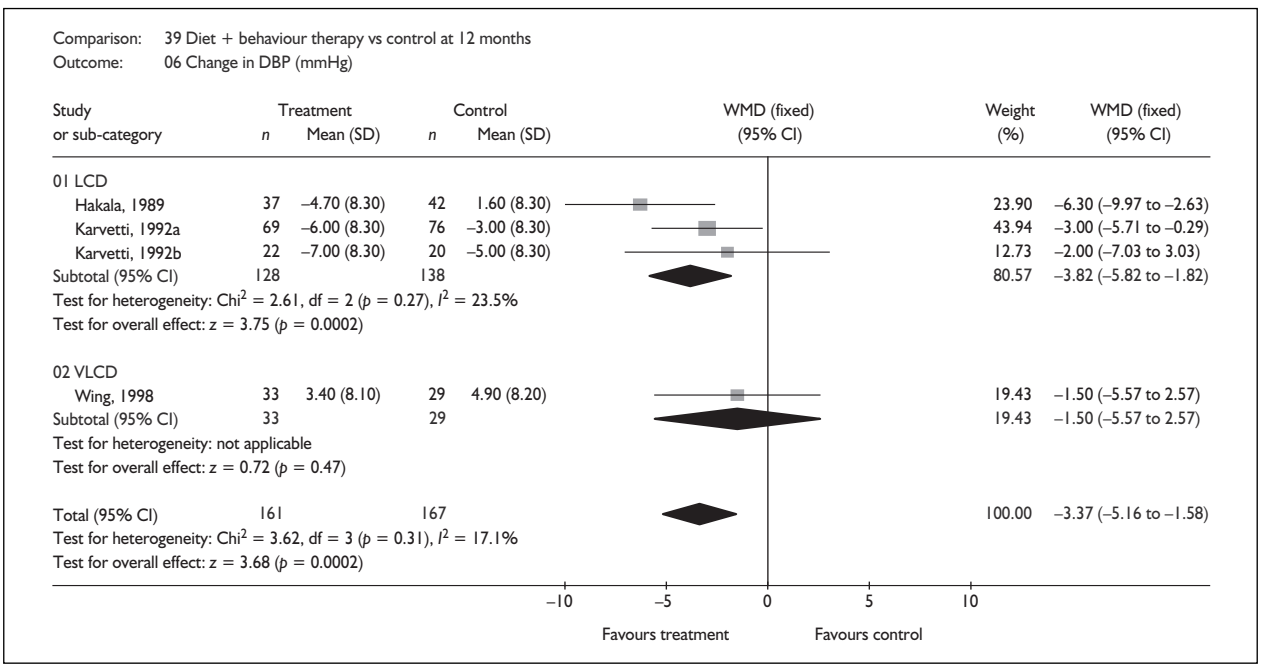


FIGURE 147

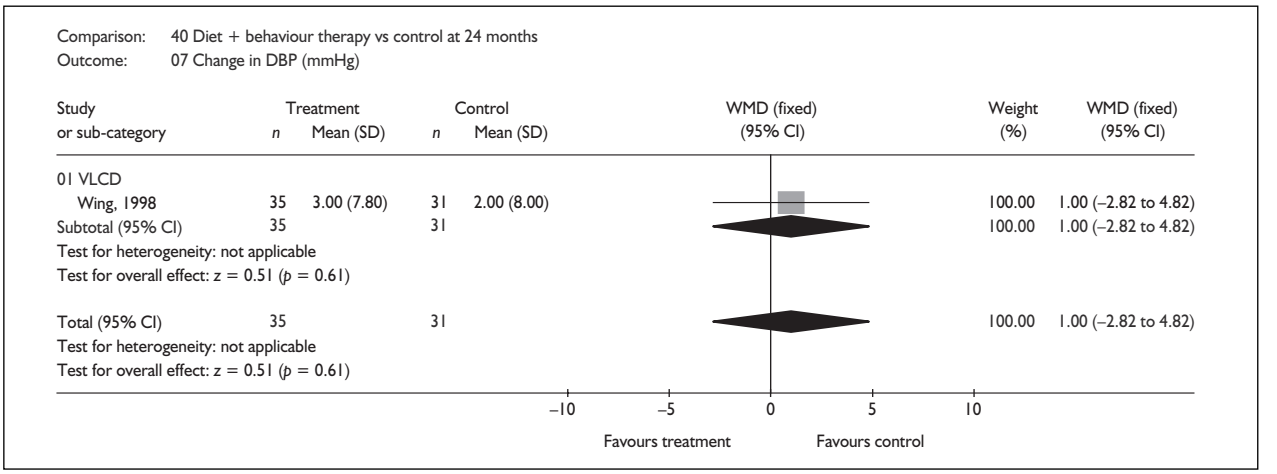


FIGURE 148

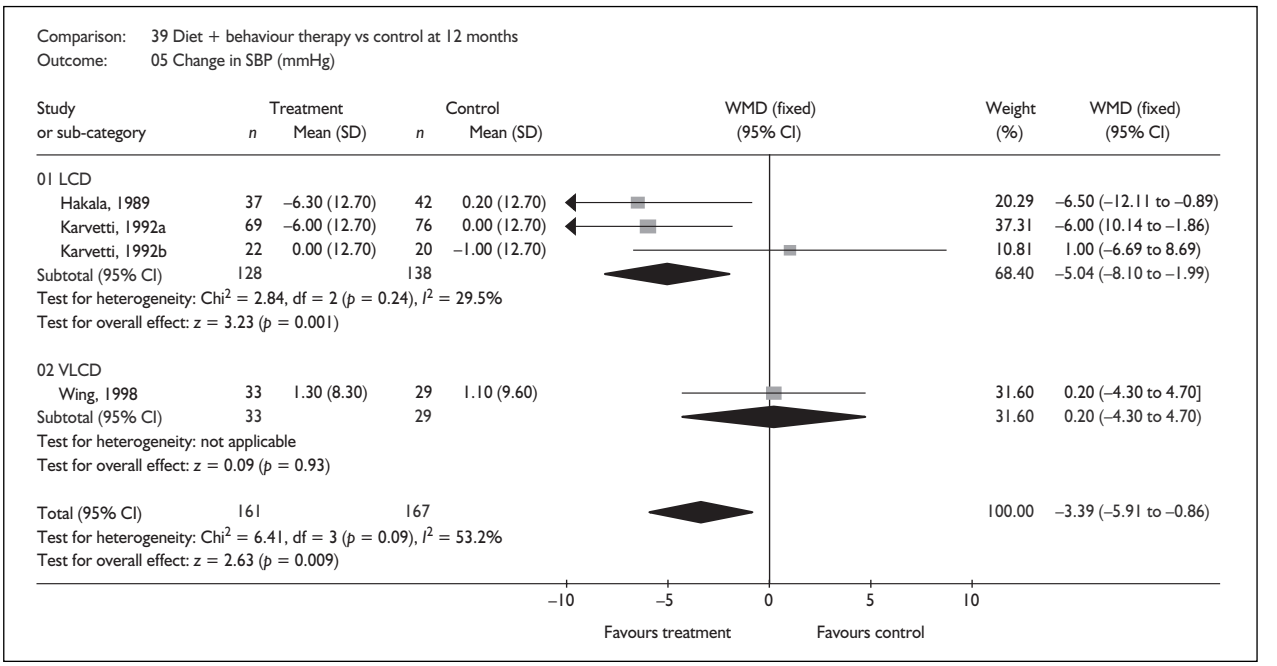


FIGURE 149

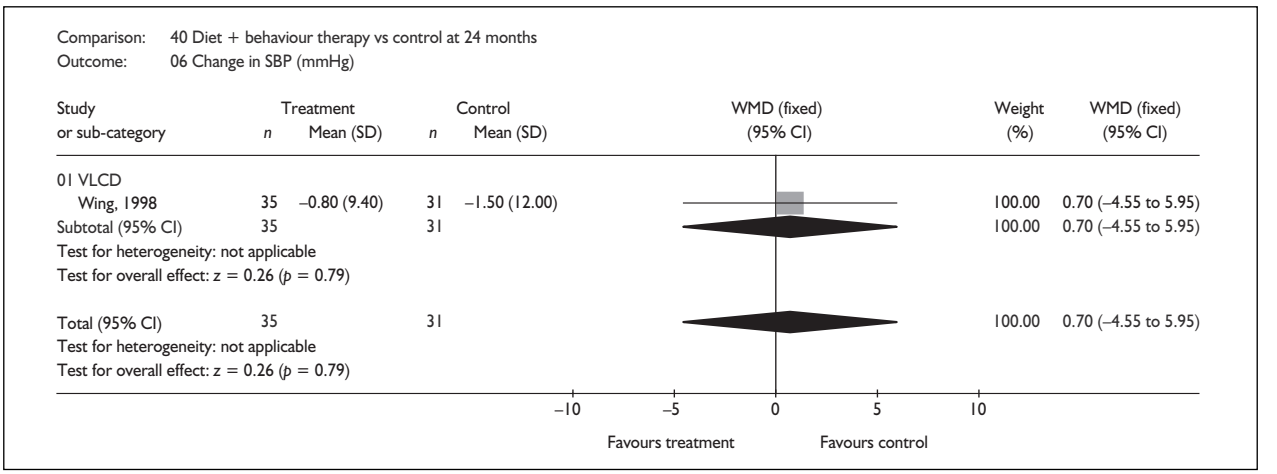


FIGURE 150

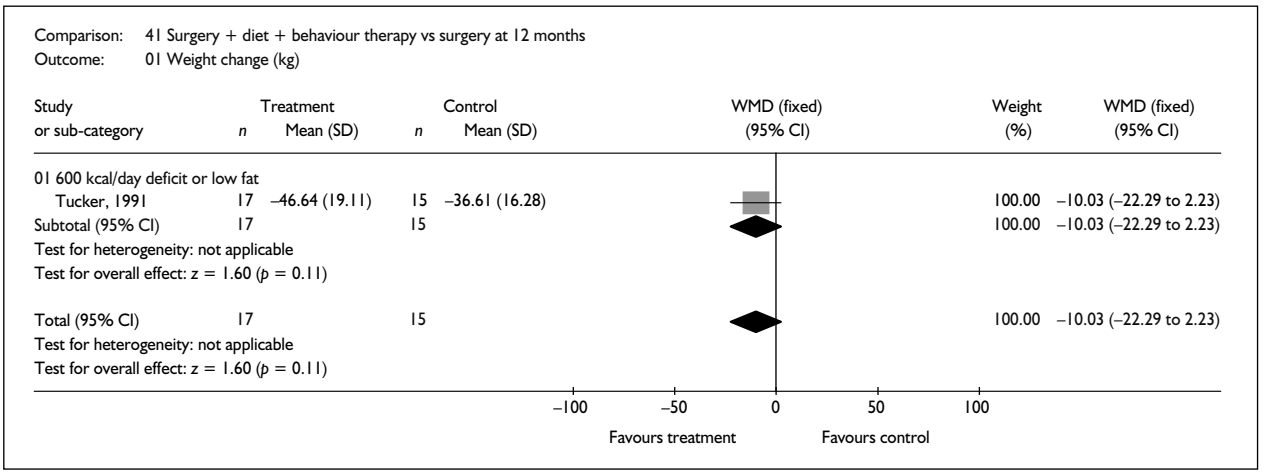


FIGURE 151

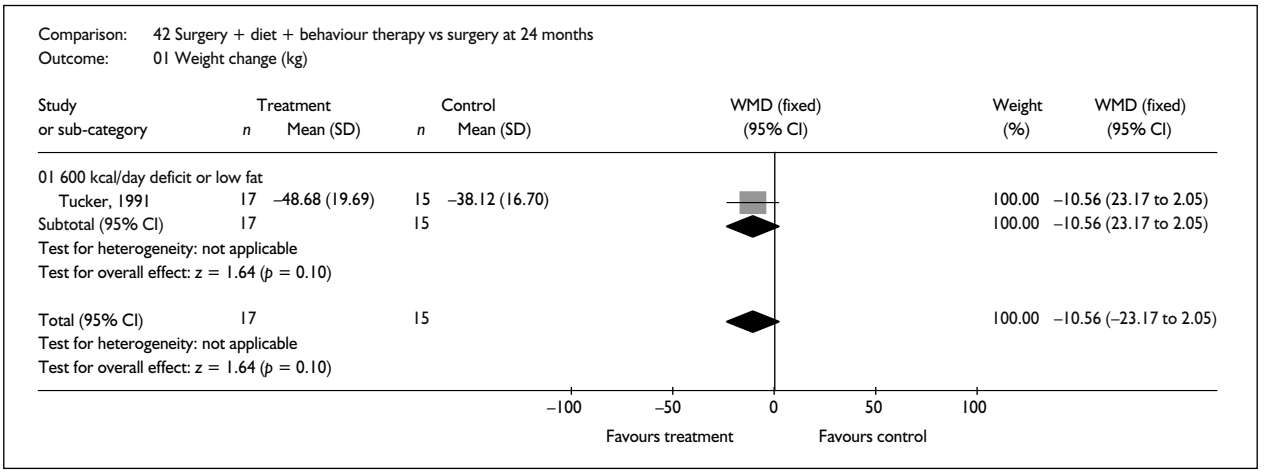


FIGURE 152

Effects of surgery and diet and behaviour therapy versus surgery

Description of study

One RCT compared the effect of behaviour therapy and dietary information with minimal intervention after bariatric surgery.[179] Change in weight at 12 and 24 months was provided, but no data were provided for risk factors.

It was unclear whether an ITT analysis had been used. Dropouts were 47% overall at 2 years. Mean BMI was 48.9 kg/m^2 in the group receiving diet and behaviour therapy postsurgery and 47.6 kg/m^2 in the minimal treatment group post-surgery. Participants were randomly assigned to treatment groups preoperatively and both groups were contacted the same number of times.

Review results

At 12 months diet and behaviour therapy compared with the minimal intervention was associated with a WMD weight change of –10.03 kg (95% CI –22.29 to 2.23 kg) and at 24 months of –10.56 kg (95% CI –23.17 to 2.05 kg). The number of participants in the study was small (*Figures 151* and *152*).

Effects of diet and behaviour therapy and exercise versus control

Description of studies

Twelve RCTs provided change in weight at 12 months or longer.[176–178,180–224] Of these 12 studies, ten provided change in weight at 12 months.[176,177,180–196,204–224] Five studies provided change in weight at 18 months,[178,182–186,197–224] four studies at 24 months,[176,177,187–193,204–224] two studies at 30 months[182–186,210–224] and one study at 36 months.[204–209]

Data were provided for lipids, blood pressure, fasting plasma glucose and HbA_{1c} at 12 and 24 months. Data on blood pressure were also provided at 18 and 36 months. One cluster RCT provided change in HbA_{1c} at 18 months.[178]

Two studies evaluated a population with hypertension[181,210–224] and two studies evaluated people with high–normal blood pressure.[197–209] Two studies recruited people with type 2 diabetes,[178,187–193] and another study recruited people with one or two biological parents with type 2 diabetes.[176,177] One study recruited people with abnormal oral glucose tolerance tests.[194]

Eleven of the studies recruited both genders, and one study recruited women only.[180] One study recruited married Mexican–American women with at least one preschool-aged child[180] and one study recruited Pima Indians from Arizona.[195]

Two studies assessed participants using an ITT approach.[176,177,196] It was unclear whether this approach had been used in another six studies.[178,181–193,197–209]

In two studies baseline weight appeared to differ between groups.[181,196] A high dropout rate at 12 months of 49% overall was reported in the study by Cousins and colleagues.[180] Reported mean BMI ranged from 30.2 kg/m^2 [194] to 36.5 kg/m^2 [195] and reported mean body weight ranged from 80 kg[181] to 93.6 kg.[204–209]

The duration of active treatment was 10 weeks for one study,[178] 12 months for five studies[180,181,187–195] and ranged from 18 months to 36 months for five studies.[176,177,182–186,197–224]

The control arms in most of the studies received considerably less contact compared with the active treatment, except in the studies by Laitinen and colleagues[187–193] and Kaplan and colleagues.[178] All control groups received minimal treatment, except for the study by Narayan and colleagues[195] where the control group received 12 monthly group meetings to discuss Pima culture and actively contribute to newsletters, and Kaplan and colleagues gave ten weekly information presentations on diabetes.[178] Active treatment ranged from seven visits in 12 months[187–193] to 53 visits in 12 months.[195] The study by Lindahl and colleagues[194] included one initial month's full board in a wellness centre with a follow-up stay at 12 months for the active treatment group. The number of participants in each study varied from 15 participants in one group[196] to 596 in another group.[204–209]

Seven studies used a 600 kcal/day deficit or low-fat diet,[187–224] four studies used an LCD[178,180–186] and one study used a VLCD for the initial 8 weeks then an LCD.[176,177]

Review results

Diet, behaviour therapy and exercise compared with control from 11 studies was associated with an overall WMD weight change at 12 months of –4.00 kg (95% CI –4.47 to –3.54 kg) (*Figure 153*). There was evidence of statistical heterogeneity, such that the results should be particularly treated with caution. The VLCD was associated with greater weight loss than the 600 kcal/day deficit or low-fat diets, but data were only derived from one VLCD study. Only one study was associated with a weight gain in the active treatment group.[195] Diet, behaviour therapy and exercise in four trials was associated with an overall WMD weight change at 18 months of –3.40 kg (95% CI –3.84 to –2.97 kg) and at 24 months of –3.00 kg (95% CI –3.59 to –2.40 kg) (*Figures 154* and *155*).

Diet, behaviour therapy and exercise was associated with a WMD weight change at 30 months of –4.68 kg (95% CI –6.08 to –3.28 kg, two trials) and at 36 months of –2.00 kg (95% CI –2.66 to –1.34 kg, one trial) (*Figures 156* and *157*).

At 12 months and at 18 months diet, behaviour therapy and exercise was associated with a significant beneficial effect on DBP and SBP (*Figures 158–165*). Changes in blood pressure were no longer statistically significant at 24 months, but were significant for SBP at 36 months and of borderline significance for DBP at 36 months. Triglycerides were also significantly decreased at 12 and 24 months, and HDL cholesterol significantly increased at 12 months (*Figures 166–177*).

Results for risk factors in people with hypertension or type 2 diabetes are presented in *Tables 7* and *8*.

In the cluster RCT by Kaplan and colleagues,[178] the authors reported that at 18 months participants' weight was "essentially constant" in the LCD, behaviour therapy and exercise group. Change in weight was not reported for the control group at 18 months. At 18 months the diet, behaviour therapy and exercise group was associated with a mean change in HbA_{1c} of –1.48% compared with 0.36% in the control group. The authors reported that for 100 participants receiving the diet, exercise and behaviour therapy programme 4.7 well-years would be produced, compared with the control (0.047 well-years for each participant, where 0 = death and 1 = optimal function).[178]

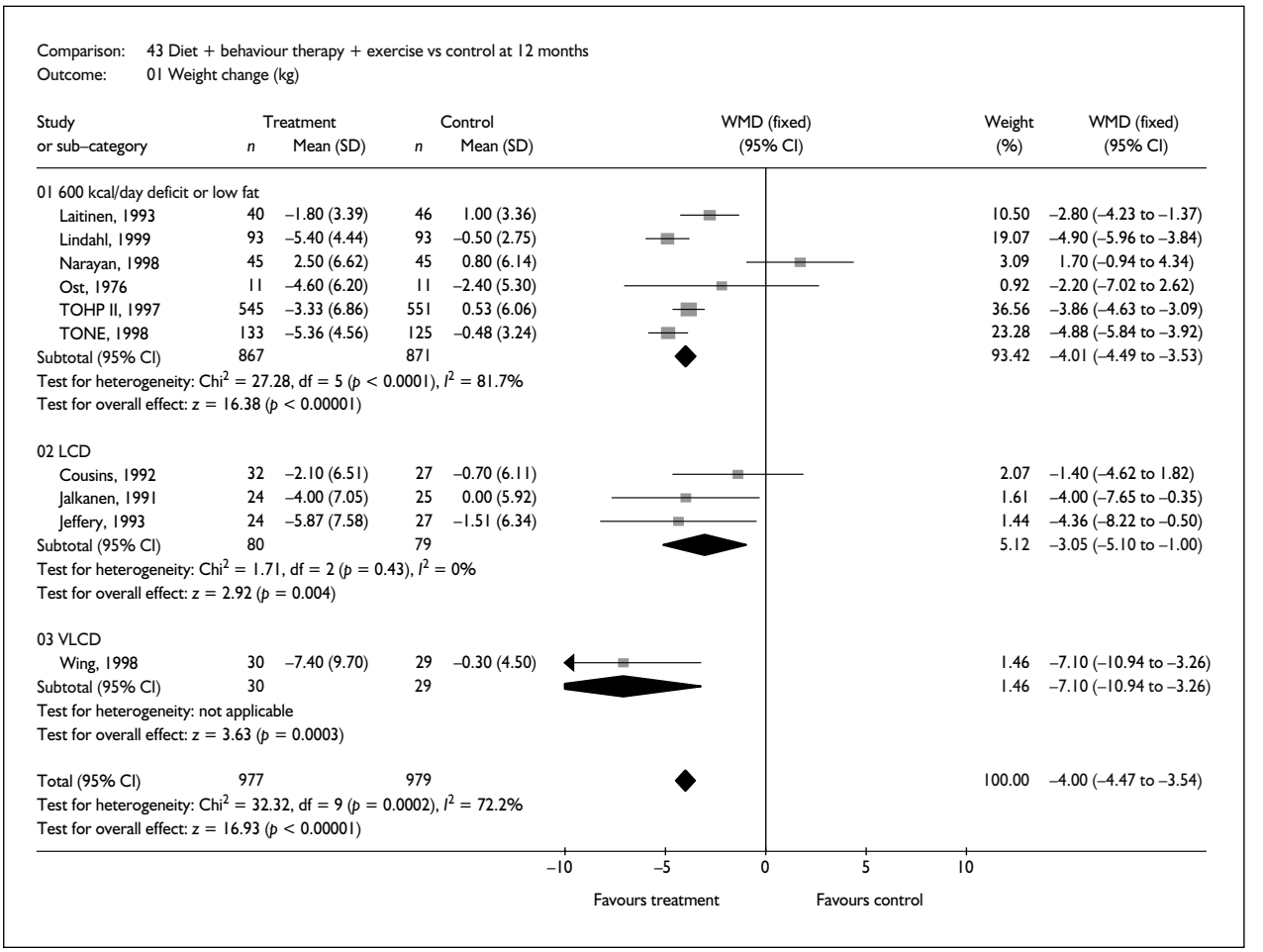


FIGURE 153

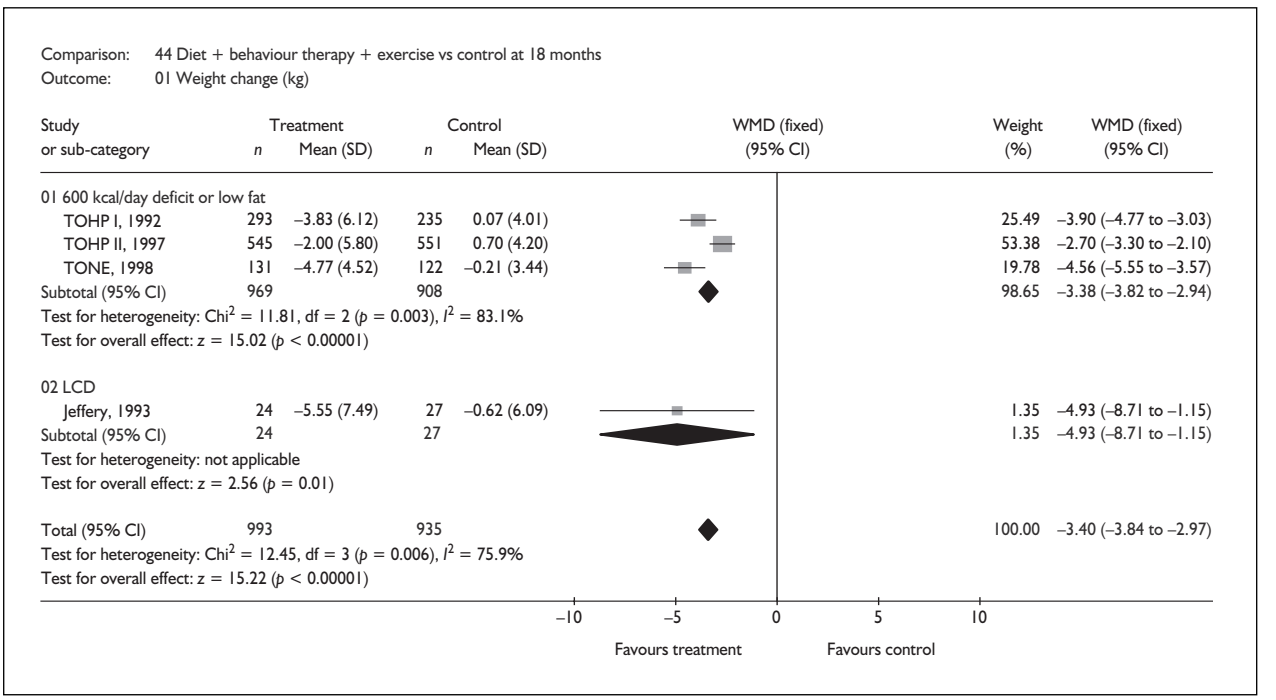


FIGURE 154

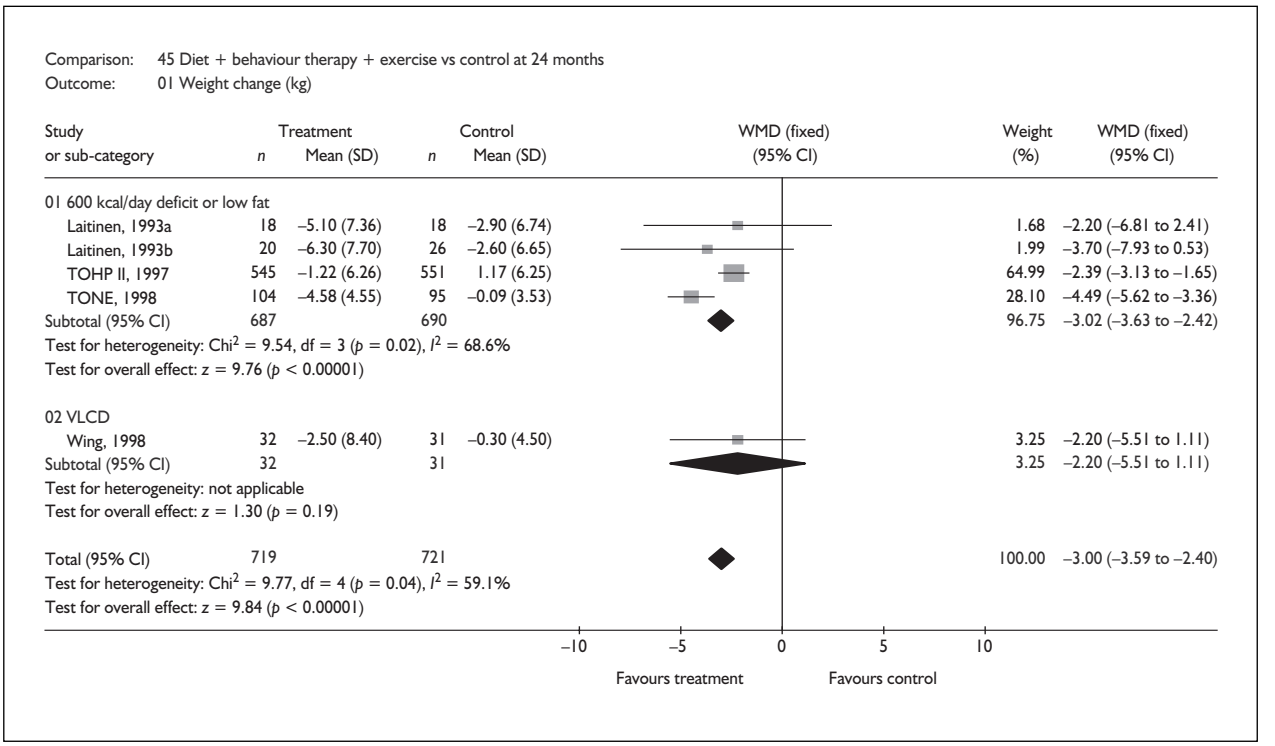


FIGURE 155

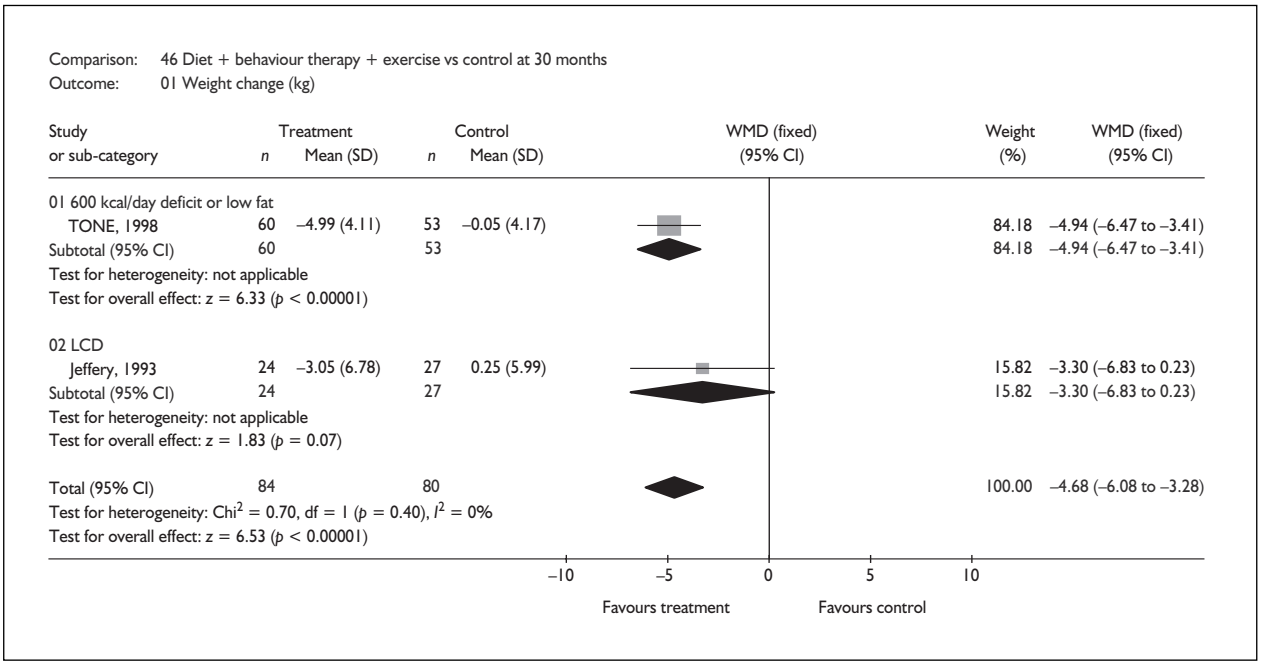


FIGURE 156

In the study by Wing and colleagues,[176,177] two out of 40 control participants and five out of 40 participants assigned diet, exercise and behaviour therapy developed type 2 diabetes mellitus at 2 years.

Two participants with MI were reported in the active treatment group and four in the control group (which includes non-obese participants) of the Trial of Non-pharmacological Interventions in the Elderly (TONE) study.[210–224] Two participants

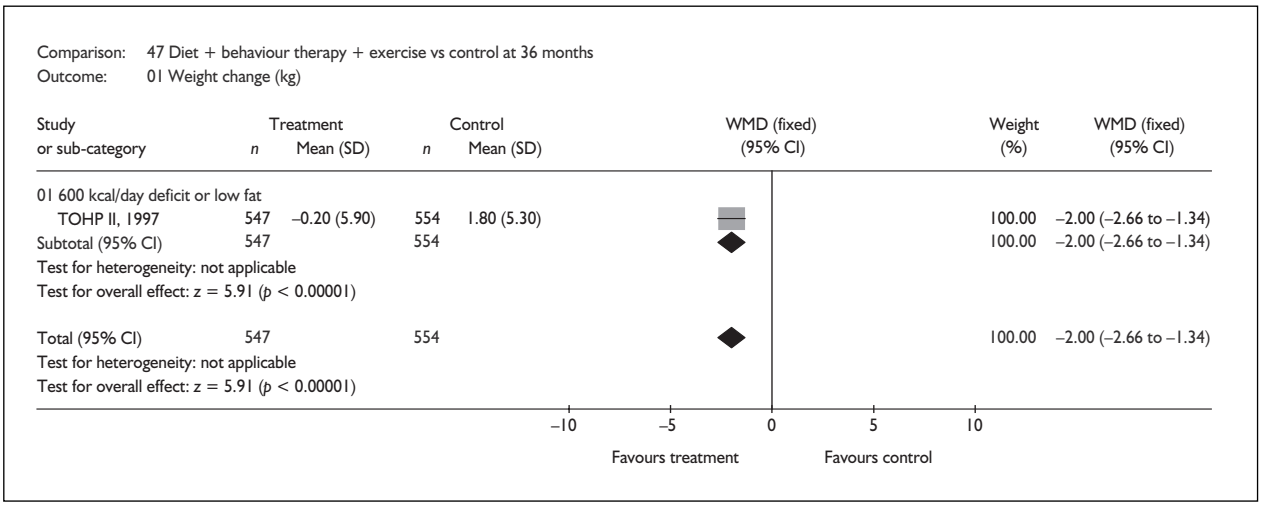


FIGURE 157

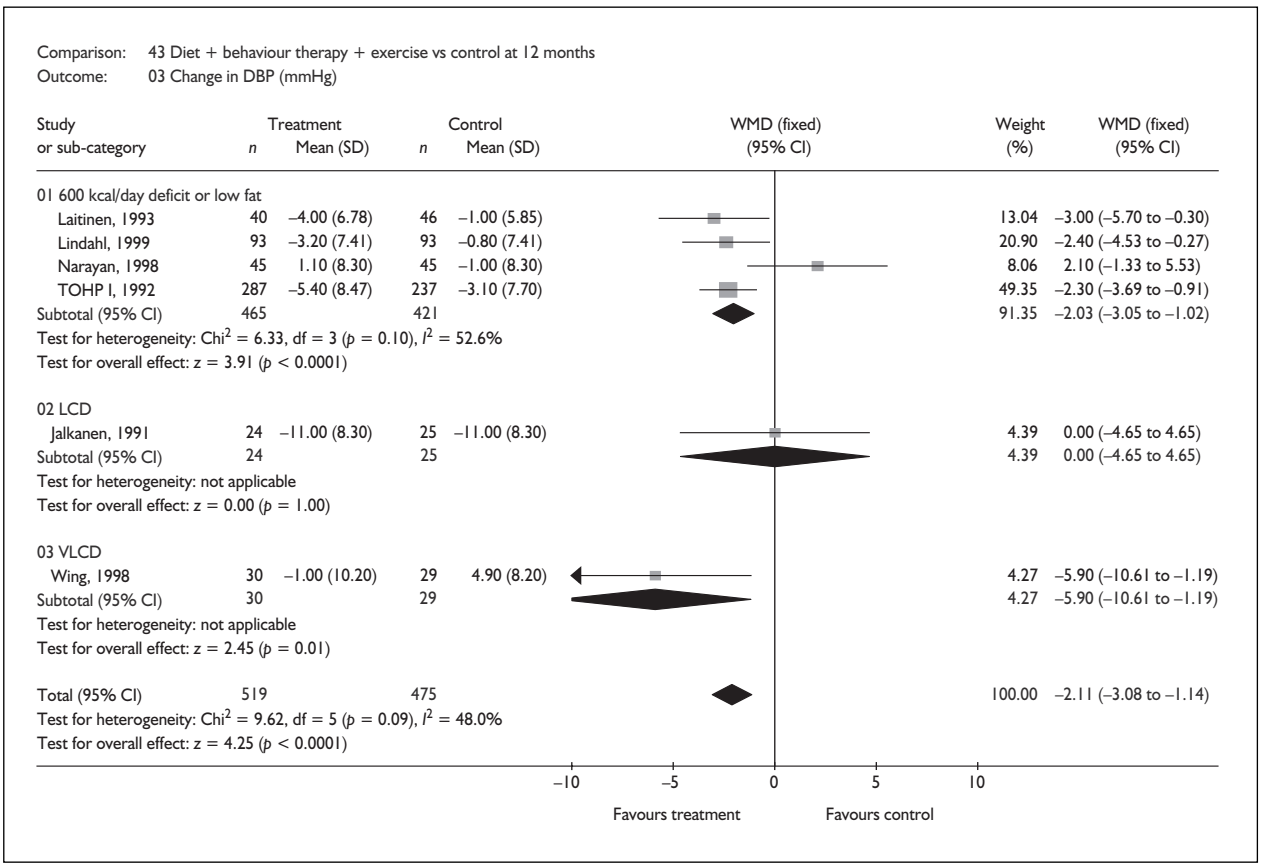


FIGURE 158

with cerebrovascular accident were also reported in the control group (which includes non-obese participants), and none in the intervention group. In the TONE study the hazard ratio for the primary end-point (recurrence of hypertension or cardiovascular events) was 0.65 (95% CI 0.50 to 0.85%) for those randomised to weight loss alone compared with controls. One participant with breast cancer and one with pancreatic cancer were reported, but it was unclear which groups these people came from.

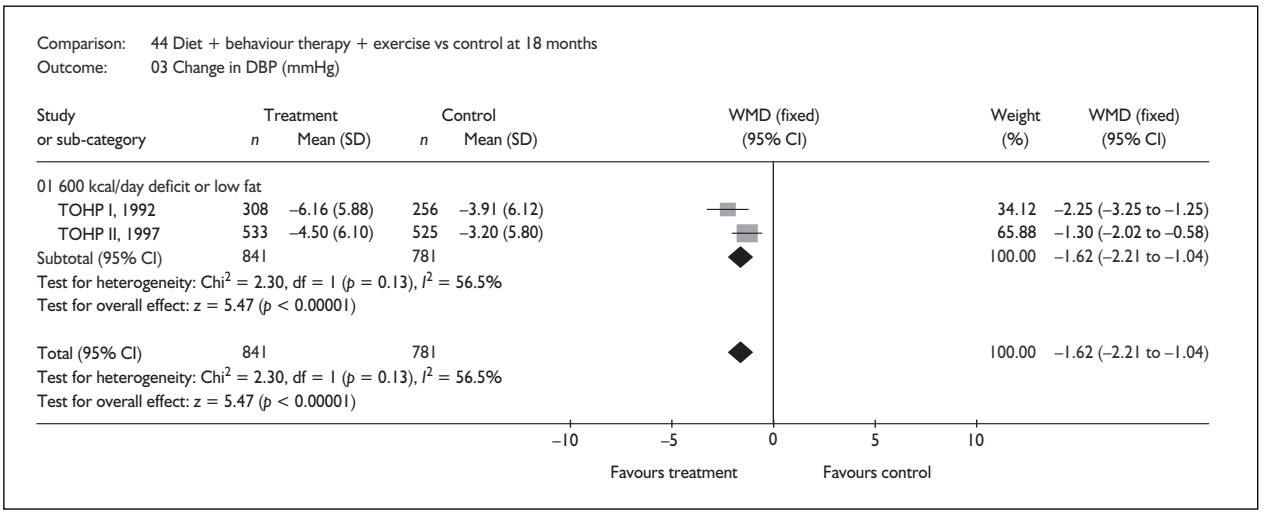


FIGURE 159

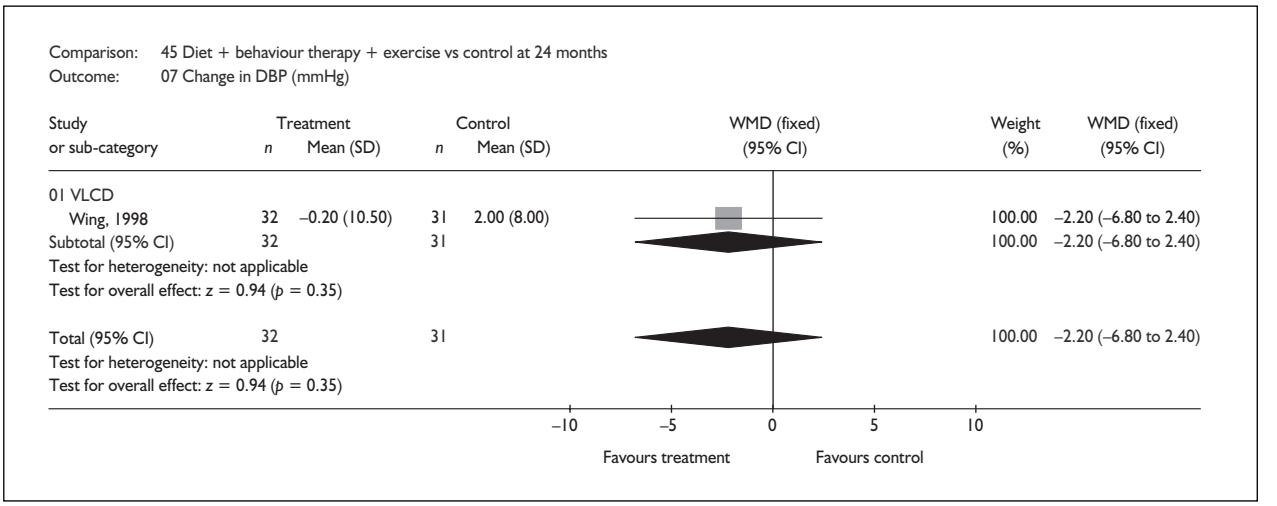


FIGURE 160

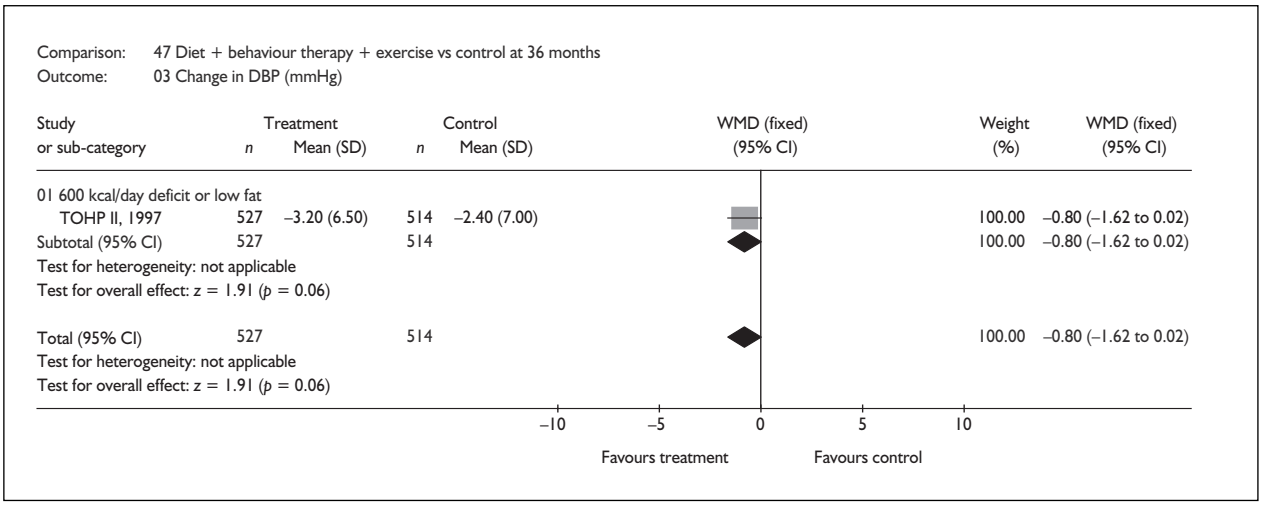


FIGURE 161

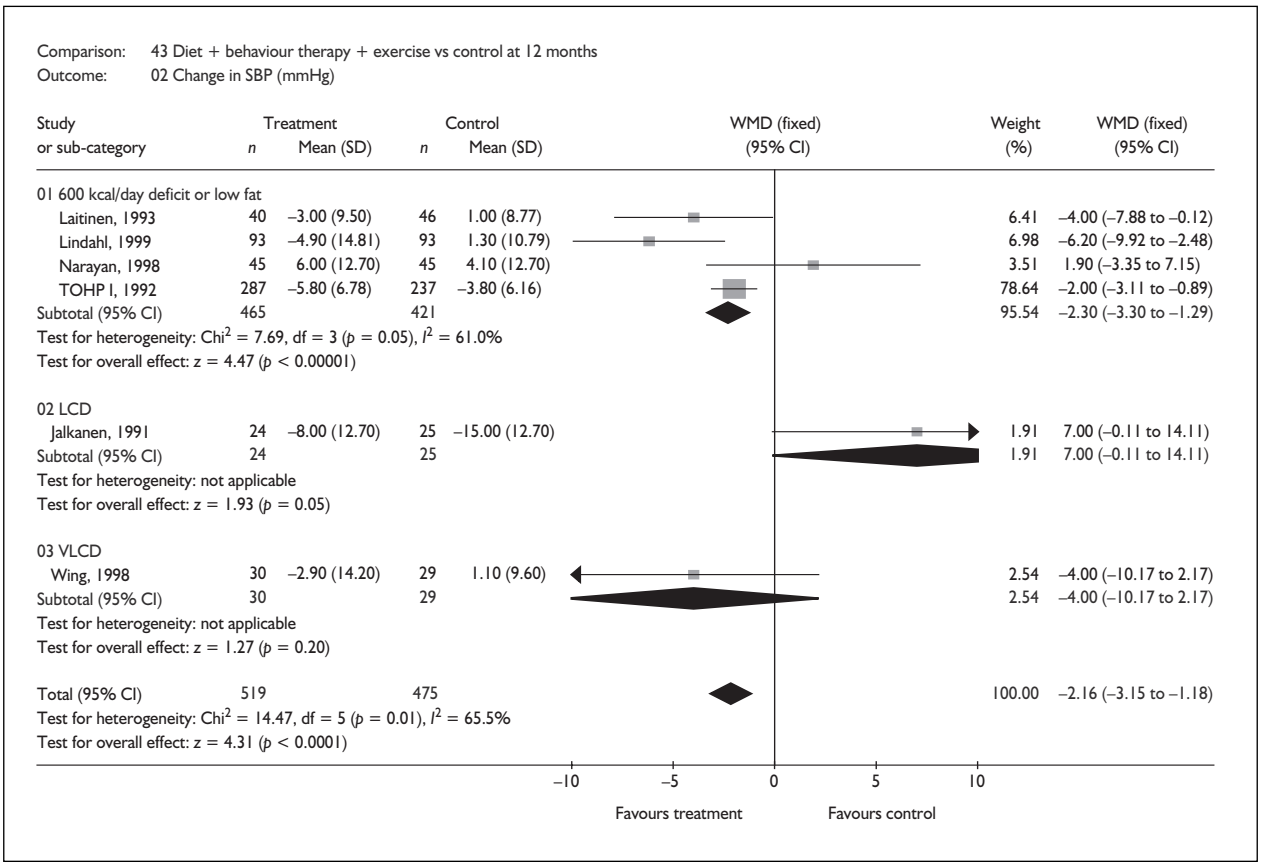


FIGURE 162

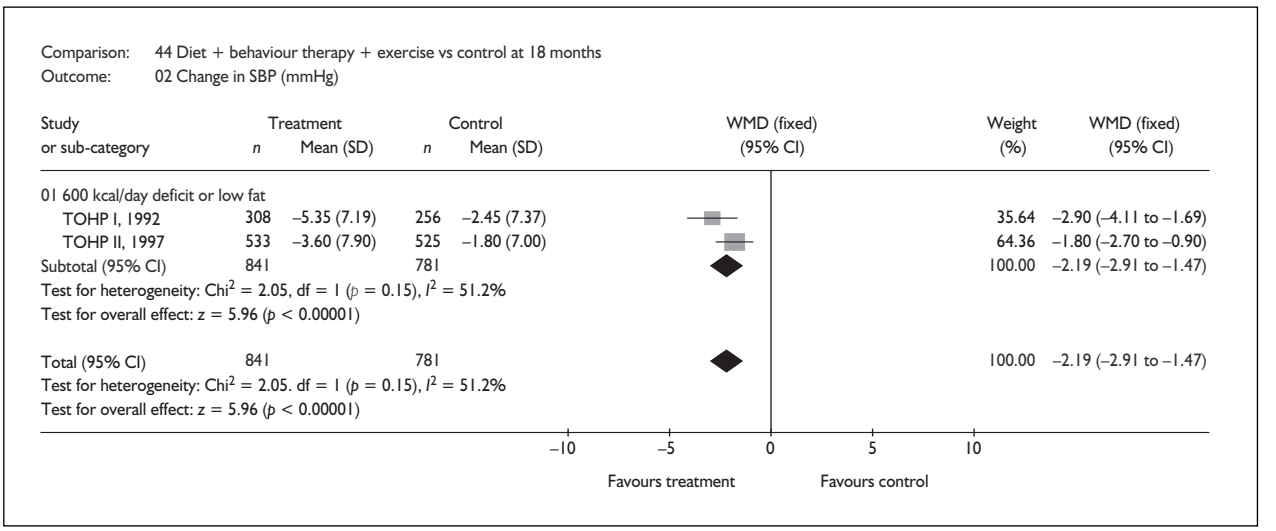


FIGURE 163

One death was reported in the intervention group and none in the control group of Trials of Hypertension Prevention (TOHP) I.[197–203] The relative risk for developing hypertension for the intervention group was 0.66 (95% CI 0.46 to 0.94%).

In TOHP II[204–209] five people randomised to weight loss died (three cardiovascular disease deaths) and two people in the usual care group died. The relative risk of developing hypertension for the weight loss group was 0.87 ($p = 0.06$) at 48 months.

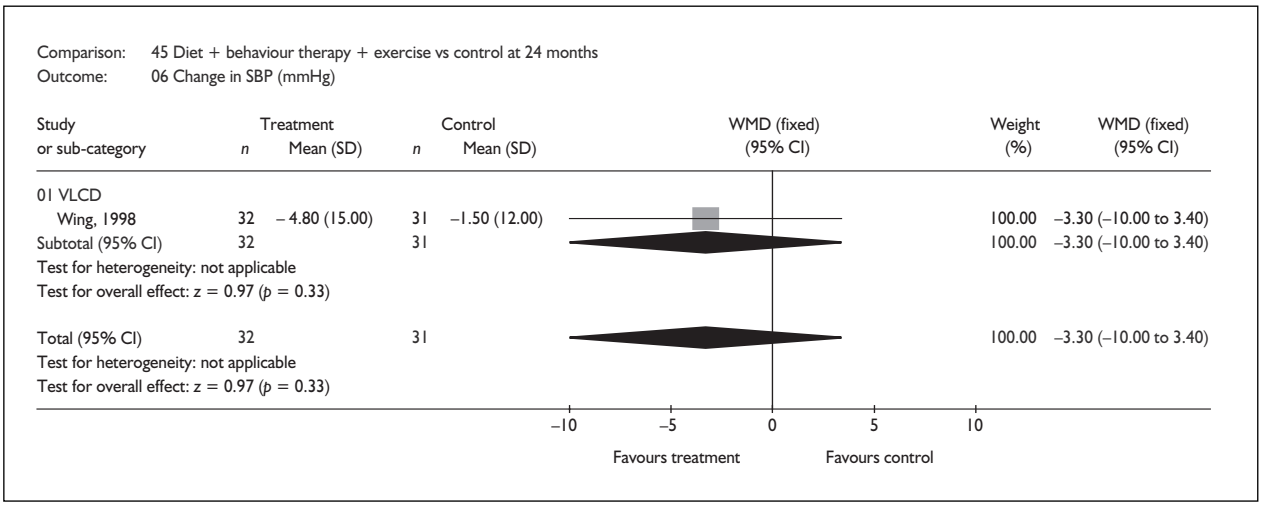


FIGURE 164

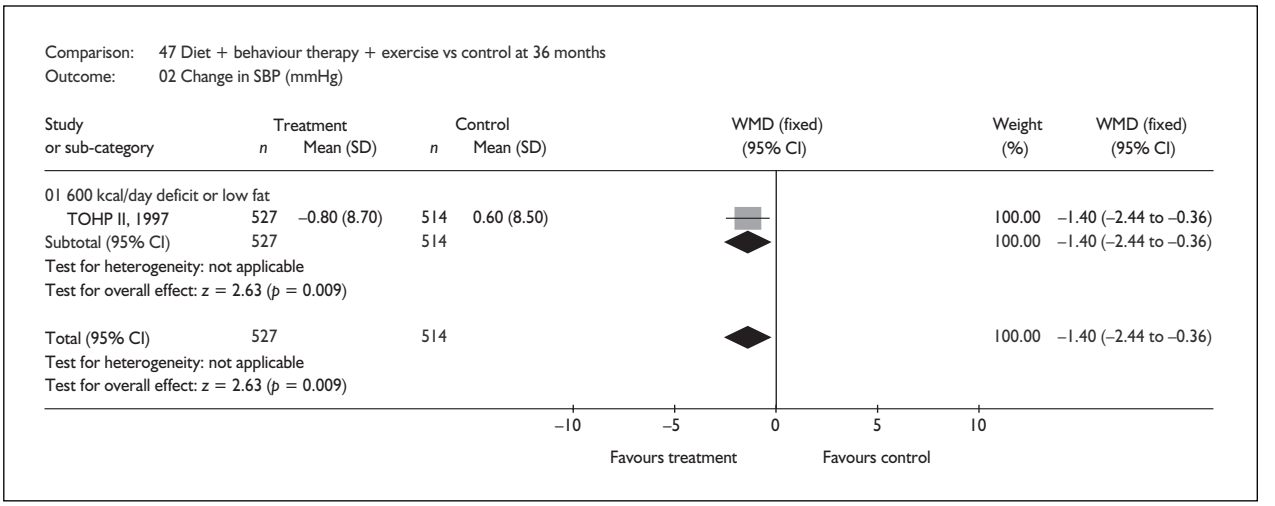


FIGURE 165

Effects of family versus individual treatment

Description of studies

Seven RCTs assessed the effects of family versus individual treatment and provided change in weight at 12 months or longer.[180,225–231] Four studies provided change in weight at 12 months,[180,225–228] two at 18 months,[230,231] one at 24 months,[226,227] one at 43 months[229] and one at 48 months.[226,227] Only the study by Wing and colleagues[230] provided data on risk factor changes (HbA_{1c} and fasting plasma glucose at 18 months).

Three studies assessed change in weight using an ITT approach[226,227,229,231] and in one other study this was possibly done.[230] The treatment received by all participants in each study was similar except for the mode of delivery, which was either family based or individually based. The treatment received across studies varied. Four studies used LCD, behaviour therapy and exercise interventions for all participants.[180,226,227,230,231] The study by Pearce and colleagues[228] used an LCD and behaviour therapy, and only advised participants to increase physical activity if weight was not lost. Rosenthal and colleagues[229] used a 'slim chance in a fat world' weight loss programme and behaviour therapy and Black and Lantz[225] used behavioural contracts that focused on changing eating and exercise habits.

Three studies recruited married women, with the family intervention arm consisting of spouses.[225,228,229] One study recruited married Mexican–American women with at least one preschool-aged child, with the family intervention arm consisting of spouses and separate classes for

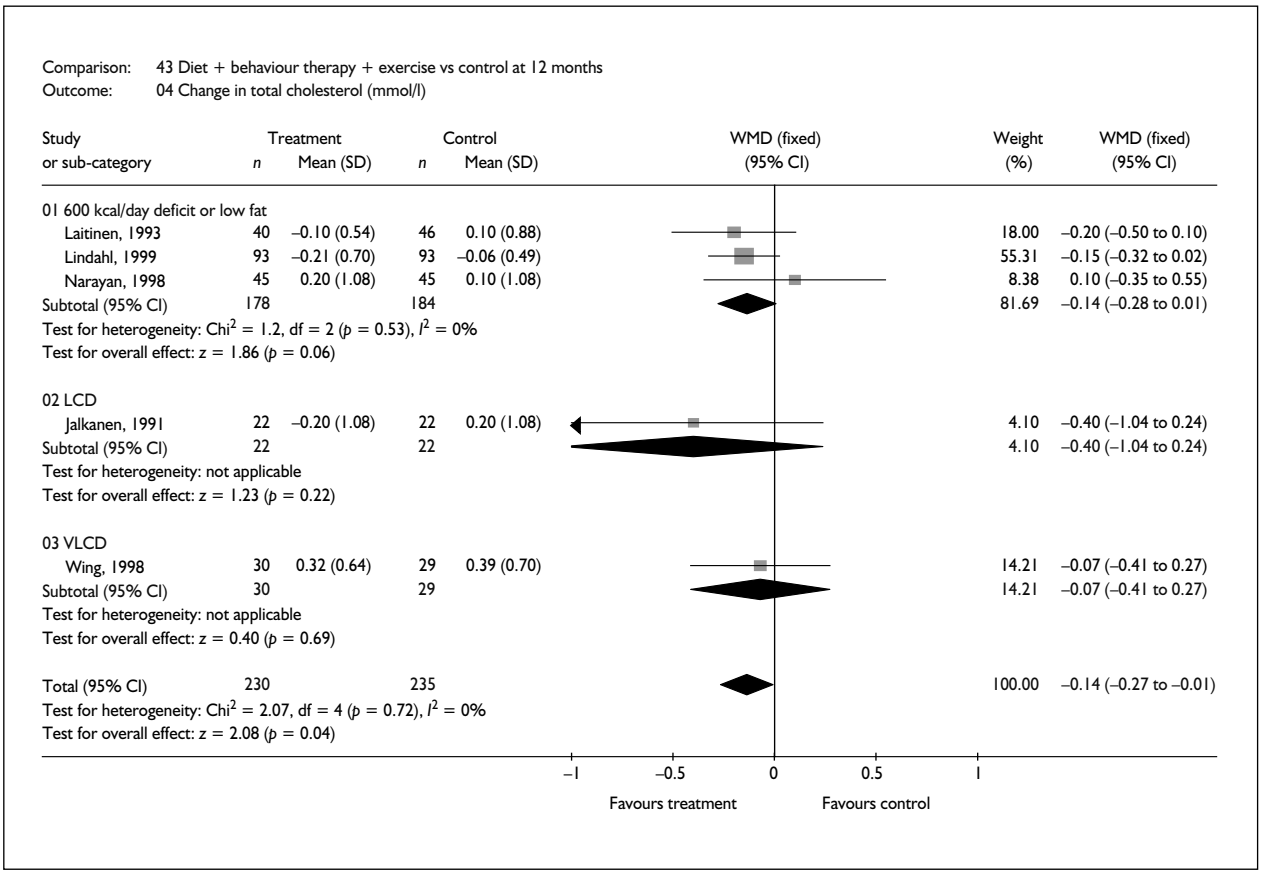


FIGURE 166

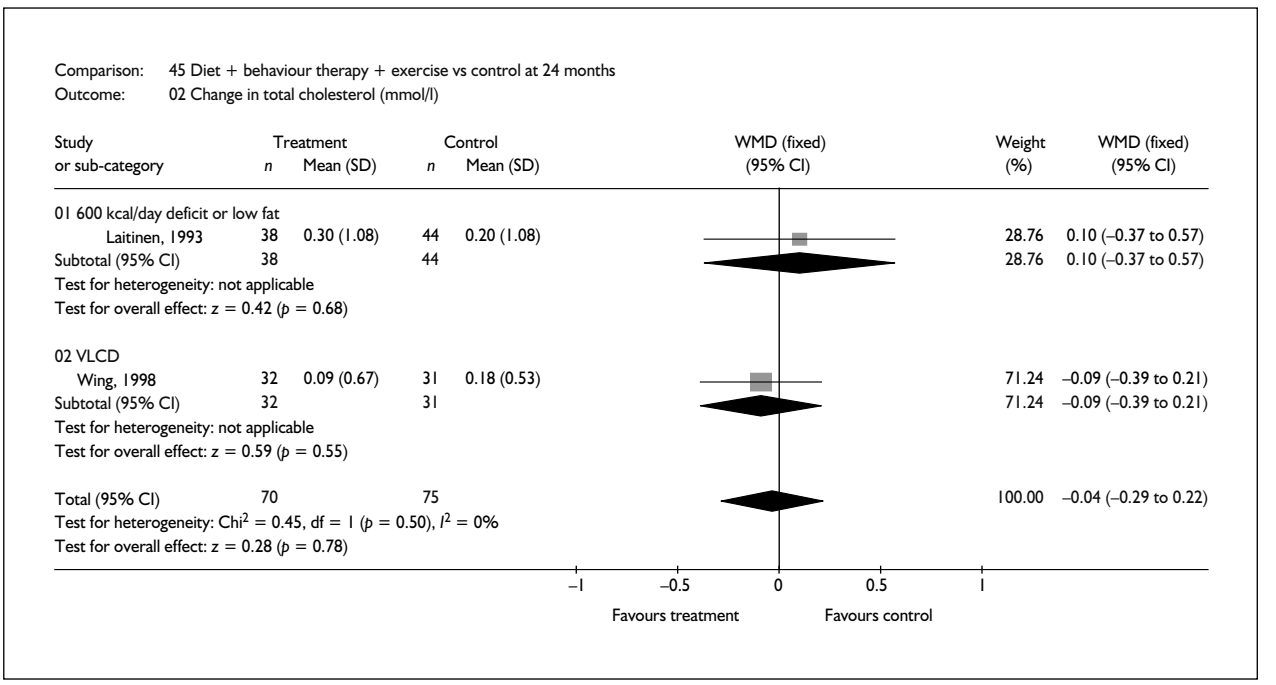


FIGURE 167

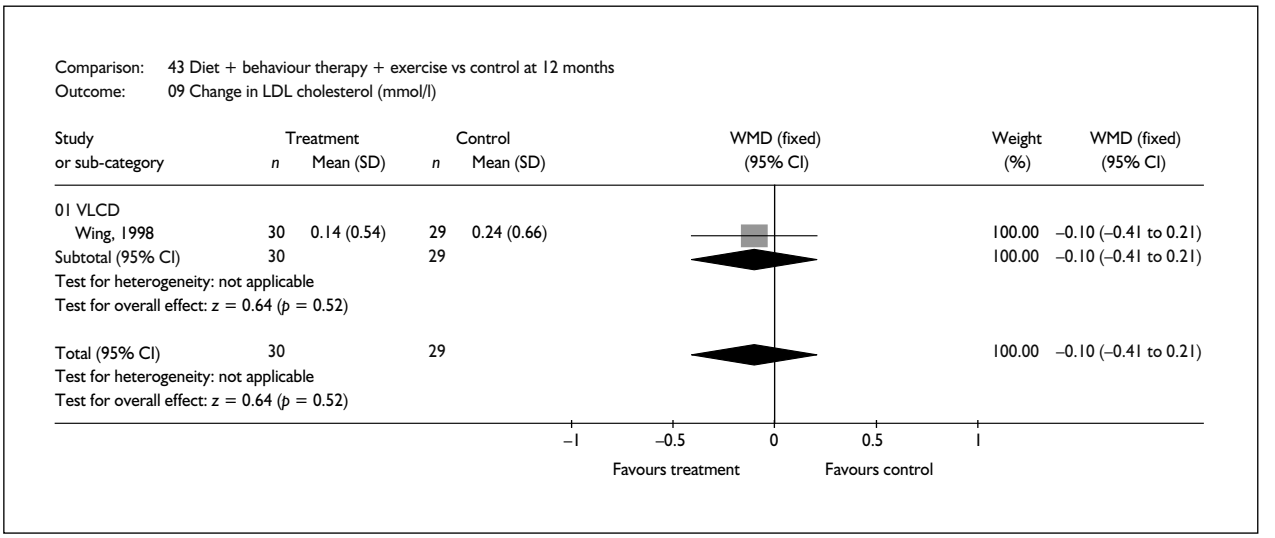


FIGURE 168

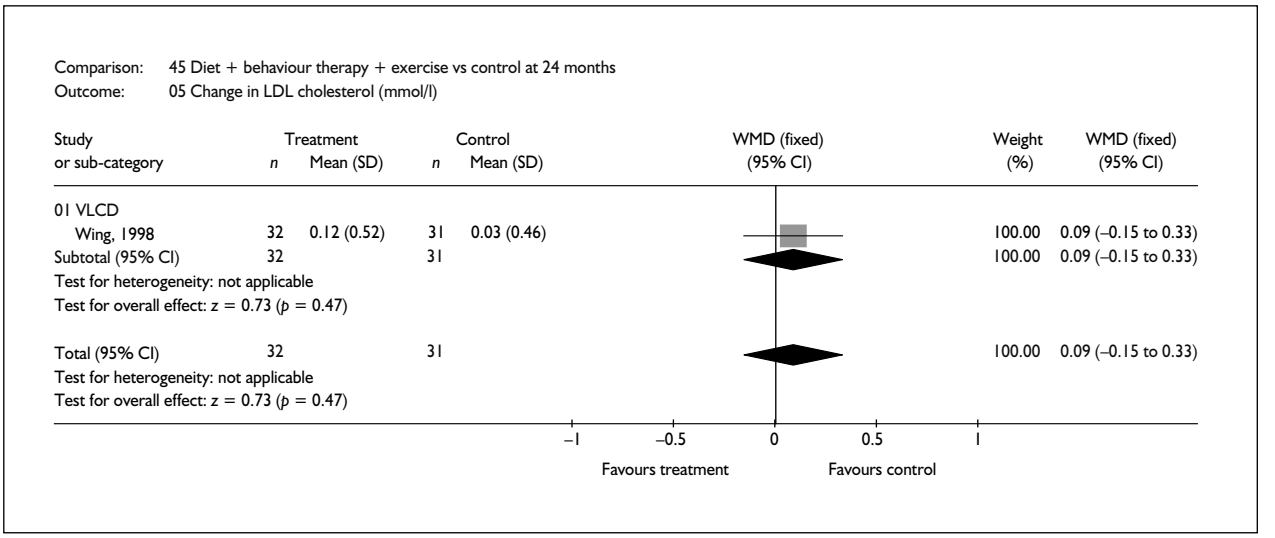


FIGURE 169

their children.[180] Murphy and colleagues[226,227] recruited married couples with either gender receiving treatment, with or without spouses, and one- or two-party contingency contracts. Wing and colleagues[230] also recruited people of either gender with type 2 diabetes with their overweight spouses. Wing and colleagues[231] recruited either gender with or without four friends or four team members.

The period of active treatment ranged from 10 weeks[225–228] to 12 months.[180] Two studies combined data from treatment arms. Rosenthal and colleagues[229] combined full husband involvement and partial husband involvement and compared mean change in weight with participants receiving individual treatment. Wing and colleagues[231] combined data from participants recruited alone and participants recruited with friends (but relationships were not acknowledged in the treatment) compared with combined data from participants assigned to a team of four members and participants recruited with four friends. Dropout rates at 1 year ranged from 8%[228] to 49%.[180] Dropout rates were 66% at 2 years and 74% at 4 years.[226,227]

Reported mean BMI ranged from 27.6 kg/m^2 [229] to 36.6 kg/m^2,[230] and reported mean weight was 77.3 kg[225] and 87.4 kg.[228]

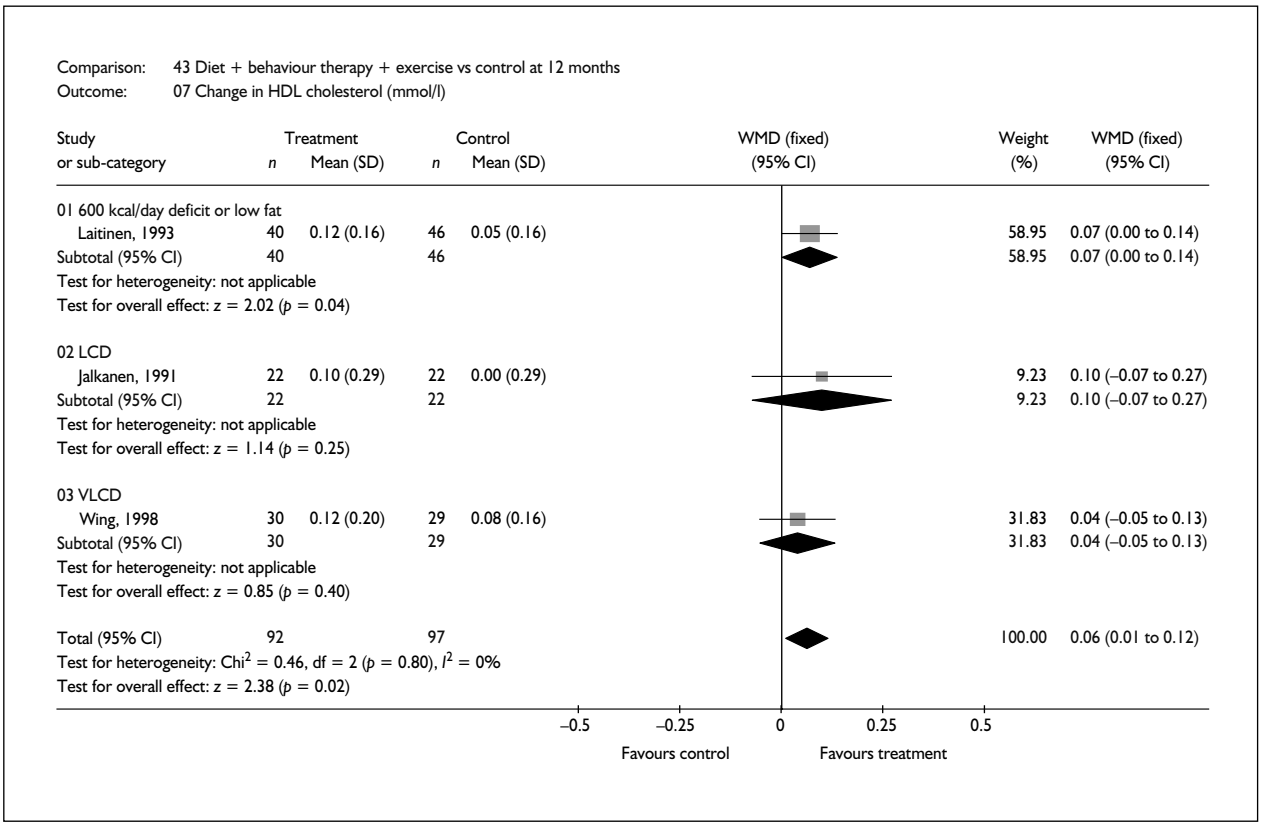


FIGURE 170

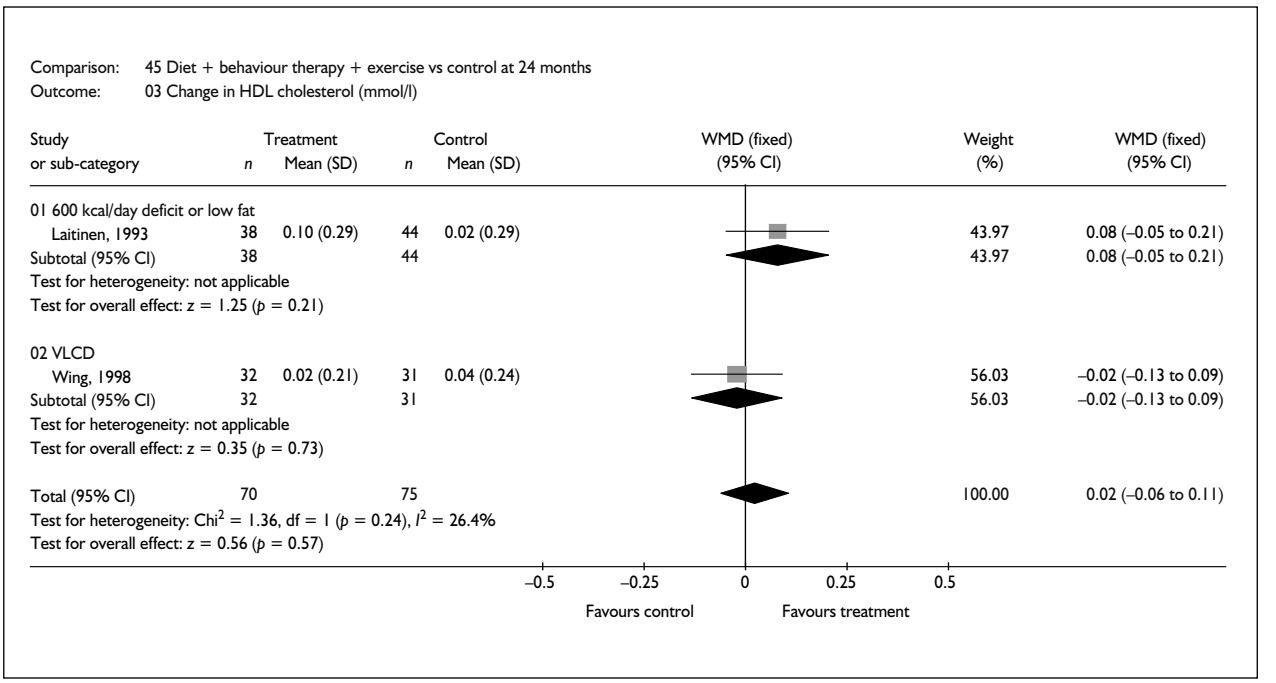


FIGURE 171

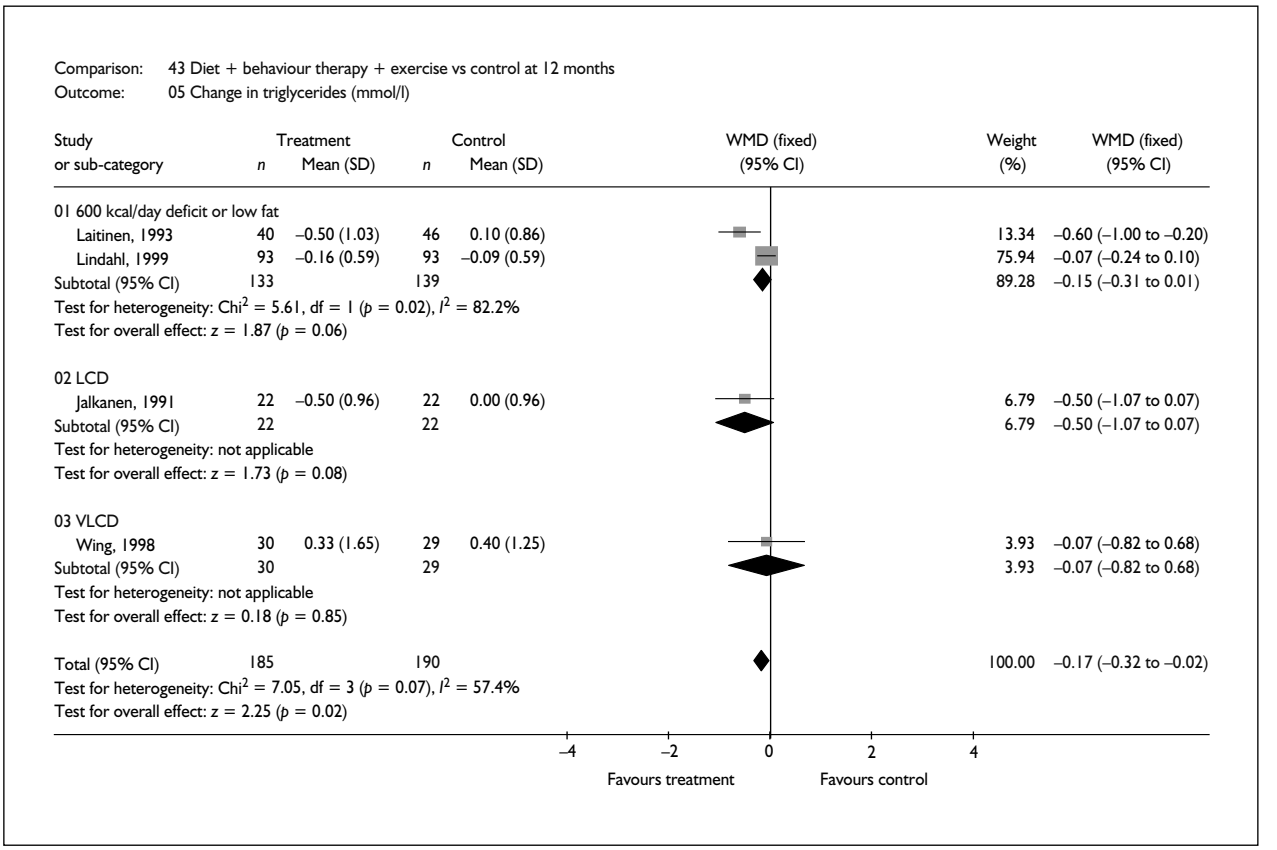


FIGURE 172

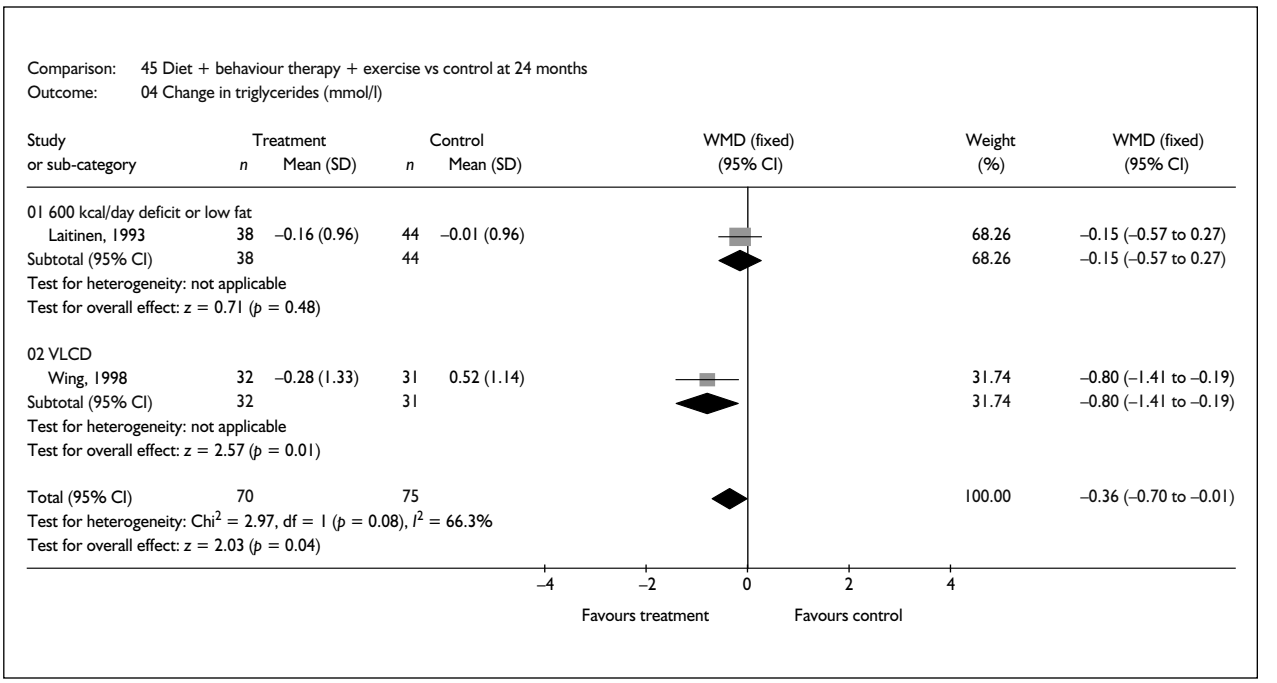


FIGURE 173

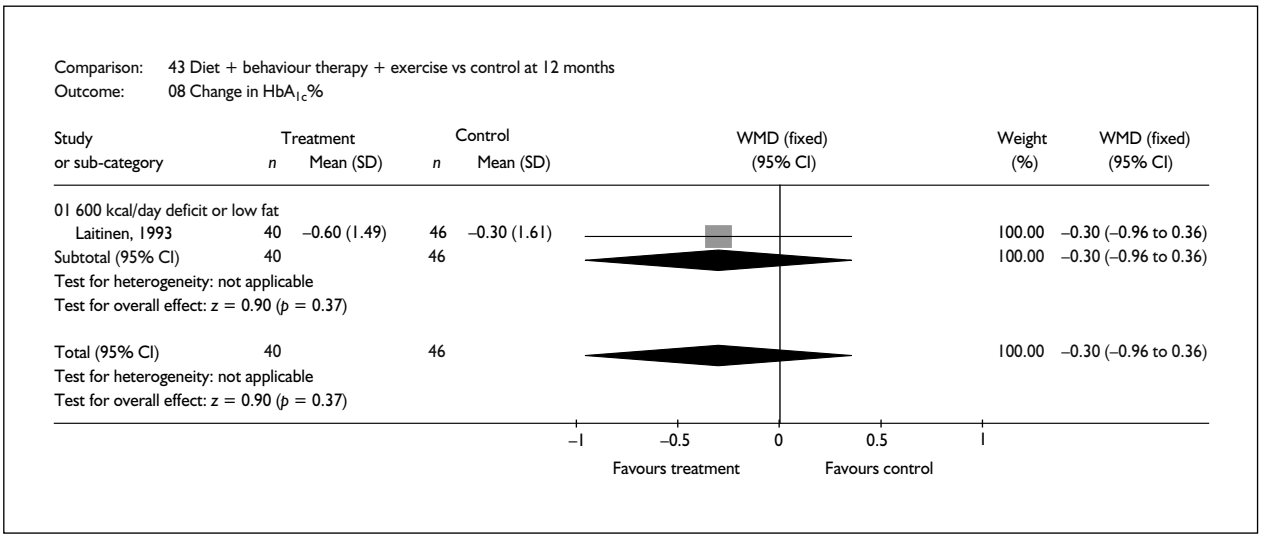


FIGURE 174

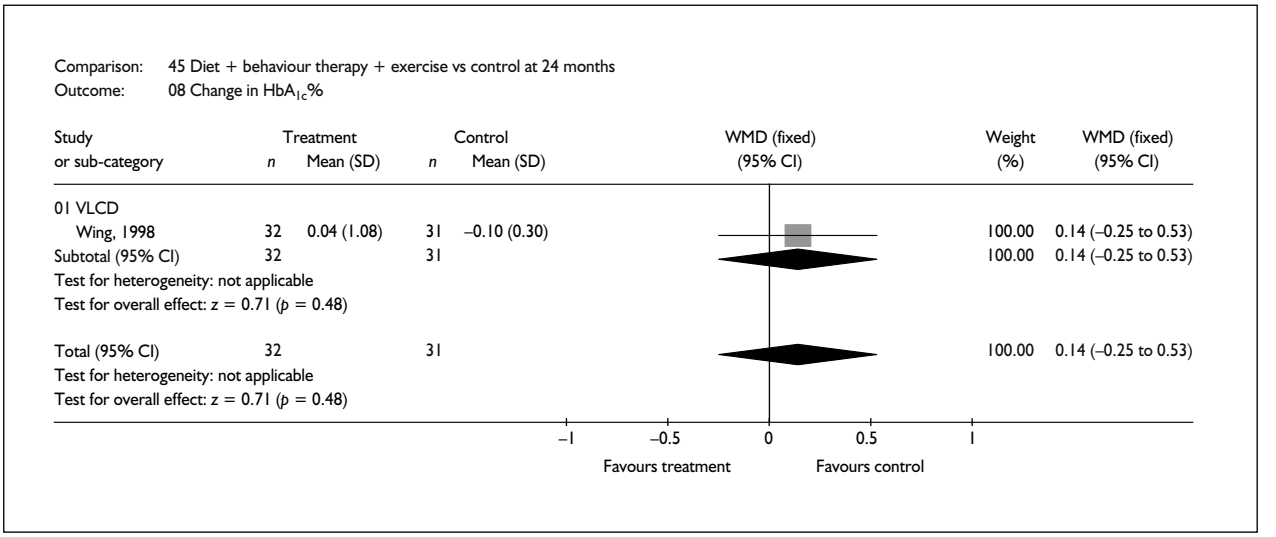


FIGURE 175

Review results

The family-based intervention from four studies was associated with an overall WMD weight change at 12 months of –2.96 kg (95% CI –5.31 to –0.60 kg) (*Figure 178*). At 18 months two family-based intervention studies were associated with an overall WMD weight change of –1.08 kg (95% CI –3.04 to 0.87 kg) (*Figure 179*). At 24 months one family-based study was associated with an overall WMD weight change of –5.61 kg (95% CI –10.98 to –0.24 kg) (*Figure 180*). At 43 months one family-based study was associated with an overall WMD weight change of –0.75 kg (95% CI –6.95 to 5.45 kg) and at 48 months –1.55 kg (95% CI –7.88 to 4.78 kg) (*Figures 181* and *182*); however after 18 months the number of participants contributing to this comparison was very small.

At 18 months Wing and colleagues[230] were unable to demonstrate any difference between family and individual approaches for weight change, HbA_{1c} or fasting plasma glucose (*Table 9*), in a study with a small number of participants (*Figures 183* and *184*).

There were no reported deaths or serious adverse events in any of the included studies.

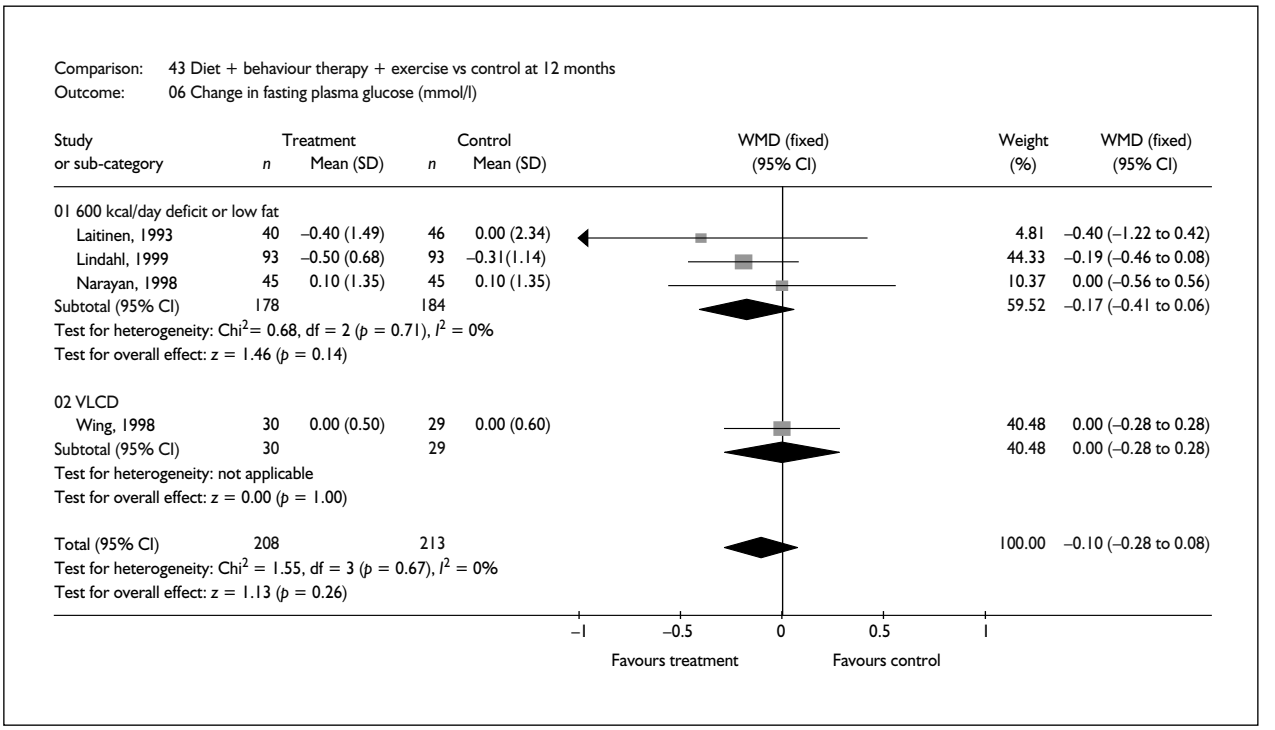


FIGURE 176

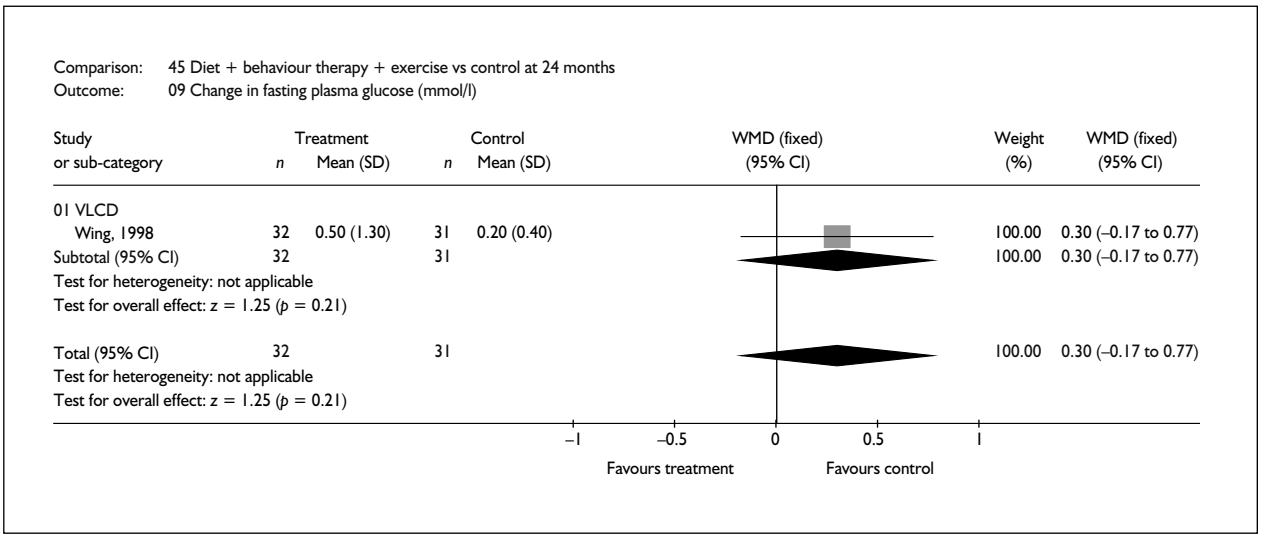


FIGURE 177

Effects of group versus individual treatment

Description of studies

Four RCTs assessed the effects of group versus individual treatment and provided change in weight at 12 months or longer.[232–235] Three studies provided change in weight at 12 months.[232,234,235] One study provided change in weight at 18 months,[233] and one at both 24 and 60 months.[232] No data were provided for changes in risk factors.

One of the four studies assessed change in weight using an ITT approach.[232] Straw and colleagues[235] rerandomised participants at week 11 to one of two maintenance conditions. Dropout rates ranged from 64% overall at 69 weeks in the study by Jones[233] to zero at 1 year in the group treatment

TABLE 7 *Effects of diet, behaviour therapy and exercise versus control on weight and risk factors in populations with hypertension*

	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)
12 months	–4.82	–0.40	0.10	–0.50	7.00	0.00
WMD (95% CI)	(–5.75 to –3.89)	(–1.04 to 0.24)	(–0.07 to 0.27)	(–1.07 to 0.07)	(–0.11 to 14.11)	(–4.65 to 4.65)
No. of studies	*n* = 2	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1
18 months	–4.56					
WMD (95% CI)	(–5.55 to –3.57)					
No. of studies	*n* = 1					
24 months	–4.49					
WMD (95% CI)	(–5.62 to –3.36)					
No. of studies	*n* = 1					
30 months	–4.94					
WMD (95% CI)	(–6.47 to –3.41)					
No. of studies	*n* = 1					

TABLE 8 *Effects of diet, behaviour therapy and exercise versus control on weight and risk factors in populations with type 2 diabetes*

	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)	Fasting plasma glucose (mmol/l)	HbA_{1c}%
12 months	–2.80	–0.20	0.07	–0.60	–4.00	–3.00	–0.40	–0.30
WMD (95% CI)	(–4.23 to –1.37)	(–0.50 to 0.10)	(0.00 to 0.14)	(–1.00 to –0.20)	(–7.88 to –0.12)	(–5.70 to –0.30)	(–1.22 to 0.42)	(–0.96 to 0.36)
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1
24 months	–3.01	0.10	0.08	–0.15				
WMD (95% CI)	(–6.13 to 0.10)	(–0.37 to 0.57)	(–0.05 to 0.21)	(–0.57 to 0.27)				
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1				

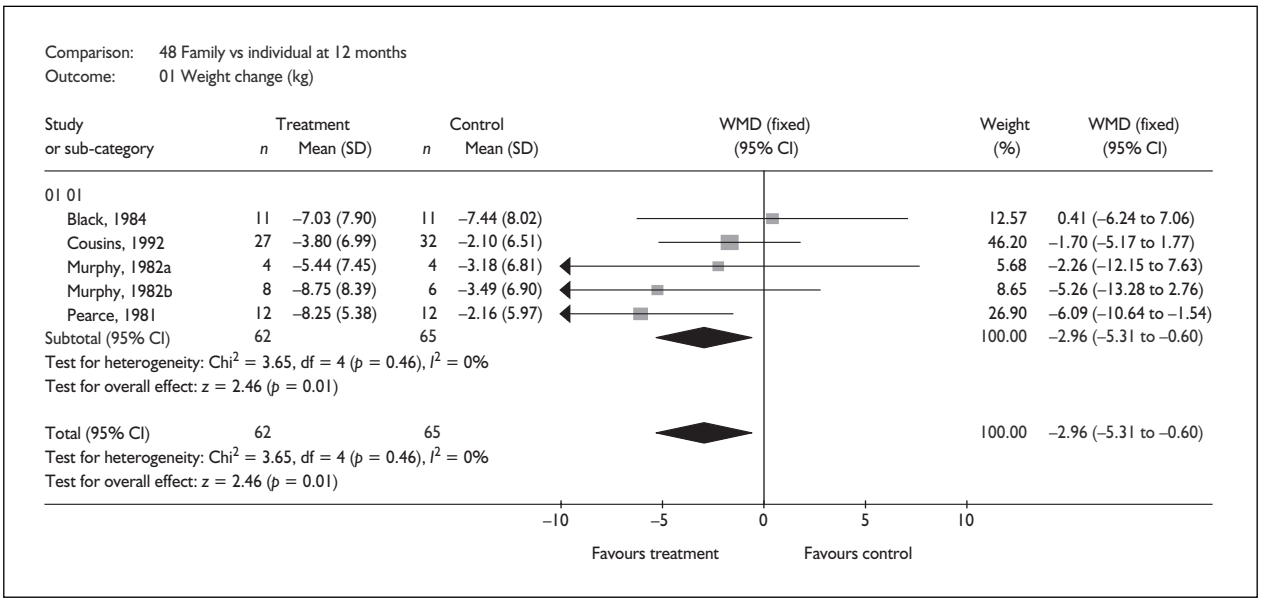


FIGURE 178

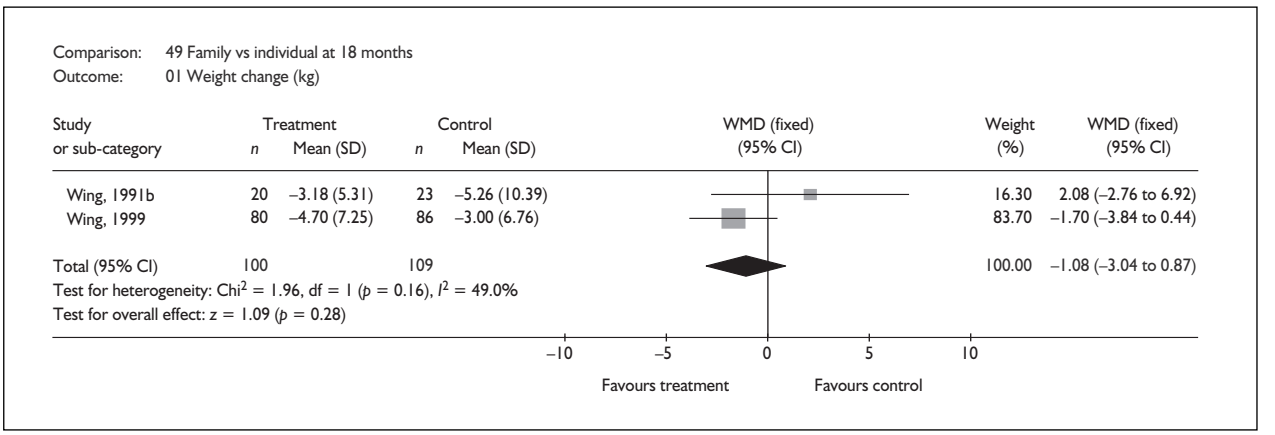


FIGURE 179

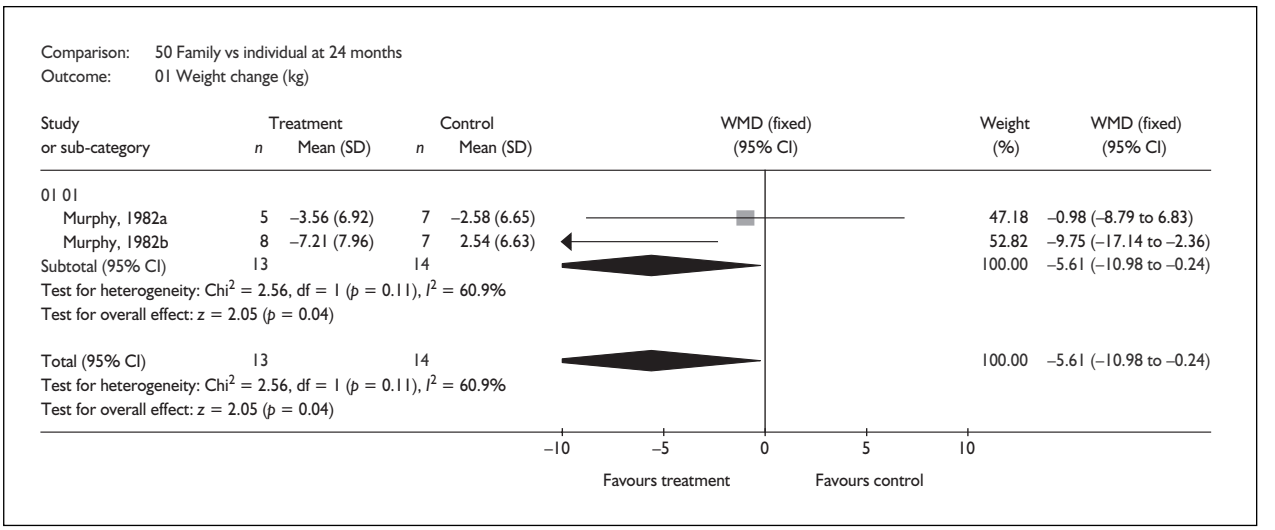


FIGURE 180

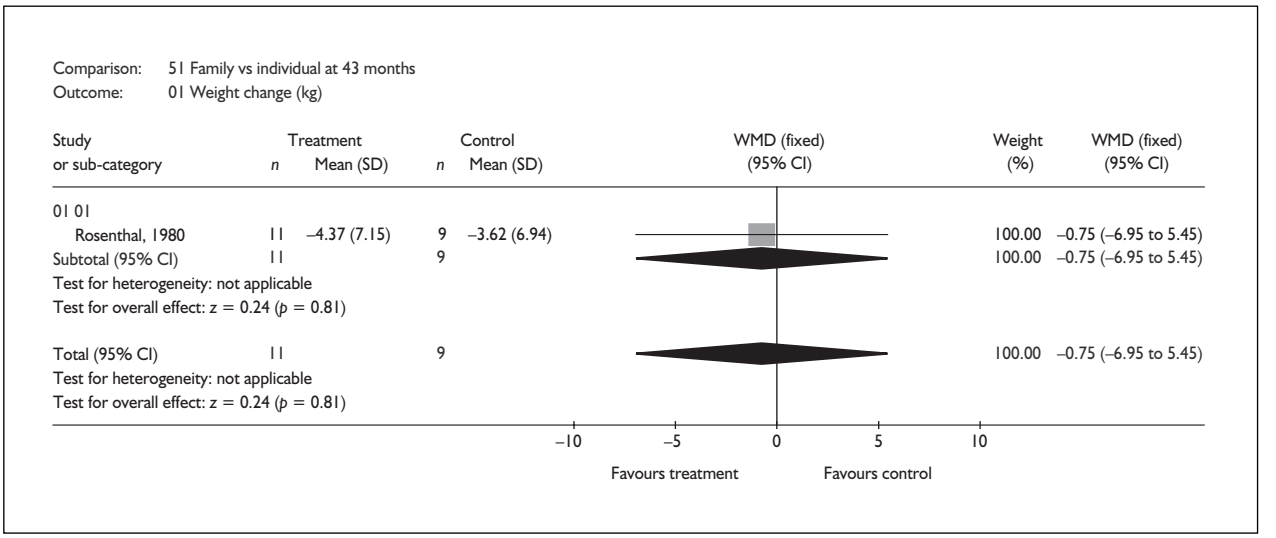


FIGURE 181

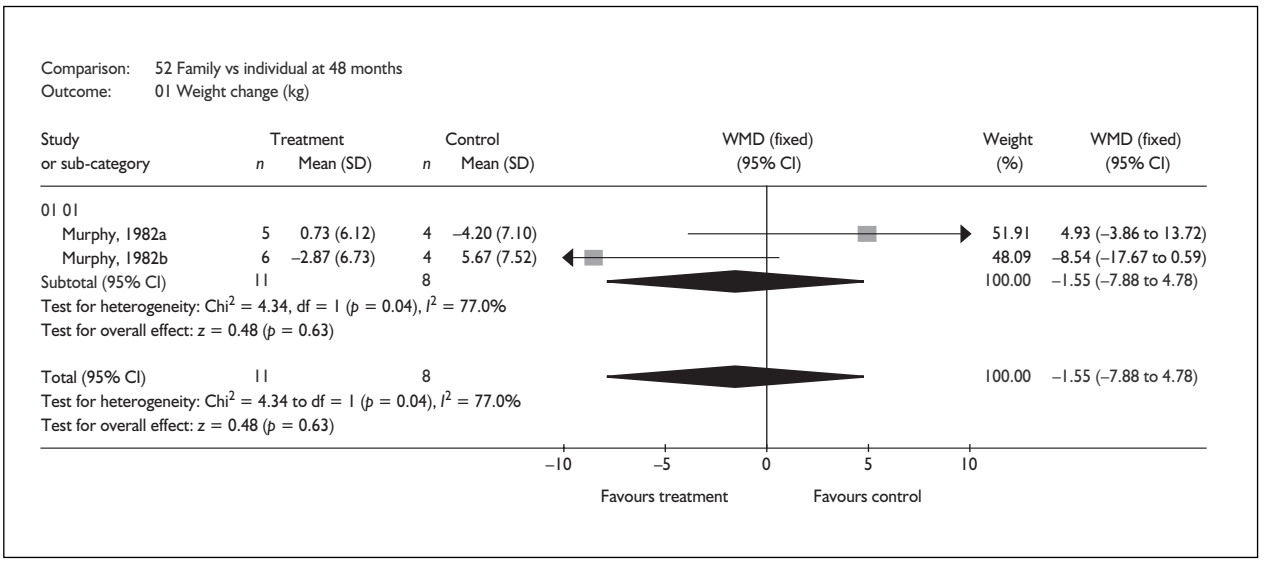


FIGURE 182

TABLE 9 *Effects of family versus individual treatment on weight and risk factors in people with type 2 diabetes*

	Weight (kg)	HbA_{1c}%	Fasting plasma glucose (mmol/l)
18 months	2.08	0.60	1.39
WMD (95% CI)	(–2.76 to 6.92)	(–0.78 to 1.98)	(–1.04 to 3.82)
No. of studies	*n* = 1	*n* = 1	*n* = 1

by Hakala and colleagues.[232] The treatment received by all participants in three of the studies was similar except for group or individual administration.[233–235] The participants receiving group counselling in the study by Hakala and colleagues[232] received an additional initial 2-week inpatient stay of intensive LCD, behaviour therapy and exercise plus more frequent follow-up visits and additional individual contacts.

The treatment varied across the four studies from group versus individually administered LCD[233,234]

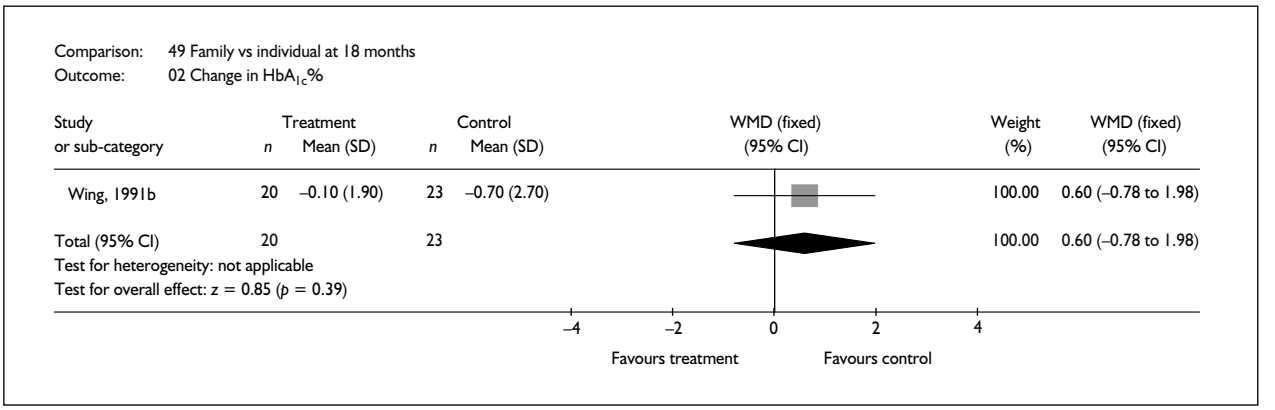


FIGURE 183

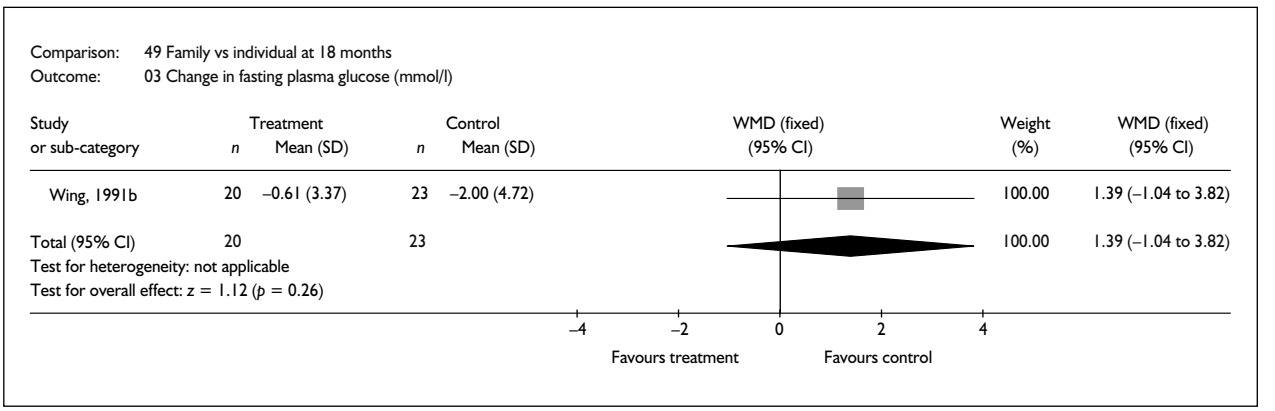


FIGURE 184

to group versus individually administered LCD plus behaviour therapy plus exercise.[232] The study by Straw and Terre[235] assessed group versus individual treatment followed by a maintenance period of weight checking from week 11 to month 12 and group versus individual treatment followed by individual problem solving.

Three of the four studies recruited women only.[233–235] Reported mean BMI ranged from 33.5 kg/m^2 [234] to 43 kg/m^2.[232] The study by Straw and Terre[235] did not report BMI, and reported mean body weight was 85.2 to 86.6 kg.

Review results

Compared with individual treatment the group administered intervention for three studies was associated with an overall WMD weight change at 12 months of 1.59 kg (95% CI –1.81 to 5.00 kg) (*Figure 185*).

At 18 months group treatment compared with individual treatment was associated with a WMD weight change of 0.74 kg (95% CI –4.21 to 5.69 kg), based on one study (*Figure 186*).[233] At 24 and 60 months the study by Hakala and colleagues[232] produced less weight loss in a group setting than in an individual setting: WMD weight change 8.10 kg (95% CI 2.19 to 14.01 kg) at 24 months and 4.40 kg (95% CI –3.51 to 12.31 kg) at 60 months (*Figures 187* and *188*). The confidence intervals are wide, reflecting the small number of participants contributing to these comparisons.

Two participants who were seriously ill with cancer dropped out during the maintenance phase of the study by Straw and Terre,[235] but their group status was unclear.

Effects of diet and exercise versus diet

Description of studies

Five studies assessed the added effects of exercise to diet and provided change in weight at 12 months or longer.[115–121,142–145,153,236] One of these five studies was a pilot consisting of only 24 participants;[153] this was a pilot for another study included in this comparison.[153] One of these

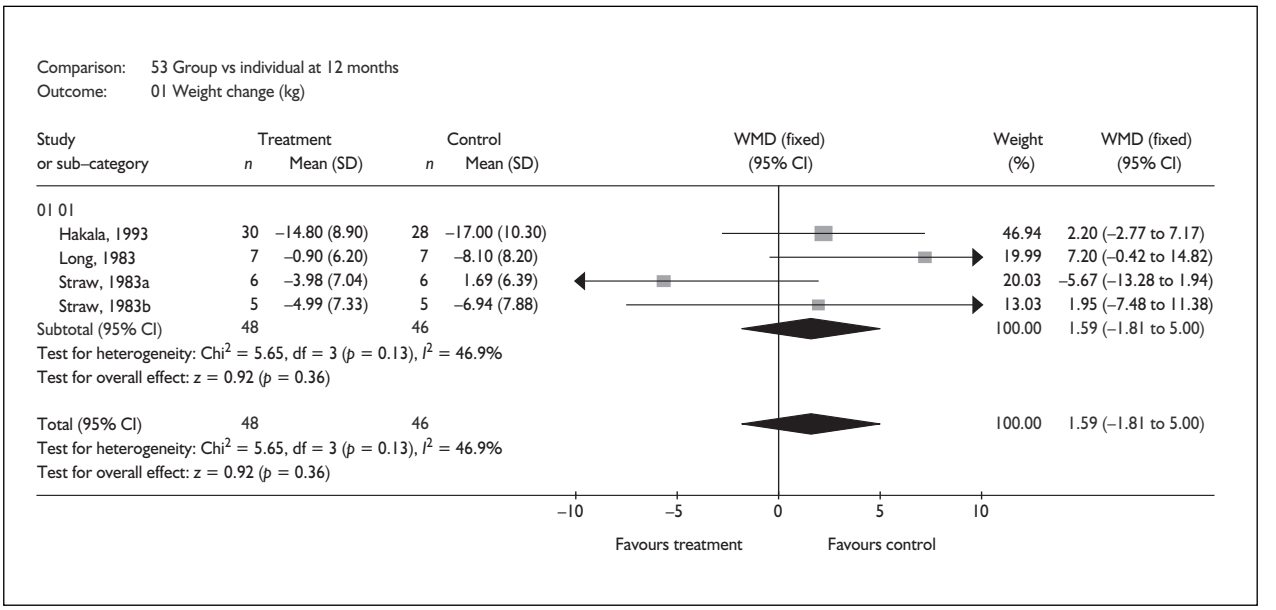


FIGURE 185

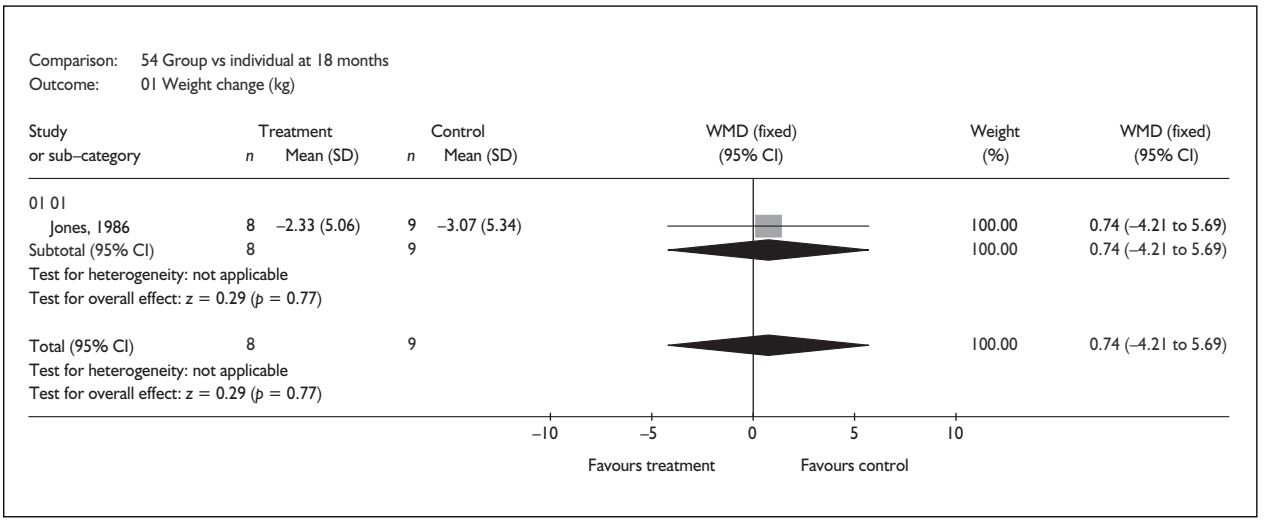


FIGURE 186

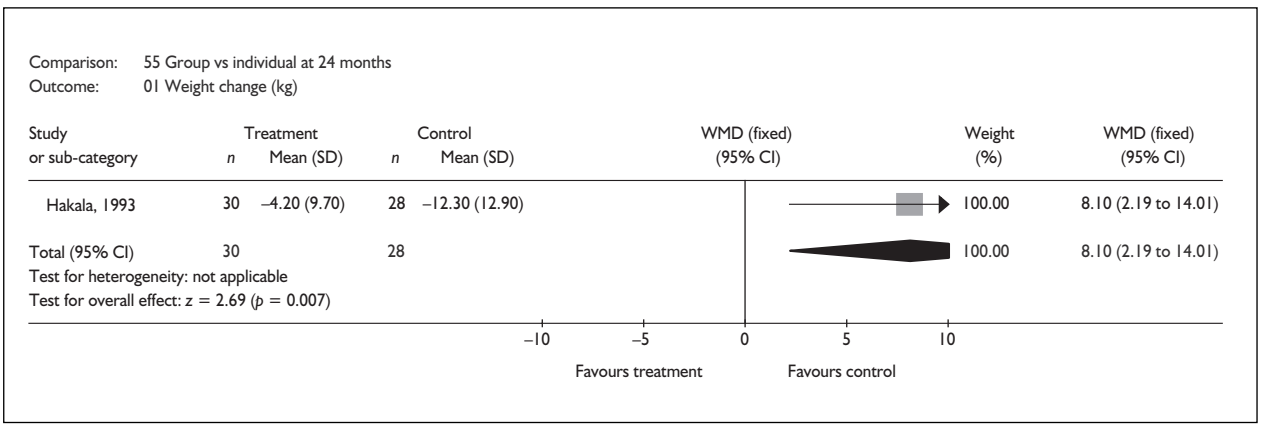


FIGURE 187

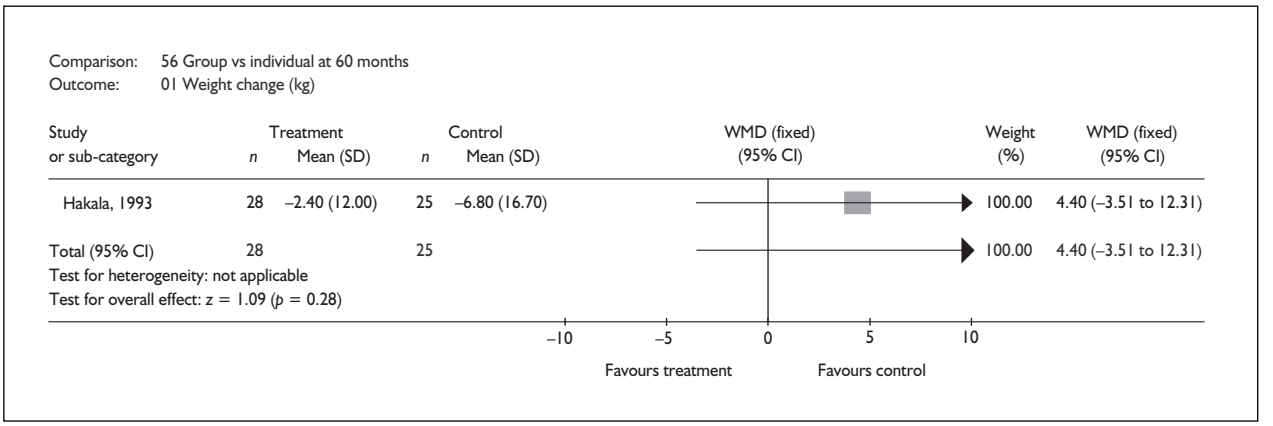


FIGURE 188

five studies was a cluster RCT which provided change in weight at 12 months.[236]

The ODES[115–121] involved a male population with a cardiovascular disease risk profile. Results in the study by Wood and colleagues[142–145] were presented separately for men and women.

Two studies provided change in weight at 12 months,[115–121,142–145] two studies provided change in weight at 18 months[153] and one study provided change in weight at 36 months.[153] Data were provided for all lipids, blood pressure and fasting plasma glucose at 12 months and for blood pressure at 18 months.

Two studies possibly assessed change in weight using an ITT approach, but this was unclear.[153] Dropout rates at 12 months ranged from 5% in the ODES[115–121] to 18% in the study by Phenix.[236]

The amount and duration of exercise received by participants varied across studies. In the ODES[115–121] the diet and exercise group received supervised endurance workouts which progressed to 1-hour sessions, three times per week at 60–80% maximum heart rate for 12 months. In the study by Wood and colleagues[142–145] the diet and exercise arm received aerobic exercise which progressed to 45 minutes, three times per week at 60–80% maximum heart rate for 12 months. In the pilot study by Pavlou and colleagues[153] the diet and exercise groups received supervised exercise for 90 minutes three times per week at 85% maximum heart rate for the initial 12 weeks only. In the main trial by Pavlou and colleagues[153] the diet plus exercise groups received supervised exercise for 90 minutes three times per week at 85% maximum heart rate for the initial 8 weeks only.

The diets also varied between studies: two studies used a 600 kcal/day deficit or low-fat diet.[115–121,142–145] The pilot study by Pavlou and colleagues[153] used an LCD and a PSMF and the main trial by Pavlou and colleagues[153] used an LCD, PSMF, 420 kcal/day diet (assumed PSMF) or a 800 kcal/day VLCD.

Reported mean BMI ranged from 27.9 kg/m^2 for women only in the study by Wood and colleagues[142–145] to 34.8 kg/m^2 in the main study by Pavlou and colleagues.[153]

Review results

Diet and exercise compared with diet alone for two studies was associated with an overall WMD weight change at 12 months of –1.95 kg (95% CI –3.22 to –0.68 kg) (*Figure 189*).[115–121,142–145] At 18 months diet and exercise compared with diet in the two studies by Pavlou and colleagues[153] was associated with an overall WMD weight change of –7.63 kg (95% CI –10.33 to –4.92 kg) (*Figure 190*). At 36 months diet and exercise compared with diet in the pilot study by Pavlou and colleagues[153] was associated with an overall WMD weight change of –8.22 kg (95% CI –15.27 to –1.16 kg) (*Figure 191*). The confidence intervals for these comparisons are wide, reflecting the small number of participants.

Two studies demonstrated beneficial effects of adding exercise to diet at 12 months for HDL cholesterol (WMD 0.1 mmol/l, 95% CI 0.06 to 0.14 mmol/l) and triglycerides (WMD –0.18 mmol/l, 95% CI –0.31 to –0.06 mmol/l) (*Figures 192–196*).[115–121,142–145] One study found statistically significant falls in DBP and SBP after 18 months,[153] but these were not seen in other studies at 12 months (*Figures 197–200*). The

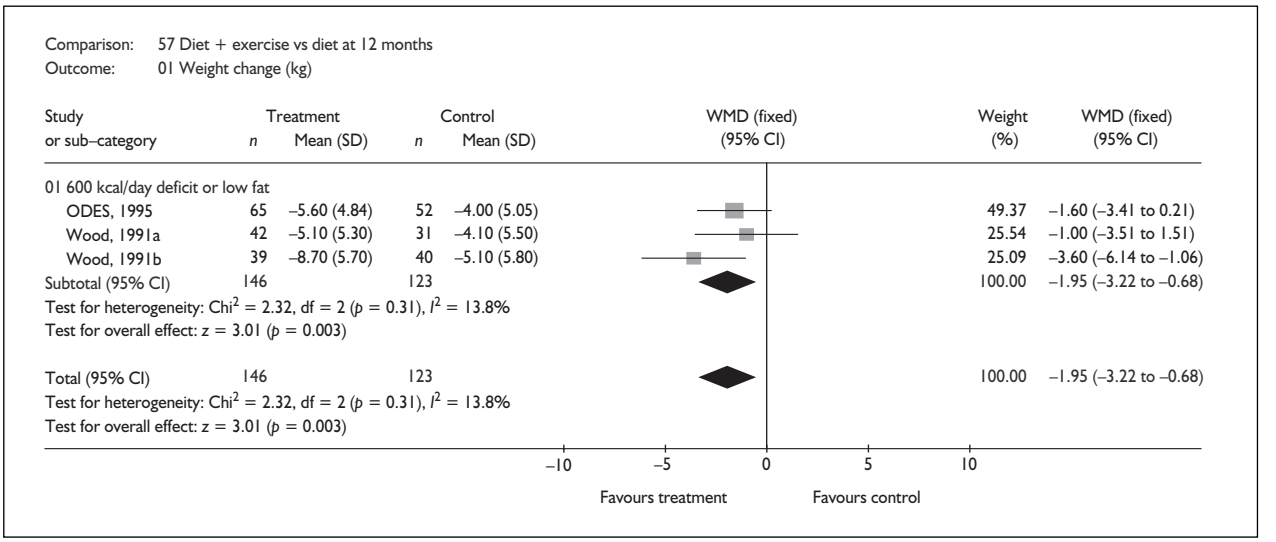


FIGURE 189

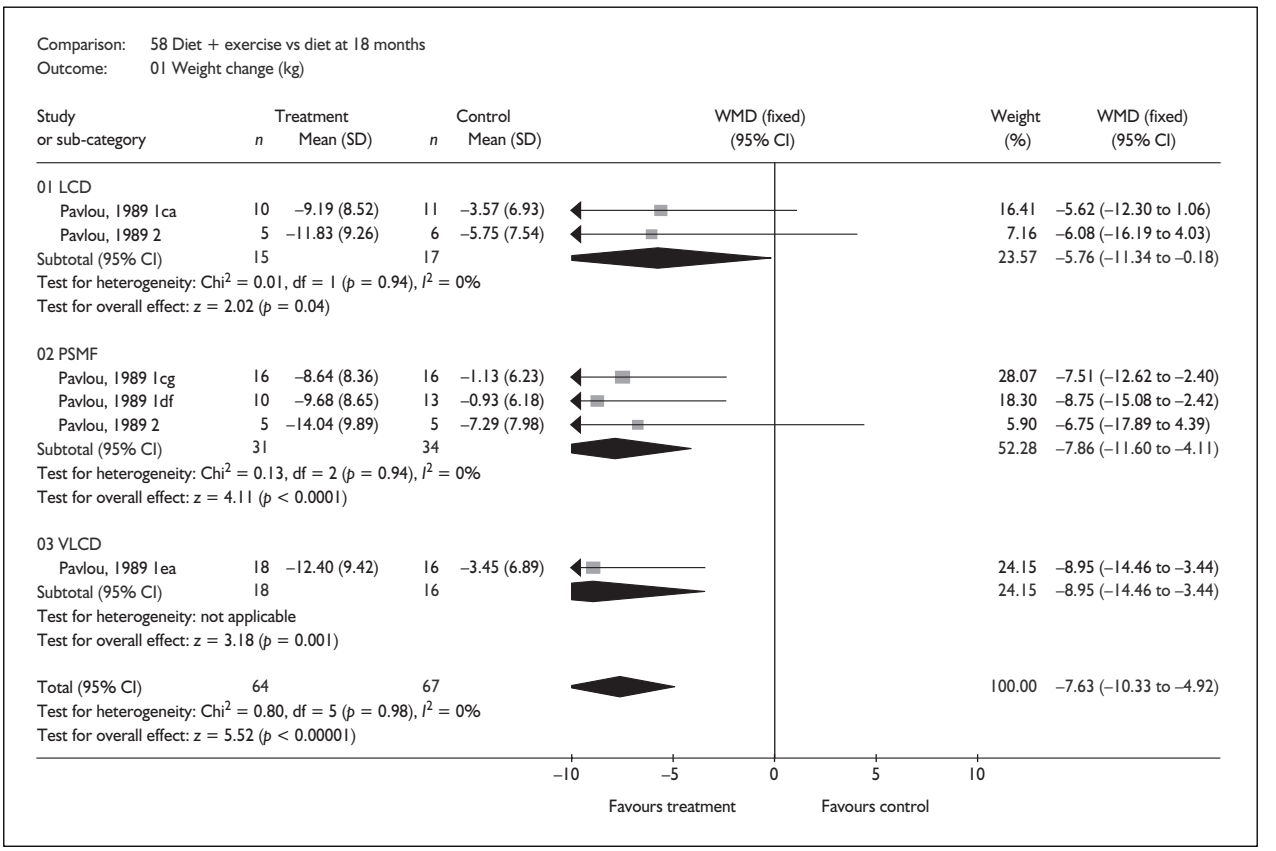


FIGURE 190

results from the ODES[115–121] with male participants at risk of cardiovascular disease are shown in *Table 10*.

The cluster RCT[236] recruited women only. Mean body weight ranged from 76 kg in one of the eight arms to 86 kg in another arm. Results were analysed using an ITT approach. Active treatment was 8 weeks for all participants of groups used in analysis for this review. The added effect of exercise to an LCD was associated with a weight loss at 12 months of –5.32 kg compared with –4.82 kg in the diet-only group.

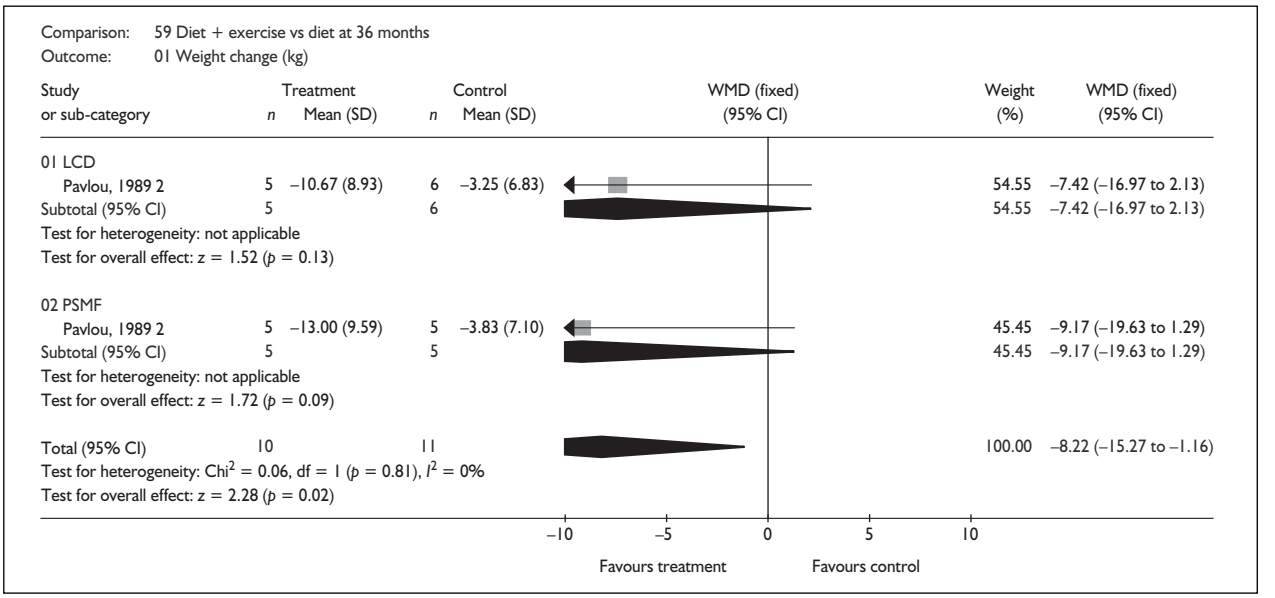


FIGURE 191

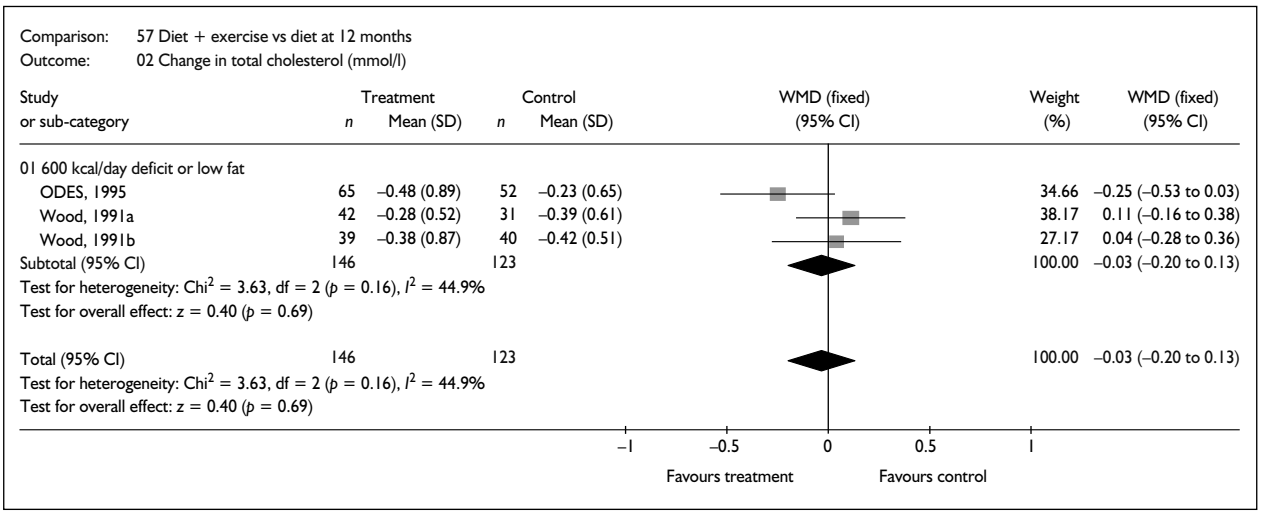


FIGURE 192

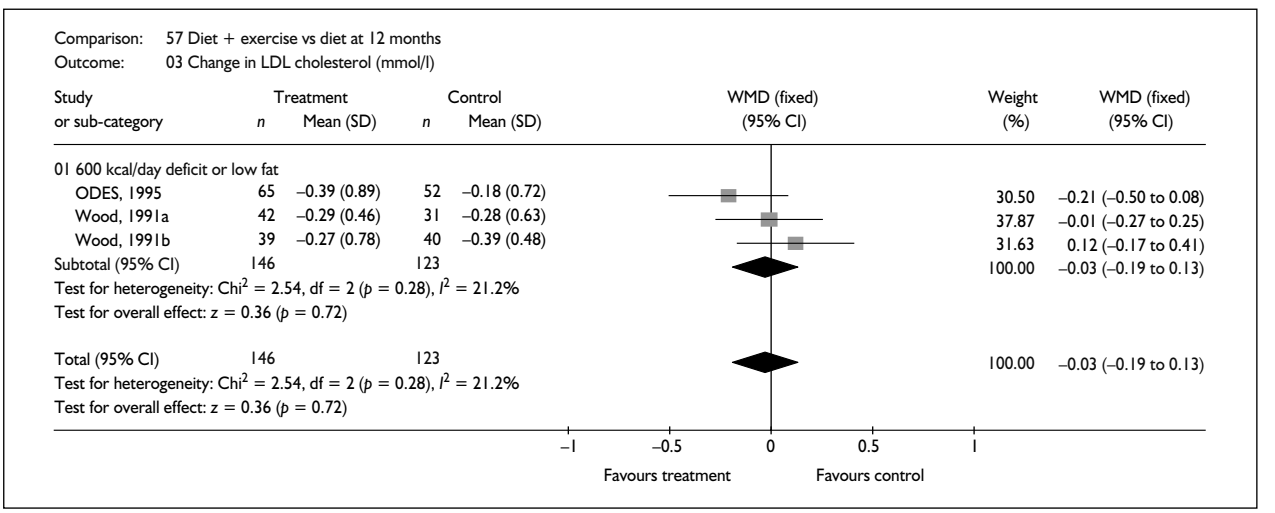


FIGURE 193

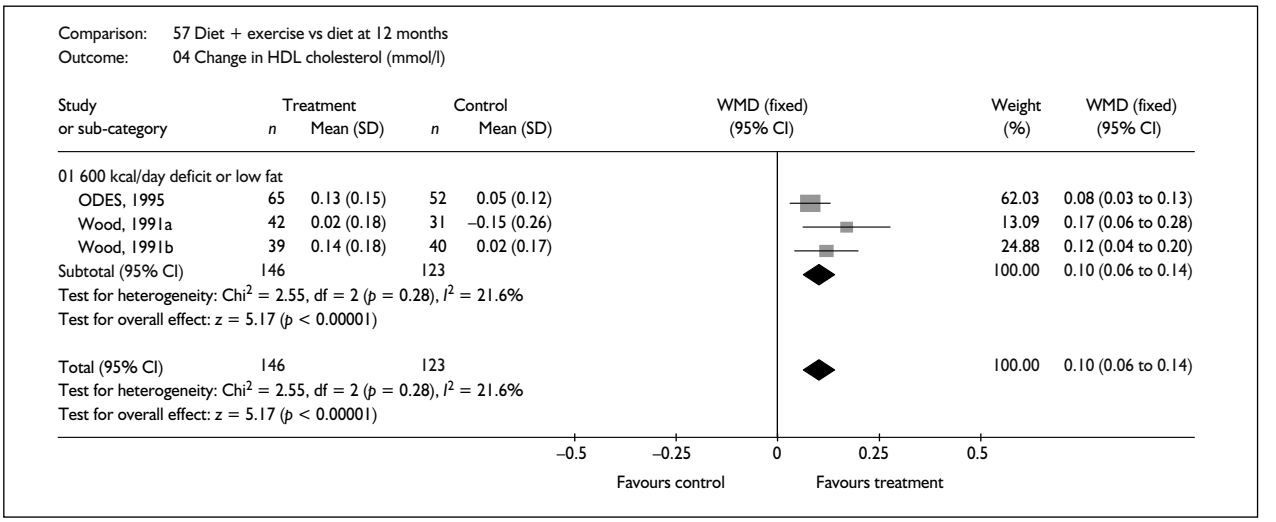


FIGURE 194

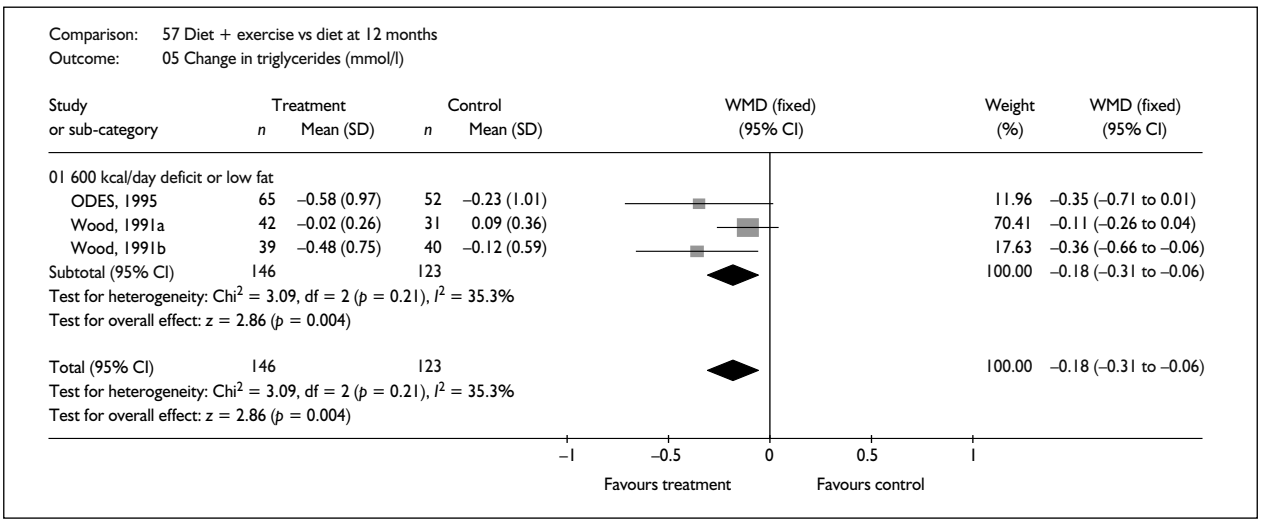


FIGURE 195

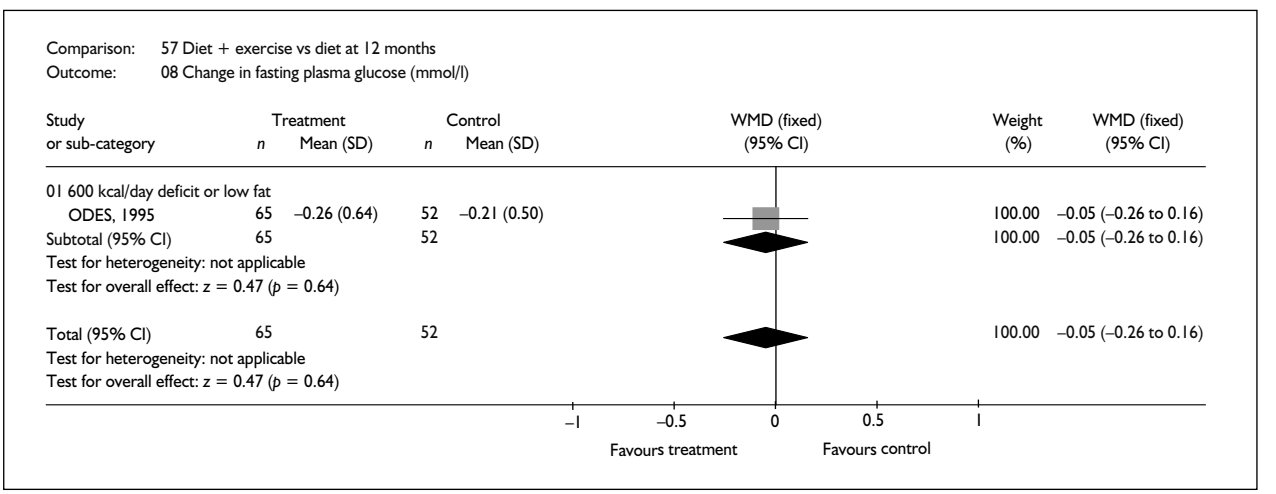


FIGURE 196

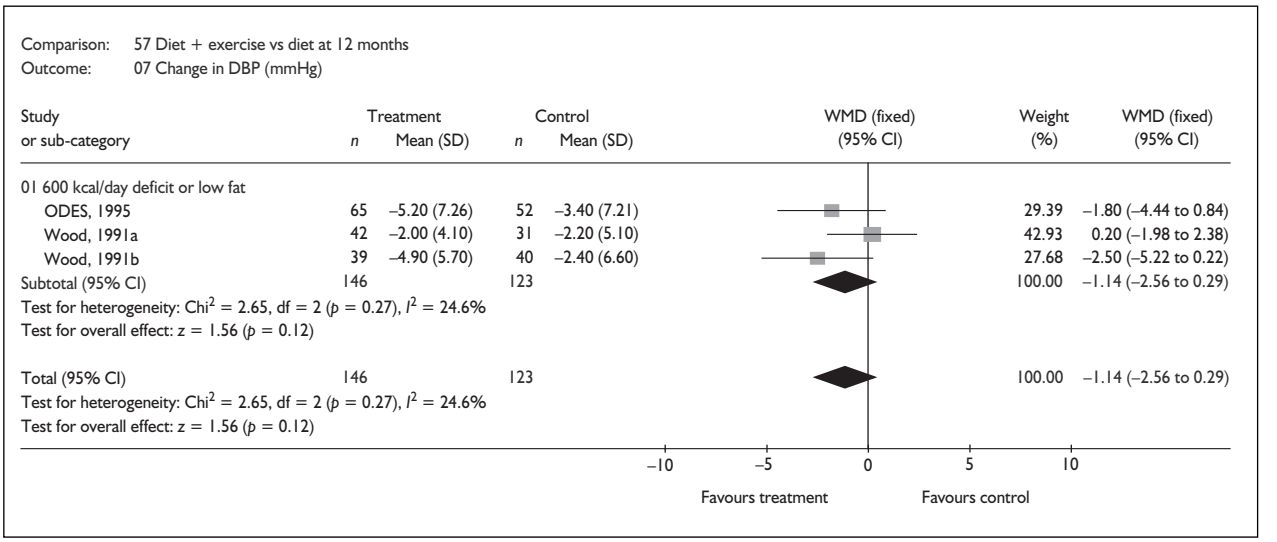


FIGURE 197

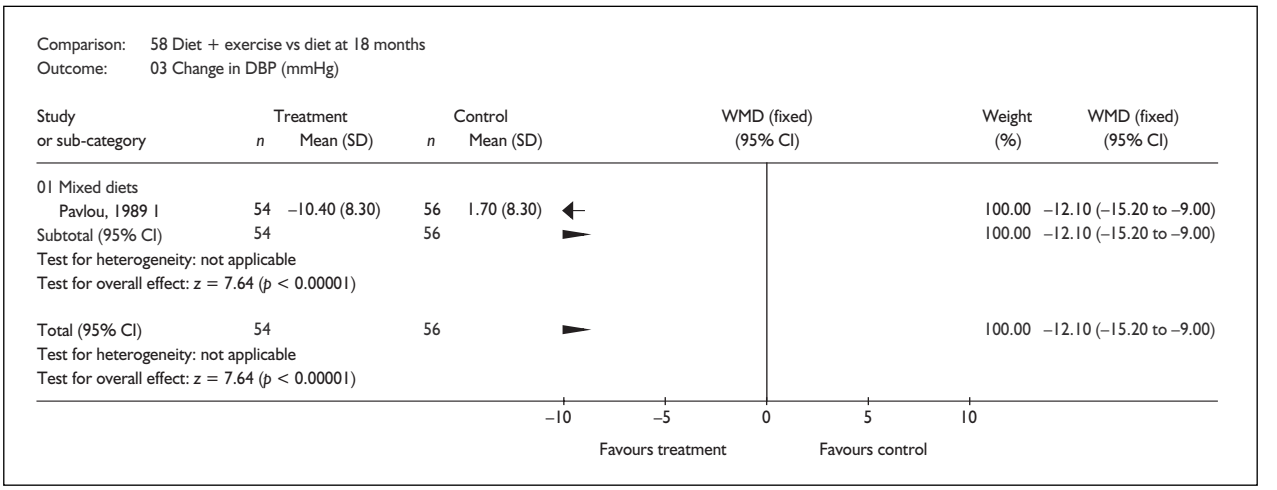


FIGURE 198

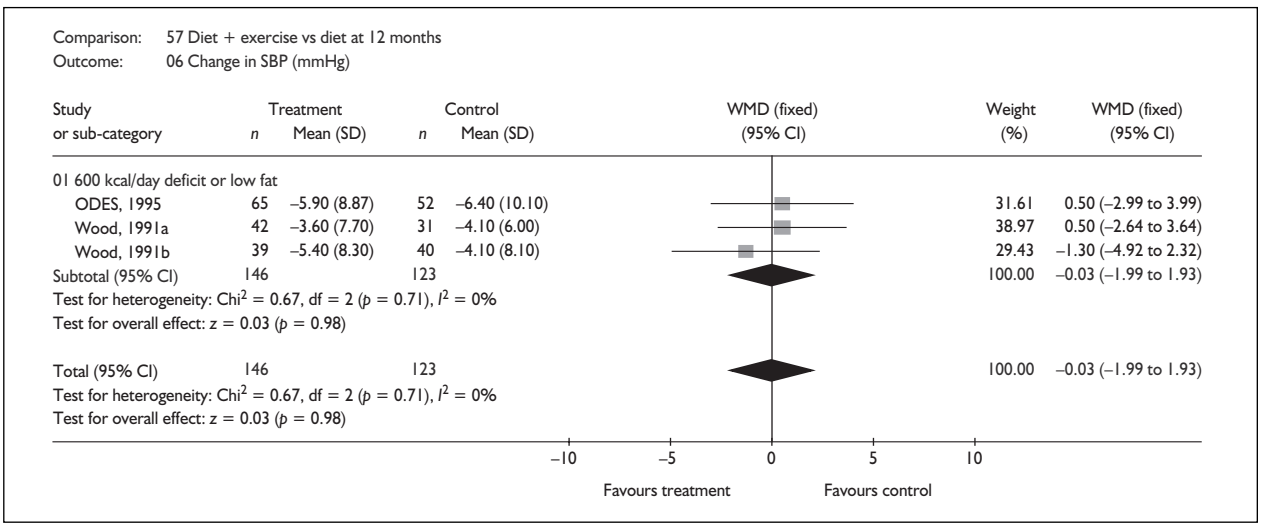


FIGURE 199

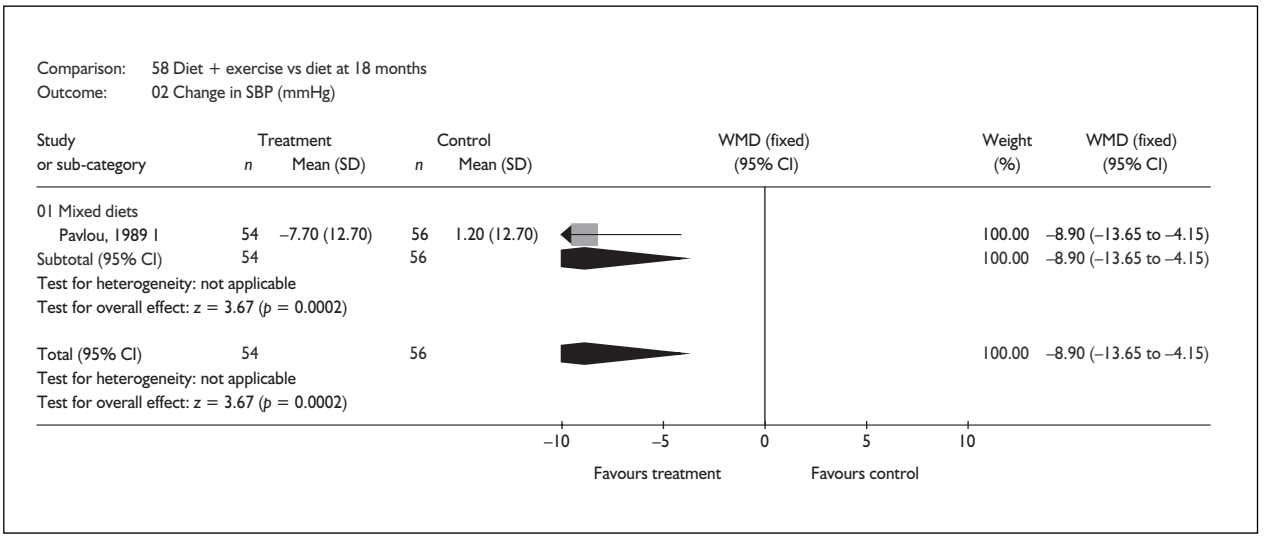


FIGURE 200

Two cases of cancer and one cardiac event were reported in the ODES,[115–121] but the treatment allocation was not stated.

Effects of diet and behaviour therapy versus diet

Description of studies

Four RCTs assessed the added effects of behaviour therapy to diet and provided change in weight at 12 months or longer.[159–162,233,234,236] Three studies provided change in weight at 12 months,[159–162,234,236] one at 18 months,[233] and one at 36 and 60 months.[159–162] No data were provided for risk factors at any time-point.

Only one study used an ITT approach.[236] Numbers of participants allocated to treatment and therefore dropout rates were unclear in one study.[159–162] Jones and colleagues[233] reported a dropout rate at 69 weeks of 64% overall.

Three studies used an LCD and behaviour therapy versus LCD alone.[233,234,236] One of these studies evaluated these comparisons both in a group setting and on an individual basis.[233] Wadden and colleagues[159–162] used a PSMF of 400–500 kcal/day during months 2 and 3, with and without behaviour therapy. In this study participants in the PSMF and behaviour therapy group had an additional 9 weeks of initial active treatment and were then followed up at more frequent intervals than the PSMF-only group. Active treatment phases ranged from 8 to 17 weeks. Three of the four studies recruited women only.[233,234,236]

Reported mean BMI ranged from 33.5 kg/m^2 [234] to 39.4 kg/m^2.[159–162]

Review results

The additional effect of behaviour therapy on diet was associated with an overall WMD 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) (*Figures 201–204*). Thus, there was significant added effect of behaviour therapy on weight change at 12 and 18 months, but not at 36 or 60 months. The number of participants contributing to the comparisons decreased over time and so the sustained effect of behaviour therapy cannot really be assessed.

In the cluster RCT by Phenix,[236] where meeting time was the unit of randomisation, mean body weight in the groups ranged from 76 to 86 kg. Phenix evaluated the added effects to diet of two forms of behaviour therapy, which were overt behaviour therapy and cognitive behaviour therapy. The added effect of overt behaviour therapy to an LCD was associated with a weight change at 12 months of –3.26 kg compared with –4.82 kg in the diet-only group. The added effect of cognitive behaviour therapy to an LCD was associated with a weight change at 12 months of –6.68 kg compared with –4.82 kg in the diet-only group.

No deaths or serious adverse events were reported in any of the included studies.

TABLE 10 *Effects of diet and exercise versus diet on weight and risk factors in men at risk of cardiovascular disease*

	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	TGs (mmol/l)	SBP (mmHg)	DBP (mmHg)	Fasting plasma glucose (mmol/l)
12 months	–1.60	–0.25	0.08	–0.21	–0.35	0.50	–1.80	–0.05
WMD (95% CI)	(–3.41 to 0.21)	(–0.53 to 0.03)	(0.03 to 0.13)	(–0.50 to 0.08)	(–0.71 to 0.01)	(–2.99 to 3.99)	(–4.44 to 0.84)	(–0.26 to 0.16)
No. of studies	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1	*n* = 1

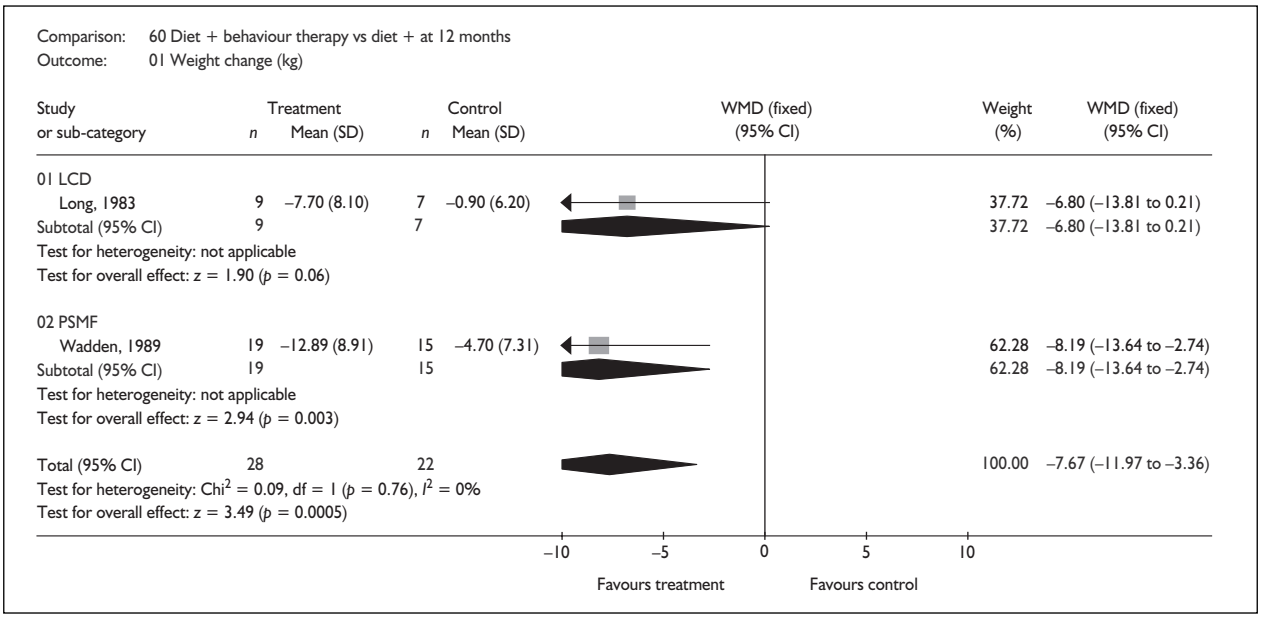


FIGURE 201

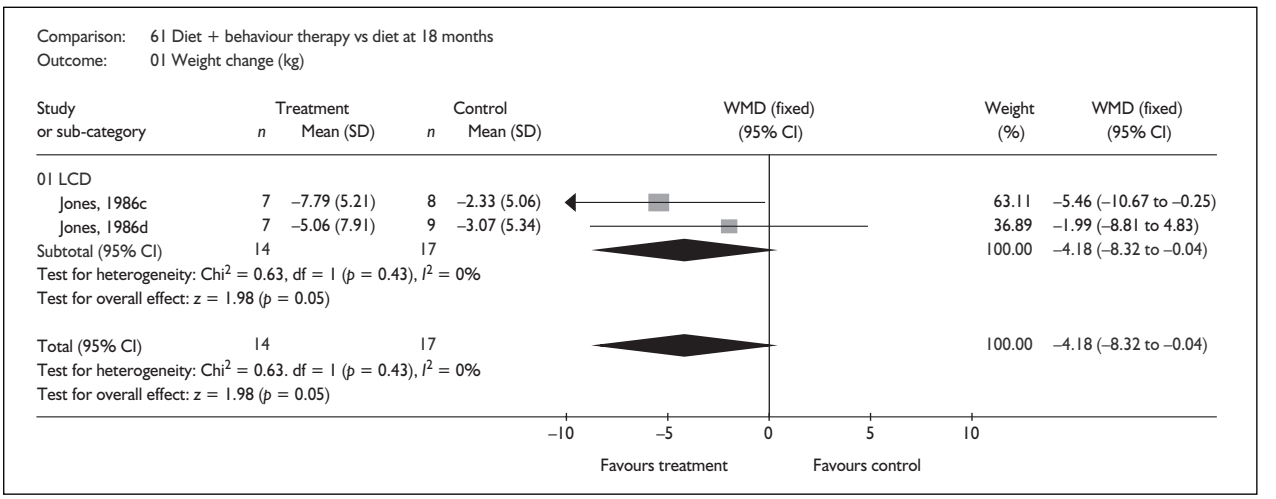


FIGURE 202

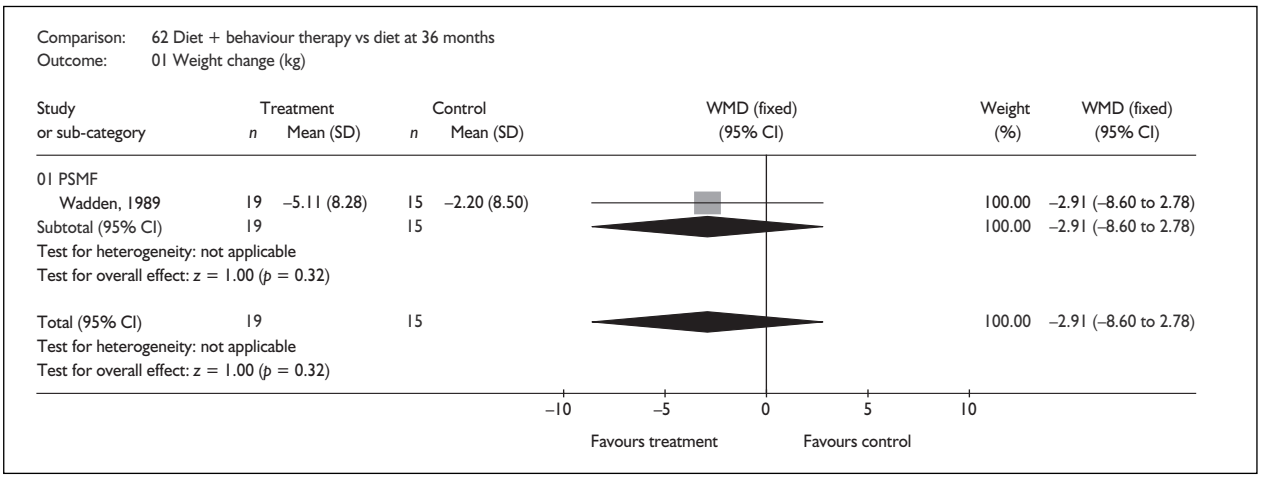


FIGURE 203

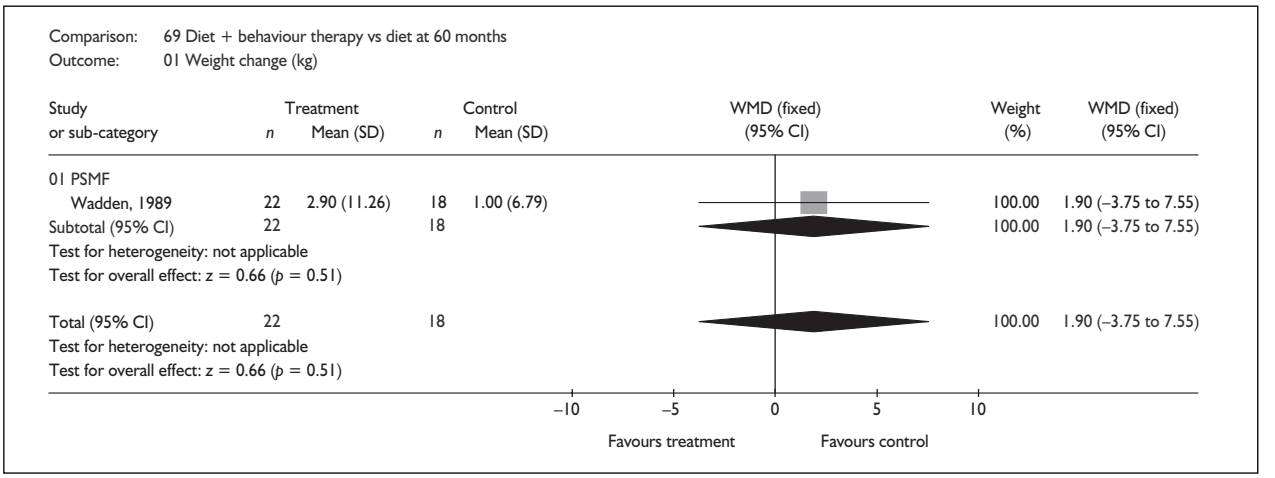


FIGURE 204

Effects of diet and behaviour therapy and exercise versus diet and behaviour therapy

Description of studies

Seven RCTs assessed the added effect of exercise to diet and behaviour therapy and provided change in weight at 12 months or longer.[176–178,236–245] Two of these were cluster RCTs.[178,236] One cluster RCT provided change in HbA_{1c} at 18 months.[178] Data were available for lipids, blood pressure, fasting plasma glucose and HbA_{1c} at 12 and 24 months.

Three studies assessed data using an ITT approach.[176,177,236,239] Wing and colleagues carried out three of the studies, which recruited obese type 2 diabetics[245] or obese people with at least one biological parent with type 2 diabetes.[176,177] The cluster RCT by Kaplan and colleagues[178] also recruited people with type 2 diabetes.

Three studies recruited women only.[236,239–244] Reported mean group BMI ranged from 38.2 kg/m^2 [245] to 35.7 kg/m^2.[176,177] Reported mean group body weight ranged from 80.4 kg[236] to 106.9 kg.[245]

In five of the eight studies participants received equal contact visits.[178,236–238,245] In the other three studies the exercise component accounted for the extra contact visits.[176,177,239–244]

Three studies used a VLCD initially before using an LCD,[176,177,239–244] three studies used a 600 kcal/day deficit or low-fat diet[178,237,238,245] and Phenix[236] used a LCD.

The study by Wing and colleagues[245] used a placebo exercise for participants in the diet and behaviour therapy group. Wadden and colleagues[240–244] compared three kinds of exercise group with no exercise, using step, strength and aerobic exercise.

The number of participants in treatment arms ranged from 11[236] to 43.[237,238] Overall dropouts at 2 years ranged from 40% to 52%.[237–244]

Review results

The added effect of exercise to diet and behaviour therapy was associated with a WMD weight change at 12 months of –3.02 kg (95% CI –4.94 to –1.11 kg) and –2.16 kg (95% CI –4.20 to –0.12 kg) at 24 months (*Figures 205 and 206*). Few studies presented changes for risk factors, with the only statistically significant result for the added effect of exercise being for LDL cholesterol at 24 months (WMD change 0.28 mmol/l, 95% CI 0 to 0.56 mmol/l) (*Figures 207–222*).

In the cluster RCT by Phenix[236] exercise, diet and cognitive behaviour therapy was associated with a mean weight change at 12 months of –1.13 kg compared with –6.68 kg in the diet and cognitive behaviour group. Exercise, diet and overt behaviour therapy was associated with a mean weight change at 12 months of –5.19 kg compared with –3.26 kg in the diet and overt behaviour therapy group.

In the cluster RCT by Kaplan and colleagues[178] the authors report that "weight was essentially constant" at 18 months in participants in the LCD and behaviour therapy plus exercise group. At

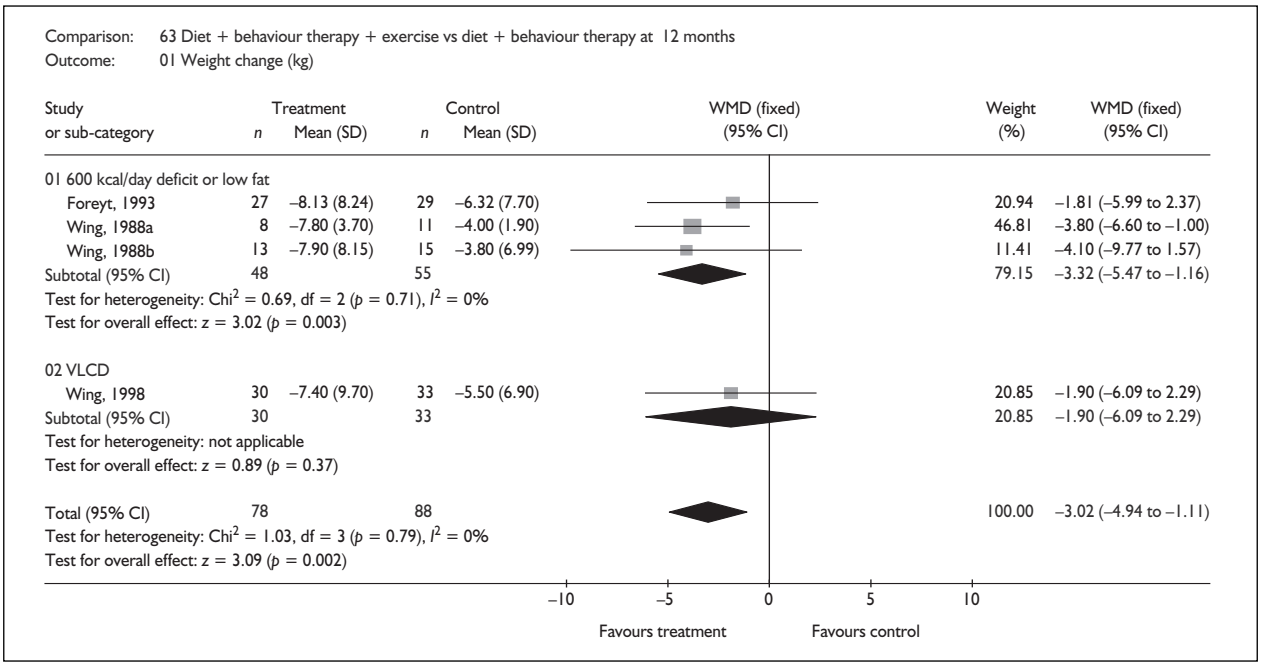


FIGURE 205

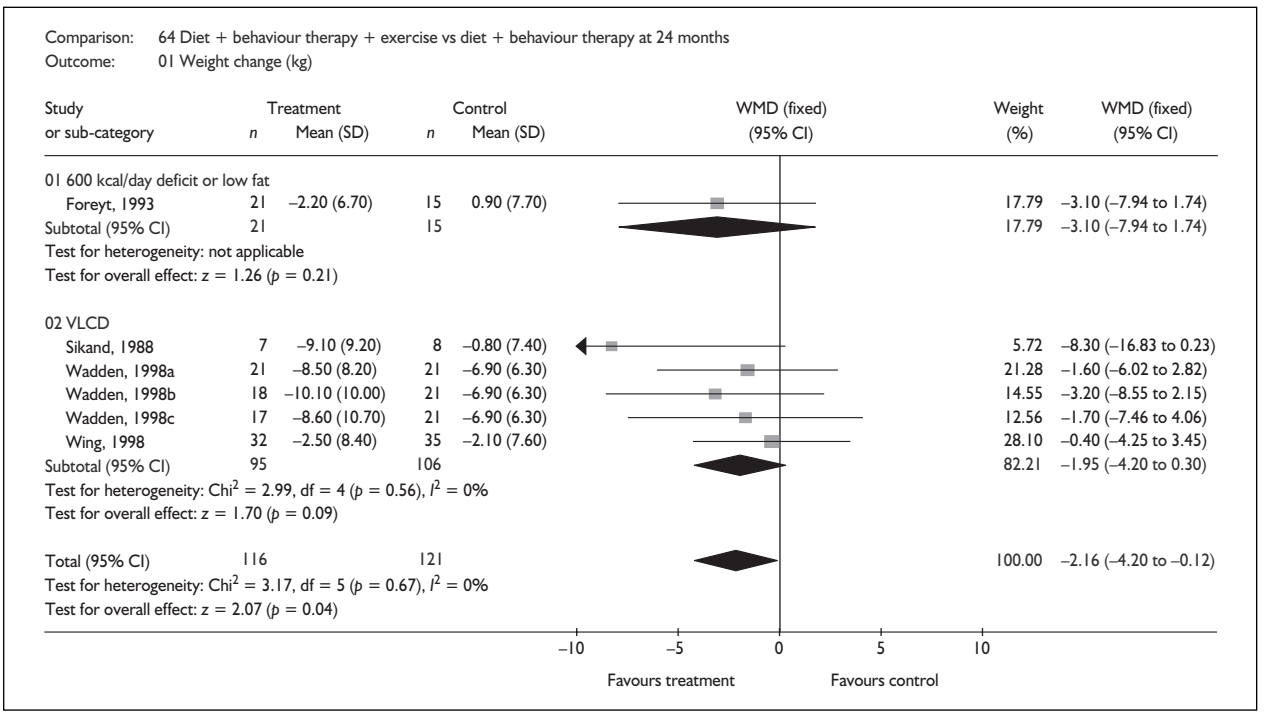


FIGURE 206

18 months the diet and behaviour therapy group was associated with a mean weight loss of –1.68 kg. At 18 months the added effect of exercise to diet and behaviour therapy was associated with a decrease in HbA_{1c} of –1.48% compared with –0.46% in the diet and behaviour therapy group. The added effect 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.

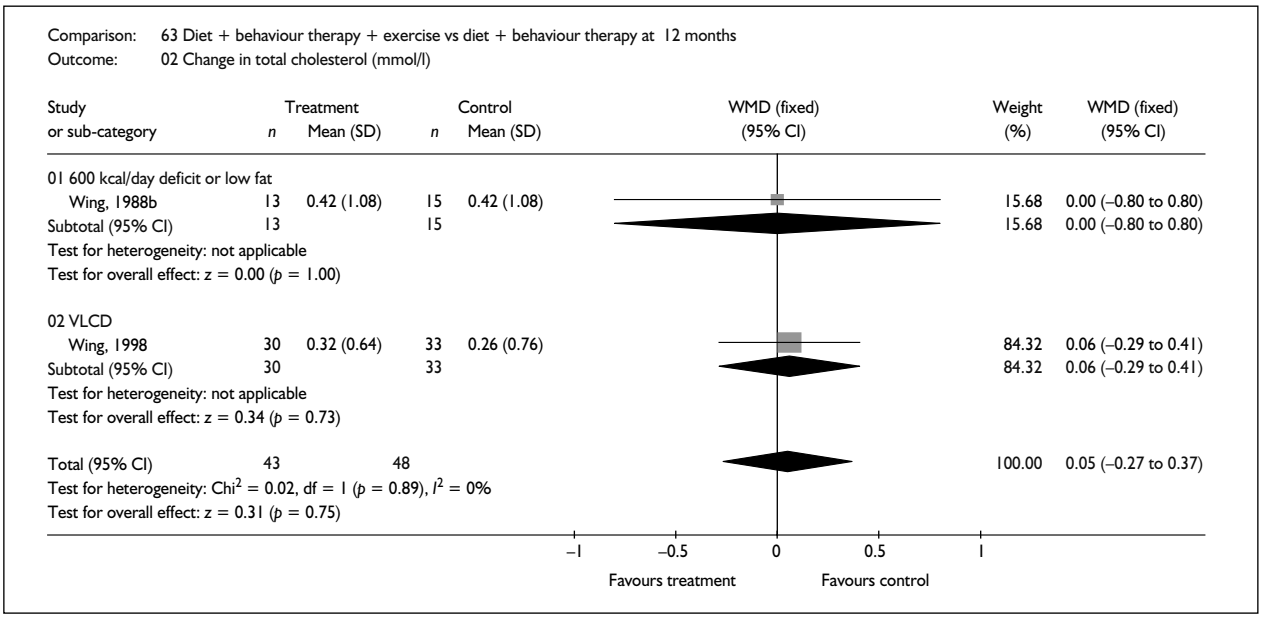
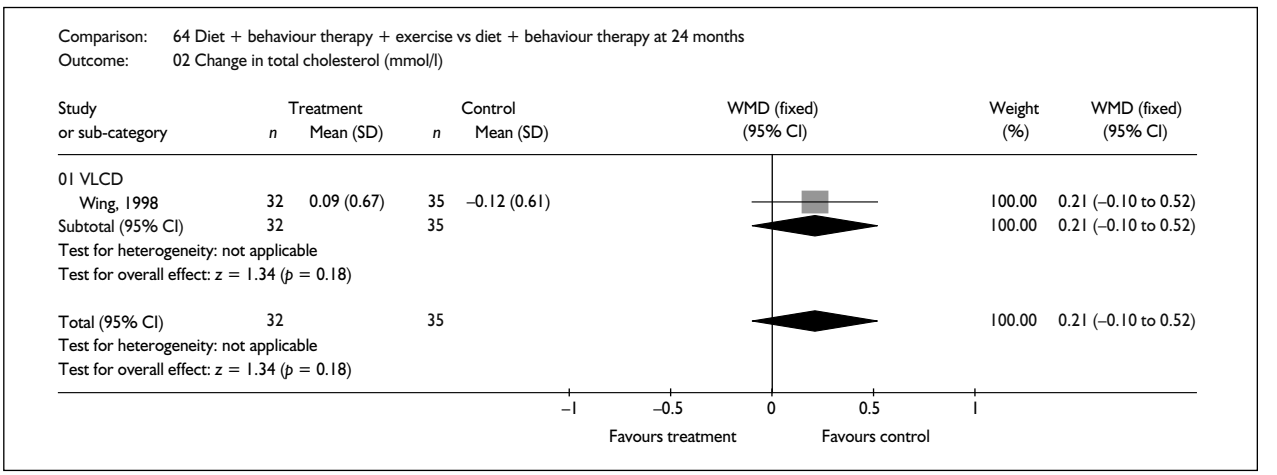


FIGURE 207



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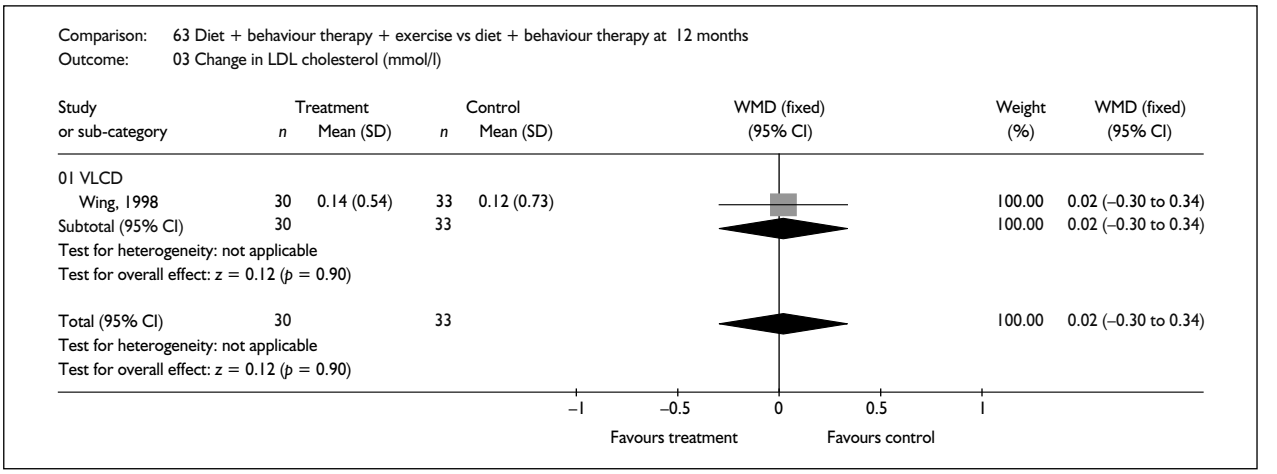

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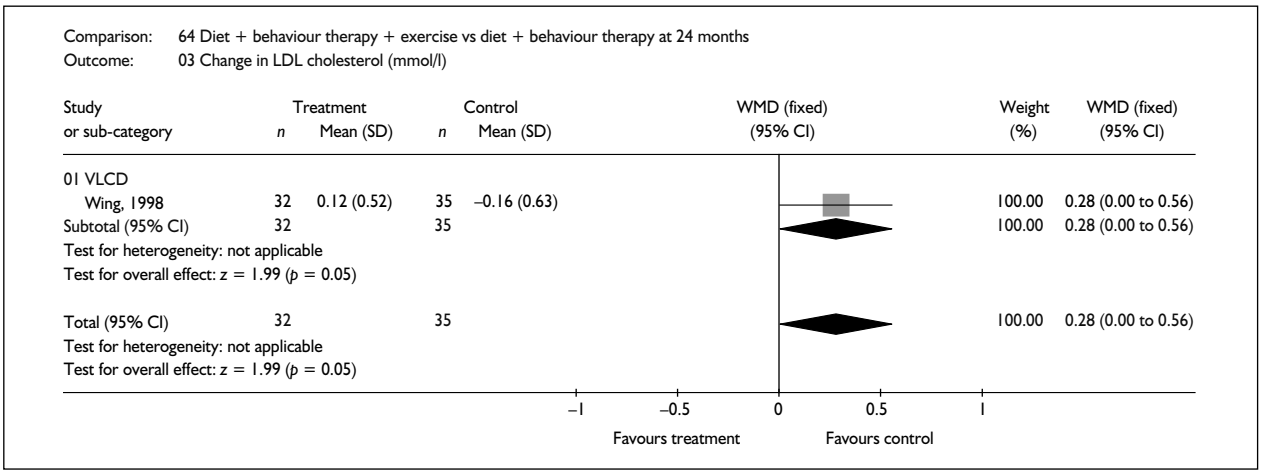
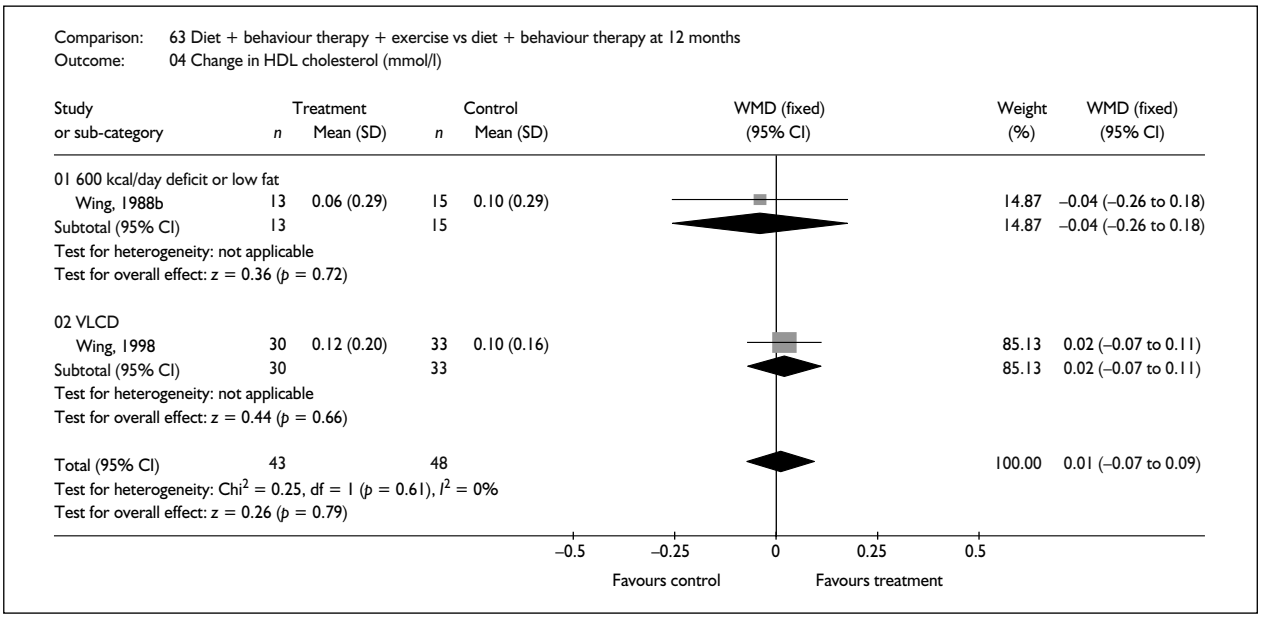


FIGURE 210



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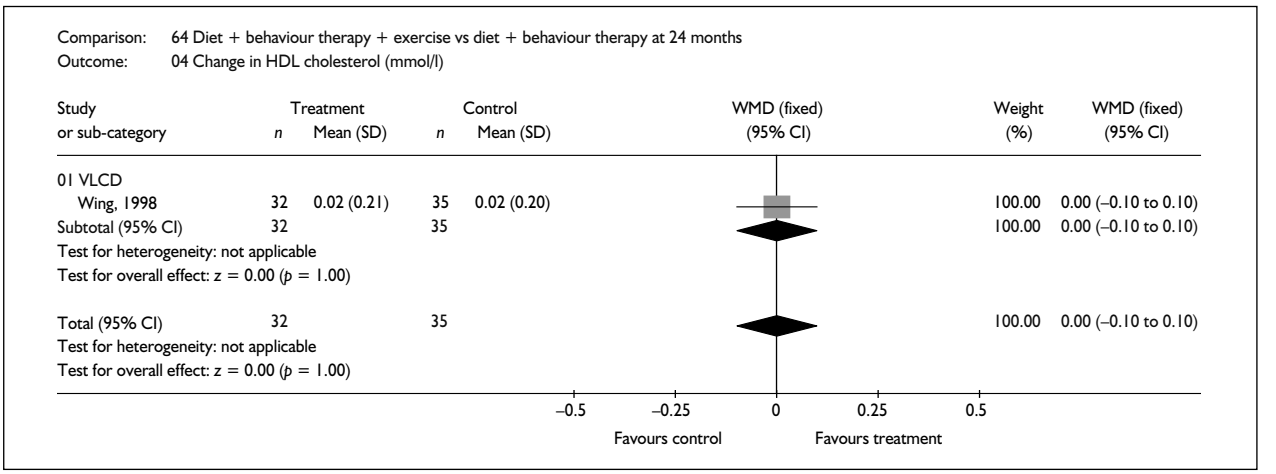

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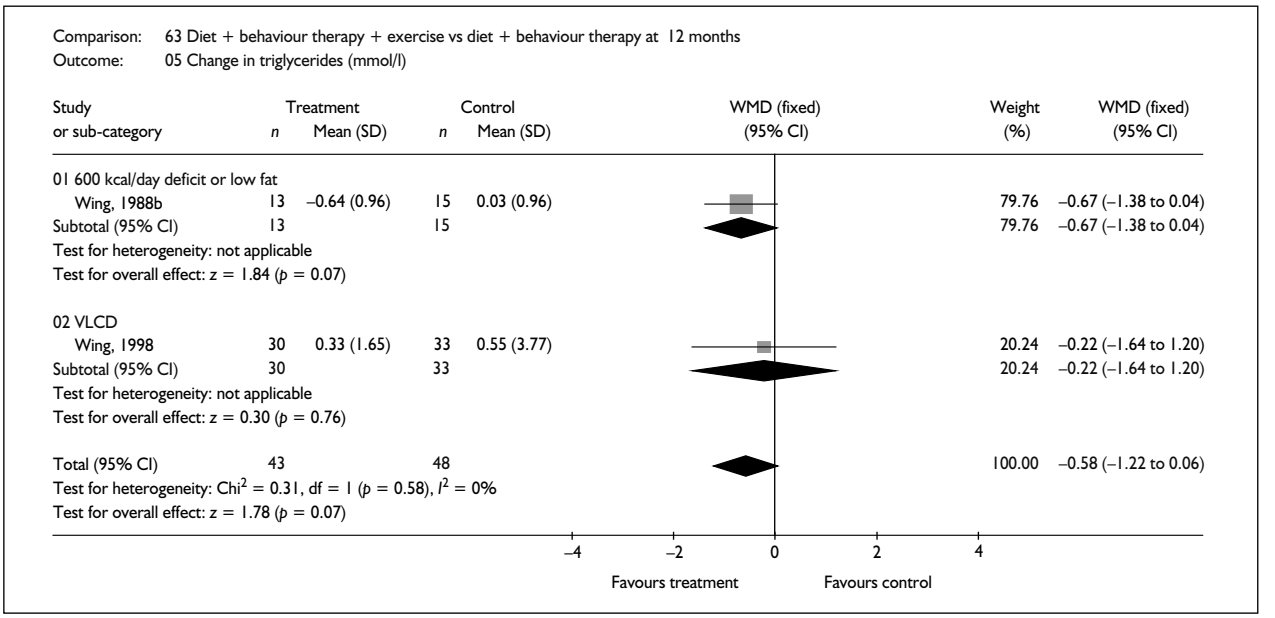

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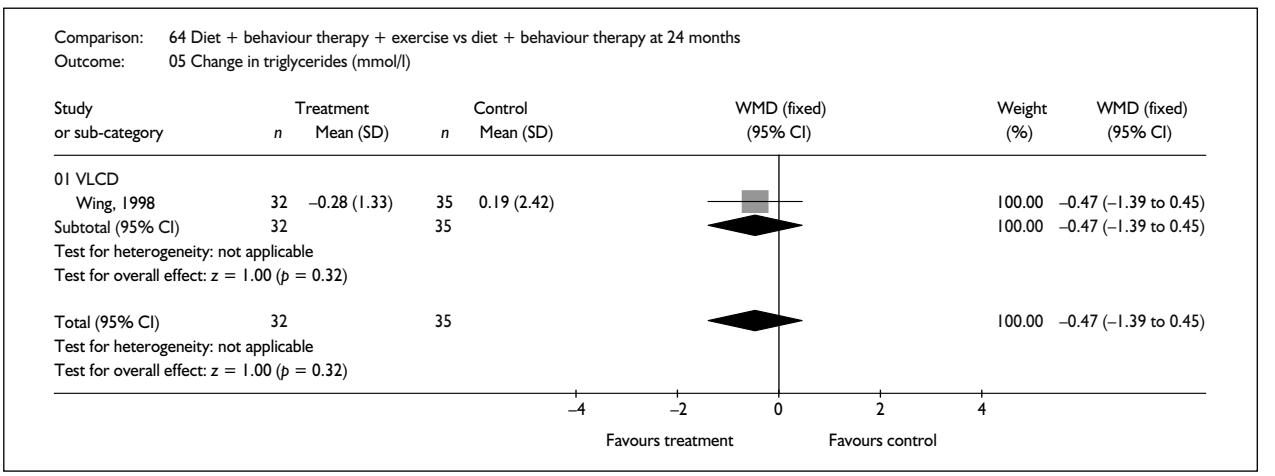

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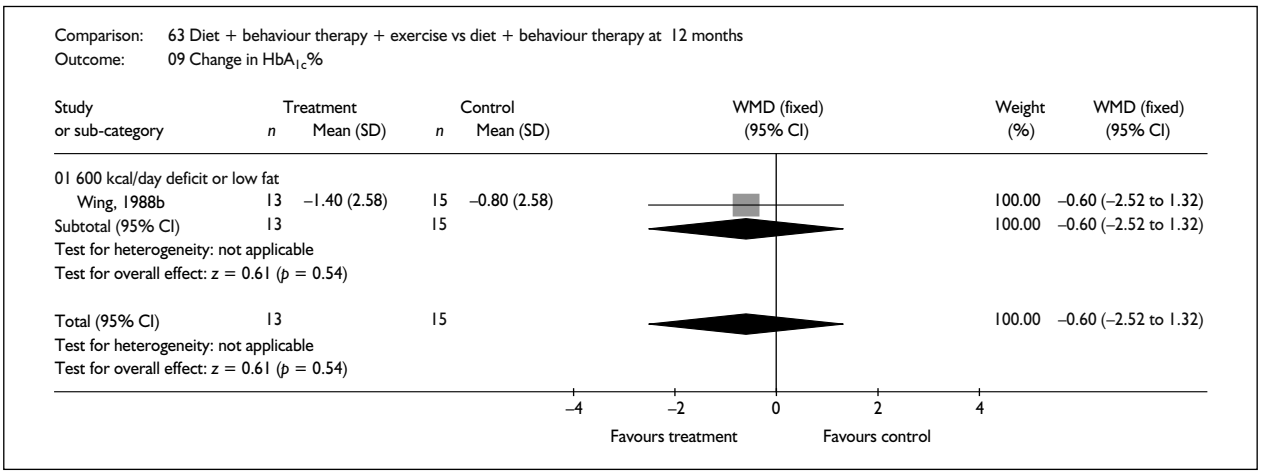

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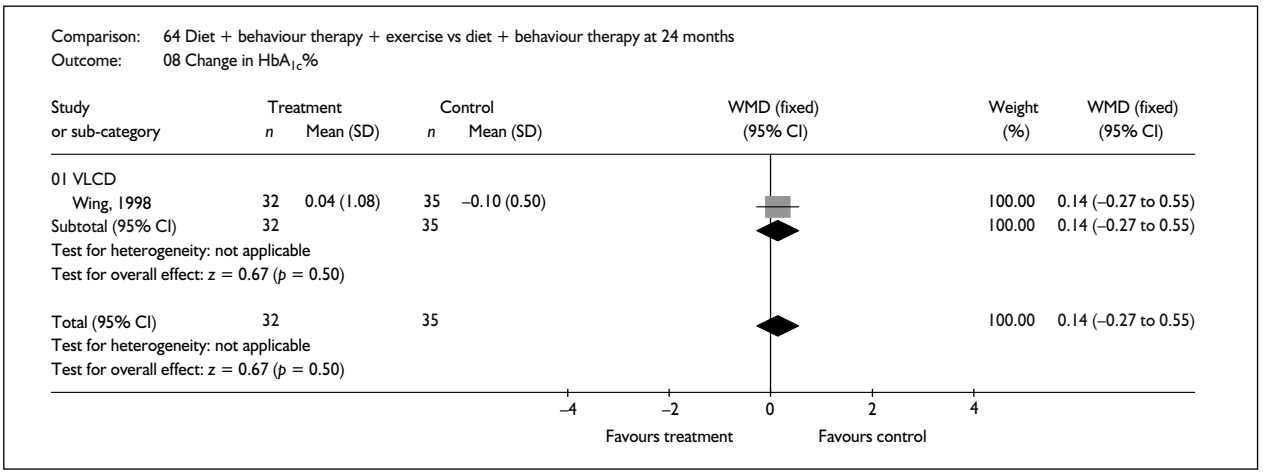

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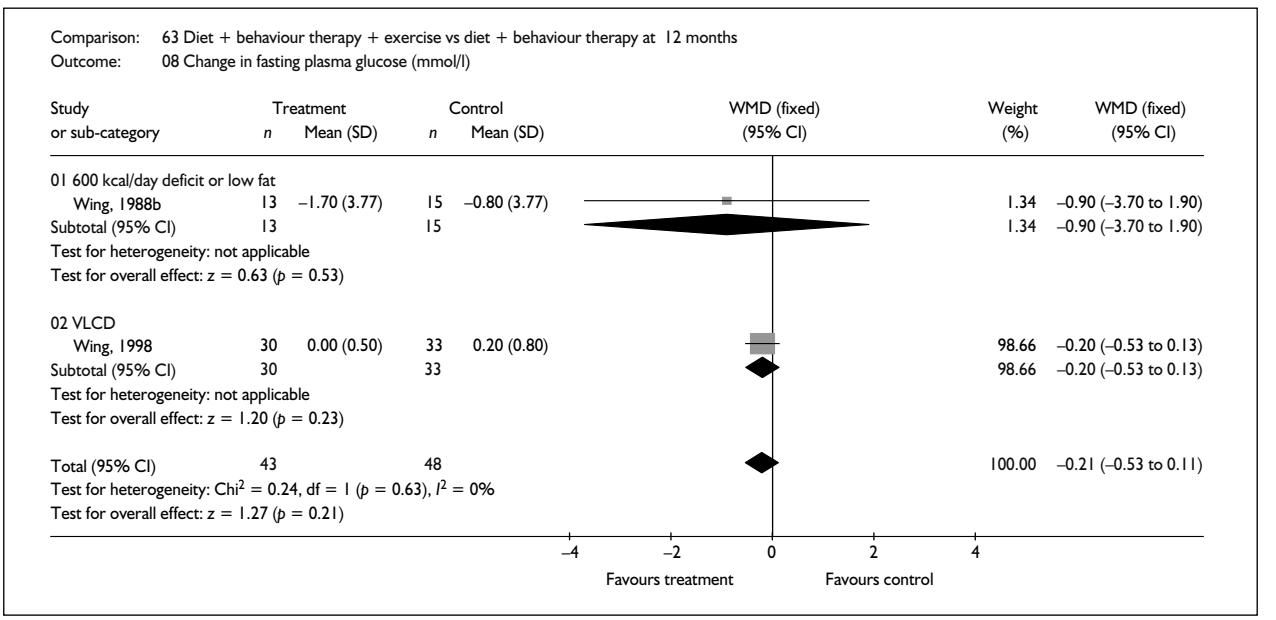
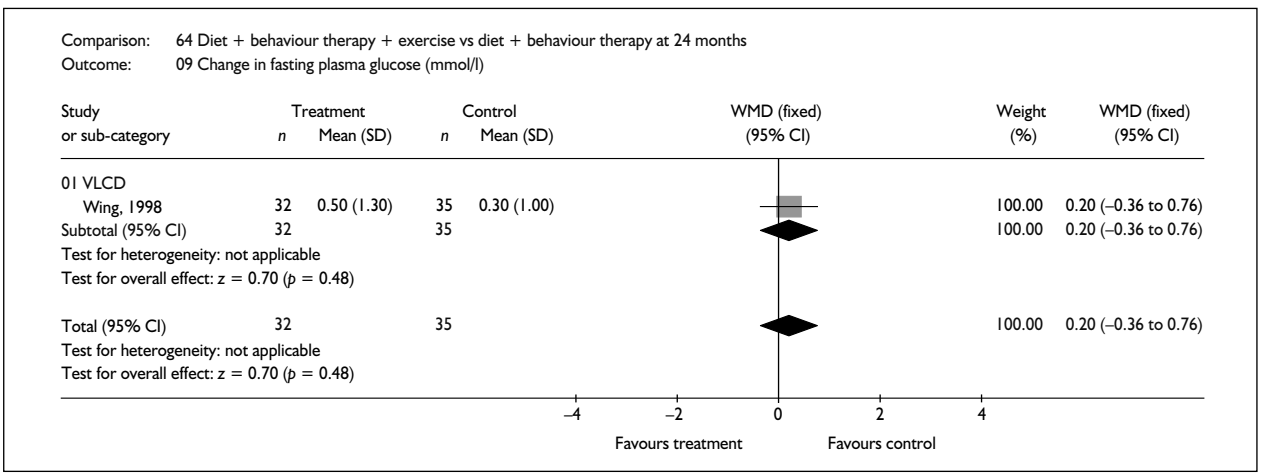


FIGURE 217



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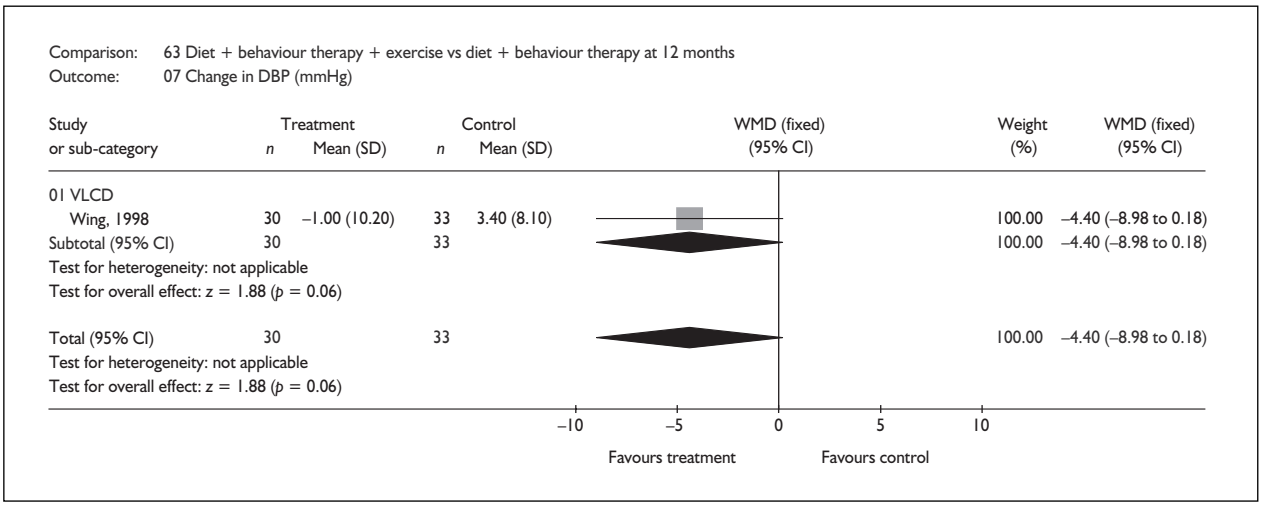

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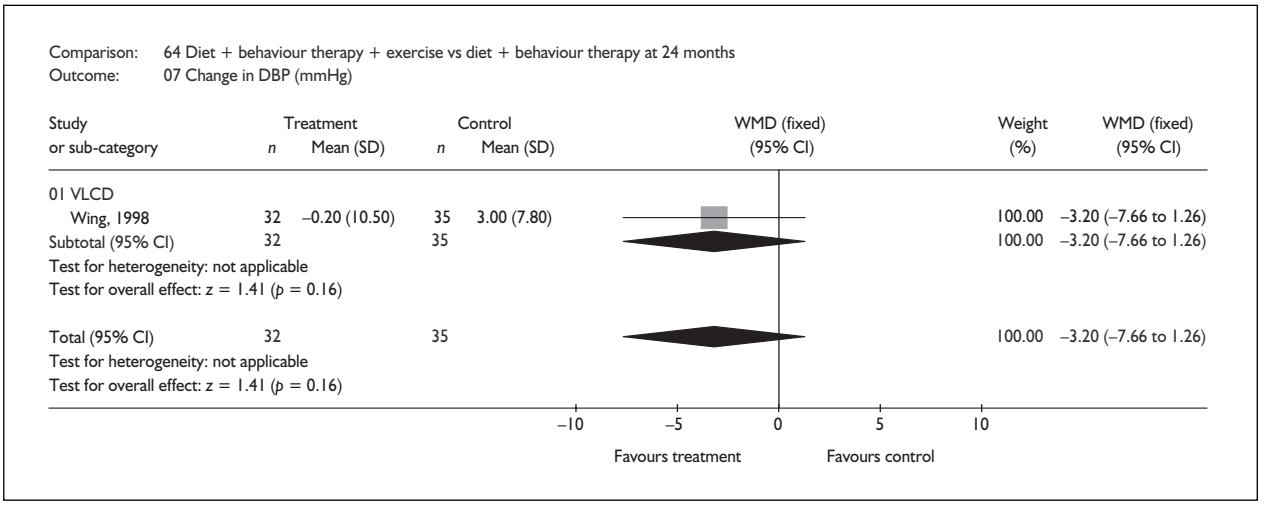

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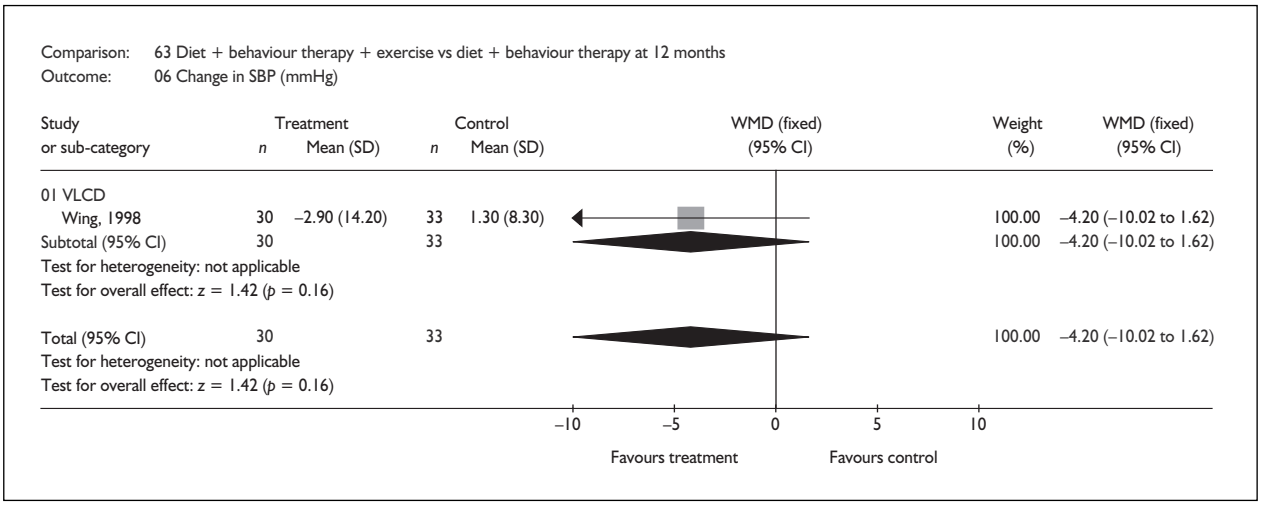


FIGURE 221

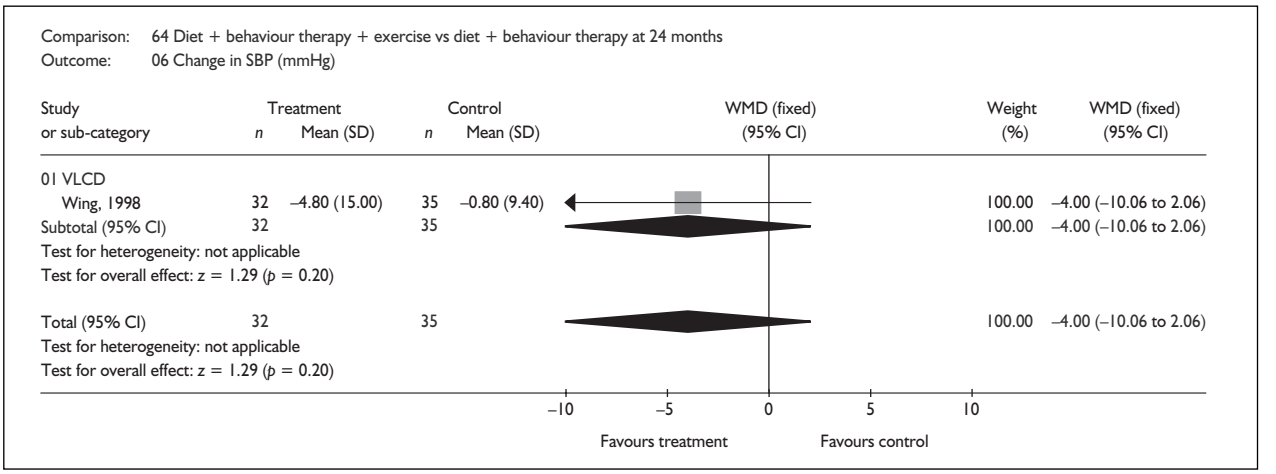


FIGURE 222

Effects of diet and behaviour therapy and exercise versus diet and exercise

Description of study

One cluster RCT assessed the added effects of two forms of behaviour therapy to diet and exercise and provided change in weight at 12 months, where participants were randomised by appointment time.[236] Overt behaviour therapy focused on self-control, including self-monitoring strategies, stimulus control, cue reduction, slowing the rate of eating, coping and problem solving. Cognitive behaviour therapy focused on modifying maladaptive eating behaviour, including cognitive restructuring and relapse prevention techniques.

The study recruited women only. Mean body weight ranged from 76 to 86 kg. Results were analysed using an ITT approach. Active treatment was 8 weeks for all participants of groups used in this review.

Review results

The added effect of overt behaviour therapy to diet and exercise was associated with a mean weight change at 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 at 12 months of –1.13 kg compared with –5.32 kg in the diet and exercise group.

Effects of diet and behaviour therapy and exercise versus diet in an obese population with type 2 diabetes

Description of studies

Two studies assessed the added effect of behaviour therapy and exercise to diet.[236,246] Blonk and colleagues[246] provided change in weight and HbA_{1c} at 12, 18 and 24 months, and change in total cholesterol at 12 months. One cluster RCT provided change in weight at 12 months.[236]

Blonk and colleagues[246] used an ITT analysis. All participants underwent a 3-month run-in period before randomisation where they were instructed not to alter their diet. The study recruited participants with type 2 diabetes. Median BMI at baseline was 31.3 kg/m^2 in the diet, behaviour therapy and exercise group and 32.8 kg/m^2 in the diet-only group. All participants were seen every 2 months for dietary advice regarding a 500 kcal/day deficit diet. The diet, behaviour therapy and exercise group received an additional 43 contact visits over 24 months. Dropouts were 12% overall at 24 months.

Review results

There was insufficient evidence to suggest that the added effect of behaviour therapy and exercise to diet was related to greater weight loss or reduction in reported risk factors at 12, 18 or 24 months (*Figures 223–229*). The WMD weight change was –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. For the added effect of exercise and diet for HbA_{1c} the results at 12 months were –0.38% (95% CI –1.77 to 1.01%), 18 months –0.20% (95% CI –1.59 to 1.19%) and 24 months –0.41% (95% CI –1.80 to 0.98%). For cholesterol at 12 months only, the change was –0.30 mmol/l (95% CI –3.51 to 2.91 mmol/l). One participant withdrew from the diet, behaviour therapy and exercise group owing to mesothelioma.[246]

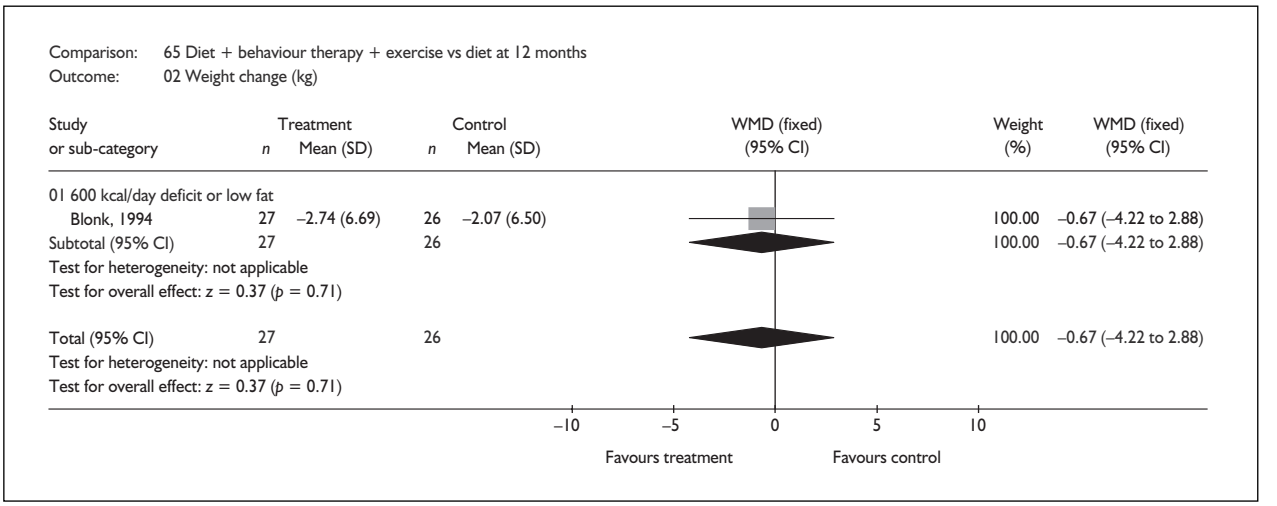
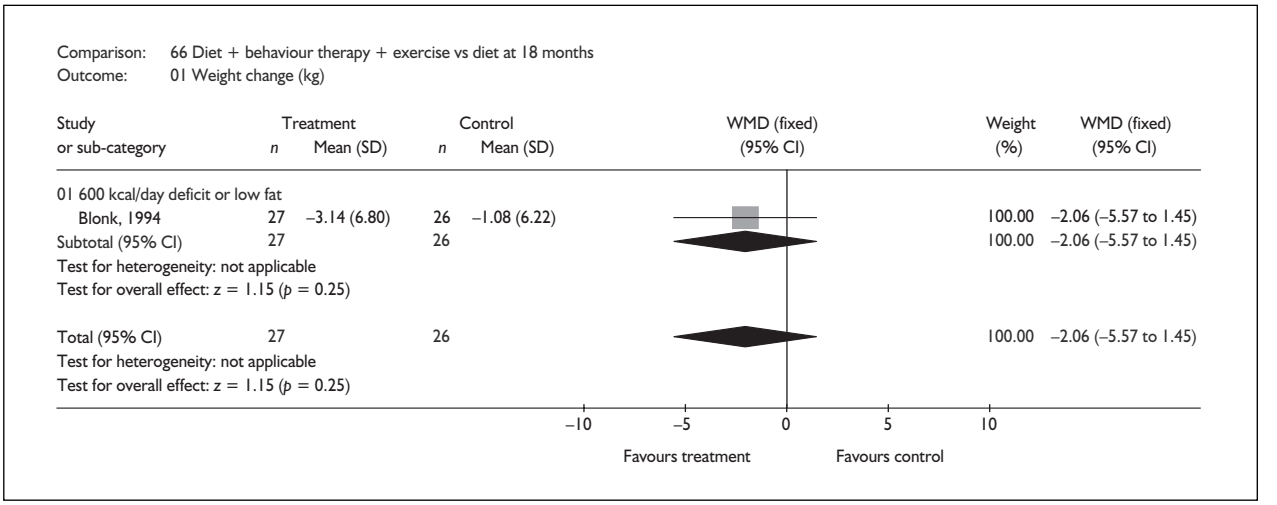


FIGURE 223



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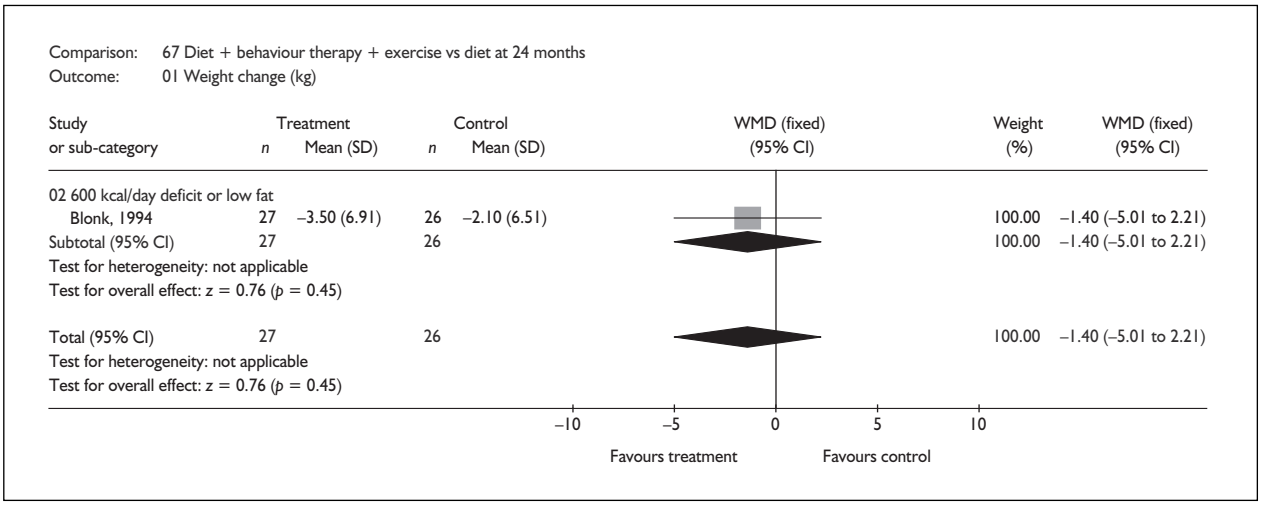
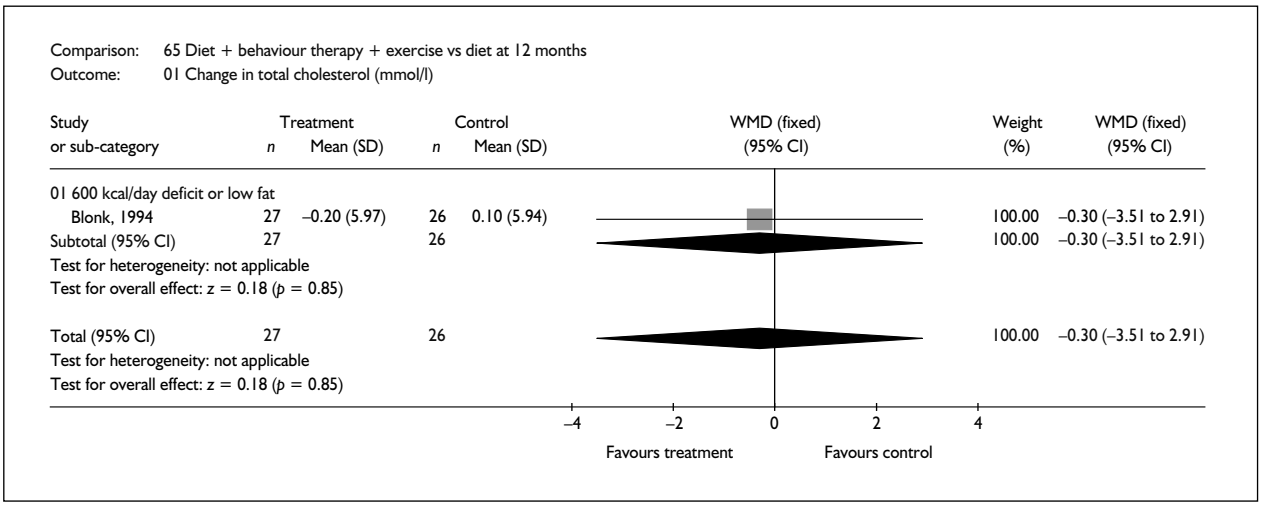


FIGURE 225



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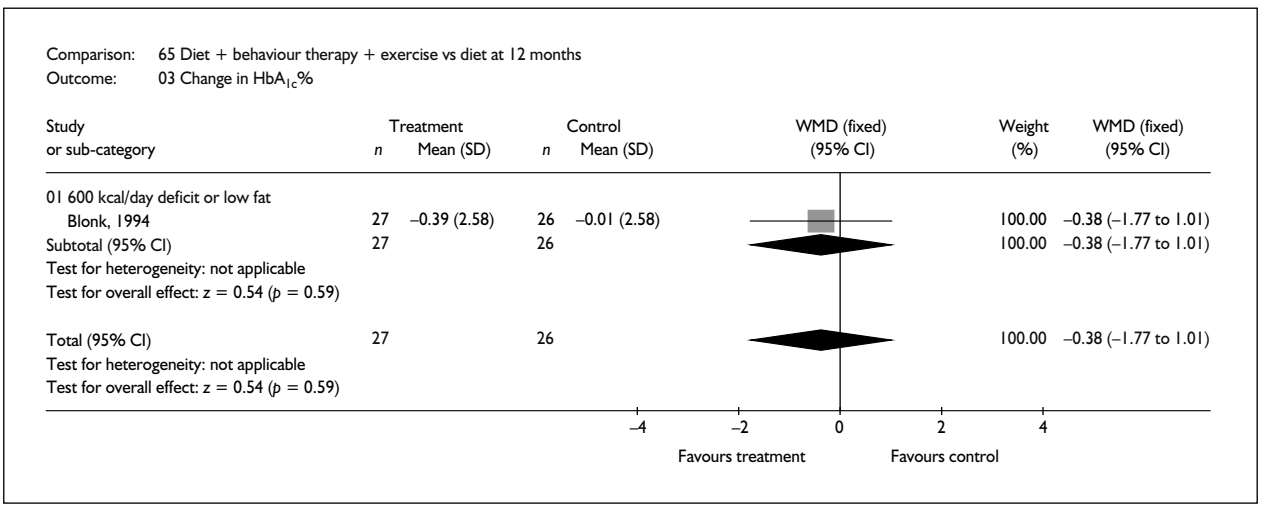

FIGURE 227

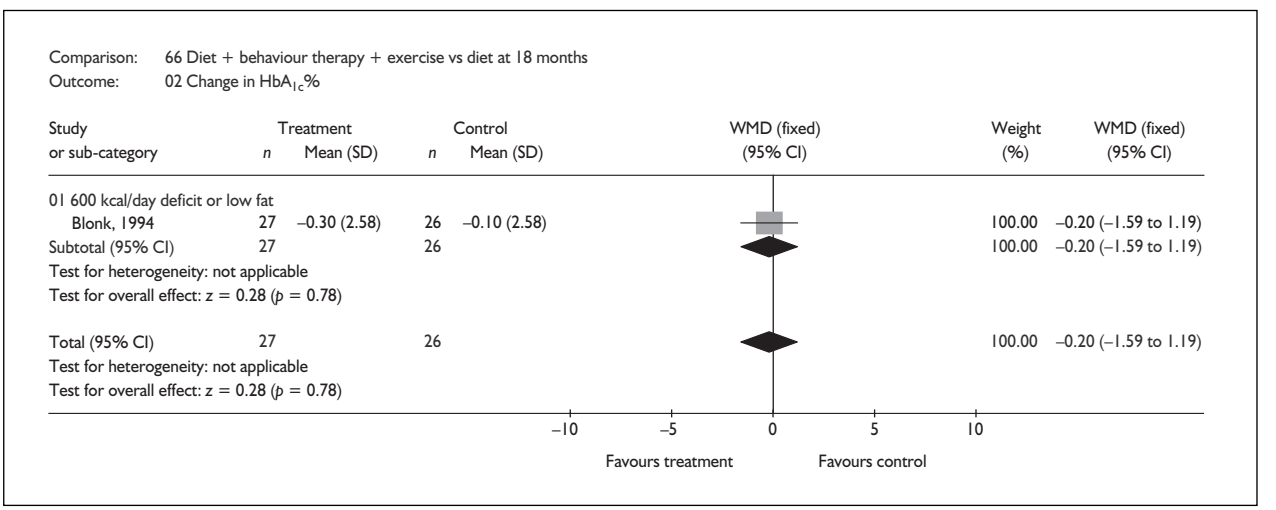

FIGURE 228

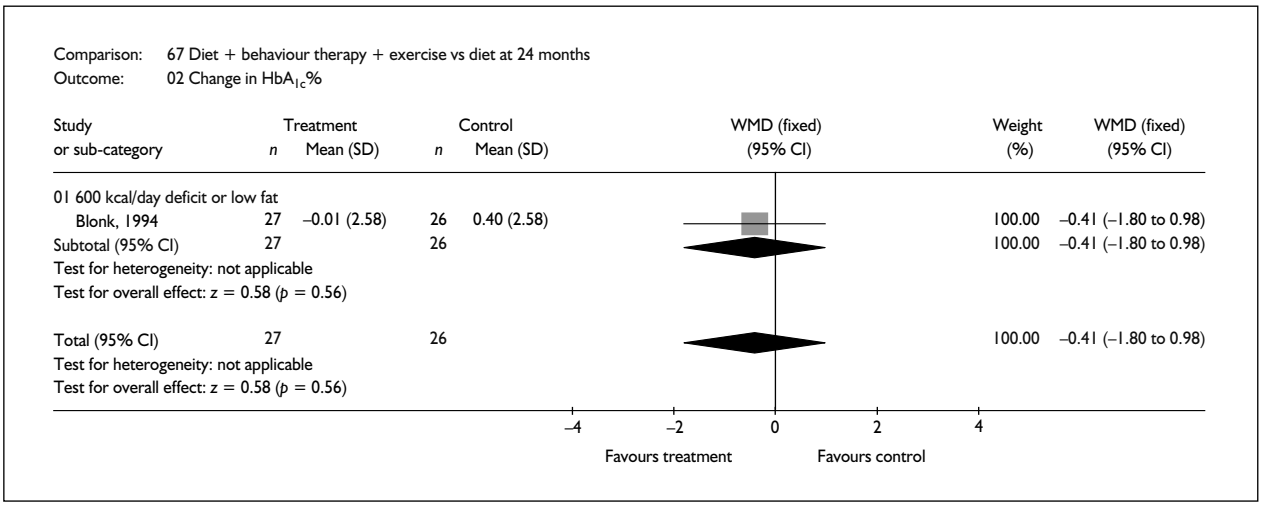

FIGURE 229

The cluster RCT[236] recruited women only. Mean body weight ranged from 76 kg in one of the eight arms to 86 kg in another arm. Results were analysed using an ITT approach. Active treatment was 8 weeks for all participants of groups used in analysis for this review. The added effect 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 added effect 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 added effect 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.

Effects of sibutramine, low-calorie diet, exercise and behaviour therapy versus sibutramine, low-calorie diet and exercise

Description of studies

Wadden and colleagues[247] assessed the added effect of behaviour therapy, where all participants received LCDs, exercise and 10–15 mg sibutramine daily. Following on from this study, Wadden and colleagues conducted a 16-week RCT[248] which evaluated the added effect of orlistat.

Wadden and colleagues[247] used both a conventional and a more conservative ITT analysis in which participants who discontinued treatment were assumed to gain 0.3 kg per month after leaving the study. The study included an LCD of 1200–1500 kcal/day for participants in two arms of the study. The other arm received a 1000 kcal/day portion-controlled diet for the first 16 weeks before receiving the same LCD as the other participants. All participants received identical exercise prescriptions. The added effect of behaviour therapy was tested in both groups receiving differing LCDs. Data were presented individually for the three groups for weight, but risk factor data on blood pressure and lipids were combined for all groups.

All participants were women with an overall BMI at baseline of 37.7 kg/m^2. The participants receiving a portion-controlled diet had no dropouts at 12 months.

Review results

Behaviour therapy was associated with a WMD weight change at 12 months of –10.69 kg (95% CI –14.22 to –7.16 kg). The number of participants in the study was small (*Figure 230*).

One participant was withdrawn from the 10–15 mg sibutramine plus conventional LCD, exercise and behaviour therapy group owing to an increase in blood pressure.

Further comparisons

Added effect of any intervention over diet

Comparing all treatments assessed as an adjunct to diet at 12 months (*Figure 231*), behaviour therapy was associated with the greatest WMD weight change of –7.67 kg (95% CI –11.97 to –3.36 kg), although confidence intervals are wide, and SSRIs were associated with the least WMD weight change of –0.33 kg (95% CI –1.49 to 0.82 kg).

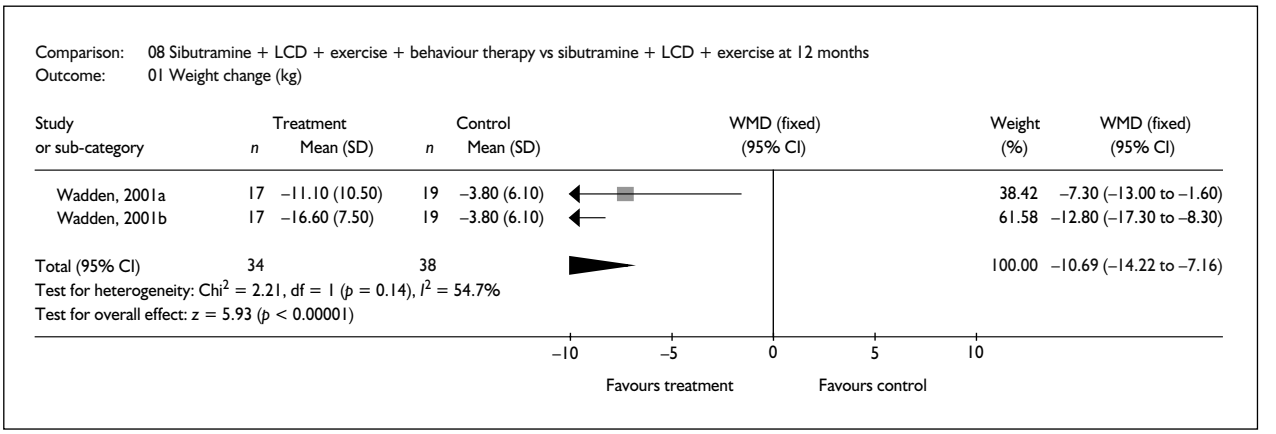

FIGURE 230

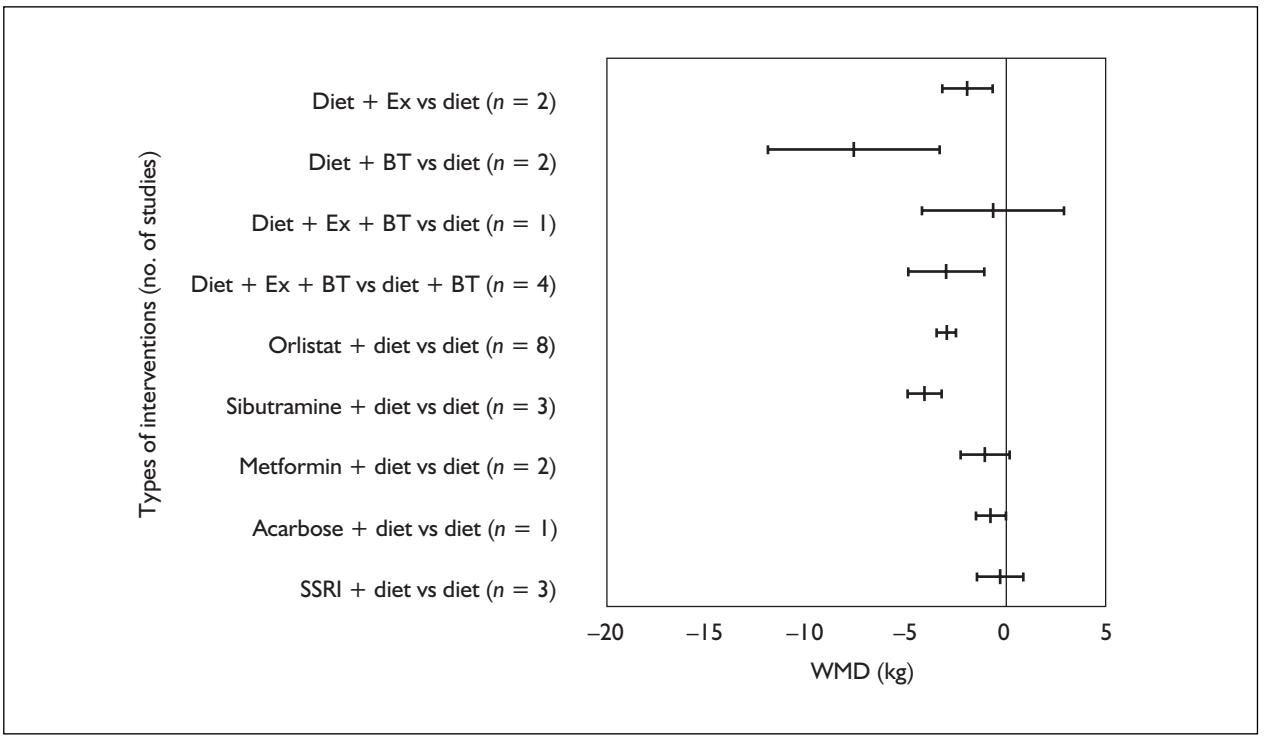

FIGURE 231 *Added effect of exercise (EX), behaviour therapy (BT) or drugs on weight at 12 months*

Sibutramine was associated with a WMD weight change of –4.12 kg (95% CI –4.97 to –3.26 kg), orlistat –3.01 kg (95% CI –3.48 to –2.54 kg), exercise –1.95 kg (95% CI –3.22 to –0.68 kg) and –3.02 kg (95% CI –4.94 to –1.11 kg), metformin –1.09 kg (95% CI –2.29 to 0.11 kg), acarbose –0.79 kg (95% CI –1.53 to –0.05 kg) and behaviour therapy plus exercise –0.67 kg (95% CI –4.22 to 2.88 kg).

At 18 months (*Figure 232*), exercise was associated with improved weight loss when added to diet, and the additional behaviour therapy was just significant. At 24 months (*Figure 233*), orlistat was associated with enhanced weight loss when added to diet, and exercise enhanced weight loss when added to diet and behaviour therapy.

The effect of exercise was similar at 36 months (*Figure 234*). At 60 months (*Figure 235*) behaviour therapy as an adjunct to diet could not be shown to prevent weight gain.

At 12 months orlistat added to diet was associated with lowered DBP and SBP, HbA_{1c}, total cholesterol and glucose (*Figures 236–240*), whereas

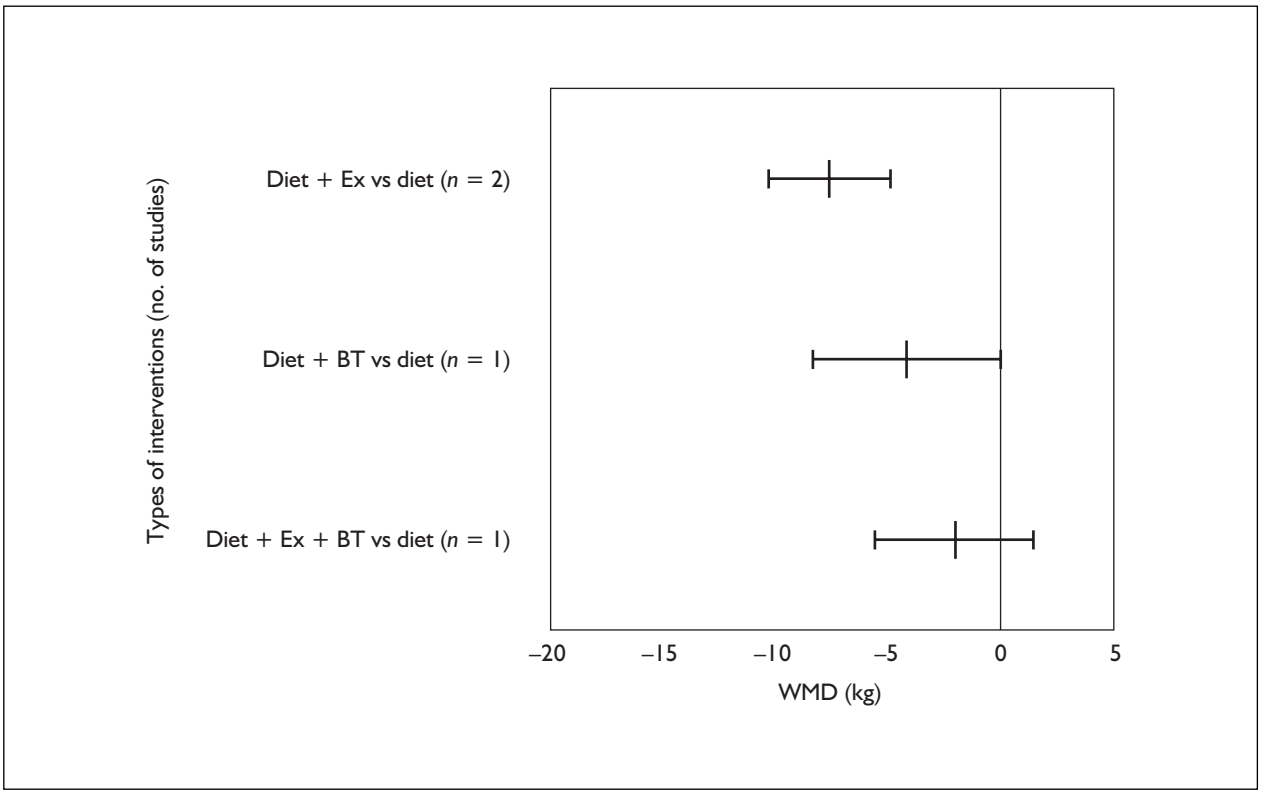

FIGURE 232 *Added effect of exercise and/or behaviour therapy on weight at 18 months*

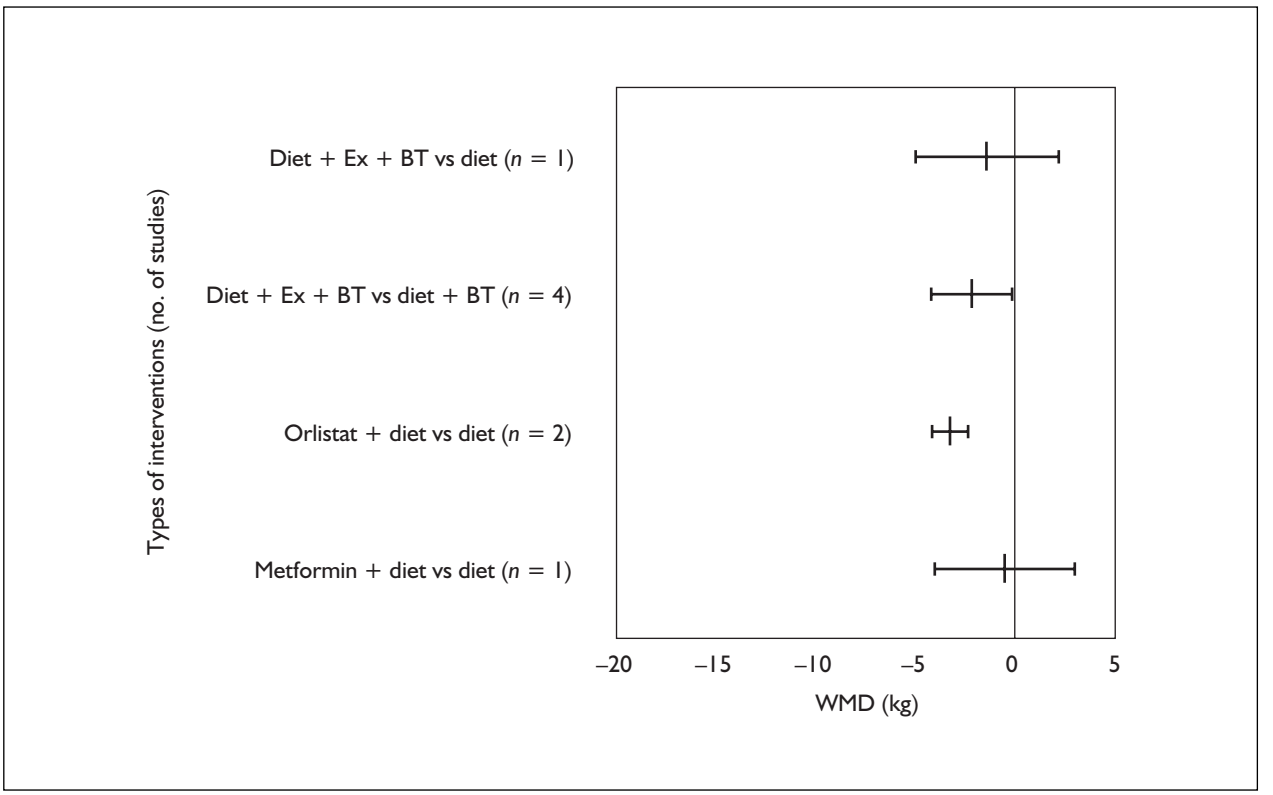

FIGURE 233 *Added effect of exercise and/or behaviour therapy, or drugs on weight at 24 months*

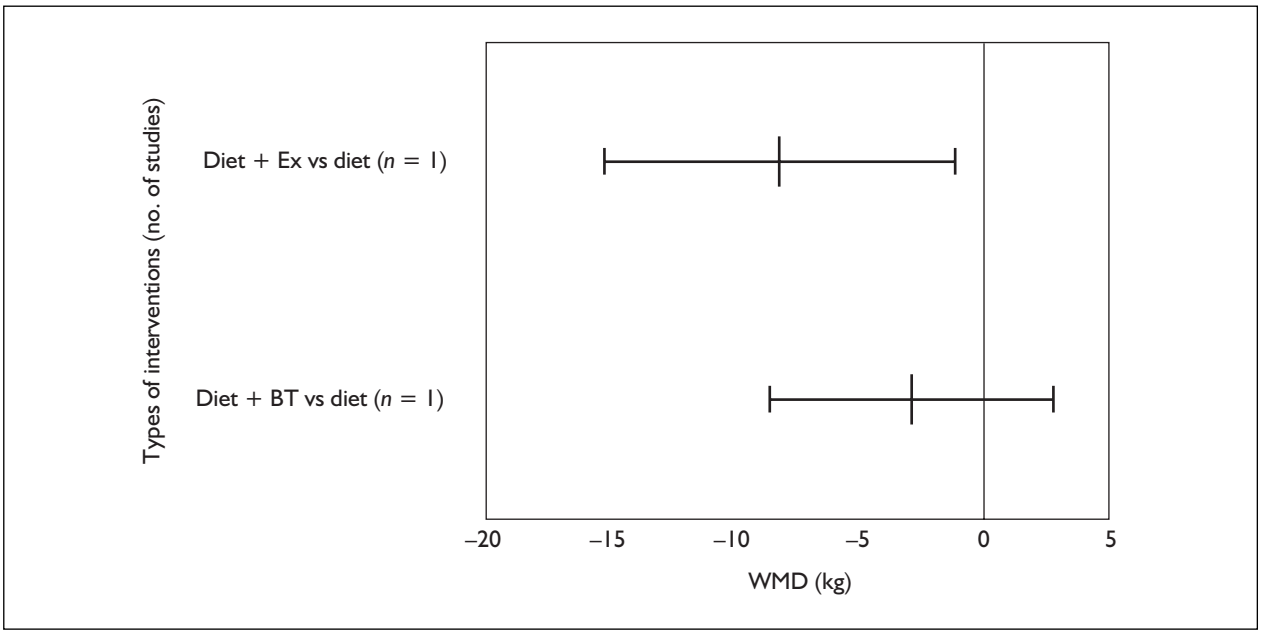

FIGURE 234 *Added effect of exercise or behaviour therapy to diet alone on weight at 36 months*

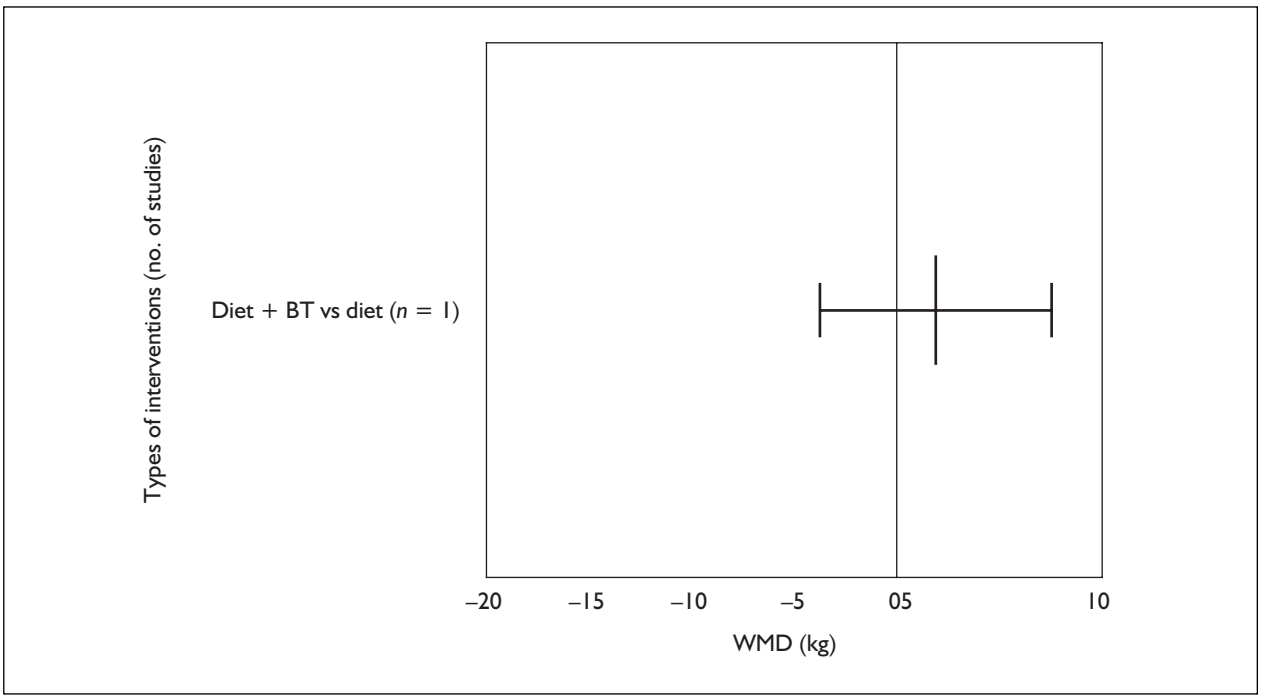

FIGURE 235 *Added effect of behaviour therapy to diet alone on weight at 60 months*

sibutramine increased DBP (*Figure 236*). At 12 months acarbose added to diet was associated with lowered HbA_{1c} and glucose (*Figures 238* and *240*).

Only one study[246] assessed the added effect of behaviour therapy and exercise to diet and was unable to demonstrate any significant effect on weight (*Figures 231* and *233*) or any risk factor at 12 months (*Figures 238* and *239*) and 24 months.

The addition of exercise to diet and behaviour therapy was associated with significantly increased weight loss at 12 and 24 months (*Figures 231* and *233*).

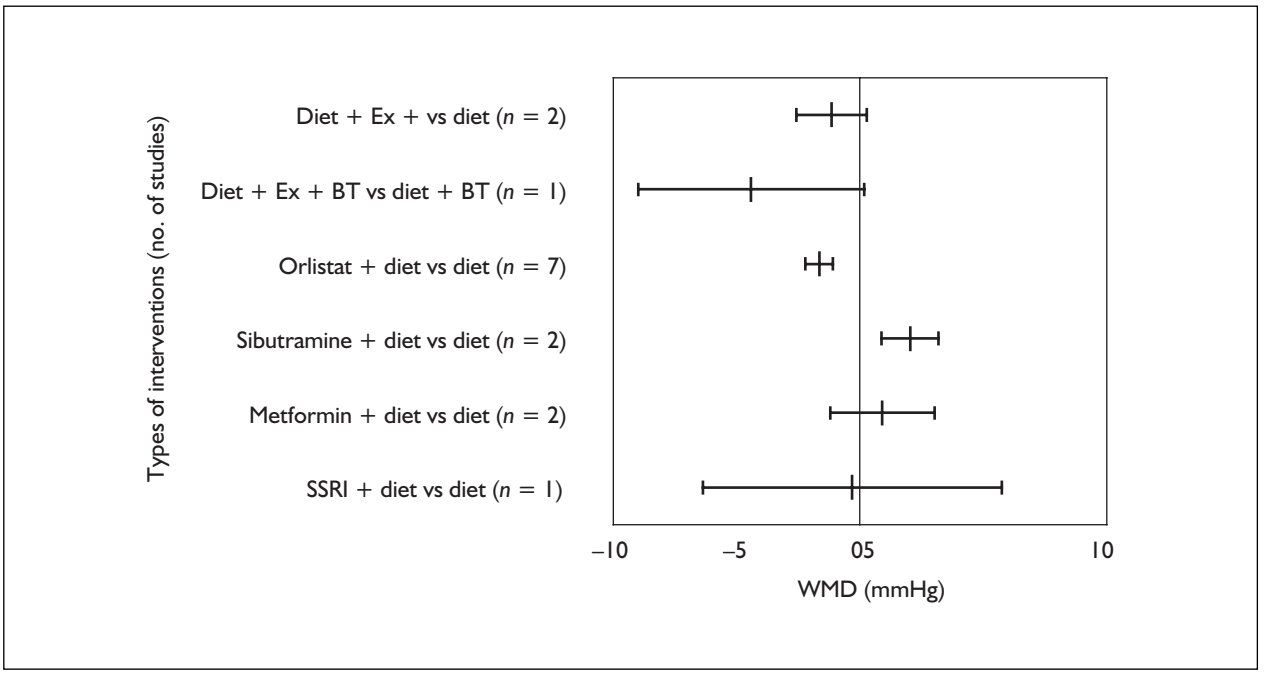

FIGURE 236 *Added effect of exercise, behaviour therapy or drugs on DBP at 12 months*

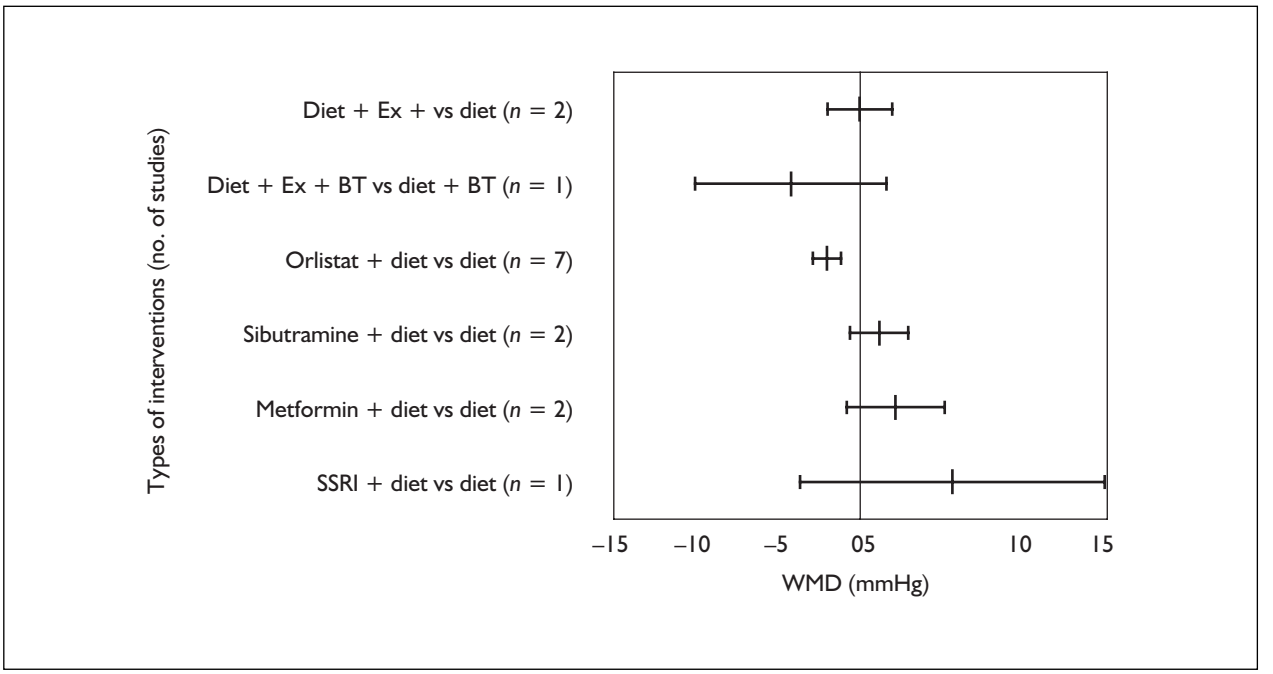

FIGURE 237 *Added effect of exercise, behaviour therapy or drugs on SBP at 12 months*

Comparisons of treatments versus control

Few studies compared LCD or VLCD with control, but there was a trend for these diets to produce more weight loss at 1 year than the 600 kcal/day deficit or low-fat diet (*Figures 241* and *242*). One VLCD study was associated with the greatest WMD weight change at 12 months of –13.40 kg (95% CI –18.43 to –8.37 kg). At 24 and 36 months there was some suggestion that LCDs were more effective than 600 kcal/day deficit diets (*Figures 243* and *244*).

Diet and exercise, diet and behaviour therapy, and diet, behaviour therapy and exercise were all associated with significantly greater weight loss than control at 12 months (*Figure 241*).

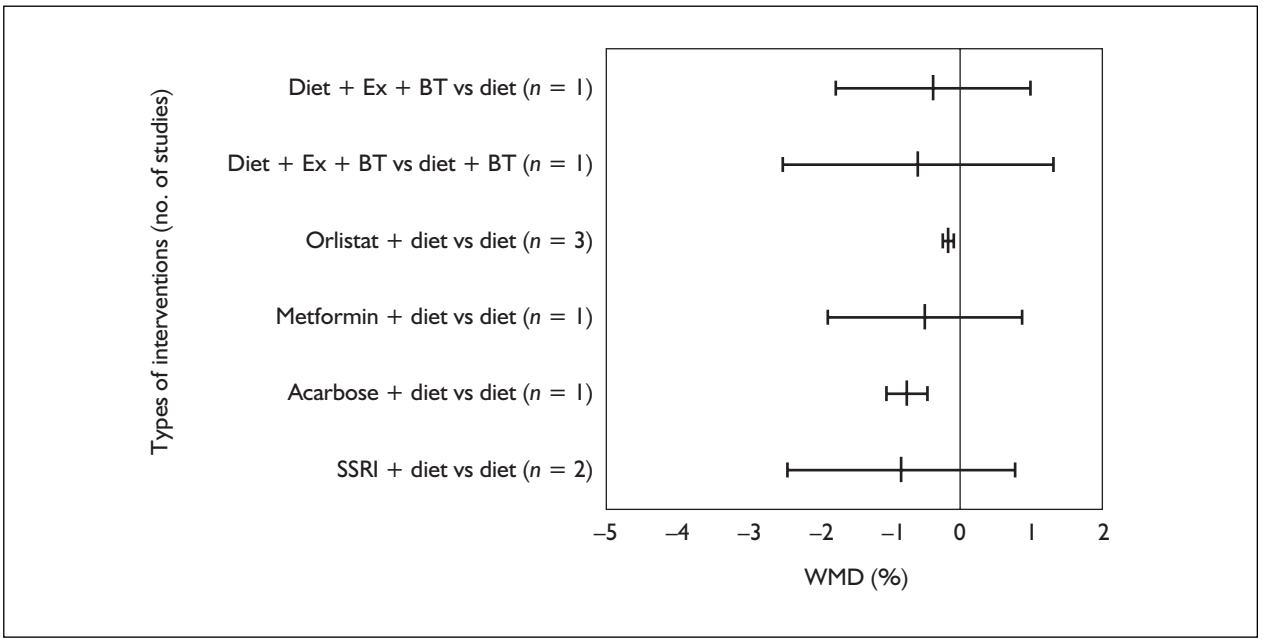

FIGURE 238 *Added effect of exercise, behaviour therapy or drugs on HbA_{1c} at 12 months*

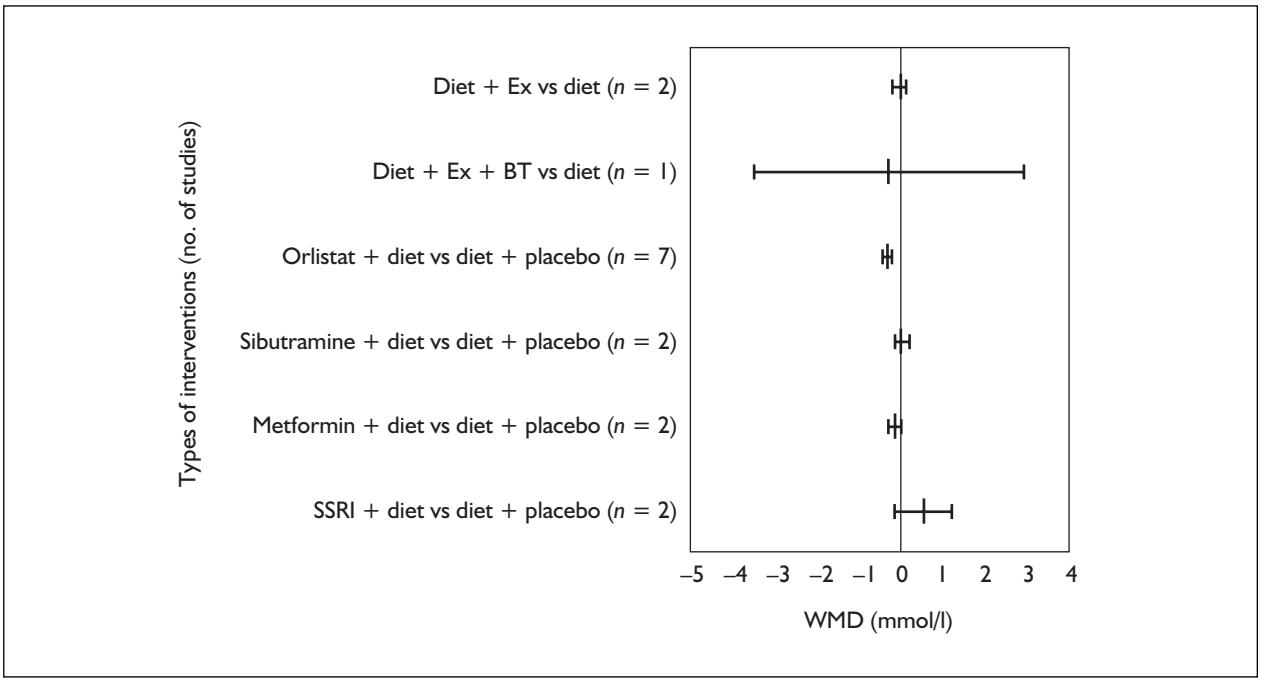

FIGURE 239 *Added effect of exercise, behaviour therapy or drugs on total cholesterol at 12 months*

In terms of mode of delivery (*Figure 245*), participants appeared to lose less weight in a group setting than when receiving treatment on an individual basis at all time-points, and this reached statistical significance at 24 months. Participants also appeared to lose more weight when accompanied by their spouse or a friend than when unaccompanied, and this was statistically significant at 12 and 24 months.

Discussion

Methodology

Results from the literature search demonstrate that it was necessary to search several electronic databases and undertake focused handsearching in order to locate reports of RCTs.

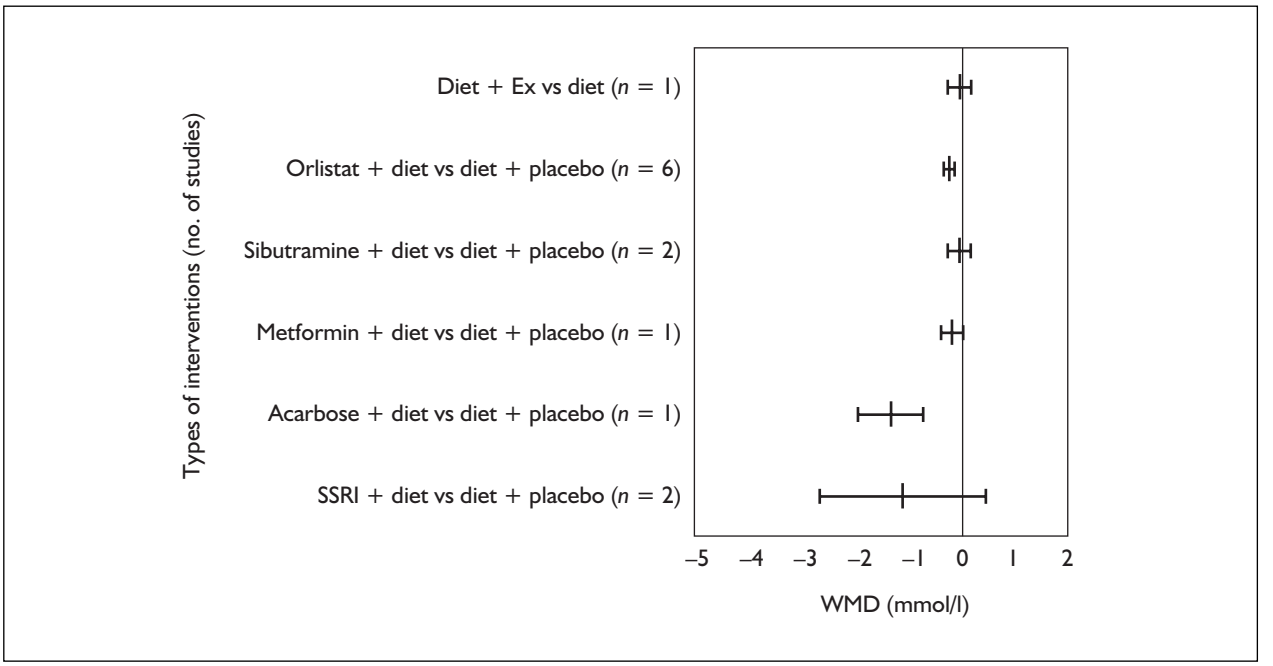

FIGURE 240 *Added effect of exercise, behaviour therapy or drugs on fasting plasma glucose at 12 months*

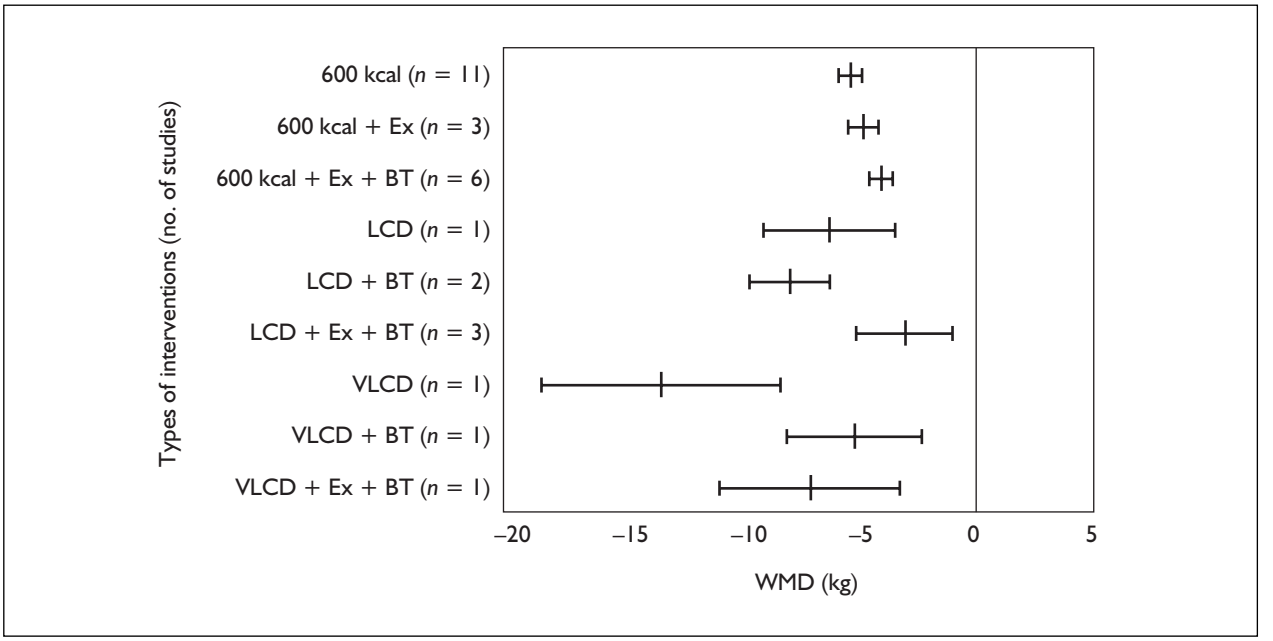

FIGURE 241 *Interventions versus no intervention on 12-month weight*

In assessing reports, of included RCTs, difficulties were encountered. Some reports failed to provide a detailed description of the interventions, such that it was difficult to classify the diets, or determine whether exercise or behaviour therapy was given. Few trials clearly reported methods of randomisation. All the drug trials were reported as double blind, but did not clearly indicate who was blinded. It was assumed this meant the participant and healthcare provider were blinded.

Some trials used a pretreatment phase and analysed outcomes from the start of this phase, rather than the start of randomisation. As a result some weight changes from randomisation had to be estimated. Standard deviations often needed to

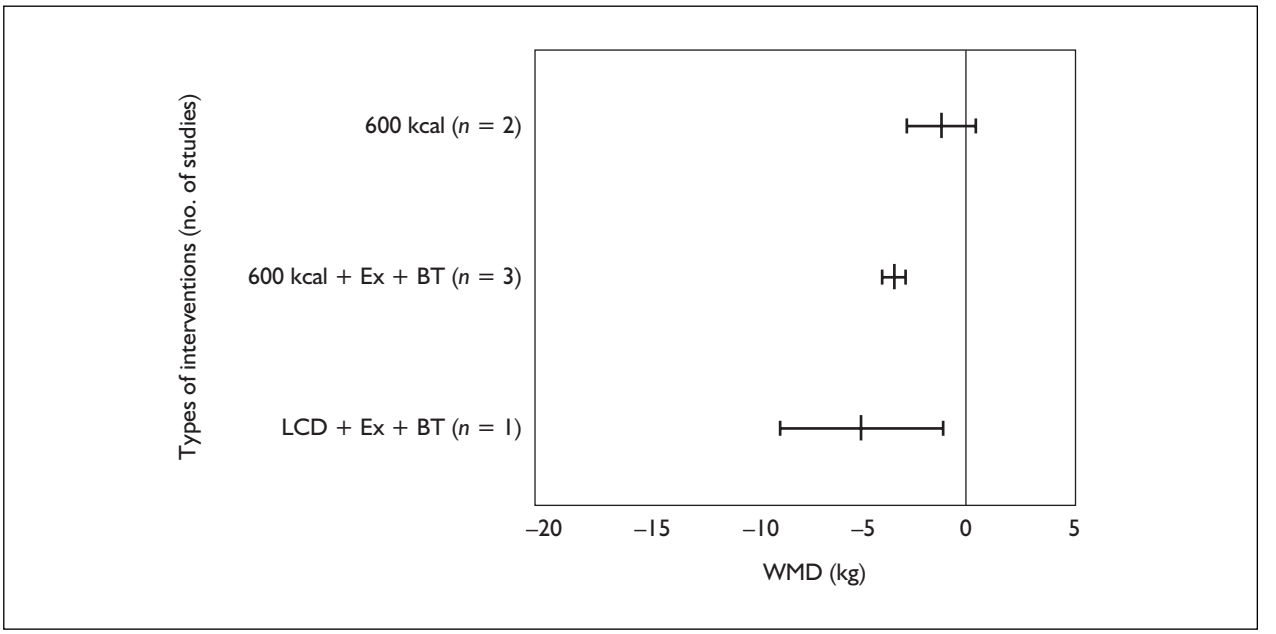

FIGURE 242 *Interventions versus no intervention on 18-month weight*

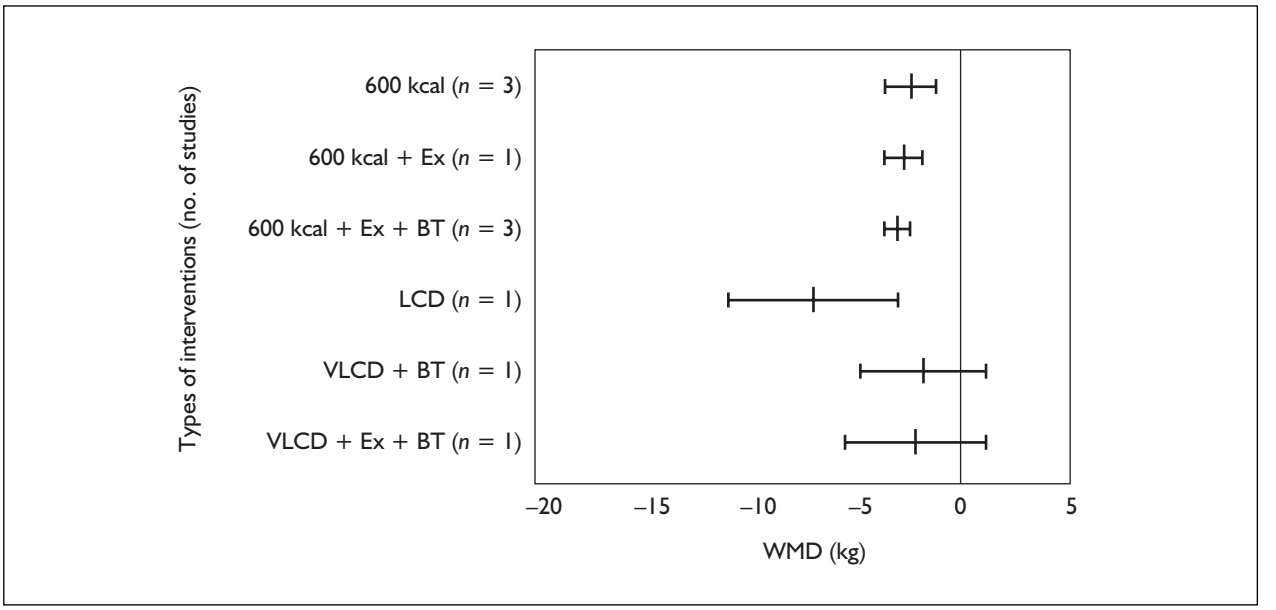

FIGURE 243 *Interventions versus no intervention on 24-month weight*

be imputed for weight and risk factor outcomes, as data were not provided in the papers. The impact of these estimates on the results is unclear. Sensitivity analyses could be used to assess whether any of these assumptions affected the results. Often participants in different arms of trials did not receive equal numbers of contacts. It could be argued that contact time rather than the specific elements of the intervention affected participants' weight and consequently risk factor outcomes.

Most non-drug studies failed to assess risk factor outcomes and to provide follow-up for longer than 12 months. With the exception of the drug studies and studies recruiting people with diabetes and hypertension, the sample sizes of the studies were too small to detect meaningful differences. A priori power calculations to estimate sample sizes are recommended for future RCTs. The fact that few statistically significant changes for risk factors could be demonstrated may well reflect the low statistical power of such studies, rather than a lack of effect.

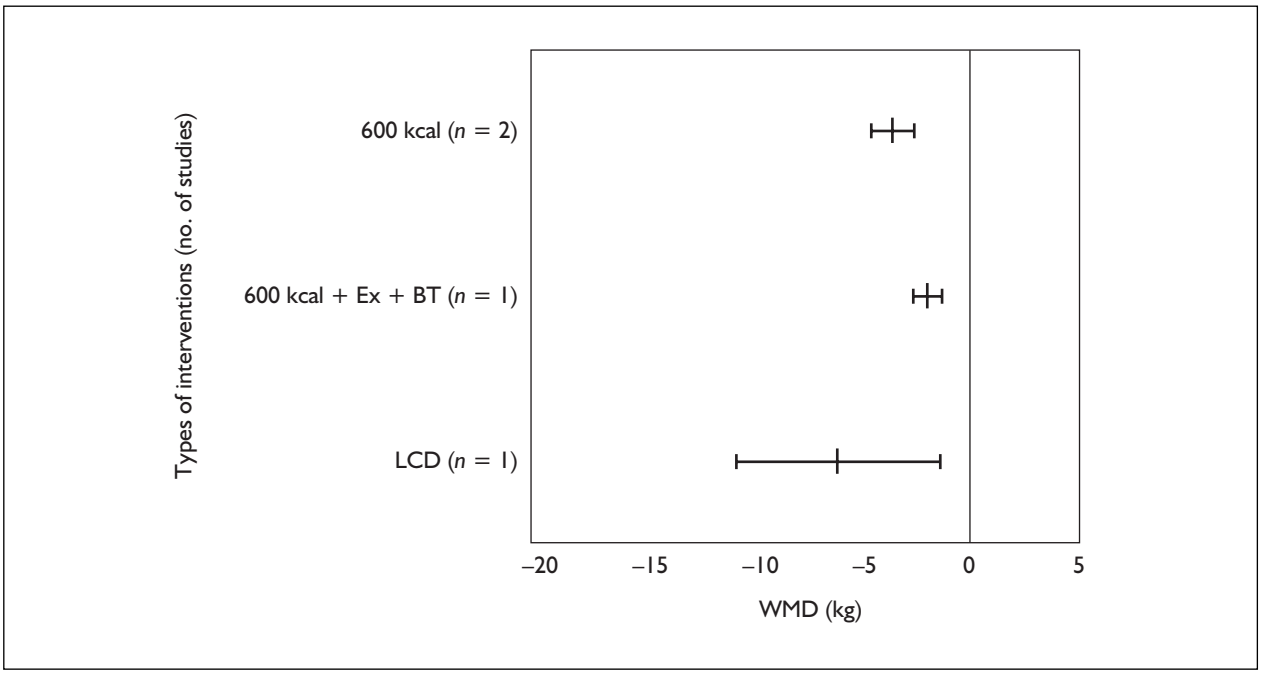

FIGURE 244 *Interventions versus no intervention on 36-month weight*

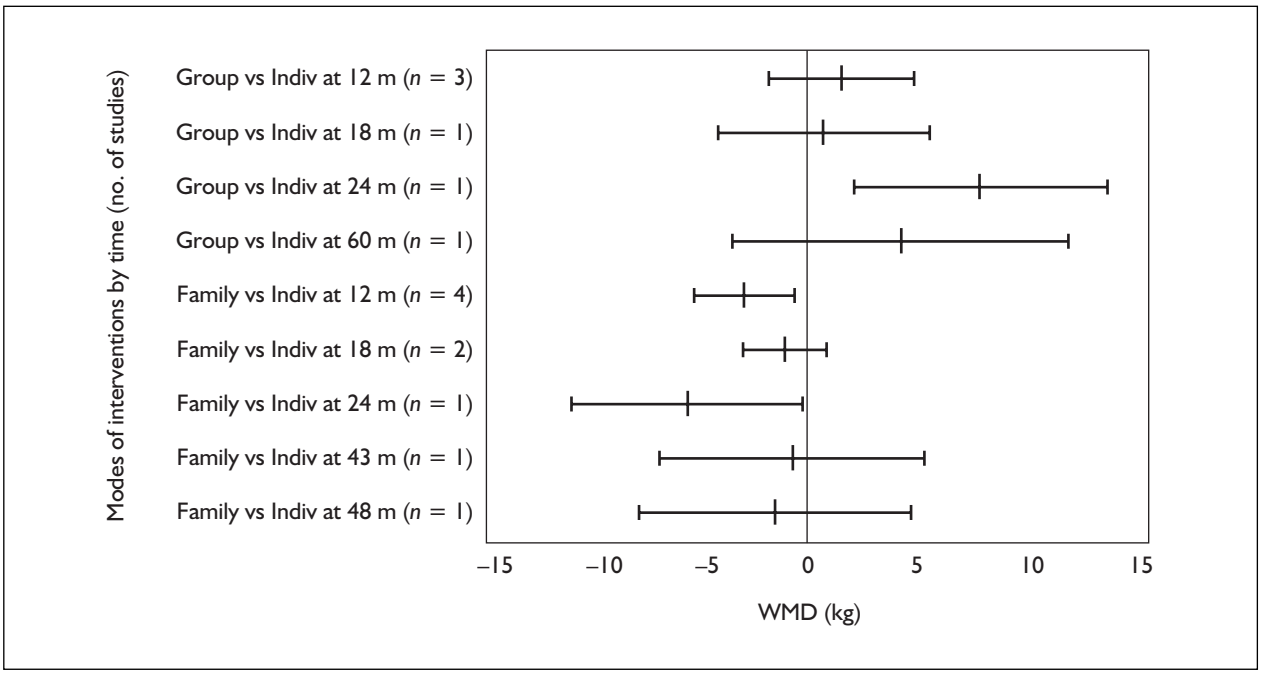

FIGURE 245 *Effect of mode of delivery on weight over time. Indiv, individual; m, months*

Appendix 11 summarises the quality assessment of the included RCTs, from which it is clear that ITT analysis was rarely performed. Future studies could also be improved by vigorous chasing up of dropouts. The method of including dropouts in final analyses by using an LOCF approach carries an inherent danger of overestimating group weight loss. Most people will regain weight after dropping out. It might be better to presume that dropouts return to baseline weight or regain weight at a certain rate that matches the natural history of obesity from time of dropout to the trial end-point.

Few reports gave clinical outcomes, quality of life data or economic outcomes. If the value of interventions other than weight loss or risk factor data is to be assessed, for example psychological effects or costs to society, it is vital that future RCTs assess such outcomes.

The studies often recruited from very select population groups. More studies are required in older and more obese populations (BMI $> 40\,kg/m^2$), populations outside North America, primary care rather than specialist obesity clinics, and groups at risk of developing complications from obesity, or already possessing co-morbidities.

Systematic review

A summary table of weight loss results is presented in Appendix 12. In general, few studies reported outcomes past 1 year, and many of the RCTs had small numbers of participants and thus had low statistical power. Weight change data were in some cases skewed, with a few people losing a lot of weight. In such cases the assumptions behind the WMD analysis may not hold.

Drug interventions

Orlistat and sibutramine

Orlistat and sibutramine were associated with similar weight changes at 12 months, –3.01 kg (95% CI –3.48 to –2.54 kg) for orlistat and –4.12 kg (95% CI –4.97 to –3.26 kg) for sibutramine. These weight changes were little changed at later time-points, –3.26 kg (95% CI –4.15 to –2.37 kg) at 24 months for orlistat and –3.40 kg (95% CI –4.45 to –2.35 kg) at 18 months for sibutramine. However, the data for sibutramine at 12 months represent weight loss studies and at 18 months weight maintenance in the STORM study.[64–70] These weight changes appear small, but are comparable to those in other trials where beneficial clinical outcomes occurred, for example prevention of diabetes in the FDPS[167–171] and reduction in the need for hypertensive medication in the DISH study.[99–103] However, similar weight losses are not necessarily associated with the same change in risk factors.

Orlistat and sibutramine appear to have different effects on lipids and blood pressure. Weight reduction with sibutramine was associated with a significant beneficial effect on HDL cholesterol and triglycerides at 12 months of 0.10 mmol/l (95% CI 0.04 to 0.15 mmol/l) for HDL cholesterol and –0.16 mmol/l (95% CI –0.26 to –0.05 mmol/l) for triglycerides, but not on any other risk factors. However, in the orlistat weight reduction studies, triglycerides were the only risk factor that orlistat did not appear to affect. Orlistat for weight reduction was associated with decreased total cholesterol at 12 months (–0.34 mmol/l, 95% CI –0.41 to –0.27 mmol/l), decreased LDL cholesterol at 12 months (–0.29 mmol/l, 95% CI –0.34 to –0.24 mmol/l), and decreased HDL cholesterol at 12 months (–0.03 mmol/l, 95% CI –0.05 to –0.01 mmol/l).

In the sibutramine weight reduction studies, an increase in blood pressure at 12 months was observed of 1.16 mmHg (95% CI –0.60 to 2.93 mmHg) for SBP and of 2.04 mmHg (95% CI 0.89 to 3.20 mmHg) for DBP. In the weight reduction studies of orlistat, however, a fall in both SBP (–2.02 mmHg, 95% CI –2.87 to –1.17 mmHg) and DBP (–1.64 mmHg, 95% CI –2.20 to –1.09 mmHg) was observed.

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.

Only one RCT assessed weight change 3 months after sibutramine was stopped, and reported weight regain amongst the active treatment participants at nearly twice the rate of the placebo group.[58] Future drug studies need to assess weight and risk factor change after cessation of the drug.

Present UK NICE guidelines[23] recommend that orlistat is prescribed only after a weight loss from dieting of 2.5 kg over the preceding month, in people with a BMI $\geq 28\,kg/m^2$ with risk factors or BMI $\geq 30\,kg/m^2$ without risk factors. It is recommended that orlistat only be continued if weight loss is over 5% in the first 3 months of treatment, and 10% in the first 6 months. Treatment is not usually continued beyond 1 year and never beyond 2 years. Similarly, for sibutramine, the NICE guidelines[24] recommend use for people with a BMI $\geq 27\,kg/m^2$ with risk factors, or $\geq 30\,kg/m^2$ without risk factors. It is advised that treatment continuation requires a 2-kg weight loss in the first 4 weeks and a 5% weight loss from the start of treatment in the first 3 months. Sibutramine treatment is not recommended beyond 12 months. None of the orlistat or sibutramine trials adhered to these recommendations, which would reduce the proportion of overweight and obese eligible for long-term drug treatment. Those selected for

long-term drug treatment might be more responsive to drug treatment.

Metformin

Metformin was relatively ineffective as therapy for weight reduction, at 12 months –1.09 kg (95% CI –2.29 to 0.11 kg) and at 24 months (–0.50 kg, 95% CI –4.02 to 3.02 kg). The UKPDS[85–93] showed that metformin was associated with less weight gain over 15 years than diet alone, although the WMD was not significant. However, metformin was associated with significantly decreased all-cause mortality and MI-related mortality at 10 years in the UKPDS.[85–93]

Metformin was associated with a significant beneficial effect over diet for total cholesterol at 12 months (–0.17 mmol/l, 95% CI –0.32 to –0.02 mmol/l) and 24 months (–0.72 mmol/l, 95% CI –1.30 to –0.14 mmol/l), although the 12-month data are based on one small study.[84] Metformin was associated with improved glycaemic control. Fasting plasma glucose decreased at 12 months (–0.20 mmol/l, 95% CI –0.40 to 0 mmol/l) and 5 years (–1.30 mmol/l, 95% CI –1.91 to –0.69 mmol/l), and HbA_{1c} was improved at 5 years (–1.08%, 95% CI –1.50 to –0.66%) and 15 years (–2.31%, 95% CI –3.85 to –0.77%). Metformin showed a trend towards increased SBP and DBP at 12 and 24 months.

SSRIs and acarbose

At 12 months there was insufficient evidence to suggest SSRIs for weight reduction (–0.33 kg, 95% CI –1.49 to 0.82 kg) or for risk factor reduction. The one acarbose study was associated with a significant beneficial effect on glycaemic control, with an observed decrease in HbA_{1c} (–0.76%, 95% CI –1.05 to –0.47%) and fasting plasma glucose (–1.36 mmol/l, 95% CI –1.96 to –0.75 mmol/l) in type 2 diabetics over 12 months.[94–98] Acarbose had limited effect on weight reduction over 12 months (–0.79 kg, 95% CI –1.53 to –0.05 kg).

Drug studies overall

There were no studies which assessed the added effect of drug treatment to a combination of diet, exercise and behaviour therapy. Guidelines recommend the use of orlistat and sibutramine only as an adjunct to diet, exercise and behaviour therapy.[18]

One study[247] assessed the added effect of behaviour therapy to sibutramine, diet and exercise. Weight change at 12 months of –10.69 kg (95% CI –14.22 to –7.16 kg) was observed. This result is in line with the effect of adding behaviour therapy to diet in the non-drug trials. Future trials should investigate adding lifestyle interventions to drug treatment.

The majority of drug studies used a low-fat or 600 kcal/day deficit diet for all participants. The placebo arms of the drug studies were associated with less weight loss than the active treatment arms of studies using a low-fat or 600 kcal/day deficit diet. This might suggest that participants in drug studies do not adhere to the diet as effectively, relying on the action of the drug or placebo. This could enhance the effect of the active drug treatment in such trials.

Dietary interventions

Of all the diets VLCDs were associated with the most weight change at 12 months (–13.40 kg, 95% CI –18.43 to –8.37 kg) compared with no treatment; however, this is based on one small study by Stenius-Aarniala and colleagues.[148] The same trial observed some beneficial effects on control of asthma. There were no longer term data comparing VLCDs with no treatment past 12 months. No risk factor changes were available for VLCDs compared with no treatment. Studies directly comparing VLCDs with LCDs or 600 kcal/day deficit or low-fat diets were small and unable to demonstrate statistically significant differences in weight, although there was a trend for the VLCDs to produce more weight loss.

There was a trend for LCDs to produce more weight loss than low-fat or 600 kcal/day deficit diets at 12, 24 and 36 months, based on studies that compared these diets with no treatment. However, in the only trial that directly compared these two diets the trend was in the opposite direction.[149] No risk factor data were available to allow comparisons between LCDs and low-fat or 600 kcal deficit diets. Difficulties in classification of some diets may account for some of these findings.

There was no evidence to suggest that PSMF diets were to be preferred to LCDs or VLCDs for weight loss, although one study suggested improved glycaemic control in type 2 diabetes.[154,155]

A low-fat or 600 kcal/day deficit diet was associated with significant weight changes at 12 months (–5.31 kg, 95% CI –5.86 to –4.77 kg), 24 months (–2.35 kg, 95% CI –3.56 to –1.15 kg) and 36 months (–3.55 kg, 95% CI –4.54 to –2.55 kg). There was an associated improvement in blood pressure, lipids and fasting plasma glucose with this diet at 12 months. Very limited data on risk

factors after 12 months were available, with a trend for blood pressure to be decreased by these diets at 36 months. Data from DISH,[99–103] HOT,[107] HPT[108–114] and Swinburn and colleagues[128,129] suggest that this diet can prevent the development of diabetes, improve blood pressure control and reduce antihypertensive medication for up to 3 years.

The low-fat or 600 kcal/day deficit diet category contained the greatest number of RCTs (12) in any one comparison, and is the diet most commonly advised in the NHS.

Diet; diet and exercise; diet and behaviour therapy; diet, exercise and behaviour therapy versus control

Weight loss was greater in all comparisons at 12 months than at 24 months, except for LCD where weight loss was little changed between 12 and 24 months. Based on comparisons of interventions versus control for weight, there was no clear evidence to confirm the benefit of adding exercise and/or behaviour therapy to diet for weight loss. However, because the study interventions differed so much it is not possible to draw conclusions about the added effect of exercise and/or behaviour therapy to diet for weight loss. The RCTs where the added effects of exercise and/or behaviour therapy were directly evaluated are discussed below.

No clear pattern emerged for risk factors when comparing these differences between interventions versus control treatment. However, the FDPS[167–171] suggested that diet and exercise can prevent the development of diabetes in people with impaired glucose tolerance (IGT).

The TONE,[210–224] TOHP I and II studies[197–209] examined the effect of diet, exercise and behaviour therapy. The TONE study[210–224] was associated with a 35% reduction in hypertension or cardiovascular events. Both TOHP I[197–203] and TOHP II[204–209] were associated with significant reductions in the numbers of people developing hypertension.

Exercise and behaviour therapy as adjuncts to diet

The addition of a planned programme of exercise to diet was associated with an additional weight change of –1.95 kg (95% CI –3.22 to –0.68 kg) at 12 months. Only the very small studies by Pavlou[153] examined exercise as an adjunct to diet after 12 months. These found a continuing weight change of –7.63 kg (95% CI –10.33 to –4.92 kg) at 18 months and –8.22 kg (95% CI –15.27 to –1.16 kg) at 36 months. At 12 months there was an associated improvement in HDL cholesterol (+0.10 mmol/l, 95% CI 0.06 to 0.14 mmol/l) and triglycerides (–0.18 mmol/l, 95% CI –0.31 to –0.06 mmol/l). Other risk factors were not significantly changed by the addition of exercise at 12 months, although the small study by Pavlou and colleagues[153] suggested lowered SBP and DBP at 18 months.

The addition of an exercise programme to diet and behaviour therapy was also associated with enhanced weight change (–3.02 kg, 95% CI –4.94 to –1.11 kg) at 12 months and at 24 months (–2.16 kg, 95% CI –4.20 to –0.12 kg). There were no statistically significant associated changes in risk factors for this comparison.

The addition of behaviour therapy to diet was associated with greater weight change at 12 months (–7.67 kg, 95% CI –11.97 to –3.36 kg) than adding exercise (–1.95 kg, 95% CI –3.22 to –0.68 kg); however, the number of participants in the studies with added behaviour therapy was very small. The added effect of behaviour therapy was still just significant at 18 months (–4.18 kg, 95% CI –8.32 to –0.04 kg), but not at 36 or 60 months.

Two studies[236,246] examined the added effect of exercise and behaviour therapy to diet, and were unable to demonstrate any significant changes in weight or risk factors at 12 or 18 months.

These data suggest that a prescribed exercise regimen or behaviour therapy makes an important contribution to weight loss, and is important in long-term weight maintenance. There is less evidence to determine whether both behaviour therapy and exercise should be added to diet, for modification of weight or risk factors. However, results from the TONE,[210–224] TOHP I and II studies[197–209] suggest benefits to clinical outcomes from diet, exercise and behaviour therapy. To some extent there are 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.

Modes of delivery

Family therapy was associated with more weight change than individual treatment at 12 months (–2.96 kg, 95% CI –5.31 to –0.60 kg) and 24 months (–5.61 kg, 95% CI –10.98 to –0.24 kg). However, there was insufficient evidence to suggest that individual therapy was more effective in

producing weight loss compared with group therapy, although the observed direction of effect was towards individual therapy. This has important cost implications for service delivery.

Overall discussion

In general, drug trials provided the clearest pointers to the management of obesity in adults, because they had sufficient statistical power to detect outcomes, unlike non-drug studies. Orlistat was associated with slightly less weight loss, but had a more beneficial effect on risk factors than sibutramine. Metformin, however, was the only drug that had a study designed to evaluate mortality and showed an association with beneficial effects on mortality.

There were very few data on risk factor changes for diets, other than for the low-fat or 600 kcal/day deficit diet, despite some suggestion that VLCDs and LCDs were associated with more weight loss. The low-fat or 600 kcal/day deficit diet was associated with benefits on weight, risk factors and clinical outcomes, such as the prevention of diabetes and improvement in hypertension, and effects appeared to persist for up to 3 years.

Exercise or behaviour therapy added to diet was associated with greater weight loss, especially in the long term. The FDPS[167–171] provided evidence that diet and exercise together could prevent type 2 diabetes. There was no comparable evidence available for the effect of a diet and behaviour therapy without exercise on diabetes. Most of the exercise programmes provided in the studies here were supervised. Activities included walking, jogging and cycling, and were usually tailored to produce 60–80% of the maximum heart rate, with typical sessions being 20–90 minutes three times a week. Behaviour therapy varied between trials, but often included self-monitoring, slowing the rate of eating, reducing eating cues, responding to social pressures, preplanning and relapse prevention techniques. Trained psychologists were often used to deliver these techniques.

Exercise programmes and behaviour therapy are not well established for the management of obesity in the NHS. Consideration needs to be given to how the interventions used in the trials described here could be implemented in the UK, given that the trials were mostly undertaken in the USA or Scandinavia. Exercise and behaviour therapy are not necessarily mutually exclusive, although the very limited current evidence would suggest exercise as the first approach.

The effect of exercise and behaviour therapy added to diet on weight and risk factors was less clear; the TONE,[210–224] TOHP I and II studies[197–209] found an association with improved clinical outcomes from behaviour therapy and exercise added to a low-fat or 600 kcal/day deficit diet.

The weight changes produced by RCTs of drug or lifestyle interventions are less than those found in the review of surgical interventions,[27] where between 23 and 37 kg more weight was lost 2 years after surgery compared with conventional treatment. However, the participants in surgical studies averaged around 120 kg, whereas participants in the trials examined here averaged around 80–100 kg in weight, with BMIs rarely above 40 kg/m^2.

Despite the smaller weight losses with the drug or lifestyle interventions, there was evidence of clinical benefit, in terms of diabetes and hypertension.

Future RCTs should have adequate statistical power to determine long-term outcomes, which should include not only weight, but also risk factors, morbidity and mortality, quality of life and economic outcomes. The methodological quality of such trials should be improved and the results should be reported according to the guidelines of the CONSORT statement.[249]

More studies are needed in high-risk populations, whether defined by BMI (> 40 kg/m^2), ethnic group, older age, risk factors or co-morbidities.

Drug trials should include lifestyle interventions, such as behaviour therapy and exercise, in addition to diets as standard management. As the prescription of drugs for the management of obesity may be limited by time, drug trials should follow up participants after cessation of the drug trial.

As this review was limited to adults with a BMI ≥ 28 kg/m^2, it did not assess the interventions examined in this systematic review for people with lower BMIs, that is, for the prevention of obesity. The authors strongly recommend that such a review be undertaken, which should include community interventions that have been excluded by the BMI cut-off. There was also insufficient time in this review to examine the effects of exercise or behaviour therapy alone, which should be undertaken.

Further questions that should be asked include what type of exercise or behaviour therapy is best, what frequency of contact is best, what type of diet in the long term is appropriate and what is the role for booster sessions.

Addendum

Since this systematic review of RCTs was completed many more eligible trials have been published. Major ongoing and recently reported trials are listed in Appendix 9.

The XENDOS trial evaluated the use of xenical (orlistat) compared with placebo in the prevention of type 2 diabetes in people with obesity, with or without impaired glucose tolerance.[250] The trial reported a relative risk reduction for type 2 diabetes of 37.3%[251] with the use of orlistat. As a consequence of this trial the product licence for orlistat has recently been revised to allow prescription for more than 2 years. NICE guidelines for orlistat are unchanged.[23] Other orlistat trials[252,253] have found the use of orlistat in people with type 2 diabetes was associated with improved diabetic control, reduced cardiovascular risk factors and reduced use of medications for type 2 diabetes, including insulin, compared with placebo.

A further trial of 20 mg sibutramine compared with placebo has examined effectiveness in people with obesity and hypertension well controlled by angiotensin-converting enzyme inhibitors with or without thiazide diuretic therapy.[254] Participants treated with sibutramine lost 4.5 kg over 52 weeks, compared with 0.4 kg in the placebo group. Hypertension remained well controlled in both groups, but after 52 weeks the differences between placebo and sibutramine groups for both mean SBP and DBP were approximately 3 mmHg, in favour of the placebo group.

The Diabetes Prevention Program[255–257] compared 3234 people with elevated fasting and postglucose load plasma glucose to metformin and usual care; placebo and usual care; or low-fat diet, exercise and behaviour therapy. After an average follow-up period of 2.8 years, the lifestyle intervention was associated with a reduction in the incidence of type 2 diabetes by 58% (95% CI 48 to 66%) and metformin by 31% (95% CI 17 to 43%) compared with placebo. The lifestyle intervention was significantly more effective than metformin.

In the Stop-NIDDM trial,[258] the use of acarbose 100 mg three times daily compared with placebo was evaluated in people with obesity and impaired glucose tolerance over a mean follow-up period of 3.3 years. The reported difference in body weight was 0.77 kg (95% CI 0.01 to 1.54 kg) in favour of acarbose. The relative hazard of developing diabetes was reduced by acarbose (0.75, 95% CI 0.63 to 0.90).

Chapter 3

Epidemiological review and modelling

Introduction

Obesity is now being recognised as a chronic disease and described as an escalating epidemic by the World Health Organization (WHO).[1] Evidence suggests that a weight loss of 10% is often associated with marked clinical improvement in co-morbidities.[259] A review by Pi-Sunyer[260] looked at studies that lasted for more than a year and demonstrated that even modest weight loss has a beneficial impact on the risk factors and disease states associated with obesity. However, there is a lack of evidence from long-term investigations on the effects of weight loss.

For the long-term epidemiological evidence, a systematic review to identify the effects of reduced BMI on long-term health outcomes was conducted and associated statistical modelling conducted.

Protocol development

A protocol was formulated for the epidemiological systematic review (Appendix 15). The protocol describes the objectives, the inclusion and exclusion criteria for considering studies for the review, including type of studies, the type of participants, the type of outcome measured, the search strategy for the identification of studies and the methods of the review.

Criteria for considering studies in this review

Types of studies

Studies were eligible for inclusion if they were prospective or cohort studies on people with BMI of 28 kg/m^2 or more. A cut-off BMI of 28 was chosen to include those borderline overweight people about to become obese. Initially, studies with a long-term follow-up of 5 years were to be included in the review. However, studies having at least 5 years of follow-up were only found for surgical interventions. Hence, non-surgical studies with a minimum follow-up of 2 years were also included in this review. To allow weight change to be estimated, only studies that had at least two measurements of body fat (e.g. weight, BMI or waist–hip ratio) were included in the review. The studies were also required to have at least one of the specified outcomes (e.g. mortality from all causes). There were no language restrictions in considering studies for inclusion. The original protocol specified that studies with a follow-up of 80% would be included in the review. During the review process it became apparent that, although studies reported follow-up periods over a long time, the number of people who were followed up at the end of the study was often very small. Consequently, studies with lower percentages of follow-up were included in the review.

Studies on children and people with bulimia were excluded. Population-based studies with small subgroups of people with obesity were also excluded owing to very small sample sizes.

Although not one of the primary objectives, studies on weight cycling were also included to measure the effect of weight cycling on the outcome measures.

Types of participants

All participants from the age of 18 to 70 years were included. The upper age limit of 70 years was judged to be appropriate owing to the potential confounding effect of old age on BMI and subsequently on the health risks associated with obesity.

The results of this review will be applied to the UK population. Consequently, studies were restricted mainly to those using Caucasian populations. However, studies with African–Americans, Japanese Americans and British Asians were also considered, recognising that these ethnic minorities were likely to have adopted the culture and dietary habits of Caucasian people and in turn may have similar risks of obesity-related illness.

Types of outcome measures

The health consequences of obesity vary from premature death to co-morbidities, with considerable impact on the quality of life with social and economic implications. A brief literature search was undertaken and opinions of clinical experts were obtained before the outcome measures of the review were finalised.

Based on the prevalence of the conditions in the general population and the relative risk of developing these conditions in people with obesity, the outcome measures sought are listed in the protocol (Appendix 15), for example, mortality from all causes, morbidity and CHD.

Systematic literature search

Systematic electronic bibliographic database searching

The electronic databases MEDLINE, EMBASE, CINAHL and HealthSTAR were searched. The search terms were identified by investigating the MeSH terms (indexing system used in each database) as well as text word searching (searching words in the titles and the abstracts). The search strategy adopted for each of the four databases is included in Appendix 16. Search terms for economic modelling were included in the MEDLINE search. Because of time constraints the search terms were restricted to those for epidemiological modelling only in other databases.

Other methods used to identify prospective studies

Reference lists of all the included studies and review articles were checked to identify any other relevant studies. Authors of identified studies were approached for further details if required, especially for details of people with obesity within general population samples.

Methods of review

Management of potentially eligible studies

All potentially eligible studies were entered into reference managing software package Reference Manager 9 with a unique reference identifier. One-hundred abstracts and study titles were read independently by two researchers. Subsequent consultation gave a check for consistency. Thereafter, the remaining abstracts were split between the two researchers. However, regular consultation between the researchers meant continual clarification regarding inclusion queries. During the course of the epidemiological search any articles relevant for the economic modelling were sent to the economist for evaluation and inclusion.

Quality assessment of the studies

Full articles of all the studies that met the selection criteria were obtained and assessed for methodological quality. Initially, assessments were carried out independently by two researchers. After a high level of consistency had been attained, assessment was undertaken by one researcher and crossed over for checking. Any doubts about the inclusion of a study were resolved by discussion.

Data extraction and storage

A data extraction form was designed and piloted on 13 studies. This was double-checked and changes were made where necessary. The final version of the data extraction form may be found in Appendix 17.

The data from the eligible studies were entered onto a Microsoft Access database to accommodate both quantitative and qualitative information. The studies were grouped according to the outcomes specified in the protocol.

Epidemiology statistical methods

The aim for this review was to investigate how weight differences related to differences in health outcomes in the long term. Where results from studies could be quantitatively combined, statistical meta-analysis was undertaken to determine the effect of weight loss over a number of studies. In these cases the results were initially tested for evidence of heterogeneity before the studies could be combined.

Homogeneity/heterogeneity

One of the basic assumptions for combining fixed effects models is whether it is reasonable to assume that all the studies to be combined are estimating a single underlying population parameter. To assess this, one of the most common tests for heterogeneity has been used for this part of our review. This method is as introduced in Chapter 8 of the HTA review on "Systematic reviews of trials and other studies" by Sutton and colleagues.[261]

The process tests the hypothesis:

$$H_o\colon \theta_1 = \theta_2 = \ldots = \theta_k$$

where θ_I are the underlying true treatment effects of the corresponding ith studies; versus the alternative that at least one of the effect sizes θ_I differs from the remainder.

To do this one needs to calculate

$$Q = \sum_i^k w_i T_i^2 - \frac{(\sum_i^k w_i T_i)^2}{\sum_i w_i}$$

TABLE 11 *Total number of possible prospective studies identified by the literature search*

Source/database	Years searched	No. of abstracts
MEDLINE	1966 to May 2001	6038
EMBASE	1980 to May 2001	1054
HealthSTAR (excluding MEDLINE)	1975 to December 2000	15
CINAHL	1982 to April 2001	460
Total		7567

where k is the number of studies being combined, T_i is the treatment effect estimate in the ith study and w_i is the weight of that study, usually the inverse of the sampling variance.

The test statistic Q is approximately distributed as a chi-squared distribution with k–1 degrees of freedom. Consequently, if the value of Q exceeds the upper critical value of the chi-squared distribution with k–1 degrees of freedom then the observed variance in the study effect sizes is significantly greater than the other studies and H_o of homogeneity would be rejected in favour of the alternative hypothesis.

Methods of estimating measures of spread

Many of the studies selected in this review reported their results as means with standard deviations or standard errors. The analysis required the weight differences and each outcome difference (for RCTs this implies comparisons to baselines rather than the traditional comparison to control groups). However, several papers did not provide mean differences per se, only giving the means of each variable at each time-point with some measure of spread about those means. The straight differences of these means acted as estimates of the mean differences, albeit crudely since the sample sizes were not always the same at the beginning and end of the studies. In these cases a measure of spread also needed to be estimated.

Methods of estimating standard deviations were developed for each variable by investigating the relationship between observed means of differences and associated standard deviations. Work based on the RCTs section in this review by colleagues (Appendices 13 and 14) has shown fairly simple relationships. These relationships were re-examined for longer term studies and are given in Appendix 26.

Statistical modelling

In some instances it was possible to model the effects of weight loss on certain health outcomes. Correlation and linear regression, to predict weight differences from each of the outcome differences, were considered. Weighted linear regression and simple linear regression were compared. However, many of the comparisons were simple and sometimes were only descriptive, given the very different types of measures and trial designs.

Results of systematic literature search

The total number of possible relevant studies identified by the systematic search of epidemiology literature is given in *Table 11*.

Included and excluded eligible studies

In total, 7567 abstracts and titles were read and 288 possibly useful studies were identified. Full papers of the identified articles were obtained and critically appraised. Many full papers proved not to fulfil the eligibility criteria for inclusion in the review (e.g. no actual weight loss was recorded or the follow-up time was too short). After critical appraisal 39 potentially eligible prospective studies were identified.

These studies were not always conducted on people with obesity only, but sometimes were for general and community populations with a subgroup of people with obesity. For eight such studies these subgroup results were not presented separately as required for this review. The authors of these eight studies were contacted requesting information specifically on the subgroup of people with obesity. Two authors provided the relevant information in time, but the other six subgroup studies were reluctantly excluded from the review.

Out of the 33 remaining studies that were eligible for the review, five studies were not analysed owing to the information in their result sections being incomplete for the present purposes. Although associated authors were contacted the information remained incomplete at the time of writing and so

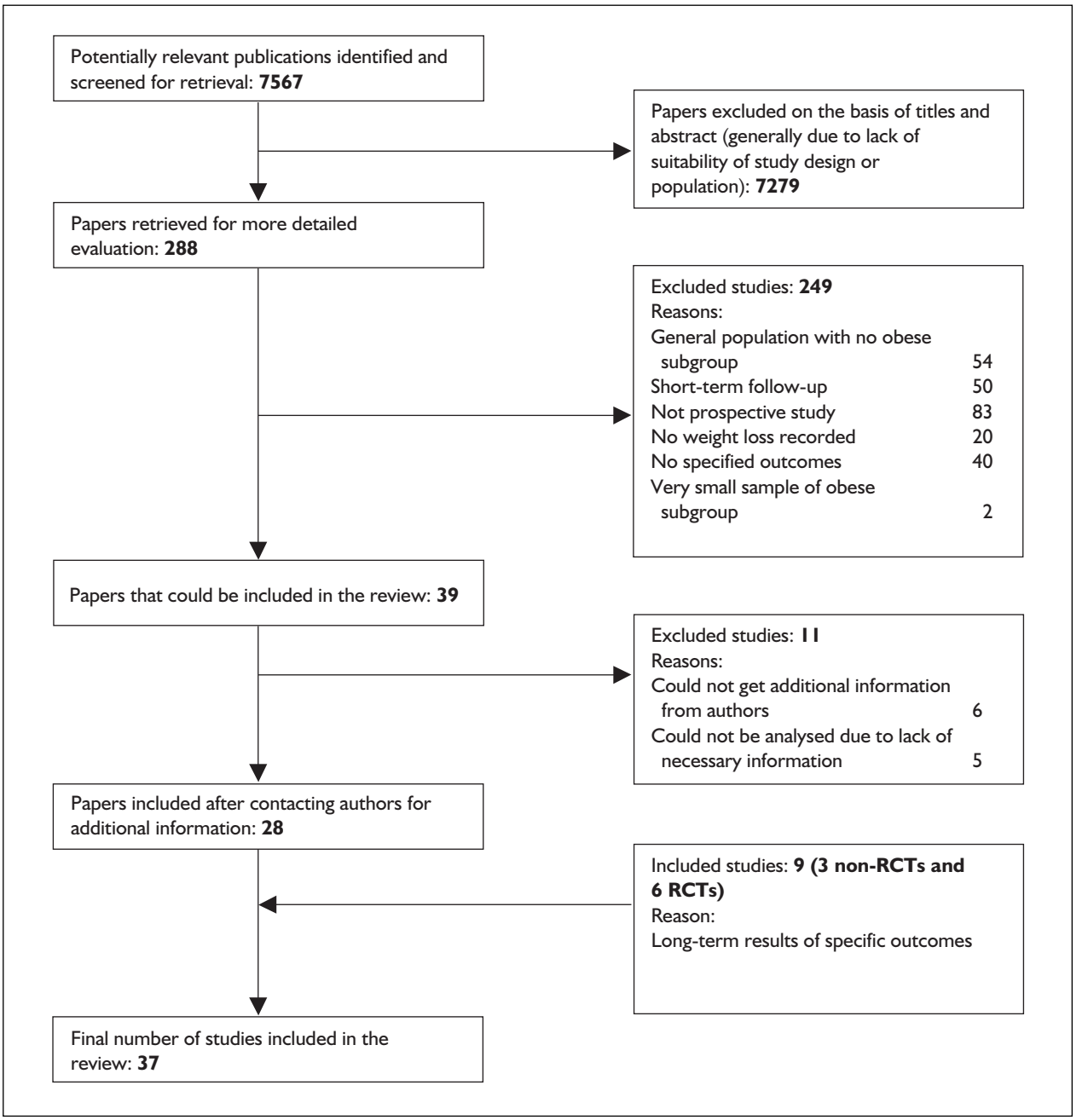

FIGURE 246 *Flow diagram of the epidemiology systematic review*

these studies were excluded from the review. The 11 excluded studies (six with a subgroup of people with obesity, five with inadequate information) are listed in Appendix 18. Although the remit for the review was prospective cohort studies, a few controlled trials were identified as having long-term results for the specified outcomes. These trials were included in the review provided there was weight loss for the specific groups from the trial. The controlled trials included both randomised and non-randomised trials. Consequently, three non-randomised trials and six randomised trials were included. This gave a final total of 37 studies included in this review. The epidemiology review selection process is summarised in *Figure 246* as a flow diagram.

Description of eligible studies

There were no studies identified on the outcomes such as cholelithiasis, arthritis, cancers, asthma, non-alcoholic steatohepatitis (NASH), urinary incontinence and bone fractures. For stroke, only one study was identified, which could not be analysed because of a lack of necessary information

TABLE 12 *Summary of the number of studies for each outcome*

Outcome	No. of studies analysed
Sleep apnoea	3
Mortality	5
Diabetes mellitus	15
Coronary heart disease	1
Lipids	13
Psychological well-being	2
Co-morbidity (multiple)	1
Hypertension	14

in the published paper. The initial protocol was designed to perform statistical modelling for the effect of weight loss on long-term health outcomes. However, many of the studies did not present the information in a form that allowed for such modelling. For some outcomes there was even difficulty in comparing the data because different methods and measurements were used in individual studies.

In the prospective cohort studies, the study populations were often broken into groups (e.g. men/women, intentional/unintentional weight loss, and amount of weight lost and time to lose weight). The results of this review are presented similarly using their groupings. For the analysis of the trials, comparison was made to the baseline rather than to any control group. This approach is very different to most Cochrane type reviews conducted on RCTs, since in this part of the review the focus was on weight loss per se and its long-term effect on various health outcomes, and not on how the weight loss was achieved.

Several studies measured more than one outcome. Here the outcomes are treated independently; consequently, studies may be included more than once. *Table 12* summarises the number of studies for each outcome as specified in the protocol.

Diabetes mellitus, hypertension and lipids had the largest number of studies. For the rest of the outcomes, very few studies were identified that had long enough follow-ups. The characteristics of the 37 studies that were included in the review are summarised in Appendix 19a, along with details of the outcomes reported for each of the studies.

Methodological quality of studies

Out of the 37 studies that had some aspects that could be analysed, 25 studies had for the present purposes complete results and could be satisfactorily analysed. Of the other 12 studies, two[262,263] had small follow-up proportions of about 30–40%. In addition, eight studies[163,264–270] had no sample size for the subgroup of people with obesity clearly stated, although in most cases confidence intervals of the outcome indices were given so that the precision could be gauged. Two studies[271,272] had problems in their reporting. For example, the follow-up time reported was wide (3 months to 7 years) and no specific measurements were reported. In general, the quality of reporting was poor, and although authors were contacted, few responded with the necessary information in time for the analysis.

Although the average follow-up time of some studies made them eligible for the review, the number of patients who were followed up at the end was low. Many studies did not report the number of patients followed up (or percentage follow-up) at the end of the study (Appendix 19a), nor did they provide details of the loss to follow-up. The omission of the standard deviations and basic information about the studied samples, for instance the setting of the study or the demographic details, was very common.

Some studies[273–275] either had self-reported weight loss by questionnaire or this was undertaken retrospectively, or both. This study design in itself can be a source of selection bias and recall bias. In some long-term follow-up studies there was not enough information about the status of weight or BMI in the period between the baseline and the final follow-up. Therefore, whether weight loss was maintained, cycled or regained could not be determined.

Appendix 27a shows the results of the quality assessment form (at the end of the data extraction form given in Appendix 17) for all the studies that were included in this review. As can be seen from Appendix 27b the highest quality scores are for the RCTs or similar studies (*Table 40*).

There seems to be a time factor whereby the most recent studies had higher scores. *Table 41* in Appendix 27b indicates that most of the studies did not adequately justify their sample sizes or describe the losses to follow-up. There was also some doubt as to whether some of the studies allowed for the passage of time.

Results of the review

Results of the review were analysed according to the predetermined outcomes to assess the long-term effect of weight loss on various health

conditions. The studies varied tremendously with respect to size, from some being population based with approximately 50,000 participants to specific trials that only considered tens of people. The population-based studies, although large in their own right, did not always have many people suffering from obesity.

Mortality

Five studies examined mortality with various subgroups and causes of mortality.[267,273–276] The representation was fair, with the largest group having about 3000 people and the smallest group having over 300. All-cause mortality, CVD-related mortality, cancer-related mortality, diabetes mellitus (DM)-related mortality and mortality due to obesity-related cancers were represented. The data were also analysed by gender; amount of weight lost [less than or more than 9kg (20 lb)]; time in which the weight was lost; and whether weight loss was intentional, unintentional or unknown.

Three out of these five studies were undertaken by Williamson and colleagues[273–275] and assessed weight loss by a retrospective questionnaire. This methodology could have had a bias in the initial participant selection and also recall. The study by Rumpel and colleagues[276] did not have any specific target population and whether the weight loss was intentional or unintentional is unclear. To calculate relative risk, in most cases the subgroups were compared with similar obese groups with no weight loss. However, one study by Rumpel and colleagues[276] used a referent group comprising people within the 'normal' weight range who were weight stable over the period of the trial.

The mortality results were all recorded as relative risks (RR) with 95% confidence intervals. Where possible the results from the different studies were combined using meta-analysis provided homogeneity could be assumed (as detailed in the Epidemiology statistical methods section, p. 128). To assess this the test statistic Q is calculated. This requires the estimates for each study of the relative risks and their associated standard errors. The latter are calculable from the 95% confidence interval given with each relative risk result. The standard error of the natural logarithm of odds ratios was calculated from knowledge of the confidence interval and the sample sizes of the studies.[261] This method was adapted for calculating the standard errors of natural logarithms of the relative risks. Hence, in the equation detailing Q in the epidemiology statistical section, the T_i values are the corresponding mean values of the natural log of the relative risk for the ith study with the weights being the inverse squared of the calculated associated standard errors.

All-cause mortality

All five studies in this review that had mortality results examined all-cause mortality. A subgroup of women with obesity who had intentional weight loss with some obesity-related illness demonstrated on average a significant reduction of 20% in the risk of death regardless of the amount of weight lost (Appendix 20, *Figure 251*). For men and women who had obesity, DM and intentional weight loss the reductions in mortality were better still (RR 0.75, 95% CI 0.67 to 0.84). Otherwise, however, the relative risk confidence intervals were wide and spread about 1, indicating non-significance. Considered altogether, the subgroups in the different studies did not display evidence of homogeneity (Q 59.10, $p = 0.001$); thus, the studies were not combined. When analysed by gender, the effect of intentional weight loss on mortality was significantly more beneficial in women (on average 20% better) than in men. The variability among studies in the male subgroup was not significant, so a combined estimate was calculated (combined result, RR 1.06, 95% CI 1.02 to 1.11) (Appendix 20, *Figure 252a, b*). Unintentional weight loss appeared to be associated with increased risk of death (combined results, RR 1.07, 95% CI 1.01 to 1.14) (Appendix 20, *Figure 253b*), although the lower limit of the CI is close to 1. This could be due to unintentional weight loss being associated with undiagnosed illness or hidden pathology. There was a significant reduction in mortality rates in people with obesity who also had either an obesity-related illness or a general illness, if the weight was lost intentionally within a year (combined result, RR 0.93, 95% CI 0.88 to 0.98) (Appendix 20, *Figure 254a*). These subgroups in Appendix 20, *Figure 254a* (e.g. men/women, intentional/unintentional weight loss, more than or less than 9 kg lost) are of borderline heterogeneity, but the combined result is quoted for a generalised impression. For those with no obesity-related illness, the risk of mortality appeared to increase if the weight was lost over a prolonged period. The relative risk of the worst case, for prolonged time of weight loss, was 1.40 (95% CI 1.02 to 1.93) (Appendix 20, *Figure 254b*). This could be attributed to people with obesity manifesting obesity-related illness or going through psychological stress losing weight over prolonged periods. Men, in particular those who took longer periods to lose weight, irrespective of amounts of weight lost, had an associated increased risk of mortality from all causes (RR 1.48,

95% CI 1.22 to 1.80) (Appendix 20, *Figure 254b*). The quantity of weight lost could not be shown to have any effect on mortality.

Mortality due to obesity-related illness

Only one study[274] examined mortality due to obesity-related illness, which was for women only. For women who admitted to an obesity-related illness, intentional weight loss of any amount was associated with decreased risk of obesity-related illness mortality (Appendix 20, *Figure 255*). If patients did not admit to an obesity-related illness, there was an increase in obesity-related cancer mortality if they lost less than 9 kg. This may have been due to hidden pathology, such as cancer, or perhaps these people did not lose enough weight. The study did not give any definition of obesity-related illness, but it was presumed to be mainly hormone related.

Cancer-related mortality

Cancer-related mortality was examined in two studies, one for men and one for women, both by Williamson and colleagues using the same population database. Women suffering with obesity, but no other apparent illness, who unintentionally lost weight or lost only small amounts of weight, had a slightly increased risk (Appendix 20, *Figure 256*) of mortality due to cancer. In contrast, women with obesity and obesity-related illness, regardless of the amount of weight lost, saw a decreased risk of cancer mortality which was significant if weight was lost intentionally (RR 0.63, 95% CI 0.43 to 0.93) (Appendix 20, *Figure 257a*). However, in men with obesity, intentional and unintentional weight loss was associated with a marginal increase in cancer mortality (RR 1.19, 95% CI 1.06 to 1.33) (Appendix 20, *Figure 257b*). Weight lost within a year may reduce mortality risk from cancer, particularly in women. For men, weight loss taking more than a year may be harmful (Appendix 20, *Figure 258a, b*).

CVD-related mortality

Four studies[273–276] examined CVD-related mortality. Again, three studies were undertaken by Williamson and colleagues[273–275] and indicated similar results. The other study[276] is notably different. The reference group people were within the normal weight range; hence, regardless of weight change in people with obesity, their risks will be larger than those in the normal weight group.

For people with obesity and diabetes, intentional weight loss demonstrated a decreased risk of CVD mortality of 28% (RR 0.72, 95% CI 0.63 to 0.82) (Appendix 20, *Figure 259*). When women and men were considered separately there was no significant effect of weight loss on CVD mortality (Appendix 20, *Figure 260a, b*). However, when the time of the weight loss was considered, differences became apparent. There was a decreased risk if weight was lost in under a year (RR 0.92, 95% CI 0.86 to 0.98) (Appendix 20, *Figure 261a*) and an increased risk of CVD mortality if the weight was lost over a longer period than a year (RR 1.16, 95% CI 1.07 to 1.25) (Appendix 20, *Figure 261b*).

Diabetes mellitus-related mortality

Two studies, again by Williamson and colleagues, examined DM-related mortality.[273,274] The studies indicate differences between the identified subgroups (Appendix 20, *Figure 262*).

Women with obesity and obesity-related illness, whose weight loss was intentional, irrespective of the amount of weight lost, had a significant decrease in the risk of DM-related mortality of about 30% (confidence intervals range from 10% to 60%). Similarly, for men with obesity and some general illness, an intentional weight loss was associated with a decreased risk of DM-related mortality of about 30% (confidence intervals range from 5% to 50%) (Appendix 20, *Figure 262*). All subgroups showed a significant decrease in DM-related mortality if weight was lost in less than a year (RR 0.57, 95% CI 0.47 to 0.68) (Appendix 20, *Figure 263a*). There was some benefit even when the weight was lost over more than a year (RR 0.78, 95% CI 0.64 to 0.96) (Appendix 20, *Figure 263b*).

Summary of mortality results

Women with obesity-related illnesses, who had intentional weight loss, irrespective of the amount of weight lost, had a reduced risk of mortality due to all causes, CVD-, cancer- and DM-related mortality. There was a significant benefit if weight was lost quickly, within a year. Men with general illness, who lost weight intentionally, had a reduced risk of DM-related mortality of about 30%. However, weight loss had no apparent effect on CVD-related mortality for men and was associated with an increased risk of mortality due to cancer.

Diabetes mellitus

Fifteen studies examined DM. Based on the age group that was included in this review, it has been assumed that the DM relates specifically to type 2 diabetes mellitus. Some studies had initially about 500 participants, while others were very small

(e.g. $n = 19$). The larger ones tended to have higher dropout rates. Three studies were non-randomised trials,[277–279] five were RCTs[37,41,45,168,176] and seven were prospective cohort studies.[266,268,269,271,272,280,281] Six studies examined surgical interventions, six had non-surgical interventions (orlistat, or diet and exercise) and three had no interventions at all.

Similar analysis was conducted by six of the studies which assessed the risk of developing DM. They reported their outcomes as odds ratios, relative risks or hazard ratios and for this review were considered together.[168,176,268,269,278,280] These results showed that people with obesity who had some intervention for obesity had a significantly decreased risk of developing DM (Appendix 21a). Surgical interventions appeared to have a greater impact on DM than non-surgical interventions. People who initially lost weight and then regained their weight may have an increased risk of developing DM. Their associated relative risk at 1.30 was raised, but confidence intervals were wide (95% CI 0.70 to 2.40).

Seven studies examined glucose differences with weight differences. One study by Hess and Hess[271] had to be considered with caution. This study reported a drop in glucose of 8.25 mmol/l. This high fall in glucose might suggest that it does not refer to the fasting plasma glucose level (Appendix 21b).

Initially, when all the studies were included there seemed to be a strong linear relationship between weight loss and the difference in glucose levels. However, this was highly sensitive to the result from the paper by Hess and Hess[271] (Appendix 21b, *Graph a*). Removing this study left a very weak, non-significant relationship with one other outlier[281] (Appendix 21b, *Graph b*). By considering only the smaller glucose differences (Appendix 21b, *Graph c*) the fasting plasma glucose levels do seem to be lowered by weight loss in a linear fashion. The model is given in Appendix 21b, Regression. The larger weight losses that were excluded for this analysis have larger glucose reductions than would be predicted by this model, suggesting a non-linear relationship with extrapolation. Predictions from this model could grossly underestimate glucose drops when weight losses are large, that is, the model is conservative.

Two studies reported only the improvement in DM status.[272,266] All the people who showed improvement in glucose status or DM control were either diabetic or people with IGT. This improvement in DM status, while not being one of the outcomes of this review, was indicated by several other studies.

A study by Watts and colleagues[281] from the USA reported that a group of people with DM suffering from obesity, some of whom lost weight by diet intervention, had no corresponding changes in glucose levels, whereas others who also had similar weight losses did have reduced glucose levels. They suggested that losing weight with diet should begin to improve DM status within 2–3 months. If there is no improvement by a 'diet only' intervention during this period, then additional drug treatment might be necessary to control the diabetes.

Summary of diabetes results

Some interventions for obesity, particularly surgery, seemed to reduce the risk of developing DM and improved DM status, if people had impaired glucose tolerance or diabetes. People with obesity who lose and regain weight may have an increased risk of developing DM.

Lipids

There were 13 studies that examined lipids. They were all relatively small studies with subgroups never higher than $n = 323$ and as low as $n = 7$. One study[282] examined weight cycling, with a non-surgical intervention.

There were three non-surgical prospective cohort studies,[283–285] four non-surgical RCTs[41,45,84,176] and five prospective studies with a surgical intervention.[271,272,277,286,287]

Non-surgical weight cyclers (Appendix 22a, Table 31)

Definitions of weight cycling groups used in this study are given in Appendix 28. People who lost a reasonable amount of weight and maintained this loss (including partial cyclers) had increases in HDL (albeit non-significant owing to the small subgroup sizes). In comparison, people who were small or large cyclers, those who did not lose weight and the weight gainers had either little change in HDL levels or a detrimental drop. Cholesterol differences were mixed with non-significant changes.

Non-surgical prospective studies (Appendix 22a, Table 32)

These observational studies indicated significant weight losses associated with significant cholesterol improvement. However, significant reduction in HDL cholesterol was also observed.

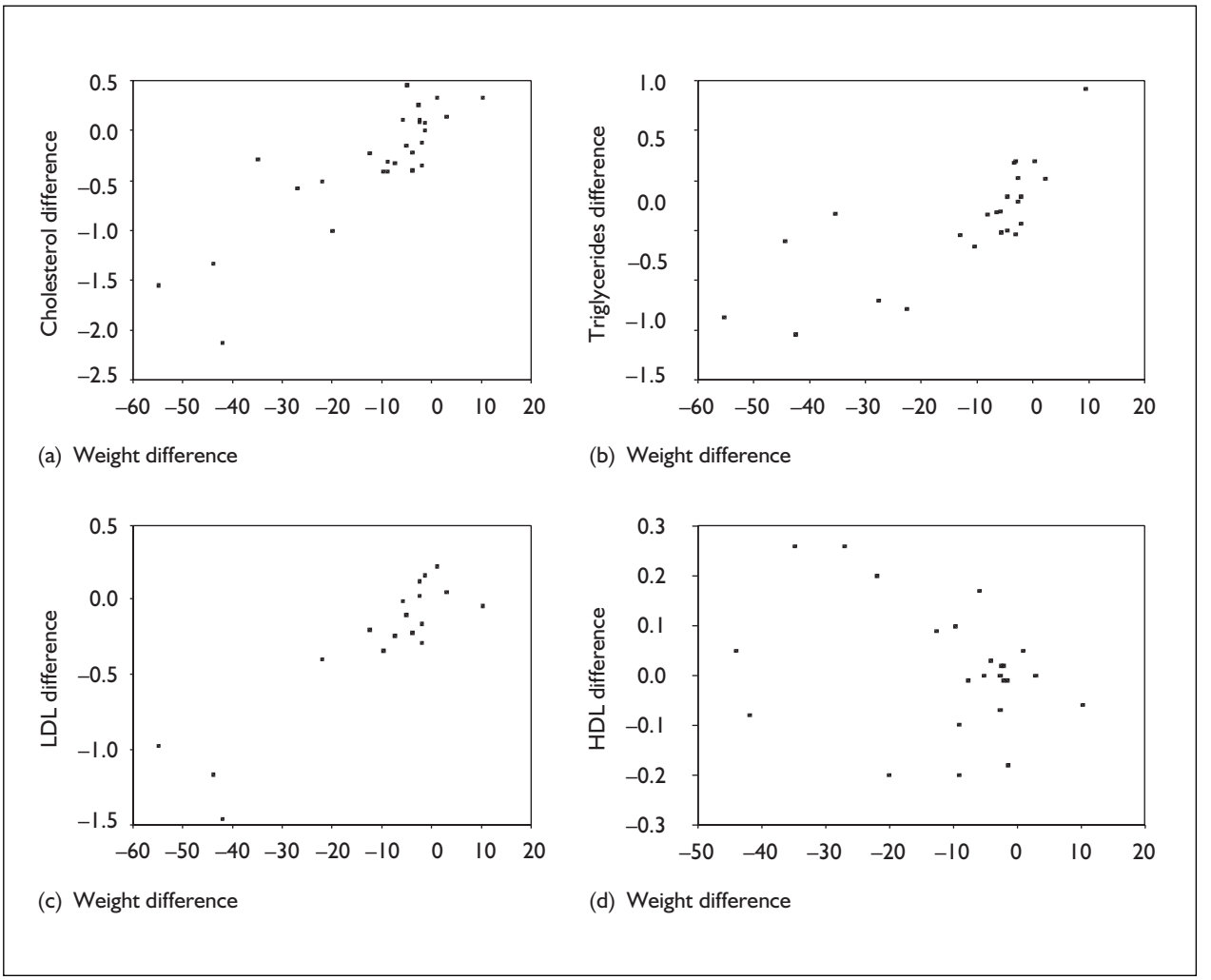

FIGURE 247 *Mean differences of weight in kg versus (a) cholesterol, (b) triglycerides, (c) LDL and (d) HDL (all mmol/l)*

Non-surgical RCTs (Appendix 22a,* Table 33*)
The long-term RCTs demonstrated significant weight losses with drug interventions. The relationship between weight loss and cholesterol levels seemed mixed. The study with the greatest weight loss (weight loss of 7.6 kg with orlistat and diet) had a statistically significant reduction in cholesterol, whereas another study with a weight loss of 5.1 kg (diet only) was associated with an increase in cholesterol.

Surgical interventions (Appendix 22a,* Table 34*)
All of these were prospective studies. Overall weight loss was significantly associated with reduced cholesterol and often increased HDL levels. One study only reported the overall improvement in hypertriglyceridaemia and hypercholesterolaemia. This study could not be analysed other than as a percentage improvement in the condition.

Regression analysis of changes in lipids with weight losses
All the appropriate studies were considered together, to determine whether changes in weight were related to changes in lipid measurements. Scatter graphs showing the relationship between weight changes and lipid changes are given in *Figure 247* (also in Appendix 22b i–iv as part of the whole analysis). As can been seen, LDL cholesterol has the strongest positive relationship (bivariate correlation $r = 0.903$, Appendix 22b iii), followed by total cholesterol (bivariate correlation $r = 0.856$, Appendix 22b i).

Total cholesterol is examined here as the most informative measure. Regression results are presented in Appendix 22b i, along with graphs and plots that aid assessment of other linear regression assumptions (the residuals should be

normal and independent). The resulting linear regression model gives the prediction equation:

Total cholesterol diff. = 0.07009 + 0.03210 (Weight diff.)

For instance, on average, 10 kg weight loss indicates a 0.25 mmol/l drop in total cholesterol.

Similar results are presented in Appendix 22b ii–iv for average differences of triglycerides, LDL and HDL cholesterol. Weight loss compared with differences in HDL, although slightly positive, was weak and non-significant.

Appendix 26 shows that for lipid outcomes standard errors were reasonably constant, ranging from 0.03 to 0.60 (Appendix 22a). In contrast, the precision of the mean weight differences was linear with mean weight differences and here ranged between 0.2 and 5.0. To account for this and the fact that the observations are mean values of studies of varying sizes, weighted least squares regression analysis was conducted. However, as the results were similar only the simple linear regression analysis results are reported and should only be used as a gauge rather than a precise estimate.

Summary of lipid results

The assessment of the studies individually and the final model above indicate that weight loss for people with obesity may lead to lowering of their cholesterol levels. It seems to be the amount of weight lost that is important.

Hypertension

Fourteen studies examined hypertension. Eleven of the studies had actual values for DBP and SBP. The remaining three studies[266,272,288] were more descriptive and only reported improvements in the condition or decreased medication. As for the results for lipids, the study sizes were fairly small, although varied. The largest subgroup had $n = 323$ people in it and the smallest had $n = 7$.

Blood pressure

Those studies that reported measurements for DBP and SBP were considered first. One study examined weight cycling with a non-surgical intervention,[282] two studies were non-surgical prospective cohort studies,[283,285] four were non-surgical RCTs[37,45,84,176] and four studies examined surgical interventions.[262,263,277,278]

Non-surgical weight cyclers (Appendix 23a, Part i)

Only the partial weight cyclers had significant weight loss and significant reduction in both DBP and SBP. The large successes (i.e. sustained weight loss) had significant weight loss but a non-significant drop in both DBP and SBP. The sample size for this group was only 14. Those classed as 'small successes' had weight loss of 5.9 kg, but with only seven people in the group this was not significant.

Non-surgical prospective study (Appendix 23a, Part ii)

Significant weight losses were related to significant reductions in DBP and SBP.

Non-surgical RCTs (Appendix 23a, Part iii)

In general, weight losses were related to DBP and SBP reductions (mostly statistically significant), although one study did not demonstrate this.[45]

Surgical intervention (Appendix 23a, Part iv)

Large weight losses were associated with DBP and SBP reductions, except for two studies.[263,278] Sjostrom and colleagues[278] showed that in spite of a good weight loss (20.1 kg) there was a statistically significant increase in SBP. The study by Carson and colleagues[263] showed that people who had obesity and hypertension with an average weight loss of 40.5 kg had a non-statistically significant reduction in DBP. They gave no results for SBP.

Regression model

Stepwise multiple linear regression was used to investigate appropriate studies that had weight changes with (1) DBP difference and (2) percentage DBP difference. The models were developed selecting from independent variables *initial weight*, *weight difference* or *%weight difference*, and *follow-up time*. Weighted least squares analysis was also conducted with similar results, and thus is not reported.

Two subgroups with extreme weight loss, both from the study by Carson and colleagues,[263] with surgical patients, had initial weights of >130 kg and weight losses of >40 kg. Unfortunately, these two data points significantly influenced the linearity of the relationship between *weight difference* and *diastolic blood pressure difference*, as can be seen from the correlation results in Appendix 23b. Consequently, the stepwise multiple linear regression was conducted excluding these atypical observations. Although many terms were allowed,

all the models selected one term (*weight difference* or *%weight difference*), implying simple linear regression models.

The models were developed to include a constant term and then constrained to go through the origin; that is, zero weight change = zero blood pressure change. This was carried out mainly because many of the estimates for the constant terms were not seen to be significant and also because such models suggested that no weight change means no blood pressure change, which is a reasonable assumption in this case.

The best fit for DBP difference was with percentage weight difference alone (r = 0.698, Appendix 23b). However, actual weight difference has almost as good a fit and is easier to interpret (r = 0.675, Appendix 23b i). This implies that 10-kg loss will give a 3.7-mmHg drop in DBP. When forced to go through the origin (Appendix 23b ii), this is amended such that 10-kg weight loss is expected to give a 3.6-mmHg drop in DBP.

A similar process was conducted for SBP. In this case, excluding the extreme weight loss studies by Carson and colleagues[263] did not particularly improve the linearity between SBP changes and weight loss. In fact, SBP differences were only slightly significantly related to percentage weight differences (Appendix 23c i and ii). The best fit was again SBP compared with percentage weight difference (10% weight loss leads to a 6.1-mmHg drop in SBP). However, the fit is very weak (adjusted R^2 = 0.144) (Appendix 23c iii) .

Descriptive studies on hypertension

Five studies (Appendix 23d) demonstrated other results related to hypertension. These were mostly descriptive but indicated improvement in the condition of hypertension with weight loss.

Summary of hypertension results

Interpretation of the individual studies and the regression model indicated that blood pressure reductions may result after weight loss. More specifically, a 10-kg weight loss may result in a 3.6-mmHg drop in DBP, but this may not extrapolate to the studies with larger weight losses. Indications are that such weight losses would have smaller DBP reductions in the long term than this model would predict. The model for SBP with weight loss per se was not significant, although a drop is indicated. Comparing percentage weight loss with SBP showed that a 6.1-mmHg drop might be expected with a 10% weight loss.

Co-morbidities

Two studies identified investigated weight loss and improvements in co-morbidities (including DM, hypertension and sleep apnoea) both after surgery for obesity.[265,289] Neither study was of sufficient quality to be statistically manipulated, nor was additional information available for either study. Consequently, the following review was based on descriptive interpretation of the studies.

Study by Wittgrove and Clark[289]

People with obesity had laparoscopic Roux-en-Y gastric surgery from 1993 to 1999. The study described 500 people who all had a BMI of greater than 35 kg/m^2. They participated in a multistage educational and information programme preoperatively to improve compliance. They were followed up prospectively from 3 to 60 months by physical examination and telephone evaluation. The number of co-morbidities in the 500 people was 1752 preoperatively. The authors claim that 80% of the people lost 50% or more of their excess body weight, which persisted up to 60 months postoperatively. The total number of co-morbidities was reduced overall by 96%, to 71 after surgery. Persisting postoperative co-morbidities tended to be markedly reduced in severity. However, the time at which these results were measured post-operatively was not clearly defined. It is uncertain whether the 96% reduction in co-morbidities occurred immediately after the surgery or at the end of the 60-month follow-up period, or for how many people this occurred. There was no measure of variability in weight before and after surgery.

Study by Holt and colleagues[265]

Fifty people (12 men and 38 women) with a mean weight of 131 kg (range 74–216 kg) had vertical banded gastroplasty between 1981 and 1985, with ages ranging from 12 to 54 years. Many of them had complications as a result of obesity. At 2 years the excess weight loss was 60% overall. Although the length of follow-up was mentioned as being between 2 and 5 years, the actual number of people followed up at 5 years (the criterion for this review of surgical interventions) was uncertain. The authors claimed that at some stage of the study after surgery 72% of people reported that their medical conditions due to obesity were improved and quality of life was described for many as "more like normal people".

Summary of co-morbidities

Both of these studies indicate an improvement in obesity-related co-morbidities with weight loss. However, any exact relationship is unclear from the information available in either of the papers.

Psychological well-being

Two studies were identified that looked at the effects of weight loss on psychological well-being in people with obesity.[163,270] One study had a non-surgical intervention[163] and the other had a surgical intervention.[270]

Study by Foster and colleagues[163]

In this study 55 people with a mean BMI of 39.1 kg/m^2 and mean age of 41 years participated. The participants underwent 18 months of treatment of VLCD, a deficit diet and relapse prevention programme. Maximum weight loss of an average of 21.1 kg occurred 6 months after treatment. However, at the end of the follow-up (57.5 ± 10.1 months) (mean ± SD) they averaged 3.6 ± 10.9 kg above baseline weight and the majority of the patients experienced at least two cycles of weight loss and regain. In spite of a slight weight gain overall their psychological measures seemed to be significantly improved by the programme (Appendix 24, *Table 35*). The only factor that improved with the initial weight loss and returned to similar levels to those before the programme was restraint.

Study by van Gemert and colleagues[270]

Sixty-two people who suffered from morbid obesity participated in the study. The demographics of the sample (mean ± SD) show that the mean overall BMI was 47.8 ± 7 kg/m^2 and the mean age was 33.1 ± 9.4 years. All the participants underwent either a gastric bypass or vertical banded gastroplasty. Three psychometric tests Scale of Interpersonal Behaviour (SIG) the Dutch Shortened Minnesota Multiphasic Personality Inventory (NVM) and the Dutch Personality Inventory (NPV)] were undertaken before surgery and the mean follow-up of the patients was 85.9 ± 48.1 months. The psychometric tests were repeated at the end of the follow-up. Surgical treatment resulted in a reduction of the mean overall BMI to 32.0 ± 7.1 kg/m^2. Before surgery these people were negative and introverted compared with the normal population and this significantly improved after surgery (Appendix 24, *Tables 36–38*).

Summary of psychological well-being

The two studies shown here used different programmes for weight loss and different measures of psychological well-being, which makes combining their results difficult. However, both studies show that weight loss improved the psychological status of people who suffer from obesity.

Sleep apnoea

Three studies relating to sleep apnoea were identified.[264,290,291] One study, by Peppard and colleagues,[290] had no intervention and involved people only some of whom were obese. Specific information regarding people with obesity was separated out and forwarded by the authors on request. The other two studies, by Charuzi and colleagues[264] and Sugerman and colleagues,[291] involved people with obesity who had undergone surgical interventions.

Study by Peppard and colleagues[290]

This study included 268 people who had obesity. However, only 36 people had significant weight loss (10% or more) during the 4 years of follow-up. The results of this small group showed a slight but non-significant reduction in sleep apnoea events per hour (Appendix 25).

Study by Charuzi and colleagues[264]

This study presented full results (weight losses and sleep apnoea differences) for only six out of 51 people after 7 years of follow-up. These people had some reduction in both weight and apnoeic episodes per hour (Appendix 25).

Study by Sugerman and colleagues[291]

This study involved 126 people who had either obesity hypoventilation syndrome and/or sleep apnoea syndrome. These people had an average BMI of 56 kg/m^2. About half of the people were followed up for between approximately 3 and 7 years. The average percentage weight loss was 26–31%. The results showed that 76% of people with obesity hypoventilation syndrome and 66% with sleep apnoea syndrome before surgery became asymptomatic at the end of the follow-up (Appendix 25).

Summary of sleep apnoea

Altogether, these studies indicated that weight loss was associated with an improvement in sleep apnoea and related syndromes. However, given the small numbers of people followed up by Peppard and colleagues[290] and Charuzi and colleagues,[264] it was only the paper by Sugerman and colleagues[291] that gives any quantifiable results.

Weight cycling

Weight cycling is defined as intra-individual variability in body weight about a time-dependent regression slope.[292] It is also called 'yo-yo' dieting, weight fluctuation and weight variability. The high prevalence of obesity in affluent societies coupled with the lean aesthetic ideal has resulted in increased rates of dieting. Many individuals

TABLE 13 *Studies on weight cycling for people with obesity*

Authors (year)	Country	Outcome	Sample size	Follow-up time	Weight measure
Foster *et al.* (1996)[163]	USA	Psychological well-being	55 patients	57.5 ± 10.1 months	BMI = 39.1 ± 6.4 (weight 105.8 ± 16.6 kg)
Wing *et al.* (1995)[282]	USA	Lipids and blood pressure	148 at follow-up	30 months	Approx. 134% of IBW

engage in repeated attempts to lose weight and it is often assumed that weight reduction is beneficial to health. However, recent studies have raised concerns over the harmful effects of weight cycling on health.

During the search for epidemiological evidence, several studies were found that investigated the effects of weight cycling. However, only two studies investigated the evidence of effects of weight cycling on health outcomes for people with obesity. These papers are detailed in *Table 13*.

Study by Foster and colleagues[163]

This study gave results for a non-surgical intervention for obesity. The authors were interested in the effects of weight loss patterns on psychological well-being. The tables in this study quote results as mean ± SD. The participants saw a maximum weight loss of 21.1 ± 8.4 kg after 6 months. At the end of the follow-up period (approximately 60 months), however, 33% were within 5 kg of their baseline weight, 80% were more than 5 kg above baseline and only 17% were more than 5 kg below baseline. Most participants had at least two cycles of weight loss/regain and admitted that they dieted only when they exceeded their baseline weight. In spite of overall weight gain, the authors concluded that weight cycling did not affect mood, binge eating, restraint, disinhibition or hunger.

Study by Wing and colleagues[282]

This was a prospective cohort study with a non-surgical intervention. Their definitions of weight cycling groups are presented in Appendix 28. These results have been considered previously in the context of weight loss rather than the current focus of weight cycling.

Cholesterol

There was no significant difference between weight cyclers, gainers and losers.

HDL cholesterol

Participants who lost more than 9 kg at the end of the follow-up had a significant increase in HDL. This included the group who were classed as partial cyclers.

Blood pressure

Both DBP and SBP for partial cyclers were seen to be significantly decreased. Those people who maintained their weight with similar overall weight loss did not have significant reductions in blood pressure.

Summary of weight cycling

The two studies that examined weight cycling in people with obesity suggested psychologically detrimental effects due to weight cycling and, provided weight is lost, partial cycling may aid physiological improvements.

Discussion of the epidemiology results

While some short-term health outcomes are better determined immediately after weight loss, for example fertility, polycystic ovary syndrome (PCOS) and urinary incontinence, the focus of this review was on the long-term health outcomes. This was defined as looking at the effects after 5 years initially, but given the lack of studies except for surgical interventions this was reduced to include studies with follow-up for 2 years or more.

Mortality was reported by five studies suitable for this review, of which three were by the same group of authors (Williamson and colleagues) using the same cohort study. As an outcome, mortality is relatively easy to track from registers of births and deaths, with the follow-up of people in the studies often being high (approximately 90%). The relatively long period of follow-up (8–20 years) achieved by these studies may be accounted for by the use of such registers. The approach of the studies by Williamson and colleagues to establish weight loss was to issue a questionnaire retrospectively asking about weight changes over the previous 3 years. This in itself may introduce recall bias. In addition, weight change patterns after this questionnaire up to death were unknown

and may have had an even bigger impact on their type of mortality.

Mortality was the most consistently recorded outcome, using relative risks, with all but one of the studies using a group of weight-stable people suffering from obesity as the reference group. Although age was always adjusted for, the relative risks in each study (even those by Williamson) were otherwise adjusted differently.

With these limitations in mind the studies indicated that intentional weight loss seemed to reduce significantly all types of mortality for women if they had an obesity-related illness. The same could not be said of men, where weight loss either appeared to have no effect (CVD) or seemed to increase the risk of mortality (cancer). Both men and women had reduced risk of diabetes-related mortality after some weight loss.

The gender divide, with the exception of diabetes, could be a result of women being more frequent visitors to healthcare. Men tend not to seek medical attention, particularly between the ages of 20 and 45 years.[293] Consequently, hidden pathology may go undiagnosed in men more easily than for women, particularly for the cancers, which often are initially asymptomatic. The decrease in diabetes-related mortality in men could be a direct result of attending their doctors for their obvious diabetes symptoms.

The time taken to lose weight was also seen as a factor. A prolonged period usually increased the risk of mortality. This could be due to the psychological stress of the actual process of losing weight, or to the fact that the obesity-related problems were being allowed to manifest over a longer period, or both.

For diabetes mellitus, 15 studies included people suffering from obesity, who had had weight loss at some stage. The results were presented in several different ways. Studies reported risk of developing diabetes after weight loss as odds ratios, relative risks or hazard ratios. These were mostly adjusted for age and gender. Other variables were also adjusted, although not consistently. Other studies gave actual measurements of plasma glucose (usually stated as being fasting glucose) before and after weight loss, or had an associated glucose difference measure.

Weight loss for those suffering from obesity seemed to reduce the risk of developing diabetes for both men and women, more so if there had been some intervention for the obesity. This is particularly so for surgical interventions probably related to larger amounts of weight loss, which were more easily maintained. Where there was weight loss and then regain there was some evidence that the risk of developing diabetes increased. For those with either diabetes or impaired glucose tolerance their diabetic status was often seen to improve after weight loss. The relationship between glucose levels and weight differences, although positive, is not reliably definable from the evidence reviewed. A model was developed to predict the glucose levels after weight loss, but excluded extreme glucose differences. This indicated a drop of 0.04 mmol/l in glucose levels for every 10 kg loss in weight. However, with only seven observations the robustness of this model is in doubt and would in any case underestimate the levels for those who were able to lose large amounts of weight by whatever means.

A similar number of studies (13 altogether) was identified presenting lipid measures. Of interest here were differences in levels of cholesterol, LDL and HDL cholesterol after weight loss for those who were initially suffering from obesity. The measurements were fairly consistent between the studies despite there being a mixture of RCTs, prospective cohort studies, with surgical intervention, non-surgical intervention or no intervention at all.

Considered altogether, the studies showed that the relationship between weight loss and LDL cholesterol difference was positive and linear (bivariate correlation $r = 0.903$). The correlation with cholesterol difference was similar ($r = 0.851$). A model was developed suggesting that a loss of 10 kg would give an expected drop in cholesterol of 0.25 mmol/l. This would roughly equate to a fall in cholesterol of about 5%, half that previously quoted.[17,294] The current review has tried to relate long-term weight loss with long-term health outcomes (at least 5 years for surgical interventions and a minimum of 2 years for the other studies), whereas guidelines do not specify the follow-up times.[17]

The review identified 14 studies where weight loss and the relationship with hypertension in the long term were reported for people with obesity. Again, the studies were fairly similar in their measurements but lacked sufficient evidence for those with larger weight losses. Excluding these extreme weight changes indicated that a 10-kg weight loss might result in an expected 3.6-mmHg drop in DBP. The

model for SBP with weight loss per se was not significant, although a drop was indicated. Comparison of SBP change with percentage weight loss showed a weak association, suggesting an expected drop of 6.1 mmHg in SBP for a 10% weight loss.

These results, like those for the lipids, differ from those in current guidelines.[17] These state that a 10-kg loss in weight will give a drop of at least 10 mmHg in both DBP and SBP. The current review has not shown a lowering in blood pressure of that order for long-term weight loss. It has been suggested that a levelling off of blood pressure reduction could be happening where, despite the large amounts of weight loss sometimes seen after surgical interventions for obesity, the blood pressure levels do not drop any further. Another possible reason given was that the longer follow-up times for the surgical studies could be influencing the final blood pressure and although not seen to be significant here, may allow for the gradual creeping back up of blood pressure despite an overall large weight loss.[278] All that can be concluded from this review is that the large weight losses experienced by the people with obesity who were surgically treated did not result in blood pressure drops proportional to those treated by non-surgical means.

The two studies of co-morbidities after surgical interventions for weight loss did not provide sufficient quantitative information. However, descriptively they indicated an improvement for various co-morbid conditions when weight loss was achieved.

Similarly, there were two papers for psychological well-being as a measure of health. Although different measures were used both studies indicated that weight loss improved the psychological status of people with obesity.

The studies that were identified for sleep apnoea did not provide adequate information for modelling; however, they implied that weight loss improved episodes of sleep apnoea in people with obesity.

Only one study examined the relationship between stroke and obesity. This study measured weight change, but only reported the relative risks associated with weight gain compared with people with stable weight.

This review found little evidence of the effects of weight cycling on people with obesity. The two papers that were found indicated no harmful psychological or physiological effects from weight cycling.

An important methodological limitation arising from this review was the varied definitions of the outcomes and weight measurements. For example, the papers presented weight measurement as actual weight, BMI, percentage excess weight and/or waist–hip ratio. Even the definition of obesity varied. In addition, the measurement of health outcomes was not always explicit and/or did not always use the same indices. Statistical adjustments varied in all the papers. This was particularly noticeable for the mortality papers citing relative risks, where even the same authorship used different adjustments. Differences between gender, age, smoking status and possibly initial BMI category would seem to be worthwhile adjustments. Making too many adjustments has the effect of making the resulting model too data specific.

The studies recorded weight with outcome measures at the start of the study and then again at some stage at follow-up. However, some measured actual values whereas others measured the differences, the latter being the ideal requirement for this review. Differences with appropriate measures of variation (standard deviation or standard error of differences) required estimation for some studies. This problem highlights another difficulty. It is easier to take group summary results than rigorously to follow individuals to ensure paired differences, particularly for longer term studies where dropouts are often an issue. Researchers need to track individuals to obtain paired measurements, which may also reduce loss to follow-up.

This review was based on long-term follow-up studies where it was assumed that the outcome measurements were taken at the end of the study period. However, many studies did not specify the time when the outcomes were measured in relation to the follow-up period.

Research and funding bodies should be committed to structured long-term follow-up strategies so that the long-term effects of short-term interventions can be assessed accurately.

Addendum

An additional literature search was carried out on MEDLINE from 2001 to April 2003, to update the findings of this review. Using the same inclusion

and exclusion criteria, abstracts of studies were screened for any relevant studies. These included trials and prospective studies, provided the results were for outcomes in the long term. Studies that did not mention the follow-up time in the abstract or had wide follow-up times were not pursued on this occasion. Many of the studies complement the findings of this epidemiology review with respect to the association of weight loss and health outcomes in the long term (see Appendix 19b).

A study on sleep apnoea syndrome showed that improvement in sleep apnoea was highly correlated with weight loss,[295] although the number of participants with weight loss was small. A paper by Sanchez-Cabezudo and colleagues[296] indicated that, despite complications, surgical methods of weight reduction often improved preoperative illnesses and hence quality of life.

Three papers based on the same RCT, looking at food substitutes, reported benefits for lipid levels at least 2 years after weight loss,[297–299] as did results from another RCT,[300] and a non-randomised trial after 5 years.[301] A surgical paper by Arribas and colleagues[302] also reiterated this relationship for larger weight losses.

Improvements in plasma glucose and other diabetes-related outcomes, as a result of weight loss, were reinforced by ongoing results from Ditschuneit and colleagues,[297,299] and the ongoing Swedish Obesity Study (SOS).[303] The long-term benefits of weight loss from surgery were reflected in a reduction of medication for diabetes.[302]

The SOS has also shown that weight loss results in reductions in the incidence of and medication for CVD.[303,304] Two other RCTs[208,297,299] and two non-randomised studies[301,302] indicated that weight loss was associated with lowering of hypertension and/or blood pressure in the long term.

A study by Gregg and Williamson and others,[305] independent of the data used in this review by Williamson and colleagues, reiterated the importance of establishing the intentionality of weight loss, with regard to mortality rates in overweight and obese people. The advantage of weight loss with respect to mortality, even for those suffering from obesity, has been debated in the recent literature,[13,306] with intentionality playing an important role in the arguments.

To avoid weight gain and to ensure compliance, a high degree of close follow-up was advocated in a recent surgical study by Wolf and colleagues[307] with respect to long-term surgical complications. This message extends to the understanding of the effects of weight loss in the long term on health outcomes, particularly since such studies often suffer from poor follow-up.

Chapter 4

Systematic review of economic evaluations

Methods

Search strategies

Studies that reported both costs and outcomes of treatments for obesity were sought from three sources:

- identification of studies as part of the literature searches conducted for the effectiveness portions of this report
- a search on the NHS Economic Evaluation Database (with the final search conducted in early March 2002)
- a search on each of the following bibliographic databases: MEDLINE (1966–2002), EMBASE (1980–2002), PsycINFO (1967–2001), Science and Social Science Citation Indexes (1981–2002), CINAHL (1982–2001), Applied Social Science Index and Abstracts (ASSIA) (1987–2002) and Health Management Information Consortium (HMIC) Database (to 2002/01). Search strategies for identification of economic evaluation studies were formulated using a combination of controlled vocabulary terms, where available, and free text terms (see Appendix 29). These strategies were subsequently combined with those designed for identification of effectiveness studies in each database. The final search was conducted early in March 2002.

Inclusion and exclusion criteria

To be included, studies had to compare treatments for obesity in terms of both health service costs and effectiveness or had to be a systematic review that covered such studies. Studies reported in languages other than English were not included in the review. A single economist assessed all abstracts for relevance. Full papers were obtained and formally assessed for all studies that appeared potentially relevant.

Data extraction

Following the HTA reviews by O'Meara and colleagues,[25,26] the following data were extracted for each included study and are provided in Appendices 30–34 (by type of intervention):

- study identification information
  - author and year
  - the intervention studied
  - the type of economic evaluation
  - the country of origin and currency reported
- the intervention study design and main outcomes
  - fuller description of treatment
  - numbers receiving or randomised to each intervention
  - outcomes studied
- sources of data
  - efficacy data
  - prevalence, mortality and morbidity (if measured)
  - cost data
  - quality of life (if measured)
- methods and study perspective
- results
  - costs
  - benefits
  - incremental cost-effectiveness/utility ratio (ICER)
- sensitivity analyses
- additional comments.

Quality assessment

A single economist assessed included studies against the following ten criteria, which were also used in the HTA reviews by O'Meara and colleagues:[25,26]

- well-defined question
- comprehensive description of alternatives
- effectiveness established
- relevant costs and consequences identified
- costs and consequences measured accurately
- costs and consequences valued credibly
- costs and consequences adjusted for differential timing
- incremental analysis of costs and consequences
- allowance made for uncertainty in estimates of costs and consequences
- results and discussion included all issues of concern to users.

Appendices 35–37 contain the results of the quality assessment for all economic evaluation studies in which modelling was performed (i.e. not systematic reviews of existing economic evaluations).

Data synthesis

Data from any included studies were summarised and critiqued by a single economist to identify

common results, variations and weakness between the studies. No formal attempt was made to synthesise quantitatively the data from the identified studies, although the summary to this section provides a rough comparison of results from the selected studies. These data were then interpreted alongside the results of the systematic review of effectiveness so that conclusions could be drawn on the relative efficiency of various treatments for obesity.

Results

In total, 16 reports of studies eligible for inclusion were identified from the review of the literature. *Table 14* classifies the studies according to type of study and type of intervention. The search identified four systematic reviews of economic evaluations, six cost–utility analyses, eight cost-effectiveness analyses, and one cost-minimisation analysis. With respect to type of intervention, the search identified seven studies pertaining to pharmacological interventions (orlistat, sibutramine and metformin), seven pertaining to surgery and four pertaining to lifestyle interventions (diet, exercise and behaviour therapy).

One non-systematic review of the literature, written by Hughes and McGuire[320] is worth noting because it provides a useful overview discussion of economic analysis of obesity as well as concise definitions of the different types of economic evaluation. These authors note that at the time of their study (1997), most of the voluminous published literature pertaining to the economics of obesity consisted of cost of illness or burden of illness studies. While such work, which has increased since 1997, is important in understanding the economic magnitude of the problems of obesity and the vast amount of resources engaged in treating the disease and associated problems, Hughes and McGuire only identified two economic evaluations. Of these two, only one[314] was deemed to be a sufficiently rigorous economic evaluation to be included in this systematic review. It is not surprising, therefore, that most of the studies identified in *Table 14* are from the period following 1997.

It is also worth noting some studies that were not included in *Table 14*, as several are particularly relevant for understanding the costs of interventions or implications of weight loss for certain types of costs. Some economic evaluations

TABLE 14 *Economic evaluations of treatments for obesity by type of intervention*

	Type of intervention				
Type of study	**Orlistat**	**Sibutramine**	**Metformin**	**Surgery**	**Lifestyle (diet, exercise, behaviour therapy)**
Systematic reviews of economic evaluations	O'Meara, 2001[25]; Foxcroft, 1999[308]	O'Meara, 2002[26]		Clegg, 2002[27]	
Cost–utility analysis	Foxcroft, 2000[308,309]	BASF Pharma/Knoll, 2000 (unpublished)		Clegg, 2002[27] Nguyen, 2001[310]	Kaplan, 1987, 1988[178,311a]; Salkeld, 1997[312a]
Cost-effectiveness analysis	Lamotte, 2002[313]		Clarke, 2001[87]	Martin, 1995[314]; Sjostrom, 1995[315a]; Segal, 1998[316a]; van Gemert, 1999[317a]	Johannesson, 1992[318]; Segal, 1998[316a]
Cost-minimisation analysis				Chua, 1995[319]	

Studies are identified by first author and year of publication.
O'Meara (2001)[25] indicated that Foxcroft and Ludders[308] was the only economic evaluation of orlistat published up to June 2000.
O'Meara (2002)[26] indicated that no economic evaluations of sibutramine were published up to 2000 and that an unpublished company submission from BASF Pharma/Knoll was the only cost–utility model available at the time of their systematic review.
[a] NHS Centre for Research and Dissemination (University of York) structured abstract available.

were not included because they considered a very narrow range of costs. Three studies of nutritional or lifestyle interventions[127,321,322] were not included because they only measured intervention costs. While these studies provide comparative information between interventions on effectiveness and on average intervention cost per intermediate outcome, such as the cost per kilogram of weight lost, they do not provide broader guidance on incremental cost per life-year saved, since they do not track health service use impacts as a result of the interventions. Other studies that looked at the long-term effects of weight loss on particular costs, such as pharmaceutical costs in obese subjects[303] may be helpful in developing economic models but do not, per se, provide a basis for comparison of different interventions from a more comprehensive economic perspective.

Economic evaluations of orlistat

In the most recently published systematic review of orlistat, O'Meara and colleagues[25] searched 19 electronic databases up to June 2000. The search strategy in the present review identified two additional economic evaluations of orlistat published since June 2000, although one of them[309] was a cost–utility analysis conducted as part of the systematic review by Foxcroft and Ludders[308] that was reviewed by O'Meara and colleagues. One company submission (Roche 2000[323]) that included a cost–utility analysis was provided to O'Meara and colleagues as well as to this review team. The company submission was declared as commercial in confidence, however, and therefore cannot be discussed.

The economic evaluation component of the two systematic reviews[25,309] relied on effectiveness evidence from three RCTs that focused on outcomes related to mean weight loss or the proportion of patients who lost greater than 5% of their initial body weight[33,34,41,42,52–56] Foxcroft and Milne provided a succinct summary of the three RCTs as well as a reanalysis of the efficacy data on an ITT basis.[309] The three RCTs all assessed intervention with 120 mg of orlistat three times a day in combination with a hypocaloric diet. The control groups received a placebo plus diet. The run-in period of dieting before initiation of treatment with orlistat was 4 or 5 weeks, and follow-up for the trials was 1 year[33,34] or 2 years[41,42,52–56]. None of these three RCTs implemented the licensing requirements for weight loss, so the data do not necessarily relate to the results that would be obtained under licensed application. Earlier sections of this report summarise and comment on the results. The perspective for all studies was that of the health service provider/payer.

Cost estimates[309] included initial consultation and laboratory tests, four outpatient consultations per year and drug cost. The number of consultations seems quite low, as ten studies of orlistat reviewed in the effectiveness portions of this report indicate that the average number of outpatient consultations is substantially higher, for example 11 in 1 year[48,49] to 25 in 2 years.[52–56] Annual average treatment costs per person per year were estimated at £7344 in 1998. Foxcroft and Milne[309] paid particular attention to the estimated effects on cardiovascular risk factor measures, concluding that the estimated improvements were small and that their long-term benefits were not known. They also cited a lack of evidence of the short-term, small to moderate weight reductions on morbidity and mortality, and concluded that one could only assume longer term benefit of weight loss if that weight loss was sustained. Because of this conclusion, they estimated effects of orlistat only on short-term quality-adjusted life-years (QALYs) (i.e. benefits directly attributable to weight loss) and did not include any long-term estimates of impact on QALYs.

The literature is largely lacking good estimates of orlistat or, more broadly, of weight reduction on quality of life. Foxcroft and Milne[309] used a procedure to estimate the change in QALYs based on the Index of Health Related Quality of Life (IHQL). They estimated the short-run gain in QALYs over a 2-year treatment period with orlistat to be 0.0160 QALYs per year. The resulting cost per QALY gained was £45,881, with an estimated range from £19,452 to £55,391 in their base-case analysis.

The recent study by Lamotte and colleagues,[313] which was funded by Roche Pharmaceuticals, was a cost-effectiveness analysis that focuses on obese patients with type 2 diabetes. The authors noted that they were not able to predict the independent effect of weight loss on the incidence of complications and death. Instead, they used estimated improvements in risk factors associated with the use of orlistat and the accompanying weight loss to estimate potential changes in morbidity and mortality over a 10-year follow-up period. They used a Markov model to estimate the ICER for four groups of obese patients with type 2 diabetes: patients with no complications, patients with hypercholesterolaemia, patients with arterial hypertension (AHT), and patients with both types of complication. The outcome measure was life-

years gained from using orlistat over diet plus a placebo. They assume that weight was fully regained in 5 years after termination of the 2-year orlistat treatment period. Cost-effectiveness estimates were in year 2000 Euros.

Not surprisingly, the cost-effectiveness of orlistat in the diabetic population was better than in the general population, and was also better for the patients with complications. For diabetic patients without complications, the cost per life-year gained was €19,968. For persons with both hypercholesterolaemia and AHT, the cost per life-year gained was €3462. Lamotte and colleagues[313] performed several sensitivity analyses, including an assumption that all weight was regained within 2.5 years instead of 5 years. The cost per life-year gained for patients without any complications and with both types of complication, respectively, only increased to €26,527 and €4565. Since their model seemed to assume that the benefits from the risk factors accrue in all years until the weight is regained, the shorter period provides some assurance that the cost per life-year gained in obese patients with other diseases may still be affordable to society.

Economic evaluations of sibutramine

A systematic HTA review conducted by O'Meara and colleagues[26] identified no published economic evaluations of sibutramine and provided a critique of one cost–utility model submitted by a pharmaceutical company (BASF Pharma/Knoll 2000, company submission). As no further economic evaluations were identified by the current search, their review of the company submission remains the sole assessment of the economic implications of sibutramine. The key points from their review are summarised below.

The company submission model (BASF Pharma/Knoll 2000, company submission) incorporated three specific effects of sibutramine-induced weight loss: the effect on CHD risk, the effect on the incidence of diabetes and the direct effect on quality of life. The model assumed that all weight was regained by 5 years following the trial. The individual estimates of cost per QALY for each of the three components were £32,000 for the CHD reduction, £58,260 for the diabetes incidence reduction and £14,700 for the direct weight loss. The combined cost per QALY gained from the three influences was estimated at £7860. O'Meara and colleagues expressed concern that the utility values used in the study were not sufficiently justified and in particular may have represented an inappropriately high gain in QALY per kilogram of weight loss. Their overall estimate of the cost per QALY for sibutramine versus a placebo was £10,500. They noted that a sensitivity analysis using lower utility gain values resulted in a cost per QALY of £38,674 (ostensibly for the combined effect of all three components, although this point was not clear).

Economic evaluations of metformin

Obesity may not only increase the risk of type 2 diabetes (as considered, for example, in the cost–utility model of sibutramine discussed above) but also increase the risk of diabetes-related events for obese patients with type 2 diabetes. Therefore, the cost-effectiveness of metformin in blood glucose control versus conventional diet therapy is relevant for the economic evaluation of treatments for obesity. As part of the UKPDS, Clarke and colleagues[87] conducted an economic evaluation of the cost-effectiveness of metformin in obese type 2 diabetic patients. They used a fairly wide definition of obesity by studying patients who were more than 120% of their ideal weight, which translated roughly into people with a BMI in excess of 25.6 kg/m^2, although the mean BMI among people who actually enrolled in the study was 31.7 kg/m^2. A total of 342 patients received intensive blood-glucose control with metformin, while a control group of 411 patients received conventional treatment consisting primarily of diet in addition to standard treatment for diabetes. Median follow-up was 10.7 years for the economic evaluation. The economic evaluation focused on life-years gained as an outcome measure due to the lack of data on estimates of QALYs for people with diabetes. Costs and outcomes were both discounted at 3 and 6%. Metformin was estimated to result, on average, in cost savings of £258 per person (6% discount rate) with a gain in life-years of 0.6 per person (3% discount rate). The reduction in costs was not statistically significant. An acceptability curve approach to account for uncertainty in the data resulted in an estimate (using a 6% discount rate for both costs and outcomes) of a 71% chance that metformin is cost saving, and a 95% chance that the cost per life-year gained was less than £1600.

Economic evaluations of surgery

In conducting a systematic review of surgery for people with morbid obesity, Clegg and colleagues[27] identified and reviewed four economic evaluations[314,315,317,319] which are each described briefly below. Two of the four studies identified focused on the obese population rather than the morbidly obese population, which was defined as people with a BMI of 40 kg/m^2 or greater. Their

review also included an extensive list of cost studies that were deemed not to be economic evaluations as well as their own economic model of the cost–utility of surgical treatment for morbidly obese patients. The present systematic review identified two additional economic evaluations of surgery; one was a study by Segal and colleagues[316] of a range of interventions to assess the cost-effectiveness of primary prevention of NIDDM (type 2 diabetes) that included an analysis of surgery for morbidly obese individuals, and the second was a study by Nguyen and colleagues[310] of laparoscopic versus open gastric bypass surgery in morbidly obese people. Appendix 33 provides key data extraction for each study, and Appendix 36 provides a summary of quality assessment. The only study discussed in this section that used data for the UK was the cost–utility model constructed by Clegg and colleagues,[27] so the external validity of the other six studies may be limited for the UK, especially with respect to costs.

Martin and colleagues[314] compared Roux-en-Y gastric bypass surgery with a VLCD in the obese population. They focused on an outcome of weight (pounds) lost and reported average cost-effectiveness ratios (dollars per pound lost) rather than ICERs. The authors reported that after 7 years all non-surgical patients regained the weight lost and concluded that surgical treatment appears to be more cost-effective at producing and maintaining weight loss. Yet the study suffers from a number of weaknesses, including the following points: costs for medical and surgical complications were not included; cost of follow-up was not included; patient selection may have occurred because the patient profile differed between the two groups; and approximately 50% of patients were lost from each group by the fifth year of follow-up.

van Gemert and colleagues[317] compared vertical banded gastroplasty with no treatment for morbidly obese patients using a cost-of-illness prevalence-based model, where the data for the 'no treatment' came from the obese population. Direct health service costs including the costs of complications and revisions were included, although the costs of co-morbidities attributable to morbid obesity were not included. The authors included the costs of productivity losses and found that vertical banded gastroplasty resulted in total cost reductions and improvements in quality of life, resulting in a situation of dominance of surgery over non-treatment. It is notable, however, that the direct costs of surgery were US$5865 while the productivity gain was estimated at US$2765 per year, so the finding of dominance is not surprising.

Chua and Mendiola[319] compared laparoscopic vertical banded gastroplasty with open gastric bypass surgery and with open Roux-en-Y gastric bypass in the obese population. This was a very preliminary study, however, in that it focused on the costs of the three different surgical approaches and did not include any long-term follow-up. The study did determine from a cost-minimisation viewpoint that the laparoscopic surgery was the least cost of the three techniques, as the cost of the longer operating time was more than offset by short hospital lengths of stay following surgery. Lacking follow-up data on weight loss and complications, however, the study offers no insights into broader cost-effectiveness or cost–utility implications of the three surgeries.

The fourth economic evaluation of surgery identified in the systematic review[27] was conducted by Sjostrom and colleagues.[315] The authors compared three types of surgery (gastric banding, vertical banded gastroplasty and open gastric bypass) with conventional treatment (which was not clearly described) over a 2-year follow-up period. The authors noted improvements in health-related quality of life over 2 years in surgery patients, but not in the control patients. Additional benefits noted for the surgery patients included reductions in cardiovascular risk factors, a lower rate of incidence of new diabetes cases, a higher rate of cure of hypertension, and a lower rate of sick leave during the second year of follow-up. ICERs and cost–utility ratios were not calculated, and the authors instead noted that 10-year follow-up data should be pursued to determine the economic implications including the effect of improvements in disease risk status. As noted earlier, however, data from Sjostrom and colleagues[278] indicate that there is no evidence of a long-term effect on the incidence of hypertension.

Based on their systematic review results, Clegg and colleagues[27] conducted an economic evaluation of four different treatments: Roux-en-Y gastric bypass, vertical banded gastroplasty, adjustable gastric banding and non-surgical management. For the gastric bypass, they assumed that 36% of original weight was lost in the first year and that the weight loss was maintained over time. For vertical banded gastroplasty, they assumed that patients lost 25% of their weight in the first year but regained 2% of their original weight in each subsequent year, based on their review of

effectiveness data. For the adjustable gastric banding, they assumed an initial weight loss of 20% of original weight, but that weight loss continued beyond year 1 up to a loss of 33% of original weight by year 5. They assumed no weight loss for non-surgical patients, which may not be realistic. For their base case, they assumed that patients weighed 135 kg or had a BMI of approximately 45 kg/m^2 at the start of the analysis.

Based on a review of the health-related quality-of-life literature as well as their own work using the IHQL, they hypothesised potential differences in quality of life under best and worst case scenarios. They included gains from avoiding diabetes in their estimates based on an assumption of 10% prevalence of diabetes among the morbidly obese, but did not include gains from reduced hypertension because of lack of evidence that the effects on hypertension are long lasting rather than transient.[278] They also did not assume any change in life expectancy for their base case, although based on evidence from the UKPDS they assumed a gain of 0.29–0.6 life-years per patient for their best case scenario.

They developed estimates of the costs of surgery, including complications and postdischarge care, by combining estimates of resource use with unit cost measures. They ran their model for a hypothetical cohort of 100 patients for 20 years following surgery. Weight loss ceased after 5 years and the impact of reduction in diabetes incidence ended after 8 years. They discounted costs at 6% and QALYs at 0%, 1.5% and 6%.

Relative to usual care, the model of Clegg and colleagues[27] resulted in higher QALYs and higher costs for all three types of surgery. The main source of averted costs in their model was costs associated with avoided diabetes. The cost per additional QALY from surgery rather than conventional treatment was £10,237 for vertical banded gastroplasty, £8527 for adjustable gastric banding and £6289 for Roux-en-Y gastric bypass. Adjustable gastric banding had the highest costs and a negligible improvement in QALYs relative to gastric bypass. The cost per additional QALY from gastric bypass rather than vertical banded gastroplasty was £742. These estimates are based on a number of assumptions, and therefore sensitivity analyses were conducted on a range of factors pertaining to procedure costs and effects. The results from these analyses indicated that surgery was a cost-effective alternative to non-surgical management, although the estimate of the cost per additional QALY varied. In considering their results, the authors noted that NICE guidance places the cost per additional QALY of orlistat[23] at £46,000 and the cost per additional QALY of sibutramine in the range of £15,000–30,000.[24] Subject to a number of caveats (including the fact that the estimates for orlistat and sibutramine are not for the morbidly obese subgroup of patients), the benefits from surgical treatment of morbid obesity may be worth the cost.

Clegg and colleagues[27] highlighted the potential advantages in utility gains and cost per additional QALY for gastric bypass versus other surgery or conventional treatment. Segal and colleagues[317] similarly found that gastric surgery resulted in increased life-years, including diabetes-free life-years, which presumably have a higher quality of life than non-diabetes-free life-years, and that the cost per life-year gained in 1997 Australian dollars was Aus$4,600. Segal and colleagues modelled the cost-effectiveness of a range of interventions including several lifestyle approaches with the specific goal of assessing primary prevention of type 2 diabetes (which is apparently why the study was not identified in the systematic review of surgery for morbid obesity[27]). The full description of this study is deferred until the next section.

Given the evidence in favour of the cost-effectiveness of gastric surgery, a recent study by Nguyen and colleagues[310] reports on an RCT of laparoscopic versus open gastric bypass that assessed the implications of these two approaches for outcomes, quality of life and costs. The study randomly assigned 155 morbidly obese people to the two treatments and followed them for 1 year after surgery. A range of clinical outcomes, including complications during and after surgery as well as quality of life at 1, 3, 6, and 12 months following surgery, were measured. The study considered direct hospital costs and also apparently measured indirect costs related to time lost from work. The study did not, however, appear to include follow-up treatment costs during the year after surgery, and there is virtually no information provided about how the indirect costs were measured.

Nguyen and colleagues[310] found that laparoscopic surgery had higher operating costs but shorter hospital stays. There was no statistically significant difference in direct hospital cost, indirect costs or total costs between the two procedures. Complication rates were also not statistically different, although quality of life was higher at various interim points during the year following

surgery for laparoscopic patients relative to open gastric bypass patients. It is notable that laparoscopic gastric bypass resulted in fewer intensive care unit stays, shorter hospital stays, faster recoveries and an earlier return to work than did open surgery. No effort was made to determine the implication of these differences on QALYs, and the measured quality of life differences did disappear by the end of the year. However, these gains may be valuable to patients, and the lack of significant differences in costs may mean that laparoscopic surgery is cost-effective relative to open gastric bypass.

Economic evaluation of lifestyle interventions

The literature search did not identify any systematic reviews of economic evaluations of lifestyle interventions of diet, exercise or behaviour therapy. While the pharmacological and surgical interventions for obesity have been accompanied in a few cases by explicit economic evaluation, the trials related to lifestyle interventions have either rarely included an economic evaluation or not focused exclusively on obese people or on the problems of obesity. The search used a broad perspective by including economic evaluations of interventions that were not necessarily targeted exclusively at obese people, but instead may have been directed at people for whom obesity is often a serious complication or subsequent disease, or both. The three studies identified addressed problems of obesity among two groups of people: one study[178,311] targeted people with type 2 diabetes, and two studies[312,316] targeted overweight individuals living in the community who in particular might be identified as at risk of sequelae of obesity (e.g. type 2 diabetes, CVD) through general practice.

The earliest economic evaluation of lifestyle interventions identified in this review was by Kaplan and colleagues.[178,311] This study analysed the effect of four interventions (diet and behaviour therapy, exercise and behaviour therapy, diet and exercise and behaviour therapy, and a control group receiving general diabetes education only) in a single-centre RCT of 76 obese non-insulin-dependent diabetics. Participants were followed for a total of 18 months. Key outcome measures included HbA_{1c} and quality of well-being.

Cost measures focused on intervention treatment costs, although possible effects on medication use were also assessed and found not to occur. All weight lost with any of the interventions was regained by the end of the 18-month follow-up period. The combined diet/exercise/behaviour therapy group had a marginally significant improvement in HbA_{1c} levels, and the diet/behaviour therapy and combined diet/exercise/behaviour therapy groups had significant modest improvements in quality of life.

The diet/exercise/behaviour therapy group had an estimated annual improvement in quality of life of 0.092, resulting in a cost per additional well year of life of US$10,870 in 1986. Because general health service use costs were not tracked, this estimate may be an overestimate of the actual cost per additional well year of life since such costs might have been greatest for the control group. However, the small sample size and short follow-up period limit the study findings.

Because obesity significantly increases the risk of onset of type 2 diabetes, it is possible that interventions targeted towards obese people may reduce the incidence of type 2 diabetes. Segal and colleagues[316] used a Markov model approach over a 25-year postintervention period to assess the cost-effectiveness of six different treatments for obesity: (1) intensive diet and behavioural therapy for the seriously obese, (2) intensive diet and behavioural therapy for women with previous gestational diabetes mellitus, (3) surgery for the seriously obese with BMI >40 kg/m^2 or excess weight of 45 kg, (4) group behavioural therapy for overweight men, (5) advice from a GP, and (6) a media campaign with community support. Possible states within the model were normal glucose tolerance (NGT), IGT, and type 2 diabetes. Costs were in 1997 Australian dollars. Assumptions were made about the baseline health status, transition rates and the effectiveness of the interventions. The authors found that surgery for the severely obese saved the greatest number of life-years, but also had the highest ICER of Aus$4,600 for persons with IGT and Aus$12,300 in a more general population with 10% IGT and 90% NGT. The individual diet and behavioural therapy approaches as well as GP advice resulted in costs per additional year of life of roughly Aus$1000–2600, depending on the initial risk status of participants. The group behavioural therapy and media campaigns were cost saving, as was the intensive diet and behavioural therapy in high-risk seriously obese people. The media programme, however, was assumed to be successful in only 1% of the population, and net benefit amounts from the interventions that were cost saving were not reported. Therefore, the return from other interventions that were found to

be cost saving, such as intensive diet and behavioural therapy among severely obese people with IGT, may be greater than the net benefit from the media campaign.

The calculations by Segal and colleagues rested on a number of assumptions, and in many ways the analysis is largely hypothetical. The effectiveness apparently was assumed to extend over the full follow-up period, and the percentage of people assumed to have a successful intervention was quite high (e.g. 33% for intensive diet and behavioural therapy). In contrast, even the longest trials of dietary interventions only follow participants for up to 5 years, and since many intervention group members regain a lot of the weight during the 5-year follow-up period, the effectiveness may be overstated by Segal and colleagues. Yet, the analysis was also conservative in a number of ways. The analysis only offset programme costs with the expected reduction in direct diabetes treatment costs and did not incorporate any other reductions in costs due to reduced medication or reduced incidence of CVD. In total, the basic framework for the analysis was useful, and further refinement and estimation of the model may be helpful.

Obesity also increases the risk of CVD, so that interventions targeted towards obese people may have benefits in terms of prevention of the disease and associated costs. Johannesson and Fagerberg[318] used data from a trial of diet versus drug treatment for hypertension (with atenolol as the first drug of choice) in a sample of obese men in Sweden. The analysis used a computer simulation based in part on risk equations for stroke and CHD from the Framingham Heart Study and also used a willingness to pay approach in a cost–benefit analysis. The sample was small and the findings are somewhat equivocal. Five simulations were conducted under different assumptions about the effect of risk factor changes on the risk of CHD. Drug treatment was cost saving relative to diet in three out of the five different simulations, but in the simulation where all three risk factors reduced the risk of disease, diet was estimated to result in an additional year of life for 46,000 Swedish crowns (year 1991). The main contribution of the study may be to emphasise that a range of contributions may occur from behavioural interventions and that in some cases or under some assumptions the effects may be better than drug treatment.

In a more extensive study, Salkeld and colleagues[312] conducted a cost–utility analysis using data from a trial of two lifestyle interventions administered within a general practice setting (a video, and a video plus written self-help materials) versus routine care. The study targeted people with one or more modifiable CVD risk factors, including BMI > 25 kg/m^2, as well as other factors such as smoking, and it is important to note that the intervention materials focused on three factors: smoking cessation, healthy eating and physical activity. Therefore, the results of the study are potentially affected by confounding from both the other risk factors and components of the intervention targeted towards those risk factors. The presence of obesity was high among the study population, with a mean BMI of 30 kg/m^2.

The authors used a model based on risk equations for CHD and stroke from the Framingham Heart Study. The video was found not to increase the outcomes of life-years or QALYs in the general at-risk population identified in the study, and the video plus self-help did not increase the outcomes in a more narrowly identified high-risk population (with very high blood pressure or total cholesterol). The estimated cost per life-year saved or cost per additional QALY was extremely high in the general at-risk population for the video plus self-help, at Aus$152,128 and more than Aus$11 million per additional QALY for males and females, respectively. The best results obtained were in a sensitivity analysis that assumed that high-risk individuals who changed behaviour maintained the change over 2 years, which resulted in a cost per additional QALY of Aus$4,342. The main lessons from the study may be that the cost-effectiveness of lifestyle interventions is often going to be relatively poor unless the interventions are targeted towards people at high risk of developing disease and unless the behaviour is maintained over time.

Summary

In total, a number of fairly recent studies have attempted to assess the cost per life-year saved or cost per additional QALY from a range of treatments for obesity. *Table 15* provides a very rough conversion of the results from selected recent studies to current (2001) UK pounds sterling. Such conversions and comparisons of cost-effectiveness results from different studies are subject to a number of qualifications. It is possible to document certain differences between studies (e.g. specific target population and length of time used in follow-up). However, translating ICER results from one country's currency to another

TABLE 15 *Comparison of selected base-case cost-effectiveness estimation/modelling results (studies published after 1996)*

Target (modelled) population	Intervention	Comparator	Source (first author, year of publication)	Years modelled or followed	Original currency and year of cost data	Outcome measure	Cost per additional unit of outcome in original currency	Cost per additional unit of outcome in original year £	Cost per additional unit of outcome in year 2001 £[a]
Obese people with type 2 diabetes									
No complications	Orlistat	Diet (unspecified)	Lamotte, 2002[313]	10 years modelled	Euros 2000	Life-years	€19,968	£12,522	£12,760
Hypercholesterolaemia	Orlistat	Diet (unspecified)	Lamotte, 2002[313]	10 years modelled	Euros 2000	Life-years	€7,407	£4,645	£4,733
AHT	Orlistat	Diet (unspecified)	Lamotte, 2002[313]	10 years modelled	Euros 2000	Life-years	€7,388	£4,633	£4,721
Hypercholesterolaemia and AHT	Orlistat	Diet (unspecified)	Lamotte, 2002[313]	10 years modelled	Euros 2000	Life-years	€3,462	£2,171	£2,212
Morbidly obese									
BMI ≥ 45 kg/m^2	Vertical banded gastroplasty	No weight loss	Clegg, 2002[27]	20 years modelled	UK pounds 2000	QALYs	£10,237	£10,237	£10,432
BMI ≥ 45 kg/m^2	Adjustable gastric banding	No weight loss	Clegg, 2002[27]	20 years modelled	UK pounds 2000	QALYs	£8,527	£8,527	£8,689
BMI ≥ 45 kg/m^2	Roux-en-Y gastric bypass	No weight loss	Clegg, 2002[27]	20 years modelled	UK pounds 2000	QALYs	£6,289	£6,289	£6,408
BMI ≥ 45 kg/m^2 or 45 kg excess, 10% IGT, 90% NGT	Gastric bypass surgery	No intervention	Segal, 1998[316]	25 years modelled	Australian dollars 1997	Life-years	Aus$12,300	£5,527	£6,277
BMI ≥ 45 kg/m^2 or 45 kg excess with IGT	Gastric bypass surgery	No intervention	Segal, 1998[316]	25 years modelled	Australian dollars 1997	Life-years	Aus$4,600	£2,067	£2,329
Seriously obese people									
100% IGT	VLCD and individual therapy	No intervention	Segal, 1998[316]	25 years modelled	Australian dollars 1997	Life-years	Cost saving (VLCD and therapy dominates)	NA	Cost saving (VLCD and therapy dominates)

continued

TABLE 15 *Comparison of selected base-case cost-effectiveness estimation/modelling results (studies published after 1996) (cont'd)*

Target (modelled) population	Intervention	Comparator	Source (first author, year of publication)	Years modelled or followed	Original currency and year of cost data	Outcome measure	Cost per additional unit of outcome in original currency	Cost per additional unit of outcome in original year £	Cost per additional unit of outcome in year 2001 £[a]
10% IGT, 90% NGT	VLCD and individual therapy	No intervention	Segal, 1998[316]	25 years modelled	Australian dollars 1997	Life-years	Aus$2,600	£1,168	£1,316
Type 2 diabetics									
>120% of IBW or > approximately 25.6 kg/m^2 BMI	Metformin	Diet	Clarke, 2001[87]	Median follow-up 10.7 years	UK pounds 1997	Life-years	Cost saving (metformin dominates)	NA	Cost saving (metformin dominates)
People in general practice at very high risk of CVD									
DBP >95 mmHg or total cholesterol > 6.5 mmol/l (mean BMI > 30 kg/m^2)	Educational video	No intervention (usual care)	Salkeld, 1997[312]	Lifetime	Australian dollars 1994	QALYs	Aus$29,574	£14,066	£17,386

[a] The conversion is done by first converting to UK pounds in the original year of the data using midyear intrabank conversion rates from www.itools.com and then inflating as appropriate using the following pay and price index rates for hospital and community health services from www.ukc.ac.uk/pssru:[324] 1997/98, 1.7; 1998/99, 4.0; 1999/00, 4.5; 2000/01, 1.9.

NA, not applicable.

assumes that important factors, such as underlying characteristics of the study population that may be related to study effectiveness and patterns of health service use, are the same across the two countries. The conversion also assumes that patterns of health service treatment have not changed over time, although the problems from this assumption are reduced by limiting the assessment to fairly recent studies.

While remembering these caveats, the comparisons in *Table 15* are potentially helpful and interesting. First, the combination of the costly implications of obesity for development of CVD and type 2 diabetes means that interventions targeted towards high-risk obese individuals (e.g. those with diabetes or IGT, those with hypertension or high risk for CVD, or those who are morbidly obese) are likely to result in costs per additional life-year or QALY of no more than £13,000 in most cases. The only entry in *Table 15* with a higher ICER was for the intervention in a general practice setting modelled by Salkeld and colleagues.[312] This return on investment of healthcare resources is at least as good as many other disease treatments, and is lower than the cost-effectiveness estimates considered by NICE in existing decisions on recommendations for use of some of the treatments (see NICE website[23,24]). Furthermore, as is clear from the table as well as common knowledge, the greater the targeting towards higher risk individuals, the lower the cost per additional unit of outcome. Finally, one study provided reasonably rigorous evidence of cost-saving from treatment with metformin.[87]

The estimated (year 2001) cost-effectiveness of gastric bypass surgery in the morbidly obese population was extremely similar for two studies: £6408 per QALY and £6277 per life-year. Three points are relevant. First, the two estimates are for different outcome measures but imply approximately a value of 0.87 QALYs for morbidly obese people (if one equates the two estimates). This value may very well be within the plausible values of quality of life for morbidly obese people. Second, targeting of surgery to morbidly obese people with IGT would be even more cost-effective at £2329 per additional year of life. Third, since both Clegg and colleagues[27] and Segal and colleagues[316] modelled open Roux-en-Y gastric bypass surgery, the cost-effectiveness may be modestly improved based on the evidence of greater benefit at the same cost for laparascopic versus open gastric bypass surgery.[310] This latter gain, however, is likely to be considerably smaller than the reduction in cost per additional life-year from targeting surgery to people with IGT.

Finally, it is important to remember that components of the individual studies may affect the results. In particular, the estimates of costs and effects are both subject to varying degrees of uncertainty, and the estimates in *Table 15* are undoubtedly accompanied by confidence intervals that are potentially quite large. A further example pertains to the fact that the drug trials of orlistat and sibutramine (and, to a lesser extent, surgery) tended to have very high dropout rates. Some of these analytical models used effectiveness estimates based on data for completers (as discussed in detail in the effectiveness sections of this report), so that results may understate actual cost per additional unit of outcome (e.g. life saved).

Some of the studies used conservative assumptions to avoid overestimating the cost-effectiveness. For example, Clegg and colleagues[27] did not include gains from reduced hypertension because of lack of evidence that the effects on hypertension are long lasting rather than transient.[278] This approach may be reasonable, yet other researchers[185,208] cite evidence that even when people regain weight after initial loss, there is a period of reduced risk of hypertension that may confer at least some short-term benefits. Therefore, it may be reasonable to use the Framingham logistic risk equations to estimate benefits in reduced stroke and CHD from weight loss and improvements in blood pressure and cholesterol, as done in some studies,[312,318] but given the evidence of weight regain it is likely to be best to incorporate such reductions in short-term rather than long-term estimates. In total, however, the evidence in *Table 15* is indicative of benefits from a range of treatments for obesity for which society may be willing to pay.

Chapter 5

An economic model of the cost-effectiveness of lifestyle treatments for obesity

Overview

As discussed in the systematic review of economic evaluations, several recent analyses show that intervention in high-risk individuals may result in improvements in life-years or QALYs for a relatively modest increase in healthcare costs. In the case of metformin for diabetics, treatment may even result in cost savings. Yet caution is needed in applying these results to policy. Most of the studies use follow-up data from a very short period, particularly the studies of pharmaceutical interventions, and the effects of relatively short-term or fluctuating changes in weight or clinical indicators such as blood pressure and cholesterol are simply not known. Furthermore, one study of lifestyle interventions in general practice[312] showed that the cost-effectiveness of such interventions is often going to be relatively poor unless the interventions are targeted towards persons at high risk of developing subsequent or worsened disease and unless the behaviour is maintained over time. Therefore, the desire to treat obesity, especially in a preventive manner, should be balanced with an understanding that it is the sequelae of obesity that result in evidence-based justification for intervention rather than obesity per se.

This chapter extends these considerations by providing a simple economic model of the effectiveness of lifestyle interventions in preventing the onset of diabetes among people with IGT.

The focus is on the onset of diabetes for several reasons. First, diabetes is widely recognised as a major cause of health service use. The Cost of Diabetes in Europe – Type 2 (CODE 2) study[325] estimates that the total current annual NHS cost of type 2 diabetes is £1.8 billion or 4.1% of total NHS expenditure. Second, although the National Audit Office indicated that hypertension accounts for the most cases of disease attributable to obesity in England, type 2 diabetes has the highest proportion of cases of the disease attributable to obesity (at 47% compared with 35% for hypertension) and the annual cost per case of diabetes is almost three times as high as the estimated annual cost per case of hypertension (£467 versus £170 in 1998).[2] Third, the prevalence of diabetes is projected to increase owing to trends of increasing obesity (although increasing obesity will also increase rates of other diseases or risk factors such as blood pressure).

The focus is also on lifestyle interventions for several reasons. First, GPs are often in a position to offer guidance on treatments to obese people who have not yet developed diabetes, CVD or other diseases for which the risk is increased by obesity. Although general recommendations on losing weight and increasing exercise should be routine for any overweight or sedentary individual, effective programmes for lifestyle changes in diet, exercise and behaviour can be both intensive and expensive. Therefore, an awareness of the cost-effectiveness of such programmes among people identified as high risk (according, for example, to glucose tolerance or blood pressure) can provide important guidance for appropriate targeting of such interventions to individuals. Furthermore, results from the effectiveness review described earlier showed that one long-term study of lifestyle interventions[167–171] had significant benefit regarding effects on the onset of diabetes. Since economic evaluations have not yet been published from this study, the use of modelling techniques can provide insight into the potential cost-effectiveness of the interventions.

Description of the intervention and published effectiveness

Tuomilehto and colleagues[167–171] (referred to as the FDPS in the effectiveness review) estimated the effect of a lifestyle intervention consisting of a low-fat diet and exercise on the onset of diabetes among 522 middle-aged overweight Finnish people with IGT. Study enrolment occurred between 1993 and 1998. The intervention group was given detailed dietary recommendations (to limit the total intake of fat to less than 30% of energy consumed and of saturated fat to less than 10%, and to increase fibre to at least 15 g/1000 kcal, as well as advice about specific food types) and

TABLE 16 *Approximate cumulative prevalence rates of diabetes by treatment group in study by Tuomilehto and colleagues*[168]

Years since baseline	Total subjects still at risk of diabetes	Intervention		Control	
		Estimated prevalence rate	95% CI	Estimated prevalence rate	95% CI
1	507	2	0.5 to 3.5	6	3 to 9
2	471	6	3 to 9	14	10 to 19
3	374	9	4 to 13	21	15 to 27
4	167	11	6 to 15	23	17 to 29
5	53	20	8 to 32	34	21 to 47
6	27	20	8 to 32	43	25 to 55

Source: Estimated from Figure 2 in the original publication.[168]

asked to undertake moderate exercise for at least 30 minutes per day. Intervention group members had seven sessions with a dietitian during the first year and quarterly meetings thereafter. Supervised exercise sessions were also offered; during the first year the rate of participation varied from 50 to 85% at different centres. Control subjects received oral and written information about diet and exercise at a baseline visit.

The results from the randomised trial were reviewed in an earlier section of this report, but the finding of most importance for the model is that the risk of diabetes was significantly reduced by 58% in the intervention group. Furthermore, the reduction in the incidence of diabetes was directly linked to changes in lifestyle. *Table 16* provides the estimated rates of prevalence of diabetes in the two groups as well as 95% confidence intervals by the number of years since baseline. Only a very small number of subjects was both followed and still at risk of developing diabetes for the full 6-year follow-up period presented, so the estimated difference in prevalence was not statistically significant in the fifth and sixth years of follow-up. Additional analyses showed that the reduction in the onset of diabetes was significantly greater among people in either the treatment or control group who were successful in achieving dietary and exercise goals than among people who did not achieve such goals. The intervention group lost significantly more weight than the control group during both the first and second years following baseline, although there was some weight regain during the intervention group in the second year of the study. There was also some improvement in other risk factors during the first year of follow-up, but data for subsequent years were not reported, so it is not known how well reductions in these other risk factors were sustained over the follow-up period.

A Markov model to estimate cost-effectiveness

A Markov model is composed of a set of defined states of health between which a patient can move over successive periods. Transition probabilities are used to allow a patient to move within and between these states of health. A patient can be in only one state of health at any time and can make only one transition per cycle. The cycle is a discrete period spent in each state of health before transition to a successive state of health. A relevant period is chosen for the length of the cycle and the cycles then link together to create a Markov chain. Length and quality of life may vary across the different states, and the total cost is determined by the occurrence or recurrence of different states and the length of time in various states.

Although the effectiveness of the intervention might differ in the UK from the results in Finland because of a range of social or cultural factors, estimation using the effectiveness results in combination with estimates of UK costs provides a useful benchmark. *Figure 248* depicts the simplified Markov model used to estimate the cost-effectiveness of a lifestyle intervention similar to the one studied by Tuomilehto and colleagues. The model enables estimation of a typical patient's costs and outcomes for the lifestyle treatment versus no intervention (beyond provision of standard information) over a defined period. The Markov model includes a number of considerations, as described below.

- For both the intervention and control treatment groups, the Markov model embodies four different states: a state of impaired glucose tolerance; a state of onset of type 2 diabetes, a state of continuing type 2 diabetes; and death.

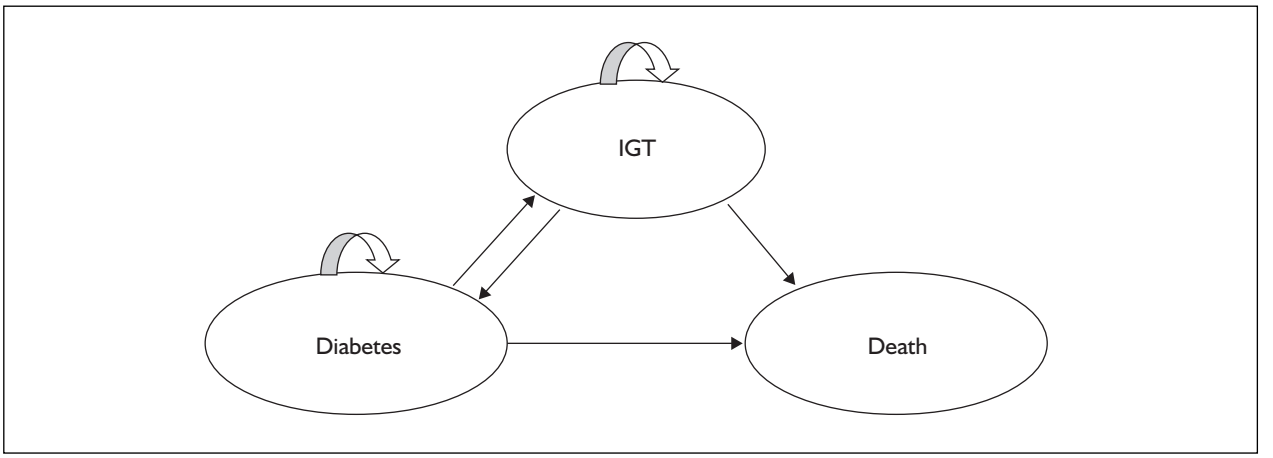

FIGURE 248 *Simplified Markov model states for lifestyle treatments for people with IGT*

(*Figure 248* combines the states of onset and continuing diabetes for simplicity.)

- The length of each period in the model is 1 year.
- All people start the model with IGT. They may leave to the state of onset of diabetes or to death according to specified transition probabilities.
- Revision from the state of diabetes (onset or continuing) to IGT is allowed, but is assumed to have a very small likelihood (1%) based on data from Segal and colleagues.[316]
- For simplicity, the possibility of exit from IGT or diabetes to a state of NGT is not incorporated into the model. Such a transition is possible and was incorporated into the model by Segal and colleagues.[316] Therefore, the current model provides a conservative estimate of the cost-effectiveness.
- Death is the only absorbing state in the model (i.e. the only state from which people cannot exit). The probability of death is based on a person's age, gender and diabetes status. The probability of death increases with age and with the onset of diabetes.
- The lifestyle intervention does not have the states of complications that would accompany a drug or surgical intervention. Complications from any other treatments for diseases are assumed to be reflected in the expected costs associated with being in each state.

Although weight loss is not explicitly incorporated into the model, weight loss has the potential additional benefit of reducing the risk of co-morbidities (and associated undesirable associated effects such as reduction in quality of life, increased use of healthcare resources and increased risk of death). Implications of impacts on other diseases besides diabetes are considered in sensitivity analyses.

DATA 4.0 software (TREEAGE Software), was used to estimate the Markov models using cohort analysis (rather than Monte Carlo simulation). The remainder of this section discusses the transition probabilities, outcome estimates (e.g. quality of life within a state) and costs that were used in the estimation of the model.

Transition probabilities

The two key probabilities for the model are rates of onset of type 2 diabetes and mortality rates. Transition rates from the IGT state to diabetes for up to 6 years of follow-up were constructed from *Table 16*. As stated above, the assumed rate of return to the state of IGT from diabetes was conservative at 1% per annum.

UK mortality rates by age group, gender and cause of death were obtained for 1997 from WHO.[326] More recent death rates are available from UK sources, but the WHO data enabled an adjustment in the death rate according to evidence that mortality rates from CVD are significantly higher for people with diabetes than for people without diabetes. Lee and colleagues[327] used meta-analysis methods to show that the relative risk of coronary death from diabetes was 2.58 (95% CI 2.05 to 3.26) for women and 1.85 (1.47 to 2.33) for men. These relative risk rates were used to adjust the mortality rates separately for persons with diabetes.

Outcomes data

The Markov model used a quality of life adjustment figure to weight the length of time spent in each state of health. The summation of time spent in each health state provided QALYs.

The literature pertaining to quality of life for obese people and to changes in quality of life from weight loss itself has expanded rapidly as a result of interest in the topic. Kolotkin and colleagues[328] provided a review literature from MEDLINE since 1990 on the relationship between quality of life and obesity. One major limitation, particularly for the problem at hand, is that it is difficult to separate reductions in health-related quality of life due to obesity itself from reductions due to other diseases that have a high prevalence among obese people.[329]

For this simple model, the most important distinction in qualify of life has to do with differences due to diabetes. The preference score (on a scale of 0 to 1) for diabetics of 0.90 was obtained from the Cost Utility Analysis database of Harvard University at www.hsph.harvard.edu/organizations/hcra/cuadatabase/intro.html/ This rate was slightly higher than the rate available for people with diabetes and congestive heart failure (0.87) and the rate for insulin-dependent diabetes mellitus (0.838). Unfortunately, this database does not include an estimate of quality of life for obese non-diabetic people. Clegg and colleagues[27] indicated that they could not find any estimates of health-related quality of life that are directly applicable to estimating QALYs for obese people, but they cite work indicating that under a "best case scenario" an obese person might have a quality of life of 0.94, and that an obese person losing 10% or more of their weight might have an increase in the score to 0.99. A rate of 0.96 (in the middle of this range) was arbitrarily selected for the base-case analysis for people in the IGT state, and sensitivity analyses are used to assess the implications of different QALY weights. As specified in UK guidelines for conducting health technology assessment,[330] QALYs were discounted using a rate of 1.5% per annum.

Costs

Estimates of three types of costs were required: lifestyle intervention costs, health service costs for people with diabetes and health service costs for people with IGT. Since Tuomilehto and colleagues described their intervention clearly, the intervention costs are relatively easy to estimate. Based on unit costs of healthcare calculated for the UK for 2001,[324] the dietitian cost per visit was estimated at £32. The same cost was assumed for the person leading the exercise classes, although it was assumed that these were group sessions with 20 people, that only 60% of the group attended two sessions per week during the first year and that only 30% attended during the subsequent years. The total estimated costs were £324 per person in the first year and £178 per person per subsequent year.

Lacking any data on specific health service use by study participants (intervention or control), it is necessary to use very rough estimates of direct healthcare costs. The CODE 2 study[325] estimated that the total direct healthcare costs for someone with diabetes averaged £1505. Using this average for each year of the model could be problematic if healthcare costs are relatively low at onset and increase over time. An analysis of the pattern of diabetes costs over time among persons with diabetes in a managed care setting in the USA showed, however, that among diabetics costs were substantially higher in the first year of treatment for diabetes than they were during the subsequent 9 years of treatment.[331] Higher first year costs seem likely given that people may be hospitalised at the onset of their diagnosis of diabetes and will require substantial education to learn how to care for themselves. Therefore, defining onset as the first year of treatment (although the disease may have been developing over several years before this), the costs for the year of onset of diabetes were set at one and a half times the rate of £1505 (which was used as the rate for all subsequent years of continuing diabetes treatment). These annual costs are higher than those indicated in other studies,[2,87] but the estimates from those other studies may be affected by such other factors as study inclusion criteria, estimation methodology or recent changes in technology.

Obtaining estimates of healthcare costs for people with IGT was much more difficult. A different study in a managed care setting indicated that healthcare expenditures per person with diabetes were 2.4 times more than were expenditures for a group of control subjects matched by age and gender.[332] While this ratio may not represent the specific ratio for people with IGT relative to those with diabetes and may also reflect differences in treatment patterns between the USA and the UK, the fact that matching was used means that some differences (aside from diabetes status) are controlled. Therefore, the costs for people in the IGT state were calculated at £1505 divided by 2.4, or roughly £627 per year.

Three other points about costs are relevant. First, substantial evidence indicates that healthcare costs increase dramatically during the last year of life. Therefore, a multiple of three times the annual costs of treatment for persons with diabetes was

TABLE 17 *Base-case results for a lifestyle (diet and exercise) intervention*

Years since baseline	Strategy	Cost per person	Incremental cost per person	QALYs per person	Incremental QALYs per person	ICER (Cost per additional QALY)
1	No intervention	£1,019		0.937		
	Diet & exercise	£1,287	£268	0.939	0.002	£113,905
2	No intervention	£1,779		1.849		
	Diet & exercise	£2,121	£342	1.856	0.007	£50,440
3	No intervention	£2,559		2.739		
	Diet & exercise	£2,949	£390	2.752	0.013	£29,903
4	No intervention	£3,313		3.608		
	Diet & exercise	£3,769	£456	3.627	0.019	£23,732
5	No intervention	£4,165		4.452		
	Diet & exercise	£4,665	£500	4.478	0.026	£19,049
6	No intervention	£5,023		5.273		
	Diet & exercise	£5,508	£485	5.309	0.036	£13,389

added to costs for people who died. Second, screening costs for IGT were not included separately, although they should be reflected in the estimated costs for diabetics and people with IGT. Third, the dropout rates in the Finnish study were only 7% at 2 years, compared with dropout rates between 40 and 48% in some of the trials of orlistat or sibutramine. Therefore, the internal validity of the estimates may be much higher from the Finnish study than from some of the other intervention studies reviewed in this report.

All costs are presented in 2001 UK pounds sterling. As specified in UK guidelines for conducting health technology assessment,[330] costs were discounted using a rate of 6% per annum. The perspective used in the analysis was that of the healthcare purchaser. Indirect costs attributable to obesity (e.g. costs of absence from work and of premature death) were not included. For readers interested in the potentially huge indirect costs of obesity, a report by the UK National Audit Office provides estimates.[2]

Results

Base case results

The tree representing the Markov model for the base-case analysis is provided in Appendix 38. The base-case estimates are presented in *Table 17* for a 6-year follow-up period, which was the length of follow-up available in the study published by Tuomilehto and colleagues. The base-case estimates are presented for a cohort of individuals starting at the age of 55 years (the mean age at entry into the study) with the same gender distribution from the study (33% male). The ICER, or cost per additional QALY, was £13,389 at 6 years following baseline.

Incremental costs between the intervention and treatment groups initially increase with length of follow-up, but at a decreasing rate. The incremental cost reaches a maximum in year 5 following baseline and then starts to decline, because the differential (greater) accumulation of people with diabetes and associated costs in the control group is more than offsetting the continuing lifestyle intervention costs. In contrast, the increment in QALYs increases during each year of follow-up because the rate of onset of diabetes is lower for people in the treatment group, although the absolute magnitude of the estimated increase in QALYs per person at 6 years following baseline is modest at 0.036. The initially high incremental cost per additional QALY of £113,905 occurs because of the initial investment in lifestyle change therapies in the intervention group, but the initial expenditures are subsequently offset by reduced disease treatment costs for the intervention group.

Sensitivity analysis: precision of estimates of transitions to diabetes

Table 16 showed that the confidence intervals around the transition rates become quite large beyond the fourth year of the intervention owing

to the small number of people that were followed for that duration and were still at risk of diabetes. Formal sensitivity analysis could be used to characterise the uncertainty in these estimates; however, results from another study published very recently corroborate these estimates.[255–257] In this study, 3234 non-diabetic people with IGT were randomly assigned to a lifestyle intervention (similar in focus to the one studied by Tuomilehto and colleagues[167–171] but with more initial intervention, including behaviour therapy and less reinforcement in subsequent years), metformin or a placebo. The mean follow-up was 2.8 years, but 1510 subjects were followed for 3 years and some participants were followed for 4 years. The results indicated that the lifestyle intervention reduced the incidence of diabetes by 58% overall during the follow-up period (while metformin only reduced the incidence by 31%) compared with the placebo. These very similar results from a much larger study mean that the findings by Tuomilehto may be very robust (both over time and across cultures). Therefore, the future analyses possible once longer follow-up data are available may be more relevant than detailed assessments of the implications for uncertainty in the estimates of the fifth and sixth years of data.

For assessment purposes, the ICER was calculated under two extreme value situations: (1) a pessimistic approach assuming the upper bound of the 95% confidence interval for the intervention group and the lower bound for the control group to the end of the fourth year of follow-up; and (2) an optimistic approach assuming the converse (the lower bound for the intervention group and the upper bound for the control group). The pessimistic analysis resulted in a cost of £310,593 per QALY gained for the lifestyle intervention versus control at the fourth year of follow-up. The optimistic analysis resulted in a cost of £253 per QALY gained at the fourth year of follow-up.

Sensitivity analysis: cost of intervention

The cost of the intervention was purposefully done using high rather than low estimates of cost. For example, the sessions with the dietitian were all assumed to require a full visit (ostensibly an hour). In reality, however, sessions after the first few meetings might take on average only half an hour. The analysis was rerun assuming that the intervention costs were two-thirds of the values used in the base case (£324 for the first year and £178 for subsequent years). This analysis resulted in a cost per additional QALY of £4027 at 6 years after baseline (or less than one-third of the incremental cost per QALY for the base-case analysis).

Sensitivity analysis: length of follow-up

Since the follow-up time in the study by Tuomilehto and colleagues was limited to 6 years, any estimation of the cost-effectiveness beyond 6 years is based entirely upon assumptions and is therefore very speculative. Furthermore, the fact that weight is often regained within 5 years following many of the lifestyle (as well as drug) trials reviewed earlier means that a high degree of caution should be applied in extending the results.

Given these caveats, *Figure 249* depicts the ICER over 15 years following intervention under the relatively conservative assumption that after 6 years both the intervention and control groups have the same annual rate of onset of diabetes. The rate used is the average rate per year for the 6 years of follow-up for the control group (approximately 7.2% per year), even though the intervention group is assumed to continue to meet with a dietitian four times a year. Under this assumption, the incremental cost per additional QALY continues to decline from £13,398 in year 6 to £5,825 in year 15. The rate of decline in the incremental cost per QALY tapers off considerably, however, by year 15.

If intervention group members continue to have a lower rate of onset of diabetes, then the curve in *Figure 249* would decline rapidly after year 6 and conceivably the intervention could dominate (i.e. have lower total costs and greater total effects than the control group) at some point. Yet such an outcome is only speculative, and it is also conceivable that the intervention may have only delayed rather than permanently avoided the onset of diabetes, in which case the incremental cost per QALY could conceivably increase at some point (although a more modest decline is the most likely scenario).

Sensitivity analysis: quality of life

Other parameters in the model that were subject to a great deal of uncertainty were the quality of life weights for diabetic and non-diabetic obese people. The model was re-estimated using a lower value for people with diabetes (a decrease of 0.03 to 0.87, which is the rate cited earlier for people with diabetes and CVD) and a higher value for those without diabetes (an increase of 0.03 to 0.99, which was considered earlier as a possible upper bound for people who are obese but not suffering from other severe diseases). The incremental cost per QALY at 6 years after baseline was £6933, or

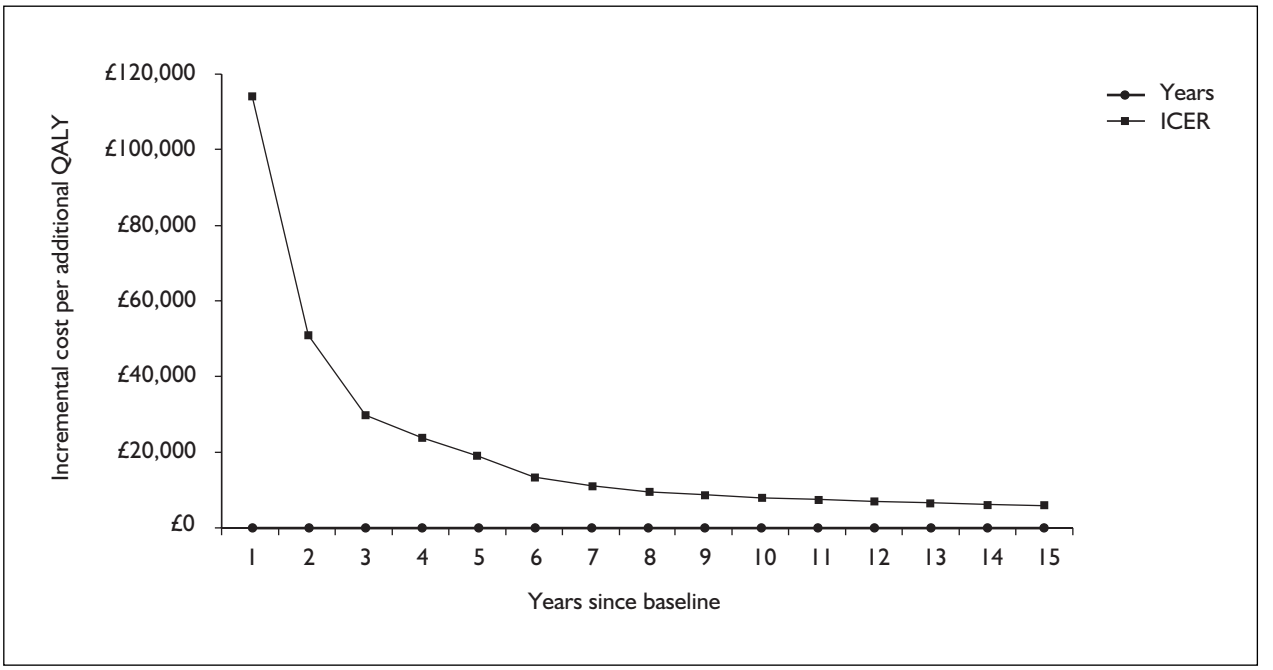

FIGURE 249 *Sensitivity analysis of extending modelling time*

almost half of the incremental cost per QALY from the base-case analysis. The magnitude of the change in the incremental cost per QALY illustrates the substantial effect that very modest changes in the value used for quality of life can have on the estimated cost-effectiveness.

Discussion

Ideally, the model estimated in this report would not only have addressed impacts on the onset of diabetes, but also have considered the impact of the lifestyle intervention on hypertension, hypercholesterolaemia and subsequent CVD. The main challenge in incorporating these considerations in economic evaluations of treatment for obesity is that it is very difficult to estimate what long-term effects may accrue from short-term weight loss or reduction in risk factors, especially since such factors often deteriorate following initial improvements. In particular, it may be best not to include gains from reduced hypertension, because of lack of evidence that the effects on hypertension are long lasting rather than transient,[278] and therefore benefits may accrue only to a self-selected group of participants who are more likely to participate in long-term lifestyle modification.[208]

The estimates provided from this economic model were conservative in a number of ways. The focus has been on the implications of lifestyle intervention for the onset of diabetes, but much overlap exists between the medical conditions associated with obesity. People with diabetes often have increased lipids and blood pressure, and reductions in lipids and blood pressure will not only decrease CVD, but also have additional benefits regarding diabetes. In total, therefore, the benefits in terms of reduced costs and improved quality of life have probably been underestimated in the model presented here, in which case the results provide an upper bound on the cost-effectiveness of lifestyle interventions.

The modelling results may also be put into perspective by comparison with the summary of systematic review results in *Table 15*. The estimated base-case 6-year incremental cost per QALY of £13,389 is only slightly higher than most of the lifetime ICERs estimates in *Table 15* (some of which are for life-years saved rather than additional QALYs). Subsequent declines in the incremental cost per QALY for a longer modelling horizon beyond 6 years mean that the attractiveness of lifestyle interventions may increase relative to other interventions. Considerations that reinforce this point include the implications of high dropout rates in some of the studies and the fact that the modelling presented here excludes benefits from reductions in CVD that probably accompany the observed benefits in reduced onset of diabetes.

The key contribution of the recent studies of lifestyle interventions[167–171,255–257] and the economic modelling results is that lifestyle interventions should clearly be among the set of treatment options considered for obese individuals with certain high-risk factors. However, further investigations will be important regarding two other important issues. First, no single treatment option is likely to be best for all individuals. For example, surgery may be the only effective and cost-effective solution for certain types of morbidly obese individuals. Therefore, a broader understanding of the incremental cost-effectiveness of different treatments for different subgroups of high-risk individuals is ultimately desirable. Second, the fact that certain treatments are cost-effective for high-risk individuals does not answer the question of the cost-effectiveness of the same interventions for lower risk obese individuals, whose treatment benefits may also be worth the cost. Resolution of that question will require, however, a better understanding of: (1) the implications of relatively short-term weight loss and improvement in risk factors (including cycling in such measures) for long-term health outcomes; and (2) the implications of both short-term and long-term weight change for quality of life.

Chapter 6
Conclusions

Implications for practice

In general, drug trials provided the clearest pointers for the management of obesity in adults, mainly because they were larger and as such had greater statistical power to detect outcomes, unlike non-drug studies. Results of trials of orlistat showed slightly less weight loss, but a more beneficial effect on risk factors than sibutramine. Metformin, however, was the only drug evaluated over more than 2 years that was able to examine effects on mortality. Metformin was the only drug that was associated with beneficial effects on mortality in obese diabetics.

There were very few data on risk factor changes for diets, particularly beyond 12 months, other than for the 600 kcal/day deficit or low-fat diet, despite some suggestion that VLCDs and LCDs may provide greater weight loss. The 600 kcal/day deficit or low-fat diet highlighted clear benefits on weight, risk factors and clinical outcomes, such as the prevention of diabetes and improvement in hypertension, and effects appeared to persist for up to 3 years.

Exercise or behaviour therapy added to diet was associated with increased weight loss, including after 12 months. The FDPS[167–171] provided evidence that diet and exercise together could prevent type 2 diabetes. There was no comparable evidence available for the effect of a diet and behaviour therapy without exercise on diabetes. Exercise programmes and behaviour therapy are not well established for the management of obesity in the NHS at all levels of care. Consideration needs to be given to how the interventions used in the trials described here could be implemented in the UK, given that the trials were mostly undertaken in the USA or Scandinavia. Exercise and behaviour therapy are not necessarily mutually exclusive, although the very limited current evidence would suggest exercise as the first approach.

Although the effect of exercise and behaviour therapy added to diet on weight and risk factors was less clear, the TONE,[210–224] TOHP I and II studies[197–209] demonstrated benefit on clinical outcomes, such as hypertension, from behaviour therapy and exercise added to a 600 kcal/day deficit or low-fat diet.

The epidemiological review analysed specific outcomes to assess the long-term effect of weight loss on mortality and co-morbidities associated with obesity. Intentional weight loss appeared to reduce significantly all types of mortality for women if they had obesity-related illness. However, the same was not found for men, where surprisingly, weight loss did not appear to be associated with a reduction in mortality due to CVD, and an increased risk of mortality due to cancer was observed. The primary exception was for diabetes-related deaths, for which weight loss was associated with a reduction in mortality in both men and women. The reason for this gender divide is unclear, but may be related to the fewer visits to a doctor by men. The striking difference in men with diabetes is the decrease in diabetes-related mortality, which may be due to attendance at their doctor for diabetes therapy.

Weight lost more quickly (i.e. within a year) in an epidemiological framework may be beneficial with respect to risk of mortality. The amount of weight loss investigated (more than or less than 9 kg) does not seem to have an additional effect on mortality, indicating that it is likely to be the weight loss itself that may be beneficial.

The epidemiological review also found that weight loss from surgical interventions in the obese was associated with a decrease in the risk of developing diabetes, more so than with non-surgical therapies. However, there was an indication that those who initially lost weight and then regained their weight may have an increased risk of developing diabetes. Although weight losses were generally associated with drops in glucose levels (that is, there was a positive relationship) this was not reliable enough to define in an equation useful for prediction.

There was also a relationship between weight loss and reduction in LDL and total cholesterol. Modelling estimated that a loss of 10 kg may lead to a reduction in total cholesterol of 0.25 mmol/l, which equates to a fall of 5% in cholesterol (which is half that previously quoted in guidelines).[17] This appears to be a long-term benefit.

Significant weight losses were also associated with reductions in blood pressure. The regression model estimated that a 10 kg loss was associated with a 3.6 mmHg reduction in DBP. The best fitting regression model for SBP related not to absolute weight loss but to percentage weight lost, such that a 10% loss was predicted to result in 6.1 mmHg reduction in SBP. Once again, this is lower than that previously quoted in guidelines,[17] where 10 kg loss was linked with a 10 mmHg fall in both DBP and SBP. The current review suggested that in surgical studies with large weight losses there was a levelling off of benefit after a certain weight loss. The longer follow-up (e.g. 8 years) in surgical studies could indicate a gradual creeping upwards of the blood pressure, in contrast to that seen for glycaemic control which maintains a benefit.

Sleep apnoea also appeared to be improved with weight loss, especially in people after obesity surgery. It is regrettable that there is very little hard evidence regarding the importance of weight loss to the risk of stroke, which remains undefined.

Psychological well-being as a measure of health would appear to improve with weight loss in those with obesity, with less negativism and introversion after weight loss.

With the costly implications of obesity for the development of diseases such as type 2 diabetes and CVD, the systematic review of economic evaluations suggested that targeting high-risk individuals was likely to result in a cost per additional life-year or QALY of no more than £13,000. This return on the use of healthcare resources is comparable to many other disease treatments.[23,24] There is also suggestive evidence of cost-saving from treatment of people with type 2 diabetes with metformin.[87] Targeting of surgery to morbidly obese people with impaired glucose tolerance is likely to be very cost-effective at £2329 per additional life-year.

Economic modelling of diet and exercise treatment over 6 years for people with IGT demonstrated high initial cost per additional QALY, but by year 4 the cost per QALY was £29,903 and by year 6 the cost per QALY was £13,389. The latter figure is comparable to the figure derived from the economic systematic review given above. A sensitivity analysis adopting a pessimistic approach gave a cost per QALY of £310,593 for year 4, while an optimistic analysis gave a figure of £253 per QALY for year 4. Assuming lower costs for the intervention produced a cost per additional QALY of £4027 at year 6, and assuming a greater impact on quality of life produced a cost of £6933 at year 6. However, these costs assume only reductions from the treatment of diabetes, and do not include potential savings from other diseases, such as hypertension. As such, estimated cost savings are likely to be conservative.

Lifestyle interventions, such as diet and exercise, appear to be comparable to other treatment options, such as drug treatment, in obese individuals with risk factors such as IGT.

Recommendations for research

Research on obesity

- More RCTs and epidemiological studies are needed in high-risk populations, particularly people with co-morbidities, cardiovascular risk factors or BMI > 40 kg/m^2. Research should also examine the influence of age, ethnic group and gender on outcomes.
- More studies are need in primary care in high-risk groups.
- Drug trials should include lifestyle interventions, such as behaviour therapy and exercise, in addition to dietary advice as standard management. As the prescription of drugs for the management of obesity may be limited by time, drug trials should follow up participants after they stop taking the drug.
- There was insufficient time in this review to examine the effects of exercise or behaviour therapy alone, which should also be reviewed for the treatment of obesity.
- Further exploration of the treatments for obesity is required to answer: what type of exercise or behaviour therapy is best, what frequency of contact is best, what type of diet in the long term is most beneficial, and what is the role for booster sessions? More research is needed to examine how high dropout rates in studies can be explained, reduced and accounted for in the analysis.
- As the review of RCTs was limited to adults with a BMI ≥ 28 kg/m^2, it has not assessed the interventions examined in this systematic review for people with lower BMIs, that is, for the prevention of obesity. The authors strongly recommend that such a review be undertaken, which would include community interventions that have been excluded by this BMI cut-off or by the fact that they were not RCTs.
- A clearer understanding of the incremental cost-effectiveness of different treatments for subgroups of high-risk individuals, e.g. surgery

for people with morbid obesity, is desirable. The cost-effectiveness of interventions for lower risk obese individuals should also be examined. To answer this question the implications of relatively short-term changes in weight and risk factors (including cycling in such measures) for long-term health outcomes and quality of life need to be determined.

Methodological research

- Future RCTs should have adequate statistical power to determine long-term outcomes, which should include not only weight, but also risk factors, morbidity and mortality, quality of life and economic outcomes.
- The methodological quality of trials should be improved and the results should be reported according to the guidelines of the CONSORT statement.[249] Greater efforts should be made to follow up participants in the RCTs. Sensitivity analyses should be undertaken to examine whether the assumptions used for this report to estimate missing parameters influenced the results. Triallists should report standard deviations or standard errors to allow data variability to be assessed and, where possible, as differences between two time-points.
- For future epidemiological studies, methods and definitions need to be more clearly agreed and defined. Long-term prospective studies also require adequate statistical power and consistent adjustments. The follow-up strategies with respect to time and the numbers of people were extremely varied and would benefit from a standard format. The CONSORT statement[249] could also be used as a starting point for guidelines for these long-term prospective studies. Within such guidelines there should be provision for long-term follow-up.
- Research and funding bodies should be committed to structured long-term follow-up strategies so that the long-term effects of short-term interventions can be assessed accurately.

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Contribution of the authors

Professor Iain Broom, Professor Adrian Grant, Professor Roland Jung, Professor Cairns Smith and Dr Alison Avenell (Clinical Research Fellow) initiated the project; Professors Broom and Jung chaired the project group. Dr Alison Avenell and Ms Tamara Brown conducted the systematic review of RCTs. Dr Lorna Aucott (Medical Statistician) and Dr Amudha Poobalan (Research Fellow) conducted the review of epidemiological studies and undertook epidemiological modelling. Dr Sally Stearns (Senior Research Fellow) reviewed the health economic literature and provided the economic model. Dr Marion Campbell (Reader) provided methodological advice. All authors helped to draft the final report.

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Appendix 1

Protocol for systematic review of RCTs

Objectives

- To review systematically treatments for the prevention and management of obesity in adults
- to examine the effect of interventions compared with no intervention
- to examine the effect of adding extra interventions, such as behaviour therapy, drugs or exercise
- to evaluate treatments from the perspective of the UK NHS.

Criteria for considering studies for this review

Types of studies

Information will be sought from RCTs of at least 1 year's duration, where the control group receives a placebo or no intervention. Comparisons between different interventions will also be examined. Only interventions that are specifically designed to produce weight loss and/or prevent weight gain will be examined. Interventions where weight loss is produced coincidentally as a result of dietary changes made, for example higher fruit and vegetable consumption to lower blood pressure, will not be examined. Trials where weight loss is the desired outcome and/or the intervention, for example to reduce a risk factor for CHD, will be examined.

Types of participants

Interventions in adults from the age of 18 years upwards will be examined. There will be no upper age limit. The following information will be recorded:

- gender of participants
- smoking status
- age
- social class
- ethnic group
- whether intervention had been specifically targeted at people with the following conditions
  - diabetes
  - hypertension
  - hyperlipidaemia
  - binge eating

  according to the definitions used by the investigators
- BMI [weight in kg/(height in m)^2], weight and height
- waist circumference.

The following will be excluded:

- studies on people with bulimia nervosa
- studies on women who are pregnant
- studies in which the average BMI is $< 28\,kg/m^2$ for all groups combined.

Types of interventions

The following interventions, lasting for any period, will be examined provided there are follow-up data provided at least 1 year after the interventions started:

- drugs, including
  - pancreatic lipase inhibitor: orlistat (Xenical)*
  - SSRIs, e.g. fluoxetine (Prozac)*
  - fibre-containing bulking agents, e.g. methylcellulose (Celevac), bran (Trifyba), isphagula husk (Fybogel, Konsyl, Isogel, Regulan), sterculia
  - cholecystokinin receptor antagonists
  - centrally active appetite suppressants, e.g. sibutramine* (Reductil, Meridia), dexfenfluramine, fenfluramine, diethylpropion, phentermine, mazindol, phenylpropanolamine
  - leptin*
  - thyroid hormones
  - α-glucosidase inhibitor: acarbose (Glucobay)
  - biguanides, metformin (Glucophage)*
  - topiramate (Topomax)
  - catecholaminergic appetite suppressants, e.g. H_2 receptor antagonists, e.g. cimetidine (Tagamet)
  - cholestyramine, diethyl aminoethyl dextran
  - ephedrine*
  - caffeine*
  - atypical β-adrenergic agonists
  - growth hormone*

- physical activity
  - endurance exercise
  - resistance training
- behavioural interventions
  - cognitive behavioural therapy
  - others, e.g. motivational interviewing
- obesity surgery
  - liposuction
  - intragastric balloon
  - jaw-wiring
  - producing malabsorption e.g. jejunoileal bypass
  - gastric restriction only, e.g. vertical stapled gastroplasty with banded outlet, gastric banding, Roux-en-Y gastrojejunostomy*
  - apronectomy.

  *If no data are available from RCTs for these key interventions, information will be sought from the following categories of studies (data in descending order of importance):

  - quasi-randomised study (at least 1 year of follow-up)
  - intervention study with concurrent control group (at least 1 year of follow-up)
  - intervention study with historical control group (at least 5 years of follow-up)
  - intervention study with no control group (at least 5 years of follow-up)

- complementary medicine including
  - hypnosis
  - acupuncture
  - herbal remedies
  - homeopathy
  - reflexology
  - aromatherapy
  - vibration therapy
- diets
  - healthy eating
  - 600 kcal/day deficit or low fat
  - low calorie (1000–1600 kcal/day)
  - very low calorie (<1000 kcal/day)
  - protein sparing (≤ 40 g of carbohydrate/day)
  - low carbohydrate, high monounsaturated fat
  - salt restriction (where compared with weight loss).

Combinations of different therapies, for example weight loss versus sodium restriction, will also be examined.

Types of outcome measures

Data on the following outcome measures will be extracted:

- mortality
  - all cause
  - CHD
  - CVD
  - cancer (all cause), breast cancer, colorectal cancer
- morbidity
  - CHD
  - CVD
  - diabetes mellitus
  - cancer (all cause), breast cancer, colorectal cancer
  - musculoskeletal (all causes)
  - psychological (all causes)
  - days off work
  - GP consultations
- participant satisfaction and quality of life
- economic outcomes
- weight loss, however measured at the start and at each time interval, e.g.
  - body weight (kg)
  - weight change (kg)
  - Percentage weight change:
    - ≤ 5% of starting weight
    - 6–10% of starting weight
    - 11–20% of starting weight
    - >20% of starting weight
  - BMI (kg/m^2)
  - change in BMI
  - percentage change in BMI
  - waist circumference
  - change in waist circumference
  - percentage change in waist circumference
- blood lipids (noting whether fasted or not)
  - total cholesterol
  - LDL cholesterol
  - HDL cholesterol
  - triglycerides
- SBP and DBP
- blood glucose control
  - HbA_{1c}
  - fasting plasma glucose
- psychological health ratings
  - Nottingham Health Profile
  - Hospital Anxiety and Depression Score
- number of dropouts at each period
- times of follow-up in the study
- compliance with treatment
- adverse events.

Search strategy for identification of studies

Electronic database searching

An electronic database search will be undertaken using:

- MEDLINE
- EMBASE
- BIOSIS
- Commonwealth Agricultural Bureau Nutrition Abstracts and Reviews
- Cochrane Controlled Trials Register, including Database of Abstracts of Reviews of Effectiveness (DARE) (CRD database of systematic reviews)
- PsycINFO
- Web of Science
- UK National Research Register
- CINAHL
- HealthSTAR
- AMED
- SPORTDiscus
- British Library Inside.

Handsearching

The following journals, including conference abstracts, will be handsearched:

- *International Journal of Obesity*, Volume 1 1977 to Volume 25 (Suppl 1) 2001
- *Obesity Research*
- *Obesity Surgery*, Volume 1 (1–4) 1991 to Volume 7 (1–6) 1997
- *American Journal of Clinical Nutrition*, Volume 18(5–6) 1966 to Volume 73(2S) 2001
- *Proceedings of the Nutrition Society*, Volume 19 1960 to Volume 59 (Oral Communications Booklet) 2000
- *Journal of Human Nutrition and Dietetics*, Volume 1 1988 to Volume 14(1) 2001
- *Journal of the American Dietetic Association*, Volume 77 1980 to Volume 90 1990

Data from abstracts will be used only if the authors are able to provide full details of the study.

Further searching

- The reference lists of previous trials and review articles will be searched.
- Books and reports covering the topic of obesity will be searched.
- Trials will be sought by communicating with experts in the field and trialists.
- Biomedical companies will be contacted for details of any other relevant RCTs, published or unpublished.
- No language restriction will be applied to eligible reports.
- Searching for references will finish at the end of April 2001. However, the following journals will be handsearched from January to the end of June 2001:
  - *International Journal of Obesity*
  - *Obesity Research*
  - *Obesity Surgery*
  - *American Journal of Clinical Nutrition*
  - *Proceedings of the Nutrition Society*
  - *Journal of Human Nutrition and Dietetics*
  - *Journal of Consulting and Clinical Psychology*
  - *Lancet*
  - *British Medical Journal*
  - *Journal of the American Medical Association*
  - *Annals of Internal Medicine*
  - *New England Journal of Medicine*
  - *Archives of Internal Medicine*.

Methods of the review

Identification of possible RCTs

All possible RCTs will be entered into Reference Manager version 9. Subject keywords and source of the article will be added.

Register of RCTs

A sample of all abstracts and study titles will be independently read by two researchers to assess subject relevance. Researchers will discuss all studies which either researcher has difficulty in assessing. RCTs relevant to the review will be assigned specific keywords on Reference Manager and the full published paper obtained or authors contacted for the full report.

Quality assessment of studies

Full copies of the first 20 studies will be independently assessed by two researchers using a standard form for quality assessment. Differences of opinion will be resolved by discussion. Thereafter, if appropriate, one researcher will assess other studies, and a second reviewer will check the data. Quality assessment will include:

- quality of random allocation concealment
- ITT analysis
- blinding of outcome assessors
- treatment and control group comparability
- comparability of other care between groups
- inclusion and exclusion criteria clearly defined
- participant blinding to allocation
- description of withdrawals and dropouts
- self-reported or objectively measured weight
- dropouts, ≤ 50% or not.

Data abstraction

Data will be abstracted independently by two researchers for the first 20 studies and any differences will be resolved by discussion. Thereafter, one researcher will assess other studies, if appropriate, and a second reviewer will check

the data. Only comparisons and outcomes identified a priori in the protocol will be included. Authors will be contacted for further details of their studies if required.

Data analysis

Where results from studies can be quantitatively combined, a statistical meta-analysis of the data will be undertaken. For dichotomous data an odds ratio will be derived, and for continuous data a WMD will be calculated (weighted by the inverse of the variance). Analyses will use a fixed effects approach. Evidence for heterogeneity across studies will be explored using the chi-squared test for heterogeneity.

Reporting

The review will be reported in the form used by the Cochrane Collaboration.

Reference

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309**:1286–91.

Appendix 2

Search strategies

In MEDLINE (1966 to 25 May 2001) and in HealthSTAR (1975 to December 2000), the first two levels of the standard Cochrane search strategy for RCTs were used, based on the strategy described by Dickersin (1994), with the following specific search terms:

1. obesity/
2. obesity in diabetes/ or obesity, morbid
3. hyperphagia/ or bulimia/
4. obes$.mp.
5. weight loss.mp.
6. overweight.tw.
7. (weight adj1 (maint$ or reduc$)).tw.
8. (los$ adj1 weight).tw.
9. (diet$ adj5 weight).tw.
10. (weight adj1 control).tw.
11. or/1-10
12. limit 11 to (newborn infant <birth to 1 month>or infant <1 to 23 months> or preschool child <2 to 5 years>or child <6 to 12 years> or adolescence <13 to 18 years>
13. 11 not 12.

Reference

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309**:1589–92.

In EMBASE (1980 to Week 19 2001) the following specific search terms were used:

1. Multicenter Study/
2. phase 2 clinical trial/
3. phase 3 clinical trial/
4. phase 4 clinical trial/
5. randomized controlled trial/
6. meta analysis/
7. crossover procedure/
8. double blind procedure/
9. single blind procedure/
10. randomization/
11. placebo/
12. drug comparison/
13. clinical study/
14. or/1-13
15. nonhuman/
16. (clin$ adj25 trial$).tw.
17. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
18. placebo$.tw.
19. random$.tw.
20. control$.tw.
21. or/16-20
22. 14 or 21
23. 22 not 15
24. obesity/
25. diabetic obesity/
26. morbid obesity/
27. hyperphagia/
28. bulimia/
29. obes$.mp.
30. weight reduction.mp.
31. overweight.tw.
32. (weight adj1 (maint$ or reduc$)).tw.
33. (los$ adj1 weight).tw.
34. (diet adj5 weight).tw.
35. (weight adj1 control).tw.
36. or/24-35
37. 23 and 36
38. limit 37 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
39. 37 not 38

In the Commonwealth Agricultural Bureau Nutrition Abstracts and Reviews (1973 to December 2000) the following specific search terms were used:

1. exp man/
2. random$.tw.
3. trial$.tw.
4. placebo$.tw.
5. volunteer$.tw.
6. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
7. or/2-6
8. 1 and 7
9. obesity.mp.
10. overeating.mp.
11. overweight.mp.
12. overfeeding.mp.
13. weight reduction.mp.
14. obesity hyperglycaemia syndrome.mp.
15. weight losses.mp.
16. weight gain.mp.

17. or/9-16
18. 8 and 17
19. obes$.tw.
20. hyperphagi$.tw.
21. bulimi$.tw.
22. weight los$.tw.
23. (weight and maint$).tw.
24. (weight and reduc$).tw.
25. (los$ and weight).tw.
26. (diet$ and weight).tw.
27. (weight and control$).tw.
28. or/19-28
29. 17 or 29
30. 8 and 30

In BIOSIS (1985 to April 2001) the following specific search terms were used:

1. random*
2. trial*
3. placebo*
4. 1 or 2 or 3
5. human (major concept term)
6. 4 and 5
7. obes*
8. hyperphagi*
9. bulimi*
10. weight los*
11. overweight
12. weight and maint*
13. weight and reduc*
14. los* and weight
15. diet* and weight
16. weight and control*
17. or/7-16
18. 17 and 6

In CINAHL (1982 to March 2001) the following specific search terms were used:

1. exp clinical trials/
2. clinical trial.pt.
3. exp random sample/
4. random assignment/
5. research.pt.
6. (clin$ adj25 trial$).ti, ab.
7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti, ab.
8. Placebos/
9. Placebo$.tw.
10. Random$.tw.
11. Volunteer$.tw.
12. Or/1-11
13. Animal studies/
14. 12 not 13
15. obesity/
16. obesity, morbid/
17. hyperphagia/
18. bulimia/
19. obes$.tw.
20. weight loss.tw.
21. overweight.tw.
22. (weight adj1 (maint$ or reduc$)).tw.
23. (los$ adj1 weight).tw.
24. (diet adj5 weight).tw.
25. (weight adj1 control).tw.
26. or/15-25
27. 14 and 26
28. limit 27 to (fetus <conception to birth> or newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
29. 27 not 28

In AMED (1985 to April 2001) the following specific search terms were used:

1. randomized controlled trials/
2. random allocation/
3. double blind method/
4. exp clinical trials/
5. (clin$ adj25 trial$).ti,ab.
6. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
7. placebo.sh.
8. placebo$.ti,ab.
9. random$.ti,ab.
10. research design.sh.
11. trial$.tw.
12. or/1-11
13. obesity/
14. bulimia/
15. obes$.mp.
16. weight loss.mp.
17. overweight.tw.
18. ((weight adj1 (maint$ or reduc$)).tw.
19. (los$ adj1 weight).tw.
20. (diet$ adj5 weight).tw.
21. (weight adj1 control).tw.
22. or/13-21
23. 12 and 22

In SPORTDiscus (1949 to March 2000) the following specific search terms were used:

1. double blind method/
2. prospective study/
3. comparative study/
4. research design/
5. placebo/
6. (clin$ adj25 trial$).ti,ab.
7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
8. placebo$.ti,ab.
9. random$.ti,ab.

10. or/1-9
11. obesity/
12. hyperphagia/ or bulimia/
13. obes$.mp.
14. weight loss.mp.
15. overweight.tw.
16. (weight adj1 (maint$ or reduc$)).tw.
17. (los$ adj1 weight).tw.
18. (diet$ adj5 weight).tw.
19. (weight adj1 control).tw.
20. or/11-19
21. 10 and 20

In the UK National Research Register (2001, Issue 1) the following specific search terms were used:

1. obesity: ME
2. obesity-in-diabetes: ME
3. hyperphagia: ME
4. bulimia: ME
5. obes*
6. weight-loss: ME
7. (weight next loss)
8. overweight
9. (weight near maint*)
10. (weight near reduc*)
11. (los* near weight)
12. (diet* near weight)
13. (weight near control)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)

In the Cochrane Controlled Trials Register (2001, Issue 1) the following specific search terms were used:

1. OBESITY: ME
2. OBESITY-IN-DIABETES: ME
3. OBESITY-MORBID: ME
4. HYPERPHAGIA: ME
5. BULIMIA: ME
6. OBES*
7. WEIGHT-LOSS: ME
8. (WEIGHT NEXT LOSS)
9. OVERWEIGHT
10. (WEIGHT NEAR MAINT*)
11. (DIET* NEAR WEIGHT)
12. (WEIGHT NEAR CONTROL)
13. (WEIGHT NEXT REDUC*)
14. (LOS* NEXT WEIGHT)
15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
16. CHILD* : ME
17. (#15 NOT #16)
18. NEOPLASMS* : ME
19. (#17 NOT #18)

In British Library Inside (April 2001) the following specific search terms were used:

1. (obes$3 or overweight) and ((trial$1 or stud$3) and random$7) not (child$3 or rat$1 or mice or mouse or hamster$1 or porcine or murine)

In the Science Citation Index (April 2001) the following specific search terms were used:

1. (obes* or overweight) and ((trial* or stud*) and random*) not (child* or rat* or mice or mouse or hamster* or porcine or murine)

In PsycINFO (1967 to May 2001) the following specific search terms were used:

1. obes*
2. hyperphagia*
3. binge eating
4. bulimi* near non-purging
5. weight near1 los*
6. weight near1 control
7. overweight
8. weight near1 (maint* or reduc*)
9. diet* near5 weight
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
11. AG = “adolescence”
12. 10 and (AG = adolescence)
13. AG = “childhood”
14. 10 and (AG = childhood)
15. AG = “infancy”
16. 10 and (AG = infancy)
17. AG = “neonatal”
18. 10 and (AG = neonatal)
19. AG = “pre-school age”
20. 10 and (AG = pre-school age)
21. AG = “school-age”
22. 10 and (AG = school-age)
23. #12 or #14 or #16 or #18 or #20 or #22
24. 10 not 23
25. PO = “animal”
26. 24 and (PO = animal)
27. 24 not 26
28. PO = “human”
29. 24 and (PO = human)
30. 26 and 29
31. 27 or 30
32. clin* near25 trial*
33. (singl* or doubl* or trebl* or tripl*) near25 (blind* or mask*)
34. placebo*
35. random*
36. control*
37. #32 or #33 or #34 or #35 or #36
38. 31 and 37

Appendix 3

Reviews searched for RCTs

Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr* 2001;**74**:579–84.

Anon. Popular diets: a scientific review. *Obes Res* 2001; **9**(Suppl 1).

Astrup A, Rossner S. Lessons from obesity management programmes: greater initial weight loss improves long term maintenance. *Obes Rev* 2000;1:17–19.

Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. The role of low-fat diets in body weight control: a meta-analysis of *ad libitum* dietary intervention studies. *Int J Obes* 2000;**24**:1545–52.

Astrup A, Ryan L, Grunwald GK, Storgaard M, Saris W, Melanson E, *et al*. The role of dietary fat in body fatness: evidence from a preliminary meta-analysis of *ad libitum* low-fat dietary intervention studies. *Br J Nutr* 2000;**83**(Suppl 1):S25–32.

Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. *Obes Rev* 2000; **1**:113–19.

Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues. *Med Sci Sports Exerc* 1999; **31**:S646–67.

Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycaemic control and body mass in type 2 diabetes mellitus. A meta-analysis of controlled clinical trials. *JAMA* 2001;**286**:1218–27.

Brown SA, Upchurch S, Anding R, Winter M, Ramirez G. Promoting weight loss in type II diabetes. *Diabetes Care* 1996;**19**:648.

Douketis JD, Feightner JW, Attia J, Feldman WF, with the Canadian Task Force on Preventive Health Care. Periodic health examination, 1999 update: 1. Detection, prevention and treatment of obesity. *CMAJ* 1999; **160**:513–25.

Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *BMJ* 1997; **314**:1666–74.

Ebrahim S, Smith GD. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. *J Public Health Med* 1998;**20**:441–8.

Fagard RH. Physical activity in the prevention and treatment of hypertension in the obese. *Med Sci Sports Exerc* 1999;**31**:S624–30.

Fogelholm M, Kukkonen-Harjula K. Does physical activity prevent weight gain? A systematic review. *Obes Rev* 2000;**1**:95–111.

Foxcroft DR, Milne R. Orlistat for the treatment of obesity: rapid review and cost-effectiveness model. *Obes Rev* 2000;**1**:121–6.

Goldstein DJ, Potvin JH. Long-term weight loss: the effect of pharmacologic agents. *Am J Clin Nutr* 1994; **60**:647–57.

Harvey EL, Glenny A-M, Kirk SF, Summerbell CD. Improving health professionals' management and the organisation of care for overweight and obese people (Cochrane Review). In *The Cochrane Library* (Issue 1). 2002. Oxford: Update Software; 2002.

Hennrikus DJ, Jeffrey RW. Worksite intervention for weight control: a review of the literature. *Am J Health Promot* 1996;**10**:471–98.

Hermansen K. Diet, blood pressure and hypertension. *Br J Nutr* 2000;**83**(Suppl 1):S113–19.

Hooper L, Summerbell CD, Higgins JP, Thompson RL, Clements G, Capps N, *et al*. Reducing or modified dietary fat for preventing cardiovascular disease (Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2002.

Johanesen K. Efficacy of metformin in the treatment of NIDDM. *Diabetes Care* 1999;**22**:33–7.

Kelley DE, Goodpaster B. Effects of physical activity on insulin action and glucose tolerance in obesity. *Med Sci Sports Exerc* 1999;**31**:S619–23.

Kelley GA. Aerobic exercise and resting blood pressure among women: a meta-analysis. *Prev Med* 1999;**28**:265–75.

Ketola E, Sipila R, Makela M. Effectiveness of individual lifestyle interventions in reducing cardiovascular disease and risk factors. *Ann Med* 2000;**32**:239–51.

Kushner RF, Foster GD. Obesity and quality of life. *Nutrition* 2000;**16**:947–52.

Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. *Biometrics* 1996;**52**:1324–33.

Mertens IL,Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obes Res* 2000;**8**:270–8.

National Task Force on the Prevention and Treatment of Obesity. Very low-calorie diets. *JAMA* 1993;**270**:967–74.

National Task Force on the Prevention and Treatment of Obesity. Long-term pharmacotherapy in the management of obesity. *JAMA* 1996;**276**:1907–15.

Nisoli E, Carruba MO. An assessment of the safety and efficacy of sibutramine, an anti-obesity drug with a novel mechanism of action. *Obes Rev* 2000;**1**:127–39.

Pirozzo S, Cameron C, Glasziou P, Summerbell C. Advice on low-fat diets for reducing obesity (Protocol for a Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2002.

Poston WS, Haddock CK, Dill PL, Thayer B, Foreyt JP. Lifestyle treatments in randomized clinical trials of pharmacotherapies for obesity. *Obes Res* 2001;**9**:552–63.

Pronk NP, Wing RR. Physical activity and long-term maintenance of weight loss. *Obes Res* 1994;**2**:587–99.

Rissanen A, Fogelholm M. Physical activity in the prevention and treatment of other morbid conditions and impairments associated with obesity: current evidence and research issues. *Med Sci Sports Exerc* 1999; **31**:S635–45.

Samsa GP, Kolotkin RL, Williams GR, Nguyen MH, Mendel CM. Effect of moderate weight loss on health-related quality of life: an analysis of combined data from 4 randomized trials of sibutramine vs placebo. *Am J Manage Care* 2001;**7**:926–7.

Sayler ME, Goldstein DJ, Roback PJ, Atkinson RL. Evaluating success of weight loss programs, with an application to fluoxetine weight reduction clinical trial data. *Int J Obes* 1994;**18**:742–51.

Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea (Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2002.

Stefanick ML. Physical activity for preventing and treating obesity-related dyslipoproteinemias. *Med Sci Sports Exerc* 1999;**31**:S609–18.

Summerbell CD, Jones LV, Glasziou P. The long-term effect of advice on low-fat diets in terms of weight loss: an interim meta-analysis. *J Hum Nutr Diet* 1998; **11**:209–17.

Summerbell CD, Ashton V, Anagnostelis B, Roberts AP. Dieting to reduce body weight for controlling hypertension in adults (Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2002.

Tang JL, Armitage JM, Lancaster T, Silagy CA, Fowler GH, Neil HA. Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects. *BMJ* 1998;**316**:1213–20.

Thompson RL, Summerbell CD, Hooper L, Higgins JP, Little PS, Talbot D, *et al*. Dietary advice given by a dietitian versus other health professional or self-help resources to reduce blood cholesterol (Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2002.

Thorogood M. Combining diet with physical activity in the treatment of obesity. *J Hum Nutr Diet* 1998; **11**:239–42.

Wing RR. Physical activity in the treatment of the adulthood overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc* 1999;**31**:S547–52.

Zavoral JH. Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens* 1998; **16**:2013–17.

Appendix 4

Trial eligibility form

Trial author and date		**Refman number**
Checked by		

	Yes	**No**	**Unclear, with details**
Randomised controlled trial			
Data available for one year or more			
Average or median starting BMI ≥ 28kg/m²			
Average or median age of all groups ≥ 18 years			
Designed to reduce weight or prevent weight gain			

	Control	**Treatment 1**	**Treatment 2**	**Treatment 3**	**Treatment 4**
Surgery					
Diet					
Exercise					
Behavioural					
Drugs, specify					
Alternative medicine					
Other					

Data available	**Yes**	**No**	**Unclear, with details**
Anthropometry			
Risk factors			

Appendix 5

Quality assessment form

Trial author and date	
Refman number	
Extracted by	
Checked by	

	POTENTIAL FOR SELECTION BIAS AT TRIAL ENTRY	**Score**	**Query/comments**
1	**Quality of random allocation concealment** A = good attempt at concealment, method should not allow disclosure of assignment (telephone, third party, etc.) B (I) = states random allocation but no description given B (II) = attempt at concealment but real chance of disclosure of assignment prior to formal trial entry (envelopes without third party involvement, random numbers table procedure not described) C = definitely not concealed (open random numbers tables or quasi-randomised, e.g. day of week, date of birth, alternation)		
	POTENTIAL FOR SELECTION BIAS IN ANALYSIS		
2	**Was there a description of withdrawals and dropouts?** A = states numbers and reasons for withdrawals B(I) = states numbers of withdrawals only B(II) = states withdrawals but no number given C = not mentioned		
3	**Was the analysis on intention to treat (or is it possible to do so on available data)?** A = yes B = possibly, but not clear C = no		
	POTENTIAL FOR BIAS AROUND TIME OF TREATMENT OR DURING OUTCOME ASSESSMENT (BLINDING)		
4	**Were patients blinded to treatment status (e.g. placebo)?** A(I) = action taken at blinding likely to be effective A(II) = blinding stated but no description given B(I) = no mention of blinding B(II) = attempt at blinding but reason to think it may not have been successful C = not blinded		

5	**Were healthcare providers 'blind' to treatment status (e.g. placebo)?** A(I) = action taken at blinding likely to be effective A(II) = blinding stated but no description given B(I) = no mention of blinding B(II) = attempt at blinding but reason to think it may not have been successful C = not blinded		
6	**Were the outcome assessors blinded to treatment status?** A(I) = action taken at blinding likely to be effective A(II) = blinding stated but no description given B(I) = no mention of blinding B(II) = attempt at blinding but reason to think it may not have been successful C = not blinded		

Appendix 6

Data extraction form

Trial author and date	
Refman number	
Extracted by	
Checked by	

Location	
Period of study	
Method of recruitment and sampling	

Participants' general description Targeted particularly at: Diabetic or impaired glucose tolerance Y/N Hypertensive Y/N Hyperlipidaemia Y/N Binge eating Y/N	
Inclusion criteria	Exclusion criteria

	YES	NO	DETAILS
Pretreatment phase?			

	YES	NO	DETAILS
Subgroup analysis?			

	YES	NO	DETAILS
Groups comparable at baseline?			

Notes	

Details of interventions

Study ID:

	Control group	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Description of intervention					
Timing of intervention period 1. Start 2. End 3. Duration 4. Number of times contacted 5. Frequency of contact					
Health professional involvement (role, timing)					
Type of intervention Individual/Group/Both					
Other details of care					

Study population baseline characteristics

Study ID:

	Control	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Overall
Sex						
Age (range, mean, SD)						
Smoking status						
Social class						
Ethnic group						
Weight kg						
Height m						
BMI (kg/m^2)						
% Ideal body weight						
Waist circumference (give units)						

Study population baseline characteristics

Study ID:

	Control	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Overall
Total cholesterol (give units)						
LDL cholesterol (give units)						
HDL cholesterol (give units)						
Triglycerides (give units)						
Systolic blood pressure (mmHg)						
Diastolic blood pressure (mmHg)						
HbA_{1c} (%)						
Fasting plasma glucose (give units)						
Psychological health ratings						

Participant flow for weight data only

Study ID:

	Control	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Overall
Number eligible						
Number assigned/ selected to each group						
Numbers present for weight at time=						
Numbers present for weight at time=						
Numbers present for weight at time=						
Number assessed at end of study, with details						
Number completed at end of study						
% dropout at end of study						
Number dead at end of study						

	Control	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Period of active intervention					
Maximum length of trial (includes intervention period)					

Outcomes (use a different page for each time of follow-up, starting at one year)

Study ID: Timing:

Outcome	Statistics	Control	*N* =	Treatment 1	*N* =	Treatment 2	*N* =	Treatment 3	*N* =	Treatment 4	*N* =
Deaths											
Morbidity											
Adverse events											
Compliance											
Quality of life											
Economic											

Outcomes (use a different page for each time of follow-up, starting at one year)

Study ID: Timing:

Outcome	Statistics and who measured	Control	*N* =	Treatment 1	*N* =	Treatment 2	*N* =	Treatment 3	*N* =	Treatment 4	*N* =
Weight (kg)											
Height (m)											
BMI (kg/m^2)											
% Ideal body weight											
Waist circumference (give units)											

Outcomes (use a different page for each time of follow-up, starting at one year)

Study ID: Timing:

Outcome	Statistics and who measured	Control	*N* =	Treatment 1	*N* =	Treatment 2	*N* =	Treatment 3	*N* =	Treatment 4	*N* =
Total cholesterol (give units)											
LDL cholesterol (give units)											
HDL cholesterol (give units)											
Triglycerides (give units)											
Systolic blood pressure (mmHg)											
Diastolic blood pressure (mmHg)											
HbA_{1c} (%)											
Fasting plasma glucose (give units)											
Psychological health ratings											

Appendix 7

References to included studies

*Indicates primary reference to study.

Apfelbaum, 1999 (published data only)
Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E. Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med* 1999;**106**:179–84.

BIGPRO 1, 1996 (published data only)
*Fontbonne A, Andre P, Eschwege E. BIGPRO (Biguanides and the Prevention of the Risk of Obesity): study design. A randomized trial of metformin versus placebo in the correction of the metabolic abnormalities associated with insulin resistance. *Diabete Metabolisme* 1991;**17**:249–54.

Bard JM, Charles MA, Juhan-Vague I, Vague P, Andre P, Safar M, *et al*. Accumulation of triglyceride-rich lipoprotein in subjects with abdominal obesity: the biguanides and the prevention of the risk of obesity (BIGPRO) 1 study. *Arterioscler Thromb Vasc Biol* 2001; **21**:407–14.

Charles MA, Morange P, Eschwege E, Andre P, Vague P, Juhan-Vague I. Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. Biguanides and the Prevention of the Risk of Obesity. *Diabetes Care* 1998;**21**:1967–72.

Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F, *et al*. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 1996; **19**:920–6.

Bitsch, 1987 (published data only)
Bitsch M, Skrumsager BK. Femoxetine in the treatment of obese patients in general practice. *Int J Obes* 1987; **11**:183–90.

Black, 1984 (published data only)
Black DR, Lantz CE. Spouse involvement and a possible long-term follow-up trap in weight loss. *Behav Res Ther* 1984;**22**:557–62.

Blonk, 1994 (published data only)
Blonk MC, Jacobs MAJM, Biesheuvel EHE, Weeda-Mannak WL, Heine RJ. Influence on weight loss in type 2 diabetic patients: little long-term benefit from group behaviour therapy and exercise training. *Diabet Med* 1994;**11**:449–57.

Breum, 1995 (published data only)
Breum L, Bjerre U, Bak JF, Jacobsen S, Astrup A. Long-term effects of fluoxetine on glycemic control in obese patients with non-insulin-dependent diabetes mellitus or glucose intolerance: influence on muscle glycogen synthase and insulin receptor kinase activity. *Metabolism* 1995;**44**:1570–6.

Broom, 2001a (published and unpublished data)
*Broom I, Wilding J, Stott P, Myers N, on behalf of the UK Multimorbidity Study Group. Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *Int J Clin Pract* 2002;**56**:494–9.

Broom I. Randomised trial of the effect of orlistat on body weight and CVD risk profile in overweight and obese patients with co-morbidities. *Int J Obes* 2001; **25**(Suppl 1):S106.

Wilding J. Early response to orlistat treatment predicts long-term success in overweight and obese patients with co-morbidities. *Int J Obes* 2001:**25**(Suppl 1):S108.

Broom, 2001b (published and unpublished data)
Broom I, Hughes E, Dodson P, Reckless J, on behalf of the Orlistat UK Study Group. The role of orlistat in the treatment of obese patients with mild to moderate hypercholesterolaemia: consequences for coronary risk. *Br J Cardiol* 2001;**9**:460–8.

Chiasson, 1994 (published data only)
*Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, *et al*. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1994;**121**:928–35.

Rodger NW, Chiasson J-L, Josse RG, Hunt JA, Palmason C, Ross SA, *et al*. Clinical experience with acarbose: results of a Canadian multicentre study. *Clin J Invest Med* 1995;**18**:318–24.

Wolever TM, Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, *et al*. Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes. *Int J Obes Relat Metab Disord* 1997;**21**:756–63.

Wolever TMS, Chiasson J-L, Josse RG, Hunt JA, Palmason C, Rodger NW, *et al*. No relationship between carbohydrate intake and effect of acarbose on HbA_{1c} or gastrointestinal symptoms in type 2 diabetic subjects consuming 30–60% of energy from carbohydrate. *Diabetes Care* 1998;**21**:1612–18.

Wolever TMS, Radmard R, Chiasson J-L, Hunt JA, Josse RG, Palmason C, *et al*. One-year acarbose treatment raises fasting serum acetate in diabetic patients. *Diabet Med* 1995;**12**:164–72.

Cohen, 1991 (published data only)
Cohen MD, D'Amico FJ, Merenstein JH. Weight reduction in obese hypertensive patients. *Fam Med* 1991;**23**:25–8.

Cousins, 1992 (published data only)
Cousins JH, Rubovits DS, Dunn JK, Reeves RS, Ramirez AG, Foreyt JP. Family versus individually oriented intervention for weight loss in Mexican American women. *Public Health Rep* 1992;**107**:549–55.

Davidson, 1999 (published data only)
*Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, *et al*. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial [published erratum in *JAMA* 1999;**281**:1174]. *JAMA* 1999; **281**:235–42.

Foreyt J. A 2-year multicenter study of the effects of orlistat (Xenical) on weight loss and disease risk factors. *Obes Res* 1997;**5**:53S.

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Appendix 8

Tables of included studies

TABLE 18 *Included orlistat studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Broom, 2001[a]	**Randomisation**: minimisation algorithm: primary criterion was primary defined cardiovascular risk factor, secondary criterion was study centre, then BMI (28–34.9 or 35–39.9 or ≥ 40 kg/m^2) and weight loss in 2-week pretreatment phase (≤ 2 kg vs > 2 kg). Allocation concealment:[a] B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 54 GP surgeries and 12 hospital clinics in UK **Period of study**: before August 2001 **Inclusion criteria**: men and non-pregnant women, 18–80 years, BMI ≥ 28 kg/m^2, at least one of the following: IGT (serum glucose ≥ 8.0 mmol/l, 2 hours after a standard OGTT), hypercholesterolaemia (total serum cholesterol ≥ 5.2 mmol/l or LDL cholesterol ≥ 4.2 mmol/l at screening); hypertension (sitting DBP 90–105 mmHg); compliance 60% or more throughout the study **Exclusion criteria**: lactation, women of childbearing potential not using adequate contraception, MI, coronary artery bypass graft, percutaneous coronary angioplasty in prior 3 months, gastrointestinal surgery for weight reduction, active gastrointestinal disorders, e.g. peptic ulcer disease or malabsorption syndromes, pancreatic disease, history of postsurgical adhesions, excessive alcohol intake or substance abuse, participants who required any drug that may alter body weight or plasma lipids, e.g. appetite suppressants, lipid-lowering resins, retinoids and fish oil supplements, administration of systemic steroids (other than HRT) not permitted, concomitant pharmacotherapy for type 2 diabetes, hypertension or hypercholesterolaemia not permitted **Gender**: 409 women, 113 men **Age** (years): mean (SD) a: 46.7 (11.4), b: 45.3 (11.5) BMI (kg/m^2): mean (SD) a: 37.1 (6.4), b: 37.0 (6.2) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 13 times (baseline then at monthly intervals) **Description of intervention**: a + b: 2 weeks pretreatment phase consisting of single-blind placebo and 600 kcal/day deficit (min. 1200 kcal/day), 30% energy intake from fats, food and beverage intake diary; deficit diet continued postrandomisation to month 6 then reduced a further 300 kcal/day to week 52 a: 120 mg orlistat 3 times daily with main meals b: placebo 3 times daily with main meals **Allocated**: a: 265, b: 266 **Completed**: a: 186, b: 161 at 12 months **% Dropout**: a: 30%, b: 40% at 12 months **Assessed**: a: 259, b: 263 at 12 months ('ITT')	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, adverse events, compliance, deaths	SDs for change in risk factor outcomes at 12 months calculated. SDs for change in HbA_{1c} and mean and SD change in fasting plasma glucose at 12 months obtained from Roche report **Sponsorship**: Roche Pharmaceuticals

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Broom, 2001[b]	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 12 outpatient clinics in UK specialising in obesity and/or dyslipidaemia **Period of study**: before August 2001 **Inclusion criteria**: either gender, ≥ 18 years, women of childbearing potential if using adequate protection, BMI ≥ 30 kg/m^2, total plasma cholesterol ≥ 6.5 mmol/l, or plasma LDL cholesterol ≥ 4.2 mmol/l **Exclusion criteria**: MI or major surgery in past 3 months, gastrointestinal or pancreatic disease, type 1 diabetes, uncontrolled hypertension, history of carcinoma, gastrointestinal surgery for weight loss, postsurgical adhesions, bulimia or laxative abuse, drug or alcohol abuse, treatment with drugs altering appetite or lipid concentrations, fish oil supplements, retinoids, systemic steroids (other than sex hormone replacements) or anticoagulants **Gender**: 83 women, 54 men **Age** (years): mean (SD) a: 52.1 (9.2), b: 51.0 (10.5) **BMI** (kg/m^2): mean (SD) a: 36.5 (5.48), b: 37.1 (6.27) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 52 weeks contacted 11 times (baseline, every 4 weeks to week 24, then at weeks 30, 36, 44 and 52) **Description of intervention**: a + b: 600 kcal/day deficit diet from each of 5 major food groups with 30% calorie intake from fat, maximum 300 mg/day cholesterol; advice on physical activity a: orlistat 120 mg 3 times daily with main meals for 52 weeks (double-blind to week 24 then open-label design weeks 25–52) b: placebo 3 times daily with main meals for first 24 weeks then orlistat 120 mg 3 times daily in open-label design for weeks 25–52 **Allocated**: a: 71, b: 71 **Completed**: a: 34, b: 43 at 52 weeks **% Dropout**: a: 52%, b: 39% at 52 weeks **Assessed**: a: 66, b: 71 at 52 weeks ('ITT' LOCF; 5 participants excluded)	**Length of follow-up**: 52 weeks **Outcomes**: weight data, total cholesterol, LDL cholesterol, fasting plasma glucose, adverse events	SDs calculated and denominators assumed correct **Sponsorship**: Roche Products Limited

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Davidson, 1999	**Randomisation**: 75% orlistat: 25% placebo, stratified (< 2 kg or ≥ 2 kg weight loss during 4 weeks lead-in before randomisation), participants treated with orlistat 120 mg (a) rerandomised at end of year 1. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 18 US research centres **Period of study**: October 1992–October 1995 **Inclusion criteria**: either gender, >18 years, BMI 30–43 kg/m^2, adequate contraception in women of childbearing potential, all vitamin and mineral preparations were discontinued 8 weeks prior to start of study, ≥ 75% treatment compliance by capsule count during 4-week run-in period, ≥ 70% treatment adherence in year 1 to continue to year 2 **Exclusion criteria**: weight loss > 4 kg in previous 3 months, frequently changed smoking habits or had stopped smoking in past 6 months, history or presence of substance abuse, excessive alcohol intake, significant cardiac, renal, hepatic, gastrointestinal, psychiatric or endocrine disorder; drug-treated type 2 diabetes mellitus, concomitant use of medications altering appetite or lipid levels **Gender**: 741 women, 139 men **Age** (years): mean (SEM) a: 43.3 (0.6), b: 44.0 (0.7) **BMI** (kg/m^2): mean (SEM) a: 36.5 (0.9), b: 36.2 (0.1) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 24 months, contacted 23 times (baseline, every 2 weeks to week 16, then every 4 weeks to week 52, then every 8 weeks to week 104) **Description of intervention**: a + b: 500–800 kcal/day deficit with 30% energy intake from fats in 4-weeks single-blind placebo pretreatment phase, then continued for 2 years; if participant still losing weight in last 3 months of year 1 then energy intake increased 200–300 kcal/day; food diaries kept by participant and used periodically for counselling with dietitian; participant encouraged to increase activity by walking briskly for 20–30 minutes/week throughout 2 years, 4 behaviour modification sessions on weight loss in year 1 then 4 weight maintenance seminars in year 2; once-daily multivitamin containing all fat-soluble vitamins (Centrum) given in year 1 only if serum vitamin values decreased to below reference range on 2 consecutive visits a: 120 mg orlistat 3 times daily for year 1 b: placebo 3 times daily for year 1 and year 2 a: rerandomised at week 52 to: c: placebo 3 times daily d: orlistat 120 mg 3 times daily e: orlistat 60 mg 3 times daily **Allocated**: a: 668, b: 224 **Completed**: a: 458, b: 133 year 1 **Assessed**: a: 657, b: 223 at 12 months (LOCF but not ITT and for weight and blood pressure data only) **% Dropout**: a: 31%, b: 41% at 12 months; b: 57%, c 31%, d: 29%, e: 33% at 24 months	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, adverse events, compliance, deaths, cancers	2-year results only stated for participants receiving placebo/placebo (group b) and orlistat 120 mg 3 times daily/orlistat 120 mg 3 times daily (groups a and d). **Sponsorship**: Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Finer, 2000	**Randomisation**: blinded code numbers randomised in blocks of 4 printed on labels of double-blind medication and supplied in identical blister packs. Allocation concealment: A **Assessor blinding**: yes **ITT**: no	**Location**: 5 UK centres **Period of study**: before February 1999 **Inclusion criteria**: either gender, ≥ 18 years, BMI 30–43 kg/m^2, women of childbearing potential if using adequate contraceptive precautions, > 75% compliance (returned tablets) during run-in phase **Exclusion criteria**: weight loss > 4 kg in 3 months before screening, history of severe systemic disease including diabetes, uncontrolled hypertension, previous gastrointestinal disease, surgery for weight reduction, history of postsurgical adhesions, history or presence of cancer, psychiatric or neurological disorder requiring chronic medications or liable to prejudice participant compliance, alcohol or substance abuse, bulimia or laxative abuse, pregnancy, lactation, postmenopausal women, amenorrhoeic <1 year, drugs capable of influencing body weight, resins for lipid lowering, anticoagulants, digoxin or lipid-soluble vitamin supplements within previous month **Gender**: 193 women, 25 men **Age** (years): mean (SD) a: 41.5 (10.5), b: 41.4 (10.0) **BMI** (kg/m^2): mean (SD) a: 36.8 (3.6), b: 36.8 (3.7) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 17 times (baseline, before and after 4-week run-in, every 2 weeks until week 12, then every month until month 12) **Description of intervention**: a + b: pretreatment phase of 4-week single-blind run-in, then 600 kcal/day deficit diet (min. 1200 kcal/day), 30% fat, alcohol 150 g/week, aimed to produce initial weight loss of 0.25–0.5 kg/week, reduced by further 300 kcal/day at week 24 until week 52 (or reduced to 1000 kcal/day if already at 1200 kcal/day) a: 120 mg orlistat 3 times daily b: placebo 3 times daily **Allocated**: a: 114 b: 114 **Completed**: a: 73, b: 66 at 12 months **% Dropout**: a: 36%, b: 42% at 12 months **Assessed**: a: 59, b: 61 at 12 months (completer analysis excluding participants who violated protocol); a: 110, b: 108 at 12 months ('ITT' LOCF, although 10 participants excluded)	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, adverse events	SDs for change in weight calculated **Sponsorship**: F Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hauptman, 2000	**Randomisation**: personal communication. Allocation concealment: A **Assessor blinding**: no details given **ITT**: no	**Location**: 17 primary care centres in USA **Period of study**: before June 1999 **Inclusion criteria**: either gender, >18 years, BMI 30–44 kg/m^2, completed 4-week pretreatment phase with 75% or more compliance (by capsule count) **Exclusion criteria**: pregnancy, lactation, women of childbearing potential not taking adequate contraception; weight loss > 4 kg last 3 months, history of significant cardiac, renal, hepatic or gastrointestinal disorders, uncontrolled hypertension or other clinically significant condition, gastrointestinal surgery for weight reduction, bulimia or laxative and/or substance abuse, abnormal laboratory measures (values ≥ 10% of reference value for the normal range and sufficient to require medical follow-up by study physician), change in smoking habits in previous 6 months, use of any drug that may influence body weight or food intake in 8 weeks before screening **Gender**: 497 women, 138 men **Age** (years): mean (SD) a: 42.6 (11.68), b: 43.2 (10.14) c: 41.6 (10.19) **BMI** (kg/m^2): mean (SD) a: 35.8 (4.38), b: 36.0 (2.90), c: 36.1 (4.37) at 4 weeks before randomisation **Baseline comparability**: yes	**Timing of active intervention**: a + b: 104 weeks, contacted 21 times (baseline, every 2 weeks for first month then every 4 weeks until week 52, then every 8 weeks until week 104) **Description of intervention**: a + b + c: 4-week single-blind placebo pretreatment phase of 1200 kcal/day diet for participants who weighed < 90 kg initially or 1500 kcal/day for participants who weighed ≥ 90 kg initially; 30% energy intake from fats, 50% CHO, 20% protein, maximum 300 mg/day cholesterol, maximum 10 alcoholic drinks/week; dietary guidance on intake from study physician at start of pretreatment only, diet continued for first 52 weeks then increased by 300 kcal/day for participants still losing weight at end of week 52 or no dietary adjustment for those whose weight was stable until week 104; participants viewed videos on behaviour modification techniques for weight control 4 times in first 52 weeks, weight management and diet pamphlets for weight maintenance given 4 times during weeks 53–104 based on 'Live for Life' programme, all participants encouraged to increase physical activity by brisk walking for 20–30 minutes 3–5 times/week; dietary records kept 10 times during study a: 60 mg orlistat 3 times daily with main meals b: 120 mg orlistat 3 times daily with main meals c: placebo 3 times daily with main meals **Allocated**: a: 213, b: 210, c: 212 **Completed**: a: 154, b: 151, c: 122 at 12 months; a: 120, b: 117, c: 91 at 24 months **% Dropout**: a: 28%, b: 28%, c: 42% at 12 months (% participants who completed 1 year greater in both orlistat groups than placebo (p = 0.001); a: 44%, b: 44%, c: 57% at 24 months **Assessed**: a: 213, b: 210, c: 212, at 12 months and at 24 months ('ITT'): a: 120, b: 117, c: 91 at 12 months and at 24 months (completer analysis)	**Length of follow-up**: 24 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, adverse events, compliance, deaths	Change in weight including SDs calculated (change from –4 weeks to week 52 minus change from –4 weeks to week 0), change in risk factors calculated from actual values, SDs also calculated **Sponsorship**: none mentioned, first author at Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hill, 1999	**Randomisation**: stratified (≤ 10%, or > 10% weight loss in pretreatment phase). Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 17 US clinical research centres **Period of study**: before August 1998 **Inclusion criteria**: either gender, ≥ 18 years, BMI 28–43 kg/m^2, lost 8% or more of initial body weight during 6-month run-in phase **Exclusion criteria**: ever had significant medical disorders, uncontrolled hypertension, recurrent nephrolithiasis, symptomatic cholelithiasis, active gastrointestinal disorders, type 2 diabetes, pancreatic disease, cancer, pregnancy, lactating women, history or presence of substance abuse, eating disorders, excessive alcohol intake, significantly abnormal laboratory test results, previous gastrointestinal surgery for weight reduction, history of postsurgical adhesions, any medications known to influence body weight, appetite or lipid concentrations taken in 8 weeks before screening **Gender**: 605 women, 115 men **Age** (years): mean (SEM) a: 46.8 (0.8), b: 46.4 (0.7), c: 46.1 (0.7), d: 45.9 (0.7) **BMI** (kg/m^2): mean (SEM) a: 32.6 (0.2), b: 32.8 (0.2), c: 32.9 (0.2), d: 32.8 (0.2) **Baseline comparability**: body weight significantly different in orlistat 60 mg 3 times daily (group c) from all other groups ($p < 0.05$) accounted for by higher proportion of men to women in group c	**Timing of active intervention**: a–d: 12 months, contacted 11 times (baseline, every 2 weeks during month 1, then every month to month 5, then every 2 months to month 12) **Description of intervention**: a–d: 6-month pretreatment phase consisting of 1000 kcal/day deficit, 30% energy intake from fat, 50% from CHO, 20% from protein, to produce weight loss of 0.5–1 kg/week; dietary counselling, 4 sessions of behavioural modification programme (University of Minnesota's Wise Weighs) and encouraged to increase activity to brisk walking for 20–30 minutes 5 times/week, standard multivitamin–multimineral tablets once daily (Centrum) from start of pretreatment to end of study a–d: from randomisation, participants prescribed maintenance diet where individual energy requirements reassessed according to body weight at week 22 of pretreatment phase; increase in energy intake prescribed to match anticipated metabolic requirements over 1 year, if participants gained weight they were encouraged to maintain this higher weight, dietary and behavioural counselling given to all, dietary records a: 30 mg orlistat 3 times daily b: placebo 3 times daily c: 60 mg orlistat 3 times daily d: 120 mg orlistat 3 times daily **Allocated**: a: 187, b: 188, c: 173, d: 181 **Completed**: a: 140, b: 138, c: 133, d: 126 **Assessed**: a: 119, b: 121, c: 116, d: 113 at 12 months (for weight outcome only) **% Dropout**: a: 25%, b: 27%, c: 23%, d: 30% at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, adverse events, compliance	All outcomes calculated from initial values to week 52 minus initial values to end of 6-month lead-in (denominators differ), SDs for weight change calculated **Sponsorship**: F Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hollander, 1998	**Randomisation**: stratified by weight loss and glucose control during 5-week pretreatment: weight loss ≤ 2 kg, glucose 5.6–8.9 mmol/l; weight loss ≤ 2 kg, glucose 9.0–12.2 mmol/l; weight loss > 2 kg, glucose 5.6–8.9 mmol/l; weight loss > 2 kg, glucose 9.0–12.2 mmol/l. Allocation concealment: A **Assessor blinding**: yes **ITT**: possibly as no denominators stated for outcomes	**Location**: 12 diabetic clinic centres in USA **Period of study**: before February 1998 **Inclusion criteria**: either gender, > 18 years, BMI 28–40 kg/m^2, type 2 diabetes, clinically stable on glyburide or glypizide for 6 months or more; HbA_{1c} 6.5–10% at screening, fasting plasma glucose 5.6–12.2 mmol/l at end of 4th week of pretreatment, blood levels of fat-soluble vitamins above lower limit of normal reference range, completion and compliance by tablet count of ≥ 70% during pretreatment **Exclusion criteria**: pregnancy, lactation, women of childbearing potential not taking adequate contraceptive measures, clinically relevant conditions, e.g. psychiatric disorders, substance abuse, cholecystitis, pancreatic disease, uncontrolled hypertension, significant complications associated with diabetes, weight loss of > 4 kg during past 3 months, history of recurrent nephrolithiasis or symptomatic cholelithiasis, gastrointestinal surgery for weight reduction, history of bulimia or laxative abuse or if they had taken any drug that may influence body weight or plasma lipids in 8 weeks before start of study **Gender**: 157 women, 164 men **Age** (years): mean (SD) a: 55.4 (8.8), b: 54.7 (9.7) **BMI** (kg/m^2): mean (SD) a: 34.5 (3.2), b: 34.0 (3.4) **Baseline comparability**: yes	**Timing of active intervention**: 12 months, contacted 14–27 times (baseline, weeks 1 and 2, then every 2–4 weeks) **Description of intervention**: a + b: 5 weeks pretreatment phase single blind with mildly hypocaloric diet, then 500 kcal/day deficit from baseline to week 52, additional diet counselling and a standardised commercially available vitamin supplement given if 2 consecutive vitamin measures fell below reference range a: 120 mg orlistat 3 times daily taken with meals b: placebo 3 times daily taken with meals **Allocated**: a: 162, b: 159 **Completed**: a: 115, b: 139 at 12 months **% Dropout**: a: 15%, b: 28% at 12 months **Assessed**: a: 162, b: 159 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, HbA_{1c}, fasting plasma glucose, adverse events	All mean and SD change in weight and risk factor outcomes obtained from Roche report **Sponsorship**: Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Lindgarde, 2000	**Randomisation**: randomisation was minimised by participants' primary defined CHD risk factor, study centre and weight loss achieved in 2-week lead-in period (≤ 1 kg, or > 1 kg). Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: possibly but unclear	**Location**: 33 primary care centres in Sweden **Period of study**: before February 2000 **Inclusion criteria**: men and non-pregnant women, 18–75 years, BMI 28–38 kg/m^2, fasting serum glucose ≥ 6.7 mmol/l, or confirmed type 2 diabetes treated with sulfonylurea or metformin but not insulin; total serum cholesterol ≥ 6.5 mmol/l and/or LDL cholesterol ≥ 4.2 mmol/l on at least 2 occasions or prescribed lipid-lowering medications; DBP ≥ 90 mmHg on at least 2 occasions or confirmed hypertensive treated with antihypertensive medication **Exclusion criteria**: insulin-treated participants, women of childbearing potential who were lactating or using inadequate contraception; MI within 3 months before screening, gastrointestinal surgery for weight reduction, active gastrointestinal disorders, e.g. peptic ulcer disease or malabsorption syndromes (with the exception of controlled lactose intolerance), pancreatic disease, history of postsurgical adhesions, excessive alcohol or substance abuse, participants requiring any drug that may alter body weight or plasma lipids, e.g. appetite suppressants, lipid-lowering resins, retinoids or fish oil supplements; systemic steroids (other than HRT) and insulin **Gender**: 239 women, 137 men **Age** (years): mean (SD) a: 53.7 (9.4), b: 53.2 (9.9) at 2 weeks prior to randomisation **BMI** (kg/m^2): mean (SD) a: 33.2 (3.0), b: 33.2 (3.1) at 2 weeks prior to randomisation **Baseline comparability**: yes	**Timing of active intervention**: 12 months, contacted 11 times (baseline, twice in first month, then monthly to month 6, then every 2 months to month 12) **Description of intervention**: a + b: 2-week single-blind placebo plus mildly hypocaloric diet consisting of 600 kcal/day deficit (minimum 1200 kcal/day), 30% energy from fat, diet continued up to month 6 when energy content reduced additional 300 kcal/day; participants also received dietary counselling as part of self-help weight control educational package including leaflets and videotape given at start of run-in phase; participants encouraged to increase physical activity by taking 30 minutes' walk each day a: 120 mg orlistat 3 times daily b: placebo 3 times daily **Allocated**: a: 190, b: 186 **Completed**: a: 159, b: 164 at 12 months **% Dropout**: a: 16%, b: 12% at 12 months **Assessed**: a: 190, b: 186 at 12 months (possibly ITT, all randomised participants included in ITT analysis, but participants withdrawn by investigators if compliance < 60%)	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, HbA_{1c}, fasting plasma glucose, adverse events, compliance, deaths	Change including SDs, in weight and risk factor outcomes at 12 months calculated (change from –2 weeks to week 52 minus change from –2 weeks to week 0), SDs for change in weight also calculated **Sponsorship**: Roche AB

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Rossner, 2000	**Randomisation**: stratified according to weight loss in pretreatment phase (stratification figures not stated). Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 14 European centres **Period of study**: before November 1998 **Inclusion criteria**: either gender, ≥ 18 years, BMI 28–43 kg/m^2, completed 4-week pretreatment phase and ≥ 75% compliance (by capsule count) **Exclusion criteria**: pregnancy, lactation, women of childbearing potential not taking adequate contraception, clinically significant conditions (excluding obesity) that might affect study outcome, > 4-kg weight loss in previous 6 months, gastrointestinal surgery for weight loss, history of postsurgical adhesions or of bulimia or laxative abuse, any drug that may influence body weight or serum lipids taken in 8 weeks before screening; uncontrolled hypertension, drug-treated diabetes mellitus, history or presence of symptomatic cholelithiasis **Gender**: 591 women, 127 men **Age** (years): mean (SD) a: 44.7 (10.7), b: 43.6 (11.4), c: 44.3 (10.8) **BMI** (kg/m^2): mean (SD) a: 35.2 (3.9), b: 34.7 (3.7), c: 35.3 (4.1) **Baseline comparability**: yes, baseline data stated for safety population only (n = 718)	**Timing of active intervention**: a + b: 24 months, contacted 18 times (baseline, every 2 weeks for first 2 months, then monthly up to month 6, then every 2 months to month 24) **Description of intervention**: a + b + c: 4-week pretreatment phase consisting of single-blind placebo and 600 kcal/day deficit, 30% energy intake from fat, all participants ceased taking vitamin supplements before study and if vitamin or β-carotene levels fell below clinical reference range on 2 consecutive measurements then participants were given supplements; at randomisation deficit diet continued and during year 2 diet was adjusted as follows: for participants who had lost ≥ 3 kg between weeks 40 and 52 daily calorie intake was prescribed at a level equivalent to estimated energy intake minus 10% kcal/day; for participants who lost < 3 kg no dietary adjustment was made a: 60 mg orlistat 3 times daily with breakfast, lunch and dinner b: 120 mg orlistat 3 times daily with breakfast, lunch and dinner c: placebo 3 times daily with breakfast, lunch and dinner **Allocated**: a: 242, b: 244, c: 243 **Completed**: a: 140, b: 159, c: 136 at 24 months **% Dropout**: a: 42%, b: 35%, c: 44 at 24 months **Assessed**: a: 239, b: 241, c: 236 ('ITT', LOCF)	**Length of follow-up**: 24 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, DBP, SBP, fasting plasma glucose, adverse events, compliance, QoL	Roche provided denominators, change in risk factors calculated, SDs calculated, weight change from randomisation to 12 months and 24 months derived from graph **Sponsorship**: F Hoffman-La Roche

continued

TABLE 18 *Included orlistat studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Sjostrom, 1998	**Randomisation**: randomisation numbers generated by sponsors (Roche) and incorporated into double-blind labelling, randomisation done in blocks of 4 to produce equal numbers in both groups, stratified by weight loss in 4-week pretreatment phase. Allocation concealment: A **Assessor blinding**: no details given **ITT**: no	**Location**: 15 European centres **Period of study**: before July 1998 **Inclusion criteria**: either gender, ≥ 18 years, BMI 28–47 kg/m^2, women of childbearing potential if using adequate contraception, > 75% compliance during pretreatment phase at end of year 1 to continue to year 2 **Exclusion criteria**: serious diseases including uncontrolled hypertension (DBP ≥ 105 mmHg) and pharmacologically treated diabetics, weight loss > 4 kg in 3 months before screening, surgery for weight reduction, history of postsurgical adhesions, bulimia or laxative abuse, use of any drug that may influence body weight or plasma lipids in past month, drug or alcohol abuse **Gender**: 567 women, 116 men **Age** (years): mean (range) a: 45.2 (20–76), b: 44.3 (18–77) **BMI** (kg/m^2): mean a: 36.1, b: 36.2 **Baseline comparability**: yes	**Timing of active intervention**: a + b: 4-week pretreatment phase, 52 weeks treatment, then reassigned for further 52 weeks treatment, contacted 25 times (baseline, every 2 weeks until week 12, then every month until month 12, then 8 visits in year 2) **Description of intervention**: a + b: 4-week pretreatment consisting of single-blind placebo 3 times daily with meals and 600 kcal/day deficit with 30% calorie intake from fats; first 24 weeks all participants continued 600 kcal/day deficit (min. 1200 kcal/day) then until week 52 reduced by additional 300 kcal/day (min. 1000 kcal/day); diet designed to cause weight loss of 0.25–0.5 kg/week and consisted of 30% calorie intake from fats, 50% CHO, 20% protein, 300 mg/day cholesterol, 3 main meals and optional snack daily, 150 mg/week alcohol; year 2 all participants advised on weight maintenance diet and not to return to hypocaloric diet; additional dietary counselling or vitamin supplements given when necessary if 2 consecutive measures were below normal range a: orlistat 120 mg 3 times daily baseline to week 104 b: placebo 3 times daily baseline to week 104 **Allocated**: a: 345, b: 343 at baseline; a: 135, b: 126 at end week 52 **Completed**: a: 284, b: 260 at 52 weeks; a: 114, b: 102 at week 104 **% Dropout**: a: 18%, b: 24% at 52 weeks; a: 16%, b: 19% at week 104 **Assessed**: a: 343, b: 340 at 52 weeks ('ITT', LOCF); a: 133, b: 123 at 104 weeks ('ITT', LOCF)	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, adverse events	Mean change in weight and risk factor data calculated from actual values, SDs calculated, assumed mean weight loss in 4 week run-in = 2.2 kg **Sponsorship**: F Hoffman-La Roche

[a] See Appendix 5.
OGTT, oral glucose tolerance test; HRT, hormone replacement therapy; CHO, carbohydrate; QoL, quality of life.

TABLE 19 *Included sibutramine studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Apfelbaum, 1999	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 12 medical centres in France with interest in obesity/endocrine disorders **Period of study**: before February 1998 **Inclusion criteria**: either gender, 18–55 years, BMI > 30 kg/m^2, weight loss of ≥ 6 kg during 4-week VLCD (220–800 kcal/day) run-in phase **Exclusion criteria**: endocrine-related obesity, type 1 diabetes, type 2 diabetes receiving insulin or fasting glycaemia > 7.8 mmol/l, supine DBP > 100 mmHg, medical illness, ECG or laboratory abnormalities disqualified at investigators' discretion, unsuccessful VLCD in previous 6 months, not more than borderline depressed on Clinical Global Impression Scale **Gender**: 127 women, 33 men **Age** (years): mean (SD) a: 36.3 (9.5), b: 39.1 (9.1) **BMI** (kg/m^2): mean (SD) a: 35.9 (6.6), b: 35.1 (5.8) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 16 times (baseline, at week 2, month 1, monthly to month 12, then at month 13 and month 15) **Description of intervention**: a + b: 1-week run-in phase for screening tests then 4 week pretreatment phase of VLCD (220–800 kcal/day, site specific); dietary counselling to reduce total calorie intake by 20–30% compared with pre-VLCD intake a: 10 mg sibutramine capsule each morning b: placebo capsule each morning **Allocated**: a: 82, b: 78 **Completed**: a: 60, b: 48 at 12 months **% Dropout**: a: 39%, b: 27% at 12 months **Assessed**: a: 54, b: 45 at 12 months (completer analysis, 6 participants in group a, 3 participants in group b excluded as 12-month assessment performed more than 6 days after last dose of trial medication) a: 81, b: 78 at 12 months ('ITT', LOCF; 1 participant in group a excluded as did not provide a postbaseline assessment of body weight)	**Length of follow-up**: 15 months **Outcomes**: weight data, LDL cholesterol, HDL cholesterol, TGs, adverse events, compliance	**Sponsorship**: none mentioned, reprints from author at Laboratoires Knoll, France
McMahon, 2000	**Randomisation**: 2:1, no other details given. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 13 sites, USA **Period of study**: before February 2000 **Inclusion criteria**: either gender, ≥ 18 years, BMI 27–40 kg/m^2, diagnosis of hypertension ≥ 12 months, adequate medical control of hypertension (mean supine DBP ≤ 95 mmHg during run-in period; variations in mean DBP measured at 3 consecutive run-in visits and variations in individual measurements during each of these qualifying run-in visits had to be within 10 mmHg); hypertension to be controlled using a constant dose of a calcium	**Timing of active intervention**: a + b: 12 months, contacted 16 times (baseline, every 2 weeks, weeks 0–8, then every 4 weeks, weeks 9–52) **Description of intervention**: a + b: 2–10-week pretreatment phase, brief general dietary counselling for weight reduction at initial run-in visit only a: sibutramine titrated 5–20 mg/day in 5-mg increments every 2 weeks to week 6, then maintained at 20 mg/day weeks 8–52 b: placebo once daily	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, adverse events, QoL	SDs calculated for change in weight and risk factors at 1 year **Sponsorship**: Knoll Pharmaceutical Co.

continued

TABLE 19 *Included sibutramine studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
		channel blocker ≥ 60 days preceding screening and during run-in period; use of a single thiazide diuretic in addition was allowed provided dose stable during same period; concomitant therapy with a single antilipidaemic agent, diuretic or β-adrenergic receptor agonist was allowed if dose stable ≥ 60 days preceding screening; women patients ≥ 2 years postmenopausal, had undergone surgical sterilisation or were using adequate contraceptive measures; ≥ 75% compliance (tablet count) during placebo run-in period **Exclusion criteria**: elevated BP secondary to concurrent medical condition (other than obesity); supine pulse rate > 95 beats/minute at baseline or supine DBP ≥ 95 mmHg at any run-in visit, history of significant cardiac disease, endocrine abnormalities, impairment of a major organ system, convulsions, severe cerebral trauma or stroke, hypersensitivity to ≥ 2 classes of drugs, adverse reactions to CNS stimulants, substance abuse < 2 years before screening, gastric surgery to reduce weight or participation in a formal weight loss programme within 3 months before screening, previous administration of sibutramine at any time or use of another investigation drug within 30 days before this study, concomitant therapy with other weight loss products **Gender**: 136 women, 88 men **Age** (years): mean (SD) a: 52.3 (10.0), b: 52.9 (8.7) **BMI** (kg/m^2): mean (SD) a: 34.5 (3.4), b: 34 (4.0) **Baseline comparability**: yes	**Allocated**: a: 150, b: 74 **Completed**: a: 79, b: 41 **Assessed**: a: 79, b: 41 at 12 months (completer analysis); a: 142, b: 69 at 12 months ('ITT' LOCF) **% Dropout**: a: 47%, b: 45% at 12 months		

continued

TABLE 19 *Included sibutramine studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Smith, 2001 Smith, 2001a: 10 mg sibutramine Smith, 2001b: 15 mg sibutramine	**Randomisation**: computer-generated randomisation list. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 12 GP centres in UK **Period of study**: before 1996 **Inclusion criteria**: either gender, BMI 27–40 kg/m^2, protocol amended to BMI 25–44 kg/m^2, 18–65 years, not lost > 3 kg in previous 3 months, seated pulse rate of ≤ 100 beats/minute, seated DBP of ≤ 100 mmHg, hypertensives if stabilised with medication for 6 months, ability to follow dietary advice during 2-week single-blind run-in period assessed by 10-cm visual analogue question scale **Exclusion criteria**: obesity of endocrine origin, diabetes mellitus, people taking laxatives, anorectic agents, diuretics (except where stabilised for ≥ 6 months), bulking agents, antidepressants or any other medication that may alter body weight, more than borderline depression assessed by Clinical Global Impressions questionnaire and Beck Depression Inventory **Gender**: 390 women, 95 men **Age** (years): 41.8 **BMI** (kg/m^2): mean (SD) a: 32.9 (4.1), b: 32.7 (3.3), c: 32.4 (3.5) **Baseline comparability**: yes	**Timing of active intervention**: a + b + c: 2-week single-blind placebo run-in period, 12 months with follow-up to 13 months, contacted 15 times (baseline, monthly to month 12, then 1 week post-treatment and 1 month post-treatment) **Description of intervention**: a + b + c: all participants given standardised dietary advice including diet sheets and advised to include 12 oz (340 g) vegetables and fresh fruit, 6 oz (170 g) bread, cereals, potatoes or rice, 10 oz (250 g) skimmed milk each day; told to substitute fried foods with low-calorie foods, a: 10 mg sibutramine once daily in the morning b: 15 mg sibutramine once daily in the morning c: placebo once daily in the morning **Allocated**: a: 161, b: 161, c: 163 **Completed**: a: 94, b: 82, c: 80 at 12 months **% Dropout**: a: 42%, b: 49%, c: 51% at 12 months **Assessed**: a: 154, b: 153, c: 157, at 12 months (for weight data, denominators varied for other outcomes)	**Length of follow-up**: 13 months **Outcomes**: weight data, total cholesterol, TGs, SBP, DBP, fasting plasma glucose, adverse events	SDs calculated, weight loss figures in abstracts do not agree with main trial report, presumed BP changes are actual values rather than percentages **Sponsorship**: Knoll Pharmaceuticals

continued

TABLE 19 *Included sibutramine studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
STORM, 2000	**Randomisation**: 3:1, computer-generated list maintained centrally. Allocation concealment: A **Assessor blinding**: no details given **ITT**: yes for weight outcome only	**Location**: 8 European specialist centres **Period of study**: before December 2000 **Inclusion criteria**: either gender, 17–65 years, BMI 30–45 kg/m^2, lost 5% or more initial weight in 6-month open weight reduction phase with < 2 kg weight gain between months 4 and 5 or months 5 and 6, women of childbearing potential if using adequate contraception, hypertensive patients stabilised on therapy **Exclusion criteria**: endocrine-related obesity, recent weight changes (loss or gain > 4 kg in past 3 months), specified disease, e.g. myxoedema, Cushing's syndrome, diabetes mellitus, significant neurological or psychological illness such as epilepsy, schizophrenia or depression, or eating disorder such as bulimia, severe somatic disease, hepatic or renal dysfunction, a history of heart failure, ischaemic heart disease, stroke, transient ischaemic attacks or unstable hypertension (persistent DBP > 95 mmHg or pulse rate > 100 beats/minute), those with significant abnormalities on ECG, patients on such drugs as anorectics, oral β-blockers, agonists such as those used for treating asthma, steroids, thyroid preparations or diuretics for non-hypertensive purposes **Gender**: 390 women, 77 men **Age** (years): mean (SD) 40.6 (10.1) **BMI** (kg/m^2): mean (SD) 36.6 (4.1) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 18 months, contacted 19 times (baseline then monthly) **Description of intervention**: a + b: 6-month open pretreatment weight reduction phase consisting of 10 mg sibutramine daily plus 600 kcal/day deficit plus 30 minutes' daily extra walking plus advice on behaviour modification a: 10 mg sibutramine daily b: placebo daily a + b: sibutramine (or placebo) increased to 15 mg if > 1 kg weight regain occurred after pretreatment phase or since last dose increase providing dose stable for minimum of 2 months, if further weight increases dose increased to maximum 20 mg daily, dose reduced by 5 mg each time if patient could not tolerate higher dose, activity and behavioural advice, 600 kcal/day deficit (EE=RMRXPAL) consisting of 45–50% CHO, 30% fat, 15–20% protein **Allocated**: a: 352, b: 115 **Completed**: a: 206, b: 57 **% Dropout**: a: 59%, b: 50% **Assessed**: a: 222, b: 62 at 12 months for cholesterol, TGs, HbA_{1c} and fasting plasma glucose; a: 350, b: 114 at 12 months for weight data (ITT, LOCF)	**Length of follow-up**: 18 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, HbA_{1c}, fasting plasma glucose, adverse events, compliance	Mean change in risk factor outcomes at 12 and 18 months postrandomisation calculated from actual values at time-points, SDs also calculated **Sponsorship**: BASF Pharma part funded

BP, blood pressure; ECG, electrocardogram; EE=RMRXPAL, energy expenditure = testing metabolic rate × physical activity level.

TABLE 20 *Included SSRI studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Bitsch, 1987	**Randomisation**: predetermined randomisation list. Allocation concealment: A **Assessor blinding**: yes **ITT**: yes	**Location**: 12 GPs with practices in southern Sjaelland, Denmark **Period of study**: before July 1986 **Inclusion criteria**: either gender, 20–75 years, obese for 1 year (20% above IBW) **Exclusion criteria**: diuretics initiated during previous 1 month or anorectics in previous 6 months; pregnant, women of childbearing age if not on pill or using intrauterine device, severe hepatic, renal or somatic diseases **Gender**: 43 women, 10 men (completers only) **Age** (years): mean 47.9, range 24–68 (completers only) **BMI** (kg/m^2): not stated (nor weight) **Baseline comparability**: yes (completers only)	**Timing of active intervention**: a + b: 16 weeks, contacted 10 times (baseline, every 2 weeks for initial 16 weeks, then at 12 months) **Description of intervention**: a + b: 1200–1600 kcal/day and written dietary instruction a: 200 mg femoxetine twice daily days 1–7, increased to 300 mg twice daily thereafter, reduced to 200 mg twice daily if clinically significant side-effects b: placebo twice daily **Allocated**: a: 36, b: 37 **Completed**: 34 **% Dropout**: 53% overall at 12 months **Assessed**: 37 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data adverse events, compliance	Baseline characteristics for all participants, excluded participants, denominators at 1 year, mean and SD for weight in each group at 1 year unclear **Sponsorship**: none mentioned, one author at Ferrosan Research Division
Breum, 1995	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: multicentred, Denmark **Period of study**: before November 1994 **Inclusion criteria**: either gender, ≥ 18 years, BMI ≥ 29 kg/m^2, fasting venous plasma glucose ≥ 7.8 mmol/l, or 2 separate plasma glucose tests ≥ 7.8 mmol/l 2 hours after oral 75 g glucose load and HbA_{1c} < 14% **Exclusion criteria**: obesity due to endocrine disorders, severe somatic or psychiatric disorder including alcohol or drug abuse, MAOIs or cyclic antidepressants in previous 2 weeks, anorectics, lactation, pregnancy including desire to become pregnant, weight loss in previous 2 months, antihypertensives, guanethidine, reserpine, clonidine, methyldopa, severe diabetic complications **Gender**: 28 women, 12 men **Age** (years): mean (SD) a: 43.6 (9.8), b: 44.3 (8.7) **BMI** (kg/m^2): mean (SD) a: 36.9 (4.5), b: 39.5 (4.7) **Baseline comparability**: glucose and HbA_{1c} levels were higher in the fluoxetine group (non-significant)	**Timing of active intervention**: a + b: 12 months, contacted 13 times (baseline, every 4 weeks) **Description of intervention**: a + b: 1194 kcal/day with at least 50% CHO, behaviour modification a: 60 mg fluoxetine daily b: placebo daily **Allocated**: a: 20, b: 20 **Completed**: a: 15, b: 14 **% Dropout**: a: 25%, b: 30% at 12 months **Assessed**: a: 15, b: 14 at 12 months (2 participants excluded due to adverse events)	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, SBP, DBP, HbA_{1c}, fasting plasma glucose, adverse events, compliance	Presumed outcome data are for completers in each treatment group as unclear. Mean change in all outcomes (except for weight and fasting plasma glucose) calculated from actual values at baseline and at 12 months, SDs calculated **Sponsorship**: Eli Lilly & Co.

continued

TABLE 20 *Included SSRI studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Goldstein, 1994	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: yes **ITT**: no	**Location**: multicentre, 10 sites in USA **Period of study**: before August 1992 **Inclusion criteria**: either gender, > 18 years, BMI ≥ 25 kg/m^2, must avoid pregnancy **Exclusion criteria**: pregnancy/lactating, appetite suppressants within past 2 weeks **Gender**: 366 women, 92 men **Age** (years): mean (SD) a: 43 (12), b: 43 (12) **BMI** (kg/m^2): mean (SD) a: 36.2 (6.5), b: 35.8 (6.7) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 12 times (baseline, biweekly weeks 0–8, monthly weeks 9–20, every 2 months weeks 21–52) **Description of intervention**: a + b: participants given individual diets aimed to produce weight loss of 0.45 kg/week, nutrition, behavioural counselling and walking programme a: 60 mg fluoxetine once daily b: placebo once daily **Allocated**: a: 230, b: 228 **Completed**: a: 99, b: 108 at 12 months **% Dropout**: a: 57%, b: 53% at 12 months **Assessed**: a: 99, b: 108 at 12 months (completers, a: excludes 6 participants who discontinued at final visit but had final weight measurement, b: includes 1 participant who did not have weight measurement at final visit) a: 230, b: 228 at 12 months (ITT, LOCF, presumed no participants failed to return for 1 postbaseline visit)	**Length of follow-up**: 12 months **Outcomes**: weight data, adverse events, compliance	**Sponsorship**: Eli Lilly and Co.
O'Kane, 1994	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: diabetic clinic at Leeds General Infirmary, UK **Period of study**: before July 1993 **Inclusion criteria**: either gender, BMI >30 kg/m^2, no significant change in weight in prior 3 months, diagnosed with type 2 diabetes for ≥ 1 year and had been prescribed weight reducing diets as part of therapy, measurable fasting serum C peptide levels **Exclusion criteria**: clinical depression/antidepressant therapy **Gender**: 13 women, 6 men **Age** (years): mean (range) a: 59.6 (51–71), b: 54.9 (23–72) **BMI** (kg/m^2): mean (range) a: 36.8 (30.7–53.0), b: 35.8 (30.1–43.2) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 14 times (baseline, every 4 weeks) **Description of intervention**: a + b: prescribed weight reducing diets a: 60 mg fluoxetine daily b: placebo daily **Allocated**: a: 10, b: 10 **Completed**: a: 7, b: 9 at 12 months **% Dropout**: a: 30%, b: 10% at 12 months **Assessed**: a: 7, b: 9 at 12 months, 1 subject excluded from fluoxetine group (a) within first month as did not fulfil entry criteria	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, TGs, HbA_{1c}, fasting plasma glucose, adverse events	Weight and risk factor outcomes presented as median and IQRs, median assumed similar to mean and SDs calculated from IQRs **Sponsorship**: Lilly Industries

continued

TABLE 20 *Included SSRI studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wadden, 1995	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: yes	**Location**: University of Pennsylvania School of Medicine, Philadelphia, USA **Period of study**: before December 1994 **Inclusion criteria**: women who had completed a 26-week VLCD and behaviour therapy programme and had lost ≥ 10% of initial weight then completed a medical evaluation **Exclusion criteria**: medications affecting weight, appetite or energy expenditure, abnormal renal or hepatic function, severe psychiatric illness **Gender**: 53 women **Age** (years): mean (SD) a: 41.7 (10.9), b: 42.4 (8.6) **BMI** (kg/m^2): mean (SD) a: 29.2 (4.3), b: 30.7 (6.1) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 54 weeks, contacted 29 times (baseline, weekly for first 4 weeks, then fortnightly to week 54) **Description of intervention**: a + b: 26-week pretreatment phase of VLCD of 420/660/800 kcal/day plus behavioural therapy, then 1500–1800 kcal/day diet, ≤ 30% fat, exercise 3–4 times/week for 20–30 minutes of walking/aerobic activity, identifying and coping with high-risk situations, developing supportive relationships, identifying maximum acceptable weight, learning to reverse small weight gains a: 50–200 mg daily sertraline titrated in first 3 weeks then maintained to week 54 b: placebo daily **Allocated**: a: 26, b: 27 **Completed**: a: 13, b: 17 at 12 months **% Dropout**: a: 50%, b: 63% at 12 months **Assessed**: a: 13, b: 17 at 12 months	**Length of follow-up**: 54 weeks **Outcomes**: weight data, adverse events	**Sponsorship**: Pfizer Central Research, National Institute of Mental Health

MAOI, monoamine oxidase inhibitor.

TABLE 21 *Included metformin studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
BIGPRO 1, 1991	**Randomisation**: double-blind, confidential balanced random lists used to allocate to every participant's number metformin or placebo. Allocation concealment: A **Assessor blinding**: no details given **ITT**: yes	**Location**: multicentre, hospital outpatient clinics in university hospitals in France **Period of study**: before December 1995 **Inclusion criteria**: either gender, women 40–60 years, men 35–60 years with high waist–hip ratio (women = 0.8, men = 0.95) **Exclusion criteria**: ischaemic heart disease (or ECG abnormal on admission), diabetes (or diagnosed by WHO criteria on OGTT), serious chronic medical treatment, serious life-threatening medical conditions, chronic treatment by drug containing metformin or a lipid-lowering drug, psychiatric disorders, impaired renal function (plasma creatinine > 130 μmol/l) **Gender**: 306 women, 151 men **Age** (years): median (range) 49 (36–65) **BMI** (kg/m^2): geometric mean (95% tolerance limit) a: 33.3 (24.6–45.1), b: 33.0.(24–45.4) **Baseline comparability**: (available for completers only) 29% family history of diabetes in placebo group compared with 19% in metformin-treated group	**Timing of active intervention**: 12 months, contacted 5 times (every 3 months) **Description of intervention**: a + b: diet and encouragement to take regular moderate physical activity to reduce insulin resistance a: 850 mg metformin twice daily b: placebo twice daily **Allocated**: a: 227, b: 230 **Completed**: a: 164, b: 160 **% Dropout**: a: 28%, b: 31% at 12 months **Assessed**: a: 164, b: 160 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose deaths, new diabetes, morbidity, adverse events, compliance	SDs calculated from CIs **Sponsorship**: LIPHA Pharmaceutical Co., National Institute of Health and Medical Research, National Health Insurance for Wage Earners

continued

TABLE 21 *Included metformin studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Teupe, 1991	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: diabetes clinic, Bad Mergentheim, Germany **Period of study**: before 1991 **Inclusion criteria**: either gender, type 2 diabetes with plasma glucose levels not normalised (fasting 6.67–10.0 mmol/l, early postprandial 10.0–13.9 mmol/l) during 2 weeks' inpatient care with intensive diet treatment (participants also belonged to an overweight group receiving behavioural therapy at time of randomisation) **Exclusion criteria**: >70 years, creatinine >1.2 mg/100 ml, liver cirrhosis, ischaemic or wasting disease, acute severe diseases **Gender**: 60 women, 40 men **Age** (years): mean (SD) a: 51.5 (10.1), b: 56 (7.6) (at hospital entry, 14 days before randomisation) **BMI** (kg/m^2): mean a: 31.57, b: 30.51 (at hospital entry, 14 days before randomisation) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 2 years, contacted minimum 19 times (baseline, week 6 and week 20, every 3 months until 2 years) **Description of intervention**: a + b: all participants received 14 days' inpatient hospital treatment consisting of a strong dietary regimen before randomisation; postrandomisation all participants given individually adapted written diet plans, daily calorie reduction of ≥ 300 kcal, 50% intake from CHO, 6 meals daily; behavioural group leader (psychologist) contacted participants by letter and telephone at weeks 6 and 20; participants received telephone counselling every 3 months and asked to submit blood sample for HbA_{1c} (if > 10% rechecked after 4 weeks, if still elevated then participant hospitalised for 5 days to check whether reason was non-compliance or failure of therapy); participants hospitalised at 1 year and at 2 years for 2-day assessment b: received maximum 1.7 g metformin daily from baseline to 2 years **Allocated**: a: 50, b: 50 **Completed**: a: 33, b: 39 at 1 year; a: 25, b: 29 at 2 years **% Dropout**: a: 50%, b: 42% at 2 years **Assessed**: a: 29, b: 25 at years 1 and 2 (all participants with metabolic failures excluded from analyses)	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, TGs, HbA_{1c}, MI, musculoskeletal adverse events, compliance	Change calculated from actual values, SDs calculated **Sponsorship**: none mentioned

continued

TABLE 21 *Included metformin studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
UKPDS, 1998	**Randomisation**: computer-generated, allocations in sealed opaque envelopes, check maintained on numerical sequence, dates of opening and results. Allocation concealment: A **Assessor blinding**: no details given **ITT**: possibly	**Location**: multicentre, UK **Period of study**: 1977 onwards **Inclusion criteria**: either gender, 25–65 years, newly diagnosed diabetes, 3 fasting plasma glucose levels mean value > 6 and < 15 mmol/l, if later mean of 3 consecutive 3-monthly fasting plasma glucose > 6 mmol/l were randomised too; ≥ 120% above IBW (Metropolitan Life Insurance tables) **Exclusion criteria**: ketonuria > 3 mmol/l, MI in previous year, current angina or heart failure, > 1 major vascular episode, serum creatinine > 175 μmol/l, severe retinopathy requiring photocoagulation, malignant increase in BP, uncorrected endocrine abnormality, occupation not allowing insulin, severe concurrent illness requiring extensive systemic treatment, inadequate comprehension **Gender**: 403 women, 350 men **Age** (years): mean (SD) a: 53 (8), b: 53 (9) **BMI** (kg/m^2): mean (SD) a: 31.6 (4.8), b: 31.8 (4.9) **Baseline comparability**: yes	**Timing of active intervention**: a + b: median 10.7 years, contacted median 44 times (baseline then 3 monthly or more frequently) **Description of intervention**: a + b: all participants received advice regarding prudent diet, 50% CHO, low saturated fat, moderate–high fibre, reduced energy if obese and aiming for IBW a: maximum 1700 mg metformin at breakfast, 850 mg at evening meal with aim to get fasting plasma glucose < 15 mmol/l, if fasting plasma glucose > 15 mmol/l the sulfonylurea added then insulin added if control still inadequate **Allocated**: a: 342, b: 411 **Completed**: a: 279, b: 309 at 5 years; a: 181, b: 200 at 10 years; a: 21, b: 22 at 15 years **% Dropout**: a: 18%, b: 25% at 5 years; a: 47%, b: 51% at 10 years; a: 94%, b: 95% at 15 years **Assessed**: a: 279, b: 309 at 5 years; a: 181, b: 200 at 10 years; a: 21, b: 22 at 15 years	**Length of follow-up**: 15 years **Outcomes**: total mortality, deaths from CVD, deaths from stroke, deaths from cancer, adverse events, HbA_{1c}, fasting plasma glucose, weight data	Report of diet and metformin arms only of UKPDS **Major sponsorship**: UK Medical Research Council, British Diabetic Association, UK Department of Health, National Eye Institute, National Institute of Digestive, Diabetes and Kidney Disease in National Institutes of Health, USA, British Heart Foundation, Novo-Nordisk, Bayer, Bristol Myers Squibb, Hoechst, Lilly, Lipha, Farmitalia Carlo Erba

TABLE 22 *Included acarbose studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Chiasson, 1994	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: 7 hospitals in Canada **Period of study**: before 1994 **Inclusion criteria**: either gender, ≥ 18 years, BMI <40 (stable for 3 months), NIDDM = 6 months, HbA_{1c} > 7% or > 6.5% (diabetics on diet alone), normal plasma creatinine and liver function tests, hypertensives if blood pressure well controlled by antihypertensive medication **Exclusion criteria**: gastrointestinal disease and/or medications likely to alter gut motility or absorption, lactose intolerance, lipid-lowering agents, glucocorticoids, any debilitating disease, thiazide diuretics or β-blockers for hypertension **Gender**: 143 women, 211 men **Age** (years): mean (SD) 57.4 (9.4) **Weight** (kg): mean (SEM) a: 84.5 (1.5) n = 130, b: 81.1 (1.3) n = 149 **Baseline comparability**: yes	**Timing of active intervention**: 12 months, contacted 5 times (every 3 months) **Description of intervention**: a + b: 6 week pretreatment phase of placebo and weight maintaining diet a: 50 mg acarbose 3 times daily taken with first bite of each meal, titrated to 100 mg, then 200 mg 3 times daily during first 6 months to achieve target 60-minutes postbreakfast plasma glucose level < 12 mmol/l, dose increased if postprandial plasma glucose > 10 mmol/l b: placebo 3 times daily **Allocated**: a: 172, b: 182 **Completed**: a: 125, b: 143 **% Dropout**: a: 27%, b: 23% at 12 months **Assessed**: a: 149, b: 167 at 12 months (participants excluded if dropped out or required increase in concomitant hypoglycaemic medication in first 60 days)	**Length of follow-up**: 12 months **Outcomes**: Weight data, HbA_{1c}, fasting plasma glucose, adverse events	Data for fasting plasma glucose and HbA_{1c} only presented for subgroups: diet alone (BMI 28.8 kg/m^2), metformin (BMI 29.4 kg/m^2), sulfonylurea (BMI 27.8 kg/m^2), insulin (BMI 30.2 kg/m^2) **Sponsorship**: Miles Canada

continued

TABLE 23 *Included non-drug studies*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Black, 1984	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Omaha and Oklahoma, USA **Period of study**: before November 1983 **Inclusion criteria**: women, married, ≥ 10% overweight, husband signed statement if requested to attend, $11 deposit refunded on attendance **Exclusion criteria**: physiological or medical problems that would inhibit weight loss **Gender**: 36 women **Age** (years): mean: 35.1 overall **Weight** (kg): 77.3 overall **Baseline comparability**: yes	**Timing of active intervention**: a + b + c: 10 weeks with follow-up to 4 years, contacted 14 times (90-minute introductory baseline visit, then 10 weekly visits of 30–90 minutes' duration, then at 1, 3 and 4 years post-treatment (218 weeks in total) **Description of intervention**: a + b + c: all participants received 90-minute introductory meeting and signed contract to complete daily food record and record of non-routine physical activity for 2 weeks, 4 behavioural contracts written during 10 weeks focusing on changing eating and exercise habits a: participants attended alone, counsellor negotiated and co-signed contracts b: husbands attended as passive observers not encouraged to help their wives, counsellor negotiated and co-signed contracts c: husbands attended and actively participated in sessions, and contracts specified ways husband could help their wives, spouse negotiated and co-signed contracts **Allocated**: a: 12, b: 12, c: 12 **Completed**: a: 11, b: 10, c: 11 at 62 weeks **% Dropout**: a: 8%, b: 17%, c: 8% at 62 weeks **Assessed**: a: 11, b: 10, c: 11 at 62 weeks	**Length of follow-up**: 4 years **Outcome**: weight data	**Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Blonk, 1994	**Randomisation**: stratified by gender, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Amsterdam, The Netherlands **Period of study**: before December 1993 **Inclusion criteria**: Either gender, type 2 diabetes (WHO), normal haematological, liver, kidney, thyroid function, BMI > 27 kg/m^2 **Exclusion criteria**: history of angina, heart failure, intermittent claudication, proliferative retinopathy, subcutaneous insulin injections, diuretics, β-blocking agents, drugs for hyperlipidaemia and any other drugs that may influence CHO metabolism, regular physical exercise training **Gender**: 40 women, 20 men **Age** (years): median (range) a: 59 (42–69) $n = 27$, b: 58.5 (29–70) $n = 26$ **BMI** (kg/m^2): median (range) a: 31.3 (27.2–44.3) $n = 27$, b: 32.8 (27.9–45.8) $n = 26$ **Baseline comparability**: yes	**Timing of active intervention**: a: 24 months, contacted 56 times (baseline then 2-monthly dietitian visit, behavioural therapy sessions once a week for first 2 months, then at 4, 8, 12, 16 and 20 weeks, exercise sessions twice a month during months 3–6 and once a week during months 9–12 and 15–18) b: 24 months, contacted 13 times (baseline then every 2 months) **Description of intervention**: a + b: all participants underwent 3-month run-in before randomisation, seen 3 times for measurements and twice by dietitian who assessed 3-day food records, all participants instructed not to change their dietary habits; postrandomisation all participants received dietary education counselling programme involving visits to the dietitian every 2 months, 500 kcal/day deficit (minimum 1000 kcal/day), 50–55% CHO, 15% protein, 30% fat (emphasising unsaturated fat), 25 g fibre and < 300 mg cholesterol/day; adherence assessed at each visit by dietary record a: participants additionally received behavioural modification strategies including self-monitoring, stimulus control, self-reinforcement, cognitive restructuring and relapse prevention training; participants also received exercise training of 30 minutes of bicycle ergometer at 60–80% maximum heart rate and then 30 minutes of various sports activities **Allocated**: a: 30, b: 30 **Completed**: a: 27, b: 26 at 24 months **% Dropout**: a: 10%, b: 13% at 24 months **Assessed**: a: 27, b: 26 at 24 months	**Length of follow-up**: 24 months **Outcomes**: weight data, total cholesterol, TGs, SBP, DBP, HbA_{1c}, adverse events	Author confirmed study participants were randomly allocated to treatment groups; median change in weight at 12, 18 and 24 months derived from graphs assumed similar to mean, SDs calculated **Sponsorship**: Dutch Diabetes Research Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Cohen, 1991	**Randomisation**: stratified by residency year and randomly assigned, group status of participant determined by status of physician, cluster randomised. Allocation concealment: B(I) **Assessor blinding**: no details **ITT**: possibly	**Location**: Lawrenceville Family Health Centre, Pittsburgh, USA **Period of study**: January 1987–1989 **Inclusion criteria**: either gender, 20–75 years, BMI ≥ 27.8 kg/m^2 for men and ≥ 27.3 kg/m^2 for women, average SBP ≥ 140 mmHg on ≥ 2 readings, or average DBP > 90 mmHg on ≥ 2 readings **Exclusion criteria**: not stated **Gender**: 22 women, 8 men **Age** (years): mean: a: 59.3, b: 59.7 **BMI** (kg/m^2): mean: a: 34.2, b: 34.0 **Baseline comparability**: yes	**Timing of active intervention**: a: 12 months, contacted 13 times (baseline then monthly) b: assessed 3 times (baseline, 6 and 12 months) **Description of intervention**: a: physicians received special instruction and materials in weight reduction methods; reviewed diet of participant using questionnaire and suggested dietary changes, gave participant diet history sheet, information and advice sheet; advised participants to reduce calorie content of diet and set short-term goals; used methods of encouragement such as reinforcement, each month reviewed participant's previous day's food intake b: participants received usual care, physicians free to refer patients for dietary advice or provide advice themselves, but did not receive any special weight reduction instructions or materials **Allocated**: a: 15, b: 15 **Completed**: a: 15, b: 15 at 12 months **% Dropout**: a: 0%, b: 0% at 12 months **Assessed**: a: 15, b: 15 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, change in number of antihypertensive medications	Cluster RCT **Sponsorship**: St Margaret Memorial Hospital

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Cousins, 1992	**Randomisation**: 3 cohorts, 1 each year, stratified by weight, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Baylor College of Medicine, Houston, USA **Period of study**: before 1992 **Inclusion criteria**: self-identified Mexican–American women, 18–45 years, 20–100% above IBW, married with at least 1 preschool-aged child **Exclusion criteria**: hypertension (DBP ≥ 115 mmHg), diabetes (fasting plasma glucose ≥ 140 mg/dl), chronic illness with diet or exercise recommendations different from those in the study **Gender**: 168 women **Age** (years): mean (SD) a: 33.6 (6.4), b: 33.8 (6.1), c: 33.8 (7.0) **BMI** (kg/m^2): mean (SD) a: 31.7 (5.0), b: 30.3 (4.5), c: 31.6 (4.9) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 37 times (baseline then weekly group sessions and 6 monthly sessions for initial 24 weeks, then 6 monthly sessions up to month 12) c: unclear but presume contacted only at baseline and at 12 months **Description of intervention**: a–c: all participants received 'Cuidando el Corazon', a bilingual manual consisting of a low-fat eating plan and behaviour modification strategies; aimed at diet of 1200 kcal (women), 30% fat (10% unsaturated fat), 20% protein, 50% CHO, < 300 mg cholesterol/day, advised regarding moderate sodium intake, cookbook of recipes for fat-modified traditional Mexican foods, behaviour modification strategies such as maintaining weight loss, problem solving and preventing relapse were described in simple terms and manual translated into Spanish a: individualised instruction by bilingual dietitian on nutrition, feedback on food records and behaviour modification techniques, group exercise, food tasting, cooking demonstrations; last 6 months group leaders focused on preventing or minimising relapse and emphasised problem-solving approach to problems of low-fat eating and exercise, where participants could enlist support of the group; taught using techniques specifically for adults with limited literacy skills b: same sessions as group a except that spouses encouraged to attend sessions (separate classes for children); manual modified to include information on partner support and to encourage family changes in eating and exercise behaviours **Allocated**: 168 overall **Completed**: a: 32, b: 27, c: 27 **% Dropout**: 49% overall at 12 months **Assessed**: a: 32, b: 27, c: 27	**Length of follow-up**: 12 months **Outcome**: weight data	Mean change in weight at 12 months calculated from actual values, SDs also calculated **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
de Waard, 1993 de Waard, 1993a: The Netherlands de Waard, 1993b: Poland	**Randomisation**: 3:2 ratio of intervention: control, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: 3 hospitals in The Netherlands and 2 oncological hospitals in Poland **Period of study**: 1987–1990 **Inclusion criteria**: women, had primary treatment for breast cancer, no signs of distant metastases, 50–69 years, postmenopausal (no menses for ≥ 1 year), overweight by ≥ 10 kg (according to Broca's 1st rule, equivalent to BMI of ≥ 27 kg/m^2) **Exclusion criterion**: initially tamoxifen use, but this exclusion criterion was subsequently omitted **Gender**: 58 women (Netherlands) 49 women (Poland) **Age** (years): no details given **BMI** (kg/m^2): minimum mean a1: 29.3 (Netherlands, $n = 30$), b1: 29.5 (Netherlands, $n = 24$), a2: 30.6 (Poland, $n = 29$), b2: 32.2 (Poland, $n = 19$) **Baseline comparability**: control group (b2) in Poland had significantly fewer women with moderate overweight ($p < 0.02$)	**Timing of active intervention**: a1 + b1: 3 years, no further details a2 + b2: 1 year, no further details **Description of intervention**: a1 + a2: participants received dietary advice from a dietitian of 1500 kcal/day (reduced to 1000 kcal/day if insufficient weight loss was noted) and psychological support b1 + b2: no details given **Allocated**: a1: 30, b1: 24, a2: 29, b2: 19 **Completed**: a1: 28, b1: 24, a2: 27, b2: 15 at 1 year; a1: 27, b1: 24 at 1.5 years; a1: 25, b1: 21 at 2 years; a1: 23, b1: 17 at 2.5 years; a1: 18, b1: 15 at 3 years **% Dropout**: a1: 40%, b1: 38% at 3 years; a2: 7%, b2: 21% at 1 year **Assessed**: a:1 28, b1: 24, a2: 27, b2: 15 at 1 year; a1: 27, b1: 24 at 1.5 years; a1: 25, b1: 21 at 2 years; a1: 23, b1: 17 at 2.5 years; a1: 18, b1: 15 at 3 years	**Length of follow-up**: 3 years (The Netherlands), 1 year (Poland) **Outcomes**: weight data, deaths (non-cancer), new breast cancer (other breast), breast cancer recurrence local and distant, new breast cancer in other breast, death from breast cancer	Median weight change calculated from graphs and assumed similar to mean, SDs calculated, data presented as 2 trials (Netherlands data only, Poland data only) because Netherlands started recruiting in 1987 and Poland in 1989 **Sponsorship**: Linthorst-Kattekamp Research Fund

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
DISH, 1985	**Randomisation**: stratified by clinical centre and obesity and randomised before consent, unbalanced randomisation to favour medication cessation groups. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: multicentred, USA **Period of study**: before 1985 **Inclusion criteria**: either gender, no SBP > 180 mmHg in past year, average DBP < 95 mmHg in past year, average of last 2 DBP ≤ 90 mmHg and neither > 95 mmHg **Exclusion criteria**: congestive cardiac failure, ECG evidence of MI, stroke, transient ischaemic attacks, creatinine ≥ 2.5 mg/dl on at least 2 occasions, personal problems, compliance with diet difficult, severe alcoholism, pregnancy, β-blockers for angina, glucocorticoids **Gender**: 116 women, 60 men **Age** (years): mean a: 56.1, b: 57.2 **Weight** (kg): mean (SD) a: 86.0 (17.3), b: 89.8 (17.8) **Baseline comparability**: yes	**Timing of active intervention**: a: 56 weeks, contacted approximately 38 times (baseline then every 2 weeks for initial 16 weeks, then monthly to week 56, plus 8 initial weekly nutritional visits, then monthly to week 56) b: 56 weeks, contacted 20 times (baseline then every 2 weeks for initial 16 weeks, then monthly to week 56) **Description of intervention**: a + b: all participants given standardised stepped withdrawal of antihypertensive medication during weeks 2–8; medication restarted if DBP 95–99 mmHg 3 times in 3 months, 100–104 mmHg twice in a month or 105 mmHg at any time a: dietary intervention began 1–2 weeks postbaseline, aim for desirable weight according to Metropolitan Life Insurance standards by decreasing calories and keeping electrolytes constant, little emphasis on exercise b: participants did not receive any dietary intervention **Allocated**: a: 87, b: 89 **Completed**: a: 67, b: 77 at 56 weeks **% Dropout**: a: 23%, b: 13% at 56 weeks **Assessed**: a: 67, b: 77 at 56 weeks	**Length of follow-up**: 56 weeks **Outcomes**: weight data, antihypertension medication status	Study also included a continue medication control and a no-medication sodium restriction group in obese population **Sponsorship**: National Heart, Lung and Blood Institute, Ayerst Laboratories, Merck Sharp & Dohme, Ciba-Geigy Corp., Boehringer Ingelheim, USV Pharmaceutical Corp., GD Searle & Co.

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
FDPS, 2001	**Randomisation**: stratified by centre, gender and mean 2-hour plasma glucose concentration (7.8–9.4 mmol/l or 9.5–11.0 mmol/l), randomly assigned by study physician with use of randomisation list. Allocation concealment: B(I) **Assessor blinding**: blinding stated **ITT**: no	**Location**: 5 centres in Finland **Period of study**: 1993–2000 **Inclusion criteria**: either gender, 40–65 years, BMI > 25 kg/m^2, IGT (2-hour plasma glucose 7.8–11.0 mmol/l), OGTT 75 g with a non-diabetic fasting glucose concentration (plasma glucose < 7.8 mmol/l), mean value of 2 OGTTs (less strict criteria used in 1% or less of total number of participants) **Exclusion criteria**: previous diagnosis of diabetes mellitus (other than gestational diabetes mellitus), people involved regularly in vigorous exercise programme, participants receiving treatment to lower plasma glucose (other than routine dietary and health advice), chronic disease making 6-year survival improbable, other medical characteristics likely to interfere with study participation, unbalanced clinical conditions, e.g. thyroid and liver disease **Gender**: 350 women, 172 men **Age** (years): mean (SD): 55 (7) **BMI** (kg/m^2): mean (SD) a: 31.3 (4.6), b: 31.0 (4.5) **Baseline comparability**: significant difference between groups regarding SBP (mmHg, SD): 136 (17) control group (b) vs 140 (18) intervention group (a) (p = 0.03)	**Timing of active intervention**: a: 2–6 years, contacted at baseline, at 1–2 weeks, at 5–6 weeks then at 3, 4 and 6 months and every 3 months thereafter b: 2–6 years, contacted at baseline then at annual intervals Mean duration of follow-up was 3.2 years for all participants **Description of intervention**: a: participants informed at start of risk factors for diabetes, 3-day food diary at baseline provided basis for dietary advice in second session, advised to reduce weight to goal of BMI < 25 kg/m^2 but in practice weight targets were 5–10-kg weight loss; advised to consume > 50% CHO, < 10% saturated fat, 20% mono- and polyunsaturated fat or up to 25% if surplus is from monounsaturated fat; < 300 mg/day cholesterol and 1 g protein/kg IBW per day, encouraged to increase fibre intake to 15 g/1000 kcal, encouraged to use low-fat milk products, low-fat meat products, soft margarine and vegetable oil rich in monounsaturated fatty acids (primarily rapeseed oil); energy content re-evaluated if no weight loss at visits, if no weight loss in first 6–12 months and BMI > 30 kg/m^2 a VLCD was considered (6–12-week duration with group meetings every 1–2 weeks); dietary advice individually tailored and person responsible for preparing meals in family invited to attend sessions (if not the participant), advice tailored to participant's educational level, participants individually guided to increase endurance exercise (programme differed between study centres), also where possible there was a supervised progressive individually tailored circuit type	**Length of follow-up**: 2–6 years (mean 3.2 years) **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, compliance, new diagnoses of diabetes, deaths, cancer	22 participants had VLCD in year 1 and 25 in year 2 of 3–8 weeks' duration and 500–800 kcal/day; before final inclusion criteria decided 4% participants included with 1 abnormal OGTT only, 6% included based on high plasma glucose (≥ 6.4 mmol/l fasting or random sample after a fast of ≥ 4 hours) together with 1 high 2-hour plasma glucose concentration; authors contacted, reply received regarding numbers of participants assessed, changes in blood pressure and lipids, calorie content of VLCD, causes of death and serious adverse events including group allocation **Sponsorship**: Finnish Academy, Ministry of

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
			resistance training twice weekly, encouraged to perform 30 minutes of daily moderate exercise, 3-day food diary kept every 3 months, 24-hour exercise diary kept every 3 months and 12-month physical activity history completed on annual visit along with 2-km walking test b: at baseline participants advised to adjust total energy intake to reduce BMI to below 25 kg/m^2, also < 30% of energy intake from fat, reduce alcohol intake and stop smoking, verbal and written dietary advice, verbal general information regarding health benefits of recreational exercise, additional routine advice at yearly follow-up where 3-day food record assessed and 2-km walking test performed **Allocated**: a: 265, b: 257 **Completed**: a: 256, b: 250 at 1 year; a: 242, b: 240 at 2 years **% Dropout**: a: 8%, b: 6% at 2 years **Assessed**: a: 256, b: 250 at 1 year; a: 242, b: 240 at 2 years (1 participant excluded at 2 years confirmation of diabetes diagnosed at baseline)		Education, Novo Nordisk Foundation, Yrjö Jahnsson Foundation, Finnish Diabetes Research Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Foreyt, 1993	**Randomisation**: random numbers table, no other details. Allocation concealment: B(II) **Assessor blinding**: no **ITT**: no	**Location**: Houston, USA **Period of study**: before 1993 **Inclusion criteria**: either gender, 25–45 years, ≥ 14 kg overweight (Metropolitan Life Insurance tables), not taking regular exercise, $100 deposit (refunded in increments according to number of sessions attended) **Exclusion criteria**: not stated **Gender**: 80 women, 85 men **Age** (years): not stated **Weight** (kg): mean (SD) a: 93.9 (20.8), b: 97.7 (22.0), c: 97.6 (25.5), d: 99.1 (16.4) **Baseline comparability**: no details given	**Timing of active intervention**: a + b + c: 12 months plus follow-up visit at 2 years, contacted 24 times (baseline, then weekly for 12 weeks, then fortnightly to week 18, then monthly to week 48, then at 2 years) c: waiting list control for 12 weeks only **Description of intervention**: a + c: Help Your Heart Eating Plan consisting of 30% fat, 50% CHO, 20% protein; energy intake adjusted so weight loss was < 1 kg/week, food diaries kept, contracts to reward behaviour change, stress management, stimulus control and goal setting based on Learn behavioural eating programme a: advised to maintain sedentary lifestyle b + c: lectures focused on physical and psychological benefits of exercise, taught a walking programme at an indoor track, graduated exercise with self-monitoring based on heart rate, breathing and effort to 'vigorous' but not 'strenuous' level; exercise increased to goal of 3–5 sessions of 45 minutes/week b: advised to maintain current eating habits **Allocated**: a: 42, b: 43, c: 42 **Completed**: a: 29, b: 30, c: 27 at 12 months; a: 15, b: 25, c: 21 at 2 years **% Dropout**: a: 64%, b: 40%, c: 50% at 2 years (only invited completers back at 2 years) **Assessed**: a: 29, b: 30, c: 27 at 12 months; a: 15, b: 25, c: 21 at 2 years	**Length of follow-up**: 2 years **Outcome**: weight data	Mean change in weight at 1 year calculated from actual values, SDs also calculated at 1 year **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Frey-Hewitt, 1990	**Randomisation**: randomly assigned within 4 consecutive cohorts of approximately 39 participants each. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Stanford University, California, USA **Period of study**: before November 1989 **Inclusion criteria**: men, 30–59 years, 120–160% IBW, non-smokers, weight stable (±2.27 kg during previous year) **Exclusion criteria**: BP > 160/100, medications known to affect lipids, plasma total cholesterol > 7.76 mmol/l or TGs > 5.65 mmol/l or exercising ≥ 3 times per week **Gender**: 155 men **Weight** (kg): mean (SD) a: 93.63 (9.16), b: 94.14 (8.8), c: 94.99 (10.63) completers only **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 25 times (every 2 weeks) c: 12 months, contact unclear, possibly twice (baseline and at 1 year) **Description of intervention**: a + b + c: energy requirements of all participants were determined by 7-day food records at baseline a: designed to reduce total body fat by about one-third, participants advised to reduce food quantity without changing relative proportions of fat, CHO, protein or alcohol; individual weight loss goals determined by amount of body fat; 300–500 kcal/day deficit to produce 0.3–0.6 kg fat loss per week; received instruction and discussed behavioural strategies for weight loss first 9 months then to stabilise at this new weight for about 2 months b: designed to reduce total body fat by about one-third, participants underwent supervised exercise classes on 3 days/week with 25 minutes of fast walking (2 miles) during first 3 months whilst gradually adding jogging increasing up to 40–50 minutes of continuous jogging and by month 6 participants advised to take additional 2 days/week of unsupervised walking or jogging; work at 65–85% maximum heart rate (equivalent to kcal output of 8–10 kcal/minute); advised not to change kcal intake or quality of diet, estimated decrease in body fat of 2–3 kg first 3 months, 4–5 kg months 3–6 and remainder during months 6–9 c: advised to keep weight stable with no added energy restriction or exercise a + b: monthly activity and 24-hour energy intake monitored, if dieters changed activity or exercisers changed energy intake for more than 3 months they were counselled to return to baseline habits **Allocated**: a: 51, b: 52, c: 52 **Completed**: a: 49, b: 51, c: 49 at 1 year **% Dropout**: a: 4%, b: 2%, c: 6% at 1 year **Assessed**: a: 36, b: 44, c: 41 at 1 year (excluded 28 participants who had incomplete or technically invalid data at baseline and 1 year)	**Length of follow-up**: 1 year **Outcome**: weight data	**Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hakala, 1989	**Randomisation**: randomly allocated according to gender, age and percentage overweight. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: Rehabilitation Research Centre of the Social Insurance Institute, Turku, Finland **Period of study**: before December 1988 **Inclusion criteria**: either gender, 25–50 years, 30–50% overweight (Finnish Adult Population 1980) **Exclusion criteria**: limiting diseases such as heart disease, essential hypertension, diabetes and other metabolic diseases; medical treatments **Gender**: 72 women, 28 men (completers only) **Age** (years): mean (SD) 38 (10) **BMI** (kg/m^2): mean (SD) 34 (4) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 10 weeks of intensive treatment, with follow-up to 1 year, contacted 16 times (once a week for initial 10 weeks then 5 sessions until end of 1 year) c: no treatment, contacted 3 times (baseline, 6 months and 12 months) **Description of intervention**: a + b + c: all participants asked not to change physical activity and weekly exercise records completed at baseline, 6 and 12 months a + b: participants received principally dietary counselling but also health and psychological counselling, with participants divided into 3 groups of 15 in each treatment group; for initial intensive 10 weeks the principles of each diet taught by simple advice, food preparation examples and demonstrations; included 3 lectures by a physician, psychologist and physiologist; food diaries completed, at start of each group class each participant weighed and diet reviewed individually; participants advised to consume 1200 kcal/day, low in fat and sugar, high in fibre and vegetables, and to use vegetable margarine instead of butter, 5 sessions after the initial 10 weeks were used for motivating and repeating instructions a: lactovegetarian diet consisting of 20–25% protein, 20–25% fat, 55–60% CHO, all low-fat milk products and higher in vegetable content than group b b: mixed diet consisting of 25–30% protein, 25–30% fat, 45–50% CHO, and moderate in meat, fish and eggs c: participants not given any advice, kept 4-day food diaries at baseline, 6 and 12 months **Allocated**: a: 46, b: 46, c: 44 **Completed**: a: 31, b: 37, c: 42 at 1 year **% Dropout**: a: 33%, b: 20%, c: 5% at 1 year **Assessed**: a: 31, b: 37, c: 42 at 1 year (ITT)	**Length of follow-up**: 1 year **Outcomes**: weight data, SBP, DBP (blood pressure outcomes for groups a + b only), compliance	Author provided lipid outcomes **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hakala, 1993	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: Rehabilitation Research Centre of the Social Insurance Institute, Turku, Finland **Period of study**: before May 1992 **Inclusion criteria**: either gender, 22–54 years, > 50% overweight (Finnish Adult Population 1980), no serious cardiovascular, metabolic or psychiatric disease **Exclusion criteria**: schizophrenia, hypothyroidism, cardiac failure **Gender**: 40 women, 20 men **Age** (years): mean (SD) 41 (8) **BMI** (kg/m^2): mean (SD) 43 (5) **Baseline comparability**: yes	**Timing of active intervention**: a: 2 years, contacted 17 times (baseline, once a month in year 1 and every 4 months in year 2, then at 5 years) b: 2 years, contacted 42 times (initial 2-week inpatient stay then weekly for 6 weeks, every other week for 10 months, then once a month in year 2, then at 5 years) **Description of intervention**: a + b: vitamin supplements recommended if weight loss > 10 kg in first 3 months a: individual counselling group consisting of 20 minutes of individual visits with same physician monthly for first 6 months, advised on weight reduction with 1200 kcal/day diet and physical activity, information given systematically in small portions, participants received information leaflets, counselling paid attention to personal characteristics, family relationships and working situation; after 6 months the sessions concentrated on follow-up of body weight changes and health status until end of year 2 b: 2 week inpatient intensive group counselling treatment in groups of 10, consisting of 15 hours of nutrition counselling, behaviour modification, 15 hours of physical activation and training, 12 hours of occupational therapy and 1 hour of individual nutrition counselling; also included a lecture and examination by a physician; participants provided with 1200 kcal/day diet of 4 low-fat, low-sugar meals/day; nutrition education based on a mixed diet, group sessions after initial 2 weeks consisted of weight, group discussion, advice and motivation; participants also given individual appointments with physician at 4-month intervals **Allocated**: a: 30, b: 30 **Completed**: a: 28, b: 30 at 1 year and at 2 years; a: 25, b: 28 at 5 years **% Dropout**: a: 7%, b: 0% at 1 year and at 2 years; a: 17%, b: 7% at 5 years **Assessed**: a: 28, b: 30 at 1 year and at 2 years: a: 25, b: 28 at 5 years	**Length of follow-up**: 5 years **Outcomes**: weight data, compliance	Author provided weight outcomes by group, as reported by gender in each group **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Hankey, 2001	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: Glasgow Royal Infirmary, Glasgow, UK **Period of study**: before December 2001 **Inclusion criteria**: either gender, 35–75 years, survived acute MI approximately 3 months before the study, participated in cardiac rehabilitation programmes at the 2 study hospitals **Exclusion criteria**: not stated **Gender**: 10 women, 44 men **Age** (years): mean (range) a: 57 (41–72), b: 57 (40–75) **BMI** (kg/m^2): mean a: 28.6 (2.8), b: 30.4 (3.9) **Baseline comparability**: BMI appears different between groups	**Timing of active intervention**: a: 12 weeks with follow-up at 52 weeks b: assessed at baseline, 12 weeks and 52 weeks **Description of intervention**: a + b: all participants received standard cardiac rehabilitation which included 1 group session of 30–60 minutes with a dietitian and 12 practical exercise sessions of approximately 30 minutes each a: 4 × 1 hour sessions of individual dietary counselling during the initial 12 weeks which included weight management advice, 600 kcal/day deficit and following Scottish dietary targets **Allocated**: a: 28, b: 26 **Completed**: a: 25, b: 25 at 52 weeks **% Dropout**: a: 11%, b: 4% at 52 weeks **Assessed**: a: 25, b: 25 at 52 weeks	**Length of follow-up**: 52 weeks **Outcomes**: weight data, deaths	Author provided unpublished report, author provided cause of deaths and group allocation, details refer to subgroup of study population with BMI > 25 kg/m^2, published report weight loss differs **Sponsorship**: Chief Scientist Office of Scottish Executive

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
HOT, 1999	**Randomisation**: block randomised according to 3 main HOT study treatment groups. Allocation concealment: B(l) **Assessor blinding**: no **ITT**: possibly	**Location**: University of Mississippi, USA **Period of study**: before September 1998 **Inclusion criteria**: either gender, > 50 years, baseline DBP > 100 mmHg **Exclusion criterion**: HOT study patients with BMI < 27. **Gender**: 53 women, 49 men **Age** (years): mean (SD) a: 57 (6), b: 59 (7) completers only **BMI** (kg/m^2): mean (SD) a: 34 (6), b: 34 (6) completers only **Baseline comparability**: weight loss group (a) significantly taller ($p = 0.05$)	**Timing of active intervention**: a: 30 months, contacted maximum 24 times (baseline, at 2-4 weeks, twice a month to 3 months then every 3-6 months to 30 months) b: 30 months, contacted 6 times (baseline, 6, 12, 18, 24 and 30 months) **Description of intervention**: a: individuals counselled by weight loss dietitian within 10 days of randomisation, included counselling on food selection and preparation, and establishing weight reduction goals, calorie and fat restriction; counselled again at 2–4 weeks and attended group support sessions twice monthly for first 3 months then every 3–6 months, weight measured at 6-monthly intervals b: participants told by research nurses that they should lose weight but received no formal diet counselling or group support, weight measured only at 6-monthly intervals **Allocated**: a: 55, b: 56 **Completed**: a: 51, b: 51 at 30 months **% Dropout**: a: 7%, b: 9% at 30 months **Assessed**: a: 51, b: 51 at 30 months	**Length of follow-up**: 30 months **Outcomes**: weight data, SBP, DBP, deaths, number of medication steps	Author contacted, reply received regarding change in weight at 12, 18, 24 and 30 months by treatment group, SDs calculated for weight change at all time-points **Sponsorship**: Astra-Merck

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
HPT, 1990	**Randomisation**: stratified by BMI (BMI < 25 kg/m^2 men; BMI < 23 kg/m^2 women; or BMI 25/23–35 kg/m^2 men and women), random allocation in 3 distinct time intervals. Allocation concealment: B(I) **Assessor blinding**: yes **ITT**: yes	**Location**: Universities of Alabama, California, Mississippi and Minnesota, USA **Period of study**: 1983–1989 **Inclusion criteria**: either gender, 25–49 years, BMI < 35 kg/m^2 or $< 150\%$ IBW (Metropolitan Life Insurance tables), DBP ≥ 76 mmHg or < 99 mmHg at first baseline visit and DBP ≤ 89 mmHg at second visit (7–30 days later) **Exclusion criteria**: antihypertensive medications or medication that may affect sodium metabolism, major chronic disease, CVD, BMI 35 kg/m^2 or more, dietary requirements incompatible with dietary counselling regimens, ≥ 21 alcoholic beverages/week, perceived unable to comply with study **Gender**: 82 women, 169 men **Age** (years): mean a: 38.0, b: 39.5 **BMI** (kg/m^2): mean a: 29.0, b: 28.0 **Baseline comparability**: unequal for genders, 40.5% women in control group (b) vs 24.8% in intervention group (a)	**Timing of active intervention**: a: 3 years, contacted approximately 38 times (assessed 3 times at baseline then at clinic visits other than those of treatment sessions, 6 times at 6-monthly intervals, treatment group sessions weekly for initial 10 weeks, every other week for next 4 weeks, then every other month to 3 years; participants also received periodic individual counselling sessions) b: 3 years, contacted 10 times (assessed 3 times at baseline then at 3, 6, 12, 18, 24, 30 and 36 months) **Description of intervention**: a: calorie restriction dietary counselling where individual goal was for participants to attain IBW and where group goal was to achieve a 5% reduction in mean body weight; participants recommended to include daily servings of low-fat milk and diary products, choose fish, poultry or lean cuts of red meat, decrease use of fats in cooking and at the table, decrease use of high-calorie desserts, snacks and beverages, limit use of alcohol and use more fresh fruit and vegetables; dietary change counselling related to meal planning and rationing, food purchase, label reading; included didactic presentation and demonstrations, token incentives, bimonthly newsletters and telephone calls if participant did not attend group maintenance sessions, daily food records b: participants received no dietary counselling **Allocated**: a: 125, b: 126 **Completed**: a: 117, b: 113 at 3 years **% Dropout**: a: 6%, b: 10% at 3 years **Assessed**: a: 117, b: 113 at 3 years (ITT)	**Length of follow-up**: 3 years **Outcomes**: weight data, SBP, DBP, drug treatment required for hypertension, compliance, deaths	**Sponsorship**: National Heart, Lung, and Blood Institute

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Jalkanen, 1991	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: North Karelia, Finland **Period of study**: before December 1991 **Inclusion criteria**: either gender, 35–59 years, DBP ≥ 95 mmHg, BMI 27–34 kg/m^2, attending hypertension clinic **Exclusion criteria**: not stated **Gender**: 19 women, 21 men **Age** (years): not stated **Weight** (kg): mean (SD) a: 86 (14), b: 80 (11) **Baseline comparability**: weight appears different between groups at baseline	**Timing of active intervention**: a: 12 months, contacted 35 times (baseline then 1.5-hour session weekly for first 6 months, then every 3 weeks for next 6 months) b: contacted 5 times (at baseline then every 3 months for measurements only) **Description of intervention**: a: 1000–1500 kcal/day diet, education on behaviour modification and exercise, choice of food, medical aspects of overweight and CVD risk factors, leaflets on reduction of salt and fat consumption and increase in exercise, 3 exercise sessions with physiotherapist, bicycle trips organised and free tickets for local swimming pool b: usual visit with nurse every 3 months, offered active treatment at end of the study period, received no personal counselling or advice **Allocated**: a: 25, b: 25 **Completed**: a: 24, b: 25 at 12 months **% Dropout**: a: 4%, b: 0% at 12 months **Assessed**: a: 24, b: 25 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, SBP, DBP	Mean change in weight and risk factors at 12 months calculated from actual values, SDs also calculated, data show no change in weight, HDL cholesterol and TGs at 12 months in control group b **Sponsorship**: none mentioned
Jeffery, 1993	**Randomisation**: randomised within centre and gender. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Pittsburgh and University of Minnesota, USA **Period of study**: before July 1992 **Inclusion criteria**: either gender, 25–45 years, 14–32 kg overweight, non-smokers, < 3 alcoholic drinks/day **Exclusion criteria**: special diets, food allergies, unable to exercise, current serious diseases, prescription medications including oral contraceptives **Gender**: not stated **Age** (years): mean a: 37.5,	**Timing of active intervention**: a + b + c + d: 18 months with follow-up at 30 months, contacted 79 times (baseline then weekly group sessions to week 20, then monthly with weekly weigh-ins) e: contacted 5 times (baseline, and 6, 12, 18 and 30 months) **Description of intervention**: a + b + c + d: group behavioural counselling including weigh-in, presentations of information by interventionist, group discussion and a review of progress; participants assigned to an individualised caloric goal of 1000 or 1500 kcal/day on basis of baseline body weight to produce estimated weight loss of 1 kg/week; participants selected a weight loss goal of 14, 18 or 23 kg, if goal reached participants had caloric goals adjusted upwards to a level estimated to maintain this body weight; primary dietary instruction emphasised importance of remaining below	**Length of follow-up**: 30 months **Outcomes**: weight data, compliance	Mean weight change at 12, 18 and 30 months derived from graph, SDs calculated **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
		b: 38.5, c: 38.1, d: 37.6, e: 35.7 **BMI** (kg/m^2): mean a: 30.9, b: 30.8, c: 31.1, d: 31.1, e: 31.1 **Baseline comparability**: yes	caloric goals, restriction of fat and increased consumption of complex CHO also stressed; participants initially instructed to walk or cycle amount equivalent to 50 kcal/day for 5 days/week, gradually increased to final goal of 1000 kcal/week; daily food records kept for first 20 weeks and for 1 week each month thereafter, which included exercise taken; behavioural techniques included stimulus control, problem-solving strategies, social assertion, short-term goal setting and reinforcement techniques for enhancing motivation, cognitive strategies for replacing negative thinking with more positive statements and constructive self-statements, relapse prevention and social support b: participants given prepackaged meals for 5 breakfasts and 5 dinners each week for 18 months, meals prepared for the calorie level specific to each participant (1000 or 1500 kcal/day); breakfasts primarily consisted of cereal, milk, juice and fruit; dinners typically consisted of lean meat, potato or rice and vegetable; for 1 or 2 days per week a frozen dinner such as Weight Watchers or Lean Cuisine was provided; participants also given meal plans, recipes and recommendations for lunches c: participants received a cash payment each week based on weight lost in relation to their weight loss goal; maximum payment $25/week if weight loss goal reached and maintained, minimum $2.50/week if did not gain weight, weight loss of 50% goal reinforced with $12.50 d: combination of all treatment groups described earlier; behavioural treatment plus food provision plus financial incentives. **Allocated**: a: 40, b: 40, c: 41, d: 41, e: 40 **Completed**: 177 at 30 months **% Dropout**: 13% at 12 months, 15% at 18 months, 24% at 30 months (did not complete all visits) **Assessed**: a: 26, b: 36, c: 35, d: 34, e: 28 at 18 months (participants who attended all 3 follow-ups at 6, 12 and 18 months)		

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Jones, 1986 Jones, 1986c: behaviour therapy given to group Jones, 1986d: behaviour therapy given to individual	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Rochdale, UK **Period of study**: before 1986 **Inclusion criteria**: women, ≥ 18 years, judged suitable by dietitian **Exclusion criteria**: diabetes, pregnancy **Gender**: 160 women **Age** (years): mean (SD) 50.3 (13.5) overall **BMI** (kg/m^2): mean (SD) 35.1 (9.2) overall **Baseline comparability**: not stated	**Timing of active intervention**: a–h: 17 weeks with follow-up 12 months later (69 weeks in total), contacted 7 times (baseline then week 1, then 4 more sessions at 4-week intervals, then 12 months post-treatment) **Description of intervention**: a–h: all participants received individualised dietary advice at first session, recommended 1000 kcal/day below energy requirements but not less than 1000 kcal/day; (treatment was extended beyond 17 weeks if further involvement thought to be warranted) a: 4 group treatment sessions in small groups of 5–7 for 60 minutes each b: participants seen individually for 10 minutes each session c: participants received leaflet at each 4 sessions regarding cue avoidance and food management, seen in group format d: participants received leaflet at each 4 sessions regarding cue avoidance and food management, seen individually e: participants completed daily food diary which was discussed at each of 4 sessions, seen in group format f: participants completed daily food diary which was discussed at each of 4 sessions, seen individually g: participants received same leaflet and completed same daily food diaries, seen in group format h: participants received same leaflet and completed same daily food diaries, seen individually **Allocated**: a: 17, b: 21, c: 20, d: 22, e: 19, f: 20, g: 20, h: 21 **Completed**: a: 8, b: 9, c: 7, d: 7, e: 6, f: 6, g: 8, h: 7 at 69 weeks **% Dropout**: 64% overall at 69 weeks **Assessed**: a: 8, b: 9, c: 7, d: 7, e: 6, f: 6, g: 8, h: 7 at 69 weeks	**Length of follow-up**: 69 weeks **Outcome**: weight data	Only groups a, b, c and d used for comparisons **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Kaplan, 1987	**Randomisation**: random assignment by group, no further details. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: possibly	**Location**: San Diego State University and University of California, USA **Period of study**: before 1987 **Inclusion criteria**: either gender, confirmation of type 2 diabetes by physician, 12-hour fasting plasma glucose > 3.63 mmol/l, $40 deposit, some of which was contingent on attendance in amounts ranging from $1 to $10 **Exclusion criteria**: heart problems or other diseases that may interfere with full participation in the study **Gender**: 45 women, 32 men (gender unknown for 1 participant who died in an accident a few days after initial assessment) **Age** (years): mean (SD) a: 54.87 (12.32), b: 53.81 (8.04), c: 56.96 (8.95), d: 54.50 (8.83) $n = 76$ **Weight** (kg): mean (SD) a: 83.87 (16.9), b: 89.21 (21.07), c: 92.05 (20.35), d: 92.16 (21.78) $n = 76$ **Baseline comparability**: yes	**Timing of active intervention**: a–d: 10 weeks with follow-up at 18 months, contacted 12 times (baseline then for 2-hour sessions weekly for first 10 weeks, then at 18 months) **Description of intervention**: a + b: all participants received the exchange diet of 1200 kcal/day and an exercise prescription a: dietician explained exchange diet, consisted of 50% complex CHO, 20% protein and 30% fat; behavioural modification treatment programme was based on modern learning theory and included goal identification, weekly individual feedback from eating behaviour diaries, cognitive restructuring, methods for controlling food consumption, cue identification, identifying positive reinforcement and brief relaxation strategies as an alternative method of coping with stress b: exercise-focused programme including goal setting, self-monitoring and target heart rates obtained from graded exercise test and set at 60–70% maximum heart rate; exercise dairies were completed weekly and graphed, exercise leaders walked with the participants (recommended exercise for all but 1 participant) and consisted of 20 minutes' stretching, 45–60 minutes' walking and 5–10 minutes' stretching from weeks 3 to 10; participants encouraged to perform these exercise sessions at least 2 more times weekly and to attend other adult fitness programme sessions; 30 minutes' exercise-focused behavioural group discussion followed the programmed exercise sessions, contracts formed in week 10 regarding maintenance of exercise c: modified version of diet intervention received by group a for the first 5 weeks, week 6 focused on exercise information, and weeks 7–10 consisted of the exercise and behaviour sessions received by group b d: 2-hour weekly presentations for first 10 weeks from various healthcare specialists giving diabetes information but no specific information on behavioural changes, information given regarding behavioural therapy, but	**Length of follow-up**: 18 months **Outcomes**: weight data, HbA_{1c} deaths, QoL, cost utility analysis	**Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
			participants did not experience any behavioural strategies **Allocated**: 78 in total **Completed**: 70 in total at 18 months **% Dropout**: 10% overall at 18 months **Assessed**: unclear		
Karvetti, 1992 Karvetti, 1992a: women Karvetti, 1992b: men	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: health centres, Turku, Finland **Period of study**: before March 1992 **Inclusion criteria**: either gender, 17–65 years, BMI $\geq$ 27 kg/m^2 **Exclusion criteria**: diabetes or other disease that would prevent compliance with programme **Gender**: 127 women, 116 men **Age** (years): mean (SD) 48 (11) completers **BMI** (kg/m^2): mean (SD) 34 (5) completers **Baseline comparability**: yes	**Timing of active intervention**: a: 6 weeks of intensive treatment, with follow-up to 1 year, contacted 13 times (1.5-hour group session once a week for initial 6 weeks, then 4 times at monthly intervals, then twice every second month to 1 year) b: no treatment, contacted twice (baseline and at 1 year) **Description of intervention**: a: participants divided into 8 subgroups of 12–18 participants led by 7 trained public health nurses who instructed and motivated participants regarding weight reduction plan, nutrition education, physical activation, dietary, health and psychological counselling; initial 6-week intensive course also included 3 separate lectures by a physician, psychologist and physiologist to support participants in weight reduction; participants advised to consume 1200 kcal/day, low in fat and sugar, moderate in milk products, cereals, meat and fish, high in vegetables; 3 meals a day plus snack in afternoon and evening b: participants not given any instructions, informed selected for weight reduction course after assessment at 1 year **Allocated**: a: 126, b: 117 **Completed**: a: 93, b: 96 at 1 year **% Dropout**: a: 26%, b: 18% at 1 year **Assessed**: a: 93, b: 96 at 1 year	**Length of follow-up**: 1 year (treatment group only follow-up for 7 years) **Outcomes**: weight data, total cholesterol, HDL cholesterol, SBP, DBP, compliance	Author provided mean and SD change in all risk factors by treatment group **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Laitinen, 1993 Laitinen, 1993a: women Laitinen, 1993b: men	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: possibly	**Location**: University Hospital, Finland **Period of study**: before 1993 **Inclusion criteria**: either gender, 40–64 years, newly diagnosed NIDDM (fasting plasma glucose ≥ 6.7 mmol/l in repeated measurements) **Exclusion criteria**: not stated **Gender**: 37 women, 49 men **Age** (years): mean (SD) a: 50.7 (7.7) men $n = 21$, 53.7 (6.3) women $n = 19$; b: 54.0 (6.6) men $n = 28$, 54.4 (6.4) women $n = 18$ **BMI** (kg/m^2): not stated by group **Weight** (kg): mean (SD) a: 88.3 (14.1), b: 88.8 (14.0) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 24 months, contacted 8 times (baseline, then at 2 monthly intervals for 12 months, then at 24 months) **Description of intervention**: a + b: all participants received basic diabetes education during 3 months before randomisation a: individually tailored diabetic diet, energy restricted with ≤ 30% from fat (≤ 10% from saturated fatty acids, ≥ 20% from unsaturated fatty acids), ≤ 300 mg cholesterol/day, increased intake of unrefined CHO: food records; recommended exercise 3–4 times/week of 30–60 minutes each session, of either walking, jogging, swimming, cycling or skiing; exercise records, behaviour modification topics, e.g. what to do instead of eating and how to manage parties; goals were weight reduction, normoglycaemia, correction of dyslipidaemias and normalisation of elevated blood pressure b: conventional routine diabetic treatment **Allocated**: a: 40, b: 46 **Completed**: a: 40, b: 46 at 1 year; a: 38, b: 44 at 2 years **% Dropout**: a: 5%, b: 4% at 2 years **Assessed**: a: 40, b: 46 at 1 year; a: 38, b: 44 at 2 years	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, SBP, DBP, HbA_{1c}, fasting plasma glucose, diabetes control	Weight only given by gender at 2 years, no data available to calculate BP change at 2 years, denominators vary between reports **Sponsorship**: Finnish Foundation for Diabetes Research, Emil Aaltonen Foundation, the Kyllikki and Uolevi Lehikoinen Foundation, North Savo Regional Fund of the Finnish Cultural Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Lindahl, 1999	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: Umea University, Sweden **Period of study**: before December 1998 **Inclusion criteria**: either gender, BMI > 27 kg/m^2, abnormal OGTT **Exclusion criteria**: already taken part in lifestyle modification programme, too physically ill to participate **Gender**: 117 women, 69 men (total number of participants included in analyses $n = 186$) **Age** (years): mean (SEM) a: 54.8 (0.94), b: 56.2 (0.85) **BMI** (kg/m^2): mean (SEM) a: 31.0 (0.33), b: 30.2 (0.33) **Baseline comparability**: fasting glucose and TGs significantly lower in intervention group a ($p = 0.0001$, $p = 0.04$ respectively) and intervention group b had a higher BMI ($p = 0.06$)	**Timing of active intervention**: a: 1 month with 4-day follow-up stay at 12 months (full board at a wellness centre for initial month) b: baseline and at 12 months **Description of intervention**: a: full board for initial month which included 140 hours of scheduled activities including aerobic exercise of low to moderate intensity for 2.5 hours daily; diet of 1800 kcal/day for men and 1500 kcal/day for women consisting of 20% intake from fat and high in fibre to produce a slow but persistent weight decline; behavioural modification strategies included stress management and relapse prevention; no alcohol was permitted and participants were strongly encouraged not to smoke; additional learning session for 4 days at 12 months b: health survey and 30–60-minute counselling session which included oral and written advice on lifestyle changes regarding impaired glucose tolerance and obesity, repeated at 12 months **Allocated**: a: 100, b: 94 **Completed**: a: 96, b: 94 at 12 months **% Dropout**: a: 4%, b: 0% at 12 months **Assessed**: a: 93, b: 93 at 12 months (not ITT)	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, TGs, SBP, DBP, fasting plasma glucose	**Sponsorship**: Swedish Medical Research Council, Swedish Council of Forestry and Agricultural Research, Swedish Council for Planning and Co-ordination of Research, Joint Committee of the Northern Sweden Health Care Region, the Heart and Chest Fund, Swedish Public Health Institute, Västerbotten County Council

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Long, 1983	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: outpatients, Coventry, UK **Period of study**: before 1983 **Inclusion criteria**: women, 18–60 years, BMI > 25 kg/m^2 **Exclusion criteria**: expectant mothers, diabetes, preoperative patients, began weight loss as inpatients, recent dramatic weight reduction **Gender**: 36 women **Age** (years): mean (range) 36.8 (18–56) overall **BMI** (kg/m^2): mean (range) 33.5 (28.9–49.4) **Baseline comparability**: yes	**Timing of active intervention**: a + b + c: 16 weeks with follow-up to 1 year post-treatment, contacted 20 times (baseline then weekly for 16 weeks then at 3, 6 and 12 months post-treatment) **Description of intervention**: a: advised regarding high-fibre diet tailored to give 1000–1200 kcal/day, seen individually by dietitian for 45 minutes initially then 15 × 15-minute sessions during initial 16 weeks, advised on weight reducing diets, nutrition, commercial slimming foods, seasonal topics and weight maintenance b: 12 x 1-hour group sessions plus 4 brief 30-minute weigh-in sessions during initial 16 weeks; diet advice same as group a and also fostered high expectation of weight loss based on group support c: 12 x 90-minute sessions held weekly for first 16 weeks with dietitian and clinical psychologist plus 4 brief weigh-in sessions; first 15–20 minutes of each group session participants given same diet advice as groups a and b; participants discussed application of behavioural strategies based on learning principles following each of 12 didactic sessions including self-monitoring, stimulus control, slowing rate of eating, generating social support, exercise, dietary planning, preplanning, individual problem solving, assertiveness and cognitive restructuring b + c: only average group weight loss reported to group, not individual weights a + b + c: all participants received same advice regarding obesity, health, nutrition and weight reduction, told successful weight loss depended on reducing calorie intake and/or increasing physical activity **Allocated**: a: 12, b: 12, c: 12 **Completed**: a: 7, b: 7, c: 9 at 68 weeks **% Dropout**: a: 42%, b: 42%, c: 25% at 68 weeks **Assessed**: a: 7, b: 7, c: 9 at 68 weeks	**Length of follow-up**: 68 weeks **Outcome**: weight data	Median weight change at 12 months assumed similar to mean and SDs calculated **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Murphy, 1982 Murphy, 1982a: couple + 1-party contracts vs individual + 1-party contracts Murphy, 1982b: couple + 2-party contracts vs individual + 2-party contracts	**Randomisation**: couples randomly assigned, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: Baton Rouge community, USA **Period of study**: before January 1982 **Inclusion criteria**: married couples, 20–80% above IBW (USDA 1969), spouse willing to attend all treatment sessions, no contraindications for restricting intake or increasing exercise (decided by physician) **Exclusion criteria**: no details **Gender**: 50 women, 25 men (n = 75, all participants attending first session) **Age** (years): mean a: 35.3, b: 39.7, c: 42.3, d: 47.5, e: 42.0, f: 39.1 (n = 75) **BMI** (kg/m^2): mean a: 31.50, b: 32.03, c: 29.94, d: 30.49, e: 31.97, f: 29.89 (n = 75) **Baseline comparability**: yes	**Timing of active intervention**: a + e: 10 weeks with follow-up to 4 years post-treatment, contacted 21 times (baseline then 11 x 1.5-hour sessions in first 10 weeks, then at 12, 15, 18, 22, 29 and 36 weeks, 1 year, 2 years and 4 years post-treatment) f: 10 weeks, contacted 12 times (baseline then 11 × 1.5-hour sessions in first 10 weeks) **Description of intervention**: a: received treatment manual which focused on 3 meals per day and occasional snacks to reduce calorie intake (minimum 1000 kcal/day) and increasing calorie expenditure through walking; participants attended alone and entered into 4 contingency contracts regarding calories and nutrition, eating habits, exercise and problem behaviours; participants self-selected rewards and punishments b: received same manual except for contingency contracts, attended alone, both participant and spouse agreed contingency contracts and spouse encouraged to participate actively in assisting with compliance and controlling rewards (mutually rewarding and/or punishing) c: received identical manual to group a, attended with spouse, participant alone responsible for contingency compliance, rewards and punishment d: received identical manual to group b, both participant and spouse attended sessions and both took part in contingency contracts e: attended alone, did not receive manual or enter into contingency contracts, group support format with therapist acting as facilitator, discussed possible strategies for successful weight loss f: waiting list control for initial 10 weeks only, no treatment received, weight measured at week 1 and week 10 **Allocated**: a: 19, b: 15, c: 14, d: 16, e: 15, f: 18 **Completed**: a: 4, b: 6, c: 4, d: 8, e: 6 at 1 year; a: 7, b: 7, c: 5, d: 8, e: 6 at 2 years; a: 4, b: 4, c: 5, d: 6, e: 6 at 4 years	**Length of follow-up**: 4 years Outcome: weight data	SDs calculated **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
			% Dropout: a: 63%, b: 53%, c: 64%, d: 50%, e: 60% at 2 years; a: 79%, b: 73%, c: 64%, d: 63%, e: 60% at 4 years **Assessed**: a: 4, b: 6, c: 4, d: 8, e: 6 at 1 year; a: 7, b: 7, c: 5, d: 8, e: 6 at 2 years; a: 4, b: 4, c: 5, d: 6, e: 6 at 4 years		
Narayan, 1998	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Pima Indians of Arizona, USA **Period of study**: before July 1997 **Inclusion criteria**: either gender, 25–54 years, BMI $\geq$ 27 kg/m^2 (men), $\geq$ 25 kg/m^2 (women), normoglycaemia (2-hour-plasma glucose $<$ 7.8 mM) **Exclusion criteria**: pregnancy or intention to become pregnant, previous diagnosis of diabetes, current self-reported physical activity $\geq$ 20 hours/week, prescribed low-fat diet, another household member already randomised to the study, evidence of ischaemic heart disease, chronic illness, current steroid, thiazide or β-blocker treatment, condition likely to interfere with informed consent **Gender**: 72 women, 23 men **Age** (years): median a: 34, b: 33 **BMI** (kg/m^2): median a: 36.5, b: 33.2 **Baseline comparability**: fasting plasma glucose significantly higher in group a ($p = 0.03$)	**Timing of active intervention**: a: 52 weeks, contacted minimum 53 times (baseline then weekly group meetings and home visits to week 52) b: 52 weeks, contacted 13 times (baseline then monthly to week 52) **Description of intervention**: a: structured activity and nutritional intervention programme by an American Diabetes Association-recommended dietitian, decrease fat intake and alcohol intake, increase fibre and increase energy expenditure by 700–1000 kcal/week by e.g. walking 10–12 hours/month and keeping activity log; behavioural techniques included role playing, modelling and problem solving, food tasting and grocery store tours b: control group with self-directed learning with Pima culture appreciation group meetings to discuss current/historical lifestyles, local speakers, participants contributed to newsletters carrying Pima poetry, stories and folklore; basic printed material regarding healthy eating and exercise information, detailed interview of 40–120 minutes on health and lifestyle **Allocated**: a: 48, b: 47 **Completed**: a: 45, b: 45 at 52 weeks **% Dropout**: a: 4%, b: 6% at 52 weeks **Assessed**: a: 45, b: 45 at 52 weeks	**Length of follow-up**: 52 weeks **Outcomes**: weight data, total cholesterol, TGs, SBP, DBP, fasting plasma glucose	Author confirmed numbers assessed in each group at 12 months, medians assumed similar to means and SDs calculated **Sponsorship**: Community Task Force, Gila River Indian Community

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
ODES, 1995	**Randomisation**: stratified by gender, sealed envelope with randomisation number and name of treatment group. Allocation concealment: A **Assessor blinding**: only blinded blood analyses **ITT**: no	**Location**: Ullevaal Hospital, Oslo, Norway **Period of study**: before September 1994 **Inclusion criteria**: either gender, 41–50 years, sedentary (exercise no more than once a week), BMI > 24 kg/m^2, DBP 86–99 mmHg, total cholesterol 5.2–7.74 mmol/l, HDL cholesterol < 1.2 mmol/l, fasting serum TGs > 1.4 mmol/l **Exclusion criteria**: overt diabetes/CVD, other disease or drugs that could interfere with the test results, treatment with antihypertensive drugs, acetylsalicylic acid, lipid-lowering diet, personal traits unsuitable for participation in the trial **Gender**: 21 women, 198 men **Age** (years): mean (SD) 44.9 (2.5) **BMI** (kg/m^2): mean (SD) a: 29.54 (3.89), b: 28.56 (3.22), c: 28.57 (3.47), d: 28.30 (3.15) **Baseline comparability**: total cholesterol and LDL cholesterol were significantly lower in both the exercise and the diet + exercise groups ($p < 0.05$)	**Timing of active intervention**: a: 12 months, contacted 4 times (baseline, 3, 9 and 12 months) b: 12 months, contacted 158 times (baseline, 3 times a week and follow-up at 12 months) c: 12 months, contacted 160 times (baseline, 3 times a week, 3, 9 and 12 months) d: contacted twice (baseline and at 12 months) **Description of intervention**: a: participants given dietary counselling with spouse at baseline and then individually at 3- and 9-month follow-up sessions; diet adapted to individual's risk profile with the main focus on energy restriction in those overweight, increase in the intake of fish products and vegetables, decrease in the intake of saturated fat, cholesterol and sugar, and salt restriction for participants with elevated BP; weight targets agreed and set, 180-item food frequency questionnaire at baseline and 12 months b: initial 8 weeks, intensity and duration of supervised endurance workouts increased progressively, then maintained at 3 times/week for 1 hour each session at 60–80% maximum heart rate as assessed at baseline using treadmill; 60% of each workout was aerobic, 25% circuit training and 15% fast walking/jogging, attendance measured and exercise log book kept c: identical diet counselling as described for group a and participants attended same exercise sessions as described in group b d: participants told not to change lifestyle and that after 1 year they would be offered dietary advice and supervised physical training a–d: all participants advised to stop smoking **Allocated**: a: 55, b: 54, c: 67, d: 43 **Completed**: a: 52, b: 49, c: 65, d: 43 at 12 months **% Dropout**: a: 5%, b: 9%, c: 3%, d: 0% at 12 months (includes 5 participants excluded) **Assessed**: a: 52, b: 49, c: 65, d: 43 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, fasting plasma glucose, cancer, deaths	Discrepancy of outcome data between trial papers **Sponsorship**: Research Council of Norway, Norwegian Council of Cardiovascular Diseases, Insurance company Vital Friskvern

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Ost, 1976	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Uppsala, Sweden **Period of study**: before January 1976 **Inclusion criteria**: either gender, ≥ 15% overweight **Exclusion criteria**: not stated **Gender**: 38 women, 7 men **Age** (years): mean 40.9 overall **Weight** (kg): mean (SD) a: 87.0 (12.4), b: 86.6 (9.4), c: 81.5 (16.1) **Baseline comparability**: significant difference at baseline in weight between groups a and c and groups b and c	**Timing of active intervention**: a: 16 weeks with follow-up at 68 weeks, contacted 22 times (baseline then 30 minutes twice a week for 4 weeks, then weekly for 12 weeks, then at 68 weeks) b: 16 weeks with follow-up at 68 weeks, contacted 10 times (baseline then 8 sessions in first 16 weeks, then at 68 weeks) c: assessed at baseline, 16 weeks and 68 weeks **Description of intervention**: a + b + c: all participants received 45-minute baseline lecture on food and nutrition a: focus of first 4 sessions was behavioural therapy consisting of situational control of overeating such as cue avoidance; focus of sessions 5–7 was 500 kcal/day deficit diet with recommended food plan (based on food exchanges) nearest to this value chosen (1000, 1200, 1500 and 1800 kcal food plans), calorie count diary completed; focus of session 8 was to increase calorie expenditure and introduction of regular physical exercise and a daily exercise record, diet and exercise designed to produce 0.7 kg of weight loss per week b: fenfluramine maximum 60 mg twice daily, nutrition and exercise advice c: waiting list control condition, participants told that they could not receive treatment at moment due to large number of applicants and would receive treatment at a later date **Allocated**: a: 15, b: 15, c: 15 **Completed**: a: 11, b: 11, c: 11 at 68 weeks **% Dropout**: a: 27%, b: 27%, c: 27% at 68 weeks **Assessed**: a: 11, b: 11, c: 11 at 68 weeks (ITT)	**Length of follow-up**: 68 weeks **Outcome**: weight data	Only groups a and c used for comparisons **Sponsorship**: Swedish Council for Social Science Research, Alfred E Benzon

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Pavlou, 1989 1 Pavlou, 1989 1ca: PSMF + Ex vs LCD + Ex Pavlou, 1989 1ce: PSMF + Ex vs VLCD (420 kcal) + Ex Pavlou, 1989 1cg: PSMF+ Ex vs VLCD (800 kcal) + Ex Pavlou, 1989 1db: PSMF vs LCD Pavlou, 1989 1df: PSMF vs VLCD (420 kcal) Pavlou, 1989 1dh: PSMF vs VLCD (800 kcal) Pavlou, 1989 1ea: VLCD (420 kcal) + Ex vs LCD + Ex Pavlou, 1989 1fb: VLCD (420 kcal) vs LCD Pavlou, 1989 1ga: VLCD (800 kcal) + Ex vs LCD + Ex	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: Boston University, USA **Period of study**: before 1989 **Inclusion criteria**: men, 26–52 years, euthyroid, free from any physical, psychological or metabolic impairment **Exclusion criteria**: not stated **Gender**: 160 men **Age** (years): mean (SD) a: 41.5 (7.59), b: 42.9 (6.63), c: 45.1 (10.0), d: 49.6 (8.4), e: 41.8 (10.44), f: 41.8 (7.57), g: 46.1 (9.33), h: 44.5 (9.6) (completers) **BMI** (kg/m^2): mean a: 32.54, b: 32.4, c: 32.07, d: 31.5, e: 30.13, f: 34.82, g: 31.89, h: 33.78 (completers) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 8 weeks plus 18 months post-treatment follow-up (weekly from baseline to week 8 then at 8 months and 18 months post-treatment) **Description of intervention**: a–h: all participants attended weekly educational sessions up to week 8 that included behaviour modification, diet and general nutrition and exercise education; all participants given multivitamins, daily food and activity record to week 8, non-caloric liquids including coffee were allowed in unrestricted amounts, a + b: BCDD where 1000 kcal/day selected from usual 4 food groups in quantities thought to meet basic requirements c + d: PSMF ketogenic diet of meat, fish and fowl used as only dietary source to provide equivalent of 1.2 high biological-value protein/kg of IBW or 1000 kcal/day, no CHO and all fat ingested came from meat, fish and fowl; 2.8 g potassium chloride daily e + f: DPC-70; assumed PSMF 420 kcal/day diet of powdered protein–CHO mix derived from calcium caseinate, egg albumin and fructose dissolved in water or other non-caloric liquid, fat content zero, fortified with vitamins and minerals to meet US Recommended Daily Allowance, mix 5 packets per day in 850 g of non-caloric liquid and consume no other nutrients; 2.8 g potassium chloride daily g + h: DPC-800; assumed VLCD 800 kcal/day diet provided in powdered form to be consumed similarly to DPC-70, provided a complete mixture of nutrients and similar nutritionally to BCDD except for fewer calories a + c + e + g: 90-minute supervised exercise programme 3 times/week from baseline to week 8 which consisted of 35–60 minutes of aerobic activity, e.g. walk–jog–run (70–85% max. heart rate), callisthenics and relaxation techniques b + d + f + h: participants to continue normal daily activity and not to participate in any form of additional supervised and/or unsupervised physical activity during initial 8 weeks	**Length of follow-up**: 86 weeks **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, SBP, DBP	Weight data derived from graph and SDs calculated **Sponsorship**: part funded by Sandoz Nutrition

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Pavlou, 1989 1hb: VLCD (800 kcal) vs LCD			**Allocated**: 160 **Completed**: a: 10, b: 11, c: 16, d: 16, e: 10, f: 13, g: 18, h: 16 at 18 months post-treatment **% Dropout**: 31% at 18 months post-treatment **Assessed**: a: 10, b: 11, c: 16, d: 16, e: 10, f: 13, g: 18, h: 16 at 18 months post-treatment (completers)		
Pavlou, 1989 2 Pavlou, 1989 2a: no Ex Pavlou, 1989 2b: Ex	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: Boston University **Period of study**: before 1989 **Inclusion criteria**: men, 26–52 years, euthyroid, free from any physical, psychological or metabolic impairment **Exclusion criteria**: not stated **Gender**: 24 men **Age** (years): mean (SD) a: 49.2 (6.48), b: 44.8 (7.84), c: 46.1 (5.14), d: 48.1 (4.65) (completers) **BMI** (kg/m^2): mean a: 31.75, b: 31.92, c: 31.11, d: 30.4 (completers) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 weeks plus 36 months post-treatment follow-up, contacted 16 times (weekly from baseline to week 12, then at 6, 8 and 18 months post-treatment) **Description of intervention**: a + b + c + d: all participants attended weekly educational sessions up to week 12 that included behaviour modification, diet and general nutrition and exercise education; all participants given multivitamins, daily food and activity record to week 12, non-caloric liquids including coffee were allowed in unrestricted amounts a + b: BCDD where 1000 kcal/day selected from usual 4 food groups in quantities thought to meet basic requirements c + d: PSMF, ketogenic diet of meat, fish and fowl used as only dietary source to provide equivalent of 1.2 high biological-value protein/kg of IBW or 1000 kcal/day, no CHO and all fat ingested came from meat, fish and fowl; 2.8 g potassium chloride daily a + c: 90-minute supervised exercise programme 3 times/week from baseline to week 12 which consisted of 35–60 minutes of aerobic activity, e.g. walk–jog–run (70–85% max. heart rate), callisthenics and relaxation techniques b + d: participants to continue normal daily activity and not to participate in any form of additional supervised and/or unsupervised physical activity during initial 8 weeks **Allocated**: 24 overall **Completed**: a: 5, b: 6, c: 5, d: 5 at 36 months post-treatment **% Dropout**: 13% at 36 months post-treatment **Assessed**: a: 5, b: 6, c: 5, d: 5 at 36 months post-treatment	**Length of follow-up**: 168 weeks **Outcome**: weight data	Weight data derived from graph, SDs calculated **Sponsorship**: part funded by Sandoz Nutrition

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Pearce, 1981	**Randomisation**: randomly assigned from stratified blocks. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: University of Manitoba, Winnipeg, Canada **Period of study**: before July 1980 **Inclusion criteria**: women, 20–60 years, ≥ 9 kg or ≥ 20% overweight (Metropolitan Life Insurance tables), doctor's permission, $50 deposit refunded on attendance of 9 out of 10 sessions and 3 follow-ups **Exclusion criteria**: involvement in another weight control programme or psychotherapy, obesity-related morbidity, e.g. diabetes, thyroid problems, colitis, ulcers, taking medication that affected water retention, appetite or metabolism, pregnant or planning pregnancy, unwilling to commit for 15 months or unwilling to pay $50 deposit, husbands unwilling to participate **Gender**: 68 women **Age** (years): mean 39.0 overall **Weight** (kg): mean 87.43 overall **Baseline comparability**: not stated	**Timing of active intervention**: a + b: 12 months, contacted 14 times (baseline then weekly for initial 10 weeks, then at 3, 6 and 12 months) **Description of intervention**: a + b + c + d: advised to reduce calorie intake to pretreatment weight × 7 in pounds (1350 kcal/day), minimum 1000 kcal/day, and advised to increase physical activity if weight not lost a + b + c: training in behavioural self-control including self-monitoring, imagery techniques, stimulus control and behaviour management methods a: cooperative spouse condition, spouses attended and actively helped wives to lose weight, spouses monitored each other's behaviour b: wives alone condition, spouses not involved and wives attended alone, wife unobtrusively monitored husband's behaviour c: non-participating spouse condition, spouse sent letter asking them to detach themselves from wife's weight losing efforts, wife attended alone and self-monitored and unobtrusively monitored husband's behaviour d: focus directed at hypothetical and underlying causes of overeating, no training on behavioural techniques, attention diverted from current behaviours to past ones e: waiting list control, participants received treatment after initial 10 weeks (therefore data not used for subsequent analyses) **Allocated**: a: 14, b: 13, c: 14, d: 13, e: 14 **Completed**: a: 12, b: 12, c: 12, d: 12 at 12 months **% Dropout**: a: 14%, b: 8%, c: 14%, d: 15% at 12 months **Assessed**: a: 12, b: 12, c: 12, d: 12 at 12 months	**Length of follow-up**: 12 months **Outcome**: weight data	Only groups a + b used for comparison **Sponsorship**: none mentioned
Phenix, 1991	**Randomisation**: cluster randomised, participants chose 1 of 7 predetermined class times, each class time was assigned 15	**Location**: California School of Professional Psychology, Fresno, USA **Period of study**: before 1990 **Inclusion criteria**: women, 18–62 years, 115–200% IBW	**Timing of active intervention**: a–f: 8 weeks and follow-up at 12 months, contacted 10 times (baseline, 2 hours each week for initial 8 weeks, then at 12 months) h: contacted at baseline and at 12 months for the purpose of this study (received same treatment as group g after acting	**Length of follow-up**: 12 months **Outcome**: weight data	Cluster RCT **Sponsorship**: none given

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
	participants in a non-random manner, 7 treatment conditions were randomly assigned to 7 times. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	(Metropolitan Life Insurance tables, 1959), non-refundable $10 materials fee, written approval by own physician, $32 deposit with refund contingent on attendance and adherence **Exclusion criteria**: participation in a weight loss programme, obesity-related health disorders, e.g. diabetes and heart disease; medications that would affect weight loss, pregnancy or planning pregnancy in next 12 months **Gender**: 105 women **Age** (years): not stated **Weight** (kg): mean (SD) a: 85.16 (17.12), b: 81.12 (14.61), c: 76.23 (10.69), d: 85.77 (14.28), e: 76.43 (8.71), f: 84.17 (22.35), g: 79.24 (11.54), h: 75.97 (12.54) **Baseline comparability**: yes	as waiting list control for initial 8 weeks, details of which are not reported) **Description of intervention**: a–f: all participants given nutrition education and advised regarding 1000–1200 kcal/day diet consisting of 65% complex CHO, 20% fat, 15% protein and 100 mg cholesterol (American Heart Association diet) a: weekly food tasting for initial 8 weeks of treatment b: overt behaviour therapy which focused on self-control including self-monitoring strategies, stimulus control, cue reduction, slowing the rate of eating, coping and problem solving c: cognitive behaviour therapy which focused on modifying maladaptive eating behaviour, including cognitive restructuring and relapse prevention techniques d: given exercise education and home exercise assignments consisting of 20 minutes of aerobic exercise 3 times/week estimated to use 200–300 kcal per session using graded intensity and working at 70–80% maximum heart rate e: same exercise as group d plus same overt behaviour therapy as group b f: same exercise as groups d and e plus same cognitive behaviour therapy as group c g: same exercise as groups d, e and f plus same overt behaviour therapy as groups b and e plus same cognitive behaviour therapy as groups c and f h: received baseline testing and assessment at 12 months and told would receive most successful active treatment of the trial after the initial 8 weeks; received same treatment at week 9 as group g (results not reported) **Allocated**: 105 in total, numbers allocated to each group at baseline not stated a: 12, b: 12, c: 12, d: 14, e: 10, f: 13, g: 11, h: 11 (total 95) at week 9 **Completed**: a: 11, b: 11, c: 10, d: 13, e: 10, f: 11, g: 10, h: 10 at 12 months **% Dropout**: 18% at 12 months **Assessed**: a: 11, b: 11, c: 10, d: 13, e: 10, f: 11, g: 10, h: 10 at 12 months		

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Pritchard, 1997	**Randomisation**: random numbers table. Allocation concealment: B(II) **Assessor blinding**: no **ITT**: yes	**Location**: University of Melbourne, Australia **Period of study**: before 1998 **Inclusion criteria**: men, 35–55 years, satisfactory cardiovascular fitness test, BMI 26–35 kg/m^2, 110–130% above IBW, otherwise healthy **Exclusion criteria**: not stated **Gender**: 66 men **Age** (years): mean (SD) a: 43.6 (6.0), b: 44.9 (6.5), c: 42.3 (4.5) 12-month completers only (n = 58) **BMI** (kg/m^2): mean (SD) a: 29.0 (2.8), b: 29.2 (2.8), c: 28.6 (2.8) 12-month completers only (n = 58) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 18 months, contacted 19 times (baseline then monthly, participants also encouraged to attend bimonthly motivational group breakfasts or lunch meetings with guest speakers or videos relevant to diet, exercise and health issues) **Description of intervention**: a: participants advised to adhere to low-fat intake of 22–25%/day and 500 kcal/day deficit, to avoid all foods rich in fat, discouraged from eating more than 1 sweet/day and more than 2 alcoholic drinks/day; personalised dietary plan designed to meet Recommended Daily Intake for use in Australia, given 'The Weight Loss Guide' by the Australian Heart Foundation, exercise restricted to prestudy level, completion of daily adherence calendar, at 13 months treatment b was added b: participants selected their own unsupervised aerobic exercise regimen of at least 3 sessions of 30 minutes each week at 65–75% maximum heart rate; initial heart rate over 33 hours of normal activity which included the selected exercise used to determine personal heart rate target zone; 11 participants walked, 2 jogged, 2 alternated jogging and swimming, 3 attended the gym and 3 rode exercise bikes, participants exercised 3–7 sessions/week, advised to avoid change in food intake, completion of daily adherence calendar, at 13 months treatment a was added c: attended monthly weight monitoring sessions where counselled to follow usual food and exercise habits, participants told would be able to enter weight loss programme at the end of this study, at 13 months treatments a + b were added **Allocated**: a: 24, b: 22, c: 20 **Completed**: a: 18, b: 21, c: 19 at 12 months **% Dropout**: a: 25%, b: 5%, c: 5% at 12 months Continued at month 13: a: 9, b: 14, c: 16 **Completed**: a: 9, b: 14, c: 16 **Assessed**: a: 18, b: 21, c: 19 at 12 months; a: 9, b: 14, c: 16 at 18 months	**Length of follow-up**: 18 months **Outcome**: weight data	Author provided unpublished report, data only used up to 12 months, discrepancy in data between reports **Sponsorship**: Victorian Health Promotion Foundation, William Buckland Foundation, Department of Medicine, University of Melbourne

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Pritchard, 1999 Pritchard, 1999a: dietitian vs control Pritchard, 1999b: doctor + dietitian vs control	**Randomisation**: random numbers tables Allocation concealment: B(II) **Assessor blinding**: no **ITT**: yes	**Location**: University general practice, Lockridge, Western Australia **Period of study**: November 1992–May 1994 **Inclusion criteria**: either gender, 25–65 years, patients with known history of type 2 diabetes, hypertension (BP > 140/90 mmHg at screening plus 2 similar recordings in past medical notes) and/or overweight (BMI > 25 kg/m^2) **Exclusion criteria**: mental illness, intellectual handicap, terminal illness, acute illness, pregnancy, taking part in other health education programmes **Gender**: 198 women, 75 men **Age** (years): 199 of 273 participants < 50 years **Weight** (kg): mean a: 91.7, b: 85.5, c: 89.1 **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted 7 times (baseline then 6 times by dietitian spread evenly over 12 months) c: contacted twice (baseline and 12 months) **Description of intervention**: a + b: counselling focused on principles of good nutrition and exercise and addressed problem areas in lifestyle and dietary patterns; counselled on food, shopping and cooking, food selection, meal planning and exercise programmes, advised to complete food records and diet history, advised to reduce total energy intake and to reduce intake from fat to ≤ 30%, CHO ≥ 50% and 20% protein; participants discouraged from smoking and to have 2 or more alcohol-free days/week with no more than 2 alcoholic standard drinks/day for women and 4 for men b: in addition participants were seen by GP at baseline and saw same GP on 2 other occasions during the 12 months for 5 minutes each time to encourage and monitor the participant c: participants received results of initial screening measurements and advised that queries were to be discussed with doctor at appointment, participants received their usual care by GP but did not receive any counselling by dietitian, mailed to reattend at 12 months **Allocated**: a: 92, b: 88, c: 90 **Completed**: a: 65, b: 48, c: 64 at 12 months **% Dropout**: a: 29%, b: 45%, c: 29% at 12 months (p = 0.022 for group b vs other groups) **Assessed**: a: 92, b: 88, c: 90 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, HbA_{1c} (type 2 diabetics only), BP (hypertensives only), costs	**Sponsorship**: Western Australian Health Promotion Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Rosenthal, 1980	**Randomisation**: stratified blocks of % overweight and age, no other details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Connecticut, USA **Period of study**: before 1980 **Inclusion criteria**: women, ≥ 10% above IBW (Metropolitan Life Insurance tables, 1970), husband and wife both willing to attend meetings every 2 weeks, willing to comply with demands of the weight loss programme, $10 commitment deposit (returned at first follow-up visit), signed medical release form certifying good health, signed form stating will not participate in concurrent obesity therapy **Exclusion criteria**: not stated **Gender**: 43 women **Age** (years): mean 34.5 overall **BMI** (kg/m^2): mean a: 27.56, b: 29.29, c: 28.80 (mean BMI for groups a + b: 28.43) **Baseline comparability**: yes	**Timing of active intervention**: a + b + c: 30 weeks, contacted 11 times (baseline then 8 × 75-minute group sessions twice monthly, follow-up at 6 weeks post-treatment and 3 years post-treatment) **Description of intervention**: a: husbands attended all 8 sessions with wives, 'Slim chance in a fat world' weight loss programme, husbands assigned readings and informed of behavioural ways in which they could help their wives to lose weight; sessions 5–8 discussed couples' specific situations b: husbands attended first 4 sessions to learn techniques for helping their wives to lose weight, then wives attended alone for following sessions, identical weight loss programme to group a c: no husband involvement, identical weight loss programme to groups a and b **Allocated**: unclear **Completed**: a: 4, b: 7, c: 9 at 3 years post-treatment (186 weeks in total) **% Dropout**: 53% overall at 3 years post-treatment **Assessed**: a: 4, b: 7, c: 9 at 3 years post-treatment	**Length of follow-up**: 186 weeks **Outcome**: weight data	Data combined for mean change in weight at 3 years post-treatment for groups a + b (full husband involvement and partial husband involvement, respectively) as no significant difference in weight loss found between these 2 groups at 30 weeks, SDs calculated **Sponsorship**: National Science Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Shah, 1996	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: University of Minnesota, USA **Period of study**: before 1996 **Inclusion criteria**: healthy, non-smoking women, 25–45 years, 20–40% above IBW **Exclusion criteria**: not stated **Gender**: 122 women **Age** (years): not stated **Weight** (kg): mean (SD) a: 79.92 (4.45), b: 79.70 (4.40) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 26 weeks plus follow-up visit at 12 months, contacted 18 times (baseline, then 16 times in first 26 weeks, then at 12 months) **Description of intervention**: a + b: all participants counselled on diet, exercise, menu planning, eating out, stimulus control, problem solving, social assertion, goal setting, relapse prevention; cooking demonstrations given, all participants advised to walk for 30 minutes on 5 days/week, all participants advised to keep a daily record of food intake and physical activity a: 1000–1200 kcal/day, fat intake ≤ 30% of total energy intake, ≤ 6 oz (170 g) meat/day (only poultry, fish and lean red meat), limit fats, oils, eggs and high-fat desserts, snacks and dairy produce, and replace with low-fat alternatives, increase complex CHO and limit simple sugars b: reduce fat intake to 20 g/day, unlimited complex CHO, limit meat, fish and poultry to ≤ 2 oz (57 g)/day, specific food recommendations otherwise the same as group a **Allocated**: 122 in total **Completed**: a: 39, b: 36 at 12 months **% Dropout**: 39% overall at 12 months **Assessed**: a: 39, b: 36 at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, QoL	Mean change in weight at 12 months calculated from actual values, SDs calculated **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Sikand, 1988	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: Baylor College of Medicine, Houston, USA **Period of study**: before April 1988 **Inclusion criteria**: women, 21–60 years, obese **Exclusion criteria**: not stated **Gender**: 30 women **Age** (years): mean (SD) a: 39.8 (9.1), b: 37.8 (8.4) **Weight** (kg): mean (SD) a: 105.6 (23.6), b: 106.6 (15.2) **Baseline comparability**: yes	**Timing of active intervention**: a: 4 months, with telephone follow-up at 2 years, contacted 34 times (baseline, twice weekly for initial 4 months, then at 2 years) b: 4 months, with telephone follow-up at 2 years, contacted 18 times (baseline, weekly for initial 4 months, then at 2 years) **Description of intervention**: a + b: all participants placed on a VLCD (calorie content not given) consisting solely of milk-based protein powder for initial 4 months, received nutritional counselling, group support and discussion of behaviour modification strategies; all participants invited to an ongoing pay-for-service programme offered at clinic sponsoring the study after active treatment period a: received structured aerobic exercise programme twice weekly for first 4 months with additional exercise encouraged on other days b: participants neither encouraged to nor discouraged from exercising **Allocated**: a: 15, b: 15 **Completed**: a: 7, b: 8 at 2 years **% Dropout**: a: 53%, b: 47% at 2 years **Assessed**: a: 7, b: 8 at 2 years	**Length of follow-up**: 2 years **Outcome**: weight data	**Sponsorship**: Ross Laboratories

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Simonen, 2000	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Helsinki, Finland **Period of study**: before August 1999 **Inclusion criteria**: men and postmenopausal women, diagnosis of type 2 diabetes in past 2 years (fasting plasma glucose ≥ 7.0 mmol/l) **Exclusion criteria**: insulin therapy, diabetic microangiopathy, hepatic or thyroid disease; unstable angina pectoris or MI; or invasive coronary artery disease treatment in previous year **Gender**: 3 women, 13 men **Age** (years): mean (SD) a: 51.1 (8.8), b: 54.3 (3.4) **BMI** (kg/m^2): mean a: 31.94, b: 32.32 **Baseline comparability**: fasting plasma glucose and HbA_{1c} differed significantly between groups ($p < 0.05$)	**Timing of active intervention**: a + b: 3 months plus follow-up at 2 years **Description of intervention**: a + b: 6 week pretreatment phase consisting of *ad libitum* diet at home while metabolic tests carried out a: participants' dose of glibenclamide adjusted so that plasma glucose < 7.0 mmol/l and biguanides discontinued; low-energy diet where participants advised to consume low-fat low-cholesterol diet for 3 months a: hypoglycaemia treatment discontinued; very low-energy diet consisting of 3 daily servings of 140 kcal/serving (Cambridge diet), 1 serving = 14.2 g protein, 15 g CHO, 2.7 g fat, essential minerals, trace nutrients and vitamins for 3 months a + b: from month 4 until month 24 diets individually tailored by dietitian to provide daily energy balance of zero **Allocated**: a: 6, b: 10 **Completed**: a: 6, b: 10 at 24 months **% Dropout**: a: 0%, b: 0% at 24 months **Assessed**: a: 6, b: 10 at 24 months	**Length of follow-up**: 24 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, fasting plasma glucose	All 16 participants analysed in aggregate, author replied, only weight data outcome used as treatment by hypoglycaemic medications differed between groups **Sponsorship**: Helsinki University Central Hospital, Finnish Diabetes Research Association, The Howard Foundation

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Stenius-Aarniala, 2000	**Randomisation**: shuffling cards with the help of someone not involved in the study. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: private outpatient centre, Helsinki, Finland **Period of study**: before January 2000 **Inclusion criteria**: either gender, 18–60 years, BMI 30–42 kg/m^2, diagnosis of asthma with spontaneous diurnal variation or a bronchodilator response of ≥ 15%, non-smoker or having stopped smoking for ≥ 2 years and before the age of 50 **Exclusion criteria**: pregnancy, history of bulimia or anorexia, unstable angina or arrhythmia, untreated thyroid disease, symptomatic liver or gallbladder disorder, any other severe disease, insulin treatment, systemic steroid treatment, history of food allergy or intolerance to any component of the study's very low-energy diet preparation (Nutrilett), e.g. soya, fish, chocolate or lactose, history of adverse reactions to peas, beans or peanuts, poor motivation **Gender**: 29 women, 9 men **Age** (years): mean (range) a: 49.7 (34–60), b: 48.3 (23–60) **BMI** (kg/m^2): mean (range) a: 35.8 (31.3–39.4), b: 36.7 (32.8–41.8) **Baseline comparability**: yes for gender, age and weight	**Timing of active intervention**: a + b: 12 months, contacted 16 times (12 × 30-minute group sessions during initial 14 weeks, then at week 14, month 6 and month 12) **Description of intervention**: a + b: 2–3 week pretreatment phase consisting of lung function tests and laboratory tests to fulfil exclusion and inclusion criteria, then 2 weeks of baseline measurements a: 14-week weight reduction programme consisting of 12 × 30-minute group sessions and including 8 weeks very low-energy diet (Nutrilett) consisting of 420 kcal/day containing daily allowances of all essential nutrients; discussed same themes as controls but at a later date so that each group had the same amount of education about asthma and allergy at end of treatment b: 12 × 30-minute group sessions during initial 14 weeks where themes chosen by participants were discussed freely **Allocated**: a: 19, b: 19 **Completed**: a: 19, b: 19 at 52 weeks **% Dropout**: a: 0%, b: 0% at 52 weeks **Assessed**: a: 19, b: 19 at 52 weeks (ITT)	**Length of follow-up**: 52 weeks **Outcomes**: weight data, lung function tests, adverse events, QoL	SDs for mean change in weight calculated **Sponsorship**: The Finnish Cultural Association, Association of the Pulmonary Disabled, Wilhelm and Else Stockmann Foundation, Nycomed Pharma

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Straw, 1983 Straw, 1983a: weigh-in maintenance Straw, 1983b: individual problem-solving maintenance	**Randomisation**: randomised by blocks on percentage fat, rerandomised at week 11 to one of 2 maintenance conditions (blocked within treatment group on basis of amount of weight lost in treatment). Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Chicago, USA **Period of study**: before 1983 **Inclusion criteria**: women, ≥ 35% of body weight as fat (skinfold caliper) **Exclusion criteria**: serious physical or emotional problems, problems that required a special diet, e.g. diabetes or hypoglycaemia, severely limited physical activity, endocrine disorder, Beck Depression Inventory score ≥ 20, schedule did not allow random assignment **Gender**: 49 women **Age** (years): mean: 39.33 *n* = 42 (completers only) **Weight** (kg): mean (SD) a: 85.16 (13.97), b: 86.73 (16.52), c: 85.44 (14.66) **Baseline comparability**: not stated	**Timing of active intervention**: a + b + c: 10 weeks, contacted 11 times (baseline then 1 hour weekly for 10 weeks) a1 + b1 + c1: 42 weeks, contacted 9 times (monthly from week 11 to 12 months) a2 + b2 + c2: 42 weeks, contacted 12 times (30 minutes twice monthly from week 11 for 3 months, then monthly to 12 months) **Description of intervention**: a + b: participants required to purchase Ferguson's book '*Learning to eat*' and to complete all assignments in it; topics included self-monitoring, stimulus control, eating style, problem solving, activity management and social support a: participants seen in groups of 8–10 b: participants seen individually c: individually tailored, individually administered behavioural treatment based on food diaries, pedometer readings and supplementary questionnaires if needed, aim for 4 miles (6.4 km)/day walking, targeted 2–3 problem areas first using stimulus control, elimination exercises, activity management techniques, relaxation, cognitive therapy, assertiveness training, cognitive ecology, snack and cue elimination techniques a1 + b1 + c1: weight check each month where received encouragement a2 + b2 + c2: individual problem solving where participants determined topic and discussed for 30 minutes twice a month, then monthly to month 12 **Allocated**: a: 18, b: 15, c: 15; at week 11 a: 12, b: 12, c: 14 **Completed**: a1: 8, b1: 8, c1: 8 at 12 months; a2: 5, b2: 5, c2: 6 (includes 2 in a1 and 2 in b1 who did not wish to be rerandomised at week 11 and so received weigh-in treatment only) **% Dropout**: 18% overall at 12 months **Assessed**: a1: 6, b1: 6, c1: 8 at 12 months; a2: 5, b2: 5, c2: 6 at 12 months	**Length of follow-up**: 12 months **Outcome**: weight data	Mean change in weight calculated from change at week 10 plus change during weeks 11–52, SDs calculated, group c1 and c2 not used in comparisons **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Swinburn, 2001	**Randomisation**: unmarked envelope system, 6 participants from 1 worksite (Pacific Islands, all women) were assigned to active treatment group a. Allocation concealment: C **Assessor blinding**: no **ITT**: no	**Location**: University of Auckland, New Zealand **Period of study**: before November 1999 **Inclusion criteria**: either gender, ≥ 40 years, IGT (OGTT, 2-hour plasma glucose 7.8–11.0 mmol/l) or high normal plasma glucose (OGTT, 2-hour plasma glucose 7.0–7.8 mmol/l) **Exclusion criteria**: not stated **Gender**: 35 women, 101 men **Age** (years): mean (SD) a: 52.5 (6.5), b: 52.0 (6.7) **BMI** (kg/m^2): mean (SD) a: 29.08 (4.47), b: 29.17 (4.02) **Baseline comparability**: yes	**Timing of active intervention**: a: 1 year with follow-up to 5 years, contacted 116 times (baseline, monthly sessions for 1 year, then at 2, 3 and 5 years) b: assessed 6 times (baseline, 6 months, 1, 2, 3 and 5 years) **Description of intervention**: a: reduced-fat *ad libitum* diet, education and identification of strategies to reduce fat intake, personal goal setting, self-monitoring through food diaries, food label reading b: usual diet, general dietary advice regarding healthy food choices given at baseline only **Allocated**: 176 in total **Completed**: a: 66, b: 70 at 1 year; a: 47, b: 57 at 2 years; a: 48, b: 51 at 3 years; a: 51, b: 52 at 5 years **% Dropout**: 24% overall at 5 years **Assessed**: a: 66, b: 70 at 1 year; a: 47, b: 57 at 2 years; a: 48, b: 51 at 3 years; a: 51, b: 52 at 5 years	**Length of follow-up**: 5 years **Outcomes**: weight data, fasting plasma glucose, deaths	**Sponsorship**: Auckland Medical Research Foundation, National Heart Foundation of New Zealand, Lotteries Medical Board, Health Research Council of New Zealand

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
TAIM, 1992	**Randomisation**: stratified within clinical centre and by race, computer allocated by coordinating centre. Allocation concealment: A **Assessor blinding**: blinded to drug status only **ITT**: no	**Location**: 3 clinical centres in USA **Period of study**: before July 1991 **Inclusion criteria**: either gender, 21–65 years, 110–160% IBW, BP untreated or BP medication discontinued 2 weeks before start of study, 1 member per household, treated DBP ≤ 99 mmHg or untreated DBP 90–104 mmHg at preliminary screening, 90–100 mmHg at first clinic visit, < 115 mmHg at second visit (prerandomisation) **Exclusion criteria**: MI during past year or history of MI, history or other evidence of stroke, bronchial asthma, diabetes mellitus requiring insulin; history or other evidence of allergy to thiazides or β-blockers, creatinine ≥ 180 μm/l at baseline, other major disease, e.g. kidney disease, liver disease, cancer, pregnancy or likelihood of pregnancy during study, lifestyle or other conditions likely to affect compliance **Gender**: 100 women, 100 men **Age** (years): mean (SD) a: 48.6, b: 46.8 **BMI** (kg/m^2): mean a: 30.45, b: 30.14 **Baseline comparability**: significantly more women than men in group a	**Timing of active intervention**: a: 30 months, contacted minimum 25 times (baseline, 10 group sessions held weekly and monthly assessment in initial 6 months then every 6–12 weeks up to a maximum of 30 months) b: contacted 5 times (baseline, and 6, 12, 18 and 24 months) **Description of intervention**: b: no change in diet and given placebo a: diet counselling and nutrition education aimed at behaviour change, related activities (exercise) aimed at weight loss to achieve blood pressure control, given individual goal of calorie intake and weight loss of 10% baseline weight or 4.5 kg (whichever greater); given placebo a + b: all participants given step-up medication if necessary to control blood pressure, administered in double-blind fashion; if DBP ≥ 99 mmHg or 90–94 mmHg at 2 visits with 3-month interval or 95–99 mmHg at 2 visits with 2-week interval then 25 mg chlorthalidone or 50 mg atenolol prescribed, if still not controlled then open-label therapy used (known antihypertensive medication) **Allocated**: a: 100, b: 100 **Completed**: not clear **% Dropout**: not clear **Assessed**: a: 57, b: 61 at years 1 and 2 (participants excluded from analysis if failed to attend all 6, 12, 18 and 24-month assessments)	**Length of follow-up**: 2.5 years minimum **Outcomes**: weight data, treatment failures, deaths	**Sponsorship**: part funded by National Institutes of Health, ICI Americas, AH Robins Company

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
TOHP I, 1992	**Randomisation**: high weight strata of TOHP I randomised. Allocation concealment: A **Assessor blinding**: no **ITT**: possibly	**Location**: multicentre trial, USA **Period of study**: before March 1992 **Inclusion criteria**: either gender, 30–54 years, high–normal DBP and not taking antihypertensive drugs for past 2 months, BP based on 3 visits 10–30 days apart with cumulative averages of 75–97, 77–94, 80–89 mmHg; BMI 26.1–36.1 kg/m^2 for men, 24.3–36.1 kg/m^2 for women **Exclusion criteria**: clinical or laboratory evidence of cardiovascular or other life-threatening or disabling diseases, diabetes mellitus, chronic renal failure, cancer, pregnancy or wishing to become pregnant, psychiatric disorders, unwillingness or inability to comply with intervention or data collection, cholesterol ≥ 6.7 mmol/l **Gender**: 179 women, 385 men **Age** (years): mean (SD) a: 43.1 (6.0), b: 42.4 (6.2) **Weight** (kg): mean (SD) a: 90.2 (13.3), b: 89.3 (13.0) **Baseline comparability**: higher proportion of men in group a than in group b ($p = 0.016$)	**Timing of active intervention**: a: 18 months, contacted at baseline then 90-minute sessions weekly for first 14 weeks, then every 2 weeks, then every month to 18 months b: assessed 5 times (baseline, and 3, 6, 12 and 18 months) **Description of intervention**: a: weight reduction intervention focused on reducing calorie intake, reducing fat, sugar and alcohol intake; shopping, cooking and food selection behaviours; moderate increase in calorie expenditure through walking briskly 4–5 times/week for 45 minutes each session at 40–55% heart rate reserve; behavioural self-management through goals, reinforcement, social support, graphing weight, problem solving, relapse prevention and coping strategies; food and exercise diaries b: no treatment received **Allocated**: a: 308, b: 256 **Completed**: a: 293, b: 235 **% Dropout**: a: 5%, b: 8% at 18 months **Assessed**: a: 547, b: 554 at 36 months (weight data only)	**Length of follow-up**: 18 months **Outcomes**: weight data, SBP, DBP, mortality, development of hypertension	Sodium reduction and stress management treatment groups excluded from analyses **Sponsorship**: National Institutes of Health, Marion Laboratories, Schering-Plough, Warner-Lambert, Albion Laboratories

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
TOHP II, 1997	**Randomisation**: stratified by clinic, randomly assigned by phone or sealed randomisation envelopes. Allocation concealment: A **Assessor blinding**: yes **ITT**: possibly	**Location**: 9 clinical centres in USA **Period of study**: December 1990–March 1995 **Inclusion criteria**: either gender, 30–54 years, 110–165% IBW or BMI 26.1–37.4 kg/m^2 (men), 24.4–37.4 kg/m^2 (women), DBP 83–89 mmHg (average of all 9 measurements), SBP <140 mmHg, completion and return of 24-hour and separate 8-hour urine collection and 3-day food record **Exclusion criteria**: medically diagnosed hypertension, history of CVD, diabetes mellitus, malignancy in past 5 years (other than non-melanoma skin cancer), other serious life-threatening illness requiring medical treatment, current use of prescription medication that affects BP and non-prescription diuretics, serum creatinine ≥ 1.7 mg/dl in men and ≥ 1.5 mg/dl in women or casual serum glucose ≥ 200 mg/dl, >21 alcoholic drinks/week, current pregnancy or intention of pregnancy **Gender**: 409 women, 782 men **Age** (years): mean (SD) a: 43.4 (6.1), b: 43.2 (6.1) **BMI** (kg/m^2): not stated by group **Weight** (kg): mean (SD) a: 93.4 (14.1), b: 93.6 (13.5) **Baseline comparability**: yes	**Timing of active intervention**: a: minimum of 36 months, contacted 3 times at baseline plus 1 individual visit, then weekly for 14 weeks, every 2 weeks for the next 6 weeks, 3–6 minimodules each year supplemented by participant-initiated contact every 2 weeks b: assessed 7 times (baseline then every 6 months for a minimum of 36 months) **Description of intervention**: a: 4 phases of programme including preintensive phase of 1–4 months' wait before start of treatment when participants advised to prevent weight gain and contacted monthly; intensive phase during initial 14 weeks with mean weight loss goal of ≥ 4.5 kg or to achieve IBW during first 6 months then to maintain weight, reduce calorie intake, count fat intake, increase physical activity to 4–5 times/week for 30–45 minutes per session at 40–55% heart rate reserve, supervised exercise in 4 of 14 initial weekly sessions; transitional phase during weeks 15–26 of treatment with behavioural skills such as individual problem solving, relapse prevention, cognitive reframing and coping imagery; extended phase from week 27 onwards consisted of minimodules including topics such as 'supermarket savvy', 'stress and time management', 'walking across America' b: no treatment received **Allocated**: a: 595, b: 596 **Completed**: a: 547, b: 554 **% Dropout**: a: 8%, b: 7% at 36 months **Assessed**: a: 547, b: 554 at 36 months (weight data only)	**Length of follow-up**: 36–48 months **Outcomes**: weight data, SBP, DBP, mortality, development of hypertension	Numbers in each group assumed for 12- and 24-month data derived from graph, SDs calculated **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
TONE, 1998	**Randomisation**: 2 × 2 factorial design, 2 overweight participants randomly assigned for every 1 non-overweight participant; stratified by weight and site. Allocation concealment: B(I) **Assessor blinding**: yes **ITT**: no	**Location**: 4 academic health centres, in USA **Period of study**: August 1992–December 1995 **Inclusion criteria**: either gender, stable health, 60–80 years, mean SBP < 145 mmHg, mean DBP < 85 mmHg, taking 1 antihypertensive medication, taking 2 antihypertensive medications if successfully stepped down before randomisation; obese strata involved people with BMI ≥ 27.8 kg/m^2 for men and ≥ 27.3 kg/m^2 for women, independent in their daily living activities, permission of personal physician, ability to alter diet and increase physical activity **Exclusion criteria**: cancer in the past 5 years, type 1 diabetes, severe hypertension, CVD, peripheral vascular disease, psychiatric illness, current or recent (in past 6 months) drug therapy for asthma or chronic obstructive lung disease, corticosteroid therapy for > 1 month, ≥ 4.5 kg involuntary and unexplained weight loss in the past year, serum creatinine > 2 mg/dl, serum potassium > 5.5 mEq/l, haemoglobin < 11g/dl, plasma glucose > 260mg/dl, volume of baseline 24-hour urine specimen < 500 ml, > 14 alcoholic drinks/week, current or planned participation in another intervention study, another member of household was a member of TONE **Gender**: 162 women, 132 men **Age** (years): mean (SD) a: 66 (5), b: 66 (4) **BMI** (kg/m^2) mean (SD): a: 31.0 (2.3), b: 31.3 (2.3) **Baseline comparability**: yes	**Timing of active intervention**: a: median 29 months contacted approximately 45 times (baseline then weekly for first 4 months, then fortnightly for the next 3 months, then monthly) b: median 29 months contacted approximately 10 times (baseline then quarterly) **Description of intervention**: a + b: antihypertensive medications withdrawn 90 days after first group intervention sessions, drug-specific tapering regimens where participants seen weekly and 3 additional fortnightly visits to confirm SBP < 150 mmHg and DBP < 90 mmHg a: the group goal was ≥ 4.5 kg weight loss in 6 months then weight maintenance; individual goals were 5–10% weight loss (depending on baseline BMI) by calorie deficit and increase in physical activity; behavioural therapy based on social action theory for lifestyle change, self-monitoring of calorie intake, eating behaviours and pulse rate; management of eating behaviours, relapse prevention; participants received individual feedback from food intake records and physical activity records, calorie counting of foods, practical advice on purchase and preparation of inexpensive foods available in supermarkets, group practice of safe, low-level exercise b: advised to maintain usual diet and physical activity, speakers led discussion on topics unrelated to blood pressure, CVD or diet **Allocated**: a: 147, b: 147 **Completed**: a: 137, b: unclear at 29 months **% Dropout**: a: 7%, b: unclear at 29 months **Assessed**: a: 133, b: 125 at 12 months; a: 131, b: 122 at 18 months; a: 104, b: 95 at 24 months; a: 60, b: 53 at 30 months	**Length of follow-up**: 29 months (median) **Outcomes**: weight data, adverse events, deaths, cancers, successful withdrawal of antihypertensive medications, MI, cerebrovascular accident	Report of 2 arms of a 4-arm study; author provided mean and SD change in weight at 12, 18, 24 and 30 months postrandomisation **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Torgerson, 1997	**Randomisation**: 100 sealed envelopes per hospital prepared in random order, no other details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: 2 Swedish outpatient clinics, NAL and Skene county hospitals **Period of study**: before April 1997 **Inclusion criteria**: either gender, 37–60 years, obese (non-surgery arm of SOS study) **Exclusion criteria**: not stated **Gender**: 74 women, 39 men **Age** (years): mean (SD) a: 47.3 (6.7), b: 46.9 (5.8) **BMI** (kg/m^2): mean (SD) a: 40.2 (3.3), b: 40.5 (4.3) **Baseline comparability**: yes	**Timing of active intervention**: a: 2 years, contacted 31 times (baseline then at 1, 2, 4, 6, 8, 12, 13, 14, 16, 18 and 20 weeks, then monthly) b: 2 years, contacted 28 times (baseline then at 1, 2, 4, 6 and 8 weeks, then monthly) **Description of intervention**: a: Modifast PSMF 456–608 kcal/day for 12 weeks then individualised hypocaloric diet of 1200–1400 kcal/day (women) or 1400–1800 kcal/day (men) consisting of 55% CHO, 15–20% protein, 25–30% fat, up to 2 years b: individualised hypocaloric diet of 1200–1400 kcal/day (women) or 1400–1800 kcal/day (men) consisting of 55% CHO, 15–20% protein, 25–30% fat, for 2 years a + b: all participants were asked to complete food records before each 6 monthly visit; all received behavioural support programme which included nutrition education and lifestyle advice, risk avoidance and coping strategies, cooking groups, physical activity groups offered such as swimming and physical training **Allocated**: a: 58, b: 55 **Completed**: a: 43, b: 44 at 2 years **% Dropout**: a: 26%, b: 20% at 2 years **Assessed**: a: 58, b: 55 at 2 years (ITT, LOCF)	**Length of follow-up**: 2 years **Outcomes**: weight data, adverse events, deaths	**Sponsorship**: Swedish Medical Research Council, Novartis Nutrition, Research and Development Committee of Älvsborg County, Sweden

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Tucker, 1991	**Randomisation**: randomly assigned before bariatric surgery, no further details. Allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: possibly	**Location**: USA **Period of study**: before July 1990 **Inclusion criterion**: accepted for bariatric surgery **Exclusion criteria**: not stated **Gender**: 21 women, 11 men (completers only) **Age** (years): mean 40.18 (n = 32) **BMI** (kg/m^2): mean (SD) a: 48.87 (11.24), b: 47.60 (7.14) n = 32 **Baseline comparability**: yes	**Timing of active intervention**: a + b: 2 years, contacted 9 times (baseline then monthly for first 6 months, then at 12 and at 24 months) **Description of intervention**: a + b: all participants watched then discussed a 13-minute videotape before surgery regarding appropriate 2-oz (60 g) meals, food groups and behavioural strategies to avoid nausea and vomiting; all participants received medical assessment monthly for first 6 months postsurgery, then at 12 and 24 months; all participants also received monthly telephone interviews for initial 6 months regarding food intake, physical activity and psychosocial functioning; food diaries completed a: participants received 12 sets of written materials concerning eating and lifestyle mailed to homes every 2 weeks for initial 6 months, and received individual behavioural consultations usually corresponding with medical assessments monthly for first 6 months, then at 12 and 24 months when had opportunity to discuss content of written materials **Allocated**: 60 overall **Completed**: a: 17, b: 15 at 2 years **% Dropout**: 47% overall at 2 years **Assessed**: a: 17, b: 15 at 2 years	**Length of follow-up**: 2 years **Outcome**: weight data	Weight change at 1 and 2 years calculated from actual values, SDs calculated **Sponsorship**: none mentioned

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Viegener, 1990	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Fairleigh Dickinson University and Franklin Delano Roosevelt VA Hospital, New York, USA **Period of study**: before October 1989 **Inclusion criteria**: women, 21–59 years, 25–99% overweight, physician's approval, $125 deposit (with return based on attendance and completion of food diaries) **Exclusion criteria**: obesity-related disorders **Gender**: 85 women **Age** (years): mean (SD) a: 47.10 (7.49), b: 47.13 (8.86) **Weight** (kg): mean (SD) a: 94.58 (12.64), b: 98.57 (15.91) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 12 months, contacted maximum of 39 times (baseline, weekly 2-hour group and individual sessions for first 26 weeks, then opportunity to attend group maintenance sessions twice monthly for 26 weeks) **Description of intervention**: a + b: all participants received behavioural therapy which included self-monitoring, stimulus control, self-reinforcement, cognitive modification and problem solving; all participants were advised to follow a regimen of programmed aerobic exercise with a target goal of 30 minutes/day for 6 days/week; all participants required to purchase a nutrition guide book and to complete daily food diary and daily exercise diary; a: 800 kcal/day diet for 4 days/week and 1200 kcal/day for 3 days/week consisting of ≤ 15% intake from fat on VLCD days and ≤ 25% fat on LCD days; each treatment session included significant focus on nutrition education with sample meals and practical guidance regarding low-fat and low-calorie foods b: 1200 kcal/day balanced deficit diet with 55% CHO, 30% fat and 15% protein **Allocated**: a: 42, b: 43 **Completed**: a: 30, b: 30 at 12 months **% Dropout**: a: 29%, b: 30% at 12 months **Assessed**: a: 30, b: 30 at 12 months	**Length of follow-up**: 52 weeks **Outcomes**: weight data, compliance	**Sponsorship**: part funded by VA Medical Research Service

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wadden, 1989	**Randomisation**: first of 2 cohorts stratified into 3 blocks based on degree overweight; no details regarding second cohort. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: University of Pennsylvania School of Medicine, USA **Period of study**: January 1983–1989 **Inclusion criteria**: Either gender, ≥ 25 kg above IBW (Metropolitan Life Insurance tables) **Exclusion criteria**: recent MI or evidence of cardiac abnormalities, history of cerebrovascular, kidney or liver disease, cancer, type 1 diabetes, severe psychiatric illness, pregnancy, contraindications to treatment by VLCD (assessed at screening), participants agreed not to participate in additional weight loss treatment before follow-up at 1 year post-treatment **Gender**: 76 women (completers only, men excluded from analyses due to small numbers) **Age** (years): mean (SEM) 42.1 (1.1) women completers only (n = 76) **BMI** (kg/m^2): mean (SEM) 39.4 (0.8) women completers only (n = 76) **Baseline comparability**: 2 cohorts significantly different regarding age (43.9 and 39.5)	**Timing of active intervention**: a: 16 weeks, contacted 25 times (90 minutes each week for 16 weeks, then months 1, 2, 3, 6, 9 and 12 post-treatment, 3 years and 5 years post-treatment) b + c: 25 weeks, contacted 39 times (90 minutes each week for 25 weeks, then 11 post-treatment visits every other week for first 2 months, then once a month for next 4 months, then every other month for last 6 months, 3 years and 5 years post-treatment) **Description of intervention**: b: 1000–1200 kcal/day diet of participants' choosing for 25 weeks, taught traditional behavioural methods of weight control which included recording eating behaviour, controlling stimuli related to eating, slowing rate of consumption, increasing lifestyle activity, nutrition education, modifying self-defeating thoughts and emotions, social support, reinforcing changes in eating and exercise behaviour a + c: 1000–1200 kcal/day for month 1, months 2 + 3, 400–500 kcal/day PSMF consisting of 3 servings of lean meat, fish or fowl and to avoid all other food with the exception of non-caloric beverages and bouillon, requested to drink at least 1.5 litres of water/day, daily supplements 3 g each of potassium and sodium chloride, and 800 mg calcium; month 4 refeeding to conventional foods, first fruit and vegetables, then bread and cereal, then fats c: in addition months 5 + 6 prescribed 1000–1200 kcal/day diet, extensive training in behaviour therapy throughout (see b); months 4, 5 + 6 addressed weight maintenance and included relapse prevention training and strategies for handling weight regain a + b + c: encouraged to increase physical activity by walking and using the stairs; diet records kept throughout active treatment; paid $10 for each visit and deposited $40 which was refunded after the 1-year follow-up visit **Allocated**: unclear **Completed**: 68 overall at 12 months post-treatment, 50 overall at 3 years post-treatment and 55 overall at 5 years post-treatment (64–66 months in total) **% Dropout**: unclear **Assessed**: 68 overall at 12 months post-treatment, 50 overall at 3 years post-treatment and 55 overall at 5 years post-treatment	**Length of follow-up**: 64–66 months **Outcomes**: weight data, depression scores, medication use (not by individual treatment group)	2 kg added to all self-reported weights, 3- and 5-year weight outcomes recalculated for participants who had additional weight loss treatment in years 1–5 post-treatment, self-reported weight at time of seeking additional therapy was subtracted from pretreatment weights, significant difference in whole sample from uncorrected changes ($p < 0.002$ at 3 years, $p < 0.005$ at 5 years post-treatment) **Sponsorship**: National Institute of Mental Health Research, MacArthur's Foundation Network on Health Promoting and Disease Preventing Behaviors

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wadden, 1994	**Randomisation**: VLCD group overselected to allow for greater attrition, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Pennsylvania, USA **Period of study**: before February 1993 **Inclusion criteria**: women, ≥ 25 kg overweight, $60 deposits ($300 refunded at 6-monthly intervals) **Exclusion criteria**: MI, cardiac problems, cerebrovascular disease, kidney or liver disease, cancer, type 1 diabetes, bulimia nervosa, psychiatric illness **Gender**: 49 women **Age** (years): mean (SD) a: 42.86 (10.12), b: 36.82 (8.87) **BMI** (kg/m^2): mean (SD) a: 38.80 (5.39), b: 40.01 (5.73) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 18 months, contacted 66 times (baseline then 90-minute small group sessions weekly for first 52 weeks, then fortnightly for weeks 53–78) **Description of intervention**: a + b: all participants received behaviour therapy consisting of keeping an eating record, stimulus control, modifying cognitions, eliciting social support (materials presented in different order for group b for initial 52 weeks); then during weeks 53–78 'upkeep' skills such as weight graphing and biography, preparing low-fat meals, continuing to exercise, relapse prevention, risk avoidance and reversing small weight gains; all participants received same exercise programme consisting of 10–20 minutes 3 times per week at 40–60% maximum heart rate, gradually increased to 20–40 minutes 3–5 times per week at 60–70% maximum heart rate by week 52 a: 1200 kcal/day balanced deficit diet for first 52 weeks, 15–20% protein, 30% fat and remainder CHO, calorie intake then adjusted for weeks 53–78 depending on participant's desired weight change (minimum 1200 kcal/day) b: week 1 advised regarding 1200 kcal/day, weeks 2–17 420 kcal/day liquid formula PSMF (70 g protein, 30 g CHO, 2 g fat) and 2 litres non-caloric fluids daily and avoidance of all other foods; week 18 conventional foods gradually reintroduced to 100 kcal/day by week 23, weeks 24–78 1200 kcal/day **Allocated**: a: 21, b: 28 **Completed**: a: 17, b: 23 at 52 weeks; a: 16, b: 21 at 78 weeks **% Dropout**: a: 24%, b: 25% at 78 weeks **Assessed**: a: 17, b: 23 at 52 weeks; a: 16, b: 21 at 78 weeks	**Length of follow-up**: 78 weeks **Outcomes**: weight data, compliance, QoL	**Sponsorship**: National Institute of Mental Health Research

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wadden, 1998 Wadden, 1998a: aerobic Ex Wadden, 1998b: strength Ex Wadden, 1998c: aerobic + strength Ex	**Randomisation**: 2 cohorts and different centres, no further details. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Syracuse University and University of Pennsylvania, USA **Period of study**: before March 1997 **Inclusion criteria**: women, > 20 kg above IBW (Metropolitan Life Insurance tables) **Exclusion criteria**: medical contraindications, bulimia nervosa, other major psychiatric disturbance, medication known to affect weight **Gender**: 128 women **Age** (years): mean (SD) 40.9 (8.6) overall (n = 118 of 128 assigned) **BMI** (kg/m^2): mean (SD) a: 36.3 (5.3) overall (n = 118 of 128 assigned) **Baseline comparability**: yes	**Timing of active intervention**: a–d: 48 weeks with follow-up at 1 year post-treatment (100 weeks), contacted 40 times (baseline then weekly for initial 28 weeks, then fortnightly for next 20 weeks, then at 100 weeks) **Description of intervention**: a–d: 925 kcal/day/diet for weeks 0–16, then 1200–1500 kcal/day to week 48; 90-minute group cognitive behavioural therapy weekly for 28 weeks then fortnightly for following 20 weeks; a: advised to continue same lifestyle activities and not to increase exercise from baseline b + c + d: 3 × 1-hour supervised exercise training/week for first 28 weeks (non-consecutive days), then 2 sessions/week during weeks 29–48 and 1 home exercise session/week b: step aerobics estimated to expend 300–400 kcal/session c: strength exercise using universal gym of Cybex equipment to expend 150–175 kcal/session, consisted of bench press, latissimus pulldown, chest fly, leg press, leg and arm curls and extensions, sit-ups and back extensions c: 40% aerobic exercise same as group b and 60% strength exercise same as group c, estimated to expend 225–275 kcal/session **Allocated**: not clear **Completed**: a: 21, b: 21, c: 18, d: 17 at 100 weeks **% Dropout**: 40% overall at 100 weeks **Assessed**: a: 21, b: 21, c: 18, d: 17 at 100 weeks	**Length of follow-up**: 100 weeks **Outcome**: weight data	**Sponsorship**: National Institute of Mental Health Research and National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wadden, 2001	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Pennsylvania School of Medicine, USA **Period of study**: before January 2000 **Inclusion criteria**: women, BMI 30–45 kg/m^2 **Exclusion criteria**: physical contraindications including type 1 and 2 diabetes, uncontrolled hypertension (> 140/90 mmHg), history of cerebrovascular, cardiovascular, kidney or liver disease; use of medication known to affect body weight (e.g. steroids), pregnancy or lactation, weight loss of 5 kg and/or use of anorectic agents in previous 6 months, use of SSRIs, MAOIs or other medications contraindicated with use of sibutramine, psychosocial contraindications including current psychotherapy, bulimia nervosa, major depression (> 25 on Beck Depression Inventory), or other psychiatric illness that significantly disrupts daily functioning **Gender**: no details given **Age** (years): mean (SD) 47.2 (9.8) **BMI** (kg/m^2): mean (SD) 37.7 (3.6) **Baseline comparability**: yes	**Timing of active intervention**: 12 months, contacted 11 times (at weeks 0, 2, 4, 8, 12, 16, 20, 24, 32, 40 and 52) groups b + c received 20 additional weekly contacts (weeks 0–20) **Description of intervention**: a + b + c: 10 mg sibutramine increased to 15 mg at week 8 if tolerated, $600 deposit, $150 returned for completing assessments at 6 and 12 months a + b: 1200–1500 kcal/day, 15% energy from protein, 30% fat, 55% CHO, encouraged to increase exercise (mainly walking) to 4–5 sessions/week for 30–40 minutes each session, 28-page healthy eating and activity guide 'On your way to fitness' b + c: additionally given behavioural strategies to achieve goals, daily records of food intake and exercise for first 16 weeks, LEARN programme for weight control, weekly group lifestyle modification sessions for first 20 weeks which included stimulus control, slowing rate of eating, social support, cognitive restructuring c: additionally given portion-controlled diet, 1000 kcal/day for first 16 weeks [(4 servings/day of nutritional supplement 160 kcal, 14 g protein, 20 g CHO, 3 g fat – OPTIFAST)] combined with evening meal of frozen food entrée, serving of fruit and green salad; then weeks 17–20 supplements reduced to 1200–1500 kcal/day of conventional foods from week 20 to week 52 **Allocated**: a: 20, b: 18 c: 17 **Assessed**: a: 19, b: 17, c: 17 at 12 months (conservative 'ITT' in which participants who discontinued treatment were assumed to gain 0.3 kg/month after leaving study) a: 19, b: 17, c: 17 at 12 months (ITT, LOCF) **% Dropout**: a: 35%, b: 28%, c: 0% at 12 months	**Length of follow-up**: 12 months **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP, adverse events, compliance	All main outcome data (excluding weight) were collapsed across 3 groups after analyses revealed no significant differences among groups at end of treatment in changes on any of these variables **Sponsorship**: National Institutes of Health, Novartis Nutrition Co., Knoll Pharmaceutical Co., American Health Publishing Co.

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1984 Wing, 1984a: concentrated behavioural booster sessions Wing, 1984b: spaced behavioural booster sessions	**Randomisation**: rerandomised after 10 weeks to 1 of 2 maintenance strategies from within blocks according to weight loss (< 4.5 kg, 4.5–9 kg, > 9 kg). Allocation concealment: B(I) **Assessor blinding**: yes **ITT**: yes	**Location**: University of Pittsburgh, USA **Period of study**: before September 1983 **Inclusion criteria**: either gender, 20–65 years, ≥ 20% overweight, $85 deposit, $35 non-refundable, $50 refunded at attendance **Exclusion criteria**: currently involved in other weight control programme **Gender**: 42 women, 6 men **Age** (years): mean (SEM) a: 44.79 (1.56), overall **BMI** (kg/m^2): mean 36.45 overall **Baseline comparability**: not stated	**Timing of active intervention**: a + b + a1 + b1: 12 months, contacted 18 times (baseline, weekly for first 10 weeks, then at weeks 14, 23, 24, 25, 26, 34 and 52) a + b + a2 + b2: 12 months, contacted 18 times (baseline, weekly for first 10 weeks then at weeks 14, 18, 22, 26, 34 and 52) **Description of intervention**: a + b: all participants underwent 10 days of pretreatment assessment before randomisation, first 4 days involved food and exercise records, days 5–7 involved individual calorie deficit (initial weight in pounds × 12 – 1000 kcal) using Slender breakfast bars and liquid, days 8–10 participants returned to conventional foods but maintained same prescribed calorie deficit a + b: postrandomisation for initial 10 weeks participants received 60–90-minute weekly sessions involving individual weigh-in, review, food diaries, presentation of a behavioural lesson (energy balance, strategies for increasing exercise, stimulus control, cognitive restructuring, self-reinforcement and relapse prevention) a: to maintain individually prescribed calorie goal (initial weight in pounds × 12 – 1000 kcal) for 5 days/week and < 750 kcal/day for 2 days/week (chosen by participant) for initial 10 weeks, could use low-calorie menu or return to using Slender bars and liquid b: to maintain individually prescribed calorie goal (initial weight in pounds × 12 – 1000 kcal) for 7 days/week a1 + b1: massed booster session at weeks 14, 23, 24, 25, 26 and 34 which included problem-solving techniques, coping strategies, nutrition and exercise topics a2 + b2: spaced booster sessions, content same as for groups a1 and b1 **Allocated**: a: 25, b: 23 **Completed**: a1: 11, b1: 12, a2: 12, b2: 9 at 52 weeks **% Dropout**: 8% overall **Assessed**: a1: 11, b1: 12, a2: 12, b2: 9 at 52 weeks	**Length of follow-up**: 52 weeks **Outcome**: weight data	Mean change in weight calculated by subtracting prerandomisation weight loss from weight change at 12 months, SDs calculated **Sponsorship**: part funded by National Institute of Arthritis, Metabolism and Digestive Diseases

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1985	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Pittsburgh, USA **Period of study**: before February 1984 **Inclusion criteria**: either gender, ≥ 20% above IBW (Metropolitan Life Insurance tables), diabetes treated by diet or oral hypoglycaemics, fasting blood sugar > 140 mg/dl on 2 occasions, or 2-hour value and 1 other value > 200 mg/dl, on OGTT, permission from own physician, $85 deposit with contingencies **Exclusion criteria**: not stated **Gender**: 33 women, 20 men **Age** (years): mean 55.1 (7.28) overall **BMI** (kg/m^2): mean (SD): 34.8 (5.10) overall **Baseline comparability**: not stated	**Timing of active intervention**: a + b: 16 weeks with follow-up at 16 months, contacted 19 times (baseline, then weekly for initial 16 weeks, then at 10 and 16 months) c: 16 weeks with follow-up at 16 months, contacted 7 times (baseline then monthly for initial 16 weeks, then at 10 and 16 months) **Description of intervention**: a + b + c: all participants given calorie intake goal calculated as pretreatment weight (in pounds) × 12 – 1000 with a minimum calorie intake of 1000 kcal/day a: nutrition education condition: basic information on nutrition, exercise and diabetes, weekly discussion of nutrition topic but no specific dietary goals; calorie cost of exercise presented but no group exercise or exercise goals; contingency contracts for attendance c: received same treatment as group a, except met monthly so participants briefly discussed 4 weekly topics at monthly visits b: behaviour modification strategies to change behaviour such as changing environment for eating and changing cognitions, and information given on nutrition, exercise and diabetes; record calories of all food and drink consumed, then monitor sugar intake to < 4 times/week, weekly fibre goal; walking stressed with goal of 100 kcal/week expenditure, group exercise at meetings, charts of group exercise, social support and group competition **Allocated**: not clear, 53 in total **Completed**: 50 overall at 16 months **% Dropout**: 6% overall at 16 months **Assessed**: 50 overall at 16 months	**Length of follow-up**: 16 months **Outcome**: weight data	Only used groups a and b for comparison, no denominators for change in weight **Sponsorship**: part funded by National Institute of Arthritis, Metabolism and Digestive Diseases

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1988a	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: yes **ITT**: no	**Location**: University of Pittsburgh, USA **Period of study**: before May 1988 **Inclusion criteria**: either gender, 30–65 years, type 2 diabetes, > 20% above IBW **Exclusion criteria**: known CHD, on medication which would affect weight loss and/or measurement of heart rate, orthopaedic problems that would limit walking, taking insulin **Gender**: 21 women, 4 men **Age** (years): mean (SD) a: 56.2 (7.5), b: 52.5 (8.9) **BMI** (kg/m^2): mean (SD) a: 38.1 (6.4), b: 37.5 (6.2) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 36 weeks with follow-up at 62 weeks, contacted 28 times (baseline then twice a week for first 10 weeks, then monthly for next 6 months, then at 62 weeks) **Description of intervention**: a + b: all participants received behavioural weight control programme including weigh-in, glucose measurement and behavioural modification lecture (slowing down rate of eating, reducing eating signals in the home, social pressures, preplanning and relapse prevention techniques); 1600 kcal/day diet with daily calorie goal to produce 1 kg week weight loss, reduce fat intake and increase complex CHO intake, food diaries; exercise twice per week as a group and once a week alone, 1 hour per session a: moderate exercise based on walking, gradually increased until participants were walking 3 miles (4.8 km) within the 1-hour session b: low-intensity exercise consisting of light calisthenics and flexibility exercises set to music, designed as placebo exercise **Allocated**: a: 12, b: 13 **Completed**: a: 8, b: 11 at 62 weeks **% Dropout**: a: 33%, b: 15% at 62 weeks **Assessed**: a: 8, b: 11 at 62 weeks	**Length of follow-up**: 62 weeks **Outcome**: weight data	**Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1988b	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: yes **ITT**: no	**Location**: University of Pittsburgh, USA **Period of study**: before May 1988 **Inclusion criteria**: either gender, 30–65 years, type 2 diabetes, > 20% above IBW **Exclusion criteria**: known CHD, on medication that would affect weight loss and/or measurement of heart rate, orthopaedic problems that would limit walking **Gender**: 21 women, 9 men **Age** (years): mean (SD) a: 56.1 (6.4), b: 55.1 (7.2) **BMI** (kg/m^2): mean (SD) a: 38.2 (6.6), b: 37.9 (6.5) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 72 weeks, contacted 53 times (baseline then 3 times/week for first 10 weeks, then weekly for weeks 11–20, then monthly to 72 weeks) **Description of intervention**: a + b: all participants received behavioural weight control programme including weigh-in, glucose measurement and behavioural modification lecture (slowing down rate of eating, reducing eating signals in the home, social pressures, preplanning and relapse prevention techniques); 1600 kcal/day diet with daily calorie goal to produce 1 kg/week weight loss, reduce fat intake and increase complex CHO intake, food diaries; exercise twice per week as a group and once a week alone, 1 hour per session a: walked 3-mile (4.8 km) route with therapist 3 times/week and instructed to exercise additionally once per week on their own b: instructed not to change baseline level of activity, 3 meetings per week were used to provide demonstrations and films of new low-calorie cooking techniques, portion size estimation and role-play; numerous social group activities to control for social aspect of exercise condition received by group a **Allocated**: a: 15, b: 15 **Completed**: a: 13, b: 15 at 72 weeks **% Dropout**: a: 13%, b: 0% at 72 weeks **Assessed**: a: 13, b: 15 at 72 weeks	**Length of follow-up**: 72 weeks **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, HbA_{1c}, fasting plasma glucose	**Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1991	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: University of Pittsburgh School of Medicine, USA **Period of study**: before January 1991 **Inclusion criteria**: either gender, 35–70 years, ≥ 30% above IBW (Metropolitan Life Insurance tables), type 2 diabetes **Exclusion criteria**: liver disease, renal disease, heart disease **Gender**: 26 women, 10 men **Age** (years): mean (SD) a: 51.9 (9.9), b: 50.6 (7.7) (completers only $n = 33$) **BMI** (kg/m^2): mean (SD) a: 38.1 (5.7), b: 37.34 (4.7) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 72 weeks, contacted 25 times (weekly from baseline to week 20, then at weeks 24, 28, 46 and 72) **Description of intervention**: a + b: all participants given instructions to diet, exercise and behaviour modification emphasised in particular; advised to increase walking and given weekly exercise goals starting at 50 kcal/week (the equivalent of a 0.5-mile (0.8-km) walk for a 67.5-kg person) increased to 1000 kcal/week (approximately 10 miles or 16 km walking/week); participants self-monitored their calorie intake and exercise daily throughout the programme, stimulus control techniques, including strategies for removing food cues from the environment, slowing the rate of eating and separating eating from other activities; also taught techniques for modifying cognitions, for relapse prevention and for self-reinforcement; all participants deposited $150 at the start which was earned back weekly for meeting homework goals a: 1000–1500 kcal/day (depending on initial weight) until week 72 unless IBW achieved; information regarding calorie content of protein, CHO and fat given, and participants advised to increase complex CHO and decrease fat intake, food choices unlimited, in line with American Diabetic Association recommendation b: month 1 same as group a, then weeks 5–12, given 400 kcal/day PSMF consisting of lean meat, fish, fowl and choice of Optifast 70 for occasional meals, week 9 other foods gradually reintroduced and calories increased so by week 17 = 1000–1500 kcal/day diet until week 72; participants on insulin started VLCD in hospital where insulin was withdrawn or sharply reduced; vitamin and mineral daily supplements **Allocated**: a: 19, b: 17 **Completed**: a: 16, b: 17 at 72 weeks **% Dropout**: a: 16%, b: 0% at 72 weeks **Assessed**: a: 16, b: 17 at 72 weeks (completer analyses)	**Length of follow-up**: 72 weeks **Outcomes**: weight data, total cholesterol, HDL cholesterol, TGs, HbA_{1c}, fasting plasma glucose, compliance	Author confirmed main study and substudy publications, mean change in risk outcomes at 72 weeks calculated from actual values, SDs also calculated **Sponsorship**: Western Pennsylvania Affiliate of the American Diabetes Association, National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1991b	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: possibly	**Location**: University of Pittsburgh, USA **Period of study**: before January 1990 **Inclusion criteria**: either gender, 30–65 years, ≥ 20% above IBW, fasting glucose ≥ 140 mg/dl, or ≥ 200 mg/dl 2 hours after oral glucose load and 1 other value ≥ 200 mg/dl, spouses 30–70 years, ≥ 15% above IBW; $150 deposit per couple **Exclusion criteria**: not stated **Gender**: 25 women, 18 men **Age** (years): mean (SD) a: 53.6 (7.7), b: 51.2 (7.3) **BMI** (kg/m^2): mean (SD) a: 35.68 (5.76), b: 36.64 (5.77) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 72 weeks, contacted 21 times (baseline then weekly for first 12 weeks, then at weeks 14, 16, 18, 20, 24, 28, 40 and 72) **Description of intervention**: a + b: all participants received behavioural weight loss programme consisting of stimulus control, problem solving, assertion, goal setting and cognitive techniques; participants advised to monitor calorie intake to 1200–1500 kcal/day with a reduction in fat intake and simple CHO and increase in fibre; stepwise goals for walking, with final goal to expend 100 kcal/week; deposit refunded according to weight loss and attendance a: spouse participated in all aspects of programme and no distinction made in treatment between participant and spouse, half of therapy sessions focused on social support and behavioural marital therapy literature, e.g. mutual positive reinforcement **Allocated**: a: 24, b: 25 **Completed**: a: 20, b: 23 at 72 weeks **% Dropout**: a: 17%, b: 8% at 72 weeks **Assessed**: a: 20, b: 23 at 72 weeks	**Length of follow-up**: 72 weeks **Outcomes**: weight data, HbA_{1c}, fasting plasma glucose	**Sponsorship**: parted funded by National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1994	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no details given **ITT**: no	**Location**: University of Pittsburgh, USA **Period of study**: before November 1993 **Inclusion criteria**: either gender, 30–70 years, > 30% or > 18 kg above IBW (based on Metropolitan Life Insurance tables), NIDDM (criteria according to National Diabetes Data Group) **Exclusion criteria**: health problems that would interfere with the use of VLCDs **Gender**: 60 women, 33 men **Age** (years): mean (SD) 51.8 (9.6) **BMI** (kg/m^2): mean (SD) 37.9 (6.3) **Baseline comparability**: yes	**Timing of active intervention**: a + b: 50 weeks plus follow-up 1 year later (102 weeks in total), contacted 52 times (weekly in groups of approximately 15) **Description of intervention**: a + b: all participants kept self-monitoring records which were reviewed at weekly group meetings, along with detailed discussion on nutrition which included focusing on reducing fat content and increasing intake of complex CHO and fibre; exercise that emphasised walking or behavioural techniques that included stimulus control, goal setting and self-monitoring of intake and exercise, preplanning, relapse prevention and modifying cognitions; included role playing and individual discussion and questions; all participants encouraged to increase walking to 2 miles (3.2 km)/day on 5 days/week; all participants kept 3-day food diaries at baseline, 6 months and 12 months; all diabetes medications discontinued at start and algorithm used to determine whether and when to restart medication; all participants given vitamin/mineral supplements throughout study; all participants deposited $150 which was refunded in full for reaching behavioural goals and attending assessments at baseline, 6 months and 50 weeks a: 1000–1200 kcal/day consisting of < 30% energy intake from fat, from baseline to week 50 b: PSMF 500 kcal/day either as liquid supplement (Optifast) or lean meat, fish or fowl for weeks 0–12 and weeks 24–36; other foods gradually reintroduced over following 4 weeks to consume 1000–1200 kcal/day at weeks 13–23 and weeks 37–50 **Allocated**: a: 41, b: 38 **Completed**: a: 38, b: 36 at 102 weeks **% Dropout**: a: 21%, b: 20% at 102 weeks **Assessed**: a: 37, b:36 at 102 weeks (completer analysis; 1 subject in group a excluded from analyses due to gastric bypass operation before follow-up visit)	**Length of follow-up**: 102 weeks **Outcomes**: weight data, medication use	Author confirmed study and substudy reports **Sponsorship**: National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1998	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: yes **ITT**: yes	**Location**: University of Pittsburgh, USA **Period of study**: before July 1997 **Inclusion criteria**: either gender, 40–55 years, non-diabetic (confirmed by OGTT), 1 or 2 biological parents with type 2 diabetes, 30–100% above IBW **Exclusion criterion**: diabetes **Gender**: 122 women, 32 men **Age** (years): mean (SD) a: 45.0 (4.7), b: 46.4 (4.5), c: 46.3 (3.8), d: 45.3 (4.9) **BMI** (kg/m^2): mean (SD) a: 36.1 (4.1), b: 36.0 (3.7), c: 35.7 (4.1), d: 36.0 (5.4) **Baseline comparability**: yes	**Timing of active intervention**: a–c: 2 years, contacted approximately 52 times (baseline, weekly for first 6 months, then every 2 weeks for next 6 months, then 2 × 6-week course during 2nd year) d: contacted at baseline, 6 months, 1 year and 2 years **Description of intervention**: a: 800–1000 kcal/day weeks 1–8, then adjusted to 1200–1500 kcal/day by week 16, food diaries reviewed and feedback given, meal plans and shopping lists, behavioural or nutritional topic given at each session b: exercise behaviour topic each week, 50–60 minute walk with therapist at each weekly meeting (second supervised walk available each week for weeks 1–10), gradually increased exercise to estimated calorie expenditure of 1500 kcal/week [e.g. 3 miles (5 km) brisk walking on 5 days/week], other activities periodically introduced to the participants such as aerobics and line dancing c: same diet as group a and same exercise as group b (equivalent to half time for each) d: participants received LEARN behavioural manual with information on healthy eating, exercise and behavioural strategies; participants encouraged to lose weight and exercise on their own, only participated in the assessments **Allocated**: a: 37, b: 37, c: 40, d: 40 **Completed**: a: 33, b: 28, c: 30, d: 29, at 1 year; a: 35, b: 31, c: 32, d: 31 at 2 years **% Dropout**: a: 5%, b: 16%, c: 20%, d: 23% at 2 years **Assessed**: a: 33, b: 28, c: 30, d: 29 at 1 year; a: 35, b: 31, c: 32, d: 31 at 2 years	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, HDL cholesterol, LDL cholesterol, TGs, SBP, DBP, HbA_{1c}, fasting plasma glucose, development of type 2 diabetes, compliance	Author confirmed main study and substudy reports **Sponsorship**: National Institutes of Health, Obesity/Nutrition Research Center, General Clinical Research Center

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wing, 1999	**Randomisation**: allocation concealment: B(I) **Assessor blinding**: no **ITT**: yes	**Location**: University of Pittsburgh, USA **Period of study**: before July 1998 **Inclusion criteria**: either gender, 25–55 years, 6.8–31.8 kg above IBW, generally good health **Exclusion criteria**: not stated **Gender**: 84 women, 82 men **Age** (years): mean (SD) a: 41.8 (9.2), b: 43.5 (7.8), c: 40.6 (8.3), d: 43.8 (8.6) **BMI** (kg/m^2): mean (SD) a: 30.6 (3.7), b: 31.8 (3.1), c: 32.1 (3.7), d: 30.3 (4.0) **Baseline comparability**: yes	**Timing of active intervention**: a–d: 16 weeks with follow-up at 16 months, contacted 18 times (baseline then weekly for initial 16 weeks, then at 16 months) **Description of intervention**: a–d: all participants advised to eat ≤ 1000 kcal/day with 22 g of fat if weighed <90.7 kg at baseline, or ≤ 1500 kcal/day with 33 g of fat if baseline > 90.7 kg; given grocery lists and meal plans weekly during initial 16 weeks, exercise prescribed in gradual increments up to 100 kcal/week expenditure [equivalent to walking for 2 miles (3.2 km) 5 days/week], food and exercise diaries completed during 16 weeks, behavioural lessons focused on problem solving, assertion, stimulus control, developing social support, dealing with high-risk situations, cognition and maintenance strategies, a: recruited alone with no effort to increase communication in group, $25 deposit refunded for attending each follow-up at months 4 and 10 b: participants assigned to a team of 4 members and given social support intervention involving intragroup activities such as calling other members of their team to provide support, group assignments and an intragroup competition with team who had largest number of its members retaining their weight loss in full from months 4–7 and months 4–10, jackpot consisted of $25 of each participant's deposit c: recruited with friends, but relationships among and between teams not acknowledged, identical programme to group a d: recruited with 4 friends who became natural team and received same social support as group b **Allocated**: a: 38, b: 48, c: 40, d: 40 **Completed**: 90 overall at 16 months **% Dropout**: 46% overall at 16 months **Assessed**: a: 38, b: 48, c: 40, d: 40 (ITT, with dropouts assumed to have returned to baseline weights)	**Length of follow-up**: 16 months **Outcome**: weight data	Groups a + b and groups c + d assessed in aggregate **Sponsorship**: National Health, Lung and Blood Institute

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wood, 1988	**Randomisation**: 4 cohorts, sealed envelopes, no further details, at end of year participants in 2 active treatment groups were randomly assigned within each condition to 2 maintenance conditions. Allocation concealment: B(I) **Assessor blinding**: no in year 1, blinded in year 2 **ITT**: no	**Location**: Stanford University, California, USA **Period of study**: before December 1987 **Inclusion criteria**: men, 30–59 years, 120–160% IBW, no regular exercise for past 3 months, non-smokers, clinically healthy, resting clinic BP < 160/100 mmHg, plasma cholesterol < 8.28 mmol/l, plasma TGs < 5.65 mmol/l, average < 4 alcoholic drinks/day, expected to reside in Stanford area for at least 1 year, normal ECG during grade treadmill test **Exclusion criteria**: orthopaedic limitations, medications known to affect BP or plasma lipids **Gender**: 155 men **Age** (years): mean (SD) a1: 44.2 (8.2), b1: 44.1 (7.8), c: 45.2 (7.2) for 131 participants assessed **Weight** (kg): mean (SD) a1: 93.0 (8.8), b1: 94.1 (8.6), c: 95.4 (10.6) for 131 participants assessed **Baseline comparability**: yes	**Timing of active intervention**: a1 + b1: 12 months, no details of frequency of contact c: contacted 3 times during 12 months (baseline then 7 and 12 months) a2 + b2: monthly mailings during year 2, telephone contact of 5–10 minutes each during months 13, 14 and 15 and at months 18, 21 and 24 a3 + b3: contacted twice (at 18 and 24 months) **Description of intervention**: a1: baseline 7-day diet recall and fat body mass used to provide individual counselling including behavioural strategies, to reduce calorie intake to produce gradual weight loss and to lose one-third of body fat (assumed a reduction of 7762 kcal = loss of 1 kg adipose tissue); no change in nutrient composition, requested to remain sedentary, included weight stabilisation for last 6 weeks b1: received supervised exercise training session to promote increase in calorie expenditure and body fat loss of one-third, consisting of 1 hour 3 times/week, including calisthenics, walking, jogging and principally running at 60–80% peak heart rate (according to treadmill test results), advised to increase routine physical activity plus 2 more sessions/week unsupervised exercise; activity logs kept and advised not to change diet including composition, weight stabilisation last 6 weeks c: participants advised not to make any changes in diet including composition, exercise or body weight, offered weight loss programme of diet and exercise at end of the study a2 + b2: participants received telephone contact during months 13, 14 and 15 and at months 18, 21 and 24 to answer any questions relevant to original weight loss treatment; 7-day food recall and physical activity recall questionnaire completed at end of year 1 and end of year 2, monthly mail contact to prevent relapses to unwanted behaviour, included supportive letter, brief self-scored assessment of particular problem area specific to original weight control treatment group and list of coping	**Length of follow-up**: 2 years **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP	First year data only used **Sponsorship**: National Heart, Lung and Blood Institute, National Institutes of Health

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
			suggestions, option of continuing with self-monitoring logs, given written information on the weight control method participants had not received in year 1, encouraged to obtain support from members of original treatment group a3 + b3: did not receive any mailings or telephone contact during year 2, assessed at 18 months and 24 months **Allocated**: a1: 51, b1: 52, c: 52 at baseline; a2: 24, a3: 20, b2: 24, b3: 22 **Completed**: a1: 49, b1: 51, c: 49 at 1 year; a2: 20, a3: 16, b2: 21, b3: 15 at 2 years **% Dropout**: a1: 4%, b1: 2%, c: 6%, at 1 year; a2: 17%, a3: 20%, b2: 13%, b3: 32% at 2 years **Assessed**: a1: 42, b1: 47, c: 42 at 1 year; a2: 20, a3: 16, b2: 21, b3: 15 at 2 years		

continued

TABLE 23 *Included non-drug studies (cont'd)*

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Wood, 1991 Wood, 1991a: women Wood, 1991b: men	**Randomisation**: 3 cohorts, stratified by gender. Allocation concealment: B(I) **Assessor blinding**: no **ITT**: no	**Location**: Stanford University, California, USA **Period of study**: before 1991 **Inclusion criteria**: either gender, 25–49 years, 120–150% IBW, BMI 28–34 kg/m^2 men, 24–30 kg/m^2 women, non-smokers, sedentary (exercise less than twice per week, < 30 minutes each time), resting BP < 160/95 mmHg, plasma cholesterol < 6.72 mmol/l, plasma TGs < 5.65 mmol/l, average <4 alcoholic drinks/day, generally good health **Exclusion criteria**: medication known to affect BP or lipid metabolism, pregnancy, lactating or taking oral contraceptive in past 6 months or planning pregnancy in subsequent 2 years **Gender**: 132 women, 132 men **Age** (years): mean (SD) 39.1 (6.4) women, 40.3 (6.3) men **BMI** (kg/m^2): mean (SD) 27.9 (2.2) women, 30.7 (2.2) men **Baseline comparability**: significant difference in DBP in men in groups a + b vs c (control) ($p < 0.001$), significant difference in total cholesterol in females group a vs control ($p \leq 0.01$), group b vs control ($p \leq 0.05$), and LDL cholesterol in females group a and group b vs control ($p \leq 0.05$)	**Timing of active intervention**: a: 1 year, contacted 25 times (baseline, weekly for first 3 months, then every other week for 3 months, then monthly) b: 1 year, contacted 181 times (baseline, 3 times/week for 1 year plus weekly for first 3 months, then every other week for 3 months, then monthly) c: contacted twice, at baseline and at 1 year **Description of intervention**: a: National Cholesterol Education Program (NCEP) step 1 diet consisting of 55% CHO, 30% fat (with saturated fat ≤ 10%) dietary cholesterol < 300 mg/day, calorie reduction, no change in exercise b: received identical diet to group a and aerobic exercise (brisk walking or jogging) at 60–80% maximum heart rate initially for 25 minutes 3 times/week increasing to 45 minutes 3 times/week by month 4, monthly activity logs kept c: instructed to maintain usual diet and exercise patterns **Allocated**: a: 87, b: 90, c: 87 **Completed**: 237 overall at 1 year **% Dropout**: a: 10%, b: 18%, c: 10% at 1 year **Assessed**: a: 71, b: 81, c: 79 at 1 year	**Length of follow-up**: 1 year **Outcomes**: weight data, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, SBP, DBP	Outcome data presented by gender **Sponsorship**: National Institutes of Health

BCDD, balanced calorie deficit diet.

Appendix 9

Characteristics of ongoing and recently completed RCTs not included in this review

Trial name or title	Participants	Interventions	Main outcomes	Date	Contact information	Notes
CHARMONT study Germany	47 participants, 18–65 years, BMI ≥ 40 kg/m^2, no significant difference between baseline values	Diet plus aqua-fitness plus behaviour therapy plus sibutramine 10 mg/day vs gastric banding	BMI, % overweight, BP, HbA_{1c}%, total cholesterol, LDL cholesterol, HDL cholesterol, plasma glucose, economic costs, QoL, post-operative complications	Ongoing 2000	Dr S Klaua, Medizinische Universitäts-Poliklinik, Charité, Humboldt-Universität Luisenstrasse 11–13a, D-10117 Berlin, Germany	Preliminary 12-month data available for 15 conservatively treated participants and 12 surgically treated participants: reduction of overweight 35% vs 48% (conservative vs surgical), all parameters of metabolism improved significantly in conservative group except BP, which increased by 3 mmHg vs decrease of –32 mmHg in surgical group, HbA_{1c} –24% vs –16% (conservative vs surgical)
Diabetes Prevention Program (DPP) 27 centres in USA	3234 participants, both genders, ≥ 25 years, BMI ≥ 24 kg/m^2 (≥ 22 kg/m^2 if Asian), IGT plus fasting plasma glucose of 5.3–6.9 mmol/l (or ≤ 6.9mmol/l if American Indians)	Intensive lifestyle modification vs standard care plus metformin vs standard care plus placebo	Development of diabetes, defects in insulin sensitivity and secretion, development and/or progression of vascular diseases and cardiovascular risk factors, weight	Completed	Diabetes Prevention Program Coordinating Center, George Washington University, 6110 Executive Boulevard, Suite 750, Rockville, MD 20852, USA dppmail@biostst.bsc.gwu.edu	Diabetes Prevention Program Group. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 1999;**22**:623–34. Diabetes Prevention Program Group. The Diabetes Prevention Program. Baseline characteristics of the randomized cohort. *Diabetes Care* 2000;**23**:1619–29. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**:393–403.
Gale Metformin to prevent weight gain in type 2 diabetic patients starting insulin, UK	Participants with type 2 diabetes, ≤ 75 years	Metformin vs placebo	Weight, waist–hip ratio, glycated haemoglobin, serum lipids, participant satisfaction	Ongoing 1998	Professor EA Gale, Department of Metabolic Medicine, Southmead Hospital, Southmead Road, Bristol BS10 5NB, UK	Information obtained from UK National Research Register. URL:http://www.update-software.com/National/

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Trial name or title	Participants	Interventions	Main outcomes	Date	Contact information	Notes
Heshka Self-help weight loss vs a structured commercial programme, 6 centres in USA	423 participants, both genders, 18–65 years, BMI 27–40 kg/m^2, not diabetics	Self-help programme and two 20-minute sessions with nutritionist vs Weight Watchers programme	Weight, waist circumference	Ongoing 2000	Dr S Heshka, New York Obesity Research Center, St Luke's/Roosevelt Hospital Center, 1090 Amsterdam Avenue, 14C, NY 10025, USA	26-week results in: Heshka S, Greenway F, Anderson JW, Atkinson RL, Hill JO, Phinney SD, *et al*. Self-help weight loss versus a structured commercial program after 26 weeks: a randomized controlled study. *Am J Med* 2000;**109**:282–7.
Kelley Orlistat in people with insulin-treated type 2 diabetes, USA	550 participants, 40–65 years, BMI 28–43 kg/m^2, type 2 diabetes, HBA_{1c} 7.5–12.0%, stable dose of insulin	Orlistat 120 mg three times daily and low-fat diet vs placebo and diet	Weight, use of diabetes medications, glycaemic control, lipids, BP, adverse events	Completed	Dr DE Kelley, 3459 Fifth Avenue, University of Pittsburgh Montefiore Hospital, N809 Pittsburgh, PA 15213, USA kelley@msx.dept-med.pitt.edu	Kelley, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J, *et al*. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. *Diabetes Care* 2002;**25**:1033–41.
Keyserling Diabetes management programme for African–American women with type 2 diabetes, 7 practices in North Carolina, USA	200 African–American women with type 2 diabetes for ≥ 3 years	Clinic and community New Leaf Programme (diet, exercise and behaviour therapy) vs clinic New Leaf Programme vs control	Weight, glycated haemoglobin, serum lipids	Ongoing 2000	Dr TC Keyserling, CB# 8140, 1700 Airport Road, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA tkeyserling@med.unc.edu	Methods in: Keyserling TC, Ammerman AS, Samuel-Hodge CD, Ingram AF, Skelly AH, Elasy TA, *et al*. A diabetes management program for African American women with type 2 diabetes. *Diabetes Educ* 2000; **26**:796–804.
Look AHEAD (Action for Health in Diabetes) Multicentre trial, USA	5000 participants, both genders, 45–75 years, BMI ≥ 25 kg/m^2, type 2 diabetes	Intensive diet, exercise and behaviour therapy, ongoing contact and weight loss medications vs diabetes support and education	Primary outcome: aggregate occurrence of severe cardiovascular events over 11.5 years; secondary outcome: vascular events, weight	Ongoing 2001	http://show.phs.wfubmc.edu/	

continued

Trial name or title	Participants	Interventions	Main outcomes	Date	Contact information	Notes
McKeigue Development and validation of a weight losing dietary intervention to reduce the risk of diabetes and CHD in South Asians, UK	72 South Asians and Europeans, both genders, 35–59 years, central obesity	Individually tailored low-fat, low-energy diet based on computer assessment vs no intervention	Weight, fat distribution, insulin response to glucose load	Unclear	Dr P McKeigue, Epidemiology, Sciences Department, Keppel Street, London WC1E 7HT, UK	Information obtained from UK National Research Register. URL:http://www.update-software.com/National/
McMahon Sibutramine in people with well-controlled hypertension, USA	220 participants, both genders, ≥ 18 years, BMI ≥ 27 kg/m^2 and < 40 kg/m^2, well-controlled hypertension on angiotensin-converting enzyme inhibitors	Sibutramine 20 mg daily and weight reduction advice vs placebo and same advice	BMI, weight, waist–hip ratio, BP, lipids, adverse events	Completed	Dr FG McMahon, Clinical Research Center, 147 South Liberty Street, New Orleans, LA 70112, USA crcadmin@acadiacom.net	McMahon FG, Weinstein SP, Rowqe E, Ernst KR, Johnson F, Fujioka K, *et al*. Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors. *J Hum Hypertens* 2002; **16**:5–11.
Meneilly Acarbose in elderly patients with diabetes, 5 centres in North America	Older people with diet-controlled diabetes	Acarbose vs placebo	Diabetic control, weight	Ongoing 2000	DR GS Meneilly, Room S169, Vancouver Hospital and Health Sciences Centre, UBC Site, 2211 Wesbrook Mall, Vancouver BC, Canada V6T 2B5 gmeneill@vanhosp.bc.ca	Subgroup data published as: Meneilly GS, Ryan EA, Radziuk J, Lau DC, Yale J-F, Morais J, *et al*. Effect of acarbose on insulin sensitivity in elderly patients with diabetes. *Diabetes Care* 2000;**23**:1162–7.

continued

Trial name or title	Participants	Interventions	Main outcomes	Date	Contact information	Notes
Miles Orlistat in people with type 2 diabetes treated with metformin, USA	516 participants, 40–65 years, BMI 28–43 kg/m^2, type 2 diabetes, HBA_{1c} 7.5–12.0%, taking metformin with or without sulfonylureas	Orlistat 120 mg three times daily and 600 kcal/day deficit diet vs placebo and diet	Weight, use of diabetes medications, glycaemic control, lipids, BP, adverse events	Completed	Dr JM Miles, Division of Endocrinology and Metabolism, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA miles.john@mayo.edu	Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, *et al*. Effect of orlistat in overweight and obese patients treated with metformin. *Diabetes Care* 2002;**25**:1123–8.
STOP-NIDDM Multicentre, international trial	1418 participants, both genders, 40–70 years, BMI 24–40 kg/m^2, impaired glucose tolerance (old WHO criteria)	Acarbose 100 mg three times daily vs placebo	Development of type 2 diabetes, cardiovascular events, BP, lipids, weight	Completed	Dr J-L Chiasson, Research Group on Diabetes and Metabolic Regulation, Research Center, CHUM, Campus Hôtel-Dieu, 3830 Rue St Urbain, Montreal, Quebec H2W 1T8, Canada, jean.lois.chiasson@umontreal.ca	Design and baseline data in: The STOP-NIDDM trial. An international study on the efficacy of an α-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. *Diabetes Care* 1998;**21**:1720–5. Chiasson J-L, Josse RG, Gomis R, Hanefeld, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**:2072–7.
XENDOS Multicentre trial, Sweden	Both genders, 30–60 years, BMI ≥ 30 kg/m^2, non-diabetic, ≥ 10% had IGT	Orlistat 120 mg three times daily and 800 kcal/day deficit diet vs diet and placebo	Development of type 2 diabetes	Completed	Professor L Sjöström, SOS Secretariat, Vita Stråket 15, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden lars.sjostrom@medfak.gu.se	Torgerson JS, Arlinger K, Käppi M, Sjöström L. Principles for enhanced recruitment of subjects in a large clinical trial: the XENDOS study experience. *Control Clin Trials* 2001;**22**:515–25. Study reviewed in: Scheen AJ. Prévention du diabète de type 2 chez le sujet obèse: premiers résultats avec l'orlistat dans l'étude XENDOS. *Rev Med Liege* 2002; **57**:617–21.

Appendix 10

References to excluded RCTs

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Adachi Y. The effect of behavioral treatment of obesity and correlates of weight loss in treatment and at 2-year follow-up. *Jpn J Behav Ther* 1989;**15**:36–55 (BMI not ≥ 28 kg/m^2).

Adolfsson B, Andersson I, Apelman J, Bengtsson B, Rossner S, Thorne A. Quality of life in obese patients before and after weight loss – behaviour modification + adjustable gastric banding (AGB) vs. AGB. *Int J Obes* 2001;**25**(Suppl 2):S122 (abstract only).

Agewall S, Fagerberg B, Berglund G, Schmidt C, Wendelhag I, Wikstrand J, *et al*. Multiple risk intervention trial in high risk hypertensive men: comparison of ultrasound intima-media thickness and clinical outcome during 6 years of follow-up. *J Intern Med* 2001;**249**:305–14 (BMI not ≥ 28 kg/m^2).

Agras WS, Telch CF, Arnow B, Eldredge K, Wilfley DE, Raeburn SD, *et al*. Weight loss, cognitive-behavioral, and desipramine treatments in binge eating disorder. An additive design. *Behav Ther* 1994;**25**:225-38 (48 weeks).

Agras WS, Telch CF, Arnow B, Eldredge K, Detzer MJ, Henderson J, *et al*. Does interpersonal therapy help patients with binge eating disorder who fail to respond to cognitive-behavioral therapy? *J Consult Clin Psychol* 1995;**63**:356–60 (24 weeks).

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Appendix 11

Table of quality assessment of included RCTs

	Quality of random allocation concealment	Description of withdrawals and dropouts	Intention to treat?	Participants blinded to treatment status?	Healthcare providers blinded to treatment status?	Outcome assessors blinded to treatment status?
Orlistat						
Broom, 2001a	B(I)	A	C	B(II)	B(II)	B(I)
Broom, 2001b	B(I)	A	C	B(II)	B(II)	B(I)
Davidson, 1999	B(I)	A	C	B(II)	B(II)	B(I)
Finer, 2000	A	A	C	B(II)	B(II)	A(I)
Hauptman, 2000	A	A	C	B(II)	B(II)	B(I)
Hill, 1999	B(I)	A	C	B(II)	B(II)	B(I)
Hollander, 1998	A	A	B	B(II)	B(II)	A(I)
Lindgarde, 2000	B(I)	A	B	B(II)	B(II)	B(I)
Rossner, 2000	B(I)	A	C	B(II)	B(II)	B(I)
Sjöström, 1998	A	A	C	B(II)	B(II)	B(I)
Sibutramine						
Apfelbaum, 1999	B(I)	A	C	A(I)	A(I)	B(I)
McMahon, 2000	B(I)	A	C	A(II)	A(II)	B(I)
Smith, 2001	B(I)	A	C	A(I)	A(I)	B(I)
STORM, 2000	A	A	A	A(I)	A(I)	B(I)
SSRIs						
Bitsch, 1987	A	B(I)	A	A(I)	A(I)	A(I)
Breum, 1995	B(I)	A	C	A(I)	A(I)	B(I)
Goldstein, 1994	B(I)	B(I)	C	A(I)	A(I)	A(I)
O'Kane, 1994	B(I)	A	C	A(II)	A(II)	B(I)
Wadden, 1995	B(I)	A	A	A(II)	A(II)	B(I)
Metformin						
BIGPRO1, 1996	A	A	A	A(I)	A(I)	B(I)
Teupe, 1991	B(I)	A	C	C	C	C
UKPDS, 1998	A	B(I)	B	C	C	B(I)
Acarbose						
Chiasson, 1994	B(I)	B(I)	C	A(II)	A(II)	B(I)
All non-drug interventions						
Black, 1984	B(I)	B(I)	C	C	C	C
Blonk, 1994	B(I)	A	A	C	C	C
Cohen, 1991	B(I)	A	B	C	C	B(I)
Cousins, 1992	B(I)	B(I)	C	C	C	C
de Waard, 1993	B(I)	B(I)	C	C	C	C
DISH, 1985	B(I)	B(I)	B	C	C	C
FDPS, 2001	B(I)	A	C	C	C	A(II)
Foreyt, 1993	B(II)	B(I)	C	C	C	C
Frey-Hewitt, 1990	B(I)	A	C	C	C	C
Hakala, 1989	B(I)	B(I)	B	C	C	C
Hakala, 1993	B(I)	B(I)	A	C	C	C
Hankey, 2001	B(I)	A	A	C	C	C
HOT, 1999	B(I)	A	B	C	C	C
HPT, 1990	B(I)	B(I)	A	C	C	A(I)
Jalkanen, 1991	B(I)	B(I)	B	C	C	C
Jeffery, 1993	B(I)	B(I)	B	C	C	C

continued

	Quality of random allocation concealment	Description of withdrawals and dropouts	Intention to treat?	Participants blinded to treatment status?	Healthcare providers blinded to treatment status?	Outcome assessors blinded to treatment status?
Jones, 1986	B(I)	B(I)	C	C	C	C
Kaplan, 1987	B(I)	B(I)	B	C	C	B(I)
Karvetti, 1992	B(I)	A	B	C	C	C
Laitinen, 1993	B(I)	B(I)	B	C	C	B(I)
Lindahl, 1999	B(I)	A	C	C	C	B(I)
Long, 1983	B(I)	B(I)	C	A(II)	C	C
Murphy, 1982	B(I)	B(I)	A	C	C	C
Narayan, 1998	B(I)	A	C	C	C	C
ODES, 1995	A	A	C	C	C	C
Ost, 1976	B(I)	A	A	C	C	C
Pavlou, 1989a	B(I)	B(I)	B	C	C	C
Pavlou, 1989b	B(I)	B(I)	B	C	C	C
Pearce, 1981	B(I)	B(II)	C	C	C	B(I)
Phenix, 1991	B(I)	B(I)	A	C	C	C
Pritchard, 1997	B(II)	A	A	C	C	C
Pritchard, 1999	B(II)	B(I)	A	C	C	C
Rosenthal, 1980	B(I)	B(I)	A	C	C	C
Shah, 1996	B(I)	A	C	C	C	C
Sikand, 1988	B(I)	B(I)	A	C	C	C
Simonen, 2000	B(I)	C	A	C	C	C
Stenius-Aarniala, 2000	B(I)	A	A	C	C	C
Straw, 1983	B(I)	A	C	C	C	C
Swinburn, 2001	C	B(I)	C	C	C	C
TAIM, 1992	A	A	C	C	C	C
TOHP I, 1992	A	B(I)	B	C	C	C
TOHP II, 1997	A	B(I)	B	C	C	A(II)
TONE, 1998	B(I)	B(I)	C	C	C	A(I)
Torgerson, 1997	B(I)	A	A	C	C	C
Tucker, 1991	B(I)	A	B	C	C	B(I)
Viegener, 1990	B(I)	B(I)	C	C	C	C
Wadden, 1989	B(I)	A	C	C	C	C
Wadden, 1994	B(I)	A	A	C	C	C
Wadden, 1998	B(I)	A	C	C	C	C
Wadden, 2001	B(I)	A	A	C	C	C
Wing, 1984	B(I)	B(I)	A	C	C	C
Wing, 1985	B(I)	B(I)	A	C	C	C
Wing, 1988a	B(I)	B(I)	C	C	C	A(I)
Wing, 1988b	B(I)	B(I)	C	C	C	A(I)
Wing, 1991	B(I)	B(I)	B	C	C	B(I)
Wing, 1991b	B(I)	B(I)	C	C	C	C
Wing, 1994	B(I)	B(I)	C	C	C	B(I)
Wing, 1998	B(I)	B(I)	A	C	C	B(I)
Wing, 1999	B(I)	B(I)	A	C	C	C
Wood, 1988	B(I)	A	C	C	C	C
Wood, 1991	B(I)	A	C	C	C	C

Appendix 12

Summary table of weight loss results

The table shows summary estimates for weight changes from RCTs of weight reduction (WMDs and 95% CI, in kg).

Comparison	12 months	18 months	24 months	30 months	36 months	48 months	60 months
Drug trials							
Orlistat added to diet	–3.01* (–3.48 to –2.54)		–3.26* (–4.15 to –2.37)				
Sibutramine added to diet	–4.12* (–4.97 to –3.26)						
SSRIs added to diet	–0.33 (–1.49 to 0.82)						
Metformin added to diet	–1.09 (–2.29 to 0.11)		–0.50 (–4.02 to 3.02)				–0.12 (–1.13 to 0.89)
Acarbose added to diet	–0.79* (–1.53 to –0.05)						
Diet trials							
600 kcal/day deficit or low-fat diet compared with control	–5.31* (–5.86 to –4.77)	–1.15 (–2.76 to 0.45)	–2.35* (–3.56 to –1.15)		–3.55* (–4.54 to –2.55)		–0.20 (–2.03 to 1.63)
LCD compared with control	–6.25* (–9.05 to –3.45)		–7.00* (–10.99 to –3.01)		–6.10* (–10.71 to –1.49)		
VLCD compared with control	–13.40* (–18.43 to –8.37)						
LCD compared with 600 kcal/day or low-fat diet	1.63 (–1.26 to 4.52)						
VLCD compared with 600 kcal/day or low-fat diet			–4.70 (–11.79 to 2.39)				
VLCD compared with LCD	–0.15 (–2.73 to 2.43)	–1.13 (–5.32 to 3.06)					
PSMF compared with LCD	–3.57 (–7.36 to 0.22)	0.69 (–1.58 to 2.96)	–2.17 (–4.88 to 0.54)		–1.51 (–5.43 to 2.41)		0.20 (–5.68 to 6.08)
PSMF compared with VLCD		2.73 (0.07 to 5.39)					

continued

Comparison	12 months	18 months	24 months	30 months	36 months	48 months	60 months
Trials of diet, exercise or behaviour therapy combinations							
Diet and exercise compared with control	–4.78* (–5.41 to –4.16)		–2.70* (–3.60 to –1.80)				
Diet and behaviour therapy compared with control	–7.21* (–8.68 to –5.75)		–1.80 (–4.77 to 1.17)				
Adding diet and behaviour therapy to surgery	–10.03 (–22.29 to 2.23)		–10.56 (–23.17 to 2.05)				
Diet, exercise and behaviour therapy compared with control	–4.00* (–4.46 to –3.54)	–3.40* (–3.84 to –2.97)	–3.00* (–3.59 to –2.40)	–4.68* (–6.08 to –3.28)	–2.00* (–2.66 to –1.34)		
Family compared with individual therapy	–2.96* (–5.31 to –0.60)	–1.08 (–3.04 to 0.87)	–5.61* (–10.98 to –0.24)			–1.55 (–7.88 to 4.78)	
Group compared with individual therapy	1.59 (–1.81 to 5.00)	0.74 (–4.21 to 5.69)	8.10 (2.19 to 14.01)				4.40 (–3.51 to 12.31)
Adding exercise to diet	–1.95* (–3.22 to –0.68)	–7.63* (–10.33 to –4.92)			–8,22* (–15.27 to –1.16)		
Adding behaviour therapy to diet	–7.67* (–11.97 to –3.36)	–4.18* (–8.32 to –0.04)			–2.91 (–8.60 to 2.78)		1.90 (–3.76 to 7.56)
Adding exercise to diet and behaviour therapy	–3.02* (–4.94 to –1.11)		–2.16* (–4.20 to –0.12)				
Adding exercise and behaviour therapy to diet	–0.67 (–4.22 to 2.88)	–2.06 (–5.57 to 1.45)	–1.40 (–5.01 to 2.21)				
Behaviour therapy added to LCD and exercise	–10.69* (–14.22 to –7.16)						

* Significant difference.

Appendix 13

Statistical methods for estimation of standard deviation of change in weight

Introduction

The following provides an equation for deriving the standard deviation for the change in weight from baseline given the absolute value of the mean change in weight since baseline.

Method

Summary statistics were provided from a series of trials representing 62 trial–treatment combinations, of which four had no data. A linear regression was made of the standard deviation of the mean change on the absolute mean change for weight.

Results

Of the 58 trial–treatment combinations, 43 reported both the mean change and the standard error of the mean change in body weight from baseline to the end of the first treatment phase, while eight only reported the mean and seven reported neither. The plot of standard deviation by the absolute value of the mean change (*Figure 250*) shows two points where both the absolute mean and the standard deviation of the mean are close to zero; both were excluded from the linear regression, giving $n = 41$. The linear regression was also repeated with observation 13, which was influential,

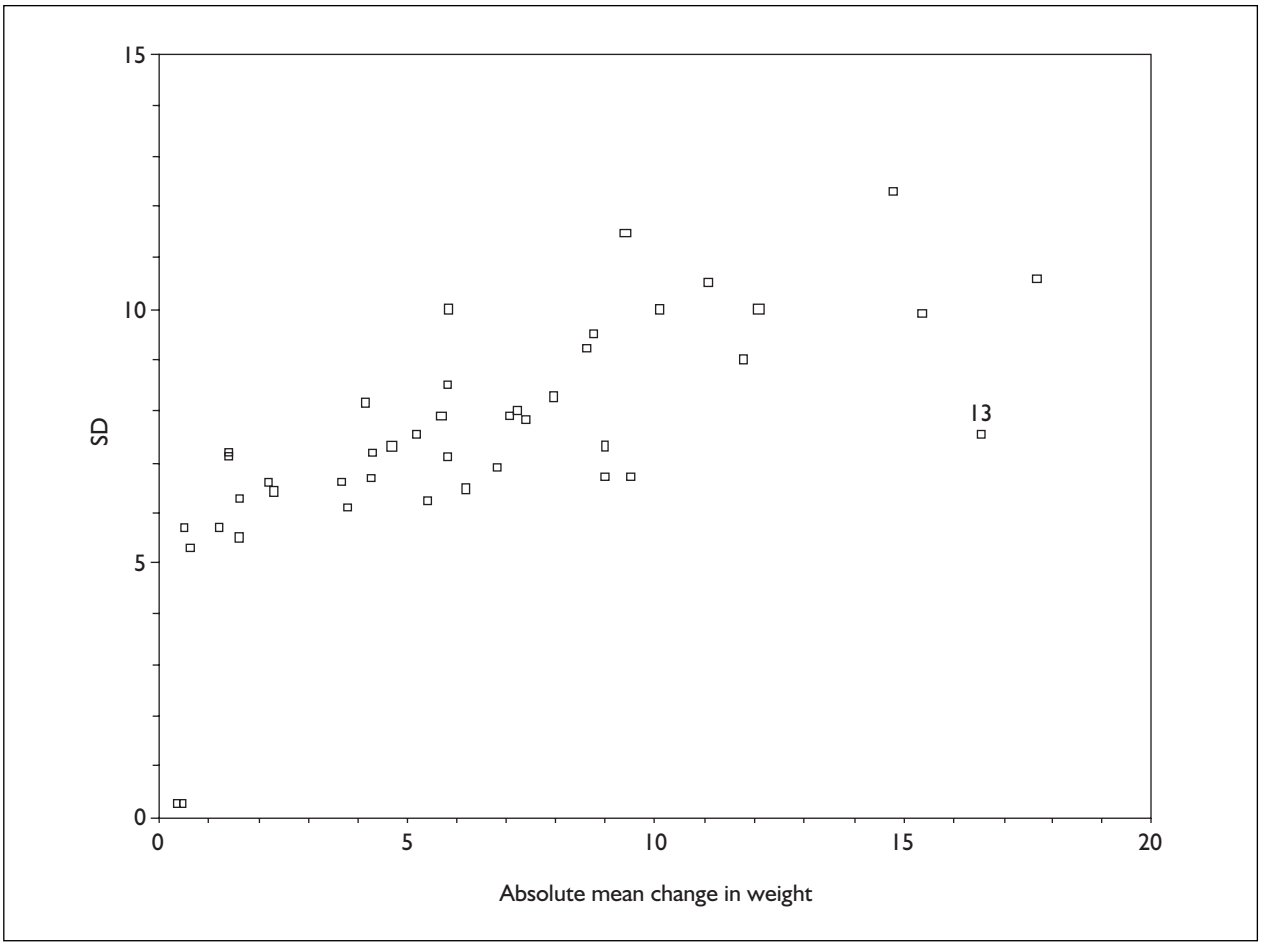

FIGURE 250 *Scatterplot of the standard deviation of the mean change in weight by the absolute mean change in weight. Observation 13 is labelled*

TABLE 24 *Summary statistics and the equations for the predicted values of the standard deviations of the two linear regressions*

n	R^2			Constant		Slope
41	53.7%	SD	=	5.915	+	0.283 * abs(mean)
40	63.4%	SD	=	5.694	+	0.328 * abs(mean)

excluded to see whether the regression coefficients changed.

Discussion

The results from the two linear regressions were similar. Diagnostic plots (not shown) suggested that the regression could be improved by allowing for the increase in variation of the standard deviation with increasing mean; however, this is unlikely to change the results.

Conclusion

When the mean change in weight since baseline (mean) is known but its standard deviation is unknown, then the equation:

$$\text{SD} = 5.915 + 0.283 * \text{absolute(mean)}$$

can be used to derive the standard deviation of the mean change (*Table 24*).

Appendix 14

Statistical methods for estimation of standard deviation of change in risk factors

Estimation of standard deviation of change in blood pressure

Introduction

The following short report describes the derivation of an equation for the standard deviation for the change in BP from baseline given the mean change in BP since baseline. Both SBP and DBP were available.

Method

Summary statistics were provided from a series of trials representing 96 trial–treatment–BP combinations. A linear regression was made of the standard deviation of the mean change on the absolute mean change for both systolic and diastolic data.

Results

Of the 96 trial–treatment–BP combinations (46 SBP and 50 DBP), 51 (25, 26) reported both the mean change and the standard error of the mean change in BP from baseline to the end of the first treatment phase, while 12 (6, 6) only reported the mean and 33 (15, 18) reported neither.

The plot of standard deviation by the absolute value of the mean change showed the systolic and diastolic data to be sufficiently different not to warrant a joint regression model. The systolic data showed greater variation amongst their standard deviations. One study reported three diastolic absolute means and the standard deviation of the mean that were close to zero and they were excluded, linear regression giving $n = 25$ for SBP and $n = 23$ for DBP (*Table 25*).

SBP

The absolute mean had no effect on the standard deviation. The overall mean for the standard deviation is reported below.

DBP

The absolute mean had no effect on the standard deviation. When two influential points were excluded there was no change in the result. The overall mean for the standard deviation is reported below.

Discussion

Only just over half of the trial–treatment–BP combinations were available for use in the regression models. Of the remaining 45, 33 had data on both the mean and standard deviation of the mean at the two time-points available. Standard deviations for the change could be derived if some assumptions on correlation were made, possibly based on the nine observations where all three standard deviations were available.

Conclusion

- Standard deviation of the mean change in SBP, use 12.7 mmHg.
- Standard deviation of the mean change in DBP, use 8.3 mmHg.

Estimation of standard deviation of change in fasting lipids and plasma glucose level control

Introduction

The following short report describes the derivation of an equation for the standard deviation for the change in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose and HbA_{1c} from baseline given the mean change since baseline.

Method

Summary statistics were provided from a series of trials representing 208 trial–treatment–blood measure combinations from 50 trial–treatment combinations. The relationship between the absolute mean change and the standard deviation of the mean change was examined for 6 types of blood measure: total cholesterol from 44 trial–treatment combinations, LDL from 30, HDL from 42, TGs from 42, fasting glucose from 30 and HbA_{1c} from 20. The relationship could be affected by whether participants were diabetic or non-diabetic, in particular for fasting glucose and HbA_{1c}.

The following analysis was done for each blood measure:

TABLE 25 *Summary statistics for the mean standard deviation of the mean change in blood pressure*

	n	Min.	Max.	Mean	SD
Systolic	25	6.80	23.97	12.7070	4.0164
Diastolic I	23	5.60	14.75	8.2958	2.1794
Diastolic II	21	5.60	9.40	7.7549	1.2773

Diastolic II was based on removing two influential data points.

TABLE 26 *Summary statistics for the standard deviations of the risk factors*

Blood measure	Mean SD	Median SD	Details
HDL	0.29	0.24	Mostly below 0.4, except for five between 0.4 and 0.6 when $n < 100$
LDL	0.74	0.71	No relationship with *n*
TGs	0.96	0.81	Mostly below 1.5, except for four between 1.5 and 3.5 when $n < 50$
Cholesterol	1.08	0.83	A narrow band of SDs. One outlier. Four higher SDs, three from small trials ($n = 30$) and one trial ($n \simeq 100$)
Fasting glucose	2.43	1.42	Clear threshold effect. One outlier (a possible typographic error). Two high values for two large studies ($n \simeq 350$). Most SDs < 2
	3.11	3.49	When $n < 30$
	1.98	0.95	When $n \geq 30$
HbA_{1c}	1.96	1.60	Clear threshold effect. SDs increase rapidly when $n < 30$
	2.70	2.10	Where $n < 30$
	0.76	0.66	Where $n \geq 30$

- plot of the number of observations versus the standard deviation
- summary statistics for the standard deviation by treatment
- where the SD varied with study size, summary statistics stratified by study size.

Results

The plots suggested that the standard deviations were quite stable, but below a threshold there were cases where some of the standard deviations were greater as the number of participants fell (*Table 26*). The threshold varied for each measure. Causes for this were not reviewed.

Discussion

The effect of study size needs to be reviewed when estimating standard deviations. For the blood lipids this appears to make little difference and either the mean or median standard deviation could be used. Erring on the side of caution would suggest using the mean value. There is, however, a study size effect for glucose and HbA_{1c}. The possibility of using the stratified SDs should be considered.

The cause of the effect of the number of observations was not reviewed. The main candidate would be treatment. Plots were reviewed but there are numerous treatments and there is no clear way in which to group them.

Appendix 15

Protocol for a systematic review of observational epidemiological evidence

Objective

The objective of this review is to look at prospective studies systematically to identify the effects of reduced BMI on long-term health outcomes with statistical modelling methodology.

Criteria for considering studies for this review

Inclusion criteria

Types of studies

- Information from all prospective or cohort studies carried out on patients with a BMI ≥ 28 kg/m^2
- minimum duration of the study for surgical follow-up at least 5 years; for studies with non-surgical follow-up, duration of study at least 2 years
- BMI measured on at least two occasions during the study period
- in MEDLINE, terms for cross-sectional studies and prevalence studies will be included in the search strategy to provide studies for economic modelling. Relevant abstracts will be sent to the economist for inclusion. In other databases the search terms for the economic modelling will be omitted
- studies published in all languages from 1966 up to April 2001
- major journals that are indexed will be reviewed up to June 2001.

Types of participants

- Studies on adults from the age of 18 years up to 70 years
- studies on populations who weight-cycle
- studies on Caucasian populations. However, studies on immigrant populations such as African–Americans, Japanese Americans and British Asians will be included.

Exclusion criteria

- Studies on people with a BMI < 28 kg/m^2
- non-human studies
- people with bulimia nervosa
- studies on children less than 18 years old, and people more than 70 years old
- population-based studies which include a small subgroup of obese patients
- Oriental, African and Asian population studies
- studies with loss to follow-up of more than 20% of the study population.

Types of outcome measures

Data will be extracted on the following outcome measures:

- mortality from all causes
- morbidity from CVD (including risk factors: blood lipids, BP)
- CHD
- cerebrovascular disease: stroke
- diabetes mellitus (including risk factor: blood glucose)
- cholelithiasis
- musculoskeletal: arthritis
- cancer: breast, colorectal, prostate, endometrial
- asthma
- sleep apnoea
- NASH
- urinary incontinence
- bone fractures
- psychological health and quality of life
- co-morbidities
- risk scoring systems.

Search strategy for identification of studies

Databases for the search

A database search for the prospective studies will be conducted using:

- MEDLINE
- EMBASE
- CINAHL
- HealthSTAR.

- Specific MeSH terms will be used and modified according to the relevant databases, in addition
  - reference lists of identified articles and review articles will be searched for further relevant prospective studies
  - authors will be contacted for details of the study if additional information is necessary.

Method of review

Identification of the studies

All possible studies will be entered into Reference Manager version 9. Subject keywords and source of articles will be added. Abstracts and study titles will be read by two researchers initially to check for consistency, and later on by one researcher. Articles on cross-sectional and prevalence studies on people with obesity and any other relevant articles will be sent to the economist for evaluation and inclusion.

Quality assessment of the studies

Full copies of the eligible studies will be obtained and assessed by two researchers initially to check for consistency, and later on by one researcher. Any doubts about the inclusion of a study will be resolved by discussion.

Data extraction

The following data will be extracted using a standard form:

- year of study
- author and country
- sample size
- age and gender of the participants
- ethnic groups of participants
- specifically targeted groups (diabetes, hypertension)
- co-morbidities
- risk factors: smoking, lipids, blood pressure, blood glucose, family history
- details of follow-up: duration, percentage of follow-up
- results: outcomes.

Statistical modelling will be done based on the evidence of effect of weight loss on long-term health outcomes from the epidemiological studies and the RCTs.

Appendix 16

Search strategies

The electronic bibliographic database MEDLINE (National Library of Medicine, the electronic version of *Index Medicus*, USA) was searched from 1966 to May 2001 using the developed search strategy for the prospective and cohort studies:

1. cohort studies/
2. prospective studies/
3. follow-up studies/
4. longitudinal studies/
5. cohort$.tw.
6. (prospective adj1 stud$).tw.
7. (follow-up adj1 stud$).tw.
8. (longitudinal adj1 stud).tw.
9. epidemiological studies/
10. (epidemiological adj1 stud$).tw.
11. (case-control adj1 stud$).tw.
12. (retrospective adj1 stud$).tw.
13. (cross-sectional adj1 stud).tw.
14. (survey or surveys).tw.
15. prevalence.tw.
16. (prevalence adj1 stud$).tw.
17. (relative adj1 (risk or risks)).tw.
18. or/1-17
19. obesity/
20. obesity in diabetes/
21. obesity, morbid/
22. overweight.tw.
23. (weight adj1 reduc$).tw.
24. (weight adj1 control$).tw.
25. (weight adj1 cycl$).tw.
26. (weight adj1 chang$).tw.
27. (waist adj3 hip adj3 (ratio or ratios) adj5 chang$).tw.
28. (body adj3 mass adj3 index adj5 chang$).tw.
29. quetelet$.tw.
30. (quetelet$ adj1 index).tw.
31. (waist adj1 circumference adj5 chang$).tw.
32. (body adj1 weight adj5 chang$).tw.
33. or/19-32
34. 18 and 33
35. limit 34 to human
36. limit 35 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
37. 35 not 36

EMBASE, the Experta Medica database produced by Elsevier Science, was searched from 1980 to week 17 of 2001. The search terms were modified according to the relevant MeSH terms:

1. prospective studies/
2. (prospective adj1 stud$).tw.
3. cohort$.tw.
4. (cohort adj1 stud$).tw.
5. (follow-up adj1 stud$).tw.
6. longitudinal study/
7. (longitudinal adj1 stud).tw.
8. (epidemiological adj1 stud$).tw.
9. or/1-8
10. obesity/
11. morbid obesity/
12. diabetic obesity/
13. overweight.tw.
14. weight reduction/
15. (weight adj1 reduc$).tw.
16. (weight adj1 control$).tw.
17. (weight adj1 cycl$).tw.
18. (weight adj1 chang$).tw.
19. (waist adj3 hip adj3 (ratio or ratios) adj5 chang$).tw.
20. (body adj3 mass adj3 index adj5 chang$).tw.
21. (quetelet$ adj1 index).tw.
22. quetelet$.tw
23. (waist adj1 circumference adj5 chang$).tw.
24. (body adj1 weight adj5 chang$).tw.
25. or/10-24
26. 9 and 25
27. Nonhuman/
28. 26 not 27
29. limit 28 to (adolescent <13 to 17 years> or child <unspecified age> or embryo <first trimester> or infant <to one year> or preschool child <1 to 6 years> or school child <7 to 12 years>)
30. 28 not 29

HealthSTAR, produced by the National Library of Medicine, was searched from 1975 to December 2000:

1. cohort studies/
2. longitudinal studies/
3. prospective studies/
4. follow-up studies/

5. cohort$.tw.
6. (prospective adj1 stud$).tw.
7. (follow-up adj1 stud$).tw.
8. (longitudinal adj1 stud).tw.
9. epidemiological studies/
10. (epidemiological adj1 stud$).tw.
11. or/1-10
12. obesity/
13. obesity in diabetes/
14. obesity, morbid/
15. overweight.tw.
16. (weight adj1 reduc$).tw.
17. (weight adj1 control$).tw.
18. (weight adj1 cycl$).tw.
19. (weight adj1 chang$).tw.
20. (waist adj3 hip adj3 (ratio or ratios) adj5 chang$).tw.
21. (body adj3 mass adj3 index adj5 chang$).tw.
22. quetelet$.tw.
23. (quetelet$ adj1 index).tw.
24. (waist adj1 circumference adj5 chang$).tw.
25. (body adj1 weight adj5 chang$).tw.
26. or/12-25
27. 11 and 26
28. (animal not human).sh.
29. 27 not 28
30. limit 29 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years> or "aged, 80 and over")
31. 29 not 30
32. limit 31 to nonmedline

CINAHL was searched from 1982 to April 2001:

1. prospective studies/
2. (prospective adj1 stud$).tw.
3. cohort$.tw.
4. (cohort adj1 stud$).tw.
5. (follow-up adj1 stud$).tw.
6. (longitudinal adj1 stud).tw.
7. epidemiological research/
8. (epidemiological adj1 stud$).tw.
9. concurrent prospective studies/
10. panel studies/
11. or/1-10
12. obesity/
13. obesity, morbid/
14. overweight.tw.
15. (weight adj1 reduc$).tw.
16. weight control/
17. (weight adj1 control$).tw.
18. (weight adj1 cycl$).tw.
19. (weight adj1 chang$).tw.
20. (waist adj3 hip adj3 (ratio or ratios) adj5 chang$).tw.
21. waist-hip ratio/
22. body mass index/
23. (body adj3 mass adj3 index adj5 chang$).tw.
24. quetelet$.tw.
25. (quetelet$ adj1 index).tw.
26. (waist adj1 circumference adj5 chang$).tw.
27. (body adj1 weight adj5 chang$).tw.
28. or/12-27
29. 11 and 28
30. animal studies/
31. 29 not 30
32. limit 31 to (pregnancy of fetus <conception to birth> or newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years> or "aged, 80 and over")
33. 31 not 32

Appendix 17

Data extraction and quality assessment form

Data Extraction Form – PROSPECTIVE STUDIES

Search database: _____

Database ID number: _____ Checked by: _____

ELIGIBILITY CHECK

	YES	NO	Unclear or other with details
Prospective study			
Obese group (at least one subgroup) BMI ≥ 28 kg/m^2			
Weight loss recorded			
Follow-up more than 2 years for non-surgical interventions			
Follow-up more than 5 years for surgical interventions			
At least one of the specified outcomes			

DATA EXTRACTION

Final database: **Final obesity HTA** Unique ID number: _____

BIBLIOGRAPHIC DETAILS

Authors _____

Journal _____

Title _____

_____

Year Volume Issue Page numbers

Country of origin _____

Reviewer 1 _____ Reviewer 2 _____

SEARCH DETAILS

MEDLINE EMBASE HealthSTAR CINAHL Other (e.g. PhD)

Identified from reference checking (which article?)

Search strategy (key MeSH terms)

SAMPLE DETAILS

Sample size	Total: Males: Females:
Sex of the sample	
Age of the sample	Mean: SD: Range: Others:
Country of the sample	
Ethnic groups	Caucasians African–Americans Japanese Americans British Asians
Socio-economic class	Class I Class II Class III Class IV Class V
Body mass index at the start of the study (BMI)	Mean: Range: WHO Class (no:) ≥ 28–29.9 30–34.9 35–39.9 ≥ 40
Waist circumference at the start of study	Mean: Range: Others:
Any others measurement at start of study	

RISK FACTORS RECORDED

Smoking	Yes	No
Family history of obesity	Yes	No
Blood pressure	Yes	No
Cholesterol	Yes	No
Blood sugars	Yes	No
Diabetes mellitus	Yes	No

INTERVENTION/PROCEDURE

Intervention	Type	Details
Was weight loss	Intentional/Non-intentional:	
Intervention before follow-up	Surgical/Non-surgical/ Combination of interventions:	

ASSESSMENT AND FOLLOW-UP

Setting of study	Hospital Community Urban/Rural General practice Obesity clinic Others	Details:
Duration of follow-up		
Number of follow-ups		Details:
Percentage of follow-up		
Are losses to follow-up described?	Yes/No	Details:
Medium employed for assessment	Specified/Non-specified	
Mode of assessment	Questionnaires Interviews Physical examination Lab investigations Others	Details of assessment:
Quantification of weight loss	% or average weight loss Change in BMI (WHO class) Change in waist circumference: Other measurement:	Details:

OTHER DETAILS

Weight cycling	Yes/No Number of cycles Average weight loss in each cycle	Details:
Risk scoring systems	Yes/No	Details:

OUTCOMES MEASURED

Number of outcomes measured ☐ **What are they?**	**Details of outcomes measured**
Mortality	
Lipids	
Blood pressure	
Coronary heart disease	
Stroke	
Blood sugars	
Gallstones	
Arthritis	
Breast cancer	
Colorectal cancer	
Prostate cancer	
Endometrial cancer	
Asthma	
Sleep apnoea	
NASH (non-alcoholic steatohepatitis)	
Urinary incontinence	
Psychological health/quality of health	
Fracture of bones	

QUALITY ASSESSMENT FORM

* Ring the appropriate code

	YES	UNCLEAR/ POSSIBLY	NO
1. Was the aim of the study clearly stated?	2	1	0
Sample:			
2. Was sample size justified?	2	1	0
3. Age of patients defined?	2	1	0
4. Measurements at start of study clearly stated?	2	1	0
5. Are measurements likely to be valid and reliable?	2	1	0
6. Risk factors recorded clearly?	2	1	0
Conduct of the study:			
7. Was intervention before follow-up defined?	2	1	0
8. Setting of the study clear?	2	1	0
9. Is mode of assessment described?	2	1	0
10. Did untoward events occur during the study?	1	0	2
Follow-up:			
11. How adequate was the follow-up?	2	1	0
12. Was follow-up long enough?	2	1	0
13. Are losses to follow-up described?	2	1	0
Analysis:			
14. Were basic data adequately described?	2	1	0
15. Do numbers add up?	2	1	0
16. Did analysis allow for passage of time?	2	1	0
17. Was statistical significance assessed?	2	1	0
Interpretation:			
18. Were the main findings interpreted adequately?	2	1	0
19. Were the null/negative findings interpreted?	2	1	0
20. Are important effects overlooked?	0	1	2

TOTAL: (add ringed scores above): _____ (A)

Maximum possible score (2 × 20) _____ (B)

OVERALL RATING (A/B expressed as %) _____ (%)
Not satisfactory (1–50%)
Moderate (51–80%)
Very satisfactory (81–100%)

Queries/Comments

Appendix 18

Excluded studies

1. Research Group of the Rome Project of Coronary Heart Disease Prevention. Eight-year follow-up results from the Rome Project of Coronary Heart Disease Prevention [published erratum appears in *Prev Med* 1986;**15**:436]. *Prev Med* 1986;**15**:176–91.
2. The Roman Coronary Disease Prevention Project: effectiveness of intervention and reduction of mortality over a 10-year period [in Italian]. *G Ital Cardiol* 1986;**16**:196–202.
3. Prevalence of overweight – behavioral risk factor surveillance system, 1987. *MMWR Morb Mortal Wkly Rep* 1989;**38**:421–3.
4. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990;**150**:153–62.
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Appendix 19

Characteristics of prospective studies included in the review, and recent papers and studies to update the epidemiology review for long-term health outcomes

Appendix 19a

Characteristics of prospective studies included in the review

First author, year	Country	Sample size	Outcomes measured	Outcome indices	Intervention	Average follow-up (years)	Percentage follow-up
Prospective studies (*n* = 28)							
Peppard, 2000[290]	USA	258 (M 140, F 128)	Sleep apnoea (AHI)	OR	None	4	72.8%
Charuzi, 1992[264]	Israel	51 (M 44, F 7)	AI	Absolute value	Surgical (bariatric surgery)	6.3	86%
Sugerman, 1992[291]	USA	126 (M 78, F 48)	AI, lung volume	AI: value; PaO_2 and PCO_2: mmHg	Surgical (VBG)	4.5	45%
Pories, 1992[266]	USA	515 (M 77, F 438)	DM, hypertension	Incidence	Surgical (gastric bypass)	11	50% at 5 years
Williamson, 1995[274]	USA	43,457 (all F)	Mortality: all cause, CVD, cancer, DM	Mortality rate ratios	None	12.9	?91%
Williamson, 1999[273]	USA	49,337 (all M)	Mortality: all cause, CVD, cancer, DM	Mortality rate ratios	None	12.9	?91%
Williamson, 2000[275]	USA	4970 (M 2509, F 2461)	Mortality: all cause, CVD, cancer, DM	Mortality rate ratios	None	12.9	91.4%
Rumpel, 1993[276]	USA	326 (all F)	Mortality: all cause, CVD, cancer, other	Relative risks (weight groups)	None	Median 13.6	?
Chaturvedi, 1995[267]	Europe	541 (M 210, F 331)	Mortality in NIDDM	Relative risks	None	8–19	?
O'Leary, 1980[272]	USA	274	DM, lipids, hypertension	% improved	Surgical (jejunal bypass)	?7 (not clear)	?84%
Ford, 1997[268]	USA	8545 (M 3220, F 5325)	DM	Hazard ratio (weight groups)	None	?10	?
Moore, 2000[269]	USA	618 (M 333, F 285)	DM	Relative risks	None	16	?
Watts, 1990[281]	USA	135	DM	Glucose: mmol/l	Non-surgical (diet)	4	?
Wannamethee, 1999[280]	UK	7735 (all M)	DM	Relative risks, incidence rate	None	Mean 16.8	91%
Wittgrove, 2000[289]	USA	500	Co-morbidities	Proportion of reduction	Surgical (gastric bypass)	3–60 months	<1% at 5 years

continued

First author, year	Country	Sample size	Outcomes measured	Outcome indices	Intervention	Average follow-up (years)	Percentage follow-up
Hess, 1998[271]	USA	440 (M 95, F 345)	Lipids, glucose	Lipids and glucose: mg/dl	Surgical (biliopancreatic diversion)	8	21% at 5 years
Wing, 1995[282] (W)	USA	202 (M 101, F 101)	Lipids, BP	Lipids: mmol/l or mg/dl; BP: mmHg	Non-surgical (VLCD, exercise and behaviour)	2.5	76%
Kauffman, 1992[283]	Spain	836 (M 714, F 125)	Lipids, BP	Correlation	Non-surgical (diet and exercise)	2	77%
Gleysteen, 1992[286]	USA	43	Lipids	mmol/l	Surgical (Roux-en-Y bypass)	5–7	77%
Rossner, 1980[287]	Sweden	29 (M 10, F 19)	Lipids	mmol/l	Surgical (jejunoileal bypass)	3.6	80% (M), 53% (F)
Ewbank, 1995[284]	UK	55	Lipids	mmol/l	Non-surgical (VLCD and behaviour)	2	82%
Foster, 1996[163] (W)	USA	48 (all F)	Psychological well-being	No. of events	Combined (surgical and non-surgical)	4.8	45%
van Gemert, 1998[270]	Netherlands	62 (M 18, F 44)	Psychological well-being	NVM, NPV and SIG scores	Surgical (VBG, gastric banding or bypass)	7.2	91%
Holt, 1987[265]	USA	50 (M 12, F 38)	Co-morbidities (lipids, DM, stress incontinence, sleep apnoea, hypertension, arthritis)	% improvement of all co-morbidities together	Surgical (VBG)	2–5	80%
Kunesova, 1998[262]	Prague	318 (M 64, F 254)	Hypertension	mmHg	Combined (surgical and non-surgical)	3.5	32.4%
Carson, 1994[263]	USA	45 (M 10; F 35)	Hypertension	% improved	Surgical (gastric bypass)	4	40% at 4 years
Foley, 1992[288]	USA	74 (M 24, F 50)	Hypertension	% improved	Surgical (Roux-en-Y, VBG)	4.2	91%
Sjostrom M, 1999[285]	Sweden	36	Hypertension, lipids	Hypertension: mmHg; lipids: mmol/l	Non-surgical	5	

continued

First author, year	Country	Sample size	Outcomes measured	Outcome indices	Intervention	Average follow-up (years)	Percentage follow-up
Non-randomised (*n* = 3) and randomised (*n* = 6) trials							
Long, 1994[279] (NR)	USA	109 (M 15, F 94)	NIDDM	Incidence rates	Surgical (bariatric vs no surgery)	6.2	40% at 6 years
Karason, 1999[277] (NR)	Sweden	39	Lipids, BP, glucose	Lipids and glucose: mmol/l; BP: mmHg	Surgical (gastric surgery vs diet)	4	92%
Sjostrom CD 2000[278] (NR)	Sweden	346 (M 118, F 228)	Hypertension, DM, BP	HT: incidence and OR; DM: prevalence, incidence and OR; BP: mmHg	Surgical (surgery vs customary treatment)	8	73%
Wing, 1998[176] (R)	USA	154 (M 32, F 122)	DM, lipids, BP	DM: values; lipids: mmol/l; BP: mmHg	Non-surgical (diet, exercise and behaviour)	2	81%
Rossner, 2000[37] (R)	Sweden	718 (M 127, F 591)	BP, glucose	BP: mmHg glucose: mmol/l	Non-surgical (orlistat and diet vs placebo and diet)	2	60%
Davidson, 1999[41] (R)	USA	880 (M 139, F 741)	Lipids, glucose, insulin	Lipids and glucose: mmol/l; insulin: pmol/l	Non-surgical (orlistat and diet vs placebo and diet)	2	45.8%
Teupe, 1991[84] (R)	Germany	100 (M 40, F 60)	BP, lipids	BP: mmHg; Lipids: mg/100 ml	Non-surgical (metformin and diet vs diet)	2	46%
Tuomilehto, 2001[168] (R)	Finland	522 (M 172, F 350)	DM	Incidence, relative risks	Non-surgical (diet and exercise vs control)	2–6 (mean 3.2)	92%
Hauptman, 2000[45] (R)	USA	635 (M 138, F 497)	Lipids, BP, glucose, insulin	Lipids and glucose: mmol/l; BP: mmHg; insulin: pmol/l	Non-surgical (orlistat and diet vs placebo and diet)	2	52%

W, study included weight cycling; NR, non-randomised trial; R, randomised trial; M, male; F, female; AHI, apnoea–hypopnoea index; AI, apnoea index; PaO_2, arterial oxygen tension; PCO_2, carbon dioxide tension; VBG, vertical banded gastroplasty.

Appendix 19b

Characteristics of recent papers and studies to update the epidemiology review for long-term health outcomes

Study and country	Participants	Interventions	Main outcomes	Date	Notes
Fisher, 2002[295] Israel	40 untreated, mean ± SD Age 47 ± 10 years, BMI 28.9 ± 4.8 kg/m^2 11 weight losers, Age 46 ± 13 years, BMI 33.3 ± 4.5 kg/m^2	Treated had dietary programme for weight loss. All had reached their target weight	BMI, sleep apnoea measures	Not given	Untreated were followed for 5 ± 2.8 years (mean ± SD). Put on some weight (not sig). Effects on sleep apnoea: 0 improved, 22 unchanged, 18 worsened Those treated were followed for 2.5 ± 2.3 years. Lost some weight (sign). Effects on sleep apnoea: 3 improved, 7 unchanged, 1 worsened
Sanchez-Cabezudo, 2002[296] Origin?	75 morbidly obese participants	BPD surgery	% EWL, < 50% was classed a failure; reasons for failure of weight loss to this extent, progression of illnesses and QoL	?	All had 5-year follow-up. Even though classed as failures, the weight lost was sufficient to cure or improve their preoperative illnesses, thus improving their QoL
Flechtner-Mors, 2000[297–299] Germany	100 participants, phase I weight loss period 3 months, phase II weight maintenance 48 months	Group A prescribed menus 1200–1500 kcal, group B food substitutes	Weight, BP, lipids, blood glucose, insulin	Seems to be ongoing	Contact with those who dropped out was attempted to obtain long-term results. 75% were followed up. At 4 years: weight loss (mean ± SEM) A: 3.2 ± 0.8%, B: 8.4 ± 0.8%. Glucose and insulin sign improved in each group. Only B had improved TGs and SBP
Arribas, 2002[302] Spain	Retrospective look at a cohort of 80 morbidly obese participants, mean age 37 years, initial mean BMI 49.5 kg/m^2	VBG surgery	BMI, hypertension, lipids DM status	1986–1994: Follow-up years for further 5 years.	Beneficial changes mainly early. Still there even for those with tendency to regain weight
Paisey, 2002[301] UK	45 participants with type II DM, BMI >30 kg/m^2, diet and exercise for 6 weeks, monthly meetings for 5 months, 6 monthly follow-up	Non-randomised 15 VLCD for at least 6 weeks, 15 intensive conventional diet (ICD), 15 non-compliers	Weight loss, lipids, hypertension, glucose	1994, 5-year follow-up	ICD weight loss slower than VLCD but better maintained at 5 years where the HDL increased in ICD group and DBP reduced

continued

Study and country	Participants	Interventions	Main outcomes	Date	Notes
Gregg, 2003[305] USA	Based on USA National Health Interview Survey and supplemental survey, after exclusions, had $n = 6391$, >36 years, BMI >25 kg/m^2	Interviews demographics, health and lifestyle, weight loss intentionality	Self-reported BMI, height, weight change in previous year, linked to National Death Index. Mortality as hazard rate ratios using no weight changes as referent	Supplemental survey 1989, deaths followed up to 1997	Attempted weight loss was associated with lower all-cause mortality, independent of actual weight change. Self-reported intentional weight loss was associated with lower mortality rates. Unintentional weight loss was associated with higher mortality rates

BPD, biliopancreatic diversion; ICD, intensive conventional diet; EWL, excess weight loss.

Appendix 20

Studies and subgroups with mortality results

TABLE 27 *List of included studies*

Graph key	Author & year	Gender	Type of weight loss	Known illness	*n*	Mean age	SD	Initial BMI	SD	Last BMI	SD
5	Williamson, 1995[274]	F	Unintentional weight loss	None given	942	52.9	6.6	30.9	4.1	26.0	3.6
			Intentional weight loss of < 20 lb	None given	2745	51.7	6.3	30.4	3.1	27.3	3.1
			Intentional weight loss of > 20 lb	None given	3018	50.8	6.4	33.1	4.4	26.6	3.6
			Unintentional weight loss	Obesity related	812	55.3	6.1	31.9	4.4	26.3	4.0
			Intentional weight loss of < 20 lb	Obesity related	1550	53.8	6.3	31.5	4.0	28.5	4.0
			Intentional weight loss of > 20 lb	Obesity related	2598	53.7	6.3	34.8	5.4	27.8	4.5
6	Williamson, 1999[273]	M	Unintentional weight loss	None given	1474	52.0	6.1	29.2	2.9	26.0	2.4
			Intentional weight loss of < 20 lb	None given	2834	51.5	5.8	29	2.2	27.2	2.2
			Intentional weight loss of > 20 lb	None given	2610	51.5	5.9	31.4	3.4	26.9	2.8
			Unintentional weight loss	General illness	917	54.4	6.3	29.7	3.1	25.5	2.8
			Intentional weight loss of < 20 lb	General illness	1310	53.4	5.9	29.1	2.4	27.2	2.4
			Intentional weight loss of > 20 lb	General illness	2614	53.6	6.0	31.6	3.7	26.7	3.0
7	Williamson, 2000[275]	M and F	Unintentional weight loss	DM	649	55.6	5.7	31.8	4.1	25.9	3.6
			Intentional weight loss	DM	1669	54.6	6.0	33.5	5.0	27.7	4.0
8	Rumpel, 1993[276]	F	Unknown weight loss intention	None given	326	58.0	14.0	> 29			
9	Chaturvedi, 1995[267]	M and F	Unknown intention lost > 2 BMI	DM	541	48.0	5.6	> 29			

20 lb = 9 kg.

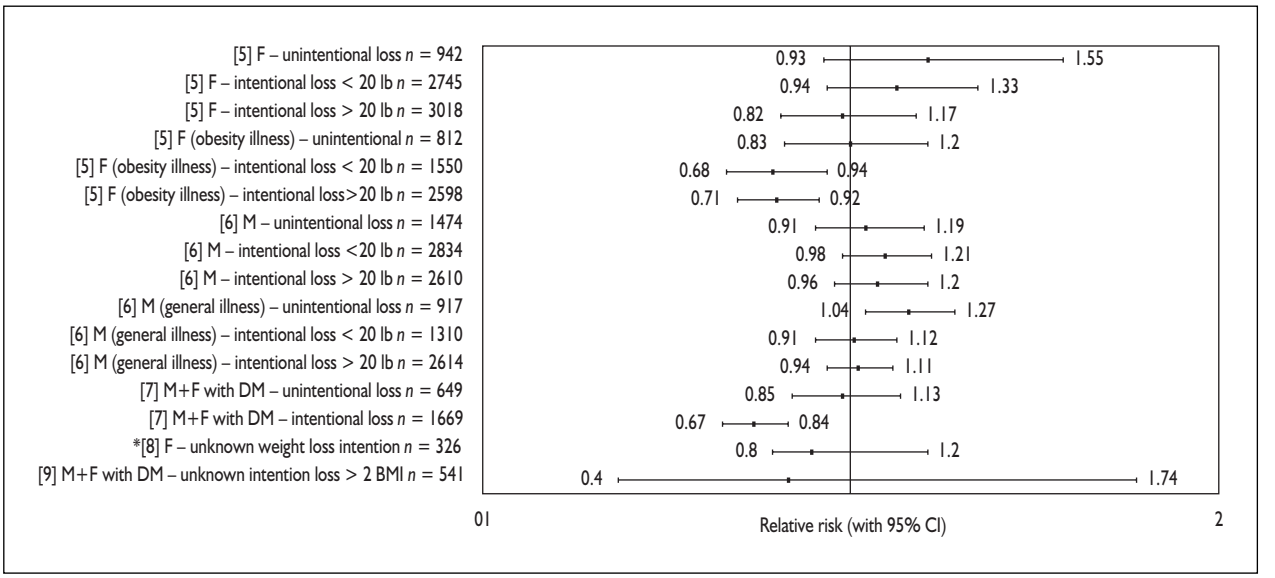


FIGURE 251 *All-cause mortality: all subgroups. Key of [study numbers] given in* Table 27. ** referent was a group that was of normal stable weight.* Q = *59.10 with 15 df: reject homogeneity at* p = *0.001*

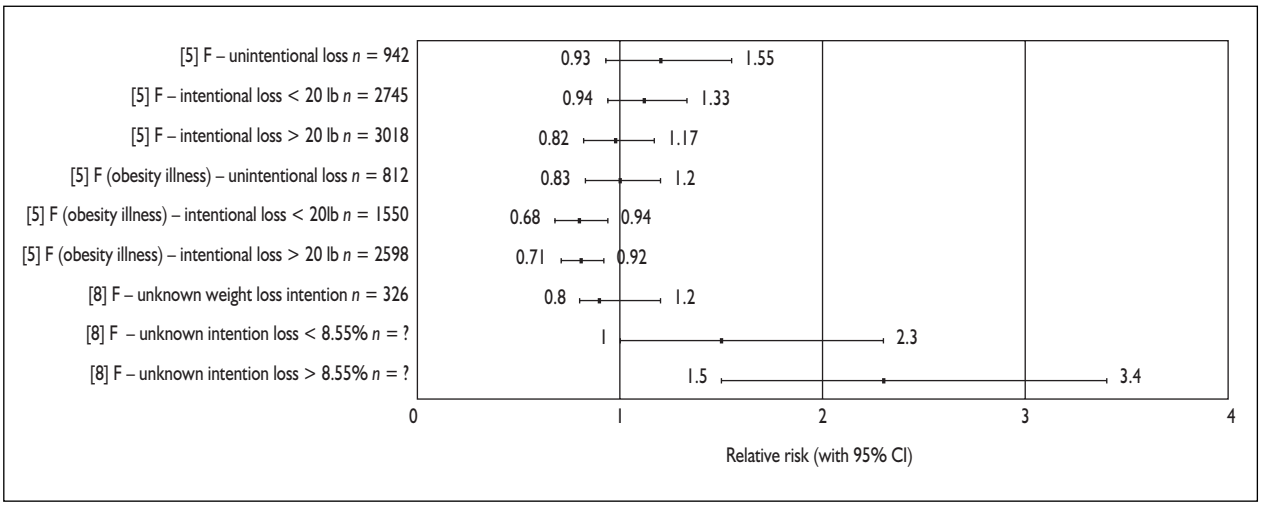


FIGURE 252(a) *All-cause mortality: women only. Key of [study numbers] given in* Table 27. Q = *40.00 with 8 df: reject homogeneity at* p = *0.001*

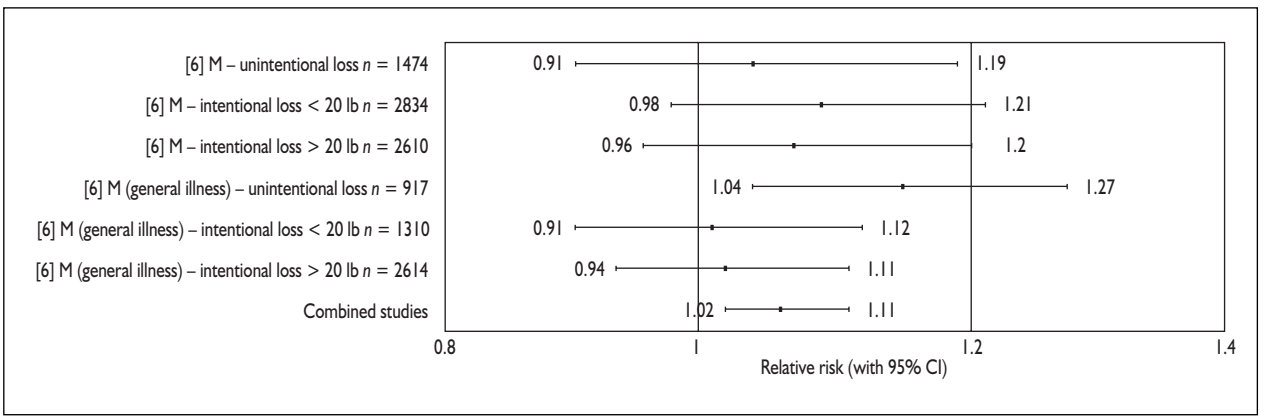


FIGURE 252(b) *All-cause mortality: men only. Key of [study numbers] given in* Table 27. Q = *4.57 with 5 df: no reason to reject homogeneity, therefore may combine study results*

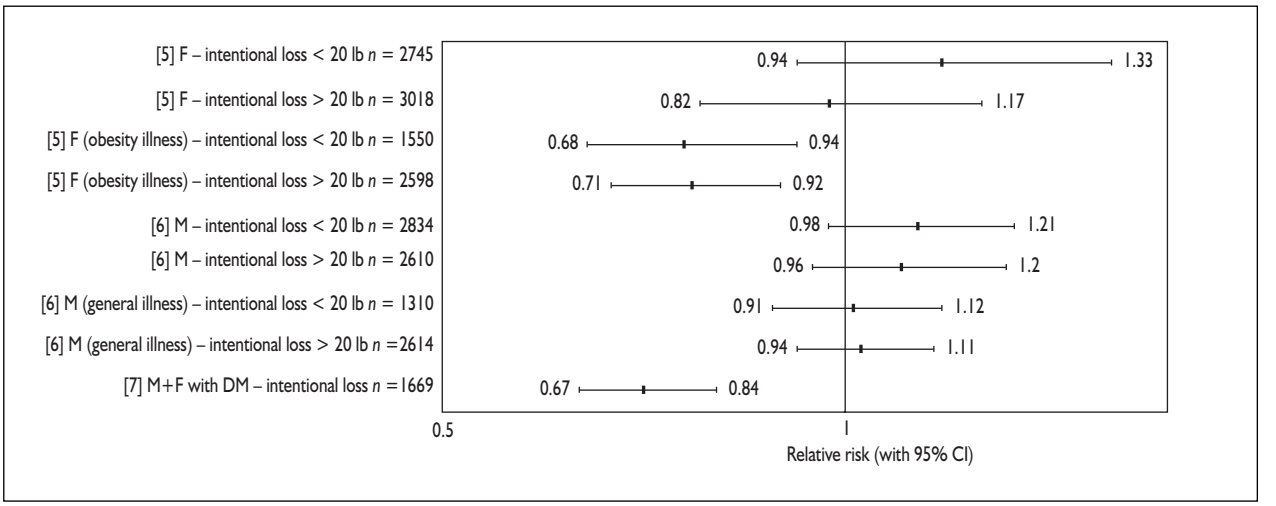


FIGURE 253(a) *All-cause mortality: intentional weight loss. Key of [study numbers] given in* Table 27. *Q = 44.99 with 8 df: reject homogeneity at* p *= 0.001*

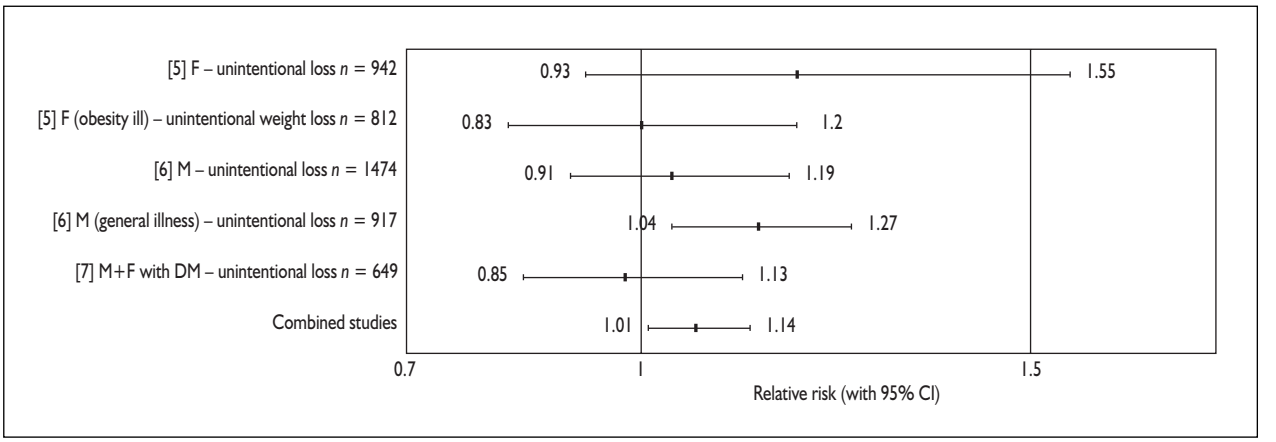


FIGURE 253(b) *All-cause mortality: unintentional weight loss. Key of [study numbers] given in* Table 27. *Q = 4.91 with 4 df: No reason to reject homogeneity, therefore may combine study results*

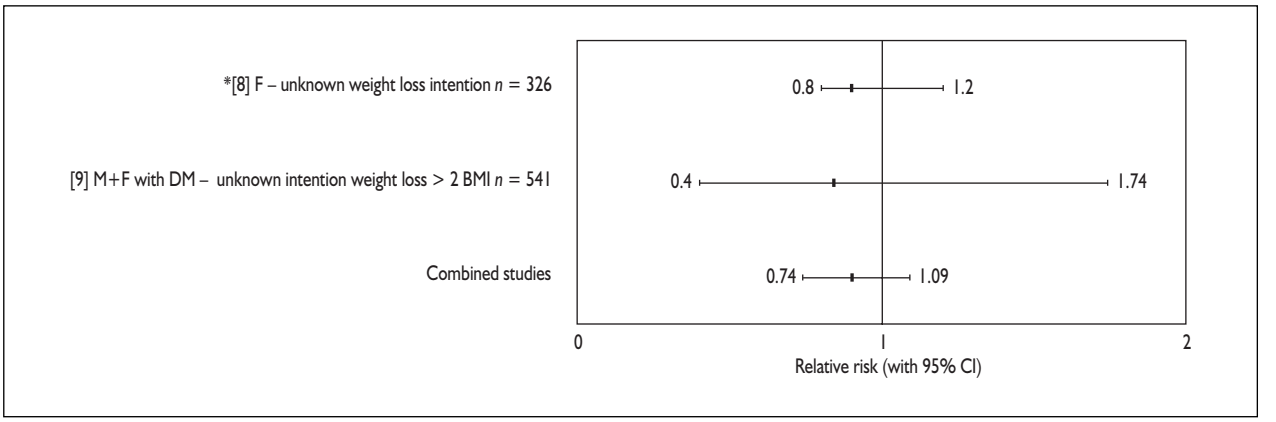


FIGURE 253(c) *All-cause mortality: unknown weight loss intention. Key of [study numbers] given in* Table 27. ** Referent is a group of normal stable weight. Q = 0.03 with 1 df: No reason to reject homogeneity, therefore may combine study results*

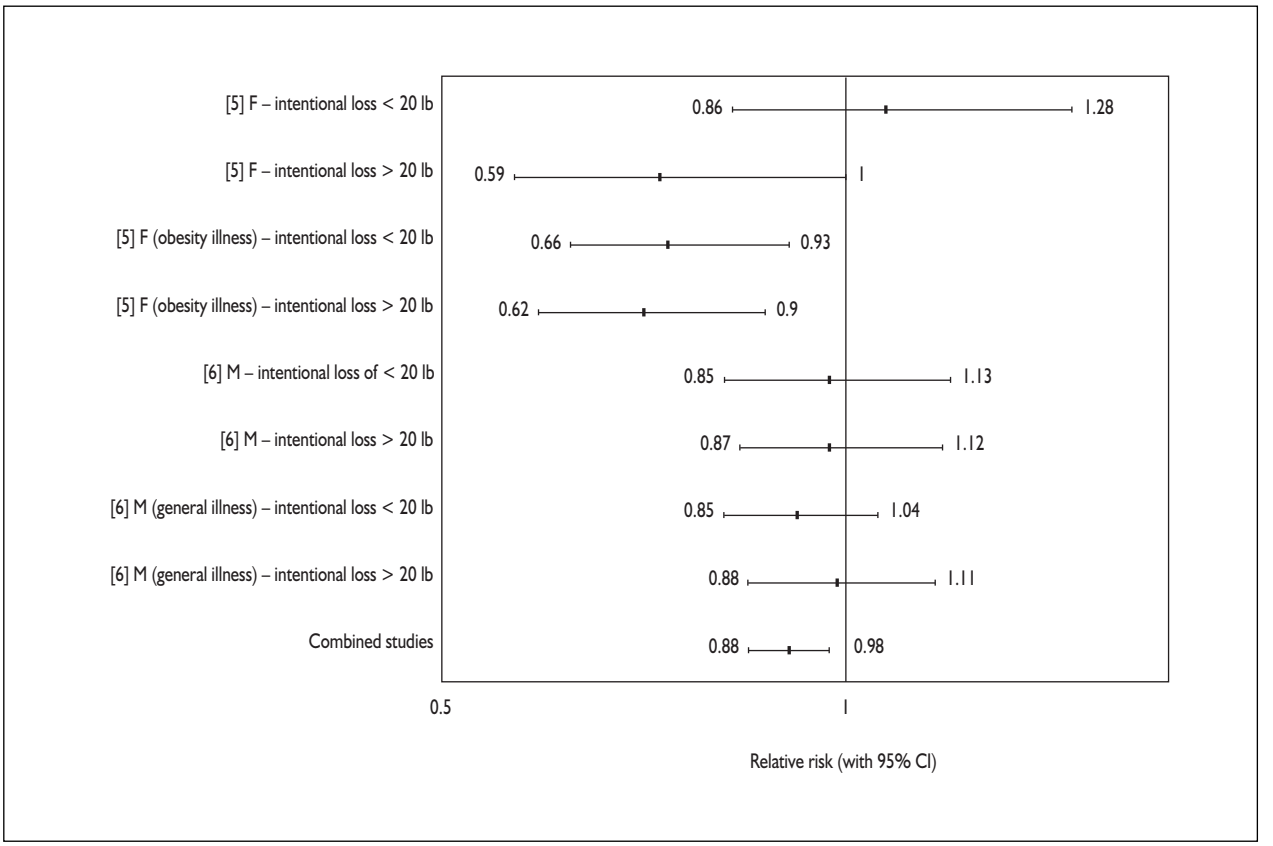


FIGURE 254(a) *All-cause mortality: weight loss within 1 year. Key of [study numbers] given in* Table 27. *Q = 14.88 with 7 df: reject homogeneity at* p *= 0.05 (nearly not significant)*

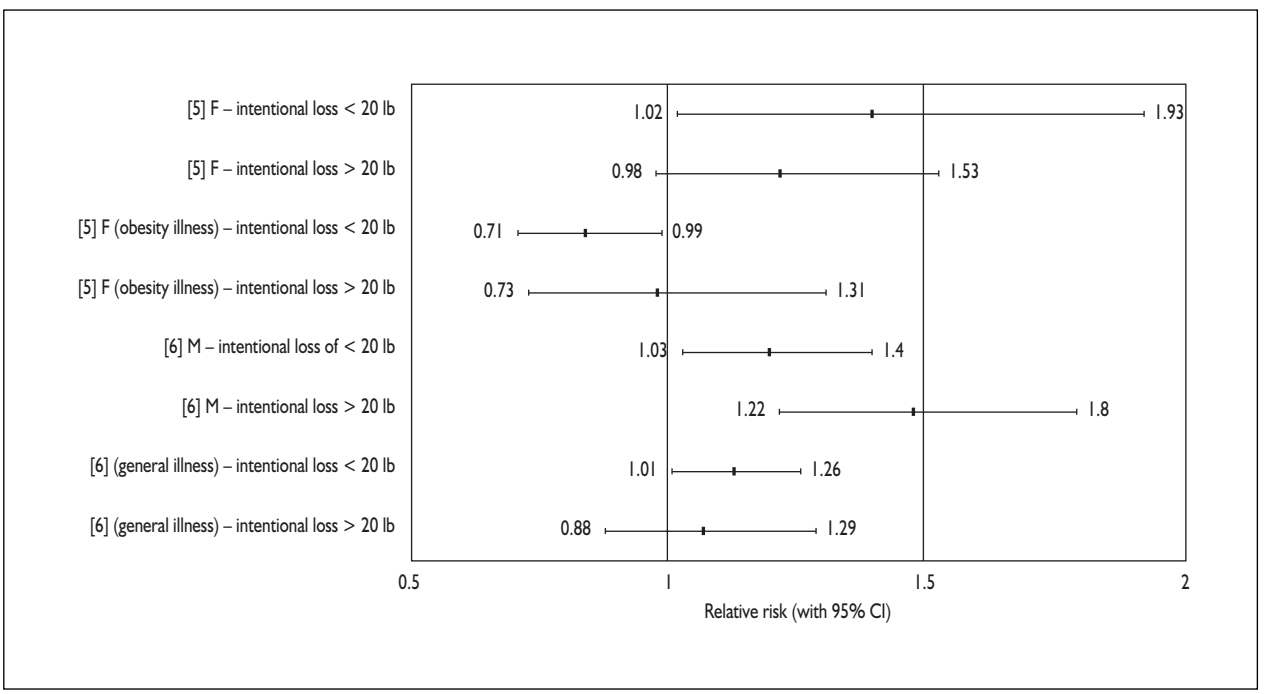


FIGURE 254(b) *All-cause mortality: weight loss taking more than 1 year. Key of [study numbers] given in* Table 27. *Q = 23.62 with 7 df: reject homogeneity at* p *= 0.01*

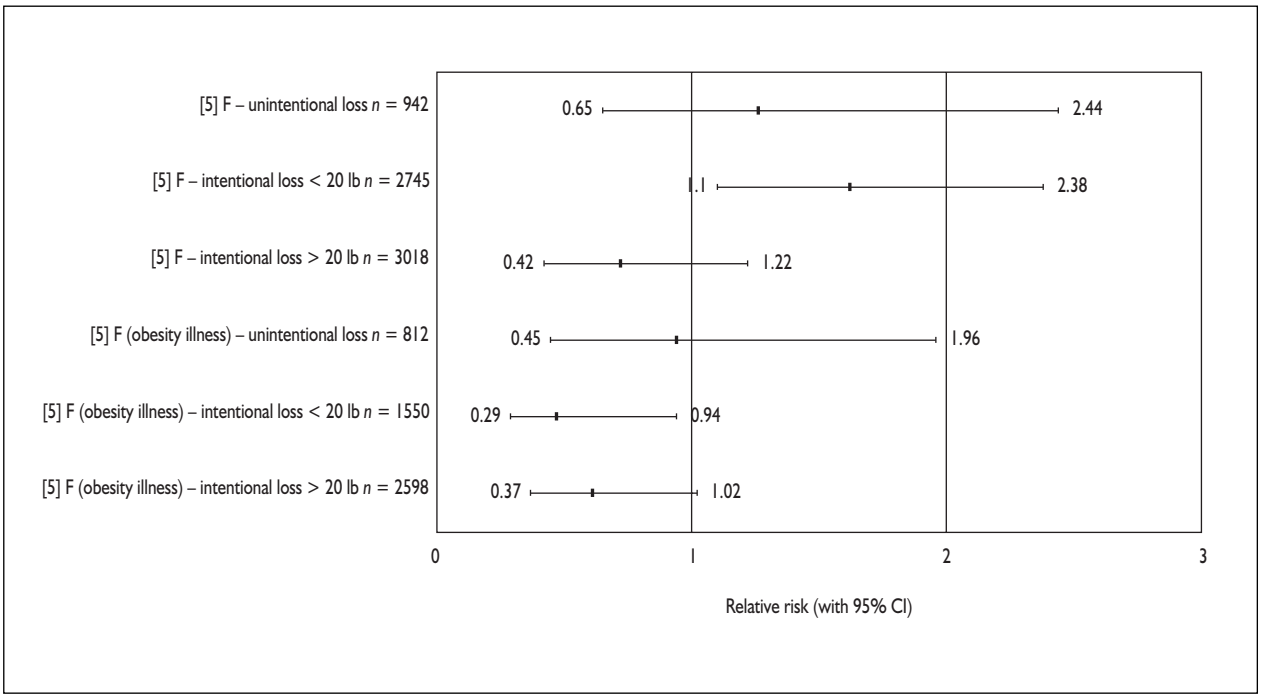


FIGURE 255 *Mortality from obesity-related illness: all subgroups. Key of [study numbers] given in* Table 27. Q = *17.47 with 5 df: reject homogeneity at* p = *0.01*

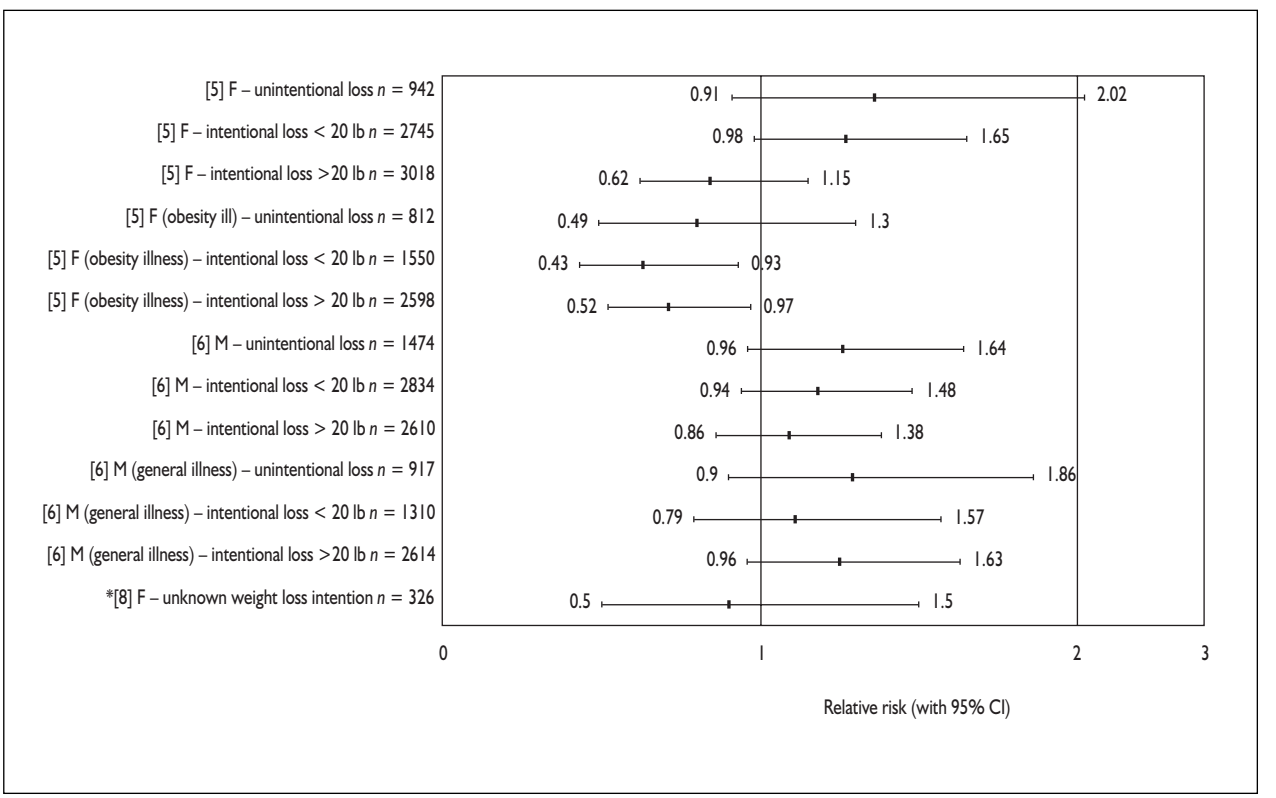


FIGURE 256 *Mortality from cancer: all subgroups. Key of [study numbers] given in* Table 27. **Referent is a group of normal stable weight.* Q = *25.61 with 12 df: Reject homogeneity at* p = *0.02*

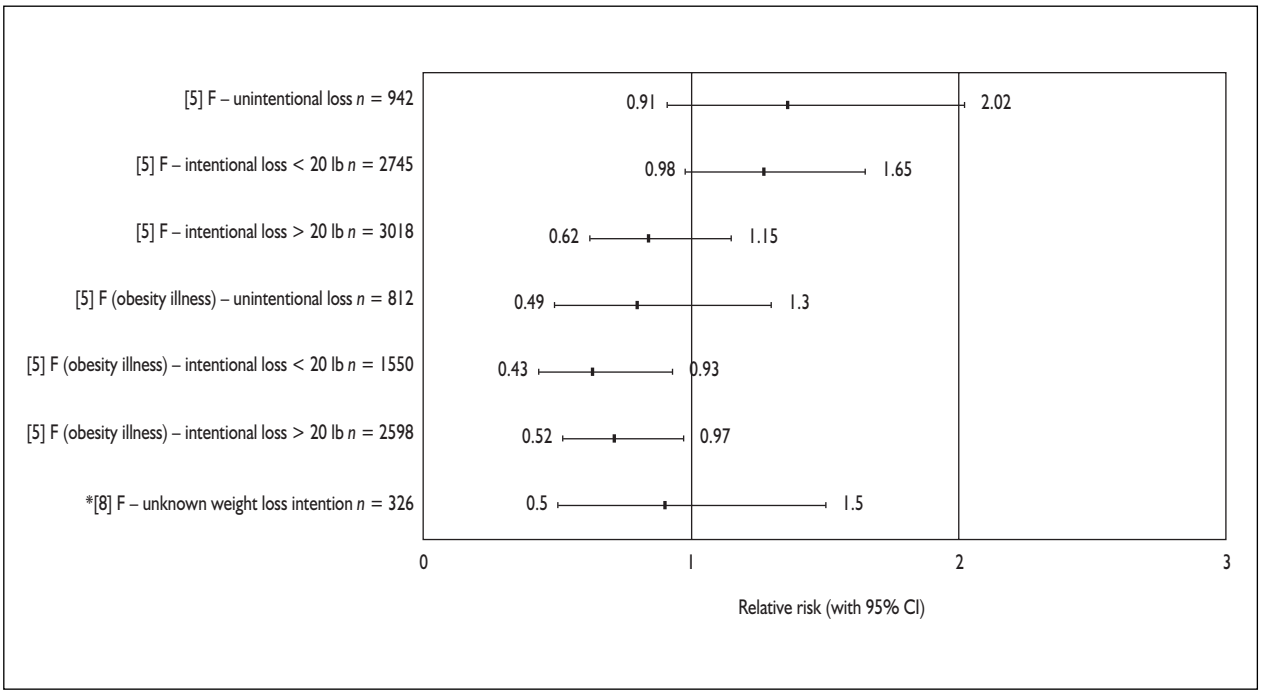


FIGURE 257(a) *Mortality from cancer: women only. Key of [study numbers] given in* Table 27. *Q = 16.58 with 6 df: reject homogeneity at* p = *0.02.*

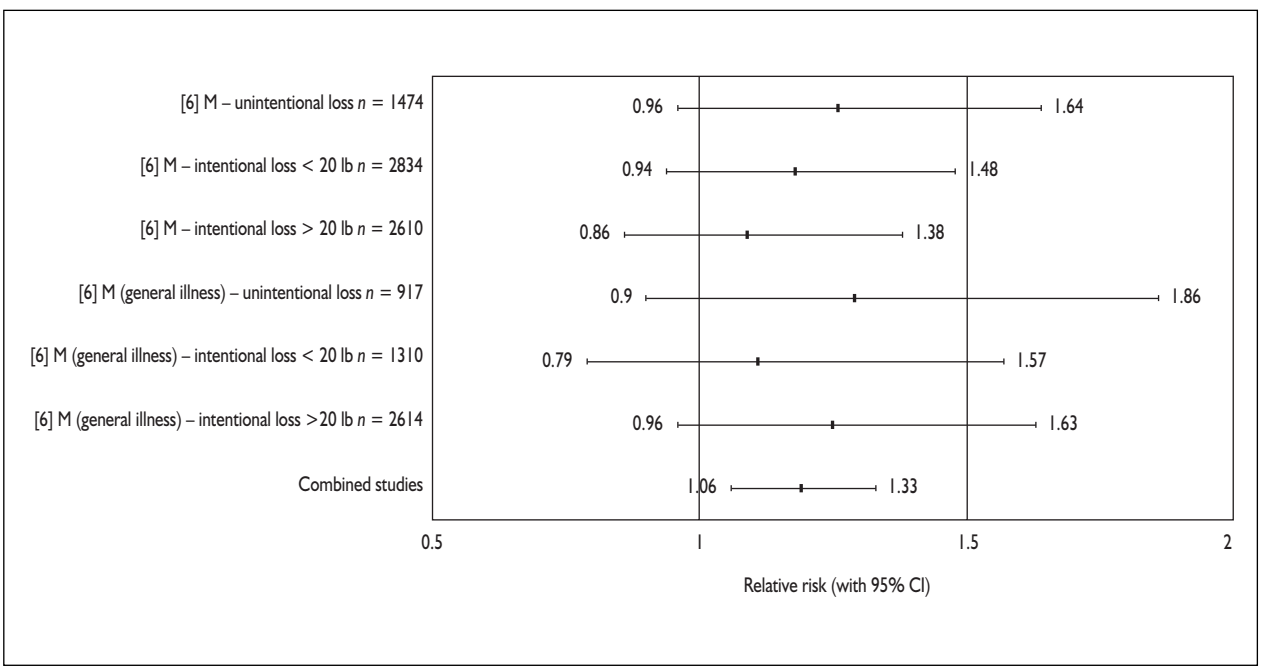


FIGURE 257(b) *Mortality from cancer: men only. Key of [study numbers] given in* Table 27. *Q = 1.19 with 5 df: no reason to reject homogeneity, therefore may combine study results*

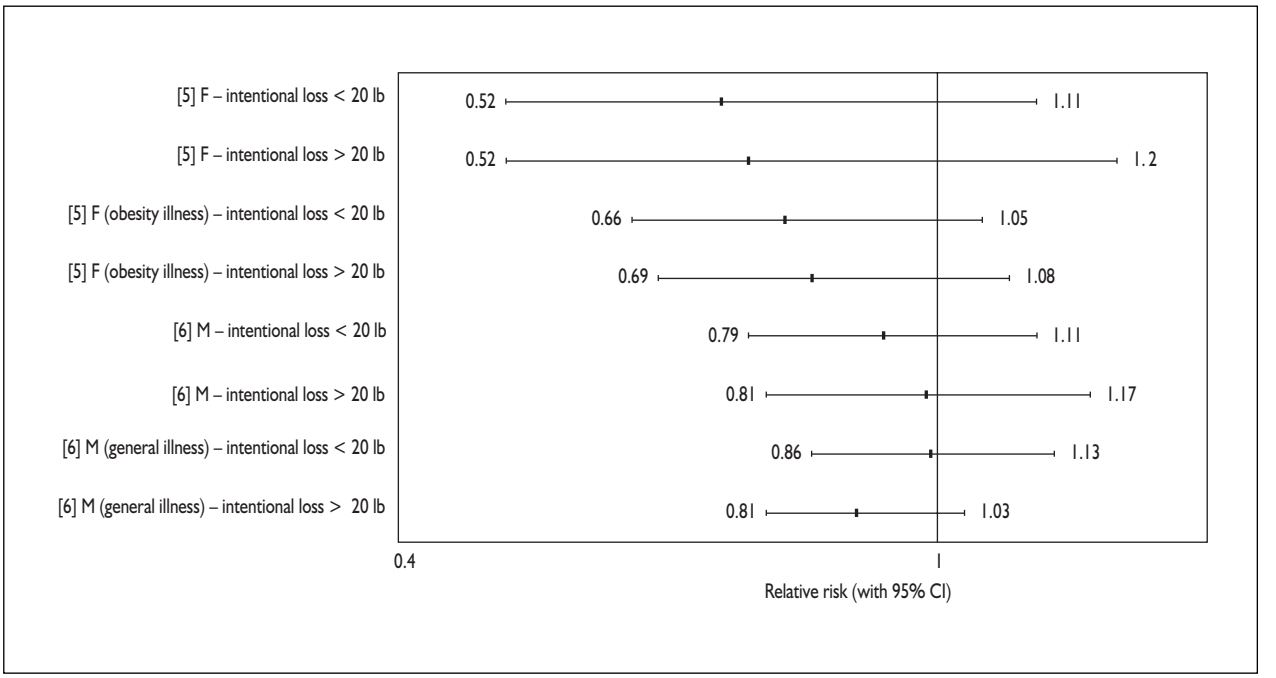


FIGURE 258(a) *Mortality from cancer: weight loss within 1 year. Key of [study numbers] given in* Table 27. Q = *18.14 with 7 df: reject homogeneity at* p = *0.02*

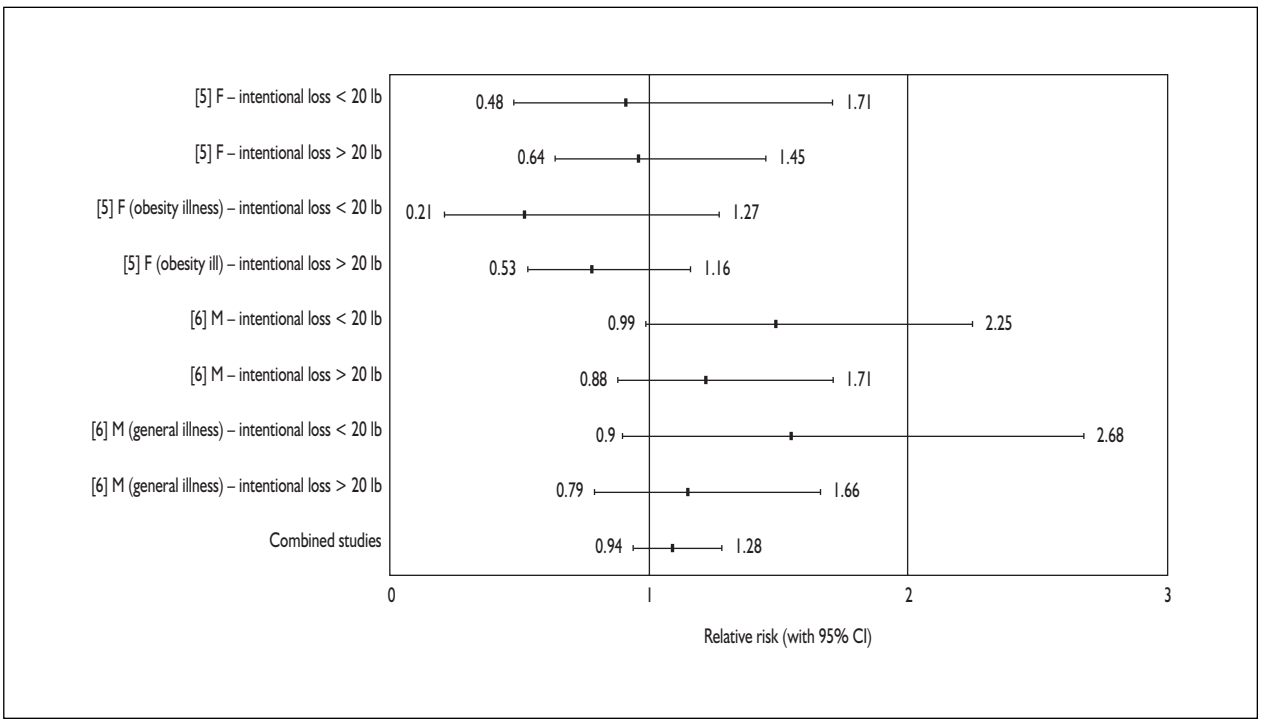


FIGURE 258(b) *Mortality from cancer: weight loss taking more than 1 year. Key of [study numbers] given in* Table 27. Q = *10.43 with 7 df: no reason to reject homogeneity, therefore may combine study results*

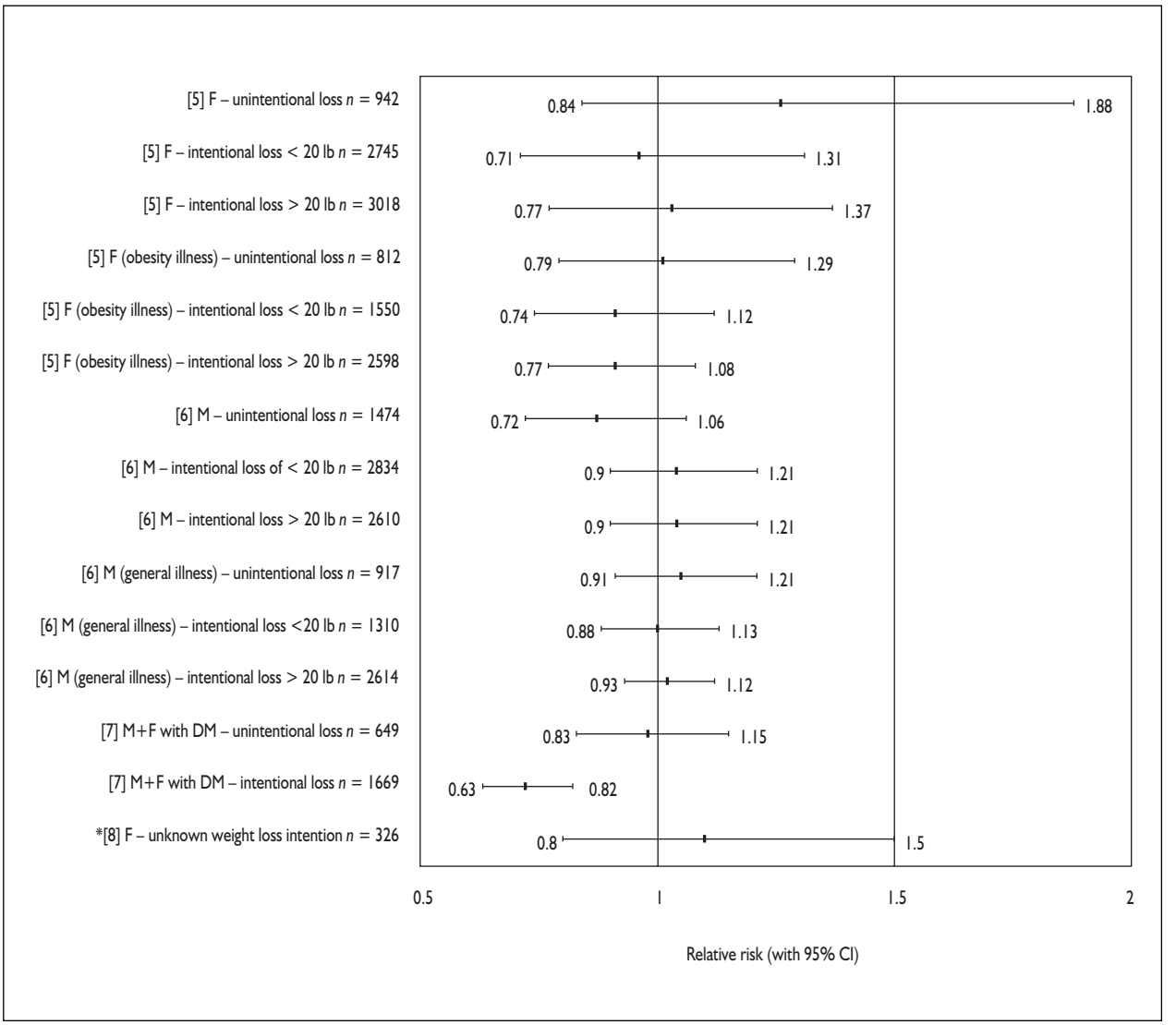


FIGURE 259 *Mortality from CVD: all subgroups. Key of [study numbers] given in* Table 27. ** Referent is a group of normal stable weight.* Q = *28.53 with 14 df: reject homogeneity at* p = *0.02*

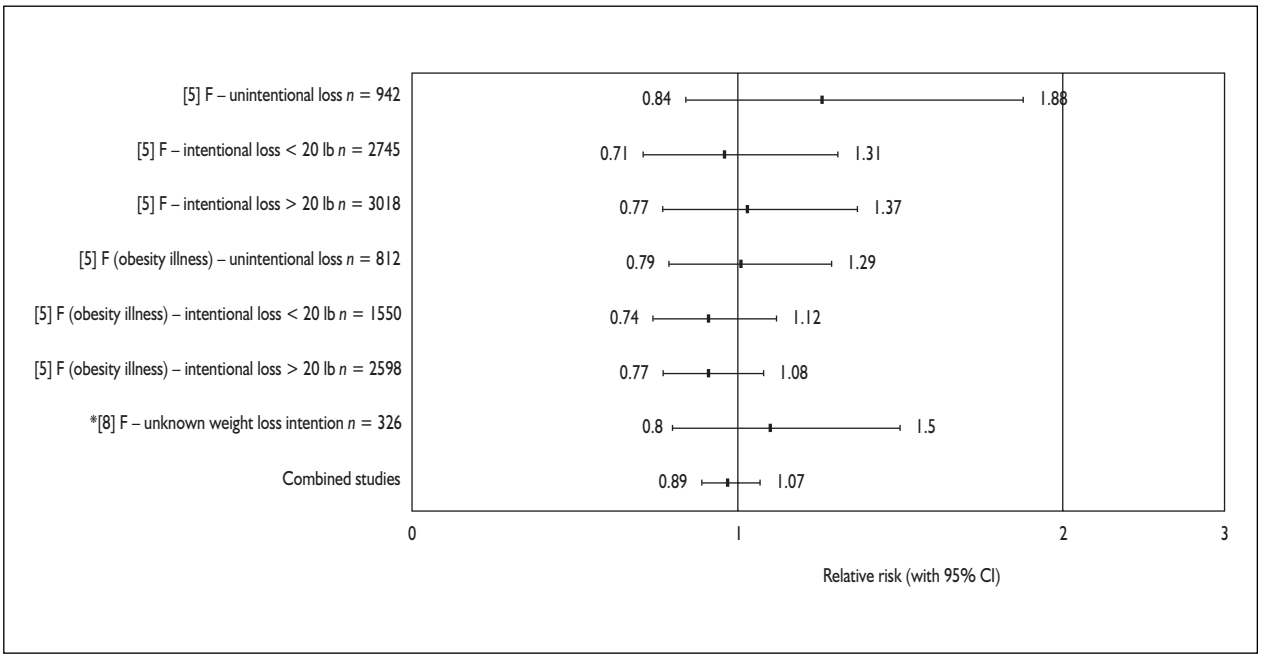


FIGURE 260(a) *Mortality from CVD: women only. Key of [study numbers] given in* Table 27. ** Referent is a group of normal stable weight. Q = 3.416 with 6 df: no reason to reject homogeneity, therefore may combine study results*

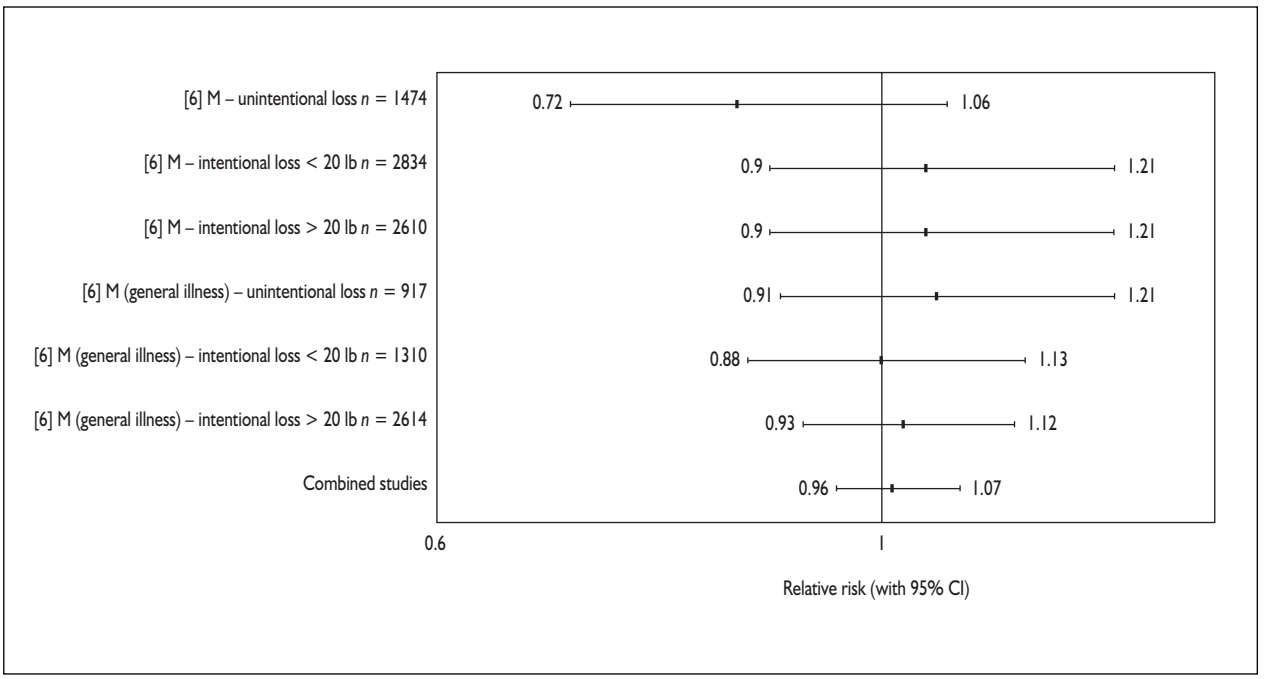


FIGURE 260(b) *Mortality from CVD: men only. Key of [study numbers] given in* Table 27. *Q = 2.93 with 5 df: no reason to reject homogeneity, therefore may combine study results*

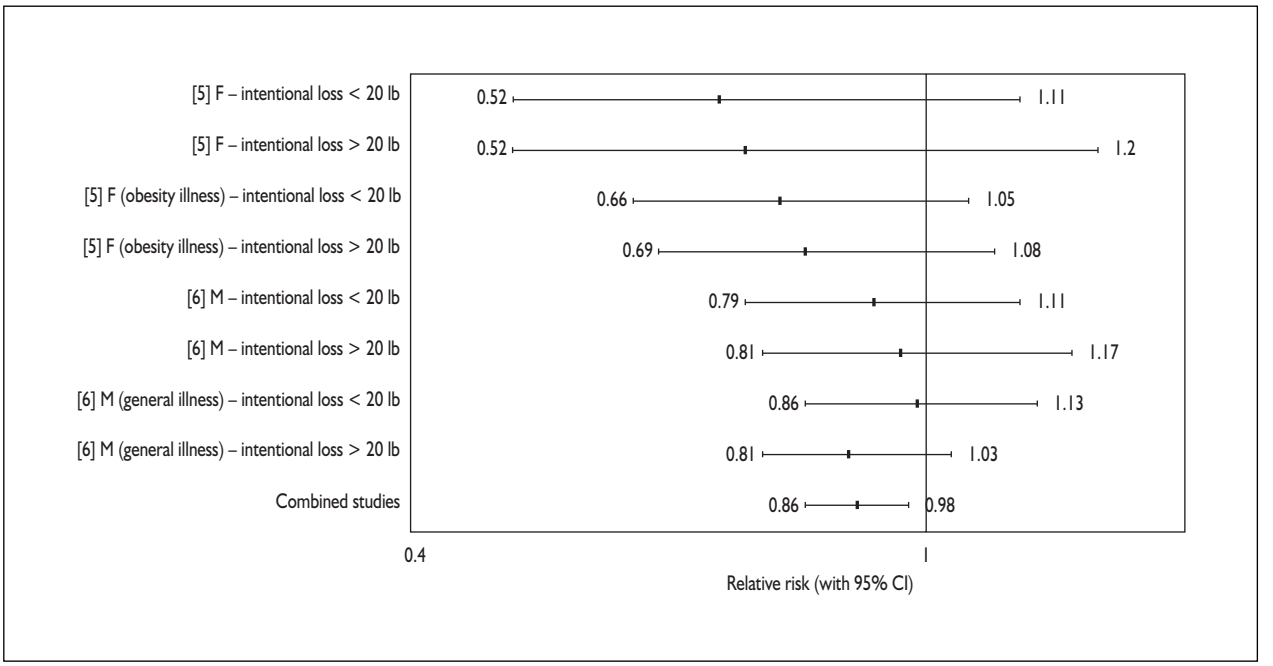


FIGURE 261(a) *Mortality from CVD: weight loss within 1 year. Key of [study numbers] given in* Table 27. *Q = 4.11 with 7df: no reason to reject homogeneity, therefore may combine study results*

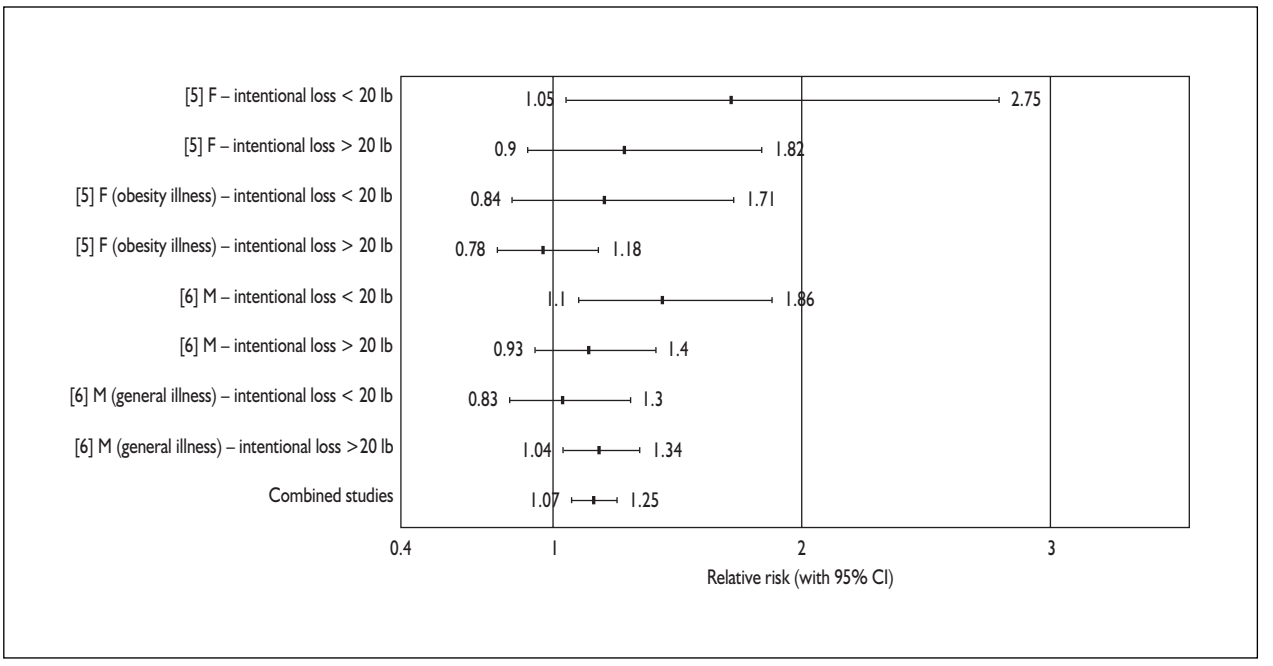


FIGURE 261(b) *Mortality from CVD: weight loss taking more than 1 year. Key of [study numbers] given in* Table 27. *Q = 9.41 with 7 df: no reason to reject homogeneity, therefore may combine study results*

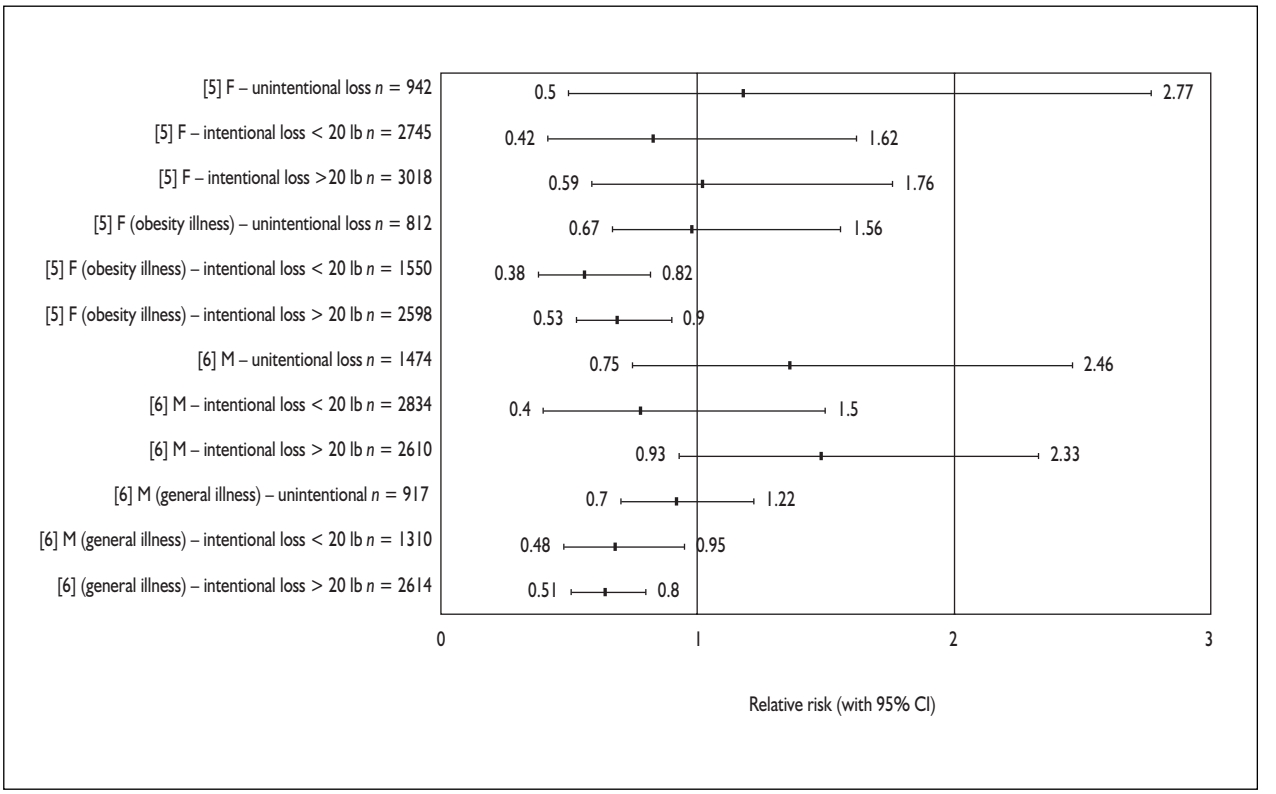


FIGURE 262 *Mortality from diabetes mellitus: all subgroup. Key of [study numbers] given in* Table 27. *Q = 22.423 with 11 df: reject homogeneity at* p *= 0.05*

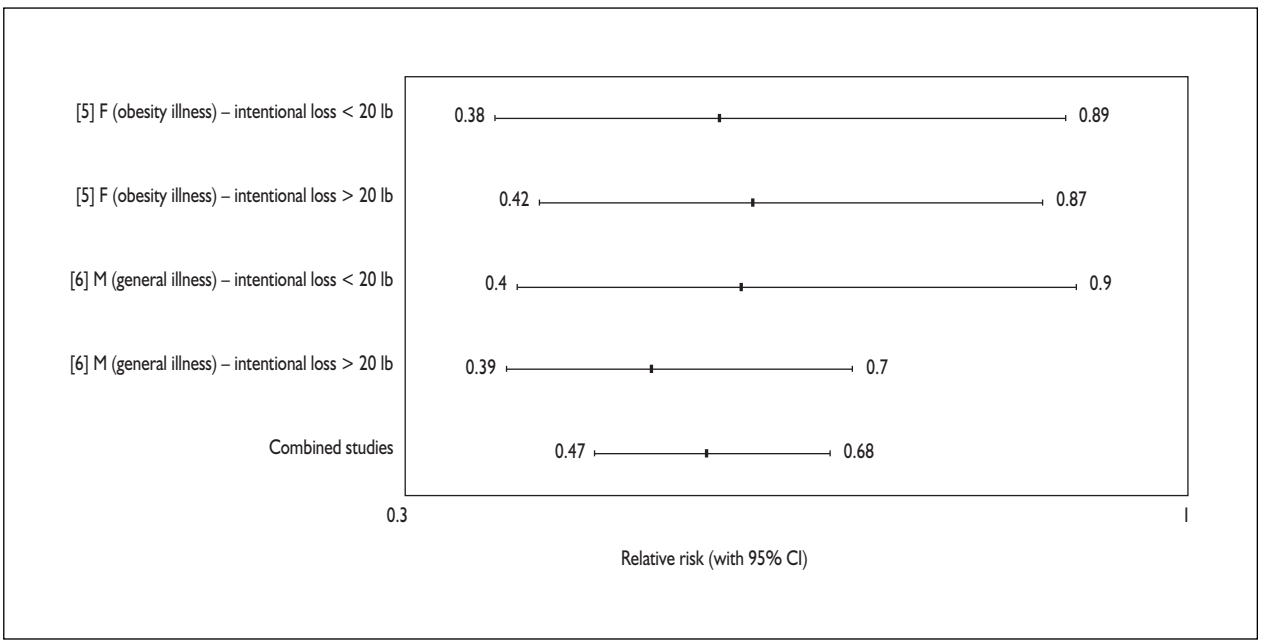


FIGURE 263(a) *Mortality from diabetes mellitus: weight lost within 1 year. Key of [study numbers] given in* Table 27. *Q = 0.58 with 3 df: no reason to reject homogeneity, therefore may combine study results*

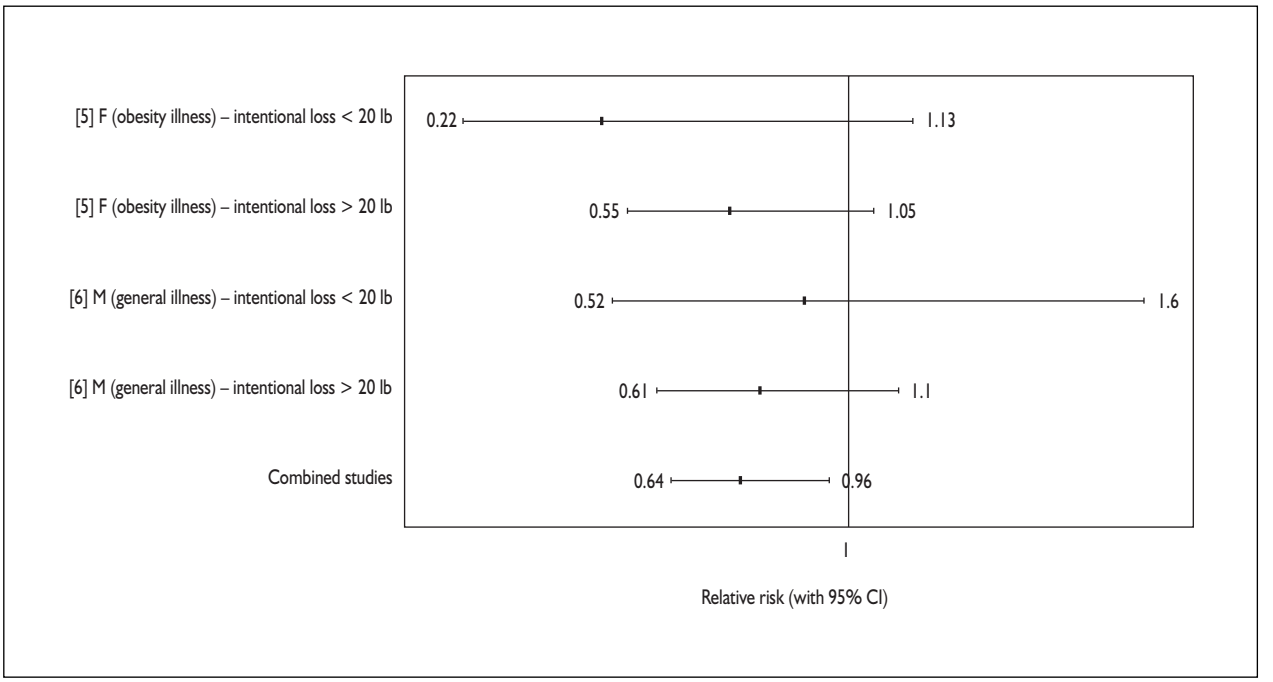


FIGURE 263(b) *Mortality from diabetes mellitus: weight lost over more than 1 year. Key of [study numbers] given in* Table 27. Q = *1.56 with 3 df: no reason to reject homogeneity, therefore may combine study results.*

Appendix 21

Diabetes mellitus studies with basic results

Appendix 21a

Diabetes mellitus ratios

TABLE 28 *Surgical interventions*

Graph key	Study	Genders	Description	Age (years)		Initial weight			Last weight or loss		
				Mean	Spread	*n*	weight	Spread	*n*	weight	Spread
4	Pories, 1992[266]	Both	Morbid obese, 27% DM	18–65		*n* = 515	135 kg	Range kg 89–257	*n* = 236 at 5 year	91 kg	Range 49–195
		Both	Morbid obese, 12% IGT	18–65							
11	O'Leary, 1980[272] (Unknown follow-up at 7 years)	Both	70% NIDDM			*n* = 274	156 kg	Range kg 95–275	All but 2 lost, 5-year plateau some regain 20–30%		
		Both	6% Insulin DM								
20	Hess, 1998[271]	Both	Morbid obese, DM insulin	Whl grp = 40		Whl grp *n* = 440	BMI = 50	BMI Range 25–77	*n* = 92? at 5 year	BMI = 30 Diff –55 kg	
		Both	Morbid obese, DM non-insulin								
28	Long, 1994[279] Non-RCT	Both	IGT (27 did not have surgery)	36	SD = 8.0	*n* = 109	BMI = 48	SD = 8.0	% loss of excess weight at 5 years = 62 (SD 4)		
29	Karason, 1999[277] Non-RCT	Both	Obese	Whl grp = 49	SD = 5.0	*n* = 19	118 kg BMI = 38	SD =15 SD = 3.6	*n* = 19 at 4 year	diff = –22 kg BMI diff = –6.8	SD = 10 SD = 3.5
30	Sjostrom CD, 2000[278] Non-RCT	Both	Obese control	47	SD = 6.0	*n* = 346	121.6 kg BMI = 42.2	SD = 16.6 SD = 4.1	*n* = 251 at 8 year	diff = –20.1 kg BMI diff = –6.8	SD = 15.7 SD = 5.4

Whl grp, whole group; Diff, difference.

TABLE 29 *Non-surgical interventions*

Graph key	Study	Genders	Description	Age (years)		Initial weight			Last weight or loss		
				Mean	Spread	*n*	weight	Spread	*n*	weight	Spread
15	Wing, 1998[176] RCT	Both	Parent(s) DM, patients normal	~45.7	SD = 4.4		BMI ~35.9	SD =4.3	*n* = ?	Lost ≥ 4.5 kg	
		Both	Parent(s) DM, patients IGT	~45.7	SD = 4.4		BMI ~35.9	SD = 4.3	*n* = ?	Lost ≥ 4.5 kg	
16	Watts, 1990[281]	Both	DM – responders	57.4	SD = 1.9	*n* = 55	94 kg	SD = 3.0	*n* = 55 14.7 (SD 2.3) months, took 1 year 50% regained	Lost ≥ 9.1 kg	
		Both	DM – non-responders	55.3	SD = 1.3		94 kg	SD = 2.0	*n* = ? 26.2 (SD 2.3) months, took 1 year 40% regained	Lost ≥ 9.1 kg	
39	Hauptman, 2000[45] RCT – drug	Both	Placebo + diet	41.6	SE = 0.7	*n* = 91	101.0 kg BMI = 36.2	SE = 0.8	*n* = 91 at 2 years	Diff= –1.54 kg	SE = 0.58
		Both	Orlistat + diet	42.6	SE = 0.8	*n* = 117	100.6 kg BMI = 36.2	SE = 1.6	*n* = 117 at 2 years	Diff = –5.16 kg	SE = 0.78
40	Tuomilehto, 2001[168] RCT	Both	DM patients diet + Ex	55	SD = 7.0	*n* = 257	BMI = 31.3	SD = 4.6	*n* = ? at 2 years	Diff = –0.8 kg	SD = 4.4
		Both	DM patients, control	55	SD = 7.0	*n* = 265	BMI = 31.0	SD = 4.5	*n* = ? at 2 years	Diff = –3.5 kg	SD = 5.5
41	Rossner, 2000[37] RCT – drug	Both	Placebo + diet	44.3	SD = 10.8	*n* = 237	97.7 kg BMI = 35.3	SD =14.6 SD = 4.1	*n* = 140 at 2 years	Diff = –4.3 kg	SD = 7.5
		Both	Orlistat + diet	43.6	SD = 11.4	*n* = 242	96.7 kg BMI = 34.7	SD = 11.4 SD = 3.7	*n* = 136 at 2 years	Diff = –7.6 kg	SD = 7.0
42	Davidson, 1999[41] RCT – drug	Both	Placebo + diet	44.0	SE = 0.7	*n* = 223	100.6 kg BMI = 36.5	SE = 0.9 SE = 0.9	*n* = 89 at 2 years	Diff = –4.0 kg	SE = 0.5
		Both	Orlistat + diet	43.3	SE = 0.6	*n* = 657	100.7 kg BMI = 36.2	SE = 0.6 SE = 0.1	*n* = 103 at 2 years	Diff = –7.6 kg	SE = 0.2

TABLE 30 *No intervention*

Graph key	Study	Genders	Description	Age (years)		Initial weight			Last weight or loss		
				Mean	Spread	*n*	weight	Spread	*n*	weight	Spread
13	Ford, 1997[268]	Both?	NIDDM	Whl grp 18–70+			BMI > 29		Lost ≥ 5 kg		
14	Moore, 2000[269]	Both	Lost/gained	40.8		*n* = 102	BMI = 30.4		*n* = 102 Lost ≥ 8 lb in 8 years then gained in next 8 years		
		Both	Lost/stable	41.5		*n* = 109	BMI = 29.3		*n* = 109 Lost ≥ 8 lb in 8 years then stable in next 8 years		
		Both	Lost/lost	41.6		*n* = 51	BMI = 30.8		n = 51 Lost ≥ 8 lb in 8 years then lost more in next 8 years		
		Both[a]	Lost/lost ≥ 8 lb	41.5			BMI = 29.5		*n* = ?? Lost ≥ 8 lb in 8 years + 0–7 lb in next 8 years		
		Both[a]	Lost/lost ≥ 16 lb	41.5			BMI = 30.2		*n* = ?? Lost ≥ 8 lb in 8 years + 8–15 lb in next 8 years		
17	Wannamethee, 1999[280]	M	Not DM	Whl grp 40–59			BMI ≥ 28		Lost ≥ 4%		

[a] Subgroup of the lost/lost group, specifying the degree of weight loss.

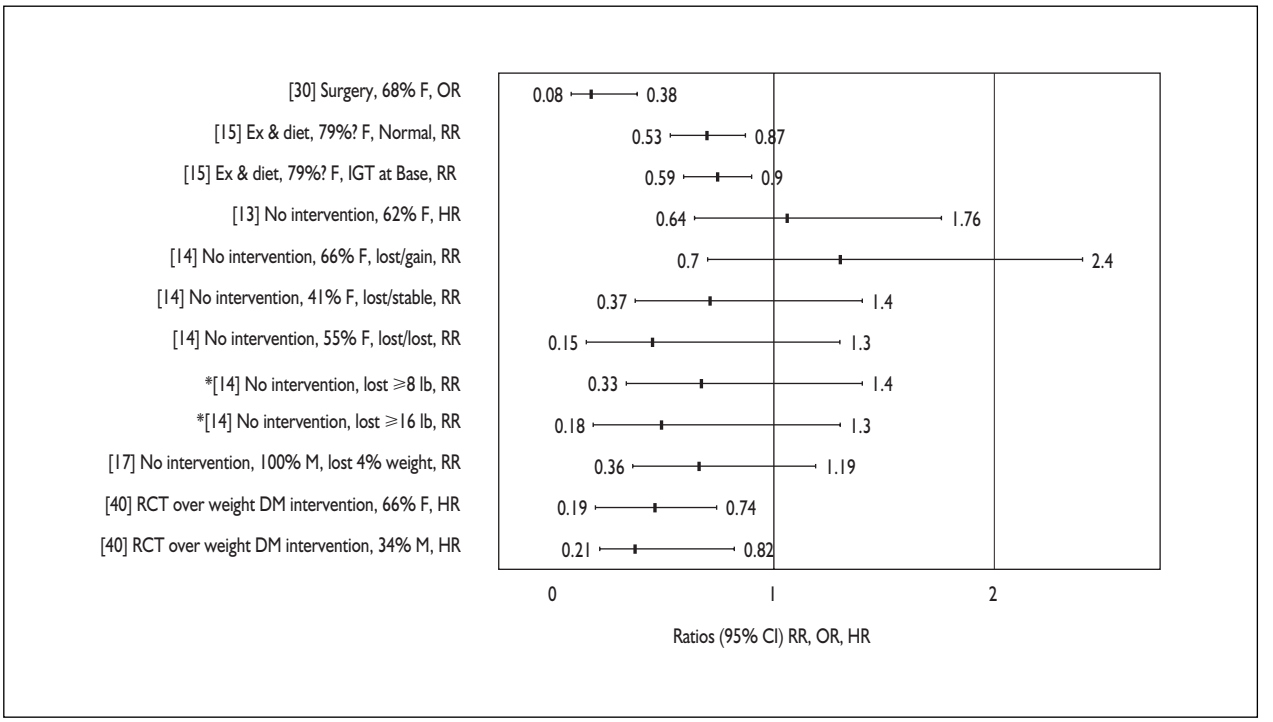


FIGURE 264 *Diabetes mellitus ratios. Key of [study numbers] given in Tables 28–30. * Non-independent subgroup. HR, hazard ratio*

Appendix 21b

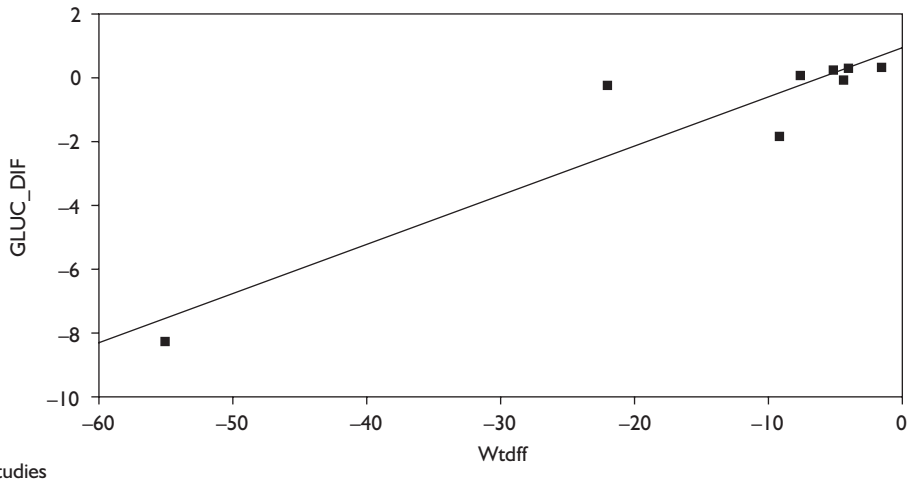
Weight differences compared with glucose differences in type 2 diabetes mellitus patients

Intervention type	Study	Description	Follow-up (months)	*n*	Weight difference (kg)	(SE)	*n*	Glucose difference (mmol/l)	(SE)
??	Watts, 1990[281]	DM non-responders	12+	80	–9.1*	**(0.98)**	80	–1.90*	**(0.15)**
RCT Drug	Hauptman 2000[45]	Placebo + diet	24	91	–1.5*	(0.58)	91	0.24	**(0.14)**
		Orlistat + diet	24	117	–5.2*	(0.78)	117	0.16	**(0.12)**
	Rossner, 2000[37]	Placebo + diet	24	140	–4.3*	(0.63)	140	–0.14	**(0.11)**
		Orlistat + diet	24	136	–7.6*	(0.60)	136	–0.07	**(0.12)**
	Davidson, 1999[41]	Placebo + diet	24	89	–4.0*	(0.50)	90	0.20	**(0.14)**
		Orlistat + diet	24	103	–7.6*	(0.20)	106	0.05	**(0.13)**
Surgery	Hess, 1998[271]	DM insulin & non	60	92	–55.0*	**(2.44)**		–8.25[a]	
	Long, 1994[279]	Non-RCT, IGT	60					–1.00	
	Karason, 1999[277]	Obese only	48	19	–22.0*	(2.29)	19	–0.30	**(0.23)**

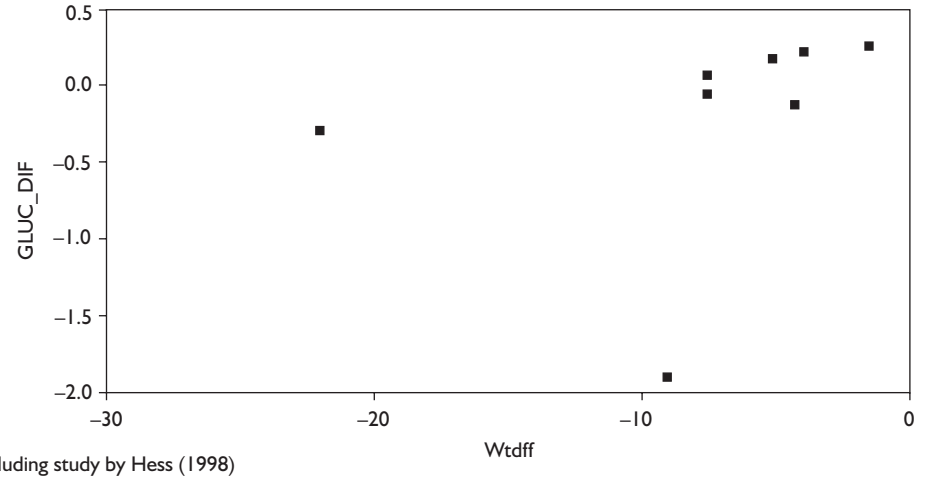
Standard errors in **bold** have been estimated as per Appendix 26.
[a] This study seems to have a large glucose difference. It may not be fasting blood sugar.
*Significant difference at $p < 0.05$.

Scatter plots: glucose difference with weight difference

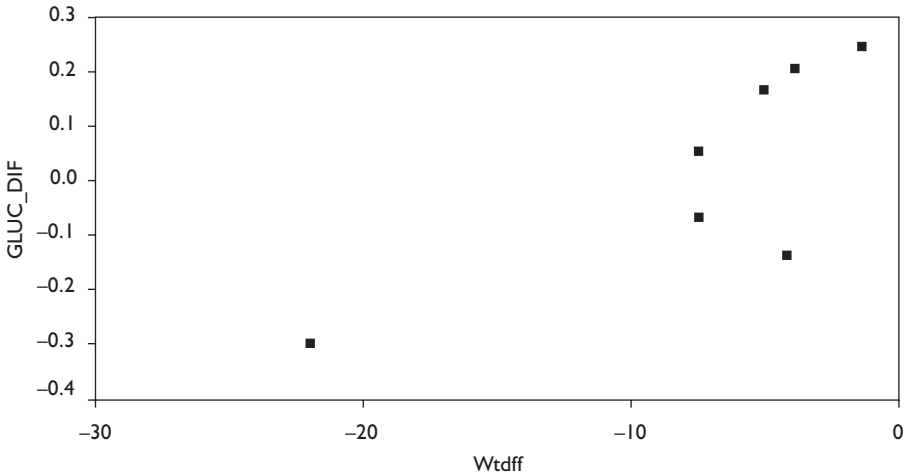
SPSS variable names: Wtdff, average weight difference subgroups; GLU_DIF, average glucose difference



(a) All studies
Correlation = 0.935 ($p < 0.001$)



(b) Excluding study by Hess (1998)
Correlation = 0.296



(c) Excluding studies by Hess (1998) and Watts (1990)
Correlation = 0.794 ($p < 0.01$)

Regression: glucose difference with weight difference (excluding Hess and Watts)

Model summary

Model	R	R^2	Adjusted R^2	SE of the estimate
1	0.794[a]	0.631	0.557	0.1324

[a] Predictors: (Constant), Wtdff.

ANOVA[a]

Model	Sum of squares	df	Mean square	F	Sig.
1 Regression	0.150	1	0.150	8.544	0.033[b]
Residual	8.764E^{-02}	5	1.753E^{-02}		
Total	0.237	6			

[a] Dependent variable: GLUC_DIF.
[b] Predictors: (Constant), Wtdff.

Coefficients[a]

	Unstandardised coefficients		Standardised coefficients		
Model	B	SE	β	t	Sig.
1 (Constant)	0.194	0.078		2.497	0.055
Wtdff	2.339E^{-02}	0.008	0.794	2.923	0.033

[a] Dependent variable: GLUC_DIF.

Conclusion: *glucose difference = 0.194 + 0.02339 (weight difference).*

Appendix 22

Lipid results

Appendix 22a

Lipid paired *t*-test results

TABLE 31 *Non-surgical weight cyclers*

Study	Follow-up (months)		*n*	Wt diff (kg)	(SE)	*n*	Cholesterol diff (mmol/l)	(SE)	*n*	TGs diff (mmol/l)	(SE)	*n*	LDL diff (mmol/l)	(SE)	*n*	HDL diff (mmol/l)	(SE)
Wing, 1995[282]	30	Gainer	15	10.30*	**(2.36)**	15	0.33	**(0.28)**	15	0.93*	**(0.40)**	15	–0.04	**(0.19)**	15	–0.06	**(0.07)**
		Stable	25	3.00*	**(1.36)**	25	0.14	**(0.22)**	25	0.18	**(0.31)**	25	0.05	**(0.15)**	25	0.00	**(0.06)**
		L cyc	31	–2.10	**(1.17)**	31	–0.34	**(0.19)**	31	–0.01	**(0.27)**	31	–0.29*	**(0.13)**	31	–0.01	**(0.05)**
		S cyc	28	–2.60	**(1.26)**	28	0.11	**(0.20)**	28	0.33	**(0.29)**	28	0.02	**(0.14)**	28	–0.07	**(0.06)**
		P cyc	28	–9.70*	**(1.69)**	28	–0.4	**(0.20)**	28	–0.38	**(0.29)**	28	–0.34*	**(0.14)**	28	0.10	**(0.06)**
		S succ	7	–5.90	**(2.92)**	7	0.11	**(0.41)**	7	–0.10	**(0.58)**	7	–0.01	**(0.28)**	7	0.17	**(0.11)**
		L succ	14	–12.60*	**(2.63)**	14	–0.23	**(0.29)**	14	–0.29	**(0.41)**	14	–0.2	**(0.18)**	14	0.09	**(0.08)**

* Significant difference at $p < 0.05$.
Bold standard errors indicate studies where the mean differences were estimated from *follow-up mean – base mean*. Standard errors were also estimated as in Appendix 26.

TABLE 32 *Non-surgical prospective/cohort*

Study	Follow-up (months)		*n*	Wt diff (kg)	(SE)	*n*	Cholesterol diff (mmol/l)	(SE)	*n*	TGs diff (mmol/l)	(SE)	*n*	LDL diff (mmol/l)	(SE)	*n*	HDL diff (mmol/l)	(SE)
Kauffman, 1992[283]	24	Spanish workplace	80	–2.20*	(0.40)	80	$r = 0.24$ $p = 0.01$										
Ewbank, 1995[284]	24	Total group	45	–13.00*	(1.79)	43	–0.60*	(0.12)							43	–0.20*	(0.05)
		Low Ex	15	–9.00*	(2.32)	15	–0.30	(0.26)							15	–0.20*	(0.08)
		Mod Ex	15	–9.00*	(3.01)	14	–0.40*	(0.16)							14	–0.10	(0.08)
		High Ex	15	–20.00*	(2.58)	14	–0.10*	(0.19)							14	–0.20*	(0.08)
Sjostrom M, 1999[285] (raw data)	24	Women	323	–1.44*	(0.40)	333	–0.02	(0.06)	319	–0.03	(0.06)				24	–0.18 *	(0.04)
		Men	221	–2.7*	(0.56)	220	–0.26*	(0.09)	213	–0.31	(0.19)				11	0.00	(0.09)

* Significant difference at $p < 0.05$.

TABLE 33 *Non-surgical RCTs*

Study (Follow-up time)	Follow-up (months)		*n*	Wt diff (kg)	(SE)	*n*	Cholesterol diff (mmol/l)	(SE)	*n*	TGs diff (mmol/l)	(SE)	*n*	LDL diff (mmol/l)	(SE)	*n*	HDL diff (mmol/l)	(SE)
Wing, 1998[176]	24	Diet + BT	35	–2.10	(1.28)	35	–0.12	(0.10)	35	0.19	(0.41)	35	–0.16	(0.11)	35	0.02	(0.03)
		Ex + BT	31	1.00	(0.84)	31	0.33*	(0.11)	31	0.33	(0.26)	31	0.22	(0.11)	31	0.05	(0.03)
		Diet + Ex + BT	32	–2.50	(1.48)	32	0.09	(0.12)	32	–0.28	(0.24)	32	0.12	(0.10)	32	0.02	(0.04)
Hauptman, 2000[45]	24	Placebo + diet	91	–1.54*	(0.58)	91	0.08	**(0.11)**	91	–0.19	**(0.16)**	91	0.17*	**(0.08)**	91	–0.01	**(0.03)**
		Orlistat + diet	117	–5.16*	(0.78)	117	–0.15	**(0.10)**	117	–0.09	**(0.14)**	117	–0.15	**(0.07)**	117	0.00	**(0.03)**
Davidson, 1999[41]	24	Placebo + diet	89	–4.00*	**(0.50)**	89	–0.22	**(0.11)**	89	0.03	**(0.16)**	88	–0.22*	**(0.08)**	89	0.03	**(0.03)**
		Orlistat + diet	103	–7.60*	**(0.20)**	106	–0.32*	**(0.11)**	106	–0.12	**(0.15)**	104	–0.24*	**(0.07)**	106	–0.01	**(0.03)**
Teupe, 1991[84]	24	Metformin + diet		25	–4.00*	**(1.42)**	25	–0.39	**(0.22)**	25	–0.25	**(0.31)**					
		Diet	29	–5.10*	**(1.39)**	29	0.46*	**(0.20)**	29	–0.27	**(0.28)**						

* Significant difference at $p < 0.05$.
Bold standard errors indicate studies where the mean differences were estimated from *follow-up mean – base mean*. Standard errors were also estimated as in Appendix 26.

TABLE 34 *Surgical*

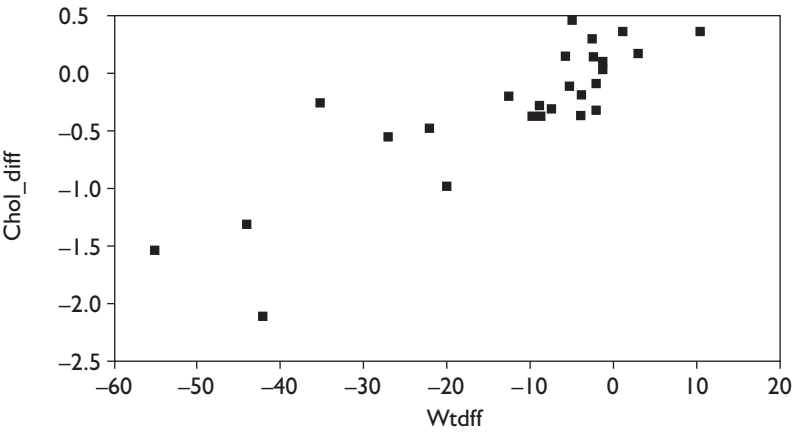
Study (Follow-up time)	Follow-up (months)		*n*	Wt diff (kg)	(SE)	*n*	Cholesterol diff (mmol/l)	(SE)	*n*	TGs diff (mmol/l)	(SE)	*n*	LDL diff (mmol/l)	(SE)	*n*	HDL diff (mmol/l)	(SE)
Hess, 1998[271]	60	78% Women	92	–55.00*	**(2.44)**	92	–1.55*	**(0.11)**	92	–0.98*	**(0.16)**	92	–0.98*	**(0.08)**	92	0.13	**(0.03)**
Gleysteen, 1992[286]	60	Women	24	–35.00*	**(3.47)**	24	–0.28	**(0.22)**	24	–0.11	**(0.31)**	24			24	0.26*	**(0.06)**
		Men	9	–27.00*	**(4.82)**	9	–0.57	**(0.36)**	9	–0.84	**(0.51)**	9			9	0.26*	**(0.10)**
Rossner, 1980[287]	24–60	Women	10	–44.00*	(4.00)	10	–1.33*	**(0.34)**	10	–0.34	**(0.48)**	10	–1.17*	**(0.23)**	10	0.05	**(0.09)**
		Men	8	–42.00*	(4.00)	8	–2.12*	**(0.38)**	8	–1.12	**(0.54)**	8	–1.47*	**(0.26)**	8	–0.08	**(0.10)**
Karason, 1999[277]	48	21% Women	19	–22.00*	(2.29)	19	–0.50 *	(0.16)	19	–0.90*	(0.21)	19	–0.40*	(0.16)	19	0.20*	(0.07)
O'Leary[272] 1980	5 years	Both	274	All but 2/274 lost weight. Plateau at 12–24 months after surgery with some weight regain by 5 years													
							Preoperative			5 years							
				Hypertriglyceridaemia			51%			88% improved, 12% unchanged							
				Hypercholesterolaemia			8%			All improved							

Appendix 22b

Weight differences compared with lipid differences

(i) Regression: weight difference versus cholesterol

SPSS variable names: Wtdff, average weight difference; Chol_diff, average cholesterol difference



Model summary[a]

Model	*R*	R^2	Adjusted R^2	SE of the estimate
1	0.856[b]	0.732	0.722	0.31450

[a] Dependent variable: Chol_diff.
[b] Predictors: (Constant), Wtdff.

ANOVA[a]

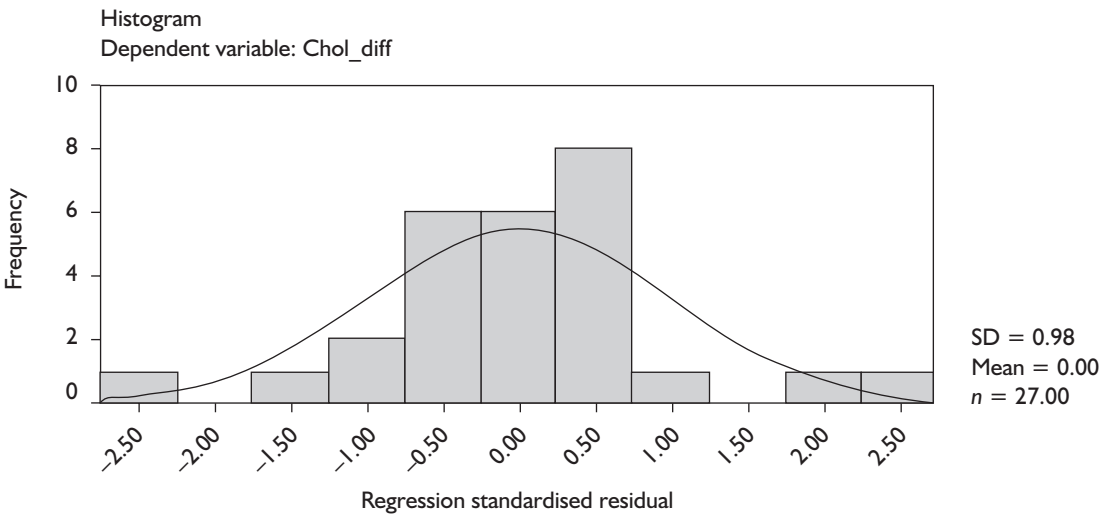
Model	Sum of squares	df	Mean square	*F*	Sig.
1 Regression	6.765	1	6.765	68.395	0.000[b]
Residual	2.473	25	0.099		
Total	9.237	26			

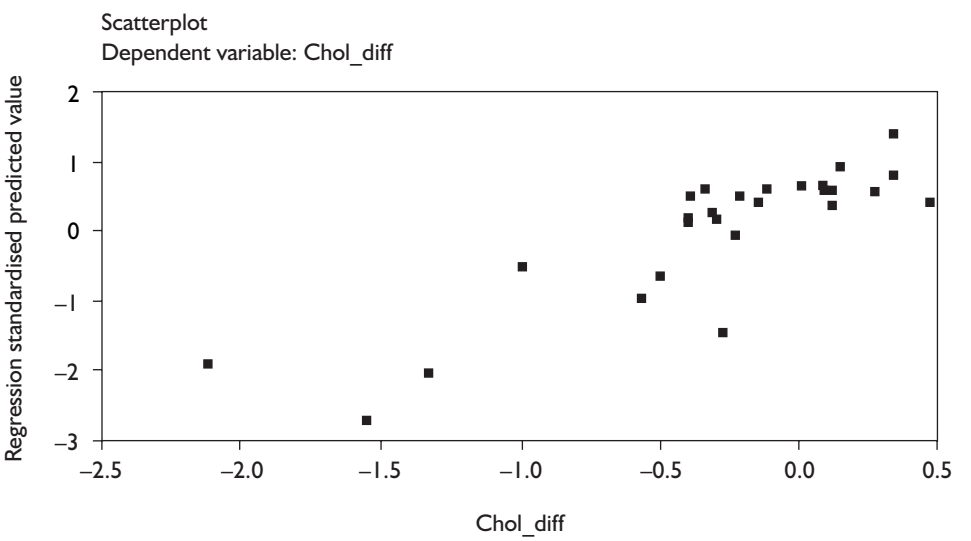
[a] Dependent variable: Chol_diff.
[b] Predictors: (Constant), Wtdff.

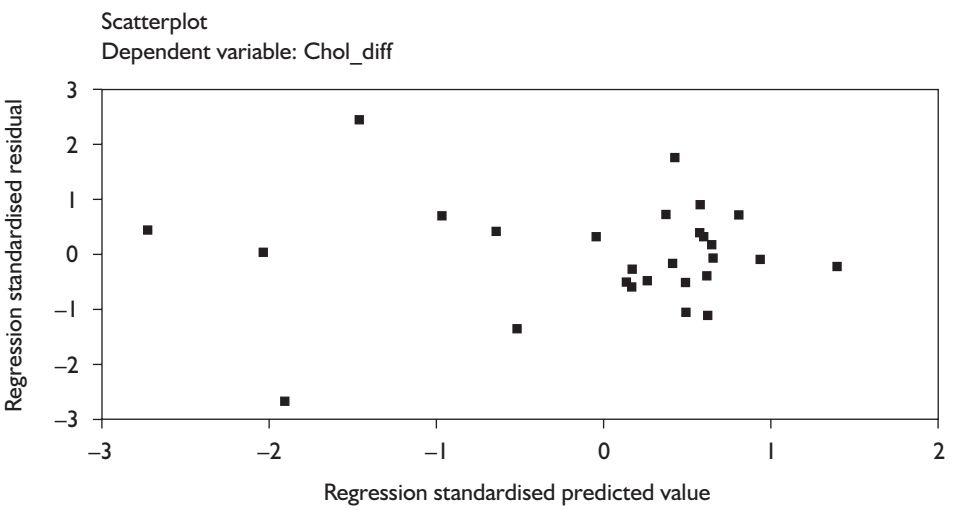
Coefficients[a]

	Unstandardised coefficients		Standardised coefficients		
Model	*B*	SE	β	*t*	Sig.
1 (Constant)	$7.009E^{-02}$	0.076		0.924	0.364
Wtdff	$3.210E^{-02}$	0.004	0.856	8.270	0.000

[a] Dependent variable: Chol_diff.

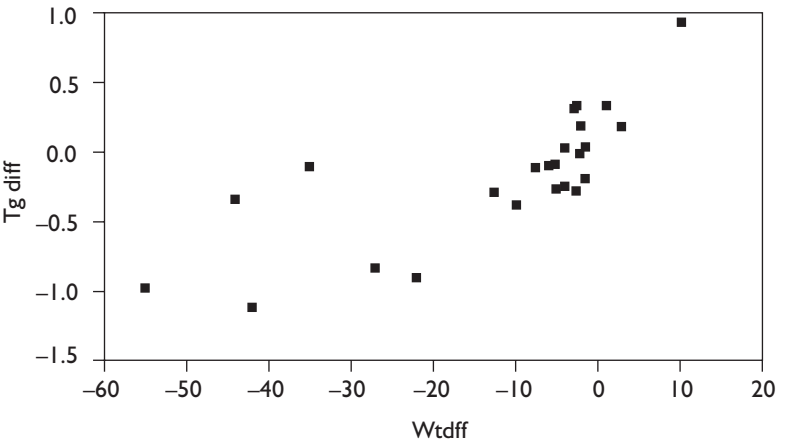

Histogram
Dependent variable: Chol_diff
Frequency
Regression standardised residual
SD = 0.98
Mean = 0.00
n = 27.00


Scatterplot
Dependent variable: Chol_diff
Regression standardised predicted value
Chol_diff


Scatterplot
Dependent variable: Chol_diff
Regression standardised residual
Regression standardised predicted value

(ii) Regression: weight difference versus TGs

SPSS variable names: Wtdff, average weight difference; Tg diff, average triglycerides difference



Model summary[a]

Model	R	R^2	Adjusted R^2	SE of the estimate
1	0.764[b]	0.584	0.565	0.30653

[a] Dependent variable: Tg diff.
[b] Predictors: (Constant), Wtdff.

ANOVA[a]

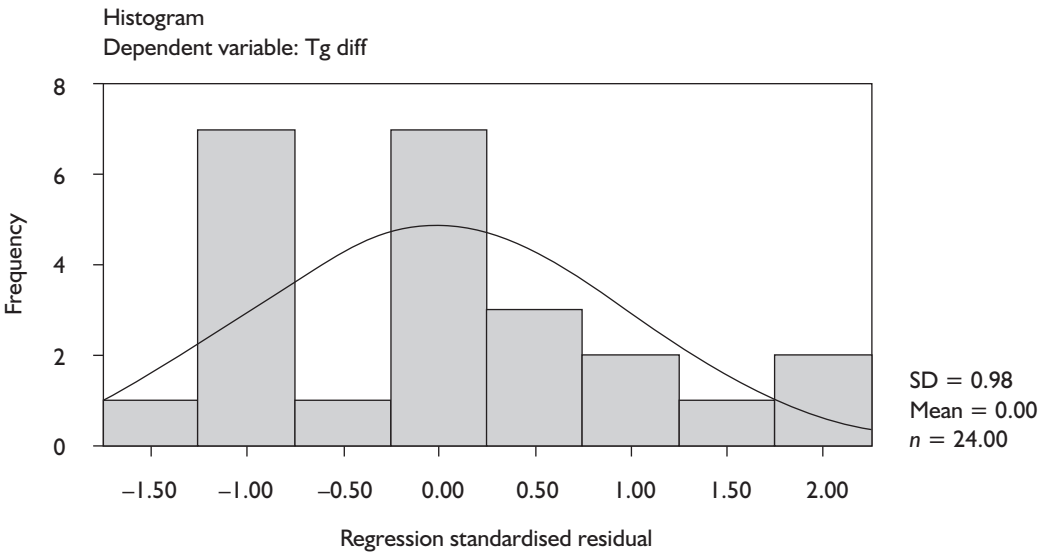
Model	Sum of squares	df	Mean square	F	Sig.
1 Regression	2.905	1	2.905	30.913	0.000[b]
Residual	2.067	22	0.094		
Total	4.972	23			

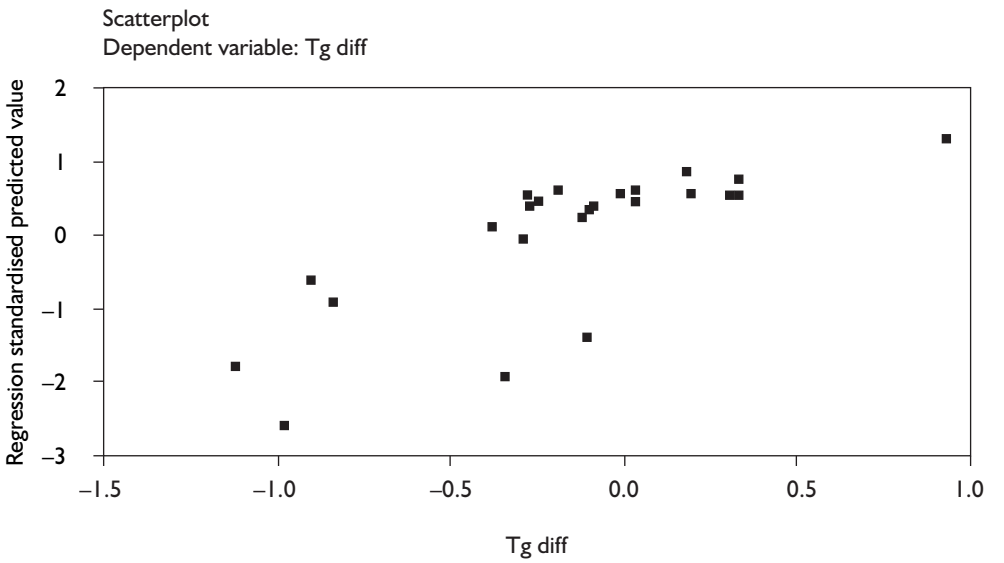
[a] Dependent variable: Tg diff.
[b] Predictors: (Constant), Wtdff.

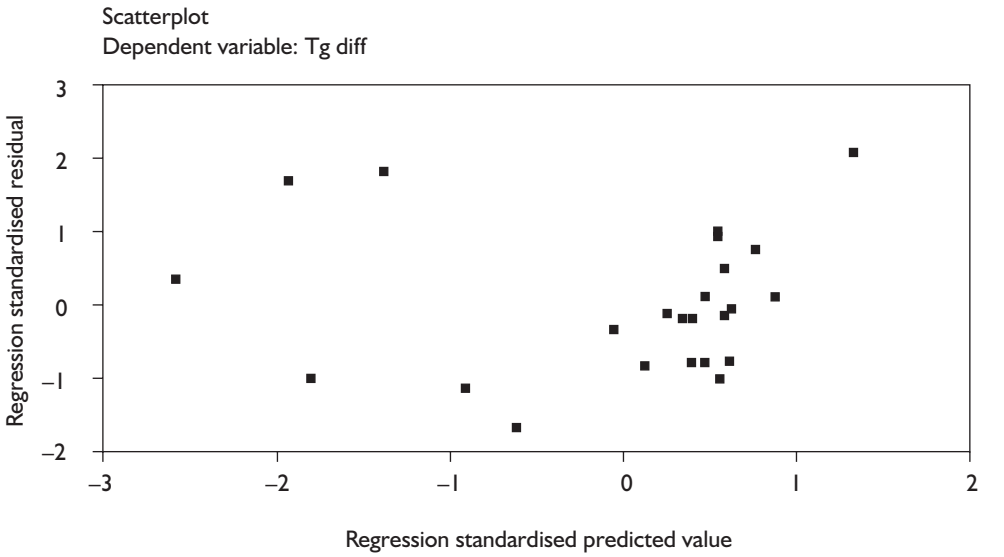
Coefficients[a]

	Unstandardised coefficients		Standardised coefficients		
Model	B	SE	β	t	Sig.
1 (Constant)	8.265E^{-02}	0.077		1.077	0.293
Wtdff	2.117E^{-02}	0.004	0.764	5.560	0.000

[a] Dependent variable: Tg diff.

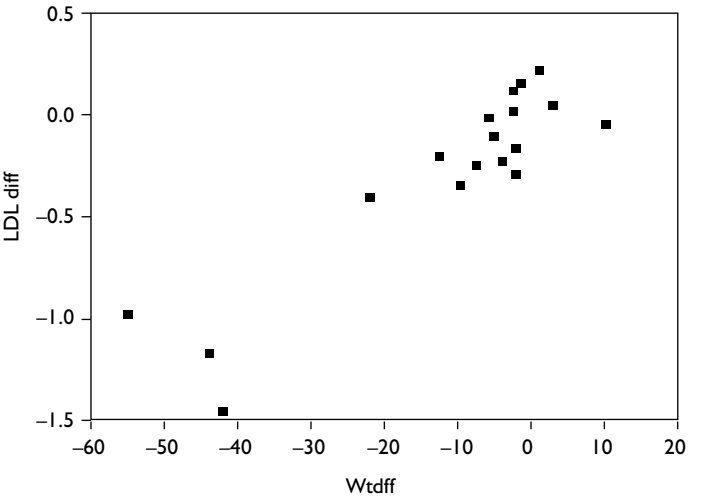

Histogram
Dependent variable: Tg diff
Frequency
8
6
4
2
0
–1.50
–1.00
–0.50
0.00
0.50
1.00
1.50
2.00
Regression standardised residual
SD = 0.98
Mean = 0.00
n = 24.00


Scatterplot
Dependent variable: Tg diff
Regression standardised predicted value
2
1
0
–1
–2
–3
–1.5
–1.0
–0.5
0.0
0.5
1.0
Tg diff


Scatterplot
Dependent variable: Tg diff
Regression standardised residual
3
2
1
0
–1
–2
–3
–2
–1
0
1
2
Regression standardised predicted value

(iii) Regression: weight difference versus LDL

SPSS variable names: Wtdff, average weight difference; LDL diff, average LDL difference



Model summary[a]

Model	*R*	R^2	Adjusted R^2	SE of the estimate
1	0.903[b]	0.816	0.804	0.20675

[a] Dependent variable: LDL diff.
[b] Predictors: (Constant), Wtdff.

ANOVA[a]

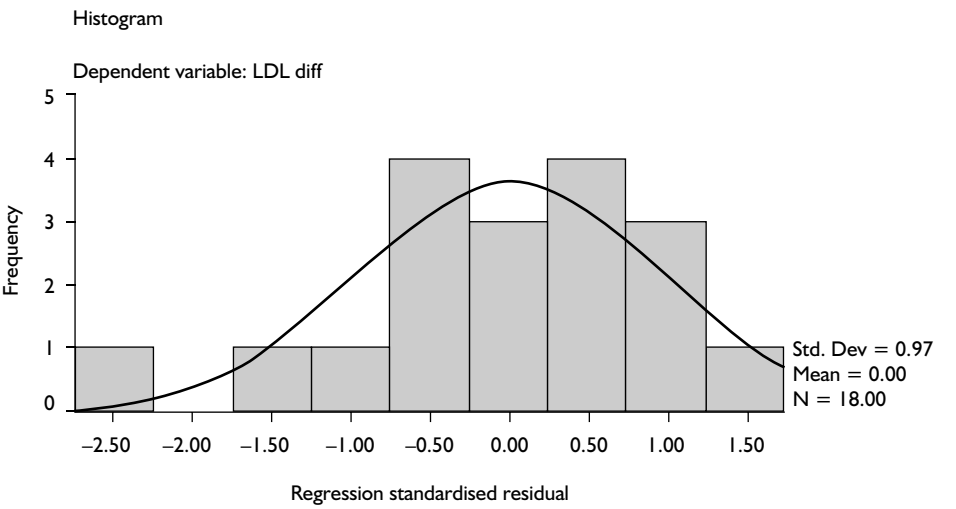
Model	Sum of squares	df	Mean square	*F*	Sig.
1 Regression	3.024	1	3.024	70.740	0.000[b]
Residual	0.684	16	0.043		
Total	3.708	17			

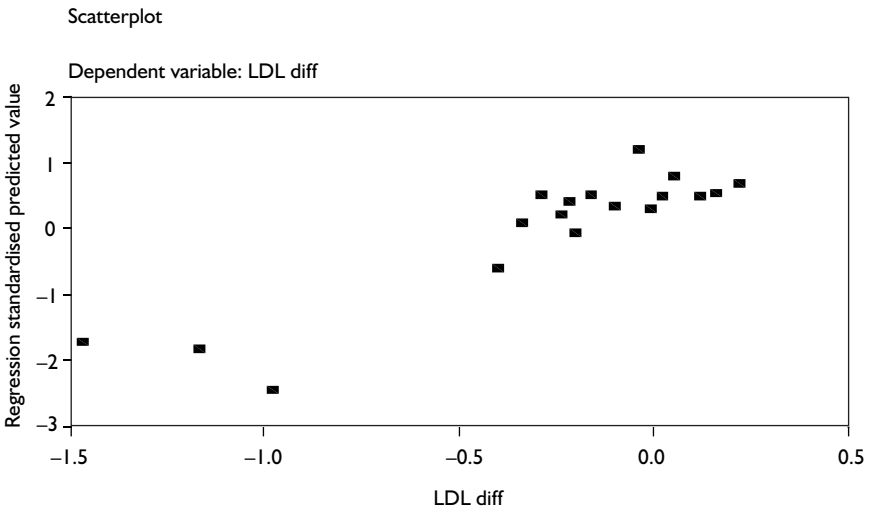
[a] Dependent variable: LDL diff.
[b] Predictors: (Constant), Wtdff.

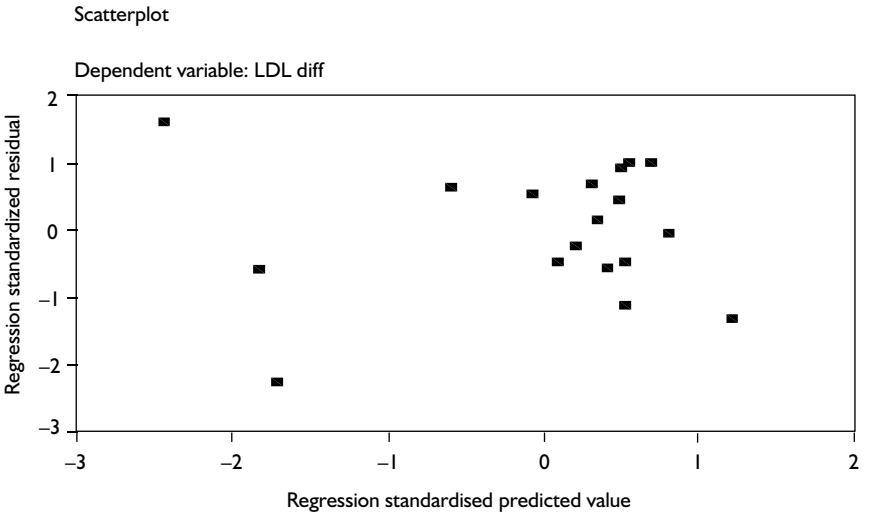
Coefficients[a]

	Unstandardised coefficients		Standardised coefficients		
Model	*B*	SE	β	*t*	Sig.
1 (Constant)	–1.206E^{-02}	0.058		–0.207	0.839
Wtdff	2.363E^{-02}	0.003	0.903	8.411	0.000

[a] Dependent variable: LDL diff.


Histogram
Dependent variable: LDL diff
Frequency
5
4
3
2
1
0
Std. Dev = 0.97
Mean = 0.00
N = 18.00
–2.50
–2.00
–1.50
–1.00
–0.50
0.00
0.50
1.00
1.50
Regression standardised residual

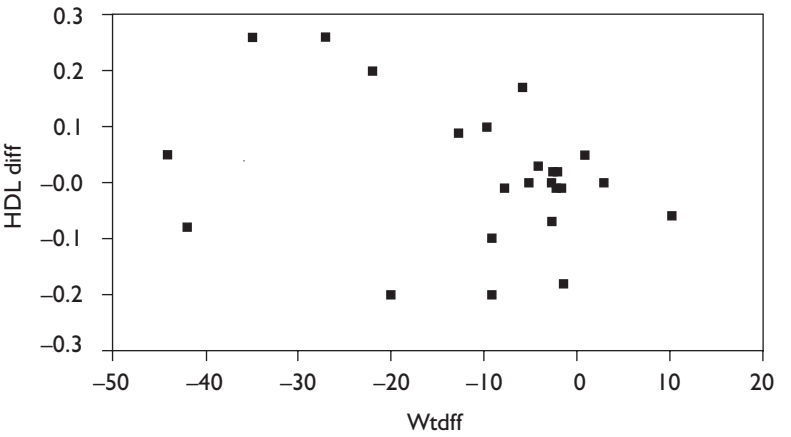

Scatterplot
Dependent variable: LDL diff
Regression standardised predicted value
2
1
0
–1
–2
–3
–1.5
–1.0
–0.5
0.0
0.5
LDL diff


Scatterplot
Dependent variable: LDL diff
Regression standardized residual
2
1
0
–1
–2
–3
–3
–2
–1
0
1
2
Regression standardised predicted value

(iv) Regression: weight difference versus HDL

SPSS variable names: Wtdff, average weight difference; HDL diff, average HDL difference

Pearson correlation = –0.308, $p > 0.05$



Appendix 23

Hypertension results

Appendix 23a

Weight differences compared with blood pressure differences for diastolic and systolic blood pressure

Intervention type		Study	Description	Follow-up months	*n*	Weight diff (kg)	(SE)	*n*	DBP diff (mmHg)	(SE)	*n*	SBP diff (mmHg)	(SE)
Prospective cohort	Part *i*	Wing, 1995[282]	Gainers	30	15	+10.30*	**(2.36)**	15	+1.5	**(2.14)**	15	–1.30	**(4.39)**
			Stable	30	25	+3.00*	**(1.36)**	25	+3.5*	**(1.66)**	25	–0.40	**(3.40)**
			Large cyclers	30	31	–2.10	**(1.17)**	31	–2.2	**(1.49)**	31	–3.10	**(3.05)**
			Small cyclers	30	28	+2.60	**(1.26)**	28	5.0*	**(1.57)**	28	0.40	**(3.21)**
			Partial cyclers	30	28	–9. 70*	**(1.69)**	28	–5.1*	**(1.57)**	28	–10.00*	**(3.21)**
			Small successes	30	7	–5.90	**(2.92)**	7	–2.4	**(3.14)**	7	–4.60	**(6.43)**
			Large successes	30	14	–12.6*	**(2.63)**	14	–4.1	**(2.22)**	14	–2.50	**(4.54)**
	Part *ii* (a)	Sjostrom M, 1999[285] (raw data)	CVD risk women	60	323	–1.44*	(0.40)	321	–5.0*	(0.76)	323	–6.00*	(1.15)
			CVD risk men	60	221	–2.70*	(0.56)	221	–2.94*	(0.86)	221	–3.66*	(1.40)
	(b)	Kauffmann, 1992[283]	Spanish workplace	24	80	–2.20*	(0.40)				80	$r = 0.2$	$p = 0.015$
RCT – diet & Ex	Part *iii* (a)	Wing, 1998[176]	Diet + BT	24	35	–2.10	(1.28)	35	+3.0 *	(1.32)	35	–0.80	(1.59)
			Ex + BT	24	31	1.00	(0.84)	31	+2.0	(1.44)	31	+0.90	(2.50)
			Diet, Ex + BT	24	32	–2.50	(1.48)	32	–0.2	(1.86)	32	–4.80	(2.54)
RCT – drug	Part *iii* (b)	Hauptman, 2000[45]	Placebo + diet	24	91	–1.54*	(0.58)	91	+1.0	**(0.87)**	91	+3.00	**(1.78)**
			Orlistat + diet	24	117	–5.16*	(0.78)	117	–1.0	**(0.77)**	117	0.00	**(1.57)**
		Rossner, 2000[37]	Placebo + diet	24	140	–4.30*	(0.63)	140	–2.7*	**(0.70)**	140	–5.10*	**(1.44)**
			Orlistat + diet	24	136	–7.60*	(0.60)	136	–2.6*	**(0.71)**	136	–6.10*	**(1.46)**
		Teupe, 1991[84]	Metformin + diet	24	25	–4.00*	**(1.42)**	25	–6.0*	**(1.66)**	25	–10.00*	**(3.40)**
			diet	24	29	–5.10*	**(1.39)**	29	–5.0*	**(1.54)**	29	–14.00*	**(3.16)**
Surgical	Part *iv*	Karason, 1999[277]	21% women	48	19	–22.0*	(2.29)	19	–10.0*	(2.75)	19	–18.00*	(4.82)
		Sjostrom C, 2000[278]	SOS	96	251	–20.1*	(0.99)	251	–1.9*	(0.90)	251	+2.90*	(1.39)
		Carson, 1994[263]	HT grp > 90 mmHg	48	18	–40.5*	(5.00)	18	–3.0	**(1.96)**			
			Norm HT	48	34	–79.8*	(5.50)	34	–4.6*	(1.90)	34	–10.70*	(3.60)
		Kunesova, 1998[262]	drug/BT/surgery(?)	24–60	103	–7.09*	(1.48)	103	–4.86*	**(0.82)**	103	–5.56*	**(1.68)**

Bold text standard errors indicate studies where the mean differences were estimated from *follow-up mean – base mean*. Standard errors were also estimated as in Appendix 26.
HT, hypertension.
* *Follow-up – baseline* paired *t*-test significance at $p < 0.05$.

Appendix 23b

Weight differences compared with diastolic blood pressure differences

Pearson correlations for DBP difference with weight difference variables

DBP difference	Follow-up (months)	All subgroups			Extreme initial weight and weight losses excluded		
		Initial weight (kg)	Weight diff (kg)	% weight diff	Initial weight (kg)	Weight diff (kg)	% weight diff
Correlation *r*	–0.281	–0.293	0.407	0.468*	–0.283	0.675**	0.698**
p-Value (2-tailed)	0.194	0.175	0.054	0.024	0.214	0.001	0.000
n	23	23	23	23	21	21	21

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Pearson correlations for % DBP difference with weight difference variables

% DBP difference	Follow-up (months)	All subgroups			Extreme initial weight and weight losses excluded		
		Initial weight (kg)	Weight diff (kg)	% weight diff	Initial weight (kg)	Weight diff (kg)	% weight diff
Correlation *r*	–0.071	–0.178	0.463	0.587*	–0.213	0.780**	0.778**
p-Value (2-tailed)	0.802	0.525	0.082	0.021	0.465	0.001	0.001
n[a]	15	15	15	15	14	14	14

[a] Some studies had no baseline blood pressures given, so % DBP could not be calculated; hence $n = 15$ and $n = 14$.
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

(i) DBP difference with weight difference (excluding > 40 kg absolute weight loss)

Diff in DBP = –0.299 + 0.340 (wt diff), i.e. –10 kg → 3.7 mmHg drop in DBP

SPSS variable names: MISWTD, average weight difference excluding extreme subgroups; DIADIFF, average DBP difference

Model summary[a]

Model	R	R^2	Adjusted R^2	SE of the estimate
1	0.675[b]	0.456	0.428	2.76781

[a] Dependent variable: DIADIFF.
[b] Predictors: (Constant), MISWTD.

ANOVA[a]

Model	Sum of squares	df	Mean square	F	Sig.
1 Regression	122.189	1	122.138	15.943	0.001[b]
Residual	145.554	19	7.661		
Total	267.693	20			

[a] Dependent variable: DIADIFF.
[b] Predictors: (Constant), MISWTD.

Coefficients[a]

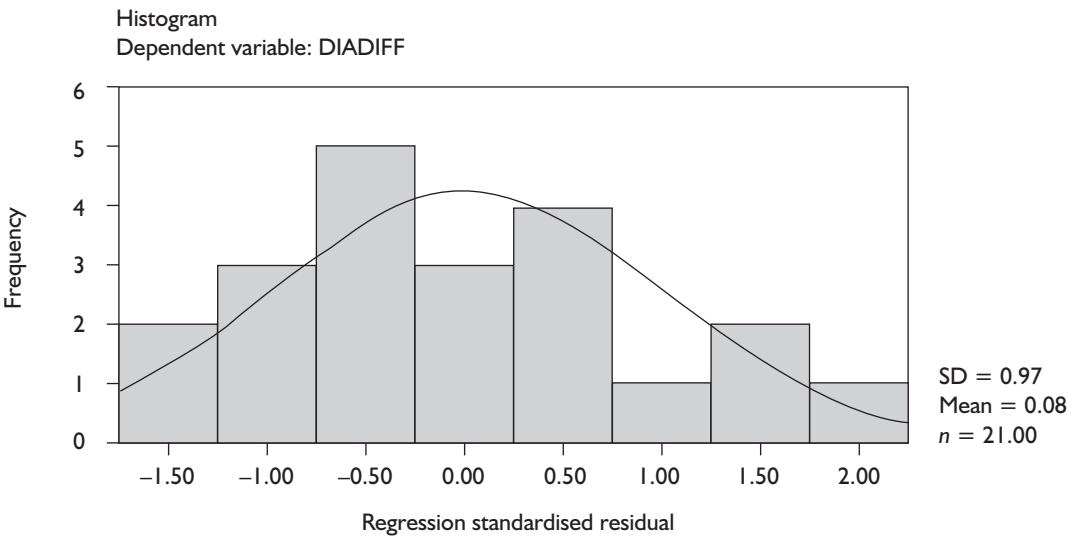
	Unstandardised coefficients		Standardised coefficients		
Model	B	SE	β	t	Sig.
1 (Constant)	–0.299	0.726		–0.412	0.685
MISWTD	0.340	0.085	0.675	3.993	0.001

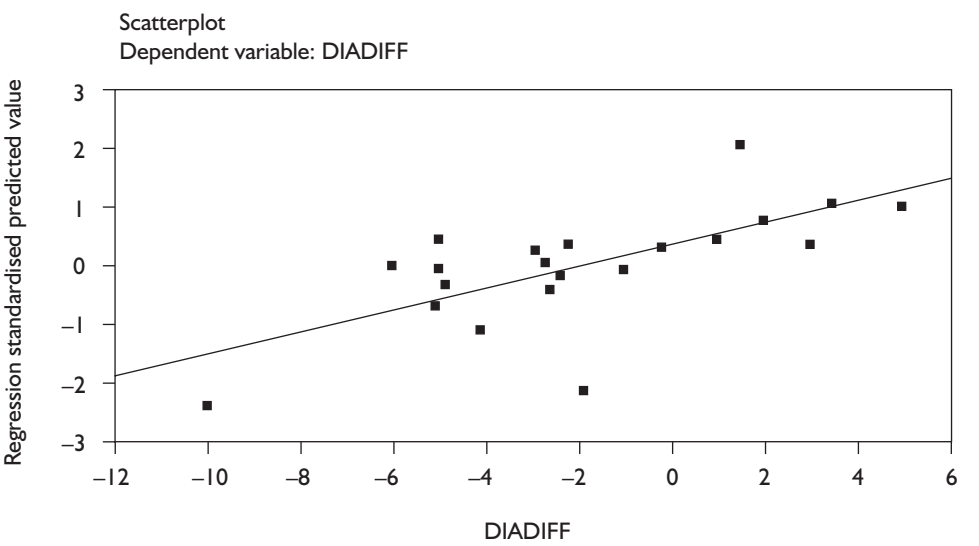
[a] Dependent variable: DIADIFF.

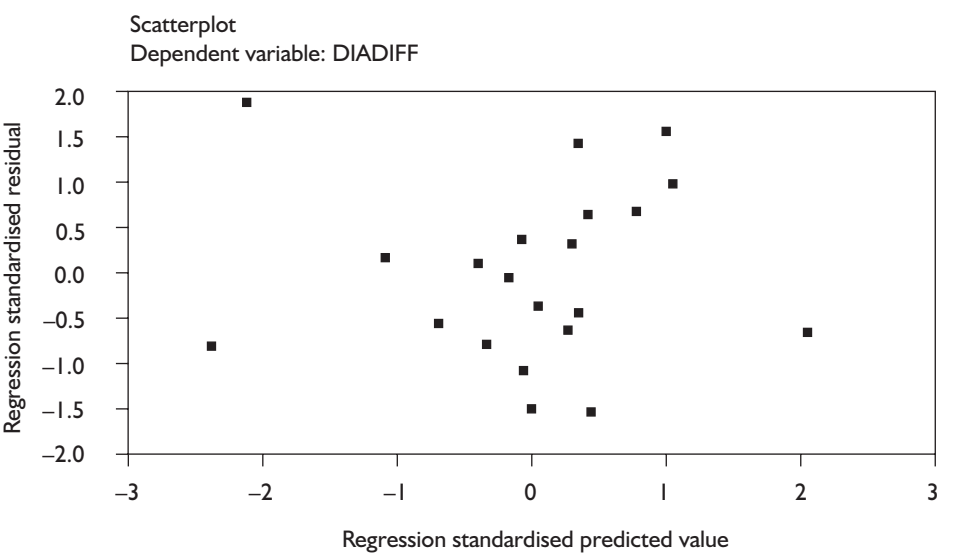
Residuals statistics[a]

	Min.	Max.	Mean	SD	n
Predicted value	–7.7900	3.2080	–1.9048	2.47122	21
Residual	–4.3389	5.2431	0.0000	2.69772	21
Std predicted value	–2.382	2.069	0.000	1.000	21
Std residual	–1.568	1.894	0.000	0.975	21

[a] Dependent variable: DIADIFF.







(ii) DBP difference versus weight difference (excluding > 40 kg losses)

Diff in DBP = 0.360 (wt diff), i.e. –10 kg → 3.60 mmHg actual drop in DBP

Model summary[a,b]

Model	R	R^2 [c]	Adjusted R^2	SE of the estimate
1	0.757[d]	0.573	0.552	2.70976

[a] Dependent variable: DIADIFF.
[b] Linear regression through the origin.
[c] For regression through the origin (the no-intercept model), R^2 measures the proportion of the variability in the dependent variable about the origin explained by regression. This cannot be compared to R^2 for models that include an intercept.
[d] Predictors: MISWTD.

ANOVA[a,b]

Model	Sum of squares	df	Mean square	F	Sig.
1 Regression	197.027	1	197.027	26.833	0.000[c]
Residual	146.856	20	7.343		
Total	343.883[d]	21			

[a] Dependent variable: DIADIFF.
[b] Linear regression through the origin.
[c] Predictors: MISWTD.
[d] This total sum of squares is not corrected for the constant because the constant is zero for regression through the origin.

Coefficients[a,b]

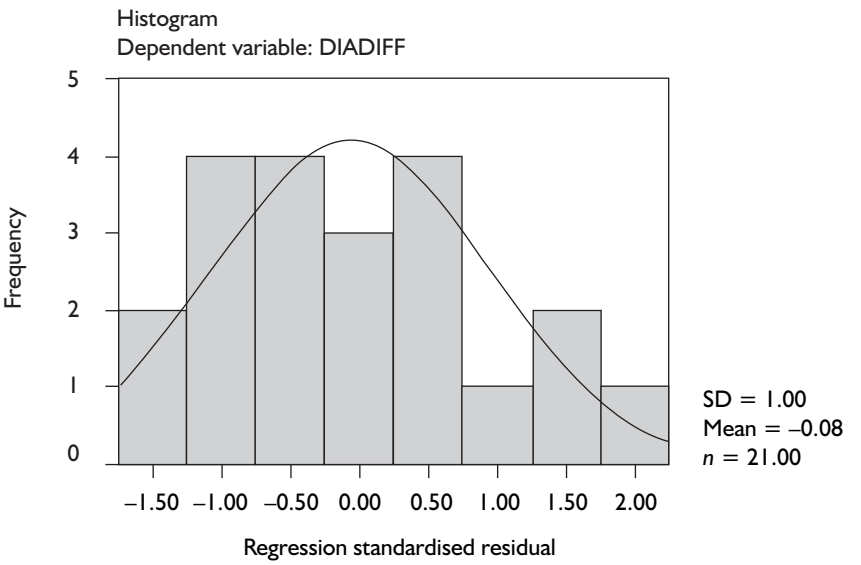
	Unstandardised coefficients		Standardised coefficients		
Model	B	SE	β	t	Sig.
1 MISWTD	0.360	0.069	0.757	5.180	0.000

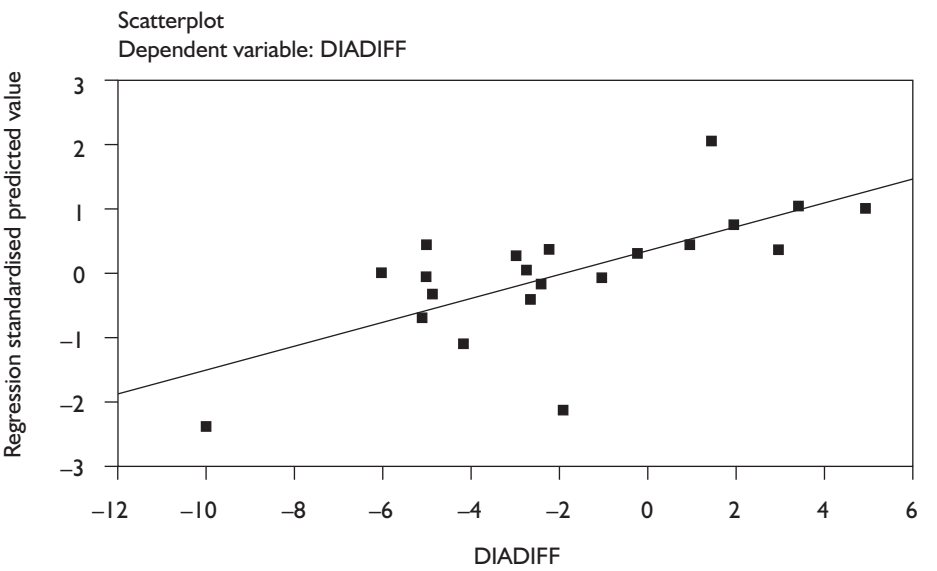
[a] Dependent variable: DIADIFF.
[b] Linear regression through the origin.

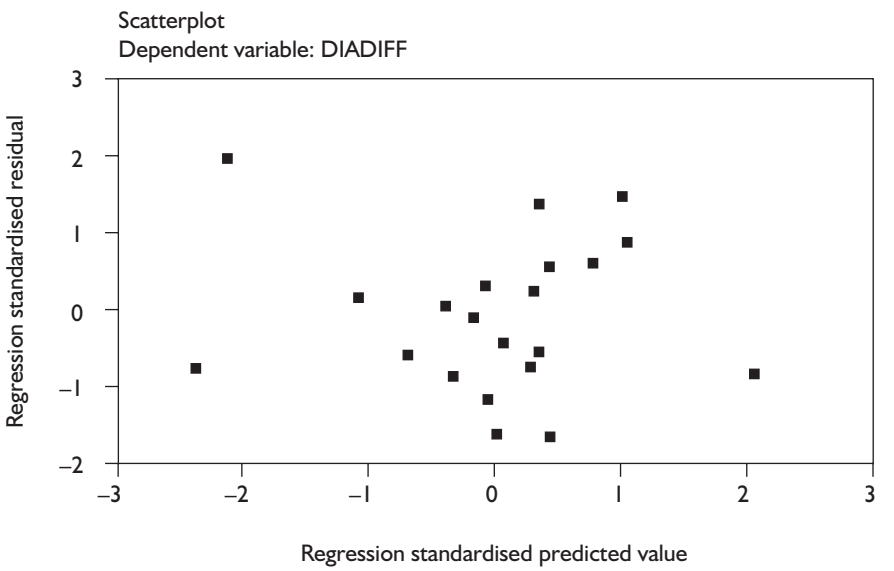
Residuals statistics[a,b]

	Min.	Max.	Mean	SD	n
Predicted value	–7.9195	3.7077	–1.6975	2.61259	21
Residual	–4.5601	5.3355	–0.2072	2.70143	21
Std predicted value	–2.382	2.069	0.000	1.000	21
Std residual	–1.683	1.969	–0.076	0.997	21

[a] Dependent variable: DIADIFF.
[b] Linear regression through the origin.





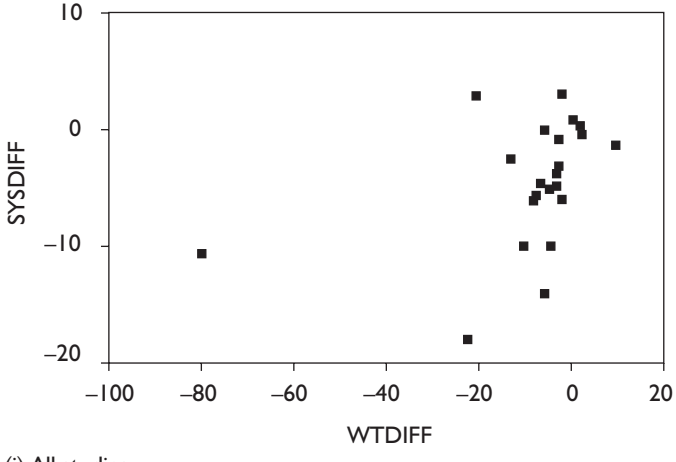


Appendix 23c

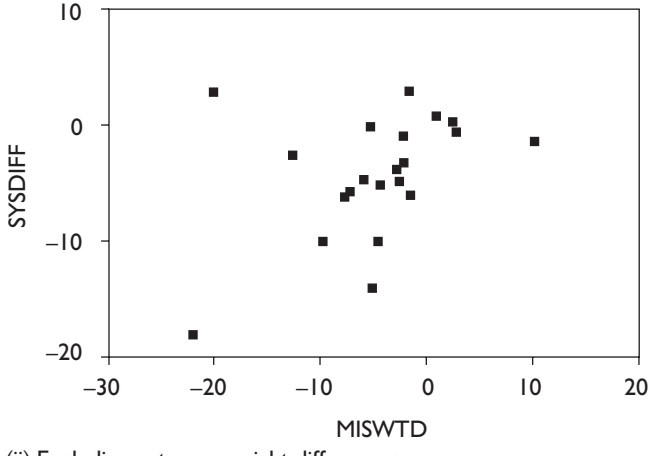
Weight differences compared with systolic blood pressure differences

(i) Scatterplots

(a) SBP versus weight differences

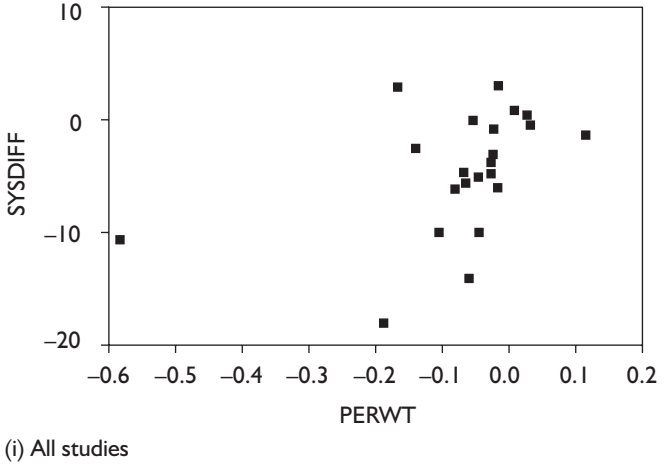


(i) All studies

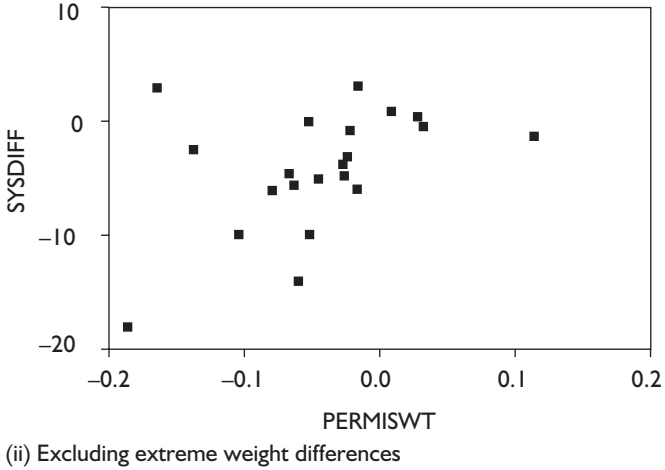


(ii) Excluding extreme weight differences

(b) SBP versus % weight differences



(i) All studies



(ii) Excluding extreme weight differences

(ii) Pearson correlations for SBP difference (raw and percentage) with weight difference variables

SBP difference	Follow-up (months)	All subgroups			Extreme initial weight and weight losses excluded		
		Initial weight (kg)	Weight diff (kg)	% weight diff	Initial weight (kg)	Weight diff (kg)	% weight diff
Correlation *r*	0.041	–0.155	0.393	0.428*	0.005	0.407	0.432
p-Value (2-tailed)	0.857	0.492	0.070	0.047	0.983	0.067	0.051
n	22	22	22	22	21	21	21

* Correlation is significant at the 0.05 level (2-tailed).

% SBP difference	Follow-up (months)	All subgroups			Extreme initial weight and weight losses excluded		
		Initial weight (kg)	Weight diff (kg)	% weight diff	Initial weight (kg)	Weight diff (kg)	% weight diff
Correlation *r*	0.015	0.180	0.491	0.502	0.080	0.498	0.509
p-Value (2-tailed)	0.960	0.538	0.075	0.067	0.538	0.070	0.063
n[a]	14	14	14	14	14	14	14

[a] Some studies had no baseline blood pressures given, so % SBP could not be calculated; hence, the number of subgroups is reduced to $n = 14$.

(iii) Regression: SBP with percentage weight difference variables (excluding > 40 kg losses)

diff in SBP = –2.719 + 33.745 (%wt diff), i.e. 10% wt loss → 6.1 mmHg drop in SBP

SPSS variable names: PERMISWT, average % weight difference excluding extreme subgroups; SYSDIFF, average SBP difference

Model summary[a]

Model	R	R^2	Adjusted R^2	SE of the estimate
1	0.432[b]	0.186	0.144	4.9395

[a] Dependent variable: SYSDIFF.
[b] Predictors: (Constant), PERMISWT.

ANOVA[a]

Model	Sum of squares	df	Mean square	F	Sig.
1 Regression	106.182	1	106.182	4.352	0.051[b]
Residual	463.568	19	24.398		
Total	569.749	20			

[a] Dependent variable: SYSDIFF.
[b] Predictors: (Constant), PERMISWT.

Coefficients[a]

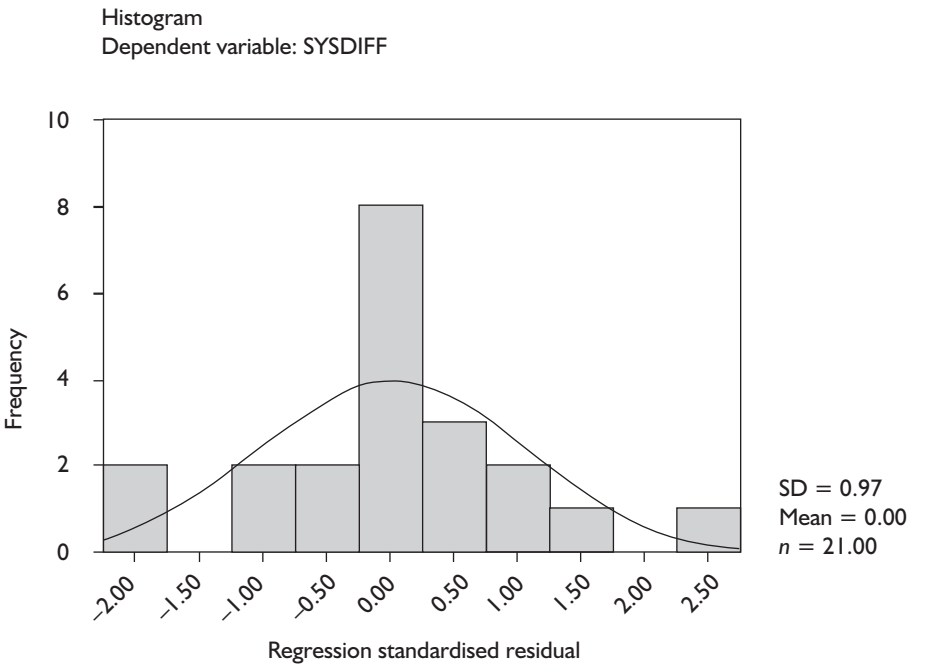
	Unstandardised coefficients		Standardised coefficients		
Model	B	SE	β	t	Sig.
1 (Constant)	–2.719	1.298		–2.096	0.050
PERMISWT	33.745	16.176	0.432	2.086	0.051

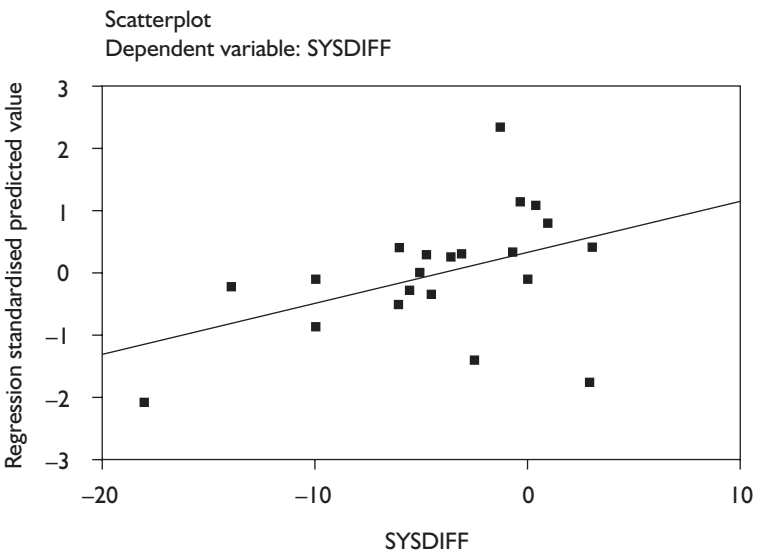
[a] Dependent variable: SYSDIFF.

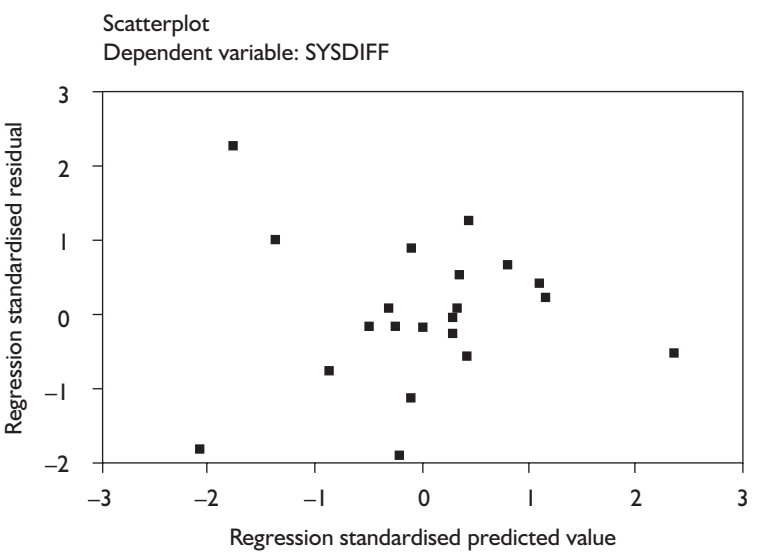
Residuals statistics[a]

	Min.	Max.	Mean	SD	n
Predicted value	–9.0107	1.2125	–4.2262	2.3042	21
Residual	–9.2819	11.1972	0.000	4.8144	21
Std predicted value	–2.076	2.360	0.000	1.000	21
Std residual	–1.879	2.267	0.000	0.975	21

[a] Dependent variable: SYSDIFF.







Appendix 23d

Other results relating to hypertension: all surgical

Study	Participant type	Follow-up years	Hypertension (HT)	Other
Pories, 1992[266]	Morbid obese	11 years overall	Baseline: *n* = 515, 301 (58.4%) had HT Follow-up: unclear when results redone 96/301 remained hypertensive	
O'Leary, 1980[272]	Obese	7 years overall	Baseline: *n* = 274, 46% were HT Follow-up: unclear when results redone 33% of those with HT at baseline improved, 66% of those with HT at baseline remained hypertensive	
Sjostrom C, 2000[278]	SOS hypertensive and obese	8 years		Baseline: *n* = 257, control *n* = 132, surgical *n* = 125 Follow-up: control *n* = 34, surgical *n* = 33; HT OR = 1.05 (0.58 to 1.89); adjusted for: gender, age, initial weight, weight, smoking status, alcohol, energy in, physical activity
Carson, 1994[263]	Hypertensive > 90 mmHg and obese	4 years	Baseline *n* = 45, had HT and 41 had medication Follow-up: HT results *n* = 18?; 12/18 resolved, 2/18 improved, 4/18 no change, 5 still on medication	Follow-up: resolved HT group BMI = 32, improved HT group BMI = 37.4, no change HT group BMI = 49.5
Foley, 1992[288]	Obese	4.2 (SE 0.2) years	Baseline *n* = 74, all HT Follow-up: *n* = 67; 44/67 (66%) resolved HT; 23/67 (34%) persistent HT	

Appendix 24

Changes in weight and psychological measures after a cycle of weight loss and regain

TABLE 35

		Baseline		6 months		Follow-up			
Variable	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	***F***	***p***
Weight (kg)	48	105.8	(16.6)	84.7	(13.2)	109.4	(20.0)	5.24	0.03
Depression	48	12.7	(8.5)	6.0	(8.9)	9.3	(8.1)	8.43	0.006
Binge eating	46	20.7	(7.8)	14.9	(7.1)	14.6	(8.2)	24.02	0.0001
Restraint	47	8.2	(3.4)	15.1	(3.4)	8.4	(4.2)	0.0001	0.99
Disinhibition	47	11.7	(2.5)	9.6	(3.1)	10.0	(3.2)	17.89	0.001
Hunger	47	7.9	(3.5)	6.2	(3.4)	5.9	(3.1)	17.31	0.001

Data from Foster *et al*. (1996)[163] Table 1.
F = ANOVA, repeated measures within-subject design. Six-month data included only to assess magnitude of changes during treatment. *F* and *p* values are for baseline and follow-up comparisons. Depression was assessed by the Beck Depression Inventory; binge eating by the Binge Eating Scale; and restraint, disinhibition and hunger by the Eating Inventory.

TABLE 36 *NVM scores of the study population before and after surgery compared with the reference group (standard values of a general Dutch population)*

	Reference		Before surgery		After surgery	
	Mean	**(95% CI)**	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**
Negativism	14.7	(14.2 to 15.2)	18.1	(15.9 to 20.3)**	16.7	(14.5 to 18.9)
Somatisation	5.3	(4.9 to 5.7)	12.8	(10.7 to 14.9)***	14.6	(12.1 to 17.1)***
Shyness	8.0	(7.6 to 8.4)	14.5	(12.1 to 16.9)***	9.9	(7.8 to 12.0)
Psychopathology	2.7	(2.5 to 2.9)	3.3	(2.5 to 4.1)	3.2	(2.5 to 3.9)
Extroversion	17.1	(16.7 to 17.5)	15.1	(13.5 to 16.7)*	16.8	(15.3 to 18.3)

Data from van Gemert *et al*. (1998)[270] Table 1.
Separate variance *t*-test for differences between the values of the study groups (before and after surgery) and the values of the reference group (*$p < 0.02$, **$p < 0.001$, ***$p < 0.001$).

TABLE 37 *NPV scores of the study population before and after surgery compared with the reference group (standard values of a general Dutch population)*

	Reference		Before surgery		After surgery	
	Mean	**(95% CI)**	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**
Inadequacy	13.9	(13.6 to 14.2)	16.8	(14.0 to 19.6)*	13.9	(11.4 to 16.4)
Social inadequacy	12.3	(12.0 to 12.6)	15.8	(13.4 to 18.2)**	9.3	(7.1 to 11.5)**
Rigidity	30.6	(30.2 to 31.0)	27.3	(25.2 to 29.4)**	27.8	(25.8 to 29.8)**
Grievance	18.2	(18.0 to 18.4)	21.2	(19.1 to 23.3)**	19.4	(17.3 to 21.5)
Self-satisfaction	13.9	(13.7 to 14.1)	12.5	(10.8 to 14.2)	13.0	(11.6 to 14.4)
Dominance	11.9	(11.7 to 12.1)	13.6	(11.5 to 15.7)	15.6	(13.7 to 17.5)***
Self-esteem	28.0	(27.9 to 28.1)	24.4	(22.2 to 26.6)**	26.5	(24.5 to 28.5)

Data from van Gemert *et al*. (1998)[270] Table 2.
Separate variance *t*-test for differences between the values of the study groups (before and after surgery) and the values of the reference group (*$p < 0.02$; **$p < 0.001$; ***$p < 0.001$).

TABLE 38 *Comparison of the SIG scores before and after surgery*

	Before surgery				After Surgery			
	Frequency of Expressing		**Tension felt**		**Frequency of Expressing**		**Tension felt**	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Positive feelings	2.7	(0.7)	2.4	(0.9)	3.1	(0.8)**	2.0	(0.9)*
Negative feelings	2.7	(0.5)	2.5	(0.8)	3.0	(0.6)*	2.2	(0.8)
Self-expression	2.7	(0.7)	2.6	(1.0)	3.1	(0.7)*	2.0	(0.9)**
Insecurity	3.4	(0.4)	2.1	(0.7)	3.5	(0.7)	1.8	(0.6)*
Total	3.0	(0.5)	2.3	(0.8)	3.2	(0.6)*	2.0	(0.7)*

Data from van Gemert *et al*. (1998)[270] Table 3.
Paired Student's *t*-test (*$p < 0.05$; **$p < 0.001$).

Appendix 25

Sleep apnoea results

Study	Description	Initial *n*	Mean age (years)	Initial weight (kg)	Follow-up (years)	Follow-up *n*	Weight change (kg)	Initial AHI events/hour	Difference in AHI events/hour
Peppard, 2000[290]	Men and women with obesity and sleep disordered breathing	268	46.6 (SD 7.4)	101.2 (SD 15.5)	4	268	+2.4 (SD 7.4)	7.4 (SD 13.1)	+2.0 (SD 12.3)
			Subgroup that lost –20% to –10% Model adjusted for age and gender			19	–20% to –10% at –20%		–3.6 (SD 15.3) –32% (95% CI –58 to 11%)
			Subgroup that lost –10% to –5% Model adjusted for age and gender			17	–10% to –20% at –10%		–2.4 (SD 6.1) –17% (95% CI –34 to 5%)
			Stable group: lost –5% to 5% Model adjusted for age and gender			129	–5% to 5% at –5% at +5%		+1.0 (SD 10.2) –9% (95% CI –18 to 2%) +9% (95% CI –2 to 21%)
Charuzi, 1992[264]	Surgical obesity and SAS	51	41.2 (SD 9.5)	138.9 (SD 24.6)	6 (SD 1.79)	42	–37.38 (estimated SD 17.76, see Appendix 26)	60.8 (SD 35.5)	*n* = 6 for full AI at 6 year. Results imply that if weight loss is maintained then AI is small (i.e. like the 1-year results)
Sugerman, 1992[291]	Surgical morbid obesity SAS and morbid SAS with hypoventilation	110		166 (SD 35)	4.5 (SD 2.3)	57	–54 kg (SD 32)	64 (SD 39) (67% severe)	32 (SD 32) 38/57 asymptomatic, 15/57 mild SAS, 4/57 still SAS and obesity hypoventilation syndrome

AI, apnoea index; SAS, sleep apnoea syndrome.

Appendix 26

Methods of estimating measures of spread

Appendices 13 and 14 provide a method of estimating standard deviations from their associated weight and health outcome differences as appropriate for RCTs. For the epidemiological review these relationships were re-examined given that some of the weight and health outcome differences were larger (as for surgical interventions) and would thus otherwise require extrapolation. This part of the review also looked at the outcomes in the longer term, which may itself alter the relationship. The models given in Appendices 13 and 14 are used as a basis.

Part A: Estimation of weight difference measure of spread

As the weight differences were gathered initially the standard deviations did not appear to have a linear relationship with their absolute weight differences, causing concern about applying a linear equation as in Appendix 13. The standard errors did at first appear to have a linear relationship with the absolute weight differences. However, as the database became complete and the spread of the differences widened, so did the relationships.

All available studies that gave weight differences and an appropriate measure of spread for these differences were amalgamated. The relationship between absolute weight differences and their associated standard deviations ($r = 0.853$) and standard errors ($r = 0.894$) were examined and found to be reasonably linear.

Although there is a slightly stronger linear relationship between the absolute weight losses and their associated standard errors, both regression models were investigated.

The assumptions of such a model require that the relationship is linear, that the observations are independent and that the residuals are normally distributed. Although the standard error model appears to have a better fit, the normality and independence assumptions were in some doubt. When examined, the residuals from the standard deviation model appear for this limited data set to uphold all of the assumptions.

Reassuringly, this fits in with the conclusion from Appendix 13. However, there are no right or wrong ways of making such estimates. The epidemiology review results, when required, used the estimates based on the model given here:

Weight diff. SD = 5.837 + 0.319 × (Absolute weight diff.)

This model has the assurance that it is similar to the RCT-based model but has been developed using the full breadth of weight differences seen in the epidemiology review.

n	Adjusted R^2	Dependent	Prediction equation
25	0.729	Weight difference SD =	5.837 + 0.319 × (Absolute weight difference)
25	0.790	Weight difference SE =	0.710 + 0.07039 × (Absolute weight difference)

Part B: Estimation of cholesterol difference standard deviation

The studies that gave cholesterol differences along with appropriate measure of spread were considered together. The relationship between cholesterol differences and their standard deviations was varied and certainly not linear. Appendix 14 estimates this as a constant of 1.08 mmol/l that will be adopted within the epidemiology review, given that none of the observed measures was larger than this and would hence be a conservative estimate.

Part C: Estimation of LDL difference standard deviation

As for cholesterol, the relationship between LDL differences and their standard deviations was non-linear and probably constant. The epidemiology data collected for LDL difference standard deviations never exceeded 0.74 mmol/l, the value suggested in Appendix 14.

Part D: Estimation of HDL difference standard deviation

Four studies gave an HDL difference with its standard deviation. Their average was 0.245 mmol/l similar to the 0.29 mmol/l estimate given by Appendix 14. With no other evidence to suggest otherwise, 0.29 mmol/l was used to estimate HDL difference standard deviations.

Part E: Estimation of TGs difference standard deviation

Four data points were available to estimate the triglycerides difference measure of spread, hence linear model was not significant. However, the constant term in Appendix 14 of 0.96 mmol/l seemed small. Instead, the average of the values in the epidemiology review (1.53 mmol/l) was used.

Part F: Estimation of glucose difference standard deviation

Although the epidemiology review gave results of fasting glucose plasma levels there were no differences with associated measure of spread. All the estimated differences were less than 7 mmol/l, thus the constant given in Appendix 14 of 1.35 mmol/l was used to estimate the standard deviations.

Part G: Estimation of DBP and SBP difference standard deviations

Intially the epiemiology review produced very few results for DBP and SBP differences with associated measures of spread. Those available compared favourably with those estimated from the RCTs given in Appendix 14. Consequently, all the estimated standard deviations of the differences for DBP and SBP were set to the constants 8.3 mmHg and 12.7 mmHg, respectively, as given in Appendix 14. Although, more studies later became available, due to time constraints it was not possible to fully explore the relationship between the mean differences and their standard deviations in order to revise this decision.

Appendix 27

Quality assessment

Appendix 27a

Quality assessment scores

TABLE 39 *Results of each quality assessment question (see Appendix 17) for each study, arranged alphabetically*

Study	Aim	Sample	Age	Measure	Valid	Risk	Intervention	Setting	Mode	Untoward	Adequate follow-up	Long follow-up	Losses	Data	Numbers	Time	Sign	Main	Null	Overlook	Total
Carson, 1994[263]	2	0	2	2	2	2	2	2	2	0	0	1	0	2	2	2	2	2	2	2	31
Charuzi, 1992[264]	2	2	2	2	2	0	2	2	2	2	2	2	0	2	0	0	2	2	2	2	32
Chaturvedi, 1995[267]	1	0	2	2	2	1	2	2	2	2	1	2	0	2	2	1	2	1	1	0	28
Davidson, 1999[41]	2	0	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	36
Ewbank, 1995[284]	2	0	2	2	2	0	2	2	2	0	2	2	2	2	2	0	2	2	0	2	30
Foley, 1992[288]	2	0	2	2	2	0	2	2	2	0	2	1	0	2	2	1	2	2	0	1	27
Ford, 1997[268]	2	0	2	2	2	2	2	2	2	0	1	2	2	2	2	2	2	2	2	2	35
Foster, 1996[163]	2	0	2	2	2	0	2	2	2	2	0	2	2	2	1	2	2	2	2	2	33
Gleeysten, 1992[286]	0	0	0	2	2	0	2	2	2	0	2	2	0	2	2	2	2	2	0	2	26
Hauptman, 2000[45]	2	1	2	2	2	2	2	2	2	1	0	2	2	2	2	2	2	2	2	2	36
Hess, 1998[271]	1	0	2	2	2	2	2	2	2	1	0	2	0	2	1	2	0	2	0	1	26
Holt, 1987[265]	1	0	2	2	1	2	2	2	2	1	2	1	0	2	1	0	0	2	2	2	27
Karason, 1999[277]	2	0	2	2	2	2	2	1	2	0	2	1	0	2	2	1	2	2	2	2	31
Kauffman, 1992[283]	1	0	2	0	2	1	2	2	2	0	2	2	1	1	0	0	2	2	0	2	24
Kunesova, 1998[262]	2	0	2	2	2	2	2	2	2	0	1	1	0	0	1	1	2	1	0	2	25
Long, 1994[279]	2	0	2	2	2	2	2	2	2	0	0	2	0	1	2	0	2	2	1	2	28
Moore, 2000[269]	2	0	2	2	2	2	0	2	2	0	2	2	2	1	1	0	1	2	2	2	29
O'Leary, 1980[272]	0	0	0	2	1	2	2	2	2	1	1	1	0	1	1	0	0	1	2	2	21
Peppard, 2000[290]	2	2	2	2	2	2	0	2	2	2	2	2	0	2	1	2	2	2	0	2	33
Pories, 1992[266]	2	0	2	2	2	2	2	2	1	1	0	2	0	1	1	0	0	2	2	2	26
Rossner, 1980[287]	2	1	2	2	2	2	2	2	2	0	2	1	0	2	2	2	2	2	0	2	32
Rossner, 2000[37]	2	1	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	37
Rumpel, 1993[276]	2	0	1	1	1	2	0	2	2	2	1	2	0	2	2	0	0	2	2	2	26
Sjostrom CD, 2000[278]	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	38
Sjostrom M, 1999[285]	2	0	2	2	2	2	2	2	2	0	1	2	0	2	2	2	2	2	1	2	32
Sugerman, 1992[291]	1	0	0	2	2	2	2	2	2	1	1	2	0	2	2	2	2	2	2	2	31
Teupe, 1991[84]	2	1	2	2	2	2	2	2	2	0	1	2	2	2	2	2	2	2	1	2	35
Tuomilehto, 2001[168]	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2	2	2	38
van Gemert, 1998[270]	2	2	2	2	2	0	2	1	2	0	2	1	2	2	2	0	2	2	2	2	32
Wannamethee, 1999[280]	2	0	2	2	1	2	2	2	2	2	2	2	0	2	2	2	2	2	0	2	33
Watts, 1990[281]	1	0	2	2	2	2	2	2	2	2	1	2	0	2	2	2	2	2	2	2	34
Williamson D, 1995[274]	1	0	2	2	2	2	2	2	2	0	2	2	2	2	2	0	1	2	2	2	32
Williamson D, 1999[273]	2	0	2	2	2	2	2	2	2	0	2	2	0	2	2	2	1	2	2	2	33
Williamson D, 2000[275]	2	0	2	2	2	2	2	2	2	0	2	2	1	2	2	2	1	2	2	2	34
Wing, 1995[282]	2	0	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2	1	2	35
Wing, 1998[176]	2	0	2	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	1	2	35
Wittgrove, 2000[289]	2	2	0	2	2	1	2	1	2	2	1	1	1	2	2	1	0	2	1	1	28

Appendix 27b

Quality assessment summaries

TABLE 40 *Quality assessment scores and percentage scores for each study (arranged from highest to lowest)*

Study	Type of study	Total score	% Score
Tuomilehto, 2001[168]	RCT, non-surgical	38	0.95
Sjostrom CD, 2000[278]	Non-RCT, surgical	38	0.95
Rossner, 2000[37]	RCT, drug	37	0.93
Hauptman, 2000[45]	RCT, drug	36	0.90
Davidson, 1999[41]	RCT, drug	36	0.90
Wing, 1998[176]	Non-RCT, non-surgical	35	0.88
Wing, 1995[282]	RCT, diet and exercise (Weight Cycling)	35	0.88
Teupe, 1991[84]	RCT, diet and drug	35	0.88
Ford, 1997[268]	Prospective	35	0.88
Williamson, 2000[275]	Prospective	34	0.85
Watts, 1990[281]	Prospective, non-surgical	34	0.85
Williamson, 1999[273]	Prospective	33	0.83
Wannamethee, 1999[280]	Prospective	33	0.83
Peppard, 2000[290]	Prospective	33	0.83
Foster, 1996[163]	Prospective, combined intervention	33	0.83
Williamson, 1995[274]	Prospective	32	0.80
Sjostrom M, 1999[285]	Prospective, non-surgical	32	0.80
Rossner, 1980[287]	Prospective, surgical	32	0.80
van Gemert, 1998[270]	Prospective, surgical	32	0.80
Charuzi, 1992[264]	Prospective, surgical	32	0.80
Sugerman, 1992[291]	Prospective, surgical	31	0.78
Karason, 1999[277]	Non-RCT	31	0.78
Carson, 1994[263]	Prospective, surgical	31	0.78
Ewbank, 1995[284]	Prospective, non-surgical	30	0.75
Moore, 2000[269]	Prospective	29	0.73
Wittgrove, 2000[289]	Prospective, surgical	28	0.70
Long, 1994[279]	Non-RCT, surgical	28	0.70
Chaturvedi, 1995[267]	Prospective	28	0.70
Holt, 1987[265]	Prospective, surgical	27	0.68
Foley, 1992[288]	Prospective, surgical	27	0.68
Rumpel, 1993[276]	Prospective	26	0.65
Pories, 1992[266]	Prospective, surgical	26	0.65
Hess, 1998[271]	Prospective, surgical	26	0.65
Gleeysten, 1992[286]	Prospective, surgical	26	0.65
Kunesova, 1998[262]	Prospective, combined intervention	25	0.63
Kauffman, 1992[283]	Prospective, non-surgical	24	0.60
O'Leary, 1980[272]	Prospective, surgical	21	0.53

TABLE 41 *Quality assessment results for each quality assessment question*

	No	Possibly/unclear	Yes
	Count	Count	Count
Aims clearly stated	2	7	28
Sample size justified	27	4	6
Age of people defined	4	1	32
Measurements clearly stated	1	1	35
Measurements valid and reliable		4	33
Risk factors recorded	6	3	28
Intervention defined initially	3		34
Setting of study clear		3	34
Mode of assessment described		1	36
Untoward events happen	20	8	9
Follow-up adequate	6	12	19
Follow-up long enough		9	28
Losses to follow-up described	21	3	13
Basic data described	1	5	31
Do the numbers add up	2	8	27
Did analysis allow for time	11	5	21
Statistical significance assessed	6	4	27
Main findings assessed ok		3	34
Null/negative findings interpreted	9	7	21
Any important effects missed	1	3	33

Appendix 28

Definition of weight cycling

The study by Wing and colleagues,[282] gave the following definitions for the different weight cycling groups:

- **gainers**: those who gained 4.5 kg from baseline to 30 months
- **stable**: those who remained within ± 4.5 kg of their baseline weight throughout the study period
- **large cyclers**: those who lost 9 kg or more during the treatment period but who returned to within ± 4.5 kg of their baseline weight at the end of the study
- **small cyclers**: those who lost between 4.5 and 9 kg during the treatment period but who returned to within ± 4.5 kg of their baseline weight at the end of the study
- **partial cyclers**: those who lost 9 kg or more during the treatment period and kept off 4.5–9 kg at the end of the follow-up period
- **small successes**: those who lost 4.5–9 kg during treatment and kept off 4.5–9 kg by the end of the study
- **large successes**: those who lost more than 9 kg during treatment and kept off more than 9 kg by the end of the study.

Appendix 29

Search strategies for the systematic review of economic evaluations

MEDLINE (1966–2002, week 4) (Ovid)

1. "costs and cost analysis"/
2. cost benefit analysis/
3. economic evaluation.tw.
4. economic analys#s.tw.
5. cost effective$.ti.
6. cost utility.ti.
7. or/1-6

EMBASE (1980–2002, week 9) (Ovid)

1. economic evaluation/
2. cost benefit analysis/
3. cost effectiveness analysis/
4. cost minimization analysis/
5. cost utility analysis/
6. or/1-5

CINAHL (1982–December 2001) (Ovid)

1. "costs and cost analysis"/
2. cost benefit analysis/
3. economic evaluation.tw.
4. economic analys#s.tw.
5. cost effective$.ti.
6. cost utility.ti.
7. or/1-6

PsycINFO (1967–December 2001) (Silverplatter)

1. 'Costs-and-Cost-Analysis' in DE
2. economic evaluation
3. economic analys?s
4. cost utility analysis
5. cost effectiveness analysis
6. cost benefit analysis
7. cost* near3 benefit*
8. cost* near outcome*
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Science and Social Science Citation Indexes (1981–2002) (Web of Science)

(obes* or weight control or weight loss or weight reduction or overweight or diet therapy) and (economic evaluation or economic analys?s or cost benefit* or cost effectiveness or cost utility)

ASSIA (1987–February 2002) and HMIC (to January 2002) (Silverplatter)

1. economic evaluation
2. economic analys?s
3. cost* near benefit*
4. cost* near outcome*
5. cost near1 effectiveness
6. cost near1 utility
7. #1 or #2 or #3 or #4 or #5 or #6

Appendix 30

Data extraction table for economic evaluations: orlistat

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Foxcroft and Ludders, 1999[308] and Foxcroft and Milne, 2000[309]. See O'Meara *et al*., 2001[25] for all other information						
Lamotte *et al*., 2002[313] **Intervention**: orlistat in type 2 diabetic patients **Economic evaluation type**: cost–utility analysis **Country and currency**: Belgium, 2000 euros	**Intervention**: 2-year treatment with orlistat with diet vs placebo with diet in 4 types of obese diabetic patients: no other conditions, hypercholesterolaemia, AHT, both conditions **Outcomes**: main outcome was life-years gained. Three clinical factors were assessed to determine changes in morbidity and mortality: reduction in HbA_{1c}, LDL cholesterol and DBP (no significant reduction found)	**Efficacy data**: Hollander *et al*., 1998[33]; Clark, 1998[333]; Koskinen *et al*., 1992[334]; UKPDS 24, 1998[88] **Mortality and morbidity**: UKPDS 38, 1998[334]	10-year Markov model with 6-month periods (20 periods total). Model assumed no complications at time of entry and that weight lost was fully regained by year 7 Costs were discounted by 3% per year. Effects were not discounted except as a sensitivity analysis Assumed (based on Hollander)[33,34] that 4.2% could stop oral antidiabetics and an additional 10.1% reduced medication by 24.8% Perspective was that of the healthcare consumer	**Costs (in year 2000 euros)**: orlistat: €881/year, metformin: €119/year 1998 euro healthcare costs by patient group: €1726 if no other conditions, €2578 if hypercholesterolaemia, €3844 if AHT, €5443 if both **Effects (life-years gained) by patient group**: 0.08 if no other conditions, 0.204 if hypercholesterolaemia, 0.227 if AHT, 0.474 if both **ICER (euros per life-year gained) by patient group**: €19,986 if no other conditions, €7,407 if hypercholesterolaemia, €7,388 if AHT, €3,462 if both	Discounting effects by 3% increased the ICER to €23,522 for the no other conditions group and to €4062 for patients with both other conditions Reducing the catch-up period to regain weight to 2.5 years increased the ICER to €26,527 for the no complications group and to €4565 for patients with both complications Effects of variation in the effect of orlistat on HbA_{1c} are provided Effects of 50% reduction in effect of orlistat on LDL cholesterol are provided	The authors note that they are not able to predict the independent effect of weight loss on the incidence of complications and death. Instead, they use the effect of weight loss on risk factors and then estimate the effect of risk factors on morbidity and mortality, i.e. assuming that improving risk factors reduces the number of complications While the model does assume that all weight is regained in 7 years, the model seems to assume that the benefits from the initial weight loss accrue for a full 7 years. In other words, the beneficial effect of orlistat on the risk factors appears to persist for 7 years in the model

Appendix 31

Data extraction table for economic evaluations: sibutramine

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
BASF Pharma/Knoll 2000, company submission. See O'Meara *et al*. 2002[26] for all other information						

Appendix 32

Data extraction table for economic evaluations: metformin

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Clarke *et al.*, 2001[87] **Intervention**: metformin in type 2 diabetic participants > 120% of IBW or approx. 25.6 kg/m^2 BMI **Economic evaluation type**: cost-effectiveness analysis **Country and currency**: UK, 1997 £	**Intervention**: 342 overweight participants were treated with an intensive blood glucose control policy with metformin, while 411 overweight patients were treated primarily with diet alone **Outcomes**: years of life gained (due to lack of reliable estimates of utility associated with different diabetes-related states)	**Efficacy data**: UKPDS **Cost data**: primary data collection of metformin dose, all other drugs used for treating diabetes or other conditions, and hospital admissions. Cross-sectional survey was used for non-inpatient healthcare resource use (home care and clinic visits or telephone calls to all providers) which was costed using national unit cost estimates	Simulation model used to estimate gains in life expectancy. Median follow-up 10.7 years. Identical hazard rates assumed beyond the trial period. Bootstrapping used to incorporate uncertainty Tobit and Poisson estimation models used to predict resource use for sensitivity analysis due to 17% non-users Estimates used non-discounted component costs as well as costs discounted at 3 and 6%. Outcomes were also discounted at 3 and 6% **Study perspective**: healthcare purchaser, so focus was on direct costs only	**Costs**: there was an estimated reduction in discounted total treatment costs since the reduced cost of complications more than offset the increased drug treatments costs. With costs discounted at 6%, the estimated cost saving was £258, but was not statistically significant (95% CI –£1171 to £655) **Outcomes**: the estimated increase in life-years from metformin was 1.0 years (0.0 to 2.1 years). Discounted at 3%, this became 0.6 years (0.0 to 1.2 years) **ICER**: metformin is cost saving at mean differences in costs and effects	Exclusion of 3 outliers did not make the estimated cost saving statistically significant An acceptability curve (discounting both costs and effects at 6%) showed there is a 71% chance that metformin is cost-saving and a 95% chance that the cost-effectiveness is < £1600 per life-year gained Other sensitivity analyses assumed a 50% increase in costs under metformin treatment (ICER = £948), a 50% decrease in costs (cost savings of £942) and doubling of costs of metformin itself (cost saving of £106). Results were robust for Tobit or Poisson estimation	Authors conclude that "cost savings are largely due to the lower hospital in-patient costs incurred secondary to the major reduction in the risk of myocardial infarction for patients on metformin", but indicate that they are not sure of the mechanism that leads to this result They postulate there are likely reductions in indirect costs and increases in intangible benefits not measured in their study

Appendix 33

Data extraction table for economic evaluations: surgery

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Martin *et al*., 1995[314]. See Clegg *et al*., 2002[27] for all other information van Gemert *et al*., 1999[317]. See Clegg *et al*., 2002[27] for all other information Chua *et al*., 1995[319]. See Clegg *et al*., 2002[27] for all other information Sjostrom *et al*., 1995[315]. See Clegg *et al*., 2002[27] for all other information						
Clegg *et al*., 2002[27] **Intervention**: three types of surgery vs conventional non-surgical treatment **Economic evaluation type**: cost–utility analysis **Country and currency**: UK, 2000 £	**Intervention**: gastric bypass, VBG and adjustable gastric banding vs conventional treatment **Outcomes**: QALYs based on estimates from literature and work by group. No adjustments made for differential effects on postoperative length of life	**Efficacy data**: systematic review. 36% weight loss for bypass, initial 25% loss followed by 2 percentage point gain per year for 5 years for VBG, initial 20% loss increasing to 33% loss by year 5 for adjustable gastric banding **Mortality and morbidity**: systematic review **QALY data**: authors' work **Cost data**: systematic review	20-year model for baseline cohort of 100 people. The cohort had an average age of 40 years and 90% were female. Average body weight was 135 kg (BMI = 45 kgm^2) Only postoperative deaths are included. Differences in the incidence in diabetes are incorporated into the model but do not affect mortality Costs and outcomes are both discounted at 6% for the base-case results The perspective is that of the health service provider. Productivity losses are not included	The cost per additional QALY through surgery rather than conventional treatment was £10,237 for VBG, £8527 for adjustable gastric banding, and £6289 for Roux-en-Y gastric bypass Adjustable gastric banding had the highest costs and a tiny improvement in QALYs over gastric bypass, so gastric bypass is preferred to adjustable gastric banding on cost per QALY grounds The cost per additional QALY from gastric bypass rather than VBG was £742	Sensitivity analyses were conducted on a range of factors pertaining to procedure costs and effects: increase in hospital length of stay, surgery cost increases, use of effectiveness rather than efficacy data, non-surgical assumptions, surgeon experience and cost of diabetes. The results from these analyses indicated that surgery was a cost-effective alternative to non-surgical management, although the estimate of the cost per additional QALY varied somewhat	The authors conclude that surgical rather than non-surgical treatment may be cost-effective for society. In the discussion, they qualify the effects of some of their assumptions. However, some of the assumptions are conservative, e.g. ignoring effects on life expectancy from reduced weight or reduced secondary disease, or the discounting of QALYs at 6%
Segal *et al*., 1998[316]: see page 437 in Appendix 34 for a review of this study.						

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Nguyen *et al.*, 2001[310] **Intervention**: laparoscopic vs open gastric bypass **Economic evaluation type**: cost–utility analysis **Country and currency**: USA, 1999 to 2001 US$	**Intervention**: from May 1999 to March 2001, 155 patients with BMI of 40–60 kg/m^2 were randomly assigned to undergo laparascopic or open gastric bypass **Outcomes**: postoperative anastomotic leak, wound-related complications, late anastomotic stricture and weight loss at 1 year. Also measured resource use during hospitalisation, time to return to activities of daily living, and QoL as measured by SF-36 scores and BAROS outcome	**Efficacy data**: trial data **Quality of life data**: postsurgery surveys using established measures **Cost data**: patient records of hospital data. Costs were estimated using the University of California, Davis, Medical Center's decision support system database. No information about determination of indirect costs was provided	**Methods**: the analysis was on an ITT basis (laparoscopic operations that were converted to open gastric bypass were analysed as laparoscopic) The method of measuring indirect costs was not indicated, although presumably it was calculated based on questions pertaining to time to return to work Discounting was not used, as the maximum follow-up period was 1 year. The year of the cost data is not clearly indicated, and it seems likely that costs may not be adjusted for inflation **Study perspective**: social, due to inclusion of direct health service costs as well as indirect costs due to lost productivity	**Costs**: laparoscopic surgery had higher operating costs but lower length of hospital stay. There were no significant differences in direct health service costs, indirect or total costs **Outcomes**: the total rate of major, minor and late complications did not vary between the treatments. Mean percentage of excess body weight lost was significantly greater at 1-year follow-up for laparoscopic patients at interim points (e.g. during the first and third months after surgery), but was not significantly different at 1 year following surgery **ICER**: incremental cost-effectiveness calculations were not provided. Costs were not significantly different, and the laparoscopic procedure resulted in significantly greater weight loss as well as some benefit in QoL measures during the recovery period	Although statistical tests were conducted for all comparisons in costs and outcome measures, no sensitivity analyses were conducted about any of the assumptions	Although the number of major complications was not statistically different between the two procedures, it is notable that laparascopic gastric bypass resulted in fewer intensive care unit stays, shorter hospital stays, faster recoveries and an earlier return to work than did open surgery. No effort was made to determine the implication of these differences on QALYs, and the measured QoL differences disappeared by the end of the year

SF-36, Short Form 36; BAROS, Bariatic Analysis and Reporting Outcome System.

Appendix 34

Data extraction table for economic evaluations: lifestyle interventions

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Johannesson *et al*., 1992[318] **Intervention**: diet vs drug treatment for hypertension in obese men **Economic evaluation type**: cost-effectiveness analysis and cost–benefit analysis **Country and currency**: Sweden, 1992 Swedish crowns (SEK)	**Interventions**: the drug intervention was a stepped-care approach with atenolol as the drug of first choice; diet. 64 men were randomised and 61 completed the study. Follow-up was for 1 year **Outcome**: life-years saved	**Efficacy data**: measurements on trial patients and data from Framingham study for stroke and coronary disease risk factors **Cost data**: costs included treatment costs minus saved costs of cardiovascular morbidity. Indirect costs were included	**Methods**: used a computer simulation model based on the Framingham logistic risk equations for stroke and CHD. Due to study design, it was not possible to base the cost-effectiveness analysis upon observed risk reduction, so a simulation approach was used. Five simulations were carried out based on a 54-year-old man at entry. LDL cholesterol and triglycerides were not included since it is uncertain whether these risk factors affect the risk for CVD after taking account of the changes in total cholesterol and HDL cholesterol Costs were discounted at 5%. Outcomes were only discounted as part of the sensitivity analysis **Study perspective**: societal perspective, as direct and indirect costs were included	**Costs**: total treatment cost was approximately SEK 8300 for the diet group and SEK 7900 for the drug treatment group **Outcomes**: after 1 year, the diet group lost 7.6 ± SD 3.1 kg while the drug group gained 0.9 ± SD 2.3 kg. DBP and HDL cholesterol had both decreased significantly in drug group relative to diet group **ICER**: in 3 simulations the drug treatment was cost saving, with greater effect at lower total cost. In 2 simulations the diet treatment was cost-effective. Both of these simulations had the same change in (expected or half of expected) for DBP and total cholesterol, and HDL changes led to a reduced risk of CHD. ICER for additional life-year saved from diet vs drug ranged from 46 to 205 K Swedish crowns	Sensitivity analyses were performed using only direct costs and alternative discounting approaches In a cost–benefit analysis, it was indicated that both treatments resulted in a loss compared with no treatment, but that the difference between the treatments was negligible	The authors conclude that non-pharmacological treatment may be less cost-effective than drug treatment, but that more studies and further methodological development are needed

continued

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Kaplan *et al*., 1987[178] Kaplan *et al*., 1988[311] **Intervention**: diet and behaviour therapy, exercise and behaviour therapy, diet and exercise and behaviour therapy, or control education about diabetes **Economic evaluation type**: cost-utility analysis **Country and currency**: USA, 1986 $	**Intervention**: 76 obese non-insulin dependent diabetics were randomised to the four treatment groups. Each group received 10 weekly education sessions about techniques related to the intervention. The diet was an exchange diet (1200 calories per day). Exercise recommendations were based on a graded exercise test **Outcomes**: paper reports on HbA_{1c}, weight, and quality of life at 18 months follow-up. Quality of life was measured using the quality of well-being scale	**Efficacy data**: data were collected at 3, 6, 12, and 18 months following baseline **Cost data**: estimated using 1986 clinical charges in the San Diego community. Treatment costs include charges for history and physical, laboratory work, sessions, and medical consultations. Indirect costs were not considered	**Methods**: change scores were used (i.e., measure at follow-up minus measure at baseline) using the method of planned comparison. (It is not clear if this means by intention to treat.) 6 patients dropped out. Aside from intervention treatment costs, the only other health service use that was tracked was medication use Costs and effects were not discounted **Study perspective**: health care purchaser (direct health service costs)	**Costs**: the costs of the diet and exercise and behaviour therapy programme were estimated at US$1000 – changes in medication use were not significantly different between the group **Effects**: diet and behaviour therapy group lost the most weight, but all lost, weight among all groups was regained by the 18 month follow-up – reduction in HbA1c at 18 months was greatest for the combined diet and exercise and behaviour therapy group ($p < 0.10$) – the increase in QALY for diet and exercise and behaviour therapy versus control education at 18 months was 0.092 ($p < 0.05$) – the diet and behaviour therapy group also had a statistically significant improvement of 0.07 units in quality of well-being **ICER**: US$10,870 per well life year	No formal sensitivity analyses of the assumptions were conducted in Kaplan 1987 With respect to changes in the quality of life, the study did report that in "planned comparisons" the combined treatment group and the diet and behaviour therapy group improvements in quality of life were significantly greater than the control group improvements Kaplan 1988 conducted a sensitivity analysis according to effectiveness of intervention and duration of benefit and found a range of estimates from US$4,503 to US$18,011 per additional well year of life	The authors conclude that benefits in terms of quality of life and HbA_{1c} appear to be independent of weight loss Small sample of self-referred individuals may limit generalisability. But analysis is conservative in that it assumes that benefits do not extend beyond 18 month follow-up and if anything the control group may have had higher other health care costs due to lack of improvement in HbA_{1c}

continued

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Salkeld *et al*., 1997[312] **Intervention**: two lifestyle interventions administered in general practice **Economic evaluation type**: cost–utility analysis **Country and currency**: Australia, 1994 Aus$	**Interventions**: 2 interventions (a video and a video plus written self-help materials) were compared with routine care in general practice. 755 participants were recruited to the study if they had one or more of a set of cardiovascular risk factors (total cholesterol, BMI $> 25\ kg/m^2$, current smoker, elevated BP). Average BMI was $30\ kg/m^2$ **Outcomes**: life-years saved and QALYs gained	**Efficacy data**: trial data were collected during 1990 and 1991 Effectiveness data related to mortality risk after an MI or stroke and QoL after CHD were from published and unpublished studies in 1994 and 1995 **Cost data**: estimated costs of interventions, including estimated changes in pharmaceutical use. Costs of treating CHD events were based on data for MI patients from the Australian GUSTO trial. Indirect costs related to production losses were also obtained from the GUSTO trial	**Methods**: the economic evaluation used a computer simulation model based on risk equations for CHD and stroke from the Framingham heart study. Lifetime costs and effects of the intervention are modelled Costs and benefits were discounted at 5% per year **Study perspective**: societal perspective	**Costs**: total discounted (net?) lifetime costs are indicated to be Aus$286 and Aus$322 for males and females in the video plus self-help group, and Aus$107 for males in the high-risk group **Outcomes**: the full study sample had no benefit in life-years saved or QALYs in the video group, and a negligible improvement in the video plus self-help group. A subgroup of high-risk individuals (DBP >95 mmHg or total cholesterol >6.5 mmol/l) had negligible improvement among males from the video **ICER**: negligible improvements in outcomes made ICERs very high: Aus$152,128 per QALY for males from video, >Aus$11 million for females from video plus self-help, Aus$29,574 per QALY for high-risk males from video	Sensitivity analyses were performed on estimated costs of productivity losses and on maintenance of behaviour change through time The authors found that eliminating the productivity losses added Aus$11,000 per life-year saved or Aus$9,000 per QALY, so it lowered the cost-effectiveness only by a small amount. The second sensitivity analysis assuming that the changes in risk factors persisted for 2 years improved the cost-effectiveness considerably from the video for high-risk males, to an ICER of Aus$5,789 per life-year saved and Aus$4,342 per additional QALY	Possible mistake in Table 4. How can gain in QALYs for males be greater than gain in life expectancy for males from video? Follow-up time was very short, and authors stressed that long-term follow-up was necessary to reduce uncertainty of results. However, without reinforcement it is unlikely that cost-effectiveness could improve Subgroup analysis using data for just obese participants was not performed but would have been relevant for this report. However, average baseline BMI was high

continued

Author, year, intervention/ evaluation type, country	Intervention and outcomes	Sources of data	Methods and study perspective	Results	Sensitivity analyses	Additional comments
Segal *et al*., 1998[316] **Intervention**: range of interventions for primary prevention of type 2 diabetes **Economic evaluation type**: cost-effectiveness analysis **Country and currency**: Australia, 1997 Aus$	**Interventions**: (I) intensive diet and behavioural modification targeted towards all seriously obese; (II) intensive diet and behavioural modification for women with previous gestational diabetes; (III) gastric bypass surgery for seriously obese; (IV) group behavioural modification for overweight and obese men; (V) GP advice for high-risk adults (e.g. BMI > 27 kg/m^2); (VI) media campaign with community support targeted at general population and overweight adults Comparison was with no intervention (NGT or standard care with IGT) **Outcomes**: reduction in diabetes years, and life-years saved	**Efficacy data**: non-systematic review of the literature, with a preference for RCTs with at least 5 years of follow-up, recorded impact on weight and diabetes status, and opinion of research team where evidence was lacking **Prevalence, morbidity and mortality data**: non-systematic review of the literature **Cost data**: intervention costs were constructed by determining programme resources and then applying unit costs, except for the group programme for overweight men, which was measured as the cost of a commercial programme. Health service use costs for management of diabetes were measured using an Australian survey of hospital costs and the Commonwealth Medical Benefits Schedule. Media effort costed for a region of 4 million people	**Methods**: a Markov approach was used to model diabetic state and survival for a 25-year postintervention period. Specific states were normal glucose tolerance, impaired glucose tolerance or NIDDM Data on 5-year transition probabilities between states, annual mortality for men adjusted for metabolic state, and annual mortality for men adjusted for overweight were used Key parameters are provided, including % successful under each intervention, reduced incidence of NIDDM, and mortality relative risk Costs and benefits were discounted at 5% Results are provided for mixed population (NGT and IGT) and IGT only **Study perspective**: healthcare purchaser	**Programme costs**: (I) AUS$2500; (II) AUS$2500; (III) AUS$15,580; (IV) AUS$195 + screening cost of AUS$382 per case found; (V) AUS$420 + screening cost of AUS$53; (VI) AUS$2 million for community of 4.5 million people Downstream cost savings for people who do not develop NIDDM were estimated at Aus$1800/year **Outcomes**: surgery for the seriously obese reduced diabetes years the most and saved the most life-years **ICER (base case)**: group behavioural therapy and media campaign for the general public had cost savings. The diet, behavioural and GP programmes had ICERs of Aus$1000–2600. Surgery for severely obese had an ICER of Aus$12,300 unless targeted to IGT patients (ICER = Aus$4600)	Sensitivity analyses were conducted on the programme effectiveness parameter for all interventions. While the estimated ICER fluctuated or changed to reflect cost savings in some cases, the greatest change in the ICER was about a 50% increase Additional sensitivity analyses were also conducted for the behavioural modification programme for the seriously obese. These included variation in the discount rate, programme cost, effect of success on incidence of NIDDM, life expectancy and baseline risk status	In the effectiveness results, no consistent relationship between reduction in diabetes life-years and life-years gained is observed; the authors speculate that this is because life-years gained reflects all-cause mortality as a function of obesity as well as diabetic state, and average excess weight and success vary across the programmes The authors make the very useful point that the population at risk of type 2 diabetes often does not have access to the level of resources available to treat type 2 diabetes The authors maintain that the level of downstream health savings is an underestimate because some costs to diabetics as well as costs of other diseases caused by obesity have not been included

continued

Appendix 35

Quality assessment table for economic evaluations: pharmacological interventions

Intervention	Orlistat	Orlistat	Sibutramine	Metformin
Economic evaluation: first author and year	Foxcroft, 1999[308]	Lamotte, 2002[312]	BASF Pharma/ Knoll, 2000	Clarke, 2001[87]
Systematic review assessing quality (if applicable)	O'Meara, 2001[25]	NA	O'Meara, 2002[26]	NA
Quality component				
Well-defined question	Yes	Yes	Yes	Yes
Comprehensive description of alternatives	Yes	Not clear	Yes	Yes
Effectiveness established	Yes	Yes	Not clear	Yes
Relevant costs and consequences identified	Yes	Yes	Yes	Yes
Costs and consequences measured accurately	Yes	Yes	Yes	Yes
Costs and consequences valued credibly	Yes	Yes	Yes	Yes
Costs and consequences adjusted for differential timing	No	Yes	Yes	Yes
Incremental analysis of costs and consequences	Yes	Yes	No	Yes
Allowance made for uncertainty in estimates of costs and consequences	Yes	Yes	Yes	Yes
Results/discussion included all issues of concern to users	Yes	Yes	Yes	Yes

Appendix 36

Quality assessment table for economic evaluations: surgical intervention for obese or morbidly obese patients

Intervention	Roux-en-Y gastric bypass vs VLCD	VBG vs no treatment	Laparoscopic VBG vs open gastric bypass	Gastric banding vs VBG vs open gastric bypass vs conventional treatment	Gastric bypass, VBG, adjustable gastric banding and non-surgical treatment	Laparoscopic vs open gastric bypass
Economic evaluation: first author and year	Martin, 1995[314]	van Gemert, 1999[317]	Chua, 1995[319]	Sjostrom, 1995[315]	Clegg, 2002[27]	Nguyen, 2001[310]
Systematic review assessing quality (if applicable)	Clegg, 2002[27]	Clegg, 2002[27]	Clegg, 2002[27]	Clegg, 2002[27]	NA	NA
Quality component						
Well-defined question	Yes	Yes	Yes	Yes	Yes	Yes
Comprehensive description of alternatives	Yes	Yes	Yes	Yes	Yes except non-surgical	Yes
Effectiveness established	Yes	Yes	Yes	Yes	Yes	Yes
Relevant costs and consequences identified	No	No	No	No	Yes	Partial
Costs and consequences measured accurately	Yes (where measured)	Yes (where measured)	Yes (where measured)	Yes (where measured)	Yes	Yes (where measured)
Costs and consequences valued credibly	Yes (direct costs)	Yes (direct costs)	Yes (direct costs)	Yes (direct costs)	Yes	Partial
Costs and consequences adjusted for differential timing	No	Yes	No	No	Yes	NA
Incremental analysis of costs and consequences	No	Yes	No	No	Yes	No
Allowance made for uncertainty in estimates of costs and consequences	No	No	No	No	Yes	Yes
Results/discussion included all issues of concern to users	Unclear	Unclear	Unclear	Unclear	Yes	Yes

The study by Segal and colleagues[316] that included surgery is assessed in Appendix 34.

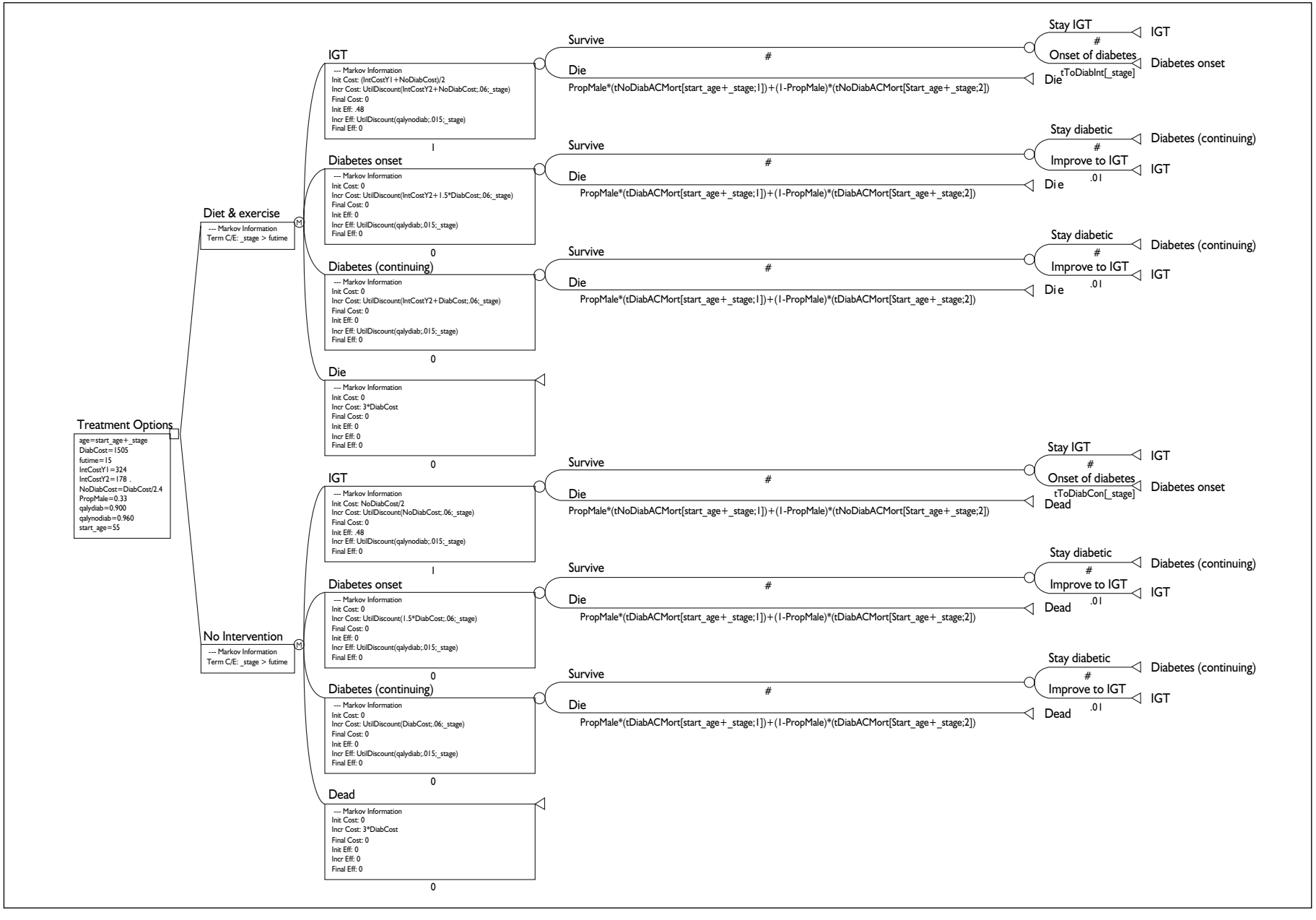
Appendix 37

Quality assessment table for economic evaluations: lifestyle interventions

Intervention	**Diet and behaviour therapy, exercise and behaviour therapy, diet and exercise and behaviour therapy, vs education on diabetes**	**Diet vs drug (atenolol) treatment for hypertension in obese men**	**Video and video plus self-help materials vs nothing for general practice patients at high risk of CVD**	**Six interventions involving diet, behavioural modification and surgery**
Economic evaluation: first author and year	Kaplan, 1987[178] Kaplan, 1988[311]	Johannesson, 1992[318]	Salkeld, 1997[312]	Segal, 1998[316]
Systematic review assessing quality (if applicable)	NA	NA	NA	NA
Quality component				
Well-defined question	Yes	Yes	Yes	Yes
Comprehensive description of alternatives	Yes	Yes	Yes	Yes
Effectiveness established	Yes	Limited	Limited	Not clear
Relevant costs and consequences identified	Partial	Yes	Yes	Not clear
Costs and consequences measured accurately	Yes (where measured)	Yes	Yes	Not clear
Costs and consequences valued credibly	Yes	Yes	Yes	Yes
Costs and consequences adjusted for differential timing	No	Yes	Yes	Yes
Incremental analysis of costs and consequences	Yes	Yes	Yes	Yes
Allowance made for uncertainty in estimates of costs and consequences	Partial	Partial	Partial	Yes
Results/discussion included all issues of concern to users	Yes	Yes	Yes	Yes

Appendix 38

DATA 4.0 tree for base-case Markov model


Treatment Options
age=start_age+_stage
DiabCost=1505
futime=15
IntCostY1=324
IntCostY2=178 .
NoDiabCost=DiabCost/2.4
PropMale=0.33
qalydiab=0.900
qalynodiab=0.960
start_age=55
Diet & exercise
--- Markov Information
Term C/E: _stage > futime
No Intervention
--- Markov Information
Term C/E: _stage > futime
IGT
--- Markov Information
Init Cost: (IntCostY1+NoDiabCost)/2
Incr Cost: UtilDiscount(IntCostY2+NoDiabCost,.06;_stage)
Final Cost: 0
Init Eff: .48
Incr Eff: UtilDiscount(qalynodiab,.015;_stage)
Final Eff: 0
1
Diabetes onset
--- Markov Information
Init Cost: 0
Incr Cost: UtilDiscount(IntCostY2+1.5*DiabCost,.06;_stage)
Final Cost: 0
Init Eff: 0
Incr Eff: UtilDiscount(qalydiab,.015;_stage)
Final Eff: 0
0
Diabetes (continuing)
--- Markov Information
Init Cost: 0
Incr Cost: UtilDiscount(IntCostY2+DiabCost,.06;_stage)
Final Cost: 0
Init Eff: 0
Incr Eff: UtilDiscount(qalydiab,.015;_stage)
Final Eff: 0
0
Die
--- Markov Information
Init Cost: 0
Incr Cost: 3*DiabCost
Final Cost: 0
Init Eff: 0
Incr Eff: 0
Final Eff: 0
0
IGT
--- Markov Information
Init Cost: NoDiabCost/2
Incr Cost: UtilDiscount(NoDiabCost,.06;_stage)
Final Cost: 0
Init Eff: .48
Incr Eff: UtilDiscount(qalynodiab,.015;_stage)
Final Eff: 0
1
Diabetes onset
--- Markov Information
Init Cost: 0
Incr Cost: UtilDiscount(1.5*DiabCost,.06;_stage)
Final Cost: 0
Init Eff: 0
Incr Eff: UtilDiscount(qalydiab,.015;_stage)
Final Eff: 0
0
Diabetes (continuing)
--- Markov Information
Init Cost: 0
Incr Cost: UtilDiscount(DiabCost,.06;_stage)
Final Cost: 0
Init Eff: 0
Incr Eff: UtilDiscount(qalydiab,.015;_stage)
Final Eff: 0
0
Dead
--- Markov Information
Init Cost: 0
Incr Cost: 3*DiabCost
Final Cost: 0
Init Eff: 0
Incr Eff: 0
Final Eff: 0
0
Survive
#
Die
PropMale*(tNoDiabACMort[start_age+_stage;1])+(1-PropMale)*(tNoDiabACMort[Start_age+_stage;2])
Stay IGT
#
Onset of diabetes
tToDiabInt[_stage]
IGT
Diabetes onset
Die
Survive
#
Die
PropMale*(tDiabACMort[start_age+_stage;1])+(1-PropMale)*(tDiabACMort[Start_age+_stage;2])
Stay diabetic
#
Improve to IGT
.01
Diabetes (continuing)
IGT
Die
Survive
#
Die
PropMale*(tDiabACMort[start_age+_stage;1])+(1-PropMale)*(tDiabACMort[Start_age+_stage;2])
Stay diabetic
#
Improve to IGT
.01
Diabetes (continuing)
IGT
Die
Survive
#
Die
PropMale*(tNoDiabACMort[start_age+_stage;1])+(1-PropMale)*(tNoDiabACMort[Start_age+_stage;2])
Stay IGT
#
Onset of diabetes
tToDiabCon[_stage]
IGT
Diabetes onset
Dead
Survive
#
Die
PropMale*(tDiabACMort[start_age+_stage;1])+(1-PropMale)*(tDiabACMort[Start_age+_stage;2])
Stay diabetic
#
Improve to IGT
.01
Diabetes (continuing)
IGT
Dead
Survive
#
Die
PropMale*(tDiabACMort[start_age+_stage;1])+(1-PropMale)*(tDiabACMort[Start_age+_stage;2])
Stay diabetic
#
Improve to IGT
.01
Diabetes (continuing)
IGT
Dead

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We look forward to hearing from you.

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