Health Technology Assessment 2012; Vol. 16: No. 5
ISSN 1366-5278

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February 2012
10.3310/hta16050

Health Technology Assessment
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R Ara,[1*] L Blake,[1] L Gray,[2] M Hernández,[1] M Crowther,[2] A Dunkley,[2] F Warren,[2] R Jackson,[1] A Rees,[1] M Stevenson,[1] K Abrams,[2] N Cooper,[2] M Davies,[2] K Khunti[2] and A Sutton[2]

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Declared competing interests of authors: KK has received funds for research or acted on advisory boards for Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. MJD has received funds for research and honoraria for speaking at meetings and has served on advisory boards for Eli Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

Published February 2012
DOI: 10.3310/hta16050

This report should be referenced as follows:

Ara R, Blake L, Gray L, Hernández M, Crowther M, Dunkley A, *et al*. What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review. *Health Technol Assess* 2012;**16**(5).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/85/02. The contractual start date was in January 2009. The draft report began editorial review in February 2011 and was accepted for publication in June 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review

R Ara,[1]* L Blake,[1] L Gray,[2] M Hernández,[1] M Crowther,[2] A Dunkley,[2] F Warren,[2] R Jackson,[1] A Rees,[1] M Stevenson,[1] K Abrams,[2] N Cooper,[2] M Davies,[2] K Khunti[2] and A Sutton[2]

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Background: Obesity [defined as a body mass index (BMI) ≥ 30 kg/m^2] represents a considerable public health problem and is associated with a significant range of comorbidities and an increased mortality risk. The primary aim of the management of obesity is to achieve weight reduction in the interests of health. For obese patients who cannot achieve or maintain a healthy weight by non-pharmacological means, drug therapy is recommended in combination with non-pharmacological interventions such as dietary modifications and exercise.

Objective: To evaluate the clinical effectiveness and cost-effectiveness of three pharmacological interventions in obese patients.

Data sources: Clinical effectiveness data used in the meta-analysis were sourced from articles identified in a systematic review of the literature. Data used to inform transitions to obesity-related comorbidities were derived from the General Practice Research Database (GPRD). The results of the meta-analysis and GPRD analyses informed the economic model supplemented by data from the Health Survey for England and other UK-specific data sourced from the literature.

Review methods: A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of orlistat, sibutramine and rimonabant within their licensed indications for the treatment of obese patients. Electronic bibliographic databases including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched in January 2009, and the reference lists of relevant articles were checked. Studies were included if they compared orlistat, sibutramine or rimonabant with lifestyle and/or exercise advice (standard care), placebo or metformin.

Results: Overall, 94 studies involving 24,808 individuals were included in the clinical meta-analysis. Eighty-three trials included data on weight change, 41 included data on BMI change and 45 and 36 studies reported on 5% and 10% body weight loss, respectively. Overall, the results show that the active drug interventions are all effective at reducing weight and BMI compared with placebo. In the case of sibutramine, the higher dose (15 mg) resulted in a greater reduction than the lower dose (10 mg). Generally, the data quality of the trials included was low with poor reporting of standard errors and standard deviations. Results from the BMI risk models derived from the GPRD showed consistent

increases in risk with increasing BMI. Adjustments for key confounders, such as age, sex and smoking status, were found to be statistically significant at the 5% level, in all risk models. Applying linear models to estimate BMI trajectories, for the diabetic cohort, an average increase in BMI of 0.040 per year for both men and women was observed. The non-diabetic cohort model showed an increase in BMI of 0.175 per year for women and 0.145 per year for men. The results of the cost-effectiveness analyses suggest that sibutramine 15 mg dominates the other three active interventions and the net benefit analyses show that sibutramine 15 mg is the most cost-effective alternative for thresholds > £2000 per quality-adjusted life-year (QALY). However, both sibutramine and rimonabant have been withdrawn because of safety concerns relating to potential treatment-induced fatal adverse events. If the proportion of patients who experienced a fatal adverse event was > 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant) the treatment would not be considered cost-effective when using a threshold of £20,000 per QALY.

Limitations: The clinical review did not include all possible lifestyle comparators, with the inclusion limited to only those trials included one of the active drug interventions. We also excluded all studies not reported in English. Although the clinical review included data from 94 studies, the quality of data was generally low, particularly in terms of the reporting of standard deviation. There was also inconsistency between the results of the mixed-treatment comparison (MTC) and the pair-wise analyses.

Conclusion: The MTC of anti-obesity treatments shows that all the active treatments are effective at reducing weight and BMI. The economic results show that, compared with placebo, the treatments are all cost-effective when using a threshold of £20,000 per QALY, and, within the limitations of the data available, sibutramine 15 mg dominates the other three interventions. This work has highlighted many areas of methodological research that could be explored, including assessing inconsistencies within a network to determine differences between the results of pair-wise and MTC analyses; the use of meta-regression methods to look for effect modifiers; exploring the effect of local publication bias; and the use of joint models to analyse the repeated measures of BMI and the time-to-event processes simultaneously.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Dominated (simple) When an intervention is less effective and more expensive than its comparator.

Dominated (extended) When the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective comparator.

Meta-analysis A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.

Odds ratio The ratio of the odds of an event occurring in one group to the odds of it occurring in another group.

Posterior distribution A representation of the knowledge associated with the true value of a population parameter after combining the prior distribution with sample data.

Prior distribution A representation of the knowledge associated with the true value of a population parameter in addition to any sample data.

Relative risk Ratio of the probability of an event occurring in an exposed group relative to the probability of it occurring in a non-exposed or control group.

Variance–covariance matrix The variance for a variable is a measure of the dispersion or spread of scores. Covariance indicates how two variables vary together. The variance–covariance matrix presents the variances on the diagonal and the covariances above or below the diagonal.

List of abbreviations

ACM	all-cause mortality
ACMM	adjusted censored mixture model
BMI	body mass index
BNF	*British National Formulary*
BP	blood pressure
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
CrI	credible interval
CVD	cardiovascular disease
EQ-5D	European Quality of Life-5 Dimensions
GP	general practitioner
GPRD	General Practice Research Database
HRQoL	health-related quality of life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
LOCF	last observation carried forward
MAE	mean absolute error
MI	myocardial infarction
MTC	mixed-treatment comparison
NIC	net ingredient cost
NICE	National Institute for Health and Clinical Excellence
OR	odds ratio
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RMSE	root mean squared error
SCOUT	Sibutramine Cardiovascular Outcomes Trial
SD	standard deviation
SPC	Summary of Product Characteristics
T2DM	type 2 diabetes
TIA	transient ischaemic attack
VAS	visual analogue scale
WHO	World Health Organization

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 in the notes at the end of the table.

Executive summary

Background

Obesity [defined as a body mass index (BMI) ≥ 30 kg/m^2] represents a considerable public health problem and the prevalence of obesity in England is reported to have increased between 1993 and 2004 from 13.6% to 24.0% among men and from 16.9% to 24.4% among women. It has been projected that 40% of Britons may be classed as obese by 2025. Overweight and obesity are associated with a significant range of comorbidities and are linked with increases in mortality.

The primary aim of the management of obesity is to achieve weight reduction in the interests of health. For obese patients who cannot achieve or maintain a healthy weight by non-pharmacological means, drug therapy is recommended in combination with non-pharmacological interventions such as dietary modifications and exercise.

Objectives

The objective of this research was to evaluate the clinical effectiveness and cost-effectiveness of pharmacological interventions compared with each other and with standard care in obese patients in primary care. Specific objectives included to analyse an existing database of clinical information from primary care; conduct a full systematic review of the published evidence on the clinical effectiveness of orlistat (Xenical®, Roche; Alli®, GlaxoSmithKline), sibutramine (Reductil®, Abbott) and rimonabant (Acomplia®, Sanofi-Aventis); undertake a full synthesis of the available evidence including the use of network meta-analysis; undertake a systematic review of the published evidence of the cost-effectiveness of the agents; use decision-analytic modelling and probabilistic sensitivity analysis to assess the relative cost-effectiveness of the three agents in terms of the incremental cost per quality-adjusted life-year (QALY) gained; and use expected value of information techniques to determine the potential benefits of future head-to-head trials of the agents.

Since the research question was formulated, two of the three pharmacological treatments have been withdrawn for safety reasons. Although the data for all three have been retained in the clinical and economic analyses, the value of information analyses exploring the potential benefits of future head-to-head trials for the agents have not been conducted.

Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of orlistat, sibutramine and rimonabant within their licensed indications for the treatment of obese patients. Electronic bibliographic databases including MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–present), Web of Science and Conference Proceedings Citation Index (1990–present), BIOSIS Previews (1969–present) and Current Controlled Trials were searched in January 2009 and the reference lists of relevant articles were checked. Studies were included if they compared orlistat, sibutramine or rimonabant with lifestyle and/or exercise advice (standard care), placebo or metformin.

All studies were assessed for quality using an extended tool initially developed by Jadad *et al.* [Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12]. Where outcome data were missing measures of precision (such as standard errors), these were derived/imputed using previously established methods. Pair-wise meta-analysis was carried out for each comparison for the outcomes of achieved 5% weight loss, achieved 10% weight loss, weight and BMI at each of three time points (3, 6 and 12 months). Mixed-treatment comparison (MTC) methods were used to compare all treatments investigated within a single model (with placebo used as the reference category throughout). The MTC analysis was conducted using a Bayesian Markov chain Monte Carlo method. A logistic regression model was used for the binary outcomes and a linear regression model for the continuous outcomes.

To appropriately populate the economic decision model described in *Chapter 5,* a UK epidemiological model of the natural history of how changes in BMI affect the risk of major clinical events (development of diabetes, myocardial infarction, stroke and death) is required together with a model of how BMI levels change as a population ages. Longitudinal data from the General Practice Research Database (GPRD) were explored to determine time-to-event outcomes for all-cause mortality, myocardial infarction, stroke and onset of type 2 diabetes mellitus (T2DM). This model of the natural history of how changes in BMI affect the risk of major clinical events was conducted in order to appropriately populate the economic decision model. Subgrouping into cohorts with or without T2DM, Weibull proportional hazards regression models were derived to obtain the estimated hazard of each event of interest. These data were also used to determine the natural trajectory of BMI over time, for cohorts with or without T2DM, using multilevel models adjusted for sex and the interaction between age and sex, with age centred at 45 years.

A cohort simulation model was developed to explore the potential cost-effectiveness of pharmaceutical treatments for obesity. The pharmacological interventions (plus diet and exercise advice) were compared with placebo (plus diet and exercise advice). Effectiveness evidence (changes in BMI) was informed by the results of the MTC analyses. Initial transitions to obesity-related comorbidities and the natural trajectory of BMI over time were informed by the GPRD analyses. Health-related quality-of-life values were modelled using European Quality of Life-5 Dimensions data derived from respondents in the Health Survey for England and all costs were UK specific.

Results

Clinical results

Overall, 94 studies involving 24,808 individuals were included in the clinical meta-analysis. A total of 83 trials included data on weight change, 41 trial data on BMI change and 45 and 36 trial data on 5% and 10% body weight loss, respectively. Generally, the data quality of the trials included was low with poor reporting of standard errors and standard deviations.

Overall, the results show that the active drug interventions are all effective at reducing weight and BMI compared with placebo. In the case of sibutramine, the higher dose (15 mg) resulted in a greater reduction than the lower dose (10 mg). Although data were limited, the combination of orlistat and sibutramine also ranked highly. Interestingly, those interventions that have now been withdrawn from use (sibutramine and rimonabant) seem to be the most effective; however, their effectiveness is outweighed by the increase in adverse events.

General Practice Research Database results

Results from the seven BMI risk models showed consistent increases in risk as a result of an increasing BMI. This pattern was evident across all models except for the diabetic cohort with outcome myocardial infarction, for which a non-statistically significant ($p = 0.838$) reduction in risk was observed. Adjustments for key confounders, such as age, sex and smoking status, were found to be statistically significant at the 5% level, in all seven risk models. More flexible survival models were investigated; however, the added complexity was deemed unnecessary.

A large variation in BMI trajectories was observed. Applying linear trajectory models showed an average increase in BMI of 0.040 per year for the diabetic cohort, for both men and women. The equivalent non-diabetic cohort model showed an increase in BMI of 0.175 per year for women; however, a statistically significant (at the 5% level) interaction between age and sex was observed, resulting in a slightly reduced increase in BMI of 0.145 per year for men. Baseline estimates (age 45 years) of BMI were similar across cohorts.

Economic results

The literature review identified 16 economic evaluations describing the costs and benefits associated with the three interventions. Compared with lifestyle advice, the mean incremental cost-effectiveness ratio for orlistat (sibutramine, rimonabant) ranged between £970 (£6941, £9303) and £59,174 (£10,042, £35,876). Although there was a wide variation in the modelling approaches and evidence used in the studies, the variable reported to have the largest effect on the results in the majority of the models was the period of weight regain modelled. Many of the models were also sensitive to changes in the values used to estimate the quality-of-life benefits attributed to weight changes, and the discount rates used. Only one study directly compared the pharmacological interventions, and the authors reported that rimonabant was cost-effective compared with either orlistat or sibutramine.

With an average cost per QALY of £557 compared with placebo, the results of the deterministic analyses suggest that sibutramine 15 mg dominates (the average costs are lower and the average QALYs are higher) the other three active interventions. The model is robust to variations in the key parameter values tested with the exception of the baseline BMI value. Although the probabilistic results show a larger range of uncertainty in the incremental QALY gain associated with both sibutramine treatments than in the QALY gain associated with orlistat, the net benefit analyses show that sibutramine 15 mg is the most cost-effective alternative for thresholds > £2000 per QALY. However, both sibutramine and rimonabant have been withdrawn because of safety concerns relating to potential treatment-induced fatal adverse events. Assuming that the adverse event occurs while on treatment, if the proportion of patients who experienced a fatal adverse event was greater than 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant) the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

Discussion

This is the first MTC of anti-obesity treatments to have been carried out. It utilises cutting-edge statistical methodology to compare treatments for which no head-to-head trials have been carried out, and hence we also present the first economic evaluation based on this evidence base.

Since the initiation of this project the Sibutramine Cardiovascular Outcomes trial has been published. The weight-loss data from this trial were not included in the MTC analysis as these were not reported for the time points of interest. However, as these data are broadly in line with

our results, their exclusion is unlikely to have changed the conclusions drawn for the effectiveness outcomes considered.

There are several limitations of the analyses presented in this work. The clinical data were poorly or inaccurately reported in many studies, which could have produced inaccuracies in the analyses. Our conservative assumptions, which were made to overcome the limitations of these data, may have underestimated the treatment effects in the MTC analyses. Although we regard the inclusion of the UK-specific data from the GPRD to be a particular strength of this work, the analyses are not without limitations because of (1) considerable inconsistencies in the clinical coding within the GPRD data set and (2) computational issues hindering more complex analyses of the substantial data sets. Finally, we were unable to accurately reflect the potential adverse event rates for sibutramine and rimonabant in the economic model, or present results separately for different subgroups, because of a paucity of effectiveness evidence in these areas.

Both sibutramine and rimonabant were effective medications for obesity management. Since their withdrawal clinicians have been limited to prescription of orlistat for weight reduction and clinicians are awaiting results of a number of new agents currently in the early stages of evaluation.

Conclusions

Currently, orlistat is the only licensed medication for the management of obesity. In clinical practice orlistat should be considered to aid weight reduction along with lifestyle interventions in those individuals who have not been successful in reducing their weight with lifestyle alone.

Our MTC of anti-obesity treatments shows that all of the active treatments are effective at reducing weight and BMI. The economic results show that, compared with placebo, the treatments are all cost-effective when using a threshold of £20,000 per QALY, and, within the limitations of the data available, sibutramine 15 mg dominates the other three interventions. However, if the proportion of patients who experienced a fatal adverse event was greater than 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant), the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

This work has highlighted many areas of methodological research that could be explored, including assessing inconsistencies within a network to determine differences between the results of pair-wise and MTC analyses; the use of meta-regression methods to look for effect modifiers; exploring the effect of local publication bias; and the use of joint models to analyse the repeated measures of BMI and the time-to-event processes simultaneously. From a clinical perspective, a long-term clinical trial for orlistat reporting hard clinical end points (cardiovascular events, onset of T2DM, incidence of cancer) would be particularly informative both from a clinical angle and to inform future economic evaluations. Clinical data from subgroups with high prevalence rates of obesity are also needed. Finally, robust long-term observational data in obese cohorts would be useful to inform the risk models that underpin the economic modelling.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Description of health problem

Prevalence

The increasing prevalence of obesity in the UK represents a considerable public health problem. The prevalence of obesity [defined as a body mass index (BMI) $\geq 30\,kg/m^2$] in England is reported to have increased between 1993 and 2004 from 13.6% to 24.0% among men and from 16.9% to 24.4% among women.[1] When waist circumference was measured in a UK adult primary care sample in 2005, 38.8% of men and 51.2% of women were classed as abdominally obese (waist circumference > 102 cm and > 88 cm, respectively).[2] It has been estimated that, among young people aged 20 years and under in England, 10% of females and 8% of males are obese.[3] Should increases in the prevalence of obesity continue at the same rate, Zaninotto *et al.*[1] predicted that the prevalence of obesity in 2012 would be 32% in men and 31% in women, with a likely higher prevalence among adults in manual social classes (43%) than in non-manual social classes (35%). Projections by the UK government's Foresight programme have postulated that by 2025 40% of Britons may be classed as obese.[3,4]

The World Health Organization (WHO) estimated in 2005 that, internationally, there were over 1.6 billion overweight adults, of whom at least 400 million were obese. They also projected that, by 2015, approximately 2.3 billion adults would be overweight and over 700 million would be obese.[5]

The estimated prevalence of overweight and obesity among male and female adults in 2010 demonstrated considerable differences by geographical region, with several hotspots of prevalence exceeding 80%, including the USA, Barbados, Dominica, Kuwait and the South Pacific islands.[5]

Groups at risk of obesity

A number of population groups are considered at increased risk of obesity. Variation in obesity by ethnic group has been described in a report published by the NHS Information Centre.[6] Data relating to obesity and overweight among ethnic minority groups were drawn from the Health Survey for England (HSE) 2004. The survey applied the definition of overweight and obesity as used in the general population. It was reported that the prevalence of obesity was higher among black Caribbean men and women, black African women, Pakistani women and Irish men than among the general population. Obesity was lower among Chinese, Indian and Bangladeshi men and women than among the general population. Groups at risk of becoming obese also include children with overweight or obese parents[7–9] and individuals giving up smoking.[10] A high prevalence of obesity has been observed in adults and children with intellectual disabilities.[11–13] An association also exists between low socioeconomic status in early life and adult obesity.[9] Data from the HSE 2007 indicated that, among women, the age-standardised prevalence of obesity and raised waist circumference increased as the quintile of equivalised household income decreased, but these measures were not related to income in men.[6]

Aetiology

Previous work by the Foresight group indicated that the energy imbalance that precedes obesity (whereby energy intake exceeds energy expenditure) is governed by what was described as a 'complex multifaceted system of determinants'.[14–16] These factors include biological propensity (such as genetic risk and the influence of early life experiences), the generation of an obesogenic external environment (based on, for example, changes in food production and lifestyle, such as increased wealth, increased sedentary lifestyle and increased availability of energy-dense foods), a life course component (whereby the risks of becoming obese may be present at an early stage of life) and a generational dimension (in which parental obesity is known to act as a significant predictor of childhood obesity).[17]

Comorbidities associated with obesity

Overweight and obesity are associated with a significant range of comorbidities, including type 2 diabetes (T2DM), hypertension, dyslipidaemia, coronary artery disease, stroke, osteoarthritis, reproductive problems, respiratory and liver conditions and cancers.[18–20] Obstructive sleep apnoea is also associated with obesity, with a potential predisposition among Asian individuals.[21,22] The National Audit Office[23] estimated the increased relative risk of the development of comorbidities among obese individuals, which is shown in *Table 1*.

Increased levels of overweight and obesity are linked with increases in mortality, with subjects who have never smoked and with no history of disease but a BMI > 40 kg/m^2 having a relative risk of death 2.7 times higher for men and 1.9 times higher for women than that among subjects with a lower BMI (between 23.5 and 24.9 kg/m^2).[24] Obesity is also associated with psychological stigma.[25] The proportion of chronic disease attributable to obesity has been predicted to undergo a considerable increase by 2050, particularly for T2DM, stroke and coronary heart disease (CHD).[3] It has been suggested that adults in the upper half of the healthy weight category (22.0 kg/m^2 < BMI < 24.9 kg/m^2) are more likely to develop health problems than their leaner counterparts and that adults should attempt to maintain a BMI of between 18.5 kg/m^2 and 21.9 kg/m^2 to minimise their risk of disease.[20]

Measurements of obesity

Obesity is frequently reported in terms of BMI. BMI is a measurement of body weight relative to height. Based on the WHO criteria, overweight is classed as a BMI of 25–29.9 kg/m^2, while obesity is defined as a BMI > 30 kg/m^2.[5] The current National Institute for Health and Clinical Excellence (NICE) clinical guideline for obesity[26] states that waist circumference may also be used in addition to BMI in adults with a BMI < 35 kg/m^2 and may be used to provide additional information on the risk of the development of comorbidities in children. Among adults, waist

TABLE 1 Relative risk of development of obesity-related comorbidities

Condition	Relative risk among females	Relative risk among males
T2DM	12.7	5.2
Hypertension	4.2	2.6
Myocardial infarction	3.2	1.5
Colon cancer	2.7	3.0
Angina	1.8	1.8
Gall bladder disease	1.8	1.8
Ovarian cancer	1.7	NA
Osteoarthritis	1.4	1.9
Stroke	1.3	1.3

NA, not applicable.

circumference can be used as an indicator of health risk, with increased risk being identified based on a waist circumference of ≥ 94 cm in men and ≥ 80 cm in women and greatly increased risk with a waist circumference of ≥ 102 cm in men and ≥ 88 cm in women.[27] Other measurements of obesity include body weight, percentage over ideal body weight, waist–hip ratio and skinfold thickness. It is worth noting that a lower cut-off point has been suggested for certain ethnic groups including South Asians.[28]

A report suggested that debate surrounded the use of standard BMI cut-offs among some ethnic groups on the basis that variation exists in the association between BMI and body fat according to ethnicity.[6] Dhaliwal and Welborn[29] and Kumar *et al.*[30] proposed that waist–hip ratio be used as a measure of central obesity because of its high precision and no bias across ethnic groups.[29,30]

Impact of health problem and significance for the NHS

Most obesity management is undertaken in primary care settings. Hospital admissions for people with obesity-related conditions place a significant burden on the health service, particularly in relation to circulatory diseases, musculoskeletal disorders and endocrine disorders including diabetes.[31]

Allender and Rayner[32] produced a new estimate of the burden of overweight- and obesity-related disease in the UK. The authors estimated that, when the rates for the burden of overweight-attributable disease were applied to mortality figures for 2003–4, over 203,000 deaths occurred in the UK as a result of diseases associated with overweight and obesity. The authors stated that it was further estimated that approximately 66,737 deaths were directly attributable to overweight and obesity, over half (54%) of these being due to CHD and 31% to stroke.

Current service provision

Management of obesity

The primary aim of the management of obesity is to achieve weight reduction in the interests of health. The Royal College of Physicians[33] described the clinical benefits of weight loss (based on a scenario of an individual weighing 100 kg losing 10% of their body weight), estimates of which included decreased blood pressure, a 10% decrease in cholesterol, a > 50% reduction in the risk of developing diabetes, reductions of 30–40% and 40–50% in diabetes-related deaths and obesity-related cancer deaths, respectively, and a 20–25% reduction in total mortality. Non-pharmacological methods for the management of obesity include dietary modification, exercise, structured education and weight management programmes. For obese patients who cannot achieve or maintain a healthy weight by non-pharmacological means, a number of pharmacological interventions exist to aid weight reduction, including sibutramine (Reductil®, Abbott), orlistat (Xenical®, Roche; Alli®, GlaxoSmithKline) and rimonabant (Acomplia®, Sanofi-Aventis). Drug therapy has been shown to be most effective when combined with dietary modification, physical exercise and behaviour change[34] and is recommended for use in the management of obesity in combination with non-pharmacological interventions. Surgical procedures, such as gastric bypass and banding, also play a role in the management of obesity.

Current service cost

The treatment of obesity and its complications is associated with significant health and social care costs, in addition to wider societal financial costs. The House of Commons Select Committee estimated that the direct health-care costs arising from the treatment of obesity and its complications ranged from £991M to £1124M in 2002. This level of expenditure represented approximately 2.3–2.6% of the total NHS spending for the period 2001–2.[35] Allender and Rayner[32] estimated the direct cost of overweight and obesity to the NHS to be £3.2B, of which the

greatest proportion was attributable to stroke (£983M), followed by CHD (£773M), hypertensive disease (£576M) and diabetes (£533M). The costs arising from overweight and obesity are likely to escalate (from the estimate for 2007 of £4.2B) in the forthcoming years if current increasing trends in the prevalence of obesity continue, with a predicted overall annual total cost to the NHS of overweight and obesity of £9.7B (based on today's prices) by 2050, representing an increase in the projected percentage of NHS costs (at £70B) from 6.0% in 2007 to 13.9% in 2050.[3]

Variation in services and/or uncertainty about best practice

The management of obesity in primary care has been described as being uncoordinated and inconsistent.[36] The Counterweight Project Team (2004) undertook a series of structured interviews with general practitioners (GPs) and practice nurses and analysed patient records from primary care settings across England and Scotland in order to investigate the range of approaches to obesity management utilised by primary care professionals. Although the majority of GPs (83%) and practice nurses (97%) reported that they would raise weight as an issue with obese patients, only 15% of GPs would spend up to 10 minutes in a weight-related consultation compared with 76% of nurses ($p < 0.001$). BMI was recorded for 64.2% of patients. GPs and practice nurses reported making patient referrals to a dietician (58% vs 59%), exercise referral schemes (50% vs 56%) and commercial weight loss agencies (41% vs 68%). Audit of obese patients' records showed the use of practice-based diet counselling (20%), dietetic (4%) and obesity centre (1%) referrals and any anti-obesity medication (2%) recorded over 18 months. Patients prescribed anti-obesity medication were more likely to be female ($p < 0.01$) and more obese ($p < 0.01$) than, but with a similar prevalence of comorbidities to, patients who were not prescribed medication.

Relevant national guidelines

Healthy Weight, Healthy Lives is a cross-government strategy for England involving a range of programmes across a number of sectors, including schools and food, physical activity, transport and the health service.[17] The strategy is focused on five areas: the healthy growth and development of children; promoting healthier food choices; promoting physical activity; creating incentives for better health; and personalised advice and support. The development of strategies for the management of obesity is also linked to requirements under the national service frameworks for CHD and diabetes.

NICE issued clinical guideline 43[26] to provide guidance on the prevention, identification, assessment and management of overweight and obese adults and children. The guidance superseded previous pieces of guidance on orlistat,[38] sibutramine[39] and surgery for morbid obesity.[40] The clinical guideline recommended that dietary changes and physical exercise should be the first options in the management of obesity before the use of pharmacological interventions is considered. Bariatric surgery was recommended if all of the following criteria were fulfilled: a BMI of $\geq 40\,kg/m^2$ (or between $35\,kg/m^2$ and $40\,kg/m^2$ in the presence of other significant disease that could be improved in the event of weight loss); all appropriate non-surgical measures have been attempted and been unsuccessful; person has or will receive intensive management in a specialist obesity service; patient is generally fit for anaesthesia and surgery; and the patient commits to requirement for long-term follow-up. In addition, bariatric surgery can be considered as a first-line option when appropriate in adults who have a BMI of $\geq 50\,kg/m^2$. Surgical intervention was not generally recommended for children or young people. In 2008, NICE guidance was issued relating to the use of rimonabant.[41] However, the marketing authorisation for this drug has since been suspended.[42]

The NHS Health Checks Programme was launched in April 2009. Designed to address health inequalities, the vascular risk assessment programme consists of systematic screening of

individuals aged 40–74 years of age for cardiovascular and T2DM risk with lifestyle interventions offered to those considered to be at risk.[43]

Description of technology under assessment

Summary of interventions

Orlistat functions by inhibiting the uptake of dietary fats by the gastrointestinal tract, whereas both sibutramine and rimonabant are centrally acting appetite suppressants. The following sections summarise the product characteristics of each of these interventions using the Summary of Product Characteristics (SPC) for each drug (obtained from the Electronic Medicine Compendium at www.medicines.org.uk; SPC not available for rimonabant) and information from the *British National Formulary* (BNF).

Sibutramine

Description of intervention

Sibutramine is a centrally acting appetite suppressant that acts as an inhibitor of the reuptake of noradrenaline and serotonin.

Licensed indications

The marketing authorisation for sibutramine was suspended following a review by the European Medicines Agency in 2010.[44] The agency concluded that the benefits of treatment with sibutramine did not outweigh the associated cardiovascular risks and that prescriptions should not be issued and that the treatment of patients receiving sibutramine should be reviewed.

Dosage and administration

Reductil was available as blue/yellow capsules containing 10 mg of sibutramine hydrochloride or as blue/white capsules containing 15 mg of sibutramine hydrochloride.

Adverse events

Possible side effects included dry mouth, taste disturbances, abdominal pain, diarrhoea, constipation, nausea, vomiting, gastrointestinal haemorrhage, haemorrhoid aggravation, tachycardia, **palpitations, hypertension**, insomnia, hot flushes, lightheadedness, paraesthesia, anxiety and panic attacks, depression, seizures, transient memory disturbance, blurred vision, sexual dysfunction, menstrual disturbances and cramps, urinary retention, thrombocytopenia, sweating, alopecia, cutaneous bleeding disorders, hypersensitivity reactions including Henoch–Schönlein purpura, rash, urticaria, angioedema and anaphylaxis, interstitial nephritis and glomerulonephritis. The following were reported rarely: headache and increased appetite on withdrawal, angle-closure glaucoma and **cardiovascular events**. The adverse events potentially relating to the withdrawal of the intervention are highlighted in bold.

Orlistat

Description of intervention

Orlistat is a lipase inhibitor that reduces the absorption of dietary fat in the gastrointestinal tract. Orlistat is available in the UK without prescription.

Licensed indications

Orlistat is indicated in combination with a mildly hypocaloric diet in the management of obesity in patients with a BMI $\geq 30\,kg/m^2$ or in overweight patients with a BMI $\geq 28\,kg/m^2$ with associated risk factors.

Dosage and administration

Xenical is available as turquoise hard capsules containing 120 mg of orlistat. Alli is available as 60-mg turquoise/dark blue hard capsules.

The recommended dose of Xenical in adults aged > 18 years is one 120-mg capsule to be taken with water immediately before, during or up to 1 hour after each main meal (up to a maximum dose of 360 mg daily).

The recommended dose of Alli is one 60-mg capsule taken three times daily with water immediately before, during or up to 1 hour after each main meal.

If a meal is missed or does not contain fat, the dose of orlistat should not be taken. Treatment should be continued beyond 12 weeks only if weight loss since the start of treatment exceeds 5% of the initial body weight (the target for initial weight loss may be lower in people with T2DM). Treatment should not exceed 6 months (Alli). Use in children aged > 12 years should be initiated by a specialist only (unlicensed use). If a multivitamin supplement is required, this should be taken at least 2 hours after the orlistat dose or at bedtime.

Contraindications

Orlistat is contraindicated in patients who:

- have chronic malabsorption syndrome
- have cholestasis
- are breastfeeding
- are undergoing concurrent treatment with ciclosporin (Alli)
- are undergoing concurrent treatment with warfarin or other anticoagulants (Alli).

Cautions

The effects of orlistat in children, the elderly and patients with hepatic or renal impairment have not been studied. Orlistat may impair the absorption of fat-soluble vitamins. Other cautions include epilepsy and pregnancy. Interactions may occur with ciclosporin, acarbose, oral anticoagulants and amiodarone.

Adverse events

Adverse events associated with the use of orlistat include the following gastrointestinal effects: oily leakage from the rectum, flatulence, liquid or oily stools, faecal urgency and incontinence, and abdominal pain/discomfort. Such gastrointestinal effects may be minimised by reducing fat intake in the diet. Other side effects include headache, tooth and gingival disorders, respiratory infections, fatigue, anxiety, menstrual disturbances, urinary tract infection and hypoglycaemia. The following have also been reported rarely: rectal bleeding, hypothyroidism, diverticulitis, cholelithiasis, hepatitis, bullous eruptions and oxalate nephropathy.

Rimonabant

Description of intervention

Rimonabant is a centrally acting appetite suppressant that acts as a cannabinoid receptor antagonist.

Licensed indications

The European Medicines Agency reported that the marketing authorisation for rimonabant was suspended across the European Union following a review by the Committee for Medicinal Products for Human Use in 2008, which concluded that the benefits of rimonabant treatment did not outweigh the risks of psychiatric adverse reactions.[42] Therefore, it was stipulated that

prescriptions should not be issued and the treatment of patients who are taking rimonabant should be reviewed.

Dosage and administration

Rimonabant was available as tablets containing 20 mg of rimonabant.

Adverse events

Reported side effects included nausea, vomiting, diarrhoea, dry mouth, anorexia, **depression**, **anxiety**, **irritability**, **nervousness**, **sleep disorders**, impaired memory, dizziness, paraesthesia, hypoaesthesia, sciatica, hot flush, asthenia, impaired attention, tendonitis, muscle cramp, pruritus and hyperhidrosis. The following were reported less commonly: hiccups, anger, aggression, **suicidal ideation** and hallucinations. The adverse events potentially relating to the withdrawal of the intervention are highlighted in bold.

The BNF stated that combination therapy involving more than one anti-obesity drug is contraindicated until additional information about efficacy and long-term safety is available.[45]

A previous systematic review of randomised controlled trial (RCT) evidence found considerable differences between orlistat, sibutramine and rimonabant in terms of discontinuation due to adverse events and underlying causes of such discontinuations.[46] Higher risk ratios for discontinuation due to adverse events were observed for patients who were treated with rimonabant and orlistat but not sibutramine in this review. The most common adverse events associated with discontinuation were gastrointestinal for orlistat (40%) and psychiatric for rimonabant (47%) (information stated as not being available for sibutramine).

Current usage in the NHS

The NICE clinical guideline for obesity[26] recommended that dietary changes and physical exercise should be the first options in the management of obesity. The use of pharmacological interventions for weight loss was not generally recommended for children younger than 12 years but the guideline stated that such measures may be used in exceptional circumstances (e.g. the presence of severe comorbidities). In children aged ≥ 12 years, treatment with orlistat or sibutramine was recommended only in the presence of severe physical or psychological comorbidities. In adults, it was recommended that orlistat be prescribed as part of an overall obesity management plan in patients with a BMI of ≥ 28.0 kg/m^2 (with associated risk factors) or ≥ 30.0 kg/m^2. It was recommended that orlistat therapy should be continued beyond 3 months only if the patient had lost at least 5% of his or her initial body weight since commencing therapy. Treatment with orlistat beyond 12 months should be made after discussing the potential benefits and limitations with the patient. The guideline also recommended that sibutramine be prescribed as part of a weight reduction plan in patients meeting one of the following criteria: a BMI of ≥ 27.0 kg/m^2 (with associated risk factors) or a BMI of ≥ 30.0 kg/m^2, with careful monitoring of weight loss and adverse events. Therapy with sibutramine was to be continued beyond 3 months only if the patient had lost at least 5% of initial body weight while taking the drug. Treatment with sibutramine was not recommended beyond the licensed duration of 12 months. Co-prescribing of pharmacological interventions for weight reduction was not recommended. As noted above, the marketing authorisations for rimonabant and sibutramine have been suspended following reviews by the European Medicines Agency.[42,44]

Anticipated costs associated with intervention

Using the latest data available,[47] *Figure 1* shows the number of items prescribed annually from 1999 to 2008 in the treatment of obesity in England. There was a substantial increase in prescribing rates for both orlistat and sibutramine following publication of guidance from

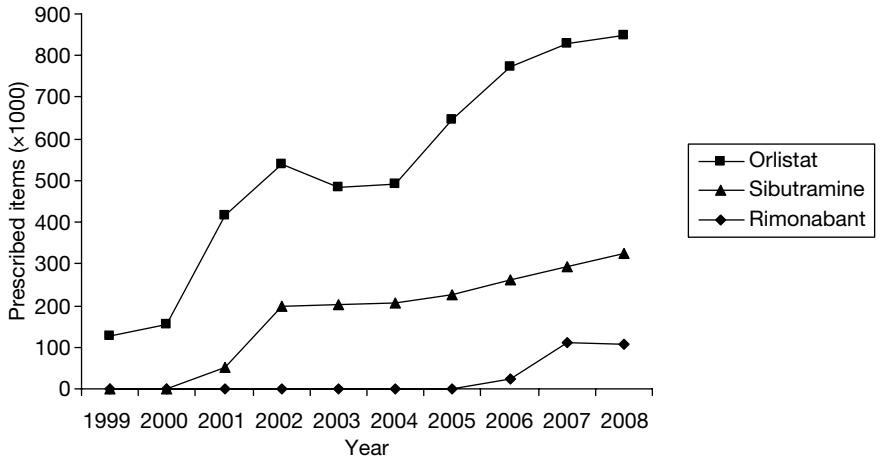

FIGURE 1 Annual number of prescription items for the treatment of obesity.

NICE in March 2001[38] and October 2001,[39] respectively. After a period of relatively steady use, prescription numbers started to increase again after the publication of revised guidance in 2004.[48]

Table 2 shows the number of items and associated net ingredient cost (NIC) of drugs for the treatment of obesity prescribed in primary care. Rimonabant became available on prescription in July 2006; thus, the figure for that year reflects just 6 months of data. In 2008, there were 1.28 million prescription items for the treatment of obesity. Overall, the total number of prescription items in 2008 was ten times the number in 1999, and the current trend is an increase of around 14% per year.

TABLE 2 Number of prescription items and net ingredient cost

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Prescription items (thousands)										
Orlistat	127	156	415	540	484	492	654	774	827	848
Sibutramine	–	–	53	196	203	208	226	263	294	325
Rimonabant								23	112	106
Total	127	157	469	737	688	699	871	1060	1233	1278
Net ingredient cost (£000)										
Orlistat	4863	6573	17,575	23,401	21,036	21,391	21,020	32,476	32,047	29,980
Sibutramine	–	–	2030	7752	8458	9314	10,984	13,654	13,093	9595
Rimonabant	–	–	–	–	–	–	–	1411	6440	5237
Total	4863	6613	19,659	31,203	29,532	30,706	38,004	47,541	51,580	44,812

Up until 2007, 'total' included other drugs that may be used to treat obesity which include mazindol, phentermine and diethylpropion hydrochloride. From 2007, only orlistat, sibutramine and rimonabant have generally been prescribed for the treatment of obesity in primary care.
Source: Prescribing Analyses and Cost (PACT) from the Prescription Pricing Division of the NHS Business Services Authority (PPD of the NHS BSA). The NHS Information Centre.

The total NIC for drugs for the treatment of obesity increased from £4.9M in 1999 to £51.6M in 2007, but fell in 2008 to £44.8M. Correspondingly, the NIC per item increased from £38 in 1999 to £42 in 2007 and then fell to £35 in 2008.

Following the withdrawal of rimonabant in 2008 and the suspension of sibutramine prescribing in 2010, it is reasonable to expect that the uptake of orlistat will increase as patients switch treatments and the alternatives available for new patients decrease. As orlistat was already the main treatment, accounting for two-thirds of all prescriptions, and the NICs per item for sibutramine (£30) and rimonabant (£50) are similar to that for orlistat (£35), it is not expected that this change in prescribing patterns will affect the observed trend in total costs. If total prescribing rates for orlistat increase at 14% (5–20%) per annum, the total annual net cost for prescriptions directly related to obesity treatment is estimated to be approximately £57.8M in 2010 and over £109M in 2015.

Chapter 2

Definition of the decision problem

The aim of this study was to evaluate the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care. The purpose of the project was to apply rigorous methods of systematic reviewing, evidence synthesis and decision-analytic modelling to evaluate the clinical effectiveness and cost-effectiveness of the three pharmacological treatments, orlistat, sibutramine and rimonabant, compared with each other and with usual care.

Aims and objectives of assessment

The specific objectives are to:

- analyse an existing database of clinical information from primary care
- conduct a full systematic review of the published evidence on the clinical effectiveness of orlistat, sibutramine and rimonabant
- undertake a full synthesis of the available evidence using network meta-analysis methods
- undertake a full systematic review of the published evidence of the cost-effectiveness of the agents
- use decision-analytic modelling and probabilistic sensitivity analysis (PSA) to assess the relative cost-effectiveness of the three agents in terms of the incremental cost per quality-adjusted life-year (QALY) gained
- use expected value of information techniques to determine the potential benefits of future head-to-head trials of the agents.

Since the research question was formulated, two of the three pharmacological treatments have been withdrawn for safety reasons. Although the data for all three have been retained in the clinical and economic analyses, the value of information analyses exploring the potential benefits of future head-to-head trials for the agents have not been conducted as we believe that conducting further studies in this area would not be possible.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Literature search

The following electronic databases were searched. Searches were carried out in January 2009. Examples of the search strategies used are given in *Appendix 1*. Where completed trials were yet to be published, we the contacted the principal investigator.

- MEDLINE
- MEDLINE In-Process & Other Non-Indexed Citations
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Health Technology Assessment Database
- EMBASE
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- NHS Economic Evaluation Database (NHS EED)
- Cochrane Controlled Trials Register
- Web of Science Proceedings
- Science Citation Index
- Current Controlled Trials
- BIOSIS.

Management of references

The results of the literature search were imported into EndNote reference managing software version X5 (Thomson Reuters, CA, USA). Duplicates were removed. Where multiple papers reported data from the same study, these were grouped together and only included once in the analysis.

Inclusion and exclusion of studies

Studies were excluded if they were not reported in English.

Study design

Only studies using a RCT design were included. Both parallel and crossover designs were included. Non-randomised studies were excluded.

Patient population

Studies with adults who were overweight or obese or at high cardiovascular disease (CVD) risk were included. High CVD risk was defined as having one or more of the following conditions: hypertension, T2DM, gestational diabetes, polycystic ovary syndrome, high cholesterol, metabolic syndrome, angina, coronary artery disease and non-alcoholic steatohepatitis. Studies were excluded if they included those with mental illness, for example binge eating, or if they included children or adolescents.

Interventions

Studies were included if they compared orlistat, sibutramine or rimonabant with lifestyle and/or exercise advice (standard care), placebo or metformin. The anti-obesity treatments had to be given at the recommended dose: orlistat 120 mg three times daily (maximum 360 mg daily), sibutramine 10 mg, 15 mg or 10 mg increasing to 15 mg once daily, rimonabant 20 mg once daily. Studies were also included if they gave orlistat and sibutramine in combination or if orlistat, sibutramine or rimonabant were given in combination with other active interventions. We excluded trials with a treatment period of < 12 weeks. We also included head-to-head comparisons of the pharmacological agents.

Outcome measures

Trials had to include one or more of the following outcome measures, measured at 3, 6 or 12 months:

- weight change from baseline
- BMI change from baseline
- number losing ≥ 5% body weight
- number losing ≥ 10% body weight.

Assessing relevancy of included studies

The titles and abstracts of all studies identified by the electronic searches were screened for inclusion by two reviewers, who each assessed half of the identified articles. The full texts of all studies found to be potentially relevant were sought and were assessed for inclusion by two independent reviewers, using the inclusion criteria outlined above. Disagreements were discussed with the project steering committee.

Data extraction

Data were extracted using a standard form by one reviewer. See *Appendix 2* for the data extraction form.

The data extracted included author, year of publication, country, population included (diabetic, with comorbidities, obese but otherwise healthy, or other), trial design, treatment length, follow-up length, study quality, interventions used, level of lifestyle/exercise advice, whether or not a wash-in period was used, if so how long and whether or not it used an active intervention, and baseline characteristics by group.

Lifestyle and/or exercise advice was categorised using the following criteria:

- standard – one visit with general dietary/exercise advice given or patients given a lifestyle leaflet
- enhanced – more than one visit or patient given more than just advice.

Because of the poor reporting of the lifestyle components of the interventions we assumed that standard advice was given if lifestyle and/or exercise advice was not mentioned, as this is standard care for overweight and obese patients. We also assumed that if diet (or exercise) advice had been given this also included advice on exercise (or diet) and therefore did not extract data on diet and exercise separately.

Outcome data were extracted in a number of formats depending on how the data were presented: data could be presented either at the arm level or as trial-level differences. For the continuous outcomes (weight and BMI change) the following data were extracted:

- arm based (data given for each intervention):
  - mean weight at baseline and follow-up with standard deviation (SD), standard error or significance levels and confidence intervals (CIs)
  - mean change from baseline with SD, standard error or significance levels and CIs
  - mean change from baseline adjusted for baseline value (ANCOVA) with SD, standard error or significance levels and CIs.

- trial based (data given as difference between interventions)
  - mean difference between interventions at follow-up with SD, standard error or significance levels and CIs.

For the binary outcomes (5% and 10% weight loss) the number achieving the target was extracted for each intervention. For all outcomes the number of participants included was also extracted.

Where possible, data from intention-to-treat analyses were extracted. If data were presented by subgroup only (e.g. data for those with and without hypertension given separately) then these were meta-analysed to give the results for the entire study population. Data were extracted only from either the manuscript text or tables (no attempt was made to extract from figures). Where data were incomplete the corresponding author of the study was contacted.

Quality assessment

All studies were assessed for quality. The quality tool used was based on that developed by Jadad *et al.*[49] with the addition of a score for allocation concealment, as suggested in Schulz *et al.*[47] The tool is described in *Table 3*.

Plan of analysis

For each outcome at each time point, pair-wise meta-analysis was initially carried out followed by a mixed-treatment comparison (MTC) (network meta-analysis).

To enable analysis, missing outcome data were derived from related statistics where feasible. Where SDs for means were not reported these were estimated from ranges, *p*-values or 95% CIs using methods reported in the *Cochrane Handbook*.[37] Where data on baseline and follow-up weight/BMI were reported rather than the change from baseline, change was calculated by deducting the baseline mean value from the follow-up mean value. SD for the change was imputed using the method described in the *Cochrane Handbook* and the correlation coefficient measurements on the same individuals were derived by taking the mean correlation for those studies that report baseline, follow-up and change SDs for weight. All SDs were converted into standard errors; those studies reporting much smaller/larger standard errors than the majority of studies were then reassessed to see if there had been errors in the reporting, that is, SDs being reported as standard errors and vice versa. Where it was not clear which methodology had been used, the more conservative estimate (i.e. the one with the largest standard error) was taken.

TABLE 3 Quality assessment criteria

Term	None	Mentioned	Described and adequate
Randomisation	(Study excluded)	1	2
Double blinding	0	1	2
Flow of participants	0	1	2
Allocation concealment	0	1	1

Pair-wise meta-analysis

Studies were pooled using random-effects models for each treatment comparison for which data were available for each of the outcomes outlined in *Outcome measures* at the time points 3, 6 and 12 months. Random-effects models were used as studies were expected to be heterogeneous. Heterogeneity was assessed using the I^2 and χ^2 statistics. Forest plots were constructed for all comparisons. All analysis was carried out in Stata version 11.0 (StatCorp LP, College Station, TX, USA).

Mixed-treatment comparison

Mixed-treatment comparison methods were used to compare all treatments under investigation for obesity and their comparators within a single model, which allowed us to make both direct and indirect comparisons (where no head-to-head trials are available).[50] Initially, all outcome measures and time points (as described for the pair-wise meta-analyses above) were checked to make sure they formed closed networks. Placebo was used as the reference category throughout. We used a logistic regression model for the binary outcomes and a linear regression model for the continuous outcomes. In all cases a burn-in of 10,000 simulations was discarded and the results are presented based on a further 40,000 simulations. Convergence was checked visually using the history plots. The goodness of fit was checked using the residual deviance. Vague priors were used for all parameters. For each treatment the percentage of times that treatment gained the highest rank across all of the simulations was also calculated. All MTC analysis was conducted using a Bayesian Markov chain Monte Carlo method using the Bayesian software WinBUGS version 1.4.3. (MRC Biostatistics Unit, Cambridge, UK).[51]

We compared the results of the pair-wise meta-analysis with the MTC and defined these as inconsistent when the MTC estimate did not fall within the 95% CI from the pair-wise meta-analysis.

Covariate analysis

For the 12-month weight change outcome we also considered exploring the effect of two covariates on the treatment effect: the proportion of participants with T2DM and the level of lifestyle advice given. Each covariate was modelled separately. The treatment covariate interactions were modelled as a separate regression coefficient for each treatment.

Sensitivity analysis

We carried out a sensitivity analysis for the 12-month weight change outcome according to the following variables: intention to treat (excluding those in which intention to treat had not been used or it was not clear which method had been used) and wash-in (excluding those studies that had used a wash-in phase). A wash-in is defined as a pretrial practice whereby all eligible patients are given an intervention (either active or placebo) for a period to test compliance; only those who comply are then randomised into the trial.

Publication bias

Publication bias was assessed visually using contour-enhanced funnel plots for all comparisons that contained five or more studies.

Clinical results

Study selection

Figure 2 shows the flow of studies. The electronic searches identified 3183 potentially relevant articles. After removing duplicates and those that were not eligible after reading the title and abstract, 161 full texts were assessed. Of these, 67 were excluded (see *Appendix 3*, *Reference list*).

Overall, 94 studies were included in the meta-analysis. Orlistat was assessed in 54 studies, 44 studies included sibutramine and five studies assessed rimonabant.

Study characteristics

The majority of trials were carried out in North America and Europe from 1995 to 2008 (*Table 4*). Overall, 24,808 individuals were included. The mean trial size was 264, ranging from 14 to 3277, and 55 trials (58.5%) included ≥ 100 participants. Two crossover trials were included, with all other trials having a parallel design. The mean length of intervention was 8.3 months (range 3–48 months). A total of 45 studies (47.9%) used enhanced lifestyle advice, with the remainder giving standard advice (49, 52.1%). A wash-in period was used in 44 (46.8%) of the studies.

Risk of bias within studies

The results of the bias assessment are given in *Table 4*. Overall, the quality of the studies included is generally low. All included studies were randomised but in only 40% of studies was the randomisation procedure described fully and adequately. In total, 22 (23.4%) studies concealed allocation. The majority of studies were double blind: 50% mentioned double blinding and 20% described their blinding adequately. Participant flow was not described in 17 (18.1%) studies.

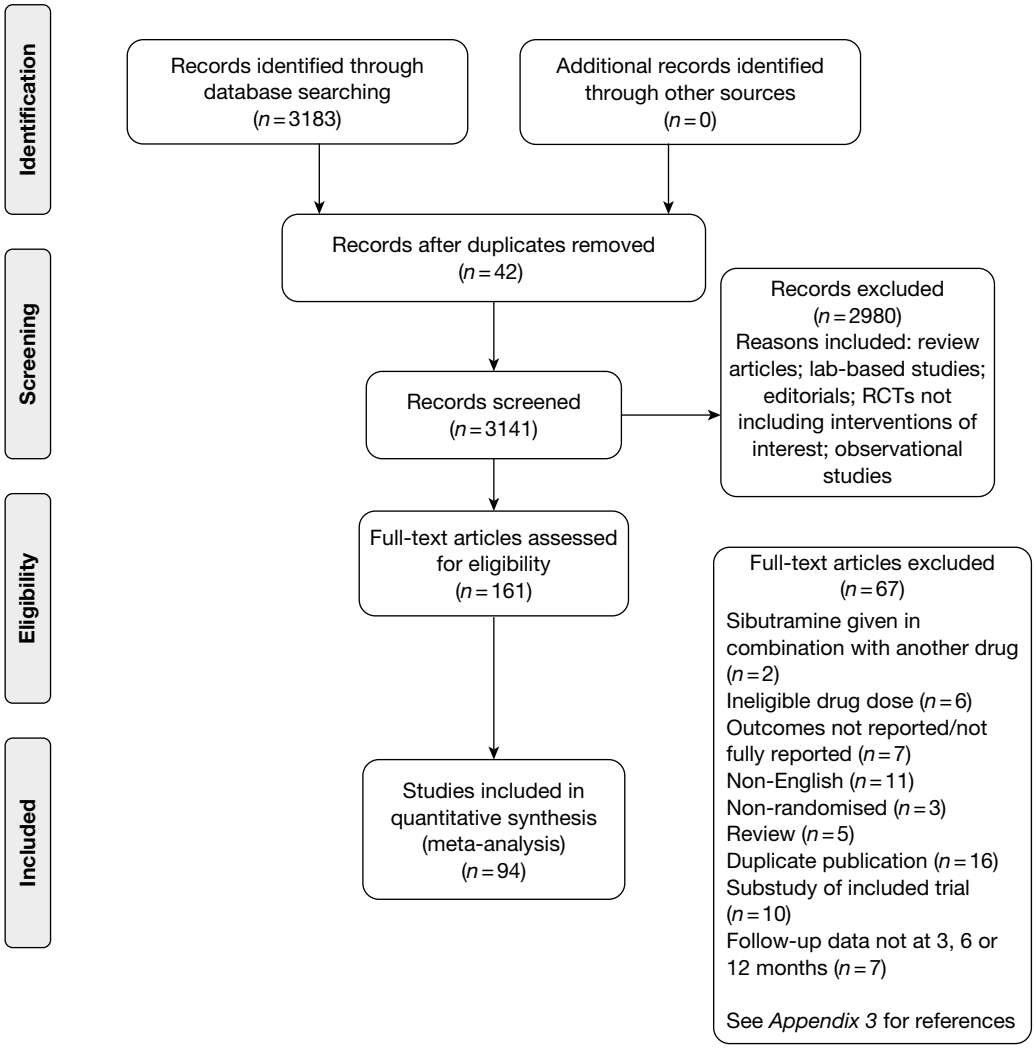

FIGURE 2 Flow diagram.

TABLE 4 Characteristics of included trials

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
5	Apfelbaum 1999[52]	Placebo	France	Parallel	12	1	0	1	2	E	NR	Y	L
		Sibutramine 10 mg									NR		
6	Audikovszky 2007[53]	Standard care	Hungary	Parallel	6	1	0	0	0	S	NR	N	NR
		Orlistat									NR		
7	Aydin 2004[54]	Standard care	Turkey	Parallel	3	1	0	0	0	S	0	Y	NR
		Sibutramine 10 mg									0		
		Orlistat									0		
8	Bakris 2002[55]	Placebo	USA	Parallel	12	1	0	1	2	E	8.0	N	L
		Orlistat									8.0		
9	Beck-da-Silva 2005[56]	Standard care	Canada	Parallel	3	1	0	0	1	S	40.0	N	L
		Orlistat									18.0		
10	Berne 2005[57]	Placebo	Sweden	Parallel	12	2	1	1	2	E	NR	Y	L
		Orlistat									NR		
11	Bloch 2003[58]	Standard care	Brazil	Parallel	3	2	1	0	2	E	38.8	N	L
		Orlistat									38.8		
12	Borges 2007[59]	Standard care	Brazil	Parallel	4	1	0	0	1	E	0	N	NR
		Orlistat									0		
13	Bray 1999[60]	Placebo	USA	Parallel	6	2	0	1	1	E	NR	Y	C
		Sibutramine 15 mg									NR		
		Sibutramine 10 mg									NR		
14	Broom 2002[61]	Placebo	UK	Parallel	6	1	0	1	2	E	19.8	N	NR
		Orlistat									30.3		
15	Broom 2002[62]	Placebo	UK	Parallel	12	2	1	2	1	S	NR	Y	L
		Orlistat									NR		
16	Chou 2007[63]	Orlistat	Taiwan	Crossover	3	1	0	0	2	S	100	N	NR
		Sibutramine 10 mg									100		
17	Cocco 2005[64]	Placebo	Switzerland	Parallel	6	2	0	1	1	E	100	N	NR
		Orlistat									100		
18	Cuellar 2000[65]	Placebo	Mexico	Parallel	6	2	1	1	2	E	17.6	N	C
		Sibutramine 15 mg									22.9		

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
19	Davidson 1999[66]	Placebo	USA	Parallel	12	2	0	1	2	E	4.5	N	L
		Orlistat									4.0		
20	Derosa 2003[67]	Placebo	Italy	Parallel	12	2	1	2	1	E	NR	Y	C
		Orlistat									NR		
21	Derosa 2004[68]	Orlistat	Italy	Parallel	12	2	1	2	2	E	100	Y	L
		Sibutramine 10 mg									100		
22	Derosa 2005[69]	Orlistat	Italy	Parallel	12	2	1	2	2	E	0	Y	NR
		Sibutramine 10 mg									0		
23	De Simone 2005[70]	Placebo	Italy	Parallel	3	1	0	1	2	S	0	N	C
		Sibutramine 15 mg									0		
24	Despres 2005[71]	Placebo	Australia, Canada, Finland, Italy, Spain, Sweden, Switzerland, USA	Parallel	12	1	0	1	1	E	100	Y	L
		Rimonabant									100		
25	Di Francesco 2007[72]	Placebo	Italy	Parallel	6	2	1	1	2	S	NR	N	L
		Sibutramine 10 mg									NR		
26	Didangelos 2004[73]	Standard care	Greece	Parallel	6	1	0	0	1	S	100	N	NR
		Orlistat									100		
27	Dixon 2008[74]	Standard care	England/UK	Parallel	12	1	0	0	1	E	0	N	NR
		Orlistat									0		
28	Drent 1995[75]	Placebo	Holland	Parallel	3	1	0	1	1	S	NR	Y	NR
		Orlistat									NR		
29	Drent 1995[76]	Placebo	Denmark, Germany, the Netherlands, Sweden	Parallel	3	1	0	1	0	S	NR	Y	NR
		Orlistat									NR		
30	Erdmann 2004[77]	Placebo	Germany	Parallel	6	2	1	1	1	S	7.8	Y	NR
		Orlistat									9.9		
31	Erondu 2007[78]	Placebo	NR	Parallel	6	1	0	2	2	S	0	Y	L
		Sibutramine 10 mg									0		
		Orlistat									0		

continued

TABLE 4 Characteristics of included trials (*continued*)

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
32	Fanghanel 2000[79]	Placebo	Mexico	Crossover	6	2	1	2	1	S	NR	Y	L
		Sibutramine 10 mg									NR		
33	Fanghanel 2003[80]	Placebo	Mexico	Parallel	6	2	1	2	1	S	NR	Y	L
		Sibutramine 10 mg									NR		
34	Faria 2005[81]	Placebo	Brazil	Parallel	6	2	0	1	1	S	NR	Y	C
		Sibutramine 10 mg									NR		
35	Finer 2000[82]	Placebo	UK	Parallel	12	2	0	2		S	0	Y	L
		Orlistat									0		
36	Finer 2000[83]	Placebo	UK	Parallel	3	1	0	1	1	S	100	Y	Y
		Sibutramine 15 mg									100		
37	Florakis 2008[84]	Standard care	Greece	Parallel	6	2	1	0	2	S	NR	Y	C
		Sibutramine 10 mg									NR		
38	Garcia 2006[85]	Standard care		Parallel	12	1	0	0	1	E	9.0	N	C
		Orlistat									26.0		
39	Gokcel 2002[86]	Sibutramine 10 mg	Turkey	Parallel	6	1	0	0	0	S	8.0	N	NR
		Orlistat									10.0		
		Metformin									12.0		
40	Grudell 2008[87]	Placebo	USA	Parallel	3	1	0	1	1	E	NR	N	NR
		Sibutramine 10 mg									NR		
		Sibutramine 15 mg									NR		
41	Guimaraes 2006[88]	Placebo	Brazil	Parallel	3	1	0	0	0	S	0	Y	NR
		Sibutramine 15 mg									0		
		Metformin									0		
42	Guy-Grand 2004[89]	Placebo	France	Parallel	6	2	1	2	2	E	19.0	N	L
		Orlistat									19.4		
43	Halpern 2002[90]	Placebo	Brazil	Parallel	6	1	0	1	1	S	NR	Y	C
		Sibutramine 10 mg									NR		

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
44	Halpern 2003[91]	Placebo	Brazil	Parallel	6	2	1	2	2	S	100	Y	L
		Orlistat									100		
45	Hanefeld 2002[92]	Placebo	Germany	Parallel	12	1	0	1	2	S	100	Y	L
		Orlistat									100		
46	Hanotin 1998[93]	Placebo	France	Parallel	3	1	0	2	2	S	NR	Y	L
		Sibutramine 10 mg									NR		
		Sibutramine 15 mg									NR		
47	Hauner 2004[94]	Placebo	Germany	Parallel	12	1	0	1	2	E	0	N	L
		Sibutramine 15 mg									0		
48	Hauptman 2000[95]	Placebo	USA	Parallel	24	1	0	1	2	S	NR	Y	L
		Orlistat									NR		
49	Hazenberg 2000[96]	Placebo	Netherlands	Parallel	3	1	0	1	2	S	NR	Y	L
		Sibutramine 10 mg									NR		
50	Hill 1999[97]	Placebo	USA	Parallel	12	1	0	1	2	S	0	Y	L
		Orlistat									0		
51	Hollander 1998[98]	Placebo	USA	Parallel	12	2	0	1	2	S	100	Y	L
		Orlistat									100		
52	Hung 2005[99]	Placebo	Taiwan	Parallel	6	1	0	1	0	S	100	N	NR
		Sibutramine 15 mg									100		
53	Kaya 2004[100]	Standard care	Turkey	Parallel	3	1	0	0	1	S	0	N	NR
		Sibutramine 10 mg									0		
		Orlistat									0		
		Orlistat and sibutramine									0		
54	Kelley 2002[101]	Placebo	USA	Parallel	12	1	0	1	2	E	100	N	NR
		Orlistat									100		
55	Kelley 2004[102]	Placebo	USA	Parallel	6	1	0	1	1	E	100	N	C
		Orlistat									100		

continued

TABLE 4 Characteristics of included trials (*continued*)

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
56	Kiortsis 2008[103]	Standard care	Greece	Parallel	3	2	0	0	1	S	0	N	C
		Orlistat									0		
		Sibutramine 10 mg									0		
57	Krempf 2003[104]	Placebo	France	Parallel	18	1	0	1	1	E	0	Y	L
		Orlistat									0		
58	Kuo 2006[105]	Placebo	China	Parallel	3	1	0	2	1	S	100	N	C
		Orlistat									100		
59	Lindgarde 2000[106]	Placebo	Sweden	Parallel	12	2	0	1	2	E	24.0	Y	NR
		Orlistat									28.0		
60	Lindholm 2008[107]	Placebo	Sweden	Parallel	6	2	1	2	1	E	NR	N	C
		Sibutramine 15 mg									NR		
61	Mathus-Vliegen 2006[108]	Placebo	Netherlands	Parallel	12	1	0	1	0	S	0	Y	C
		Orlistat									0		
62	McNulty 2003[109]	Placebo	Belgium, Canada, UK	Parallel	12	1	0	1	1	E	100	N	NR
		Sibutramine 15 mg									100		
63	Miles 2002[110]	Placebo	Canada, USA	Parallel	12	2	0	1	1	E	100	N	NR
		Orlistat									100		
64	Muls 2001[111]	Placebo	Belgium	Parallel	6	1	0	0	2	E	0	Y	NR
		Orlistat									0		
65	Ozcelik 2004[112]	Placebo	Turkey	Parallel	3	1	0	1	0	E	NR	N	NR
		Orlistat									NR		
66	Ozcelik 2005[113]	Standard care	Turkey	Parallel	3	1	0	0	0	E	0	N	C
		Orlistat									0		
67	Pathan 2004[115]	Standard care	Bangladesh	Parallel	6	1	0	0	0	S	100	N	L
		Orlistat									100		
68	Pi-Sunyer 2006[115]	Placebo	Canada, USA	Parallel	12	2	0	1	2	E	0	Y	L
		Rimonabant									0		
69	Porter 2004[116]	Standard care	USA	Parallel	12	2	0	0	0	E	7.3	N	L
		Sibutramine 15 mg									10.7		

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
70	Poston 2003[117]	Standard care	USA	Parallel	12	1	0	0	2	E	9.6	N	L
		Orlistat									12.7		
71	Poston 2006[118]	Standard care	USA	Parallel	12	1	0	0	1	E	NR	N	L
		Orlistat									NR		
72	Redmon 2003[119]	Standard care	USA	Parallel	12	2	1	0	1	E	100	N	L
		Sibutramine 15 mg									100		
73	Rossner 2000[120]	Placebo	Europe	Parallel	24	2	0	1	2	S	0	Y	L
		Orlistat									0		
74	Sarac 2006[121]	Placebo	Turkey	Parallel	3	1	0	1	0	S	NR	N	L
		Sibutramine 10 mg									NR		
75	Sari 2004[122]	Orlistat	Turkey	Parallel	6	1	0	0	1	E	0	N	C
		Sibutramine 15 mg									0		
		Sibutramine and orlistat									0		
76	Sari 2004[123]	Orlistat	Turkey	Parallel	3	1	0	0	0	E	0	Y	NR
		Metformin									0		
77	Sathyapalan 2008[124]	Metformin	UK	Parallel	3	2	0	0	1	S	NR	Y	L
		Rimonabant									NR		
78	Scheen 2006[125]	Placebo	Worldwide	Parallel	12	2	0	1	2	S	100	Y	L
		Rimonabant									100		
79	Scholze 2007[126]	Placebo	Germany	Parallel	4	1	0	1	1	S	16.7	Y	L
		Sibutramine 15 mg									12.6		
80	Serrano-Rios 2002[127]	Placebo	European	Parallel	6	1	0	1	2	S	100	N	L
		Sibutramine 15 mg									100		
81	Shechter 2006[128]	Standard care	Israel	Parallel	4	2	0	0	0	S	40.0	N	L
		Sibutramine 10mg									40.0		
82	Shi 2005[129]	Placebo	China	Parallel	6	1	0	1	2	S	NR	N	L
		Orlistat									NR		
83	Smith 2001[130]	Placebo	UK	Parallel	12	2	1	2	2	S	0	Y	L
		Sibutramine 10 mg									0		
		Sibutramine 15 mg									0		

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TABLE 4 Characteristics of included trials (*continued*)

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
84	Swinburn 2005[131]	Placebo Orlistat	Australia, New Zealand	Parallel	12	2	0	1	1	E	8.3 8.2	Y	L
85	Tambascia 2003[132]	Placebo Sibutramine 10 mg	Brazil	Parallel	6	2	0	1	1	S	0 0	Y	C
86	Tankova 2004[133]	Standard care Sibutramine 15 mg	Bulgaria	Parallel	3	1	0	0	0	S	49.0 47.0	N	L
87	Tiikkainen 2004[134]	Placebo Orlistat	Finland	Parallel	6	1	0	1	0	S	0 0	N	L
88	Torgerson 2004[135]	Placebo Orlistat	Sweden	Parallel	48	2	1	2	0	E	NR NR	N	NR
89	Turker 2006[136]	Standard care Orlistat	Turkey	Parallel	3	1	0	0	2	S	0 0	N	C
90	Van Gaal 1998[137]	Placebo Orlistat	Austria, Belgium, Brazil, Germany, Italy, Sweden, Switzerland, UK	Parallel	6	1	0	2	2	E	NR NR	Y	L
91	Van Gaal 2005[138]	Placebo Rimonabant	Europe and USA	Parallel	24	2	1	1	2	E	0 0	Y	NR
92	Vazquez Roque 2007[139]	Placebo Sibutramine 15 mg	USA	Parallel	3	2	1	2	2	E	NR NR	N	L

ID	Study	Interventions	Country	Type of RCT	Intervention length (months)	Randomisation[a]	Allocation concealment[b]	Double blinding[c]	Participant flow[d]	Diet[e]	T2DM (%)[f]	Wash-in[g]	LOCF[h]
93	Wadden 2005[34]	Standard care	USA	Parallel	12	1	0	0	1	E	0	N	NR
		Sibutramine 15 mg									0		
94	Walsh 1999[140]	Placebo	UK	Parallel	3	1	0	1	2	E	NR	N	NR
		Sibutramine 15 mg									NR		
95	Wang 2005[141]	Placebo	Taiwan	Parallel	3	1	1	2	1	E	100	N	C
		Sibutramine 15 mg									100		
96	Wirth 2001[142]	Placebo	Germany	Parallel	12	1	0	1	1	S	NR	Y	L
		Sibutramine 15 mg									NR		
97	Wirth 2006[143]	Placebo	Germany	Parallel	11	2	1	2	2	S	NR	N	NR
		Sibutramine 15 mg									NR		
98	Zannad 2002[144]	Placebo	France	Parallel	6	1	0	1	2	E	NR	N	NR
		Sibutramine 10 mg									NR		

a Randomisation: 0 = none, 1 = mentioned, 2 = described and adequate.
b Allocation concealment: 0 = none, 1 = yes.
c Double blinding: 0 = none, 1 = mentioned, 2 = described and adequate.
d Flow of participants: 0 = none, 1 = mentioned, 2 = described and adequate.
e Diet: E = enhanced, S = standard.
f T2DM: NR = not reported.
g Wash-in: Y = yes, N = no, NR = not reported.
h LOCF (last observation carried forward): L = LOCF, C = completers, NR = not reported.

Results of individual studies

Individual study results are given in *Table 5*. In total, 83 trials included data on weight change, 41 on BMI change and 45 and 36 on 5% and 10% body weight loss respectively. A total of 33 trials measured outcome at 3 months, 38 at 6 months and 35 at 1 year.

At baseline, participants had an average age of 45.5 years (SD 6.97 years), 25.7% were male, 33.2% were diabetic and the mean BMI was 34.92 kg/m^2 (SD 2.58 kg/m^2).

Results of the evidence synthesis

Pair-wise meta-analysis

5% weight loss

3 months Five pair-wise comparisons could be made, including between one and three studies each. All showed an increased odds of achieving a 5% weight loss at 3 months if taking an active drug compared with either placebo or standard care. For example, those taking sibutramine 15 mg had a sixfold increased odds of achieving this target compared with those taking placebo [number of studies = 3, odds ratio (OR) 6.65, 95% CI 3.87 to 11.43]. There was no statistically significant difference between 10 mg and 15 mg sibutramine (number of studies = 1, OR 1.26, 95% CI 0.62 to 2.57). There was no significant statistical heterogeneity for any of the comparisons. (See *Figure 14a* and *Table 7a*.)

6 months Eight pair-wise comparisons could be made, including between one and six studies each. As at 3 months, taking an active drug was superior to either placebo or standard care. Taking orlistat and sibutramine in combination increased the odds of a good outcome compared with both orlistat and sibutramine 15 mg (OR 4.60, 95% CI 1.25 to 16.97 and OR 1.31, 95% CI 0.31 to 5.51 respectively). One study compared sibutramine 15 mg with orlistat and found that sibutramine 15 mg increased the odds of having a 5% weight loss (OR 3.52, 95% CI 1.03 to 12.07). Significant heterogeneity was seen for the sibutramine 10 mg versus placebo (I^2 58.0%) and sibutramine 15 mg versus placebo (I^2 81.6%) comparisons. (See *Figure 14b* and *Table 7b*.)

12 months Seven pair-wise comparisons could be made, including between 1 and 13 studies each. As with the 3- and 6-month data, the active drugs showed an increased odds of reaching the 5% weight loss outcome compared with placebo or standard care. For example, a threefold increase in the odds was seen for orlistat compared with placebo (number of studies = 13, OR 2.81, 95% CI 2.42 to 3.27), although there was significant heterogeneity for this comparison (I^2 51.7%). The 12-month data include a comparison of rimonabant against placebo, which shows an increased odds of a good outcome for those taking rimonabant (number of studies = 4, OR 3.73, 95% CI 1.77 to 7.88); again, significant heterogeneity was seen for this comparison (I^2 95.6%). (See *Figure 14c* and *Table 7c*.)

10% weight loss

3 months One three-arm trial only gave data on 10% weight loss at 3 months comparing placebo, sibutramine 10 mg and sibutramine 15 mg. The trial showed that both 10 mg and 15 mg of sibutramine were superior to placebo and there was no difference between the two sibutramine doses. (See *Figure 14d* and *Table 7d*.)

6 months Eight pair-wise comparisons could be made, including between one and seven studies each. Comparable to the 5% weight-loss data, active treatment was better than placebo or standard care, with combination treatment (orlistat and sibutramine) being better than orlistat and similar to sibutramine 15 mg (OR 3.57, 95% CI 1.13 to 11.25, and OR 1.16, 95% CI 0.40 to 3.39 respectively). No heterogeneity was seen for any of the comparisons, apart from the sibutramine 15 mg versus placebo comparison (I^2 84.8%). (See *Figure 14e* and *Table 7e*.)

TABLE 5 Data summary of included trials[a]

			3 months				6 months				12 months			
Study	**Arms**	***n***	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**
Apfelbaum 1999[52]	Placebo	78						10			43	18	+0.5 (0.65)	
	Sibutramine 10 mg	82						32			71	44	–5.2 (0.83)	
Audikovszky 2007[53]	Standard care	61							–4.10 (0.49)	–2.24 (0.23)				
	Orlistat	78							–6.90 (0.58)	–3.47 (0.18)				
Aydin 2004[54]	Standard care	19				–2.50 (0.30)								
	Sibutramine 10 mg	22				–4.40 (0.28)								
	Orlistat	25				–3.60 (0.20)								
Bakris 2002[55]	Placebo	265									60		–2.70 (0.39)	–0.90 (0.14)
	Orlistat	267									122		–5.40 (0.39)	–1.90 (0.14)
Beck-da-Silva 2005[56]	Standard care	10			–4.39 (2.34)	–1.45 (0.69)								
	Orlistat	11			–4.65 (2.95)	–1.66 (1.00)								
Berne 2005[57]	Placebo	109									12	3		
	Orlistat	111									51	15		
Bloch 2003[58]	Standard care	101	20		–2.00 (0.32)									
	Orlistat	105	33		–3.70 (0.32)									
Borges 2007[59]	Standard care	10				–3.00 (0.77)								
	Orlistat	14				–2.90 (0.51)								
Bray 1999[60]	Placebo	148					29	0						
	Sibutramine 15 mg	152					102	53						
	Sibutramine 10 mg	150					89	26						
Broom 2002[61]	Placebo	71					13	3	–2.60 (0.46)					
	Orlistat	66					29	5	–4.40 (0.51)					
Broom 2002[62]	Placebo	266									65	29	–2.30 (0.39)	
	Orlistat	265									147	52	–5.80 (0.52)	

continued

TABLE 5 Data summary of included trials[a] (*continued*)

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Chou 2007[63]	Orlistat	29												
	Sibutramine 10 mg	27			–1.2 (0.71)[b]									
Cocco 2005[64]	Placebo	45							–2.48 (0.20)	–1.86 (0.10)				
	Orlistat	45							–5.41 (0.21)	–3.33 (0.18)				
Cuellar 2000[65]	Placebo	34			–2.07 (1.36)	–1.37 (0.51)	5	0	–0.90 (0.88)	–0.40 (0.34)				
	Sibutramine 15 mg	35			–6.86 (0.71)	–3.14 (0.26)	26	19	–14.20 (1.40)	–5.60 (0.57)				
Davidson 1999[66]	Placebo	223									97	55	–5.81 (0.67)	
	Orlistat	657									432	256	–8.76 (0.37)	
Derosa 2003[67]	Placebo	23							–4.20 (0.60)	–1.30 (0.32)			–7.60 (0.70)	
	Orlistat	27							–5.10 (0.70)	–1.10 (0.47)			–8.60 (1.00)	
Derosa 2004[68]	Orlistat	71				–1.80 (0.70)				–2.70 (1.10)				–3.90 (1.50)
	Sibutramine 10 mg	70				–1.70 (0.60)				–2.70 (1.00)				–3.60 (1.40)
Derosa 2005[69]	Orlistat	55			–4.60 (0.24)	–1.60 (0.60)			–5.50 (0.28)	–1.90 (0.80)			–8.40 (0.48)	–2.90 (1.00)
	Sibutramine 10 mg	58			–4.50 (0.20)	–1.50 (0.20)			–5.40 (0.25)	–1.80 (0.40)			–8.30 (0.42)	–2.80 (0.60)
De Simone 2005[70]	Placebo	15			–5.10 (1.73)	–1.70 (0.45)								
	Sibutramine 15 mg	14			–9.00 (1.51)	–3.30 (0.35)								
Despres 2005[71]	Placebo	342									67	25	–1.50 (0.27)	
	Rimonabant	346									202	113	–6.90 (0.33)	
Di Francesco 2007[72]	Placebo	155					43	22						
	Sibutramine 10 mg	154					97	62						
Didangelos 2004[73]	Standard care	32					6		–3.90 (0.81)					
	Orlistat	94					63		–5.60 (0.50)					
Dixon 2008[74]	Standard care	22											–1.00 (0.82)	–0.50 (0.26)
	Orlistat	18											–3.10 (0.92)	–1.20 (0.24)
Drent 1995[75]	Placebo	7			–3.00 (0.72)									
	Orlistat	7			–4.20 (1.32)									

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Drent 1995[76]	Placebo	46			–2.98 (0.38)									
	Orlistat	47			–4.74 (0.38)									
Erdmann 2004[77]	Placebo	192							–4.90 (0.34)					
	Orlistat	192							–7.40 (0.35)					
Erondu 2007[78]	Placebo	101							–2.10 (0.52)					
	Sibutramine 10 mg	100							–5.80 (0.51)					
	Orlistat	99							–5.10 (0.42)					
Fanghanel 2000[79]	Placebo	54						4	–3.56 (0.57)	–1.46 (0.23)				
	Sibutramine 10 mg	55						19	–7.52 (0.68)	–3.14 (0.28)				
Fanghanel 2003[80]	Placebo	28					11	5	–3.40 (0.76)	–1.30 (0.32)				
	Sibutramine 10 mg	29					19	7	–5.50 (0.80)	–2.20 (0.32)				
Faria 2005[81]	Placebo	43					10		–2.40 (0.64)					
	Sibutramine 10 mg	43					27		–6.80 (0.35)					
Finer 2000[82]	Placebo	114									23	6		
	Orlistat	114									38	11	–1.99 (0.82)[b]	
Finer 2000[83]	Placebo	44	0		–0.10 (0.07)									
	Sibutramine 15 mg	47	9		–2.40 (0.30)									
Florakis 2008[84]	Standard care	28			–8.90 (1.12)	–3.40 (0.35)		9	–5.60 (1.21)					
	Sibutramine 10 mg	56			–11.60 (0.64)	–4.30 (0.30)		34	–7.60 (0.70)					
Garcia 2006[85]	Standard care	23								–0.50 (0.89)				
	Orlistat	25								–3.30 (1.30)				
Gokcel 2002[86]	Sibutramine 10 mg	50							–13.00 (0.11)	–5.22 (0.31)				
	Orlistat	50							–8.00 (0.07)	–3.20 (0.19)				
	Metformin	50							–9.00 (0.10)	–3.75 (0.93)				
Grudell 2008[87]	Placebo	62			–1.60 (1.04)	–0.10 (0.25)								
	Sibutramine 10 mg	58			–5.10 (1.05)	–1.80 (0.58)								
	Sibutramine 15 mg	61			–1.80 (1.13)	–0.90 (0.25)								

continued

TABLE 5 Data summary of included trials[a] (*continued*)

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Guimaraes 2006[88]	Placebo	10			–1.00 (1.07)	–0.40 (0.35)								
	Sibutramine 15 mg	8			–5.80 (1.59)	–2.20 (0.31)								
	Metformin	8			–3.60 (0.80)	–1.50 (0.66)								
Guy-Grand 2004[89]	Placebo	505							–1.73 (0.19)					
	Orlistat	499							–4.90 (0.63)					
Halpern 2002[90]	Placebo	31					13	1						
	Sibutramine 10 mg	30					12	8						
Halpern 2003[91]	Placebo	174					30	5	–2.58 (1.46)					
	Orlistat	164					49	11	–4.24 (0.23)					
Hanefeld 2002[92]	Placebo	180									57		–3.40 (0.40)	
	Orlistat	189									97		–5.30 (0.37)	
Hanotin 1998[93]	Placebo	59	11	3										
	Sibutramine 10 mg	59	29	12										
	Sibutramine 15 mg	62	34	11										
Hauner 2004[94]	Placebo	182									72	33	–5.10 (0.51)	
	Sibutramine 15 mg	180									109	71	–8.10 (0.59)	
Hauptman 2000[95]	Placebo	212							–4.70 (0.60)		65	24	–4.14 (0.56)	
	Orlistat	210							–8.00 (0.58)		106	60	–7.94 (0.57)	
Hazenberg 2000[96]	Placebo	59	10											
	Sibutramine 10 mg	54	24		–2.2 (0.71)[b]									
Hill 1999[97]	Placebo	188											–5.93 (0.69)	
	Orlistat	181											–7.24 (0.52)	
Hollander 1998[98]	Placebo	159									36	14	–4.31 (0.57)	
	Orlistat	163									79	29	–6.19 (0.51)	
Hung 2005[99]	Placebo	24							–0.70 (0.51)	–0.20 (0.19)				
	Sibutramine 15 mg	24							–2.50 (0.80)	–0.60 (0.23)				

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Kaya 2004[100]	Standard care	27			–6.24 (0.80)	–2.52 (0.26)								
	Sibutramine 10 mg	27			–11.72 (0.71)	–4.41 (0.24)								
	Orlistat	29			–9.35 (0.52)	–3.64 (0.18)								
	Orlistat and sibutramine	21			–13.68 (0.95)	–5.12 (0.31)								
Kelley 2002[101]	Placebo	269									35	10	–1.27 (0.28)	
	Orlistat	266									87	27	–3.89 (0.27)	
Kelley 2004[102]	Placebo	22							–9.40 (1.30)	–3.30 (0.40)				
	Orlistat	17							–10.10 (1.40)	–3.60 (0.50)				
Kiortsis 2008[103]	Standard care	20			–1.80 (0.91)	–1.50 (0.47)								
	Orlistat	20			–8.30 (0.72)	–3.20 (0.32)								
	Sibutramine 10 mg	20			–8.60 (0.85)	–3.30 (0.36)								
Krempf 2003[104]	Placebo	350									102	54	–3.30 (0.50)	
	Orlistat	346									170	85	–6.30 (0.50)	–1.00 (0.30)[b]
Kuo 2006[105]	Placebo	30			–0.40 (0.30)	–0.20 (0.20)								
	Orlistat	30			–2.50 (0.60)	–1.60 (0.30)								
Lindgarde 2000[106]	Placebo	186									76	27	–4.60 (0.40)	
	Orlistat	190									103	36	–5.90 (0.40)	
Lindholm 2008[107]	Placebo	20							–2.8 (1.50)					
	Sibutramine 15 mg	21							–7.8 (1.28)					
Mathus-Vliegen 2006[108]	Placebo	14											–14.60 (1.98)	–3.40 (0.70)
	Orlistat	14											–11.90 (1.44)	–4.00 (0.46)
McNulty 2003[109]	Placebo	64									8	0	–0.20 (0.50)	–0.10 (0.20)
	Sibutramine 15 mg	68									31	10	–5.10 (0.59)	–2.00 (0.19)
Miles 2002[110]	Placebo	254									40	10	–1.80 (0.30)	
	Orlistat	250									97	35	–4.70 (0.30)	

continued

TABLE 5 Data summary of included trials[a] (*continued*)

			3 months				6 months				12 months			
Study	**Arms**	***n***	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**	**5% (*n*)**	**10% (*n*)**	**Weight loss (kg)**	**BMI loss (kg/m²)**
Muls 2001[111]	Placebo	143					56	19	–1.88 (0.37)					
	Orlistat	147					94	34	–4.66 (0.31)					
Ozcelik 2004[112]	Placebo	10			–9.00 (1.37)	–3.90 (0.47)								
	Orlistat	14			–8.50 (1.07)	–3.40 (0.38)								
Ozcelik 2005[113]	Standard care	8			–9.00 (1.68)	–3.60 (0.68)								
	Orlistat	8			–11.50 (1.73)	–4.70 (0.70)								
Pathan 2004[115]	Standard care	15							–1.10 (1.53)					
	Orlistat	21							–3.10 (0.84)					
Pi-Sunyer 2006[115]	Placebo	607									121	52		
	Rimonabant	1214									317	129	–1.30 (0.30)	
Porter 2004[116]	Standard care	220							–3.10 (0.36)	–1.10 (0.11)	42		–2.30 (0.41)	
	Sibutramine 15 mg	281							–6.80 (0.33)	–2.40 (0.12)	133		–6.20 (0.43)	
Poston 2003[117]	Standard care	52							–1.00 (0.69)	–0.40 (0.23)			–0.30 (0.68)	–0.10 (0.23)
	Orlistat	56							–5.20 (0.74)	–2.00 (0.27)			–5.60 (0.77)	–2.20 (0.27)
Poston 2006[118]	Standard care	85					5		–0.60 (0.28)		8		+1.70 (0.46)	
	Orlistat	82					26		–2.90 (0.51)		22		–1.70 (0.70)	
Redmon 2003[119]	Standard care	29											–0.80 (0.90)	
	Sibutramine 15 mg	30											–7.30 (1.30)	
Rossner 2000[120]	Placebo	237										46	–6.60 (0.44)	
	Orlistat	242										93	–9.70 (0.40)	
Sarac 2006[121]	Placebo	20			–1.99 (0.58)	–1.10 (0.26)								
	Sibutramine 10 mg	20			–5.21 (0.66)	–2.60 (0.36)								
Sari 2004[122]	Orlistat	30					15	7	–5.50 (1.06)					
	Sibutramine 15 mg	29					22	14	–10.10 (1.04)					
	Sibutramine and orlistat	30					23	15	–10.80 (0.77)					

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Sari 2004[123]	Orlistat	30			–4.80 (0.53)	–0.90 (0.23)								
	Metformin	27			–5.77 (0.48)	–2.30 (0.25)								
Sathyapalan 2008[124]	Metformin	10			–1.60 (1.31)	–0.61 (0.55)								
	Rimonabant	10			–6.20 (1.50)	–2.34 (0.35)								
Scheen 2006[125]	Placebo	348									50	7	–1.40 (0.19)	
	Rimonabant	339									166	55	–5.30 (0.28)	
Scholze 2007[126]	Placebo	84	12		–1.50 (0.50)	–0.50 (0.20)								
	Sibutramine 15 mg	87	48		–5.70 (0.50)	–2.00 (0.20)								
Serrano-Rios 2002[127]	Placebo	65					19	4	–1.70 (0.50)	–0.60 (0.20)				
	Sibutramine 15 mg	69					34	11	–4.50 (0.50)	–1.90 (0.20)				
Shechter 2006[128]	Standard care	40				–0.70 (0.16)								
	Sibutramine 10 mg	40				–3.30 (0.16)								
Shi 2005[129]	Placebo	123					33	6						
	Orlistat	124					75	25	–3.00 (0.41)[b]					
Smith 2001[130]	Placebo	163									32	11	–1.60 (0.56)	
	Sibutramine 10 mg	161									60	30	–4.40 (0.51)	
	Sibutramine 15 mg	161									87	52	–6.40 (0.54)	
Swinburn 2005[131]	Placebo	169											–0.90 (0.32)	
	Orlistat	170											–4.70 (0.59)	
Tambascia 2003[132]	Placebo	14							+0.90 (1.03)					
	Sibutramine 10 mg	17							–5.60 (0.82)					
Tankova 2004[133]	Standard care	80	12		–2.69 (0.77)									
	Sibutramine 15 mg	93	73		–7.99 (0.55)									
Tiikkainen 2004[134]	Placebo	24							–7.40 (0.20)					
	Orlistat	23							–7.30 (0.20)					

continued

TABLE 5 Data summary of included trials[a] (*continued*)

Study	Arms	*n*	3 months				6 months				12 months			
			5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)	5% (*n*)	10% (*n*)	Weight loss (kg)	BMI loss (kg/m^2)
Torgerson 2004[135]	Placebo	1637									738	340		
	Orlistat	1640									1194	672		
Turker 2006[136]	Standard care	9			–0.90 (0.80)	–0.60 (0.30)								
	Orlistat	18			–6.00 (0.20)	–2.40 (0.10)								
Van Gaal 1998[137]	Placebo	123						23						
	Orlistat	120						45						
Van Gaal 2005[138]	Placebo	305									59	22	–1.80 (0.37)	
	Rimonabant	599									305	164	–6.60 (0.29)	
Vazquez Roque 2007[139]	Placebo	23			+0.90 (0.90)									
	Sibutramine 15 mg	25			–5.40 (0.80)	–0.51 (0.35)[b]								
Wadden 2005[34]	Standard care	55											–6.70 (1.07)	
	Sibutramine 15 mg	60											–12.10 (1.27)	
Walsh 1999[140]	Placebo	9			–5.10 (1.47)									
	Sibutramine 15 mg	10			–8.10 (1.20)									
Wang 2005[141]	Placebo	30			–0.40 (0.30)	–0.20 (0.20)								
	Sibutramine 15 mg	30			–2.50 (0.60)	–1.60 (0.30)								
Wirth 2001[142]	Placebo	201									70	26	+0.20 (0.39)	
	Sibutramine 15 mg	405									263	130	–3.80 (0.31)	
Wirth 2006[143]	Placebo	49			–2.10 (0.60)	–0.70 (0.20)								
	Sibutramine 15 mg	144			–6.90 (0.30)	–2.40 (0.10)								
Zannad 2002[144]	Placebo	60					27	6	–4.60 (0.56)	–1.70 (0.21)				
	Sibutramine 10 mg	64					53	33	–9.30 (0.72)	–3.50 (0.26)				

a Data given as a count for 5% and 10% body weight loss and mean (standard error) for weight and BMI change from baseline.
b Trial-based differences reported only.

12 months Five pair-wise comparisons could be made, including between 1 and 12 studies each. Orlistat, rimonabant, sibutramine 10 mg and sibutramine 15 mg all gave an increased odds of a good outcome compared with placebo. There was significant statistical heterogeneity for the rimonabant versus placebo comparison (I^2 93.5%). (See *Figure 14f* and *Table 7f*.)

Weight change from baseline

3 months Fifteen pair-wise comparisons could be made, including between 1 and 12 studies each. Statistically significant reductions in body weight were seen for rimonabant versus metformin, orlistat and sibutramine versus orlistat, orlistat versus placebo, sibutramine 10 mg versus placebo, sibutramine 15 mg versus placebo, orlistat versus standard care, orlistat and sibutramine versus standard care, sibutramine 10 mg versus standard care, sibutramine 15 mg versus standard care and sibutramine 10 mg versus sibutramine 15 mg. As with the 5% and 10% body weight loss outcomes, active drugs were superior to placebo or standard care and combination treatment was better than orlistat alone. There was significant heterogeneity for three of the comparisons: sibutramine 10 mg versus orlistat, sibutramine 15 mg versus placebo and orlistat versus standard care. (See *Figure 14g* and *Table 7g*.)

6 months Twelve pair-wise comparisons could be made, including between 1 and 10 studies each. The majority of studies compared orlistat with placebo, showing that orlistat reduces weight by 2.23 kg from baseline compared with placebo (95% CI –3.10 kg to –1.36 kg). For the other comparisons comparable results to the 3-month data were seen. Significant heterogeneity was seen for a number of the comparisons: orlistat versus sibutramine 10 mg (I^2 90.0%), orlistat versus placebo (I^2 87.0%) and sibutramine 15 mg versus placebo (I^2 92.4%). (See *Figure 14h* and *Table 7h*.)

12 months Eight pair-wise comparisons could be made, including between 1 and 16 studies each. As previously found, all active drug comparisons with either placebo or standard care were found to result in significant weight changes, three of which showed significant heterogeneity. At this time point, sibutramine 15 mg showed a greater weight loss than sibutramine 10 mg. (See *Figure 14i* and *Table 7i*.)

Body mass index change from baseline

3 months Fourteen pair-wise comparisons could be made, including between one and nine studies each. Statistically significant reductions in BMI were seen for nine of the comparisons (rimonabant vs metformin, metformin vs orlistat, orlistat and sibutramine vs orlistat, sibutramine 10 mg vs orlistat, sibutramine 10 mg vs placebo, sibutramine 15 mg vs placebo, orlistat vs standard care, orlistat and sibutramine vs standard care and sibutramine 10 mg vs standard care). In line with the previous findings, active drug seemed to reduce weight compared with a non-active control. Data comparing sibutramine 10 mg with orlistat show that those taking sibutramine 10 mg lose on average half a kilogram more than those taking orlistat. Significant heterogeneity was present for two of the comparisons (orlistat vs placebo and sibutramine 10 mg vs standard care). (See *Figure 14j* and *Table 7j*.)

6 months Eight pair-wise comparisons could be made, including between one and three studies each. Given a lack of studies and heterogeneity of results, statistically significant differences were not observed for sibutramine 10 mg versus orlistat, orlistat versus placebo and sibutramine 10 mg versus placebo. Sibutramine 15 mg versus placebo, orlistat versus standard care and sibutramine 15 mg versus standard care followed the previous results with the active comparator showing a bigger weight loss than the inactive. (See *Figure 14k* and *Table 7k*.)

12 months Four pair-wise comparisons could be made, including either one or two studies each. Orlistat was shown to be superior to placebo and standard care. No difference was seen between orlistat and sibutramine 10 mg (OR 0.15, 95% CI –1.84 to 2.14). (See *Figure 14l* and *Table 7l*.)

Publication bias Contour-enhanced funnel plots were constructed for pair-wise comparisons where there were five or more studies included (see *Appendix 3, Figure 15*). Visual inspection of these plots is somewhat inconclusive; however, there would not appear to be any strong suggestion of systematic suppression of results based on statistical significance.

Mixed-treatment comparison meta-analysis

Table 6 shows a summary of the results of the MTC meta-analysis, with placebo as the reference group. *Figure 3* shows the network diagrams for each of the outcomes considered. *Figure 16* in *Appendix 3* shows the percentage best plots for each treatment at each time point (this is the percentage of simulations in which each treatment option came out as having the largest treatment effect).

5% weight loss

3 months Sibutramine 15 mg had the largest probability (81.4%) of being the best intervention in terms of having a 5% body weight loss, with a 10-fold odds of having a good outcome compared with placebo [OR 9.95, 95% credible interval (CrI) 3.10 to 32.71]. No statistically significant difference was found between orlistat and placebo and standard care and placebo.

6 months At 6 months the combination of orlistat and sibutramine was the most efficacious intervention compared with placebo (OR 16.99, CrI 2.45 to 62.01). No difference was found between standard care and placebo. Orlistat, sibutramine 15 mg and sibutramine 10 mg were all more beneficial than placebo.

12 months Compared with placebo, similar results were seen at 12 months to those at 3 and 6 months. With the addition of rimonabant, all active treatments were significantly better than placebo, with no difference seen between placebo and standard care.

10% weight loss

3 months Only one three-arm trial reported data on 10% weight loss at 3 months. No statistically significant differences between placebo and sibutramine 10 mg or sibutramine 15 mg were seen.

6 months The active treatments (orlistat, sibutramine 10 mg, sibutramine 15 mg and a combination of orlistat and sibutramine) were all superior to placebo. No statistically significant difference was seen between placebo and standard care (OR 2.76, 95% CrI 0.21 to 12.1).

12 months Comparable results to those seen for 5% weight loss at 12 months were seen for 10% weight loss at this time point. Sibutramine 15 mg had the largest probability (57.9%) of being the best intervention, followed by rimonabant (31.2%) and sibutramine 10 mg (10.7%).

Weight change from baseline

3 months In comparison with placebo, the active drugs were all associated with greater weight loss, ranging from a mean change of –2.65 kg (95% CrI –4.00 kg to –1.31 kg) for orlistat to –11.23 kg (95% CrI –17.17 kg to –5.15 kg) for rimonabant. No statistically significant difference was seen between placebo and standard care.

6 months As previously seen, all active treatments were associated with greater weight loss than placebo, with the combination of orlistat and sibutramine producing the greatest weight loss (–9.67 kg compared with placebo) and the largest probability (93.1%) of being the best intervention. Standard care was also more effective than placebo at 6 months (–1.95 kg, 95% CrI –3.83 kg to –0.11 kg).

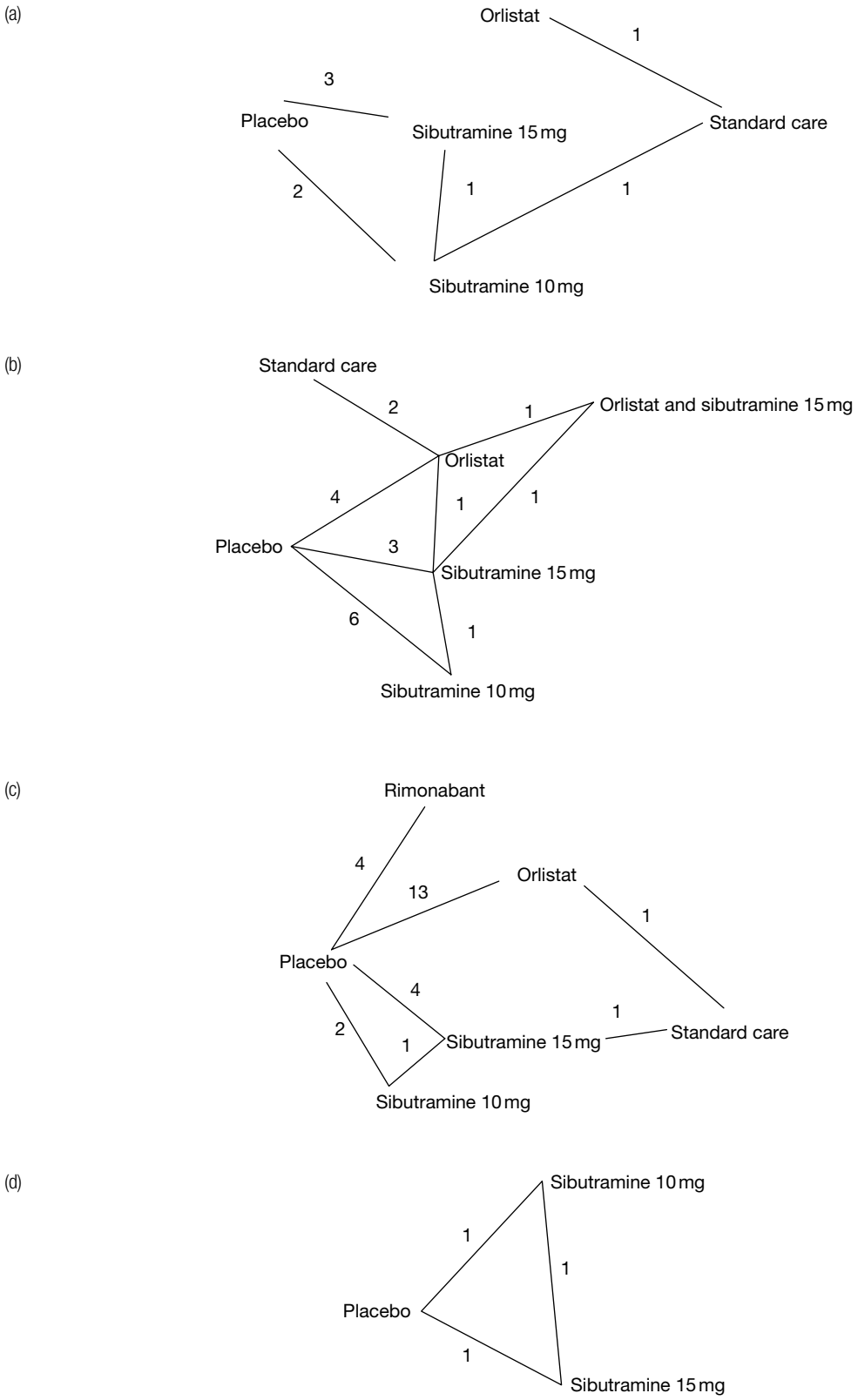
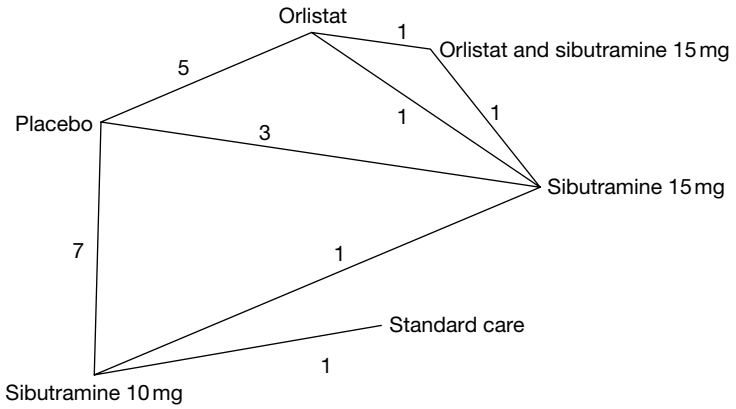
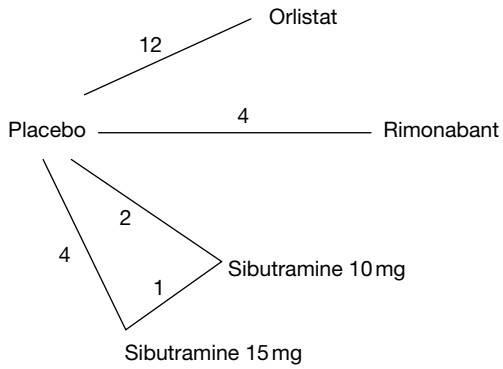


FIGURE 3 Network diagrams, showing the number of direct comparisons for each MTC analysis: (a) 5% weight loss 3 months, (b) 5% weight loss 6 months, (c) 5% weight loss 12 months, (d) 10% weight loss 3 months, (e) 10% weight loss 6 months, (f) 10% weight loss 12 months, (g) weight change 3 months, (h) weight change 6 months, (i) weight change 12 months, (j) BMI change 3 months, (k) BMI change 6 months, (l) BMI change 12 months.

(e)



(f)



(g)

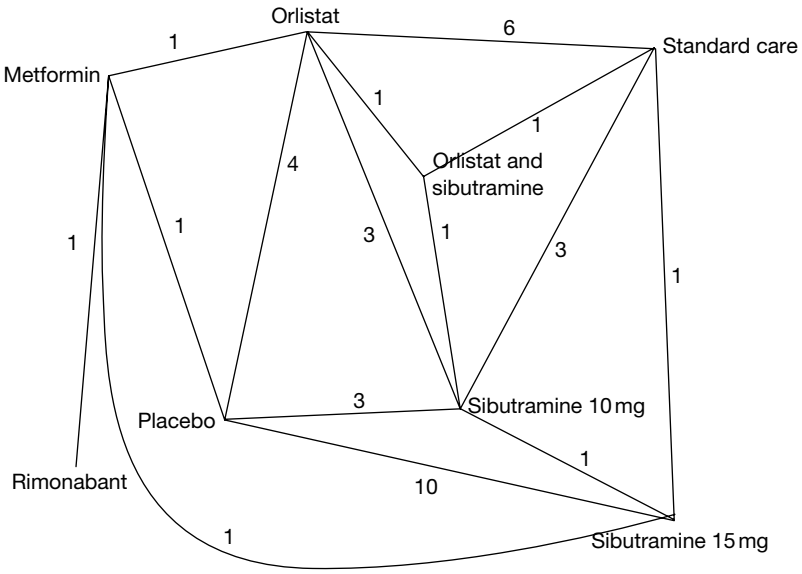
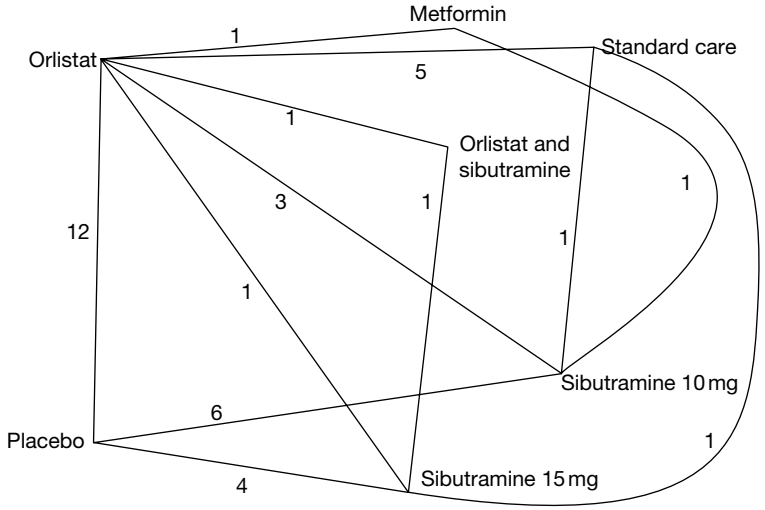
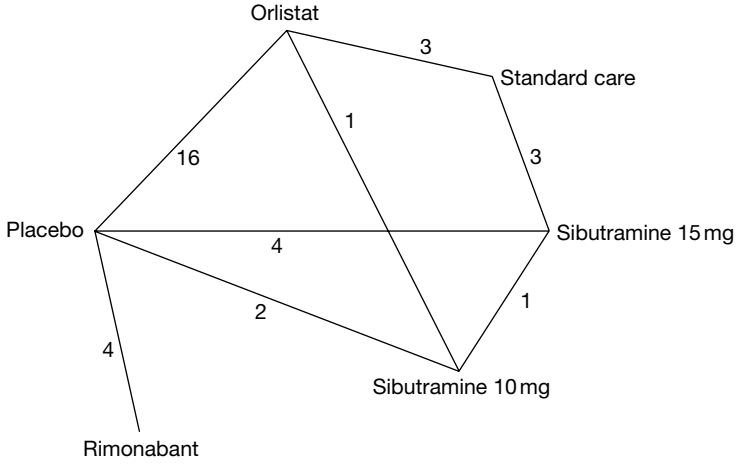


FIGURE 3 (*continued*)

(h)



(i)



(j)

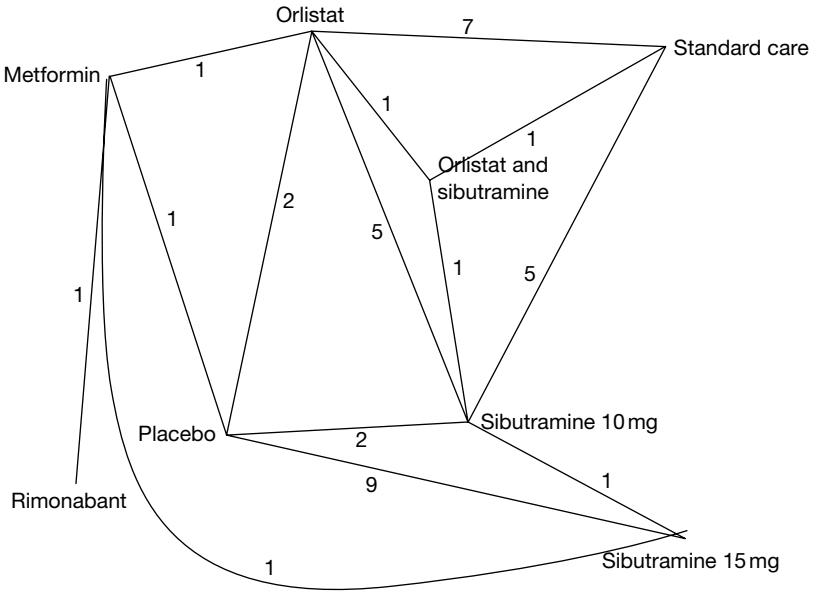
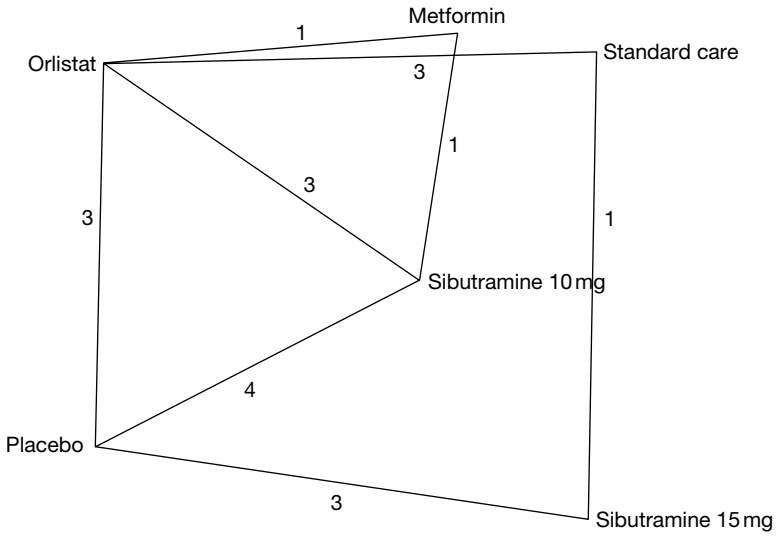


FIGURE 3 Network diagrams, showing the number of direct comparisons for each MTC analysis: (a) 5% weight loss 3 months, (b) 5% weight loss 6 months, (c) 5% weight loss 12 months, (d) 10% weight loss 3 months, (e) 10% weight loss 6 months, (f) 10% weight loss 12 months, (g) weight change 3 months, (h) weight change 6 months, (i) weight change 12 months, (j) BMI change 3 months, (k) BMI change 6 months, (l) BMI change 12 months. (*continued*)

(k)



(l)

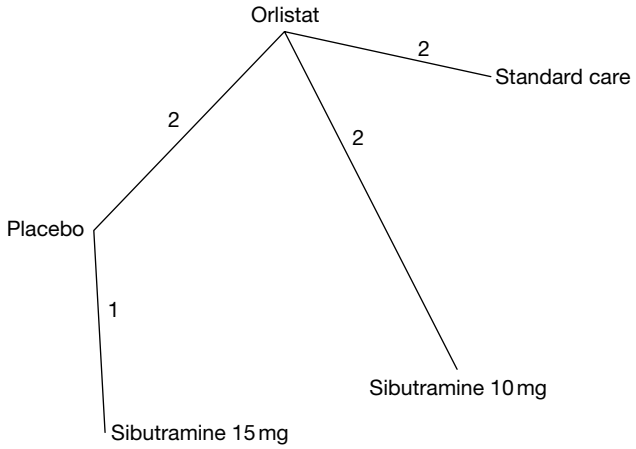


FIGURE 3 Network diagrams, showing the number of direct comparisons for each MTC analysis: (a) 5% weight loss 3 months, (b) 5% weight loss 6 months, (c) 5% weight loss 12 months, (d) 10% weight loss 3 months, (e) 10% weight loss 6 months, (f) 10% weight loss 12 months, (g) weight change 3 months, (h) weight change 6 months, (i) weight change 12 months, (j) BMI change 3 months, (k) BMI change 6 months, (l) BMI change 12 months. (*continued*)

12 months All treatments (orlistat, sibutramine 10 mg and 15 mg, and rimonabant) and standard care were superior to placebo at 12 months, with mean weight change in comparison with placebo ranging from –6.35 kg (sibutramine 15 mg) to –2.89 kg (standard care).

Body mass index change from baseline

3 months In line with the results for weight change at 3 months, all active treatments were associated with significant reductions in BMI compared with placebo. No difference was seen between standard care and placebo (0.50 kg/m^2, 95% CrI –0.51 kg/m^2 to 1.48 kg/m^2).

6 months At 6 months none of the active treatments or standard care was significantly better than placebo. For example, metformin was associated with an increase in BMI compared with placebo (0.18 kg/m^2, 95% CrI –4.05 kg/m^2 to 4.37 kg/m^2).

12 months At 12 months orlistat and sibutramine 15 mg resulted in significantly greater BMI loss than placebo. No difference was seen between sibutramine 10 mg and placebo or standard care.

TABLE 6 Mixed-treatment comparison model results unadjusted for covariates

		3 months			6 months			12 months		
Outcome	**Treatment**	**OR**	**95% CrI**	**% best ranking**	**OR**	**95% CrI**	**% best ranking**	**OR**	**95% CrI**	**% best ranking**
5% weight loss	Placebo	Reference		0	Reference		0	Reference		0
	Orlistat	3.86	0.06 to 15.11	2.5	2.95	1.62 to 4.97	0.1	2.89	2.22 to 3.72	2.0
	Sibutramine 10 mg	5.87	1.46 to 17.65	16.0	4.24	2.39 to 6.84	2.2	3.25	1.56 to 6.22	16.1
	Sibutramine 15 mg	9.95	3.10 to 32.71	81.4	6.90	3.49 to 12.99	21.5	4.06	2.51 to 6.29	47.3
	Rimonabant	–	–	–	–	–	–	3.78	2.39 to 5.79	34.5
	Orlistat and sibutramine	–	–	–	16.99	2.45 to 62.01	76.1	–	–	–
	Standard care	0.90	0.05 to 4.02	0.01	0.39	0.10 to 1.04	0	1.01	0.42 to 2.06	0
10% weight loss	Placebo	Reference		4.2	Reference		0	Reference		0
	Orlistat	–	–	–	3.10	1.44 to 6.14	0	2.43	1.72 to 3.39	0.3
	Sibutramine 10 mg	16.41	0.34 to 93.23	55.1	6.57	3.28 to 12.97	1.3	3.38	1.39 to 7.13	10.7
	Sibutramine 15 mg	14.34	0.28 to 77.43	40.7	18.83	6.70 to 48.1	54.3	5.02	2.63 to 9.12	57.9
	Orlistat and sibutramine	–	–	–	22.96	2.82 to 88.08	43.3	–	–	–
	Rimonabant	–	–	–	–	–	–	4.25	2.35 to 7.31	31.2
	Standard care	–	–	–	2.76	0.21 to 12.1	1.0	–	–	–

continued

TABLE 6 Mixed-treatment comparison model results unadjusted for covariates (*continued*)

Outcome	Treament	Mean difference	95% CrI	% best ranking	Mean difference	95% CrI	% best ranking	Mean difference	95% CrI	% best ranking
Weight change	Placebo	Reference		0	Reference		0	Reference		0
	Orlistat	–2.65	–4.00 to –1.31	0	–3.08	–4.20 to –2.03	0	–4.12	–5.07 to 3.15	0.2
	Metformin	–4.63	–7.46 to –1.68	0	–3.15	–6.51 to 0.29	0.4	–	–	–
	Sibutramine 10mg	–4.88	–6.40 to –3.43	0	–5.08	–6.55 to –3.62	1.3	–5.42	–7.36 to –3.42	16.6
	Sibutramine 15mg	–5.37	–6.59 to –4.10	0	–6.11	–8.11 to –4.23	5.3	–6.35	–8.06 to –4.63	78.2
	Rimonabant	–11.23	–17.17 to –5.15	62.6	–	–	–	–4.55	–6.20 to –2.92	5.0
	Orlistat and sibutramine	–10.18	–13.82 to –6.59	37.7	–9.67	–14.32 to –5.04	93.1	–	–	–
	Standard care	–1.36	–3.23 to 0.48	0	–1.95	–3.83 to –0.11	0	–2.89	–4.90 to –0.84	0
BMI change	Placebo	Reference		0	Reference		0.1	Reference	–	0
	Orlistat	–1.56	–2.54 to –0.58	0	–0.59	–2.60 to 1.39	7.5	–1.43	–2.67 to –0.18	1.8
	Metformin	–3.50	–5.02 to –1.87	0.6	0.18	–4.05 to 4.37	13.2	–	–	–
	Sibutramine 10 mg	–2.43	–3.33 to –1.54	0.1	–0.95	–2.89 to 1.02	16.4	–2.27	–5.08 to 0.59	33.0
	Sibutramine 15 mg	–2.25	–2.97 to –1.54	0	–1.81	–4.25 to 0.61	60.6	–2.91	–5.45 to –0.62	62.4
	Rimonabant	–6.24	–9.07 to –3.33	95.5	–	–	–	–	–	–
	Orlistat and sibutramine	–3.16	–5.22 to –1.11	3.7	–	–	–	–	–	–
	Standard care	0.50	–0.51 to 1.48	0	0.79	–2.04 to 3.72	1.3	–1.02	–3.11 to 1.12	2.8

Sibutramine 15 mg had the largest probability (62.4%) of being the best intervention in terms of BMI loss.

Comparison with pair-wise meta-analysis

The pair-wise and MTC analyses generally agreed for the two binary outcomes – 5% and 10% body weight loss. Across all outcomes, where inconsistency was seen the intervention effect size was generally in the same direction but with a different magnitude. For the continuous outcomes there was more disagreement. For example, for weight change at 3 months, there were 15 pair-wise comparisons, eight of which were consistent with the MTC results and seven of which were not, with the MTC results showing greater weight loss for the drug interventions than the pair-wise results (*Table 7a–l*).

Sensitivity analysis

Sensitivity analyses were carried out on the 12-month weight change outcome only.

Last observation carried forward

This analysis involved excluding those studies that used a per-protocol/completers analysis, or in which the method of analysis was not clear. The results including only the last observation carried forward (LOCF) studies were comparable to the main analysis including all studies (see *Appendix 3*, *Table 27*).

Wash-in

In this analysis we excluded those studies that had used a wash-in period to preselect people to be included in the trial. This led to smaller average weight reductions compared with placebo. For example, the main analysis showed that on average those taking sibutramine 15 mg lost 6.35 kg more than those taking placebo; this was reduced to 3.83 kg when the wash-in studies were excluded (see *Appendix 3*, *Table 27*).

Covariate adjusted analysis

Both the proportion of people with T2DM in the study and the level of diet and exercise advice given were added as covariates.

Type 2 diabetes

Those with T2DM lost more weight on each intervention than those without T2DM at 12 months. In those with T2DM, orlistat (mean difference –5.53 kg, 95% CrI –7.97 kg to –3.06 kg), sibutramine 15 mg (–7.17 kg, 95% CrI –11.24 kg to –3.00 kg) and lifestyle advice (–7.19 kg, 95% CrI –12.98 kg to –2.17 kg) were associated with greater weight change than placebo. For those with T2DM, the interventions with the largest probabilities of being the best were lifestyle advice (34.4%) and sibutramine 15 mg (33.9%) (*Table 8*).

Diet and exercise advice

Table 9 shows the estimates for those given standard diet and exercise advice and those given enhanced diet and exercise advice. Overall, no differences were seen between the types of diet and exercise advice. In addition, for many of the interventions (sibutramine 10 mg, rimonabant and standard care) no difference was seen between them and placebo for the standard advice.

Model fit

Table 10 shows the residual deviance for each of the models fitted above. Overall, all models had an acceptable level of fit, with the residual deviance being roughly equal to the number of unconstrained data points in all cases.

TABLE 7a Pair-wise meta-analysis results compared with MTC results: 5% weight loss 3 months

	OR (95% CI)				
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Standard care**
Placebo		–	4.07 (2.24 to 7.42)	6.65 (3.87 to 11.43)	–
Orlistat	3.86 (0.06 to 15.11)		–	–	0.52 (0.28 to 0.99)
Sibutramine 10 mg	5.87 (1.46 to 17.65)	32.31 (0.29 to 102.70)		1.26 (0.62 to 2.57)	–
Sibutramine 15 mg	9.95 (3.10 to 32.71)	35.04 (0.87 to 140.90)	2.33 (0.47 to 8.55)		0.05 (0.02 to 0.11)
Standard care	0.90 (0.05 to 4.02)	0.83 (0.08 to 3.07)	0.21 (0.01 to 0.96)	0.07 (0.01 to 0.28)	

MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7b Pair-wise meta-analysis results compared with MTC results: 5% weight loss 6 months

	OR (95% CI)					
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Orlistat and sibutramine**	**Standard care**
Placebo		2.93 (2.14 to 4.00)	4.05 (2.52 to 6.52)	6.45 (2.28 to 18.24)	–	–
Orlistat	2.95 (1.62 to 4.97)		–	3.52 (1.03 to 12.07)	4.60 (1.25 to 16.97)	0.12 (0.06 to 0.25)
Sibutramine 10 mg	4.25 (2.39 to 6.84)	1.55 (0.67 to 3.01)		1.40 (0.87 to 2.24)	–	–
Sibutramine 15 mg	6.90 (3.88 to 12.99)	2.50 (1.06 to 5.35)	1.72 (0.77 to 3.64)		1.31 (0.31 to 5.51)	–
Orlistat and sibutramine	16.99 (2.45 to 62.01)	5.90 (0.88 to 21.45)	4.28 (0.57 to 16.18)	2.58 (0.36 to 9.41)		–
Standard care	0.39 (0.10 to 1.04)	0.13 (0.04 to 0.32)	0.10 (0.02 to 0.28)	0.06 (0.01 to 0.18)	0.04 (0.004 to 0.18)	

MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7c Pair-wise meta-analysis results compared with MTC results: 5% weight loss 12 months

	OR (95% CI)					
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Rimonabant**	**Standard care**
Placebo		2.81 (2.42 to 3.27)	3.58 (1.58 to 8.09)	3.68 (2.54 to 5.33)	3.73 (1.77 to 7.88)	–
Orlistat	2.89 (2.22 to 3.72)		–	–	–	0.28 (0.12 to 0.68)
Sibutramine 10 mg	3.25 (1.56 to 6.22)	1.14 (0.52 to 2.24)		2.07 (1.31 to 3.26)	–	–
Sibutramine 15 mg	4.06 (2.51 to 6.29)	1.42 (0.83 to 2.92)	1.38 (0.62 to 2.69)		–	0.26 (0.17 to 0.40)
Rimonabant	3.78 (2.39 to 5.79)	1.33 (0.78 to 2.15)	1.31 (0.52 to 2.71)	0.99 (0.49 to 1.77)		–
Standard care	1.01 (0.42 to 2.06)	0.35 (0.15 to 0.72)	0.35 (0.11 to 0.83)	0.25 (0.11 to 0.50)	0.28 (0.10 to 0.62)	

MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7d Pair-wise meta-analysis results compared with MTC results: 10% weight loss 3 months

	OR (95% CI)		
	Placebo	**Sibutramine 10 mg**	**Sibutramine 15 mg**
Placebo		4.77 (1.27 to 17.90)	4.03 (1.06 to 15.25)
Sibutramine 10 mg	16.41 (0.34 to 93.23)		0.85 (0.34 to 2.10)
Sibutramine 15 mg	14.48 (0.28 to 77.41)	2.20[a] (0.06 to 11.46)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.

TABLE 7e Pair-wise meta-analysis results compared with MTC results: 10% weight loss 6 months

	OR (95% CI)					
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Orlistat and sibutramine**	**Standard care**
Placebo		2.54 (1.78 to 3.61)	5.52 (3.16 to 9.65)	28.28 (1.01 to 792.12)	–	–
Orlistat	3.10 (1.44 to 6.14)		–	3.08 (0.98 to 9.67)	3.57 (1.13 to 11.25)	–
Sibutramine 10 mg	6.57 (3.28 to 12.97)	2.40 (0.02 to 5.81)		2.55 (1.49 to 4.38)	–	0.27 (0.08 to 0.90)
Sibutramine 15 mg	18.83 (6.70 to 48.10)	6.69 (2.01 to 17.94)	3.09 (0.98 to 7.94)		1.16 (0.40 to 3.39)	–
Orlistat and sibutramine	22.96 (2.82 to 88.08)	7.67 (0.98 to 5.02)	3.79 (0.41 to 14.77)	1.30 (0.17 to 4.63)		–
Standard care	2.76 (0.21 to 12.10)	1.03 (0.06 to 4.57)	0.41 (0.04 to 1.67)	0.18 (0.01 to 0.79)	0.29 (0.01 to 1.44)	

MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7f Pair-wise meta-analysis results compared with MTC results: 10% weight loss 12 months

	OR (95% CI)				
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Rimonabant**
Placebo		2.30 (1.92 to 2.74)	3.59 (2.18 to 5.92)	3.96 (2.46 to 6.36)	4.21 (1.64 to 10.79)
Orlistat	2.43 (1.72 to 3.39)		–	–	–
Sibutramine 10 mg	3.38 (1.39 to 7.13)	1.44 (0.54 to 3.14)		2.13 (1.27 to 3.58)	–
Sibutramine 15 mg	5.02 (2.63 to 9.12)	2.13 (1.00 to 4.10)	1.70 (0.65 to 3.78)		–
Rimonabant	4.25 (2.35 to 7.31)	1.80 (0.89 to 3.32)	1.49 (0.49 to 3.57)	0.93 (0.37 to 1.95)	

MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7g Pair-wise meta-analysis results compared with MTC results: weight change 3 months

	Mean difference (95% CI)							
	Placebo	**Orlistat**	**Metformin**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Rimonabant**	**Orlistat and sibutramine**	**Standard care**
Placebo		–1.72 (–2.49 to –0.95)	–2.60 (–6.36 to 1.16)	–2.71 (–3.73 to –1.70)	–3.60 (–4.67 to –2.53)	–	–	–
Orlistat	–2.65[a] (–4.00 to –1.31)		–0.97 (–2.37 to 0.43)	–0.83 (–1.99 to 0.34)	–	–	–4.33 (–6.46 to –2.20)	3.62 (1.71 to 5.53)
Metformin	–4.63 (–7.46 to –1.68)	–1.98 (–4.75 to 0.91)		–	–2.20 (–5.68 to 1.28)	–4.60 (–8.50 to –0.70)	–	–
Sibutramine 10 mg	–4.88[a] (–6.40 to –3.43)	–2.23[a] (–3.52 to –0.99)	–0.24 (–3.34 to 2.68)		3.30 (0.28 to 6.33)	–	–1.96 (–4.28 to 0.36)	5.03 (2.80 to 7.27)
Sibutramine 15 mg	–5.37[a] (–6.59 to –4.10)	–2.73 (–4.36 to –1.07)	–0.74 (–3.65 to 2.06)	–0.50[a] (–2.20 to 1.29)		–	–	5.30 (3.44 to 7.16)
Rimonabant	–11.23 (–17.17 to –5.15)	–8.58 (–14.47 to –2.54)	–6.59 (–11.79 to –1.28)	–6.35 (–12.34 to –0.20)	–5.85 (–11.79 to 0.22)		–	–
Orlistat and sibutramine	–10.18 (–13.82 to –6.59)	–7.53[a] (–10.62 to –4.50)	–5.55 (–9.91 to –1.36)	–5.30[a] (–8.68 to –1.91)	–4.81 (–8.53 to –1.14)	1.05 (–5.87 to 7.69)		7.44 (5.02 to 9.86)
Standard care	–1.36 (–3.23 to 0.48)	1.29 (–0.30 to 2.82)	3.27 (0.09 to 6.36)	3.52 (1.78 to 5.26)	4.02 (2.01 to 5.97)	9.87 (3.64 to 15.91)	8.82 (5.34 to 12.28)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7h Pair-wise meta-analysis results compared with MTC results: weight change 6 months

	Mean difference (95% CI)						
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Orlistat and sibutramine**	**Metformin**	**Standard care**
Placebo		–2.23 (–3.10 to –1.36)	–4.13 (–5.02 to –3.24)	–5.54 (–9.69 to –1.39)	–	–	–
Orlistat	–3.08 (–4.20 to –2.03)		–1.90 (–5.82 to 2.02)	–4.60 (–7.51 to –1.69)	–5.30 (–7.80 to –2.73)	–1.00 (–1.24 to –0.76)	2.58 (1.84 to 3.31)
Sibutramine 10 mg	–5.08[a] (–6.55 to –3.62)	–2.00 (–3.57 to –0.42)		–	–	4.04 (3.75 to 4.33)	2.00 (0.74 to 4.74)
Sibutramine 15 mg	–6.11 (–8.11 to –4.23)	–3.03 (–5.10 to –1.06)	–1.03 (–3.39 to 1.27)		–0.70 (–3.23 to 1.83)	–	3.70 (2.74 to 4.66)
Orlistat and sibutramine	–9.67 (–14.32 to –5.04)	–6.59 (–11.05 to –2.17)	–4.59 (–9.43 to 0.17)	–3.56[a] (–8.08 to 1.02)		–	–
Metformin	–3.15 (–6.51 to 0.29)	–0.07[a] (–3.27 to 3.27)	1.93[a] (–1.10 to 5.04)	2.96 (–0.77 to 6.89)	6.52 (1.10 to 12.15)		–
Standard care	–1.95 (–3.83 to –0.11)	1.14[a] (–0.51 to 2.75)	3.14 (1.00 to 5.26)	4.17 (1.91 to 6.49)	7.73 (2.90 to 12.54)	1.21 (–2.47 to 4.78)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7i Pair-wise meta-analysis results compared with MTC results: weight change 12 months

	Mean difference (95% CI)					
	Placebo	Orlistat	Sibutramine 10 mg	Sibutramine 15 mg	Rimonabant	Standard care
Placebo		–2.55 (–2.98 to –2.12)	–4.16 (–6.99 to –1.32)	–4.14 (–4.91 to –3.38)	–3.83 (–5.76 to –1.91)	–
Orlistat	–4.12[a] (–5.07 to –3.15)		–0.10 (–1.36 to 1.16)	–	–	3.67 (1.99 to 5.35)
Sibutramine 10 mg	–5.42 (–7.36 to –3.42)	–1.30 (–3.30 to 0.74)		–2.00 (–3.45 to –0.55)	–	–
Sibutramine 15 mg	–6.35[a] (–8.06 to –4.63)	–2.23 (–4.03 to –2.23)	–0.94 (–2.96 to 1.08)		–	4.75 (3.26 to 6.24)
Rimonabant	–4.55 (–6.20 to –2.92)	–0.43 (–2.31 to 1.41)	0.87 (–1.70 to 3.42)	1.80 (–0.57 to 4.14)		–
Standard care	–2.89 (–4.90 to –0.85)	1.23[a] (–0.69 to 3.17)	2.52 (0.06 to 5.03)	3.46 (1.50 to 5.45)	1.66 (–0.87 to 4.26)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7j Pair-wise meta-analysis results compared with MTC results: BMI change 3 months

	Mean difference (95% CI)							
	Placebo	Orlistat	Metformin	Rimonabant	Sibutramine 10 mg	Sibutramine 15 mg	Standard care	Orlistat and sibutramine
Placebo		–0.51 (–2.37 to 1.35)	–1.10 (–2.55 to 0.35)	–	–1.57 (–2.27 to –0.86)	–1.38 (–1.67 to –1.09)	–	–
Orlistat	–1.56 (–2.54 to –0.58		–3.20 (–3.86 to –2.54)	–	–0.56 (–0.93 to –0.19)	–	1.36 (0.93 to 1.79)	–1.48 (–2.19 to –0.77)
Metformin	–3.50[a] (–5.02 to –1.87)	–1.94[a] (–3.42 to –0.28)		–1.73 (–3.02 to –0.45)	–	0.70 (–0.72 to 2.12)	–	–
Rimonabant	–6.24 (–9.07 to –3.34)	–4.68 (–7.47 to –1.76)	–2.74 (–5.20 to –0.37)		–	–	–	–
Sibutramine 10 mg	–2.43 (–3.33 to –1.54)	–0.87 (–1.52 to –0.23)	1.07 (–0.63 to 2.59)	3.81 (0.87 to 6.64)		0.90 (–0.34 to 2.14)	1.89 (1.30 to 2.48)	–0.71 (–1.48 to 0.06)
Sibutramine 15 mg	–2.25[a] (–2.97 to –1.54)	–0.69 (–1.75 to 0.38)	1.25 (–0.37 to 2.78)	3.99 (1.09 to 6.80)	0.18 (–0.81 to 1.18)		–	–
Standard care	0.49 (–0.51 to 1.47)	2.05[a] (1.30 to 2.81)	3.99 (2.26 to 5.57)	6.74 (3.74 to 9.58)	2.93[a] (2.12 to 3.74)	2.75 (1.63 to 3.85)		–2.60 (–3.40 to –1.80)
Orlistat and sibutramine	–3.16 (–5.22 to –1.11)	–1.60 (–3.53 to 0.37)	0.34 (–2.17 to 2.67)	3.08 (–0.40 to 6.44)	–0.72 (–2.64 to 1.22)	–0.91 (–3.03 to 1.20)	–3.65[a] (–5.56 to –1.71)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7k Pair-wise meta-analysis results compared with MTC results: BMI change 6 months

	Mean difference (95% CI)					
	Placebo	**Orlistat**	**Metformin**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Standard care**
Placebo		–0.62 (–1.78 to 0.54)	–	–0.62 (–4.44 to 3.19)	–2.19 (–4.15 to –0.23)	–
Orlistat	–0.59 (–2.60 to 1.39)		0.55 (–1.32 to 2.42)	–0.92 (–2.59 to 0.75)	–	1.41 (0.97 to 1.84)
Metformin	0.18 (–4.05 to 4.37)	0.77 (–3.03 to 4.57)		–1.47 (–3.41 to 0.47)	–	–
Sibutramine 10 mg	–0.95 (–2.89 to 1.02)	–0.36 (–2.43 to 1.80)	–1.13 (–4.64 to 2.38)		–	–
Sibutramine 15 mg	–1.81 (–4.25 to 0.61)	–1.22 (–4.07 to 1.61)	–1.99 (–6.65 to 2.68)	–0.86 (–3.86 to 2.11)		1.30 (0.98 to 1.62)
Standard care	0.79 (–2.04 to 3.72)	1.38 (–1.04 to 3.81)	0.61 (–3.80 to 5.13)	1.74 (–1.29 to 4.75)	2.60[a] (–0.49 to 5.84)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 7l Pair-wise meta-analysis results compared with MTC results: BMI change 12 months

	Mean difference (95% CI)				
	Placebo	**Orlistat**	**Sibutramine 10 mg**	**Sibutramine 15 mg**	**Standard care**
Placebo		–0.98 (–1.35 to –0.61)	–	–1.90 (–2.45 to –1.35)	–
Orlistat	–1.43[a] (–2.67 to –0.18)		–0.15 (–2.14 to 1.84)	–	1.40 (0.03 to 2.77)
Sibutramine 10 mg	–2.27 (–5.08 to 0.59)	–0.84 (–3.42 to 1.74)		–	–
Sibutramine 15 mg	–2.91[a] (–5.45 to –0.62)	–1.49 (–4.33 to 1.11)	–0.64 (–4.42 to 2.95)		–
Standard care	–1.01 (–3.11 to 1.12)	0.41 (–1.26 to 2.04)	1.25 (–1.80 to 4.27)	1.90 (–1.19 to 5.20)	

a MTC estimate does not fall within the 95% CI of the pair-wise meta-analysis.
MTC cells that are shaded light grey indicate that there are no head-to-head trials for these comparisons.

TABLE 8 Type 2 diabetes vs no diabetes at 12 months: results of MTC analysis

		T2DM			No T2DM		
		Mean difference	95% CrI	% best ranking	Mean difference	95% CrI	% best ranking
Weight change	Placebo	Reference		0	Reference		0
	Orlistat	–5.53	–7.97 to –3.06	9.2	–2.44	–4.23 to –0.60	0.5
	Sibutramine 10 mg	–3.91	–13.41 to 7.55	13.7	–2.61	–6.16 to 0.86	1.8
	Sibutramine 15 mg	–7.17	–11.24 to –3.00	33.9	–6.21	–9.77 to –2.74	86.6
	Rimonabant	–4.71	–9.09 to 0.04	8.7	–3.43	–6.63 to –0.36	10.5
	Standard care	–7.19	–12.98 to –2.17	34.4	–2.47	–5.66 to 0.77	0.6

TABLE 9 Enhanced diet vs standard diet advice at 12 months: results of MTC analysis

		Enhanced diet and/or exercise advice			Standard diet and/or exercise advice		
		Mean difference	95% CrI	% best ranking	Mean difference	95% CrI	% best ranking
Weight change	Placebo	Reference		0	Reference		0
	Orlistat	–3.49	–5.22 to –1.74	0.2	–4.38	–6.37 to –2.37	9.6
	Sibutramine 10 mg	–5.39	–9.17 to –1.71	31.9	–1.26	–5.62 to 3.02	0.1
	Sibutramine 15 mg	–5.99	–8.92 to –3.15	46.6	–6.49	–10.91 to –2.17	60.1
	Rimonabant	–4.96	–8.15 to –1.75	21.0	–4.16	–8.69 to 0.41	13.7
	Standard care	–3.23	–5.97 to –0.47	0.2	–2.74	–13.36 to 8.42	16.5

TABLE 10 Model fit assessed using the residual deviance

Outcome	Time point	Residual deviance	Data points
5% weight loss	3	13.437	13
	6	34.562	32
	12	48.981	49
10% weight loss	3	3.097	3
	6	41.919	34
	12	44.607	43
Weight change	3	59.516	61
	6	67.301	64
	12	63.079	63
Weight change – T2DM covariate	12	51.348	51
Weight change – diet covariate	12	63.156	63
Weight change – LOCF only	12	38.999	39
Weight change – wash-in	12	63.156	24
BMI change	3	55.614	53
	6	34.600	35
	12	14.227	15

Chapter 4

Epidemiological model of natural history

Introduction

To appropriately populate the economic decision model described in *Chapter 5* a UK epidemiological model of the natural history of how changes in BMI affect the risk of major clinical events [development of diabetes, myocardial infarction (MI), stroke and death] is required together with a model of how BMI levels change as a population ages.

Although a number of research studies have explored the relationship between BMI and the development of diabetes, CVD or mortality, they have had a number of limitations. They have (1) been of a retrospective or cross-sectional design[145] and therefore have only established an association or (2) used categorised BMI, for example overweight, obese, etc.,[146–150] or (3) have been conducted primarily outside the UK.[151]

Therefore, this section describes the development of both a BMI risk model for the development of diabetes, MI, stroke and death and a natural history model of BMI using the General Practice Research Database (GPRD). The use of the GPRD will enable risk to be estimated at specific levels of BMI and age. Similarly, age-specific BMI levels can be estimated. This also allows the adjustment for potentially important confounding factors in both models.

Background to the General Practice Research Database

The GPRD was established in 1987 and contains anonymised longitudinal primary care records from over 12 million patients in the UK. Of these, over 10 million are useable for research purposes, representing over 63 million person-years of observation.[152]

Patients and data preparation

The initial study population comprised 100,000 individuals drawn randomly from the GPRD subject to them (1) being ≥ 18 years of age and (2) having three or more BMI readings of over 27 kg/m^2. All patient data prior to 1980 were removed, as were any observations with missing dates. BMI readings during a pregnancy (and for the following 6 months) were removed, as were any BMI readings outside the range 25–60 kg/m^2.

The occurrence of any of four clinical events [death from any cause – all-cause mortality (ACM), MI, stroke and onset of T2DM] was then identified for each individual using Oxford Medical Information Systems (OXMIS) and READ codes.[153] As patient data were not available for all outcomes, separate patient cohorts were created for each outcome. If no events occurred, the date of an individual's last BMI reading was taken as the censoring date. Each of the ACM, MI and stroke cohorts were then subdivided into diabetic and non-diabetic cohorts. Each cohort consisted only of patients who were either diabetic or non-diabetic for their *entire* follow-up period. This aimed to reduce 'carry-over' effects from comorbidities occurring when, for example, a patient was non-diabetic but then became diabetic. This also negates the issue of a reliable

diagnosis of diabetes. A patient may be diagnosed as diabetic; however, his or her GPRD record may not reflect this for a significant period of time.

This resulted in seven overlapping cohorts, allowing the development of diabetic- and non-diabetic-specific survival models for each of the four time-to-event outcomes. Clearly, only a non-diabetic cohort was used when the time-to-event outcome was development of T2DM.

Event numbers and follow-up times are summarised in *Table 11*. Typical examples of the distribution of follow-up times for diabetic and non-diabetic cohorts can be seen in *Figures 4* and *5* respectively. In total, 90.38% of patients in the diabetic cohort, shown in *Figure 4*, had follow-up of up to 15 years. When applying the survival models in *Time-to-event analysis* (below) it is therefore unwise to apply the results beyond this range.

Covariates available for analyses included repeated measurements of BMI (kg/m^2), baseline age (years) and categorical variables (reference levels of categorical covariates are listed first): sex (female/male), aspirin treatment (no/yes), statin treatment (no/yes), blood pressure (BP)-lowering treatment (no/yes) and smoking status (non-smoker, ex-smoker and current smoker). Diabetic cohorts also included insulin treatment (no/yes) as a covariate.

Based on previous large-scale cohort studies[150,154] it was deemed sufficient to use only baseline BMI in the survival analyses (see *Time-to-event analysis*). Covariate summary statistics for each of the seven cohorts are shown in *Tables 12–18*.

Time-to-event analysis

To obtain transition probabilities for the economic decision model developed in *Chapter 5* a series of time-to-event analyses were conducted.

Methods

Weibull proportional hazards regression models were applied to each of the seven cohorts defined in *Patients and data preparation*, in order to obtain the estimated hazard of each event of interest. The hazard function of the Weibull model is given by:

$$h(t) = \lambda\gamma t^{\gamma-1} \qquad \text{[Equation 1]}$$

TABLE 11 Summary statistics for the seven cohorts showing number of events and average follow-up times

		Diabetic				Non-diabetic			
		No. of patients		Follow-up time (years)		No. of patients		Follow-up time (years)	
Outcome	Censored/ event	*n*	%	Median	Maximum	*n*	%	Median	Maximum
MI	Censored	4404	94.95	5.38	23.99	66,556	96.81	9.17	27.96
	Event	234	5.05	6.09	19.01	2192	3.19	7.51	24.45
Stroke	Censored	4400	94.16	5.39	23.99	66,688	96.62	9.17	27.96
	Event	273	5.84	5.14	18.57	2332	3.38	6.66	23.32
ACM	Censored	4264	87.47	5.34	23.99	65,376	94.02	9.34	27.96
	Event	611	12.53	7.78	19.55	4156	5.98	10.36	26.35
T2DM	Censored	–	–	–	–	69,280	85.04	9.22	27.96
	Event	–	–	–	–	12,186	14.96	7.89	25.93

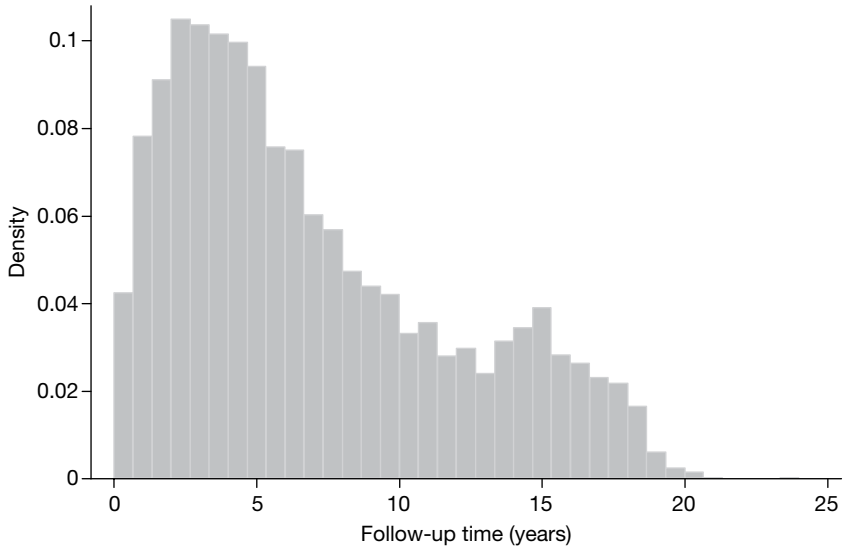


FIGURE 4 Distribution of follow-up time for the diabetic cohort with outcome ACM.

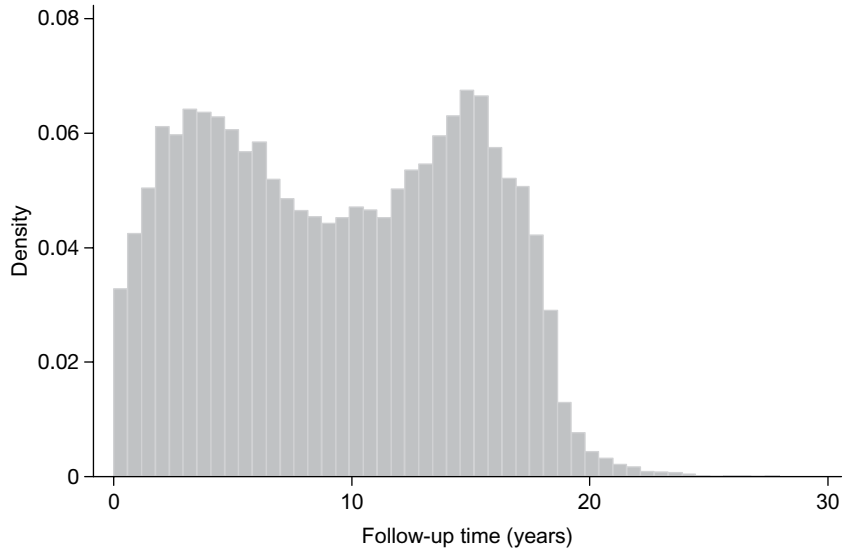


FIGURE 5 Distribution of follow-up time for the non-diabetic cohort with outcome ACM.

where $\lambda = \exp(x^T\beta)$, $\gamma = \exp(z^T\alpha)$ and z is a subset of the covariate vector x. Each β is the effect on the scale parameter, λ, with each α the effect on the shape of the hazard function, γ. Covariates investigated are defined in *Patients and data preparation*.

The scale parameter of the hazard function, λ, was allowed to depend on all covariates listed above, irrespective of statistical significance. Higher-order polynomial terms (up to power 5) of BMI and age were also investigated, based on statistical significance at the 5% level. This defined the covariate set x. The shape parameter of the hazard function, γ, was then allowed to depend on z, a subset of x, based on statistical significance at the 5% level.

All analyses were conducted in Stata version 11.0.

TABLE 12 Baseline covariate summary statistics for the ACM diabetic cohort

	Censored		Died	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	31	25 to 60	30.1	25 to 52.2
Baseline age (years)[b]	58.65	58.28 to 59.01	68.03	67.28 to 68.79
Gender				
Female	1821	87.17	268	12.83
Male	2443	87.69	343	12.31
Insulin				
No	2975	87.09	441	12.91
Yes	1289	88.35	170	11.65
Aspirin				
No	3284	88.35	433	11.65
Yes	980	84.63	178	15.37
Statins				
No	704	71.04	287	28.96
Yes	3560	91.66	324	8.34
BP treatment				
No	608	88.89	76	11.11
Yes	3656	87.23	535	12.77

a Median and range.
b Mean and 95% CI.

TABLE 13 Baseline covariate summary statistics for ACM non-diabetic cohort

	Censored		Died	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	29.8	25 to 60	30.00	25 to 57.4
Baseline age (years)[b]	45.12	45.00 to 45.24	63.82	63.46 to 64.18
Gender				
Female	40,580	95.46	1931	4.54
Male	24,796	91.77	2225	8.23
Aspirin				
No	59,524	94.91	3189	5.09
Yes	5852	85.82	967	14.18
Statins				
No	47,072	94.30	2844	5.70
Yes	18,304	93.31	1312	6.69
BP treatment				
No	29,826	97.47	774	2.53
Yes	35,550	91.31	3382	8.69

a Median and range.
b Mean and 95% CI.

TABLE 14 Baseline covariate summary statistics for MI diabetic cohort

	Censored		MI	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	31	25 to 60	29.4	25.1 to 52.2
Baseline age (years)[b]	59.44	59.08 to 59.81	61.97	60.56 to 63.37
Gender				
Female	1940	95.76	86	4.24
Male	2464	94.33	148	5.67
Insulin				
No	3150	96.45	116	3.55
Yes	1254	91.40	118	8.60
Aspirin				
No	3415	96.36	129	3.64
Yes	989	90.40	105	9.60
Statins				
No	945	96.53	34	3.47
Yes	3459	94.53	200	5.47
BP treatment				
No	673	98.97	7	1.03
Yes	3731	94.26	227	5.74

a Median and range.
b Mean and 95% CI.

TABLE 15 Baseline covariate summary statistics for MI non-diabetic cohort

	Censored		MI	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	29.8	25 to 60	29.1	25 to 53.3
Baseline age (years)[b]	45.65	45.53 to 45.77	57.29	56.81 to 57.78
Gender				
Female	41,684	98.34	704	1.66
Male	24,872	94.36	1488	5.64
Aspirin				
No	60,916	97.93	1286	2.07
Yes	5640	86.16	906	13.84
Statins				
No	49,542	99.40	301	0.60
Yes	17,014	90.00	1891	10.00
BP treatment				
No	30,512	99.83	51	0.17
Yes	36,044	94.39	2141	5.61

a Median and range.
b Mean and 95% CI.

TABLE 16 Baseline covariate summary statistics for stroke diabetic cohort

	Censored		Stroke	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	30.9	25 to 60	30.3	25 to 48
Baseline age (years)[b]	59.26	58.90 to 59.62	63.97	62.74 to 65.20
Gender				
Female	1865	93.34	133	6.66
Male	2535	94.77	140	5.23
Insulin				
No	3114	94.71	174	5.29
Yes	1286	92.85	99	7.15
Aspirin				
No	3416	95.42	164	4.58
Yes	984	90.03	109	9.97
Statins				
No	882	92.26	74	7.74
Yes	3518	94.65	199	5.35
BP treatment				
No	654	97.18	19	2.82
Yes	3746	93.65	254	6.35

a Median and range.
b Mean and 95% CI.

TABLE 17 Baseline covariate summary statistics for stroke non-diabetic cohort

	Censored		Stroke	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	29.8	25 to 60	29.6	25 to 55
Baseline age (years)[b]	45.59	45.47 to 45.70	60.42	59.94 to 60.90
Gender				
Female	41,172	97.29	1147	2.71
Male	25,516	95.56	1185	4.44
Aspirin				
No	60,879	97.60	1498	2.40
Yes	5809	87.45	834	12.55
Statins				
No	48,955	98.58	707	1.42
Yes	17,733	91.61	1625	8.39
BP treatment				
No	30,290	99.26	225	0.74
Yes	36,398	94.53	2107	5.47

a Median and range.
b Mean and 95% CI.

TABLE 18 Baseline covariate summary statistics for non-diabetic cohort with outcome T2DM

	Censored		T2DM	
Variable	***n***	**%**	***n***	**%**
Baseline BMI (kg/m^2)[a]	29.8	25 to 60	31	25 to 59.3
Baseline age (years)[b]	46.22	46.10 to 46.33	53.47	53.24 to 53.69
Gender				
Female	42,400	88.49	5513	11.51
Male	26,880	80.11	6673	19.89
Aspirin				
No	62,495	86.96	9371	13.04
Yes	6785	70.68	2815	29.32
Statins				
No	49,814	95.45	2372	4.55
Yes	19,466	66.48	9814	33.52
BP treatment				
No	30,545	94.47	1787	5.53
Yes	38,735	78.84	10,399	21.16

a Median and range.
b Mean and 95% CI.

Results

Tables 19–22 show the results from applying Weibull proportional hazard regression models to each event of interest: ACM, MI, stroke and T2DM respectively. *Tables 19–21* contain results applied separately to both diabetic and non-diabetic cohorts, whereas *Table 22* contains the results from applying a Weibull regression model to the non-diabetic cohort, with outcome T2DM. All regression coefficients and associated 95% CIs are on the log scale.

To illustrate the findings of the time-to-event analyses, we present *Table 23*, which shows the probability of experiencing each event of interest, across diabetic/non-diabetic cohort, within 5, 10 and 15 years, for a selection of covariate combinations. From *Table 23* we see that the probability of experiencing an event is higher across all covariate combinations if a patient is diabetic compared with non-diabetic.

We further illustrate this in *Figure 6*, showing the predicted survival probability curve for a woman aged 40 years who is a non-smoker and on no treatments, comparing across diabetic status and whether the patient had a BMI of 30 kg/m^2 or 40 kg/m^2 at baseline.

Sensitivity analyses

The models described and reported in the two previous sections make a number of assumptions, the most important of which are the assumption of a baseline Weibull hazard and the fact that covariates act linearly on a log-hazard scale.

The validity of both of these assumptions was assessed by using a flexible baseline hazard function[155] and restricted cubic splines[156] to model continuous terms.

For example, *Figure 7* shows predicted versus observed time to death for the diabetic cohort. *Figure 7a* shows predictions using a Weibull survival model, whereas *Figure 7b* shows predictions

TABLE 19 Results of time-to-event analysis applied to diabetic and non-diabetic cohorts with outcome ACM

	Diabetic cohort		Non-diabetic cohort	
Covariates	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
ln(λ)				
BMI	0.277	0.060 to 0.495	6.123	3.032 to 9.213
BMI^2	–3.38E-03	-6.62×10^{-3} to -1.54×10^{-3}	–0.214	–0.336 to –0.092
BMI^3	–	–	3.43×10^{-3}	1.30×10^{-3} to 5.56×10^{-3}
BMI^4	–	–	-2.100×10^{-5}	-3.490×10^{-5} to -7.080×10^{-6}
Age (years)	0.090	0.081 to 0.100	0.079	0.055 to 0.103
Age^2	–	–	3.987×10^{-4}	2.345×10^{-4} to 5.628×10^{-4}
Sex	0.410	0.236 to 0.584	1.411	1.159 to 1.663
Aspirin treatment	–0.026	–0.202 to 0.150	–0.620	–0.966 to –0.273
Insulin treatment	–0.103	–0.289 to 0.082		
Statin treatment	–0.806	–0.981 to –0.631	–1.301	–1.636 to –0.966
BP drug treatment	–0.208	–0.459 to 0.042	–0.797	–1.113 to –0.481
Smoker type				
Ex-smoker	–0.130	–0.314 to 0.054	–1.196	–1.501 to –0.891
Smoker	0.326	0.084 to 0.568	0.338	0.001 to 0.674
Constant	–17.258	–20.962 to –13.554	–80.781	–110.005 to –51.556
ln(γ)				
BMI	–	–	–0.085	–0.125 to –0.045
BMI^2	–	–	1.035×10^{-3}	4.651×10^{-4} to 1.605×10^{-3}
Age	–	–	–0.002	–0.004 to –0.001
Sex	–	–	–0.108	–0.143 to –0.074
Aspirin treatment	–	–	0.098	0.053 to 0.142
Statin treatment	–	–	0.095	0.051 to 0.139
BP drug treatment	–	–	0.114	0.064 to 0.164
Smoker type				
Ex-smoker	–	–	0.156	0.114 to 0.197
Smoker	–	–	0.041	–0.009 to 0.091
Constant	0.785	0.727 to 0.844	2.600	1.917 to 3.284

using a flexible parametric model with three degrees of freedom to model the baseline hazard. We observed only a minor improvement in prediction when using a more flexible baseline model.

Furthermore, *Figure 8* shows the hazard ratio for the age term, against age, comparing the use of splines to model age, as opposed to a log-linear term in age. Good agreement can be seen between the models, with some minor variation in the tails, indicating that linearity was satisfied.

Body mass index trajectory analysis

To investigate how BMI changes with time, we conducted multilevel modelling of the repeated measures of BMI, with age as the timescale. Trajectories were needed for both a diabetic cohort and a non-diabetic cohort so that values of BMI can be sampled from an overweight and obese population for men and women at specific ages.

TABLE 20 Results of time-to-event analysis applied to diabetic and non-diabetic cohorts with outcome MI

	Diabetic cohort		Non-diabetic cohort	
Covariates	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
ln(λ)				
BMI	–0.003	–0.035 to 0.029	0.026	0.014 to 0.037
Age (years)	0.044	0.029 to 0.058	–1.141	–2.585 to 0.303
Age^2	–	–	0.060	0.001 to 0.118
Age^3	–	–	-1.36×10^{-3}	-2.50×10^{-3} to 0.–2.14×10^{-4}
Age^4	–	–	1.41×10^{-5}	3.27×10^{-6} to 2.5×10^{-5}
Age^5	–	–	-5.51×10^{-8}	-9.51×10^{-8} to -1.50×10^{-8}
Sex	1.206	0.544 to 1.868	1.296	1.022 to 1.571
Aspirin treatment	0.638	0.374 to 0.902	1.150	0.893 to 1.406
Insulin treatment	0.609	0.337 to 0.881	–	–
Statin treatment	2.119	0.914 to 3.323	3.086	2.616 to 3.556
BP drug treatment	0.980	0.219 to 1.740	2.816	1.950 to 3.682
Smoker type				
Ex-smoker	–0.478	–0.787 to –0.169	–0.820	–1.131 to–0.508
Smoker	0.329	–0.039 to 0.697	1.072	0.792 to 1.353
Constant	–11.921	–14.045 to –9.797	–6.722	–20.759 to 7.315
ln(γ)				
Age	–	–	–0.010	–0.031 to 0.011
Age^2	–	–	1.80×10^{-4}	5.30×10^{-7} to 3.59×10^{-4}
Sex	–0.207	–0.394 to –0.019	–0.084	–0.155 to –0.014
Aspirin treatment			–0.139	–0.211 to –0.067
Statin treatment	–0.506	–0.766 to –0.246	–0.328	–0.426 to –0.230
BP drug treatment			–0.242	–0.407 to –0.076
Smoker type				
Ex-smoker	–	–	0.082	0.003 to 0.160
Smoker	–	–	–0.094	–0.175 to –0.013
Constant	0.795	0.551 to 1.040	0.903	0.321 to 1.485

Methods

Analyses were conducted using the ACM cohorts, as sample size was greatest in these data sets. Diabetic and non-diabetic cohorts were prepared as in *Patients and data preparation*; however, the repeated measures were not reduced to the baseline measurement. We excluded all patients who had a BMI measurement $< 25\,kg/m^2$ or $> 60\,kg/m^2$ at any point in their trajectory history.

Age at each BMI recording was calculated using date of measurement and year of birth. Day and month of birth were unavailable so all patients were assumed to be born on 1 July for consistency.

Initially, exploratory trajectory plots were constructed of a random sample of patients for diabetic and non-diabetic cohorts. Multilevel models were then applied. The need for random intercepts and slopes, and the correlation between them, was investigated through likelihood ratio tests. The models were restricted to allow only a linear trajectory. Each model was adjusted for sex and the interaction between age and sex, based on statistical significance at the 5% level. Age was centred at 45 years.

TABLE 21 Results of time-to-event analysis applied to diabetic and non-diabetic cohorts with outcome stroke

	Diabetic cohort		Non-diabetic cohort	
Covariates	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
ln(λ)				
BMI	0.015	–0.014 to 0.044	0.030	0.019 to 0.040
Age (years)	0.052	0.039 to 0.065	0.073	0.069 to 0.077
Sex	0.051	–0.215 to 0.318	0.664	0.427 to 0.901
Aspirin treatment	1.144	0.539 to 1.749	1.176	0.927 to 1.426
Insulin treatment	0.146	–0.119 to 0.411	–	–
Statin treatment	–0.331	–0.622 to –0.041	0.606	0.346 to 0.866
BP drug treatment	0.246	–0.243 to 0.735	0.450	0.299 to 0.600
Smoker type				
Ex-smoker	–0.400	–0.690 to –0.111	–1.627	–1.939 to –1.316
Smoker	0.376	0.040 to 0.711	0.121	–0.173 to 0.415
Constant	–9.410	–11.033 to –7.787	–12.140	–12.639 to –11.642
ln(γ)				
Sex			–0.080	–0.147 to –0.012
Aspirin treatment	–0.211	–0.415 to –0.007	–0.186	–0.260 to –0.111
Statin treatment	–	–	0.099	0.022 to 0.176
Smoker type				
Ex-smoker	–	–	0.255	0.172 to 0.338
Smoker	–	–	0.100	0.012 to 0.189
Constant	0.325	0.200 to 0.449	0.220	0.150 to 0.291

The model investigated for each cohort can be written for the *i*th observation of the *j*th patient:

$$BMI = \beta_{0ij} + \beta_{1j}(age-45)_{ij} + \beta_2 sex_j + \beta_3(age-45)_{ij} \times sex_j \quad \text{[Equation 2]}$$

$$\beta_{0ij} = \beta_0 + u_{0j} + e_{0ij} \quad \text{[Equation 3]}$$

$$\beta_{1j} = \beta_1 + u_{1j} \quad \text{[Equation 4]}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N(0,\Omega_u) : \Omega_u = \begin{bmatrix} \sigma^2_{u0} & \\ \sigma^2_{u01} & \sigma^2_{u1} \end{bmatrix} \quad \text{[Equation 5]}$$

$$e_{0ij} \sim N(0,\sigma^2_{e0}) \quad \text{[Equation 6]}$$

All analyses were conducted in Stata version 11.0.

TABLE 22 Results of time-to-event analysis applied to non-diabetic cohort with outcome T2DM

	Non-diabetic cohort	
Covariates	**Coefficient**	**95% CI**
ln(λ)		
BMI	0.607	0.392 to 0.822
BMI^2	–0.010	–0.016 to –0.004
BMI^3	5.92E-05	8.14E-06 to 1.10E-04
Age (years)	0.357	0.225 to 0.488
Age^2	–7.166E-03	–1.119E-02 to –3.146E-03
Age^3	8.160E-05	2.900E-05 to 1.343E-04
Age^4	–3.500E-07	–6.000E-07 to –1.010E-07
Sex	0.796	0.705 to 0.886
Aspirin treatment	–0.193	–0.301 to –0.084
Statin treatment	1.111	0.996 to 1.226
BP drug treatment	–0.382	–0.510 to –0.253
Smoker type		
Ex-smoker	–0.637	–0.738 to –0.536
Smoker	0.288	0.178 to 0.398
Constant	–24.356	–27.403 to –21.309
ln(γ)		
BMI	–0.011	–0.014 to –0.009
Age	–0.018	–0.019 to –0.017
Sex	–0.101	–0.127 to –0.076
Aspirin treatment	0.066	0.036 to 0.096
Statin treatment	0.177	0.141 to 0.214
BP drug treatment	0.140	0.100 to 0.180
Smoker type		
Ex-smoker	0.082	0.054 to 0.110
Smoker	–0.039	–0.071 to –0.007
Constant	1.320	1.219 to 1.421

TABLE 23 Probability of experiencing each event within 5, 10 or 15 years, across three covariate combinations

		p (event in first 5 years)		*p* (event in first 10 years)		*p* (event in first 15 years)	
Outcome	**BMI (kg/m^2)**	**D**	**ND**	**D**	**ND**	**D**	**ND**
Women, aged 40 years, no treatments, non-smoker							
ACM	30	0.00779	0.00134	0.03514	0.00717	0.08337	0.01909
	40	0.01163	0.00346	0.05209	0.01517	0.12206	0.03577
MI	30	0.00122	0.00014	0.00564	0.00062	0.01379	0.00152
	40	0.00118	0.00018	0.00545	0.00081	0.01334	0.00197
Stroke	30	0.00936	0.00181	0.02422	0.00428	0.04206	0.00709
	40	0.01084	0.00243	0.02803	0.00576	0.04859	0.00952
T2DM	30	–	0.01273	–	0.03088	–	0.05158
	40	–	0.03544	–	0.07727	–	0.12060
Women, aged 40 years, no treatments, smoker							
ACM	30	0.01078	0.00220	0.04836	0.01267	0.11364	0.03494
	40	0.01608	0.00560	0.07145	0.02599	0.16506	0.06300
MI	30	0.00169	0.00029	0.00783	0.00116	0.01911	0.00260
	40	0.00164	0.00037	0.00757	0.00150	0.01849	0.00337
Stroke	30	0.01359	0.00252	0.03507	0.00653	0.06065	0.01140
	40	0.01574	0.00339	0.04054	0.00878	0.06996	0.01530
T2DM	30	–	0.01566	–	0.03666	–	0.05994
	40	–	0.04383	–	0.09234	–	0.14109
Women, aged 40 years, statin treatment, non-smoker							
ACM	30	0.00349	0.00054	0.01585	0.00342	0.03812	0.01006
	40	0.00521	0.00133	0.02360	0.00678	0.05647	0.01752
MI	30	0.00245	0.00110	0.00618	0.00330	0.01060	0.00627
	40	0.00237	0.00143	0.00598	0.00427	0.01025	0.00811
Stroke	30	0.00673	0.00408	0.01745	0.01055	0.03038	0.01836
	40	0.00779	0.00548	0.02020	0.01417	0.03513	0.02462
T2DM	30	–	0.05658	–	0.15598	–	0.27158
	40	–	0.14547	–	0.33584	–	0.51140

D, diabetic; ND, non-diabetic.

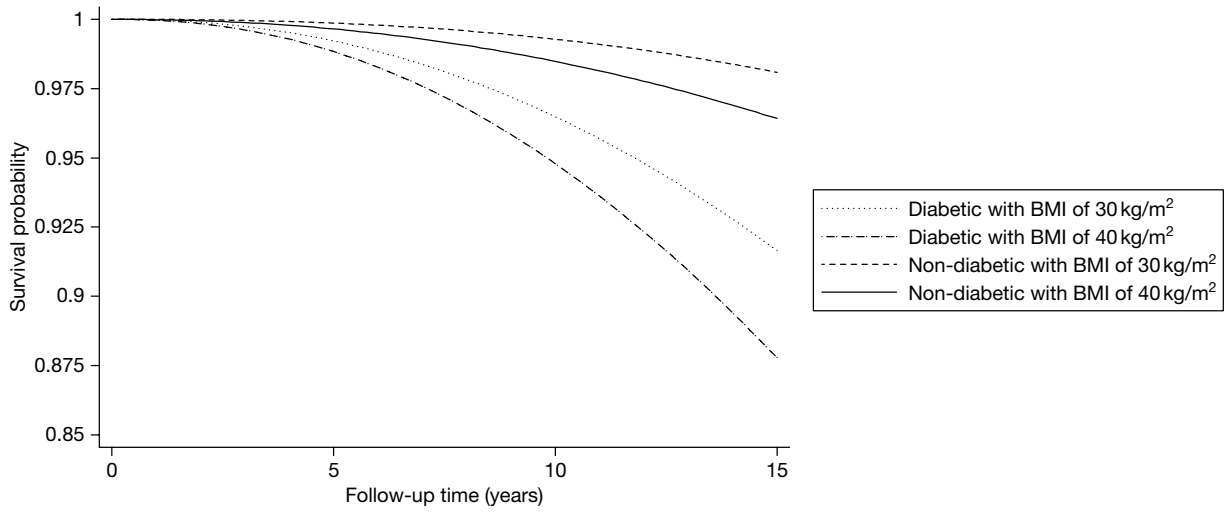


FIGURE 6 Survival probability for a women, aged 40 years, non-smoker and on no treatments.

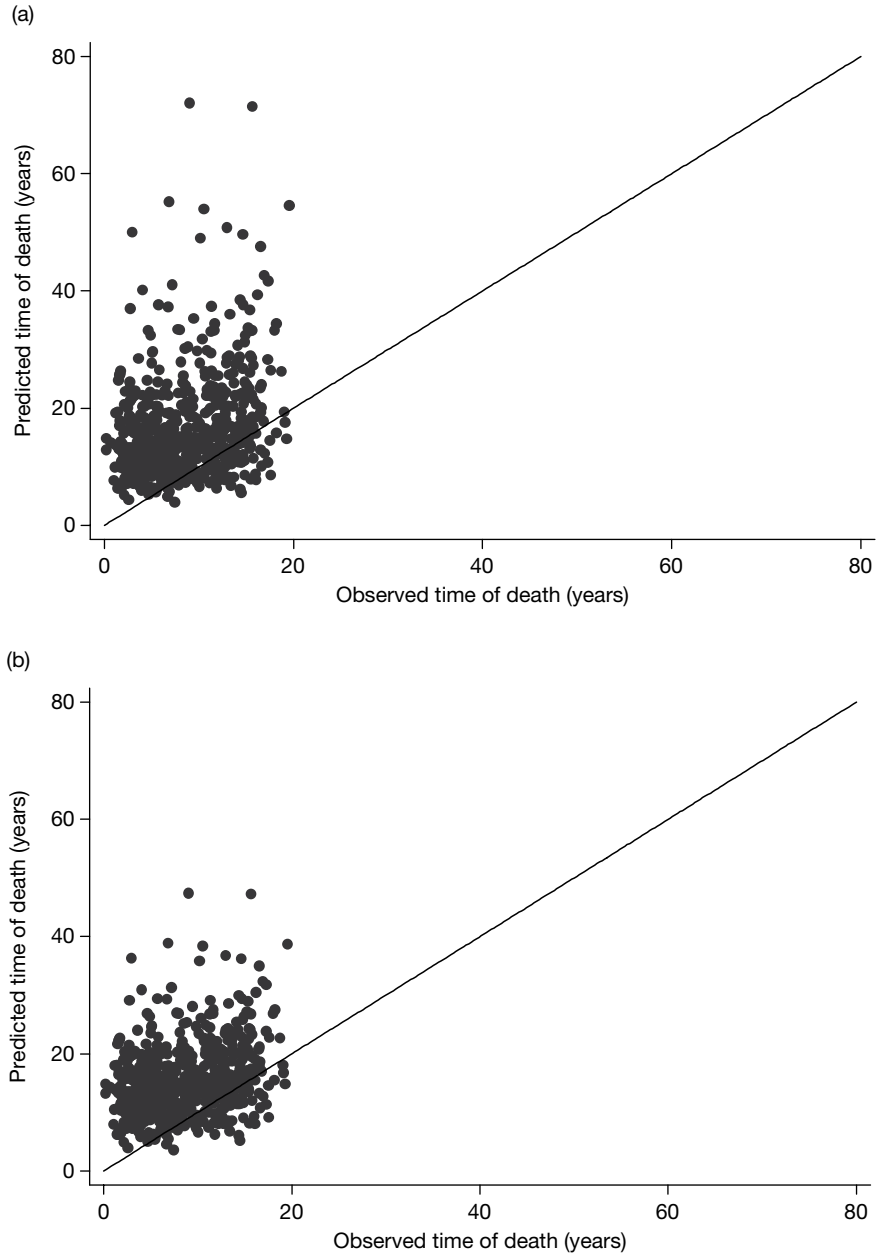


FIGURE 7 (a) Predicted vs observed time of death for diabetic patients who died, using a Weibull model. (b) Predicted vs observed time of death for diabetic patients who died, using a flexible parametric model.

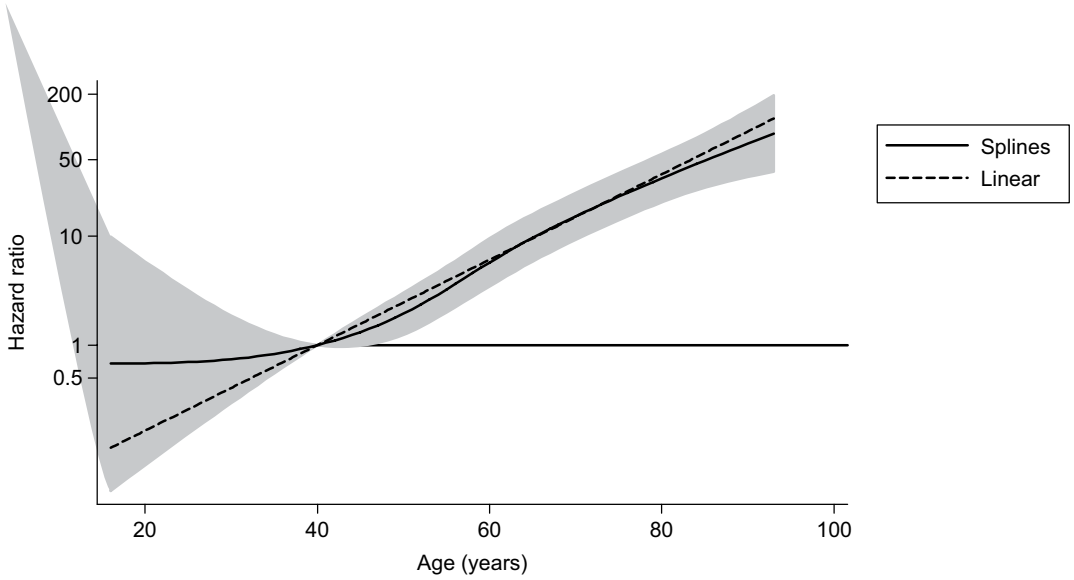


FIGURE 8 Comparing the use of restricted cubic splines and a linear term to model age. Both methods within a Weibull model.

Results

Example trajectory plots for women/men who are diabetic/non-diabetic can be seen in *Figure 9*, with the BMI trajectory for samples of 25 patients shown in each category. *Figure 9* illustrates the heterogeneity in length of GPRD history for different patients, and the potentially high level of within-subject variability seen.

Results from applying a multilevel model to each cohort can be seen in *Table 24*. Interpreting the trajectory model for the diabetic cohort, we see on average an estimated BMI score of 33.176 kg/m^2 (95% CI 32.843 kg/m^2 to 33.509 kg/m^2) for a woman aged 45 years. For a 1-year increase in age, we observe a 0.040 kg/m^2 (95% CI 0.028 kg/m^2 to 0.052 kg/m^2) increase in BMI, with sex held constant. Men, on average, have a –2.061 kg/m^2 (95% CI –2.400 kg/m^2 to –1.721 kg/m^2) lower BMI than women of the same age. The estimated correlation between slope and intercept is –0.728 (95% CI –0.746 to –0.709), indicating a decrease in slope as the intercept increases.

Summary

Results from the seven BMI risk models showed consistent increases in risk due to an increasing BMI. This pattern was evident across all models except for the diabetic cohort with outcome MI, for which a non-statistically significant ($p = 0.838$) reduction in risk for outcome MI was observed. Adjustments for key confounders such as age, sex and smoking status were found to be statistically significant at the 5% level in all seven risk models. More flexible survival models were investigated; however, the added complexity was deemed unnecessary.

Large variation in BMI trajectories was observed. Applying linear trajectory models showed an increase in BMI, on average, of 0.040 kg/m^2 per year for the diabetic cohort for both men and women. The equivalent non-diabetic cohort model showed an increase in BMI of 0.175 kg/m^2 per year for women; however, a statistically significant (at the 5% level) interaction between age and sex was observed, resulting in a slightly reduced increase in BMI of 0.145 kg/m^2 per year for men. Baseline estimates (age 45 years) of BMI were similar across cohorts.

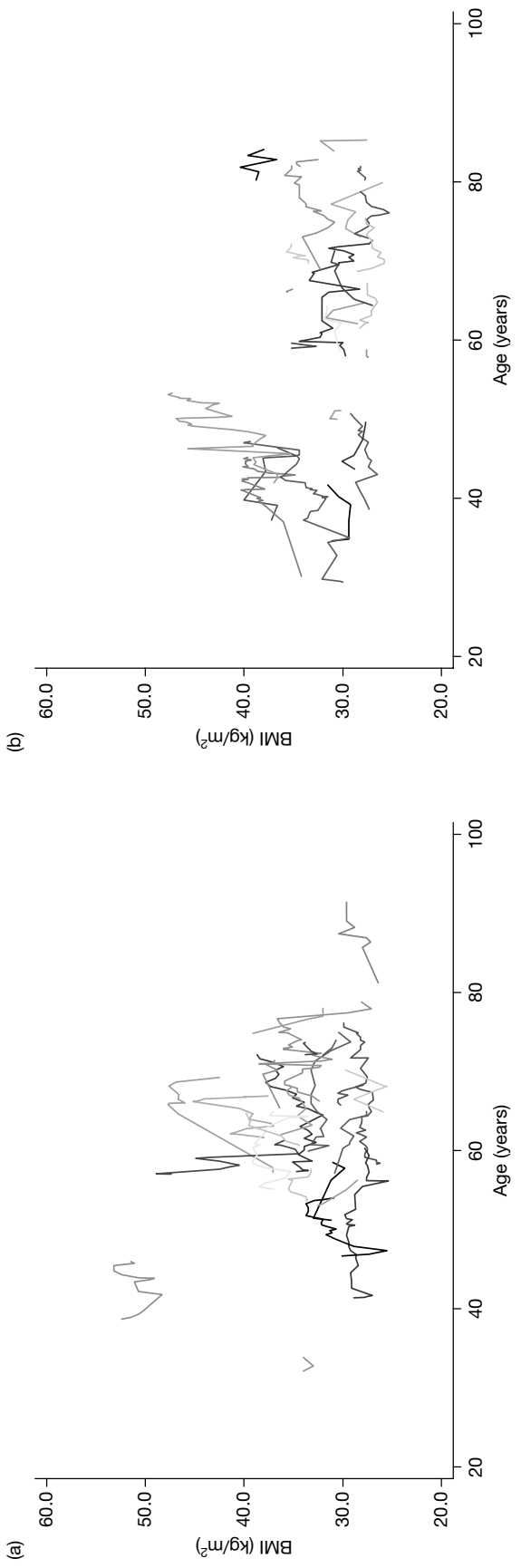


FIGURE 9 Example trajectory plots for women/men who are diabetic/non-diabetic: (a) 25 diabetic women, (b) 25 diabetic men, (c) 25 non-diabetic women, (d) 25 non-diabetic men.

TABLE 24 Multilevel regression model results for BMI (kg/m^2) (age centred on 45 years)

	Diabetic cohort		Non-diabetic cohort	
Covariate	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
Fixed effects				
Constant	33.176	32.843 to 33.509	33.132	33.071 to 33.193
Age (years)	0.040	0.028 to 0.052	0.175	0.172 to 0.178
Sex	–2.061	–2.400 to –1.721	–2.381	–2.478 to –2.284
Age*Sex	–	–	–0.030	–0.035 to –0.025
Random effects				
Level 2				
SD(Age)	0.337	0.327 to 0.348	0.241	0.239 to 0.243
SD(Constant)	7.562	7.337 to 7.793	5.590	5.552 to 5.628
Corr(Age, Constant)	–0.728	–0.746 to –0.709	0.204	0.193 to 0.215
Level 1				
SD(Residual)	1.466	1.456 to 1.476	1.692	1.688 to 1.696

Chapter 5

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Summary of studies included in this review

A systematic review of published literature describing the cost-effectiveness of pharmaceutical interventions for obesity was conducted. Searches were conducted on the following databases: MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL, NHS EED, Health Technology Assessment (HTA) and Science Citation Index. Where necessary methodological search filters were used to identify literature relating to economics and cost. Examples of search strategies used can be seen in *Appendix 1*.

From a total of 676 possible studies, 16 satisfied our inclusion criteria (see *Appendix 5*). The 16 studies (see *Appendix 4*) consisted of 14 published articles describing the results of individual cost-effectiveness evaluations, plus two reviews that included unpublished evaluations. Of these two, one was an industry submission in a single technology appraisal process and the other was a model constructed to inform a NICE obesity guideline. The studies were predominantly conducted in European settings[26,41,157–167] with two[168,169] set in the USA and one[170] in Canada. Of those studies using European settings, seven[26,41,157,159,160,163,167] were based in the UK. Discount rates for costs and benefits varied according to setting (see *Appendix 4*, *Table 28*) and one study[169] included indirect costs. Two studies[164,170] presented results in terms of cost per life-year gained, while the others presented the cost per QALY.

Ten of the studies[26,160–166,169,170] examined the costs and benefits associated with orlistat, three[41,159,168] examined rimonabant and three[157,158,167] examined sibutramine. Only one study[41] included more than one pharmacological intervention. All individuals received some form of diet and exercise or lifestyle intervention in addition to the active treatment, and two studies[166,168] also compared the pharmacological treatment with no treatment. The duration of treatment modelled was generally 1 year, although one study[41] used a lifetime of treatment, and one[169] used 6 months of orlistat weight loss followed by a 6-month maintenance period.

Ten studies[26,157,158,160–163,167–169] used obese cohorts with no comorbidities at baseline. Three studies[164,165,170] presented results for overweight cohorts with T2DM at baseline. Two studies[41,159] presented results for both of these, and one study[166] presented results for obese individuals aged between 20 and 70 years not previously treated for obesity.

Two of the studies[161,168] used a decision tree to extrapolate beyond the duration of the clinical data, three[157,158,167] used a life-table approach, six[41,159,162,164,165,170] used a Markov model and one model[166] was described as a dynamic population model. Only one evaluation[160] did not extrapolate effectiveness beyond the clinical data, and the time horizons used in the other studies ranged from 5 years[168] to a lifetime.[26,41,157–159,161,166,167,170]

Clinical pathway

Weight loss and responders to treatments

There was a wide range in the data used to represent the effectiveness of the treatments in the models. Mean weight losses for lifestyle, or diet and exercise, ranged from 1.4 kg[165] to 17.3 kg.[160]

Mean weight losses for pharmacological interventions ranged from 2.89 kg for a cohort receiving orlistat[166] to 18.91 kg for responders to orlistat.[160] Mean reductions in BMI, for lifestyle, or diet and exercise, ranged from 0.5 kg/m^2 to 2.55 kg/m^2.[159,169] Mean reductions in BMI following pharmacological interventions ranged from 1.9 kg/m^2 for a cohort with T2DM receiving rimonabant[159] to 8.49 kg/m^2 for a cohort also receiving rimonabant.[168]

Natural changes in weight over time

The majority of studies assumed that the natural trajectory of weight for obese individuals not receiving a weight-loss intervention remained constant over time. The exceptions included Roux,[168] who modelled an age-related increase in BMI of 0.26 units per annum based on Canadian health insurance registration data ($n = 29,855$),[171] and the three sibutramine models,[157,158,167] in which a natural increase of 1 kg per annum was assumed based on a 5-year study of 660 obese subjects.[172]

Weight maintenance and regain following cessation of treatment

As all studies correlated weight losses with health-related quality of life (HRQoL), morbidity and/or mortality, the length of weight maintenance and the rate of weight regain are influential variables in the models. The three sibutramine studies[157,158,167,173] modelled a monthly weight regain after cessation of treatment of 0.370 kg for the lifestyle cohort and 0.385 kg for initial responders to treatment. It was assumed that non-responders returned to the trajectory of natural history immediately after cessation of treatment. One study[158] performed a sensitivity analysis whereby weight losses for responders to treatment were maintained for 6 months after cessation of treatment, based on an open-label extension study ($n = 374$).[174] Two studies[166,169] assumed that approximately 20% of the 12-month weight loss would be maintained in the long term, while one[41] assumed that the full 12-month weight loss would be maintained over the full horizon, with a 12-month linear reduction for those who discontinued treatment. Two studies[159,168] assumed a linear rate of regain over a 1-year period, based on data from RIO trials that showed a 1-year period to reach baseline weight after re-randomisation to placebo following rimonabant.[115] Four studies[161,163,165,170] modelled a linear regain over a 3-year period, based on a NICE recommendation,[38] whereas one[164] assumed a 5-year period for regain.[175]

Comorbidities modelled

With the exception of Foxcroft,[160] who used a 1-year horizon, all models included at least one obesity-related comorbidity such as CHD/CVD or onset of T2DM (see *Appendix 4*, *Table 30*). Two[161,163] included only T2DM, whereas one[166] included additional comorbidities such as osteoarthritis, low back pain and some cancers.

Quality of life

Detail on the quality-of-life (QoL) instruments, the design of the QoL studies, the baseline utility for obese patients and the technique used to combine the QoL data in the models was limited, or not reported, in many of the studies (see *Appendix 4*, *Table 31*). Three studies[157,158,167] used a relationship between change in weight and change in QoL, whereas the rest used relationships between BMI and QoL. The latter ranged from a gain of 0.014 per unit BMI, obtained from European Quality of Life-5 Dimensions (EQ-5D) data,[159] to 0.0264 per unit BMI, obtained from a visual analogue scale (VAS).[161]

Results from published cost-effectiveness evaluations

There was a large variation in the results reported, and mean incremental cost-effectiveness ratios (ICERs) ranged from £970 to £59,174 per QALY (*Figure 10*). Compared with lifestyle advice, the mean ICERs for orlistat (sibutramine, rimonabant) ranged between £970 (£6941, £9303) and £59,174 (£10,042, £35,876). The variable reported to have the largest effect on the results in the

majority of the models was the period of weight regain modelled.[157,159,161,163,165,166,168–170] Many of the models were also sensitive to changes in the values used to estimate the QoL benefits attributed to weight changes[41,157,168,169] and the discount rates used.[41,157,159,170] Only one study[41] reported results comparing the pharmacological interventions. In this study, rimonabant was cost-effective when compared with either orlistat or sibutramine.

Independent economic evaluation

Methods

Model structure

A cohort simulation model (*Figure 11*) was developed in Simul8 version 17.0 build 2277 (Simul8 Corporation, Boston, MA, USA) to explore the potential benefits of pharmaceutical treatments for obesity. The pharmacological interventions (plus diet and exercise advice) were compared with standard care (plus diet and exercise advice). The time to death (ACM), primary MI, primary stroke and onset of T2DM were estimated using the results of the GPRD analyses (see *Chapter 4*). Taking into account current health status, age and time since previous event, annual Markov transitions to subsequent fatal and non-fatal MIs and strokes were estimated using data from the Nottingham Heart Attack Register and South London Stroke Register respectively (see *Appendix 5*).[176] Postevent health states were used to incorporate changes in HRQoL and costs associated with event-free years after the initial event.

Horizon

A lifetime horizon was used to accrue the costs and benefits associated with the alternative interventions.[177]

Discount rate

Both costs and benefits were discounted at 3.5%.[177] A NHS and Personal Social Services perspective was taken; hence, only direct health-care costs were used.[177]

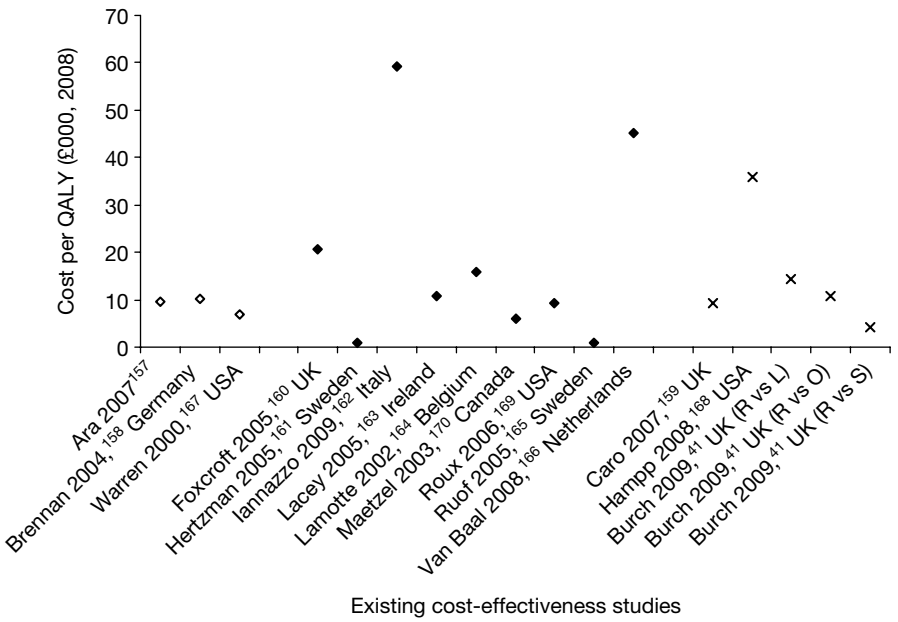


FIGURE 10 Mean ICERs in published studies. The ICERs were converted to UK£ and inflated to 2008 for comparison. R vs L, rimonabant vs lifestyle; R vs O, rimonabant vs orlistat; R vs S, rimonabant vs sibutramine.

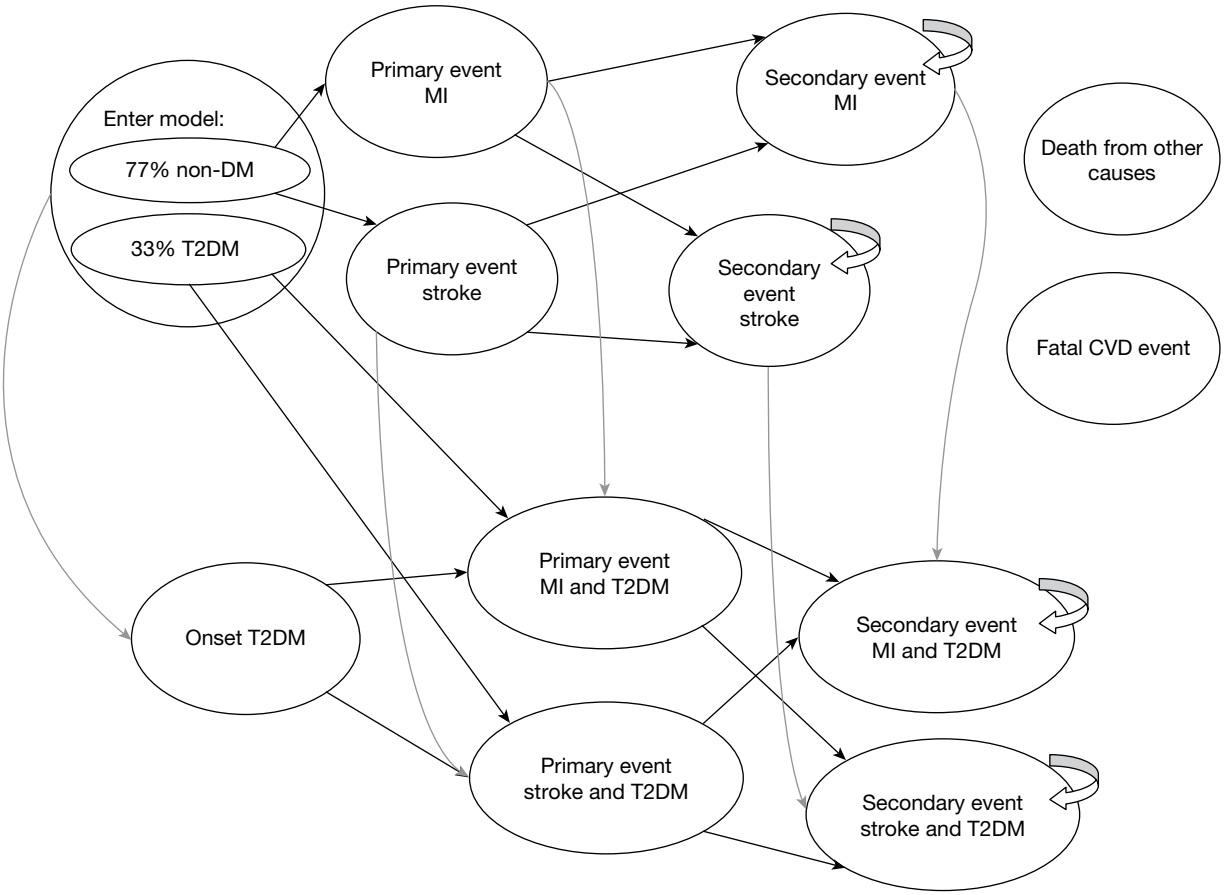


FIGURE 11 Simulation model. All are at risk of a fatal CVD death or death from other causes. DM, diabetes mellitus.

Cohort characteristics

Patients entered the model with the demographic characteristics observed in the patients recruited to the clinical studies used in the MTC (see *Chapter 3*). Hence, they had an average age of 45.5 years and a mean BMI of 34.92 kg/m^2 and 33.2% were diabetic.

Treatment alternatives

The treatments modelled were diet and exercise advice plus one of the following: no active treatment (assumed equivalent to placebo), orlistat 120 mg three times a day, sibutramine 10 mg once a day, sibutramine 15 mg once a day, rimonabant 20 mg once a day. The correlated changes in BMI at months 3, 6 and 12 from the MTC (see *Chapter 3*) informed the effectiveness of the interventions. As the full data were not available for rimonabant, the change at 12 months (–2.98 kg/m^2) was derived from the literature and the value at 6 months was interpolated.[168]

Body mass index changes

At the end of the active treatment period (i.e. at 1 year) it was assumed that any benefit of treatment was lost in a linear fashion and that BMI returned to the baseline value at 3 years after treatment cessation.[38] Sensitivity analyses were used to explore the effect on the model of using a faster rate of regain, and of assuming that BMI returned to the trajectory of natural history at 3 years after cessation of treatment.

Long-term natural changes in body mass index

After the initial 12-month period, and for anyone not receiving an active treatment, excluding the period of weight regain after stopping active treatment, BMI increased naturally over time as observed in the GPRD analyses (see *Chapter 4*).

Health measurement estimation

Life-years were weighted using the EQ-5D preference-based measure.[178] Utility measures were derived using EQ-5D data collected during the HSE.[179] Almost 60% of respondents indicated that they had no reduction in HRQoL on the EQ-5D index. An adjusted censored mixture model (ACMM), which is particularly suited for censored and non-normally distributed data,[180] was used to explore the relationship between EQ-5D scores and BMI (see *Appendix 5*).

After controlling for age, gender and health status (history and time since heart attack, stroke, angina, diabetes), the results of the regression showed an independent relationship between BMI and EQ-5D score (see *Appendix 5*). Using the individual patient-level data (see *Appendix 5*, *Table 34*), the mean error [mean absolute error (MAE), root mean squared error (RMSE)] in the full set of predicted scores was 0.0008 (0.1204, 0.1806). Subgrouping by health status, the MAEs ranged from 0.0752 (no history of any health condition) to 0.3224 (T2DM and stroke within the previous 12 months).

Health state and monitoring costs

Monitoring costs during active treatment include a surgery visit every month. Visits at baseline, 3, 6 and 12 months were with the GP, while the intervening months were with the practice nurse. Blood samples were costed for baseline and 3 months. Because of the higher risk of vascular events for sibutramine recipients, an additional extra visit for each of the first 3 months was included for BP monitoring with the practice nurse.[181] Costs were inflated to 2009 where required.[88] For the comparator cohort we assumed a meeting with the nurse at baseline.

Stroke

The costs associated with a fatal or non-fatal stroke were taken from a UK study.[182] The data were derived from a large randomised prospective trial of stroke care in the UK and resource use included hospital, primary care, health-care contacts and social services. The cost of a non-fatal stroke is dependent on the severity of the event, and so a weighted average cost was derived based on the distribution of mild, moderate and severe strokes. The cost of continuing care in the years subsequent to a stroke is based on the costs associated with discharge location (home or institution). Again, a weighted average cost was derived based on the severity of the stroke and location.[176]

Myocardial infarction

When a person experiences a heart attack, the bulk of the associated costs are incurred by their treatment in hospital. These hospital costs depend largely on whether or not a patient undergoes a surgical procedure, and on the nature of that procedure. An average cost was calculated based on the distribution of treatments received and their associated costs from the NHS reference costs.[181] It was assumed that half of patients do not undergo surgery and incur the average cost of an admission for actual or suspected MI.[183] For the remainder, it was assumed that two-thirds had coronary artery bypass surgery, and one-third a percutaneous coronary intervention. Following hospital treatment, further costs are incurred in monitoring a patient's condition and administering drug treatments. It was assumed that each patient would have outpatient visits consisting of two (three) consultations with a GP (practice nurse), and that the total annual cost for prescribed drugs would be £396.60.[176] In the years subsequent to experiencing a MI, monitoring costs were estimated to be an average of £315.11 per year, which included two GP appointments, three nurse consultations and continuing drug treatment (£131.24).[183]

Diabetes

The costs of CVD events in individuals with a history of T2DM are based on resource use in diabetic patients.[184] The annual cost of individuals with T2DM and no history of CVD includes the cost of clinical appointments, glucose tests, proteinuria and eye screening, and drug treatments.[185]

Analyses

The base case examines the costs and benefits of each intervention for a cohort of obese patients. Incremental analyses were used to identify any interventions that were dominated. An intervention is dominated if it is less effective and more expensive than its comparator and extendedly dominated when the ICER for a treatment is higher than that of the next most effective comparator. A sample size of 1,000,000 is used for the deterministic analyses (see *Appendix 5*). Because of computational limitations, 200 simulations and a sample size of 400,000 are used in the stochastic analyses. A list of assumptions used in the model is provided in *Appendix 5*. The assumptions relating to monitoring, weight regain and duration of active treatment were informed by discussions during our Advisory Group meeting, which involved potential recipients of obesity pharmacological treatments and practising clinicians.

There are insufficient data in the literature to accurately model the potential number of fatal events induced by the active treatment for either sibutramine or orlistat. Consequently, we use the estimated average costs and QALYs to determine the proportion of patients who would need to die to obtain a cost per QALY over a threshold of £20,000 per QALY.

Net benefit

Results are also presented in terms of the net benefit of the treatments. Because of potential difficulties in interpreting cost per QALY values when more than two treatments are being compared, the use of 'net benefit' is becoming more widespread. Although these results are analogous to those presented in the more traditional cost per QALY format, there is less scope for mistakes when interpreting the data as net benefit values can be directly compared across interventions. Net benefit is calculated using the formula $NB = \lambda \times QALY - cost$, where λ denotes the maximum cost that society is prepared to pay. When net benefit is positive, the treatment is cost-effective; when net benefit is negative the treatment is not cost-effective; and when net benefit is zero the cost per QALY is equal to the maximum cost per QALY that society is prepared to pay. The intervention with the highest net benefit is the most cost-effective at a given threshold.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses are applied to the following input parameters (*Table 25*) to represent the uncertainty around the model inputs when parameter values are varied simultaneously:

- change in BMI at 3, 6 and 12 months
- Weibull survival curves
- transitions to subsequent vascular events
- health-state costs
- health-state utility values
- ratio of MI to stroke deaths.

A cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness plane are included to give a measure of the uncertainly reflected by the model. *Table 25* provides the input parameters and their base-case mean values and distributions used in the model.

TABLE 25 Input parameters

Parameters	Mean	Distribution (parameters)	Source
Baseline			
Age (years)	45.5	Normal (SD 6.97 years)	Clinical review (see *Chapter 3*)
BMI (kg/m^2)	34.92	Normal (SD 2.58 kg/m^2)	
T2DM	33.2%	Beta	
Male	25.7%	Beta	
Discount rate (costs and utilities)	3.5%	Fixed	Earnshaw 2008[177]
Change in BMI (orlistat)			
Change in BMI (week 13) Change in BMI (week 26) Change in BMI (week 52)		The joint posterior distribution from the random-effects network meta-analysis analysed in WinBUGS	
Non-diabetic survival curves			
ACM	See *Table 19*	Variance–covariance matrices	GPRD (see *Chapter 4*)
Primary MI	See *Table 20*		
Primary stroke	See *Table 21*		
T2DM onset	See *Table 22*		
T2DM survival curves			
ACM	See *Table 19*	Variance–covariance matrices	GPRD (see *Chapter 4*)
Primary MI	See *Table 20*		
Primary stroke	See *Table 21*		
Transitions to subsequent cardiovascular events			
Events following primary MI	Multiple (see *Appendix 5*)	multinorminv	Ara 2009[183]
Events following primary stroke		multinorminv	Ara 2009[183]
Natural history of BMI annual progression			
Men	0.1447		GPRD (see *Chapter 4*)
Women	0.1747		
Men T2DM	0.0398		
Women T2DM	0.0398		
HRQoL			
EQ-5D scores adjusted for age, health status, BMI and sex	Multiple (see *Appendix 5*)	multinorminv	HSE[179] (see *Chapter 5*)
Drug costs (per unit)			
Orlistat 120 mg	£0.38	Fixed	BNF 2009[45]
Sibutramine 10 mg	£0.89	Fixed	
Sibutramine 15 mg	£0.89	Fixed	
Rimonabant 20 mg	£1.57	Fixed	Burch 2009[41]
Monitoring costs (per annum)			
Orlistat and rimonabant	£205.00	Fixed	Curtis 2007[181]
Sibutramine	£220.00	Fixed	
No active treatment	£7.50	Fixed	

continued

TABLE 25 Input parameters (*continued*)

Parameters	Mean	Distribution (parameters)	Source
Health-state costs			
MI (year 1)	£3835.79	Gamma	Ara 2009[183]
MI (year 1+)	£315.11	Gamma	
Stroke (year 1)	£8638.36	Gamma	
Stroke (year 1+)	£2426.92	Gamma	
T2DM (year 1)	£171.35	Gamma	Gillett 2009[185]
MI plus T2DM (year 1)	£4783.96	Gamma	Clarke 2002[184]
MI plus T2DM (year 1+)	£545.40	Gamma	
Stroke plus T2DM (year 1)	£2782.22	Gamma	
Stroke plus T2DM (year 1+)	£4298.51	Gamma	
Fatal stroke	£7899.72	Gamma	Ara 2009[183]
Fatal MI	£1266.95	Gamma	
Ratio of fatal CHD to stroke			
Appendix 5	Multiple (see *Appendix 5, Table 36*)	Beta	Scarborough 2010[186]

See *Appendix 5* for breakdown of monitoring costs used.

Univariate sensitivity analysis

The following univariate sensitivity analyses are performed to explore the sensitivity of the model results to changes in key parameters and assumptions:

SA1: Weight regain rate

For the base case we assume that at the end of the active treatment period all patients revert to their baseline BMI value in a linear fashion over a 3-year period.[38] After this they follow the trajectory of natural history. It is possible that the rate of regain would be much faster than this and we conduct a sensitivity analysis to look at the effect on the results if all patients revert to their baseline BMI by 12 months, again using a linear weight regain.

SA2: Weight regain to trajectory of natural history

The base case assumes that at the end of the active treatment period all patients revert to their baseline BMI value in a linear fashion over a 3-year period, after which they follow the trajectory of natural history.[38] It is possible that the regain would be larger than the absolute reduction achieved by the intervention, and that individuals would regain more weight than they lost. We conduct a sensitivity analysis to look at the effect on the model results if all patients revert to the trajectory of natural history over a 3-year period, again using a linear weight regain.

SA3: Longer time horizon for treatment

In the base case we assume that all patients are withdrawn from active treatment at 12 months as this is the end point for our evidence. It is possible that some individuals might continue to receive treatment beyond this period. We assume that patients continue to receive treatment for an additional 12-month period and that their BMI is maintained at the value achieved at 12 months. At month 24 they are removed from treatment and their weight reverts back to the baseline value in a linear fashion over a 3-year period.

SA4: Alternative starting age

In the base case the cohort enter the model with a starting age of 45.5 years. We perform sensitivity analyses to examine the effect on the results if the cohort enter the model at the age of 20 (60) years.

SA5: Gender

The base case uses a distribution of 74.3% women and 25.7% men as observed in the clinical data used in the MTC. We conduct sensitivity analyses using a cohort of all women (men), maintaining all other characteristics used in the base case.

SA6: Starting body mass index

In the base case, patients enter the model with a BMI of 34.92 kg/m^2 as observed in the clinical data used in the MTC. We conduct a sensitivity analysis to explore the effect on the results when patients enter the model with a lower (30 kg/m^2) or higher (40 kg/m^2) baseline BMI, maintaining all other characteristics used in the base case.

Results

Deterministic results

With an average cost per QALY of £557 compared with placebo, the results of the deterministic analyses suggest that sibutramine 15 mg dominates (average costs are lower and average QALYs are higher) the other three active interventions (*Table 26*).

However, both sibutramine and rimonabant have been withdrawn because of safety concerns relating to serious adverse events that could potentially increase the mortality rate of recipients while on treatment. With no robust data to model this increase, we explore the percentage of lives that would need to be lost for each active intervention to be considered not cost-effective compared with placebo when using a threshold of £20,000 per QALY. Using sibutramine 15 mg (see *Table 26*) as an example, a loss of > 0.2816 QALYs per person receiving sibutramine 15 mg would increase the ICER to > £20,000 per QALY [i.e. (£2967 – £2806)/(15.418 – 0.2816 – 15.128) = £20,000]. Assuming that the adverse event occurs during the first year of the model (i.e. while on treatment), if the proportion of patients who experienced a fatal adverse event was > 1.8%, the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY {i.e. (£2967 – £2806)/[15.418 × (1 – 1.83%) – 15.128] = £20,000}. For sibutramine 10 mg and rimonabant the percentage of patients would be 1.5% and 1.0% respectively (see *Appendix 5*, *Table 38*).

TABLE 26 Average life-years, costs and QALYs from the deterministic analysis

Intervention	Life-years	Cost (£)		QALYs		Cost per QALY (vs placebo) (£)
		Undiscounted	Discounted	Undiscounted	Discounted	
Placebo	75.495	5286	2806	25.123	15.128	
Orlistat	75.758	5547	3097	25.468	15.303	1665[a]
Rimonabant	75.783	5923	3478	25.499	15.317	3553[a]
Sibutramine 10 mg	75.934	5438	3011	25.637	15.376	827[a]
Sibutramine 15 mg	76.038	5372	2967	25.735	15.418	557

a Dominated by sibutramine 15 mg.

Probabilistic results

The cost-effectiveness plane (*Figure 12*) shows the individual results for each of the treatments compared with placebo, with each point representing the result of one of the Monte Carlo samples. As can be seen, each treatment would be considered cost-effective when using a cost per QALY threshold of £20,000. There is markedly less uncertainty in the QALY gain associated with rimonabant because of the different source of effectiveness data used to model changes in BMI at 6 and 12 months.

Net benefit

When assessing the net benefit of the interventions (*Figure 13*), sibutramine 15 mg is the most cost-effective alternative for thresholds > £2000 per QALY.

Sensitivity analyses

As sibutramine and rimonabant have been withdrawn, the univariate sensitivity analyses are generated comparing orlistat with placebo (see *Appendix 5*, *Table 39*). The variable that has the greatest effect on the results is the baseline BMI for the cohort (SA6). For a cohort with a baseline BMI of 30kg/m^2, the ICER increases from £1.6k to £24k per QALY. This is due to the marked decrease in QALY gain as this cohort are at a lower risk of fatal or non-fatal cardiovascular events and T2DM than those in the base-case cohort who enter the model with a mean BMI of 34.9 kg/m^2. The model results are robust to changes in the other variables tested.

Summary of cost-effectiveness

There was a large variation in the results reported in the 16 identified published economic evaluations with ICERs ranging from £970 to £59,174 per QALY when comparing the active interventions with lifestyle advice. Only one study compared the active pharmacological interventions and the reported results suggested that rimonabant would be considered cost-effective compared with either orlistat or sibutramine. These analyses were conducted before the withdrawal of both rimonabant and sibutramine.

The results of the deterministic analyses conducted for the current study show that, compared with placebo, sibutramine 15 mg dominates (the average costs are lower and the average QALYs are higher) the other three active interventions. However, sibutramine and rimonabant have both been withdrawn because of safety concerns relating to potential treatment-induced fatal adverse events. When considering the potential increase in mortality, the treatments would no longer be considered cost-effective using a threshold of £20,000 per QALY if the proportion of patients who experienced a fatal adverse event was > 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant).

Comparing orlistat with placebo, orlistat would be considered cost-effective when using a threshold of £20,000 per QALY and the model is robust to variations in the key parameter values tested with the exception of the baseline BMI value.

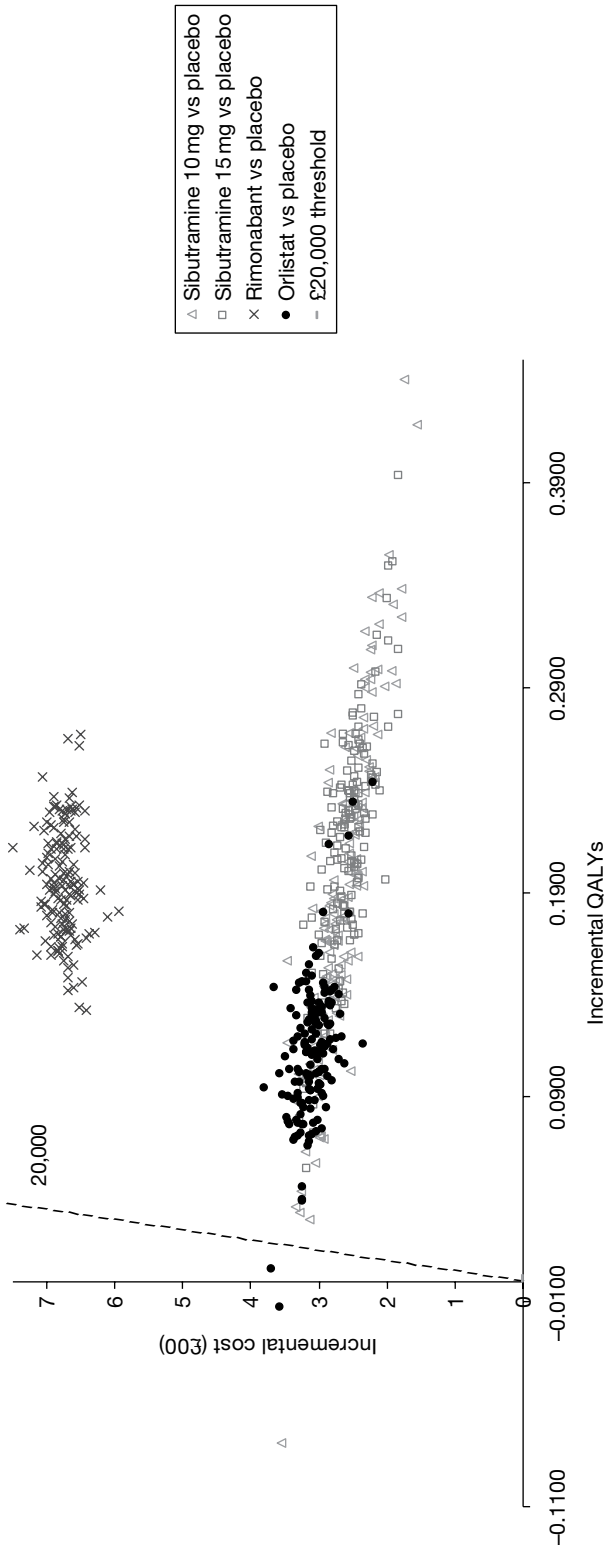


FIGURE 12 Cost-effectiveness plane.

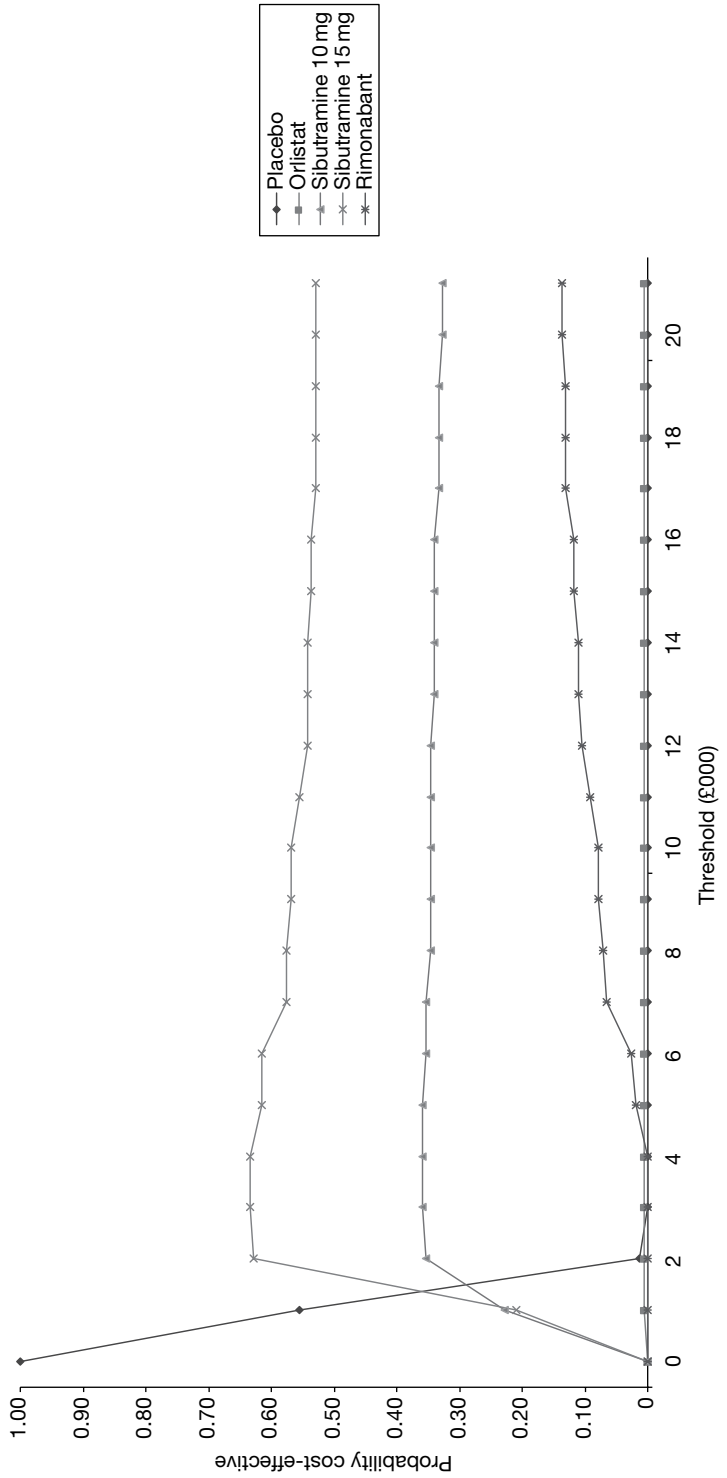


FIGURE 13 Cost-effectiveness acceptability curve.

Chapter 6

Discussion

Statement of principal findings

This is the first MTC of anti-obesity treatments to have been carried out. It utilises cutting-edge statistical methodology to compare treatments for which no head-to-head trials have been carried out. Overall, the results show that the active drug interventions are all effective at reducing weight and BMI compared with placebo. For sibutramine the higher dose (15 mg) gave a greater reduction than the lower dose (10 mg). Although data were limited, the combination of orlistat and sibutramine also ranked highly. Interestingly, those interventions that have now been withdrawn from use (sibutramine and rimonabant) seem to be the most effective; however, their effectiveness is outweighed by the increased adverse events.

A specific review of adverse events was not undertaken for a combination of reasons. First, we underestimated the size of the trial evidence base on this topic and thus the review of efficacy took much longer than we had anticipated, which had serious resource implications. Second, a preliminary assessment of the reporting of adverse event data indicated that it was very patchy and inconsistent across trials. Thus, we decided that a review of the published information only would not have been comprehensive and would have been potentially misleading. Finally, given the detailed adverse event analyses that were carried out relating to the withdrawal of two of the drugs, we felt that this aspect of the project plan had been somewhat superseded by the time we came to consider it

Results from the seven BMI risk models showed consistent increases in risk as a result of an increasing BMI. This pattern was evident across all models except for the diabetic cohort with outcome MI, for which a non-statistically significant ($p = 0.838$) reduction in risk for outcome MI was observed. Adjustments for key confounders such as age, sex and smoking status were found to be statistically significant at the 5% level in all seven risk models. More flexible survival models were investigated; however, the added complexity was deemed unnecessary.

Large variation in BMI trajectories was observed. Applying linear trajectory models showed an increase in BMI, on average, of 0.040 kg/m^2 per year for the diabetic cohort for both men and women. The equivalent non-diabetic cohort model showed an increase in BMI of 0.175 kg/m^2 per year for women; however, a statistically significant (at the 5% level) interaction between age and sex was observed, resulting in a slightly reduced increase in BMI of 0.145 kg/m^2 per year for men. Baseline estimates (age 45 years) of BMI were similar across cohorts.

The literature review identified 16 economic evaluations describing the costs and benefits associated with the three interventions. Compared with lifestyle advice, the mean ICER for orlistat (sibutramine, rimonabant) ranged between £970 (£6941, £9303) and £59,174 (£10,042, £35,876). Only one study directly compared the pharmacological interventions, and the authors reported that rimonabant was cost-effective compared with either orlistat or sibutramine.

With an average cost per QALY of £557 compared with placebo, the results of the deterministic analyses suggest that sibutramine 15 mg dominates (the average costs are lower and the average QALYs are higher) the other three active interventions. The model is robust to variations in

the key parameter values tested with the exception of the baseline BMI value. Although the probabilistic results show a larger range of uncertainty in the incremental QALY gain associated with both sibutramine treatments than in the QALY gain associated with orlistat, the net benefit analyses show that sibutramine 15 mg is the most cost-effective alternative for thresholds > £2000 per QALY. However, both sibutramine and rimonabant have been withdrawn because of safety concerns relating to potential treatment-induced fatal adverse events. Assuming that the adverse event occurs while on treatment, if the proportion of patients who experienced a fatal adverse event was > 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant) the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

Strengths and limitations of the assessment

Inconsistency was seen between the results of the MTC and the pair-wise comparisons, with a higher level of inconsistency seen for the continuous outcomes. There are many possible reasons for this. The difference in the level of inconsistency between the binary and continuous outcomes might be explained by differences in the scale on which the data are collected; the binary outcome uses percentage weight change, whereas the continuous outcome uses the absolute change. Also the binary outcomes were recorded in the same way across all trials; thus, data quality was higher and less imputation and fewer assumptions were required. The level of publication bias could also add to the level of inconsistency seen and may have positively skewed the results found.

Although this analysis has included data from 94 trials, generally the data quality of the trials included was low. Overall, there was generally poor reporting of standard errors and SDs. Many studies had reported using SDs in the methods, but had reported very low numbers in comparison with other studies and vice versa. Studies with outlying SDs/errors were reassessed and where possible data were corrected. If the publication did not make it clear which measure of variability had been used, the more conservative estimate was used. This could affect the results of the MTC, but giving larger variability to those studies that reported ambiguous results would underestimate rather than overestimate any treatment effects. The way that data were reported also varied by study. For the MTC we required change from baseline with standard error either for each treatment or between treatments. Many studies had reported absolute weight by treatment at baseline and follow-up; in these cases change from baseline was calculated and the standard error was imputed. The imputed standard error uses a correlation coefficient that was calculated using trials in which both the absolute and the change in weight had been given. No such data were available for BMI; therefore, we assumed that the change correlation for BMI would be the same as for weight.

Another limitation of this work is that we did not consider all possible comparators and therefore this is not a complete MTC analysis. Studies were limited to those that included one of the active drugs against a limited number of comparators; therefore, studies comparing lifestyle interventions alone were not included. Additionally we also excluded all studies not reported in English (11 studies); although this could have biased the results, a number of studies have suggested that excluding non-English studies has minimal impact. For example, a retrospective analysis of 50 meta-analyses including both English and non-English studies found that non-English trials tended to be smaller and of lower quality, were more likely to produce significant results and were more likely to show benefit.[187] The authors found that excluding non-English studies had a < 5% effect on the result found for around 60% of the studies assessed and led to an overall less beneficial effect in 32% of the studies. Therefore, although 11 studies were excluded from this review on language grounds, this will probably have had either little effect or a conservative effect on the results found.

Since the initiation of this project the Sibutramine Cardiovascular Outcomes (SCOUT) trial has been published.[188] This trial found that long-term use of sibutramine in those at high risk of CVD was associated with an increased risk of non-fatal MI and non-fatal stroke and this led to the suspension of the drug. This trial was not included in the MTC analysis because it did not provide weight loss data at the time points of interest. However, the weight-loss results of this trial are broadly in line with the results of the MTC and therefore the inclusion of this trial is unlikely to have changed the conclusions.

A strength of the work relative to previous evaluations in obesity is the use of UK-specific data obtained from the GPRD, which are used to determine the relationship between BMI and comorbidities in the economic models. In previous models the probabilities of comorbidities have been estimated using published algorithms,[189,190] which in general are not based on UK populations and have required assumptions and modifications to determine the links between BMI and event rates. Another strength of the work relating to the analyses of the GRPD data is the incorporation of natural changes in BMI over time. The majority of previous evaluations assumed that BMI for the comparator arm remains constant over time, the exceptions being an increase in BMI of 0.26 units per annum based on Canadian health insurance registration data ($n = 29,855$)[171] or an increase of 0.833 kg per month based on a 5-year study of 660 obese subjects.[172]

Conversely, there are clearly limitations to the GPRD analyses presented here. Baseline values of BMI were used in the modelling of time to clinical events rather than BMI trajectories. Although in theory the joint modelling of both BMI trajectories and time to clinical events could have enabled an estimate of how changing BMI levels (also allowing for measurement error and within-subject correlation), rather than BMI levels per se, changed the risk of the different clinical events,[191] there were a number of issues with adopting such an approach. The complexity of such a modelling approach, although in theory potentially attractive, requires considerable computing resources for a data set as large as this. It also relies on the validity of the BMI trajectories – something discussed with respect to the GPRD below – and ultimately such models have been shown to provide only small incremental benefits over simpler risk models. For these reasons, and as adopted by others,[150,154] we used baseline BMI levels within relatively simple Weibull parametric survival regression models to estimate the BMI risk relationships. Although more complex models could have been used, and in particular ones that relaxed the assumption of a Weibull baseline hazard and a log-linear effect of covariates, the trade-off between the added extra complexity (especially as the results of such analyses were to be used specifically as inputs into the economic decision model described in *Chapter 5*) and the very small benefit, in terms of statistical adequacy of the model, meant that a simpler approach was adopted.

Although other authors have considered the validity of diagnoses (and in particular those related to CVD) within the GPRD, and found them to be acceptable,[192] the work reported here relied not only on diagnoses, but also on both the time that such diagnoses were made and BMI levels. Both BMI levels and the recorded times of events and diagnoses were found to be highly variable, both within and between patients. Patients could have multiple BMI levels recorded on the same day that were considerably different to one another, or indeed have BMI levels recorded on different occasions but which were clinically implausible, for example BMI readings changing by over 25% within a couple of weeks. Therefore, despite extensive data cleaning and preparation as described in *Chapter 4* (see *Patients and data preparation*), such features of the GPRD, and of BMI readings in particular, should serve as a caveat for the results presented here.

A limitation of the analyses was that we were unable to explore the effects of the interventions in minority ethnic groups. Prevalence of obesity can be higher in these subgroups and their absolute risk of obesity-related comorbidities is higher than in the general UK population. Similarly, we

were unable to explore the effects of the interventions in cohorts with or without T2DM at onset of treatment as there were insufficient data to differentiate between potential changes in weight (BMI) for these subgroups.

In routine clinical practice it is unlikely that doctors will continue to prescribe treatment if patients do not respond. A limitation of the work is that we were unable to analyse changes in weight (BMI) for subgroups who responded or who failed to respond to treatment because of a lack of detailed outcomes. It is possible that this would make a difference to the cost-effectiveness results, which are estimated using the average change in BMI for a cohort irrespective of whether they respond to treatment or not.

A strength of the work is the incorporation of a function that enables us to control for health status (event free, cardiovascular events, T2DM), age, gender and BMI when estimating the HRQoL values used to determine the QALYs. The published studies exploring the costs and benefits of the obesity interventions have estimated these values using data derived from disparate sources and frequently these have involved different utility measures because of a paucity of evidence available at the time.

Chapter 7

Conclusions

Currently, orlistat is the only licensed medication for the management of obesity. In clinical practice orlistat should be considered to aid weight reduction with lifestyle interventions in those individuals who have not been successful in reducing their weight with lifestyle alone.

Our MTC of anti-obesity treatments shows that all of the active treatments are effective at reducing weight and BMI. The economic results show that compared with placebo the treatments are all cost-effective when using a threshold of £20,000 per QALY and, within the limitations of the data available, sibutramine 15 mg dominates the other three interventions. However, if the proportion of patients who experienced a fatal adverse event was > 1.8% (1.5%, 1.0%) for sibutramine 15 mg (sibutramine 10 mg, rimonabant), the treatment would no longer be considered cost-effective when using a threshold of £20,000 per QALY.

Suggested research priorities

There are many avenues of further work that could be explored but which are beyond the scope of this project. Novel methods are now available to fully assess the inconsistencies within a network[193] and could be used to explore the differences found between the pair-wise and MTC analyses. Meta-regression methods could also be used to look for effect modifiers, for example baseline weight might interact with the treatment effect seen. The effect of the level of publication bias on the results found could also be assessed. From a clinical point of view a long-term clinical trial of orlistat with a similar design to the SCOUT trial may be needed to detect long-term adverse events of this drug.

Given the high levels of variation in consistency and accuracy found in the BMI recordings from the GPRD data, it would be prudent to investigate and compare risk models based on more robust data obtained from observational studies. As discussed earlier, inclusion of ethnicity into risk models would allow further tailoring of subgroup risk profiles. Furthermore, unlimited computing resources would enable the investigation of joint models to model the repeated measures of BMI (with error) and the time-to-event processes simultaneously. Of course, as stated previously, such models may provide relatively small benefits.

In addition, clinical studies of at least 12 months' duration in subgroups with high prevalence rates of obesity would be informative for future economic evaluations, as would observational data describing the effect on BMI after cessation of treatment. Although this is the first evaluation to examine the comparative costs and benefits of the three interventions directly, given the growing prevalence of obesity, as evidence becomes available on new interventions in this area their cost-effectiveness should be compared to determine the optimal intervention.

Acknowledgements

We would like to acknowledge the assistance from our advisory team who discussed the use and relevance of the active interventions in a primary care practice from a user and provider perspective. KA is partly supported by the UK National Institute for Health Research (NIHR) as a Senior Investigator (NI-SI-0508-10061). MC is funded by a NIHR Research Methods Fellowship.

Contributions of authors

RA, KA, NC, MD, LG, AD, KK and AS contributed to the selection and inclusion of studies and the criteria used in the clinical review. LG, AD and FW extracted the clinical data, while NC, LG and AS conducted the clinical analyses including the MTC. KA, MC, and MH analysed the GPRD data set liaising with RA, LB and MS for direction relating to the economic model. RA and LB performed the cost-effectiveness review and RA, LB and MS constructed the economic model. MH conducted the HRQoL analyses. RA, KA, LB, MC, NC, LG, RJ, KK, AS and MS contributed to the report writing. AR conducted all of the literature searches.

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Appendix 1

Literature search strategies

A search strategy was constructed using a combination of Medical Subject Headings (MeSH) and free-text terms. Vocabulary was identified to describe both the condition (obesity) and the interventions (rimonabant, orlistat and sibutramine). The vocabulary was devised by the information specialist in conjunction with the research team. All synonyms, brand drug names, etc. were included.

The electronic databases searched were MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations (for latest publications), EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, CINAHL, DARE, NHS EED, HTA Database, Web of Science Proceedings, Science Citation Index and Current Controlled Trials. Searches were primarily conducted to identify evidence of clinical effectiveness (RCTs, systematic reviews) and cost-effectiveness. Methodological filters were used to identify these specific study designs where available.

Further searches were conducted to provide background information for the review including adverse events relating to the drugs and systematic reviews of lifestyle and exercise. Examples of all search strategies are provided below.

Randomised controlled trials: MEDLINE

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.
4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2
6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. 9 and 5
11. xenical.tw.
12. 96829-58-2.rn,tw.
13. reductil.tw.
14. meridia.tw.
15. 106650-56-0.rn,tw.
16. rimonabant.tw.
17. sr141716.tw.
18. acomplia.tw.
19. bethin.tw.
20. (monaslim or remonabent or riobant or slimona or rimoslim or zimulti).tw.
21. 158681-13-1.rn,tw.
22. 11 or 21 or 17 or 12 or 20 or 15 or 14 or 18 or 19 or 13 or 16 or 5
23. 22 and 9
24. Randomized controlled trials as Topic/

25. Randomized controlled trial/
26. Random allocation/
27. Double blind method/
28. Single blind method/
29. Clinical trial/
30. exp Clinical Trials as Topic/
31. (clinic$ adj trial$1).tw.
32. {singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
33. Placebos/
34. Placebo$.tw.
35. Randomly allocated.tw.
36. (allocated adj2 random).tw.
37. 35 or 27 or 25 or 33 or 32 or 28 or 36 or 26 or 34 or 24 or 30 or 29 or 31
38. 37 and 23

Randomised controlled trials: EMBASE

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.
4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2
6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. clinical trial/
11. randomised controlled trial/
12. randomization/
13. single blind procedure/
14. double blind procedure/
15. crossover procedure/
16. placebo/
17. randomi?ed controlled trial$.tw.
18. rct.tw.
19. random allocation.tw.
20. randomly allocated.tw.
21. allocated randomly.tw.
22. (allocated adj2 random).tw.
23. single blind$.tw.
24. double blind$.tw.
25. {treble or triple) adj blind$).tw.
26. PLACEBO$.tw.
27. prospective study/
28. or/10-27
29. case study/
30. case report.tw.
31. abstract report/ or letter/
32. or/29-31
33. 28 not 32
34. exp cohort analysis/
35. exp longitudinal study/

36. exp prospective study/
37. exp follow up/
38. cohort$.tw.
39. exp case control study/
40. (case$ and control$).tw.
41. or/34-40
42. 9 and 5
43. 33 or 41
44. 42 and 43
45. xenical.tw.
46. 96829-58-2.rn,tw.
47. reductil.tw.
48. meridia.tw.
49. 106650-56-0.rn,tw.
50. rimonabant.tw.
51. sr141716.tw.
52. acomplia.tw.
53. bethin.tw.
54. monaslim.tw.
55. remonabent.tw.
56. riobant.tw.
57. slimona.tw.
58. rimoslim.tw.
59. zimulti.tw.
60. 158681-13-1.rn,tw.
61. 53 or 48 or 46 or 55 or 50 or 57 or 51 or 58 or 47 or 52 or 59 or 60 or 49 or 56 or 45 or 54 or 5
    62. 61 and 43 and 9

Randomised controlled trials and systematic reviews: Cumulative Index to Nursing and Allied Health Literature

S61 S59 not S49
S60 S58 and S25
S59 S58 and S23
S58 S57 or S47
S57 S56 or S55 or S54 or S53 or S52 or S51 or S50
S56 cohort*
S55 (MH "cohort studies")
S54 control* or perspective* or volunteer*
S53 (MH "Prospective Studies")
S52 (MH "follow up studies")
S51 (MH "Evaluation Research+")
S50 (MH "comparative study")
S49 S47 and S23
S48 S47 and S25
S47 S46 or S45 or S44 or S43 or S42 or S41 or S40 or S39 or S38 or S37
S46 allocat* random*
S45 (MH "Quantitative studies")
S44 placebo* Search modes – Boolean/Phrase
S43 random allocat*
S42 (MH "random assignment")
S41 randomised controlled trial*

S40 (single or double or treble or triple) and (blind* or mask*)
S39 clinical trial*
S38 trial* Limiters – Publication Type: Clinical Trial
S37 (MH "Clinical Trials")
S26 S17 and S25
S25 S24 and S18
S24 orlistat or sibutramine
S23 S22 and S18
S22 S21 or S20 or S19
S21 rimonabant or SR141716 or acomplia or bethin or monaslim OR remonabent OR riobant OR slimona OR rimoslim OR zimulti OR 158681-13
S20 sibutramine OR reductil OR meridia OR 106650-56-0
S19 orlistat OR xenical OR 96829-58-2
S18 obesity or obese
S17 S12 NOT S15
S16 S12 NOT S15
S15 S13 or S14
S14 (MH "Animals")
S13 PT commentary OR comment OR letter OR editorial
S12 (S6 or S7 or S8 or S9 or S10)
S11 (systematic review OR systematic overview) and (S6 or S7 or S8 or S9 or S10)
S10 systematic review OR systematic overview
S9 (MH "Literature Review+")
S8 metaanaly*
S7 meta analy*
S6 (MH "Meta Analysis")

Randomised controlled trials or systematic reviews or economics: The Cochrane Library

#1 (orlistat):ti,ab,kw
#2 (sibutramine):ti,ab,kw
#3 (#1 OR #2)
#4 obese or obesity
#5 MeSH descriptor Obesity explode all trees
#6 (#4 OR #5)
#7 (#6 AND #3)
#8 xenical or 96829-58-2
#9 reductil or meridia or 106650-56-0
#10 rimonabant or sr141716 or acomplia or bethin or monaslim or remonabent or riobant or slimona or rimoslim or zimulti or 158681-13-1
#11 (#8 OR #9 OR #10 OR #3)
#12 (#11 AND #6)

Randomised controlled trials or systematic reviews: Science Citation Index and ISI Conference Proceedings

#11 #10 AND #7
#10 #9 OR #4

#9 ts=(xenical or reductil or meridia or rimonabant or acomplia or bethinmonaslim or remonabent or riobant or slimona or rimoslim or zimulti)
#8 #7 AND #4
#7 #5 OR #6
#6 ts=obesity
#5 ti=obesity
#4 #3 OR #2 OR #1
#3 ti=orlistat
#2 ti=sibutramine
#1 ti=orlistat

Systematic reviews: MEDLINE

1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw.
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).mp.
6. exp Review Literature as Topic/
7. or/1-6
8. exp *Obesity/
9. 8 and 7

Systematic reviews: EMBASE

1. exp *Obesity/
2. Meta Analysis/
3. {meta adj analy$) or metaanalys$).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. or/2-4
6. cancerlit.ab.
7. cochrane.ab.
8. embase.ab.
9. (psychlit or psyclit).ab.
10. (psychinfo or psycinfo).ab.
11. (cinal or cinahl).ab.
12. science citation index.ab.
13. bids.ab.
14. or/6-13
15. reference lists.ab.
16. bibliograph$.ab.
17. hand-search$.ab.
18. manual search$.ab.
19. relevant journals.ab.
20. or/15-19
21. data extraction.ab.
22. selection criteria.ab.
23. 21 or 22
24. review.pt.
25. 23 and 24
26. letter.pt.

27. editorial.pt.
28. animal/
29. human/
30. 28 not (28 and 29)
31. or/26-27,30
32. 5 or 14 or 20 or 25
33. 32 not 31
34. 33 and 1

Economics: MEDLINE

1. exp "costs and cost analysis"/
2. economics/
3. exp economics hospital/
4. exp economics medical/
5. exp economics nursing/
6. economics pharmaceutical/
7. exp "fees and charges"/
8. exp budgets/
9. budget$.tw.
10. cost$.ti.
11. (cost$ adj2 (effective$ or utilit$ or benefit$ or minim$)).ab.
12. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
13. (price or pricing$).tw.
14. (financial or finance or finances or finanaced).tw.
15. (fee or fees).tw.
16. or/1-15
17. orlistat/
18. sibutramine/
19. sibutramine.ti,ab.
20. orlistat.ti,ab.
21. 20 or 17 or 19 or 18
22. exp obesity/
23. obese.ti,ab.
24. obesity.ti,ab.
25. 24 or 22 or 23
26. 25 and 21
27. xenical.tw.
28. 96829-58-2.rn,tw.
29. reductil.tw.
30. meridia.tw.
31. 106650-56-0.rn,tw.
32. rimonabant.tw.
33. sr141716.tw.
34. acomplia.tw.
35. bethin.tw.
36. (monaslim or remonabent or riobant or slimona or rimoslim or zimulti).tw.
37. 158681-13-1.rn,tw.
38. 27 or 37 or 33 or 28 or 36 or 31 or 30 or 34 or 35 or 29 or 32 or 21
39. 38 and 25
40. 39 and 16

41. (value adj2 (money or monetary)).tw.
42. value of life/
43. quality adjusted life year/
44. quality adjusted life.tw.
45. (qaly$ or qald$ or qale$ or qtime$).tw.
46. disability adjusted life.tw.
47. daly$.tw.
48. health status indicators/
49. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
50. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
51. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
52. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
53. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
54. (euroqol or euro qol or eq5d or eq 5d).tw.
55. (hql or hqol or h qol or hrqol or hr qol).tw.
56. (hye or hyes).tw.
57. health$ year$ equivalent$.tw.
58. health utilit$.tw.
59. (hui or hui1 or hui2 or hui3).tw.
60. disutilit$.tw.
61. rosser.tw.
62. quality of wellbeing.tw.
63. qwb.tw.
64. willingness to pay.tw.
65. standard gamble$.tw.
66. time trade off.tw.
67. time tradeoff.tw.
68. tto.tw.
69. exp models economic/
70. *models theoretical/
71. *models organizational/
72. economic model$.tw.
73. markov chains/
74. markov$.tw.
75. monte carlo method/
76. monte carlo.tw.
77. exp decision theory/
78. (decision$ adj2 (tree$ or analy$ or model$)).tw.
79. or/41-78
80. letter.pt.
81. orial.pt.
82. comment.pt.
83. or/80-82
84. 79 not 83
85. 84 or 16
86. 85 and 39

Adverse events: MEDLINE

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.
4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2
6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. 9 and 5
11. xenical.tw.
12. 96829-58-2.rn,tw.
13. reductil.tw.
14. meridia.tw.
15. 106650-56-0.rn,tw.
16. rimonabant.tw.
17. sr141716.tw.
18. acomplia.tw.
19. bethin.tw.
20. (monaslim or remonabent or riobant or slimona or rimoslim or zimulti).tw.
21. 158681-13-1.rn,tw.
22. 11 or 21 or 17 or 12 or 20 or 15 or 14 or 18 or 19 or 13 or 16 or 5
23. 22 and 9
24. drug toxicity/
25. ae.fs.
26. (safe or safety or side effect*).tw.
27. (undesirable effect* or treatment emergent*).tw.
28. (tolerability or toxicity or adrs).tw.
29. (adverse adj2 (event or events or effect or effects or reaction or reactions or outcome*)).tw.
30. 27 or 25 or 28 or 24 or 26 or 29
31. 30 and 23

Adverse events: EMBASE

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.
4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2
6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. 9 and 5
11. xenical.tw.
12. 96829-58-2.rn,tw.
13. reductil.tw.
14. meridia.tw.
15. 106650-56-0.rn,tw.

16. rimonabant.tw.
17. sr141716.tw.
18. acomplia.tw.
19. bethin.tw.
20. (monaslim or remonabent or riobant or slimona or rimoslim or zimulti).tw.
21. 158681-13-1.rn,tw.
22. 11 or 21 or 17 or 12 or 20 or 15 or 14 or 18 or 19 or 13 or 16 or 5
23. 22 and 9
24. ae.fs.
25. (safe or safety or side effect*).tw.
26. (undesirable effect* or treatment emergent*).tw.
27. (tolerability or toxicity or adrs).tw.
28. (adverse adj2 (event or events or effect or effects or reaction or reactions or outcome*)).tw.
29. Adverse Drug Reaction/
30. exp side effect/
31. 27 or 25 or 28 or 30 or 24 or 26 or 29
32. 23 and 31

Adverse events: The Cochrane Library

#1 adverse NEAR/2 (effect or effects or event or events or reaction or reactions or outcome*)
#2 MeSH descriptor Drug Toxicity, this term only
#3 safe or safety or side effect*
#4 underirable effect or treatment emergent
#5 tolerability or toxicity or adrs
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 orlistat or sibutramine or rimonabant
#8 xenical or reductil or meridia or acomplia or bethin or monaslim or remonabent or riobant or slimona or rimoslim or zimulti
#9 7 or 8 269674
#10 MeSH descriptor Obesity, this term only
#11 MeSH descriptor Obesity, Morbid, this term only
#12 (#10 OR #11)
#13 (#6 AND #9 AND #12)

Adverse events: Science Citation Index and ISI Conference Proceedings

#16 #15 AND #11
#15 #12 OR #13
#13 ts=(adverse SAME (event or events or effect or effects or reaction or reactions or outcome*))
#12 ts=(drug toxicity or safe or safety or side effect* or undesirable effect* or treatment emergent* or tolerability or toxicity or adrs)
#11 #10 AND #7
#10 #9 OR #4
#9 ts=(xenical or reductil or meridia or rimonabant or acomplia or bethinmonaslim or remonabent or riobant or slimona or rimoslim or zimulti)
#8 #7 AND #4
#7 #5 OR #6
#6 ts=obesity
#5 ti=obesity

#4 #3 OR #2 OR #1
#3 ti=orlistat
#2 ti=sibutramine
#1 ti=orlistat

Lifestyle and exercise systematic reviews: MEDLINE

1. Life Style/
2. (lifestyle* or life style*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3. exercise.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4. *Exercise/
5. 4 or 1 or 3 or 2
6. Meta-Analysis as Topic/
7. meta analy$.tw.
8. metaanaly$.tw.
9. Meta-Analysis/
10. (systematic adj (review$1 or overview$1)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
11. exp Review Literature as Topic/
12. or/6-11
13. 12 and 5
14. *lifestyle/
15. (exercise* or lifestyle* or life style*).ti.
16. 4 or 15 or 14
17. 16 and 12

Lifestyle and exercise systematic reviews: EMBASE

1. (exercise* or lifestyle* or life style*).ti.
2. *"lifestyle and related phenomena"/ or *lifestyle/ or *lifestyle modification/
3. exp *Exercise/
4. 1 or 2 or 3
5. Meta Analysis/
6. {meta adj analy$) or metaanalys$).tw.
7. (systematic adj (review$1 or overview$1)).tw.
8. or/5-7
9. cancerlit.ab.
10. cochrane.ab.
11. embase.ab.
12. (psychlit or psyclit).ab.
13. (psychinfo or psycinfo).ab.
14. (cinal or cinahl).ab.
15. science citation index.ab.
16. bids.ab.
17. or/9-16
18. reference lists.ab.
19. bibliograph$.ab.
20. hand-search$.ab.
21. manual search$.ab.

22. relevant journals.ab.
23. or/18-22
24. data extraction.ab.
25. selection criteria.ab.
26. 24 or 25
27. review.pt.
28. 26 and 27
29. letter.pt.
30. orial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/29-30,33
35. 8 or 17 or 23 or 28
36. 35 not 34
37. 4 and 36

Lifestyle and exercise systematic reviews: Cumulative Index to Nursing and Allied Health Literature

S17 (S12 NOT S15) and (S5 and S16)
S16 S12 NOT S15
S15 S13 or S14
S14 (MH "Animals")
S13 PT commentary OR comment OR letter OR editorial
S12 (S6 or S7 or S8 or S9 or S10)
S11 (systematic review OR systematic overview) and (S6 or S7 or S8 or S9 or S10)
S10 systematic review OR systematic overview
S9 (MH "Literature Review+")
S8 metaanaly*
S7 meta analy*
S6 (MH "Meta Analysis")
S5 (S1 or S2 or S3)
S4 {MM "Life Style") or (MM "Life Style Changes")) and (S1 or S2 or S3)
S3 (MM "Life Style") or (MM "Life Style Changes")
S2 (MM "Exercise+")
S1 TI exercise* OR lifestyle* or life style*

Lifestyle and exercise: Cochrane Database of Systematic Reviews

#1 (exercise* or lifestyle* or life style*):ti
#2 MeSH descriptor Exercise, this term only
#3 MeSH descriptor Life Style, this term only
#4 (#1 OR #2 OR #3)

Economics: EMBASE

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.

4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2
6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. xenical.tw.
11. 96829-58-2.rn,tw.
12. reductil.tw.
13. meridia.tw.
14. 106650-56-0.rn,tw.
15. rimonabant.tw.
16. sr141716.tw.
17. acomplia.tw.
18. bethin.tw.
19. monaslim.tw.
20. remonabent.tw.
21. riobant.tw.
22. slimona.tw.
23. rimoslim.tw.
24. zimulti.tw.
25. 158681-13-1.rn,tw.
26. 18 or 13 or 11 or 20 or 15 or 22 or 16 or 23 or 12 or 17 or 24 or 25 or 14 or 21 or 10 or 19 or 5
27. exp SOCIOECONOMICS/
28. exp "Cost Benefit Analysis"/
29. exp "Cost Effectiveness Analysis"/
30. exp "Cost of Illness"/
31. exp "Cost Control"/
32. exp Economic Aspect/
33. exp Financial Management/
34. exp "Health Care Cost"/
35. exp Health Care Financing/
36. exp Health Economics/
37. exp "Hospital Cost"/
38. (financial or fiscal or finance or funding).tw.
39. exp "Cost Minimization Analysis"/
40. (cost adj estimate$).mp.
41. (cost adj variable$).mp.
42. (unit adj cost$).mp.
43. or/27-42
44. 43 and 26 and 9
45. 26 and 9
46. 9 and 5
47. 46 and 43

Economics: Cumulative Index to Nursing and Allied Health Literature

1. orlistat/
2. sibutramine/
3. sibutramine.ti,ab.
4. orlistat.ti,ab.
5. 4 or 1 or 3 or 2

6. exp obesity/
7. obese.ti,ab.
8. obesity.ti,ab.
9. 8 or 6 or 7
10. exp Financial Management/
11. exp *economics/
12. exp financial support/
13. exp financing organized/
14. exp business/
15. (cost or costs or economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
16. Health resource allocation.sh.
17. Health resource utilization.sh.
18. orial or letter or news).pt.
19. (10 or 11 or 12 or 13 or 15 or 16 or 17) not (14 or 18)
20. 19 and 9 and 5

Economics: Science Citation Index and ISI Conference Proceedings

#3 #2 AND #1
#2 ts=(cost* or price* economic* or budget* or fiscal* or fees* OR utilit* or value* or quality adjusted life year OR qaly)
#1 ts=(orlistat OR sibutramine OR xenical OR 96829-58-2 OR reductil OR meridia OR 106650-56-0 OR rimonabant OR sr141716 OR acomplia OR bethin OR monaslim OR remonabent OR riobant OR slimona OR rimoslim OR zimulti OR 158681-13-1)

Appendix 2

Clinical review

Data extraction form

Study details			
Endnote number		Ethnicity reported?	
First author		Language	
Year		Country	

Eligibility checklist	**Yes**	**No**	
Population >=18			If no, exclude
Population has mental illness			If yes, exclude
Population is overweight/obese or at high risk of CVD			If no, exclude
Treatment length >= 12 weeks			If no, exclude
Active intervention includes: orlistat 120mg with meals (maximum 360mg) sibutramine 10-15mg once daily rimonabant 20mg once daily			If no, exclude
Control group is lifestyle/exercise/placebo/standard care or metformin in T2DM/PCOS, or orlistat/sibutramine/rimonabant			If no, exclude
Control group is other active drug			If yes, exclude
Randomised			If no, exclude

Is the population included…… (please give percentages in boxes given)

Diabetic ☐ Co morbidities ☐ Obese but healthy ☐ Mixed/other ☐

Primary outcome						
Type of RCT	Parallel ☐ Crossover ☐ Other - State					
No of arms	2 ☐ 3 ☐ Other - State					
No of relevant arms	2 ☐ 3 ☐ Other - State					
Treatment length (m)						
Time points (m)						
Weight:	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR
BMI:	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR	T / G / GE / NR
Quality						
Randomisation	None (0) ☐ Mentioned (1) ☐ Described and (2) adequate ☐ **If none – exclude**					
Allocation concealment	None (0) ☐ Yes (1) ☐					

Double Blinding	None (0) ☐	Mentioned (1) ☐	Described and (2) adequate ☐	
Flow of participants	None (0) ☐	Described and (1) incomplete ☐	Described and (2) adequate ☐	Total score ☐
Is QoL measured	Yes ☐	No ☐		
Is there a policy for continuation?	Yes ☐	No ☐		

For greater than two-arm trials use multiple sheets

Arm 1 – Control Group

Placebo	Placebo + D	Standard care	Orlistat + D	Sibutramine + D	Rimonabant+ D
			Orlistat + E	Sibutramine + E	Rimonabant+ E
Orlistat	Sibutramine	Rimonabant	Orlistat + D&E	Sibutramine + D&E	Rimonabant + D&E
			Dietary	Exercise	

Dose:

Dietary detail:

Exercise detail:

Arm 2 – Intervention group

Placebo	Placebo + D	Standard care	Orlistat + D	Sibutramine + D	Rimonabant+ D
			Orlistat + E	Sibutramine + E	Rimonabant+ E
Orlistat	Sibutramine	Rimonabant	Orlistat + D&E	Sibutramine + D&E	Rimonabant + D&E
			Dietary	Exercise	

Dose:

Dietary detail:

Exercise detail:

Was standard dietary advice given to all participants? Yes ☐ No ☐ above standard? ☐

Advice detail:

Was standard exercise advice given to all participants? Yes ☐ No ☐ above standard? ☐

Advice detail:

Baseline data

Data should be converted to units given in table.

	Arm 1	Arm 2
No. of participants		
Age, mean		
Sex, *n* (%) male		
Systolic BP (mmHg)		
Diastolic BP (mmHg)		
Total cholesterol (mmol/l)		
LDL (mmol/l)		
HDL (mmol/l)		
Triglycerides (mmol/l)		
HbA_{1c} (%)		
Comorbidities		
Diabetes		
Previous CVD		

HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Withdrawals/adverse events

	Arm 1	Arm 2
Total withdrawals		
Discontinuation due to AE		
Heart rate for sibutramine trials		
Mean (SD)		
No. high heart rate		

AE, adverse events.

Primary outcomes

Complete one form per follow-up time per comparison Time point (months)

	Arm 1						Arm 2						Difference					
	N	Mean	SD	SE	% LCL	% UCL	N	Mean	SD	SE	% LCL	% UCL	N	Mean	SD	SE	% LCL	% UCL
Weight (kg) Baseline																		
Time point																		
Change																		
Percentage loss																		
BMI (kg/m^2) Baseline																		
Time point																		
Change																		
Percentage loss																		
Waist (cm) Baseline																		
Time point																		
Change																		
Percentage loss																		

Responders						
	r	n	%	r	n	%
>5% weight loss						
> 10% weight loss						

Notes

The data presented here is LOCF ☐ Completers only ☐ Is completer only data available? ☐

Is outcome data presented for diabetics only? ☐

Appendix 3

Clinical review analyses

Reference list

Full-text articles excluded from the review ($n = 67$).

Sibutramine given in combination with another drug (n = 2)

1. Derosa G, D'Angelo A, Salvadeo SA, Ferrari I, Gravina I, Fogari E, *et al.* Sibutramine effect on metabolic control of obese patients with type 2 diabetes mellitus treated with pioglitazone. *Metab Clin Exp* 2008;**57**:1552–7.
2. Sanchez-Reyes L, Fanghanel G, Yamamoto J, Martinez-Rivas L, Campos-Franco E, Berber A. Use of sibutramine in overweight adult Hispanic patients with type 2 diabetes mellitus: a 12-month, randomized, double-blind, placebo-controlled clinical trial. *Clin Ther* 2004;**26**:1427–35.

Ineligible drug dose (n = 6)

1. Bougoulia M, Triantos A, Koliakos G. Effect of weight loss with or without orlistat treatment on adipocytokines, inflammation, and oxidative markers in obese women. *Hormones* 2006;**5**:259–69.
2. Gentile S, Guarino G, Padovano B, Buonocunto F, Gruppo Campano Obesità. Efficacia e sicurezza di impiego di un trattamento a breve termine con orlistata in soggetti obesi. *Ann Ital Med Int* 2005;**20**:90–6.
3. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, *et al.* Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;**356**:2119–25.
4. LeCheminant JD, Jacobsen D, Hall MA, Donnelly JE. A comparison of meal replacements and medication in weight maintenance after weight loss. *J Am Coll Nutr* 2005;**24**:347–53.
5. McMahon FG, Fujioka K, Singh BN, Mendel CM, Rowe E, Rolston K, *et al.* Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 2000;**160**: 2185–91.
6. Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C. Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. *Arch Intern Med* 2001;**161**:218–27.

Outcomes not reported/not fully reported (n = 7)

1. Bach DS, Rissanen AM, Mendel CM, Shepherd G, Weinstein SP, Kelly F, *et al.* Absence of cardiac valve dysfunction in obese patients treated with sibutramine. *Obes Res* 1999;**7**:363–9.
2. Halpern A, Leite CC, Herskowicz N, Barbato A, Costa AP. Evaluation of efficacy, reliability, and tolerability of sibutramine in obese patients, with an echocardiographic study. *Rev Hosp Clin Fac Med Sao Paulo* 2002;**57**:98–102.
3. James WP, Avenell A, Broom J, Whitehead J. A one-year trial to assess the value of orlistat in the management of obesity. *Int J Obes Rel Metab Disord* 1997;**21**(Suppl. 3):24–30.

4. Kaukua JK, Pekkarinen TA, Rissanen AM. Health-related quality of life in a randomised placebo-controlled trial of sibutramine in obese patients with type II diabetes. *Int J Obes Rel Metab Disord* 2004;**28**:600–5.

5. Quilliot D, Bohme P, Zannad F, Ziegler O. Sympathetic–leptin relationship in obesity: effect of weight loss. *Metab Clin Exp* 2008;**57**:555–62.

6. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;**352**:167–72.

7. Toornvliet AC, Pijl H, Frolich M, Westendorp RG, Meinders AE. Insulin and leptin concentrations in obese humans during long-term weight loss. *Neth J Med* 1997;**51**:96–102.

Non-English (n = 11)

1. Demidova TI, Selivanova AV, Ametov AS. [The role of fat tissue in development of metabolic disorders in patients with diabetes mellitus type 2 and obesity]. [Russian]. *Ter Arkh* 2006;**78**:64–9.

2. Gao X, Sun X, Zhao N, Pan B, Jiang S, Yi D, Lu Z. Level of free fat acid could be decreased in obese subjects after 6 months' treatment with sibutramine. *Fudan Univ J Med Sci* 2002;**29**:239–43.

3. Hajdukovic Z, Jovelic A, Zivotic-Vanovic M, Raden S. [Influence of orlistat therapy on serum insulin level and morphological and functional parameters of peripheral arterial circulation in obese patients.] [Serbian.] *Vojnosanit Pregl* 2005;**62**:803–10.

4. Ivleva AI, Spiridonova IA, Maksimenko OK, Sivkova EB, Arutiunov AG. [Efficacy of orlistat in the treatment of constitutional-alimentary obesity in patients with high risk of cardiovascular complications.] [Russian.] *Kardiologiia* 2002;**42**:58–61.

5. Li R, Li Q, Luo R, Zhou B, Zhang S, Lui Z, *et al.* Effect of sibutramine in reducing body mass and its influencing factors. *Chin J Clin Rehabil* 2005;**9**:16–19.

6. Naumov VG, Lupanov VP, Dotsenko IuV, Tvorogova MG. [Six-month xenical (orlistat) therapy of patients with stable angina pectoris concomitant with obesity and hyperlipidemia.] [Russian.] *Ter Arkh* 2002;**74**:47–51.

7. Tong NW, Ran XW, Li QF, Tang BD, Li R, Yang FY, *et al.* [Effects of sibutramine on blood glucose and lipids, body fat mass and insulin resistance in obese patients: a multi-center clinical trial.] [Chinese.] *Chung-Hua Nei Ko Tsa* [*Chih Chin J Intern Med*] 2005;**44**:659–63.

8. Wang J-P, Yan Xg, Zhu X-P. Efficacy and safety of sibutramine in simple over-weighted and obese subjects. *Bull Hunan Med Univ* 2003;**28**:527–30.

9. Wu J, Lei M-X, Chen H-Ling. Serum leptin and insulin resistance in obesity and effects of sibutramine on them. *Bull Hunan Med Univ* 2003;**28**:605–7.

10. Wu J, Zhu C-L, Shao X-H, Zou D-J. Pharmacotherapeutic weight loss in treatment of overweight type 2 diabetes patients. *Acad J Second Mil Med Univ* 2006;**27**:531–4.

11. Zhao Y, Wang X, Yan Z. [A randomized, double-blind, placebo-controlled, multicenter study on sibutramine in over-weighted and obese subjects.] [Chinese.] *Chung-Hua Yu Fang i Hsueh Tsa Chih* [*Chin J Prev Med*] 2001;**35**:329–32.

Non-randomised (n = 3)

1. Lazurova I, Dravecka I, Kraus V, Petrovicova J. Metformin versus sibutramine in the treatment of hyperinsulinemia in chronically anovulating women. *Bratisl Lek Listy* 2004;**105**:207–10.
2. Pomara F, Gravante G, Russo G, Amato G. Diet associated with regular physical activity or drugs: a longitudinal study on obesity management. *Minerva Gastroenterol Dietol* 2003;**49**:141–5.
3. Sabuncu T, Nazligul Y, Karaoglanoglu M, Ucar E, Kilic FB. The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with non-alcoholic steatohepatitis. *Rom J Gastroenterol* 2003;**12**:189–92.

Review (n = 5)

1. Anderson JW. Orlistat enhances the hypocholesterolemic effects of an energy-restricted diet. *Future Lipidol* 2007;**2**:109–13.
2. Bray GA. Lifestyle and pharmacological approaches to weight loss: efficacy and safety. *J Clin Endocrinol Metab* 2008;**93**(Suppl. 1):81–8.
3. Heymsfield SB, Segal KR, Hauptman J, Lucas CP, Boldrin MN, Rissanen A, *et al.* Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 2000;**160**:1321.
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5. Leopold K, Wechsler JG. [Obesity: gradual-schedule therapy and long-term results.] [German.] *MMW Fortschr Med* 2001;**143**:I–VIII.

Duplicate publication (n = 16)

1. Bray GA, Ryan DH, Gordon D, Heidingsfelder S, Cerise F, Wilson K. A double-blind randomized placebo-controlled trial of sibutramine. *Obes Res* 1996;**4**:263–70.
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3. Hansen D, Astrup A, Toubro S, Finer N, Kopelman P, Hilsted J, *et al.* Predictors of weight loss and maintenance during 2 years of treatment by sibutramine in obesity. Results from the European multi-centre STORM trial. Sibutramine Trial of Obesity Reduction and Maintenance. *Int J Obes Rel Metab Disord* 2001;**25**:496–501.
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6. Karhunen L, Franssila-Kallunki A, Rissanen P, Valve R, Kolehmainen M, Rissanen A, *et al.* Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. *Int J Obes Rel Metab Disord* 2000;**24**:1567–72.
7. Levinson PD. Commentary. *Evid Base Med* 2001;**6**:54.

8. Mathus-Vliegen EM, Van Ierland-Van Leeuwen ML, Terpstra A. Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity. *Aliment Pharmacol Ther* 2004;**19**:601–11.

9. Patschan S, Scholze J. Obesity-related hypertension. *Cardiol Rev* 2007;**24**:32–5.

10. Phelan S, Wadden TA, Berkowitz RI, Sarwer DB, Womble LG, Cato RK *et al.* Impact of weight loss on the metabolic syndrome. *Int J Obes* 2007;**31**:1442–8.

11. Reaven G, Segal K, Hauptman J, Boldrin M, Lucas C. Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X. *Am J Cardiol* 2001;**87**:827–31.

12. Rissanen P, Vahtera E, Krusius T, Uusitupa M, Rissanen A. Weight change and blood coagulability and fibrinolysis in healthy obese women. *Int J Obes Rel Metab Disord* 2001;**25**:212–18.

13. Sibutramine significantly decreases body weight in women with PCOS. *Nature Clin Pract Endocrinol Metab* 2008;**4**:478–9.

14. Sjöström L. Analysis of the XENDOS study (Xenical in the Prevention of Diabetes in Obese Subjects). *Endocr Pract* 2006;**12**(Suppl. 1):31–3.

15. Toubro S, Hansen DL, Hilsted JC, Porsborg PA, Astrup AV. [The effect of sibutramine for the maintenance of weight loss. A randomized controlled clinical trial.] [Danish.] *Ugeskr Laeger* 2001;**163**:2935–40.

16. Vidgren HM, Agren JJ, Valve RS, Karhunen LJ, Rissanen AM, Uusitupa MI. The effect of orlistat on the fatty acid composition of serum lipid fractions in obese subjects. *Clin Pharmacol Ther* 1999;**66**:315–22.

Substudy of included trial (n = 10)

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Follow-up data not at 3, 6 or 12 months (n = 7)

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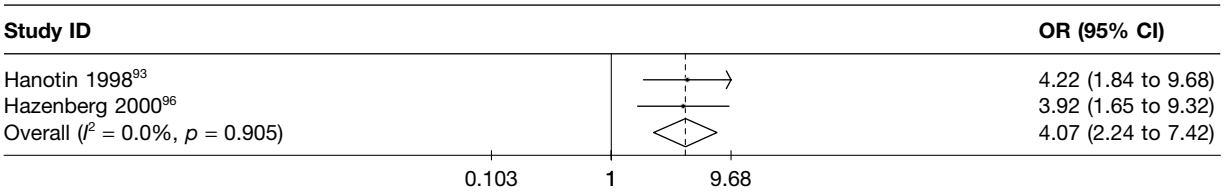
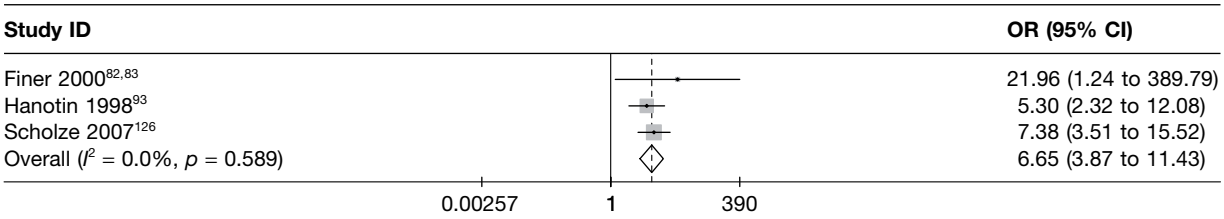
(a)

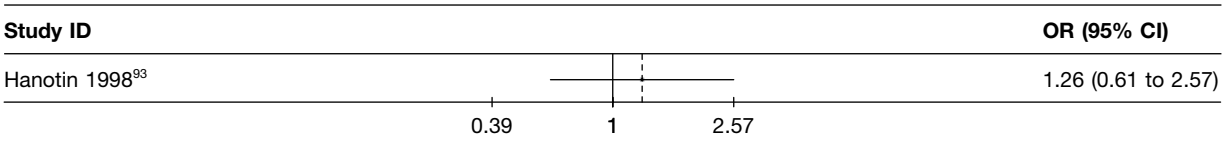
Sibutramine 10 mg vs placebo



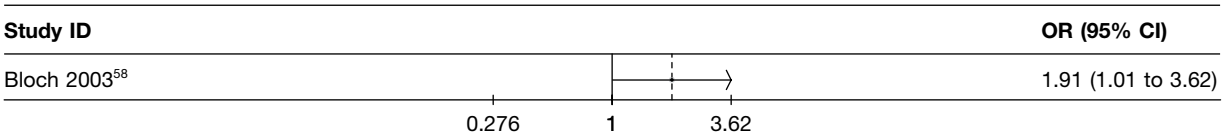
Sibutramine 15 mg vs placebo



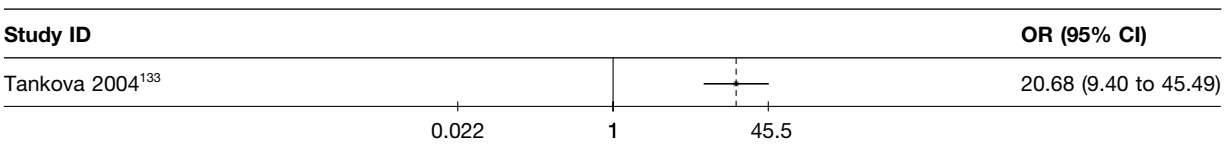
Sibutramine 15 mg vs sibutramine 10 mg



Orlistat vs standard care



Sibutramine 15 mg vs standard care



(b)

Orlistat and sibutramine vs orlistat

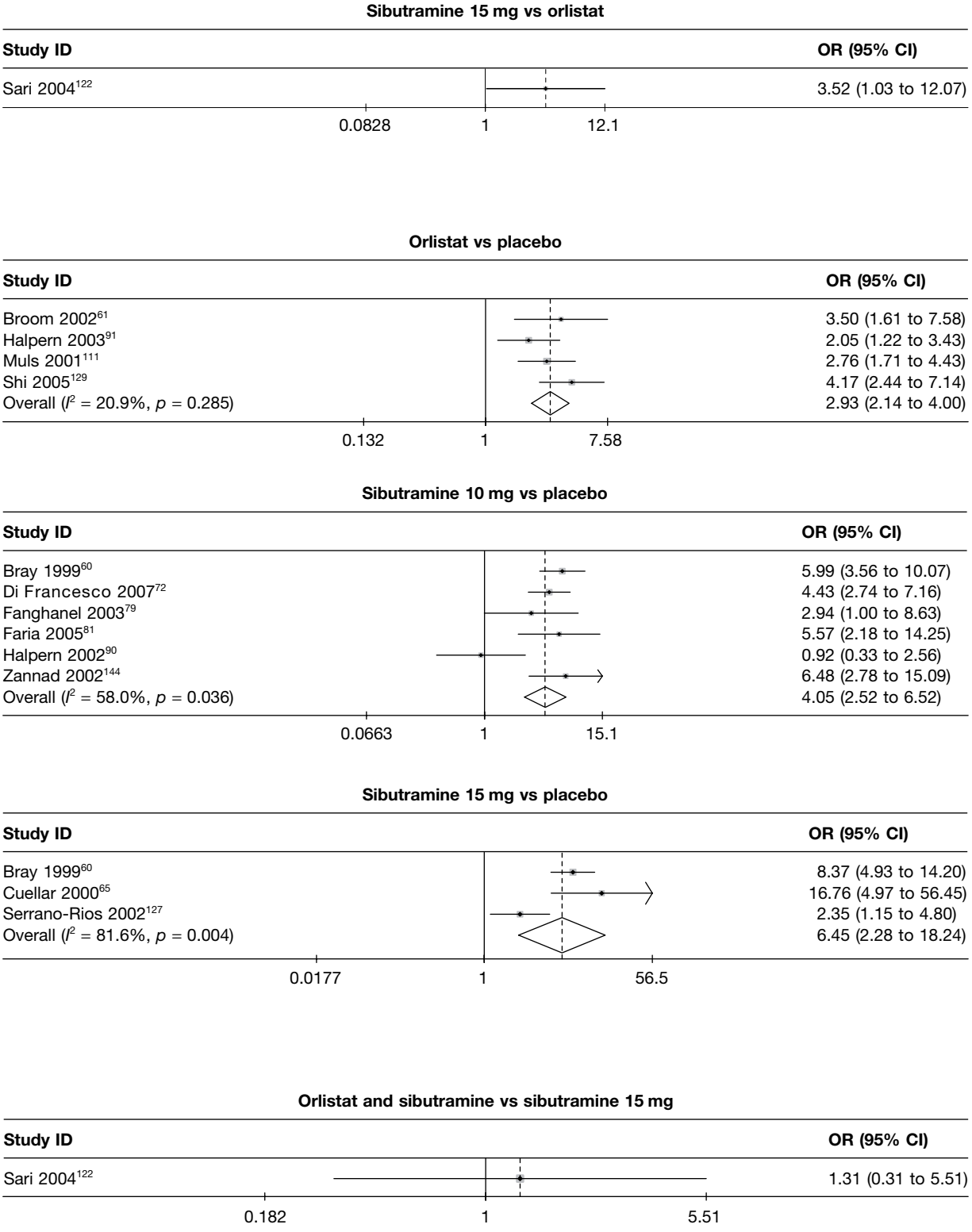
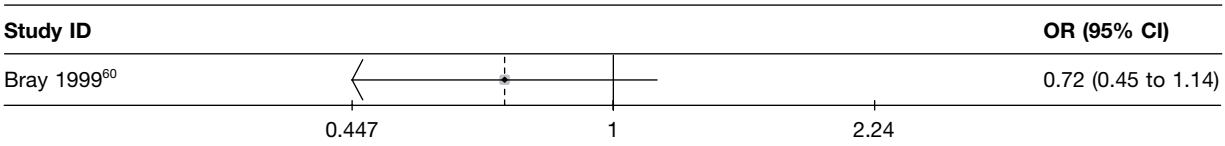


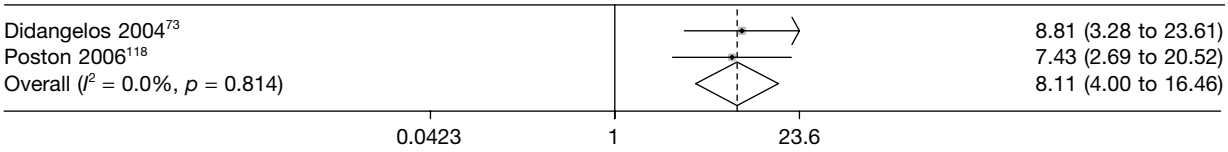
FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weight-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference.

(b) *continued*

Sibutramine 10 mg vs sibutramine 15 mg

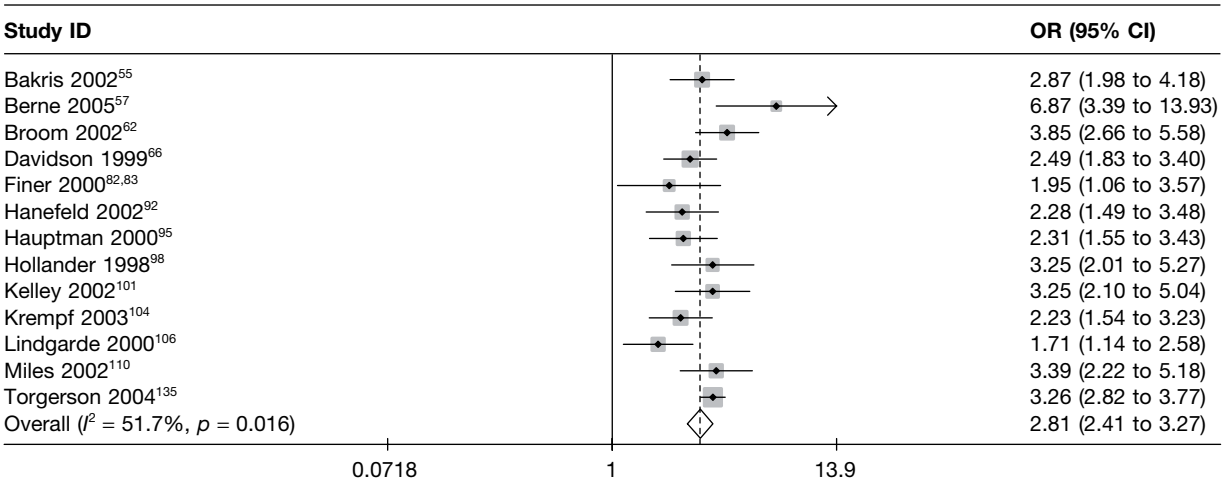


Orlistat vs standard care

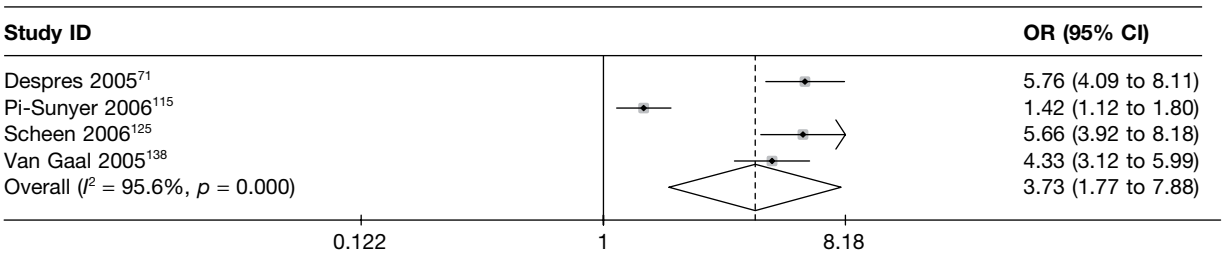


(c)

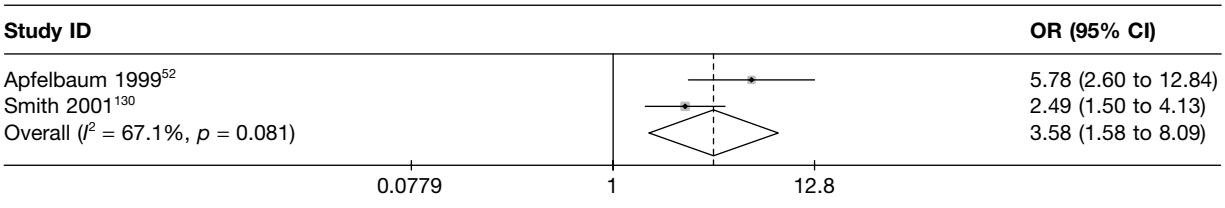
Orlistat vs placebo

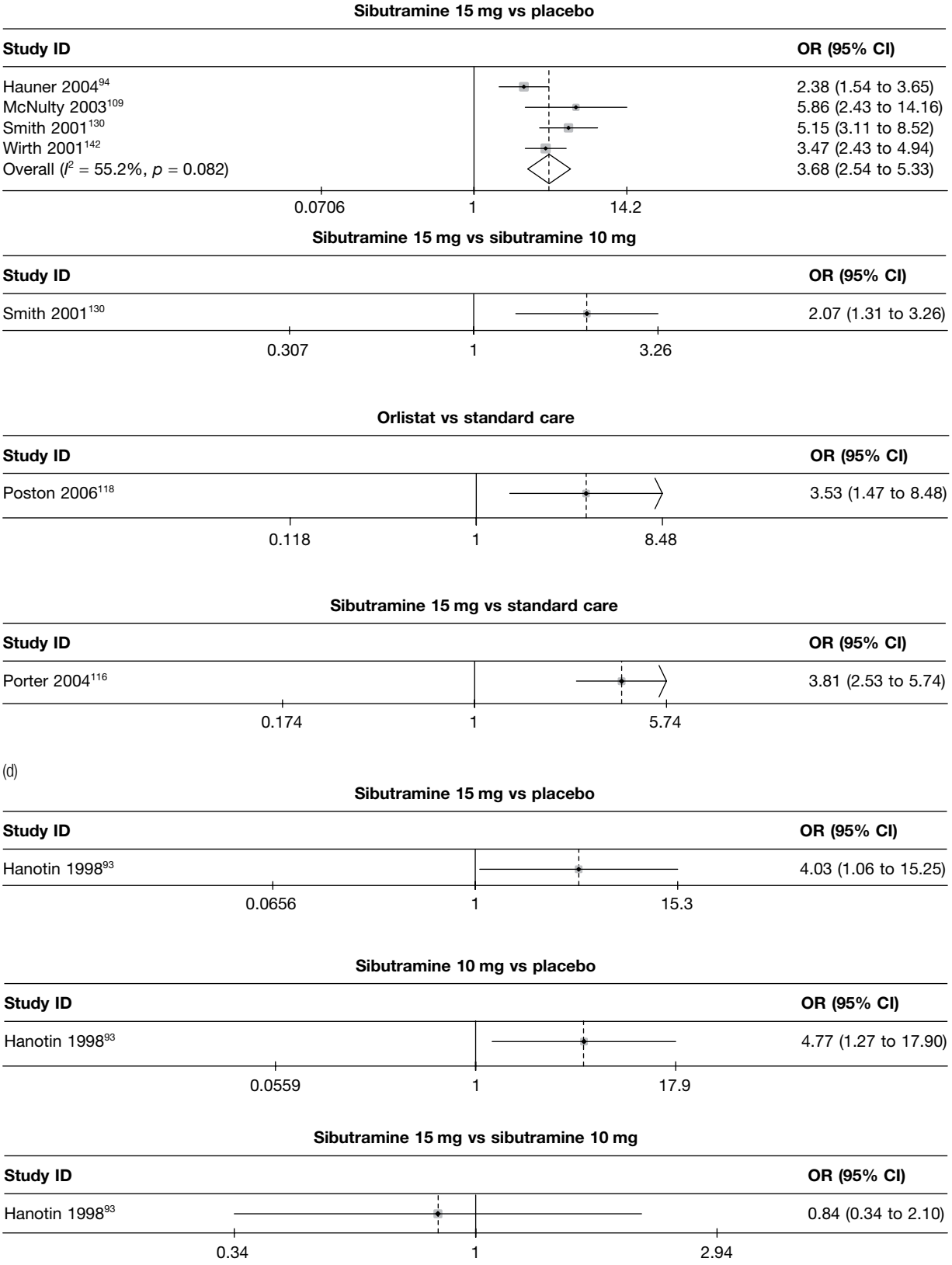


Rimonabant vs placebo



Sibutramine 10 mg vs placebo





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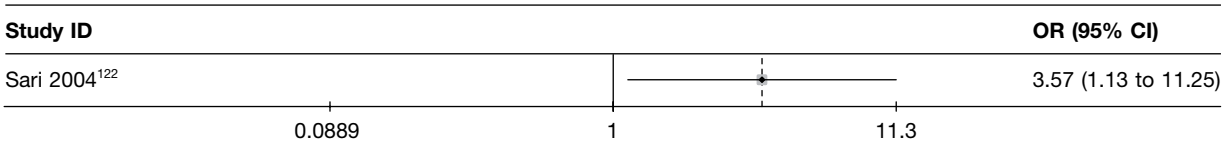
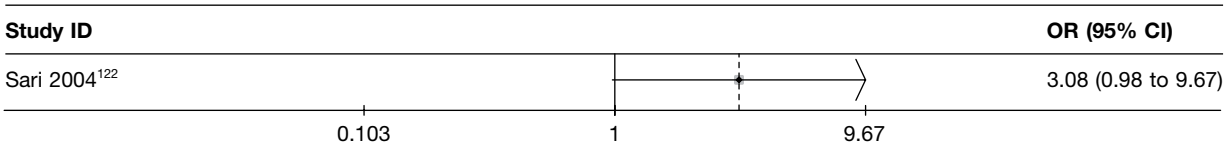
(e)

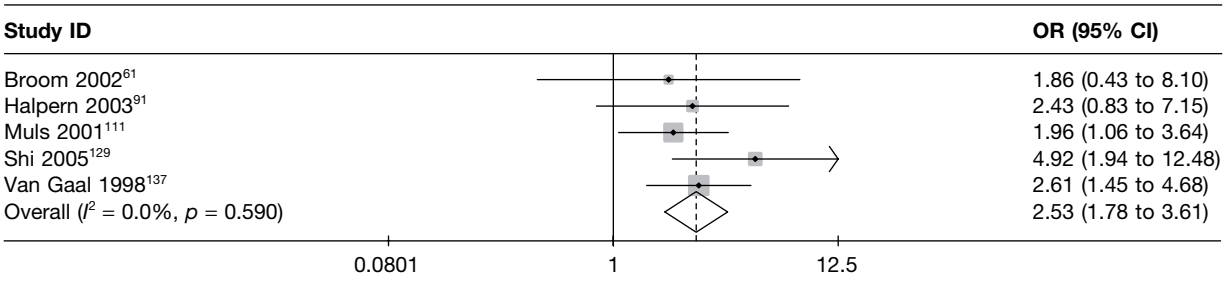
Orlistat and sibutramine vs orlistat



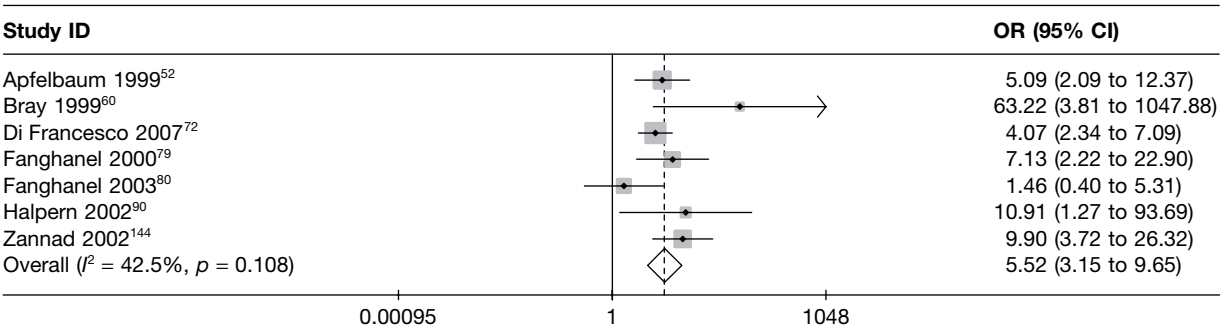
Sibutramine 15 mg vs orlistat



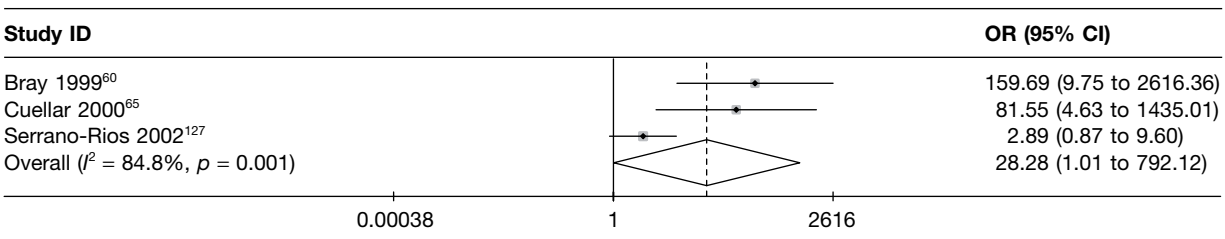
Orlistat vs placebo



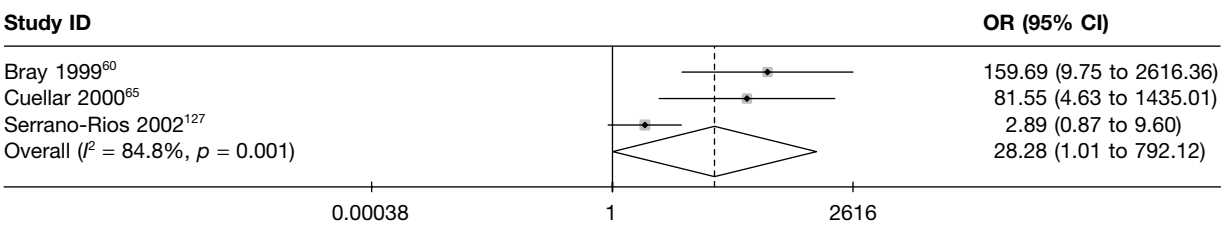
Sibutramine 10 mg vs placebo



Sibutramine 15 mg vs placebo



Sibutramine 15 mg vs placebo



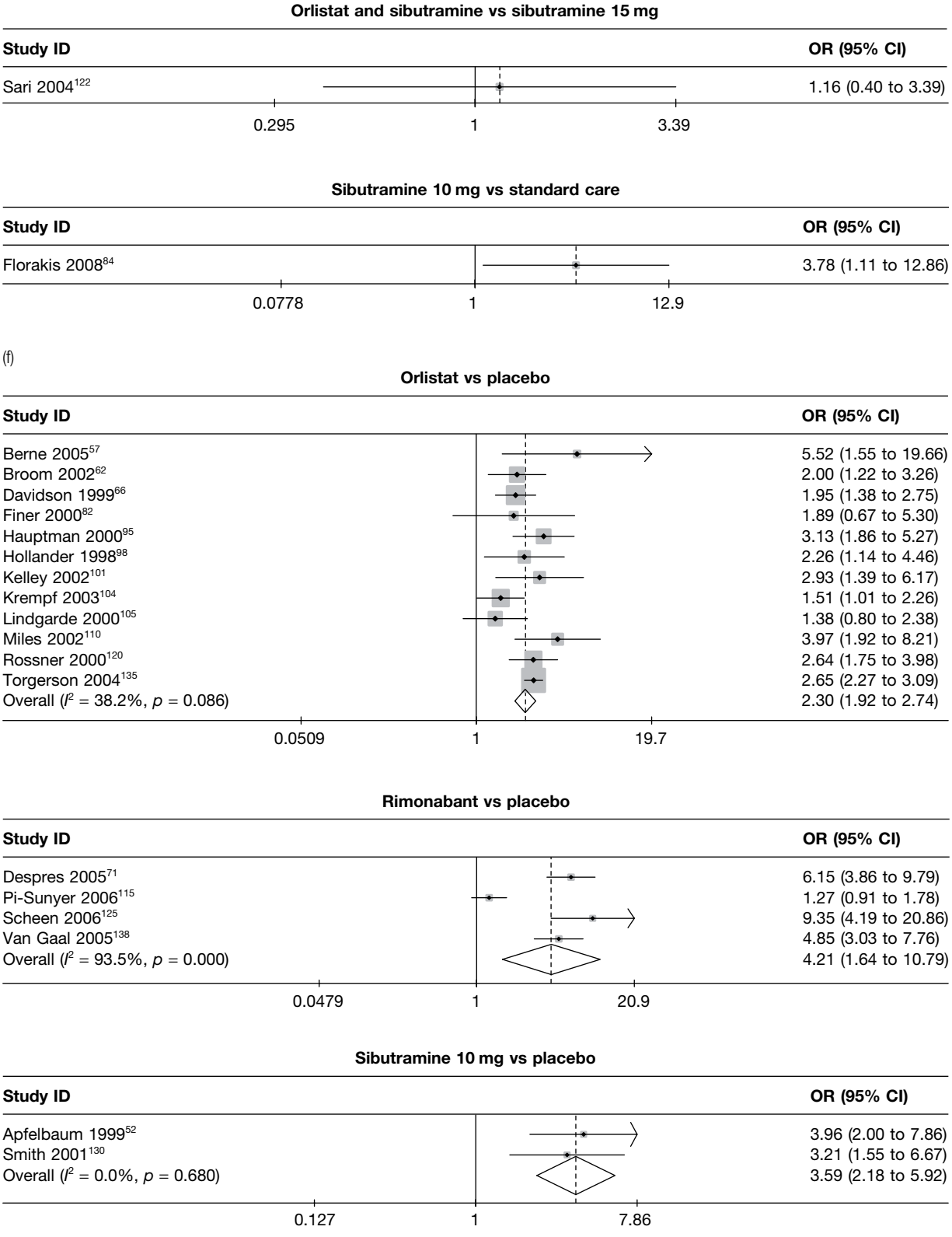
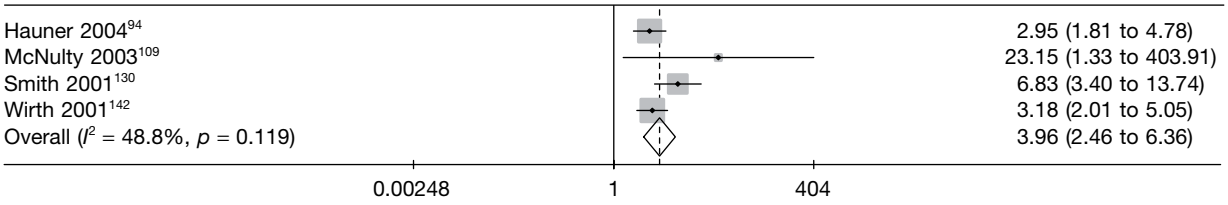


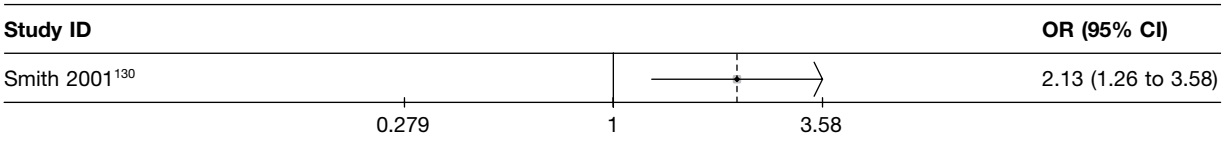
FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weight-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference. (*continued*)

(f) *continued*

Sibutramine 15 mg vs placebo

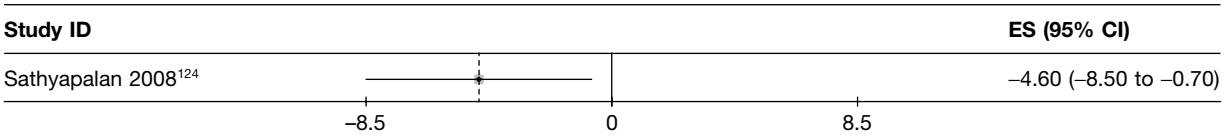


Sibutramine 15 mg vs sibutramine 10 mg

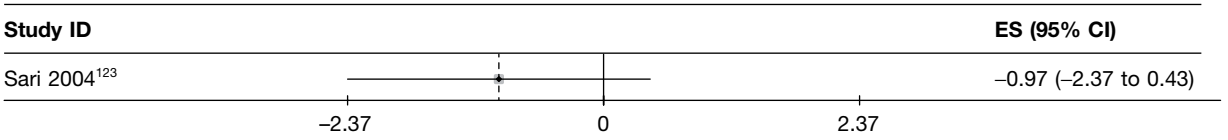


(g)

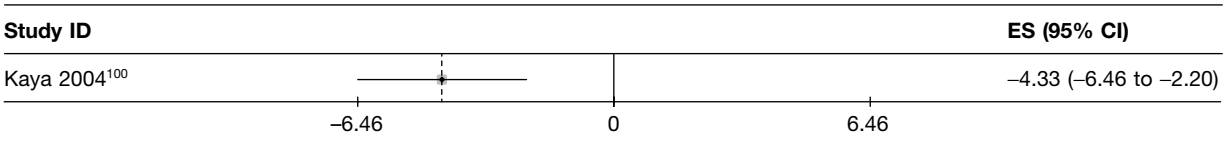
Rimonabant vs metformin



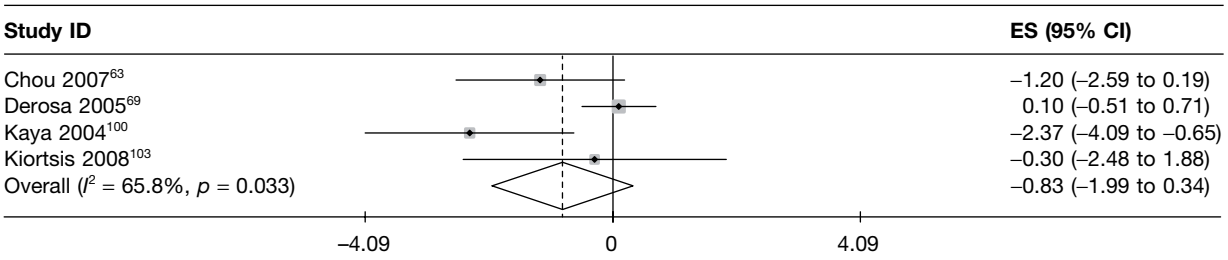
Metformin vs orlistat



Orlistat and sibutramine vs orlistat



Sibutramine 10 mg vs orlistat



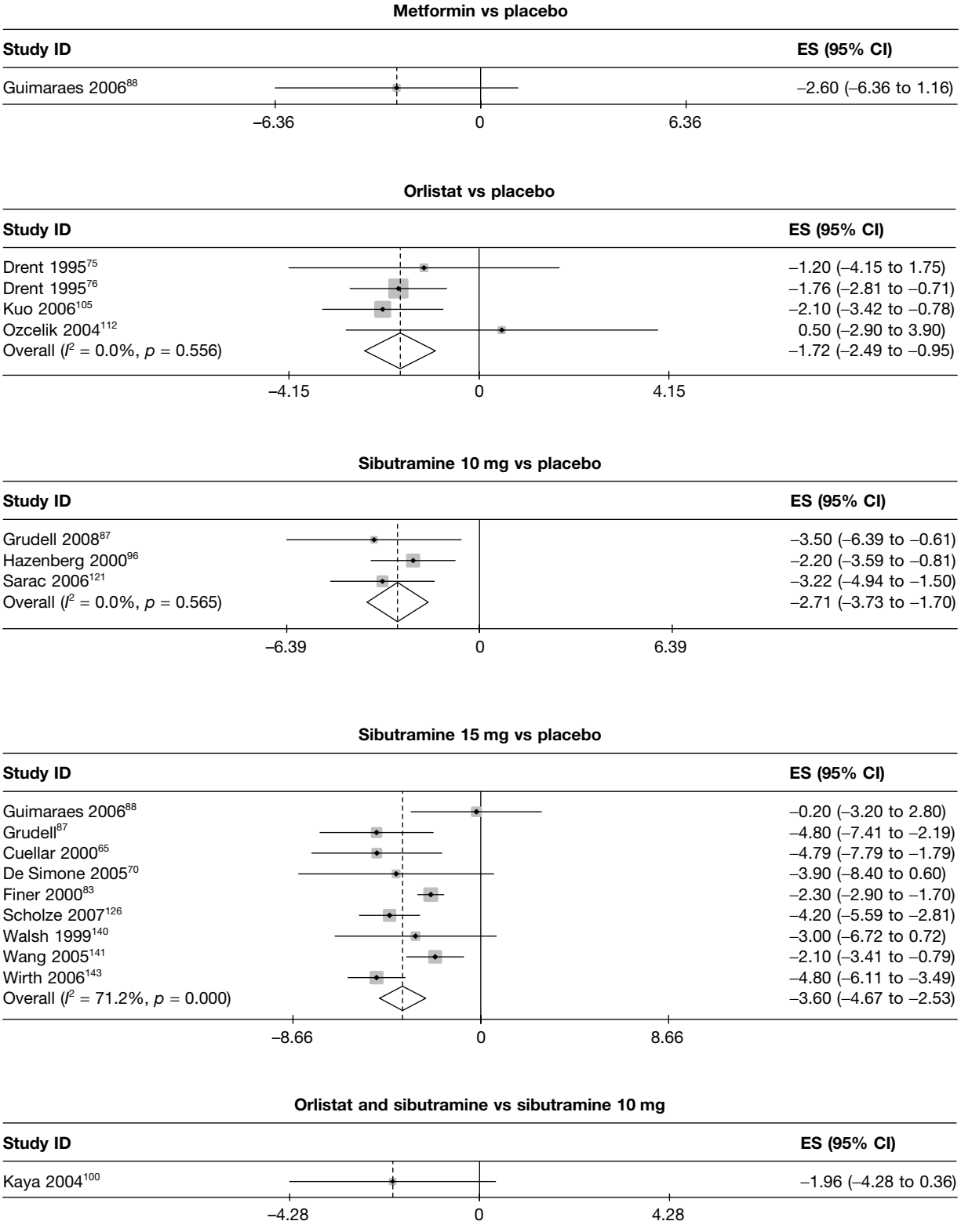
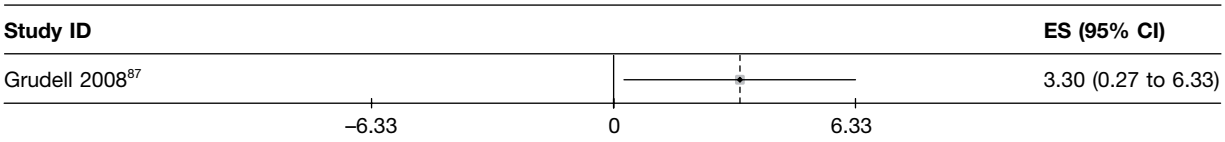


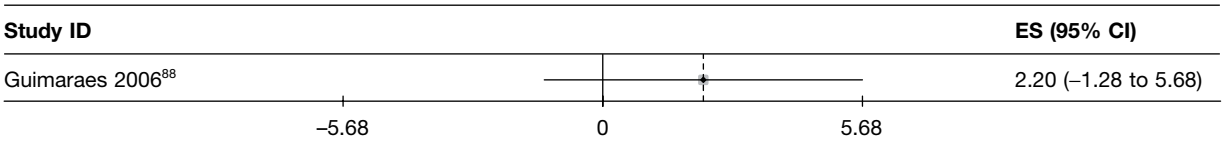
FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weigh-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference. (*continued*)

(g) *continued*

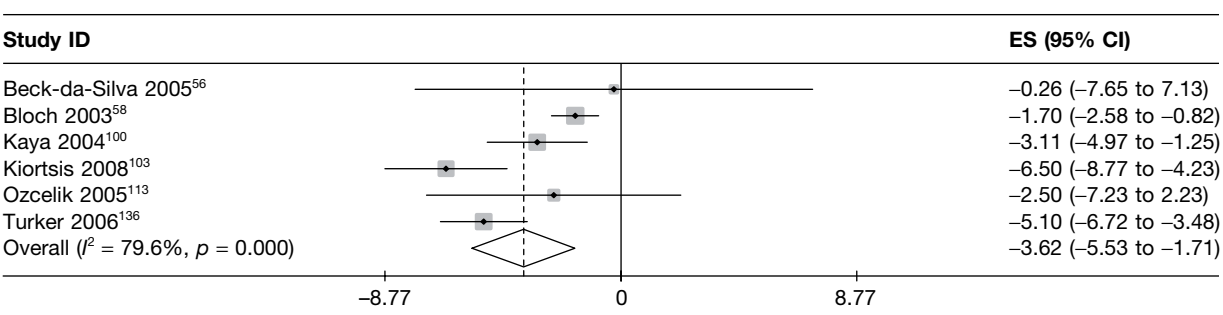
Sibutramine 15 mg vs sibutramine 10 mg



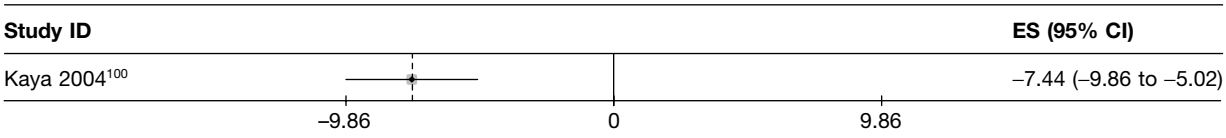
Metformin 10 mg vs sibutramine 15 mg



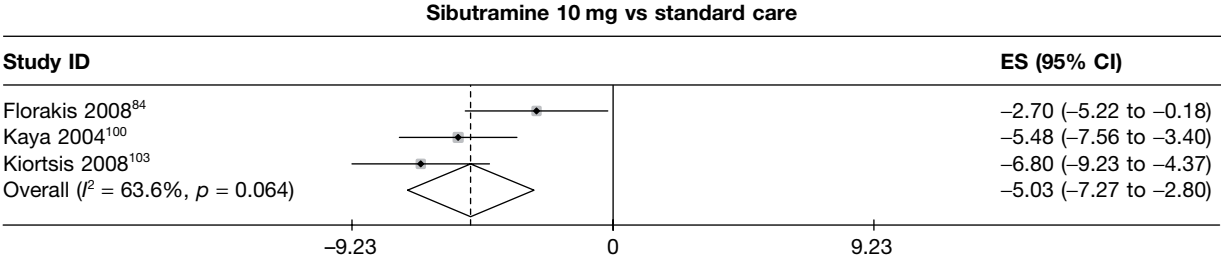
Orlistat vs standard care



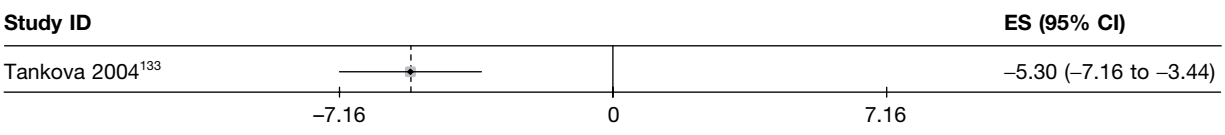
Orlistat and sibutramine vs standard care



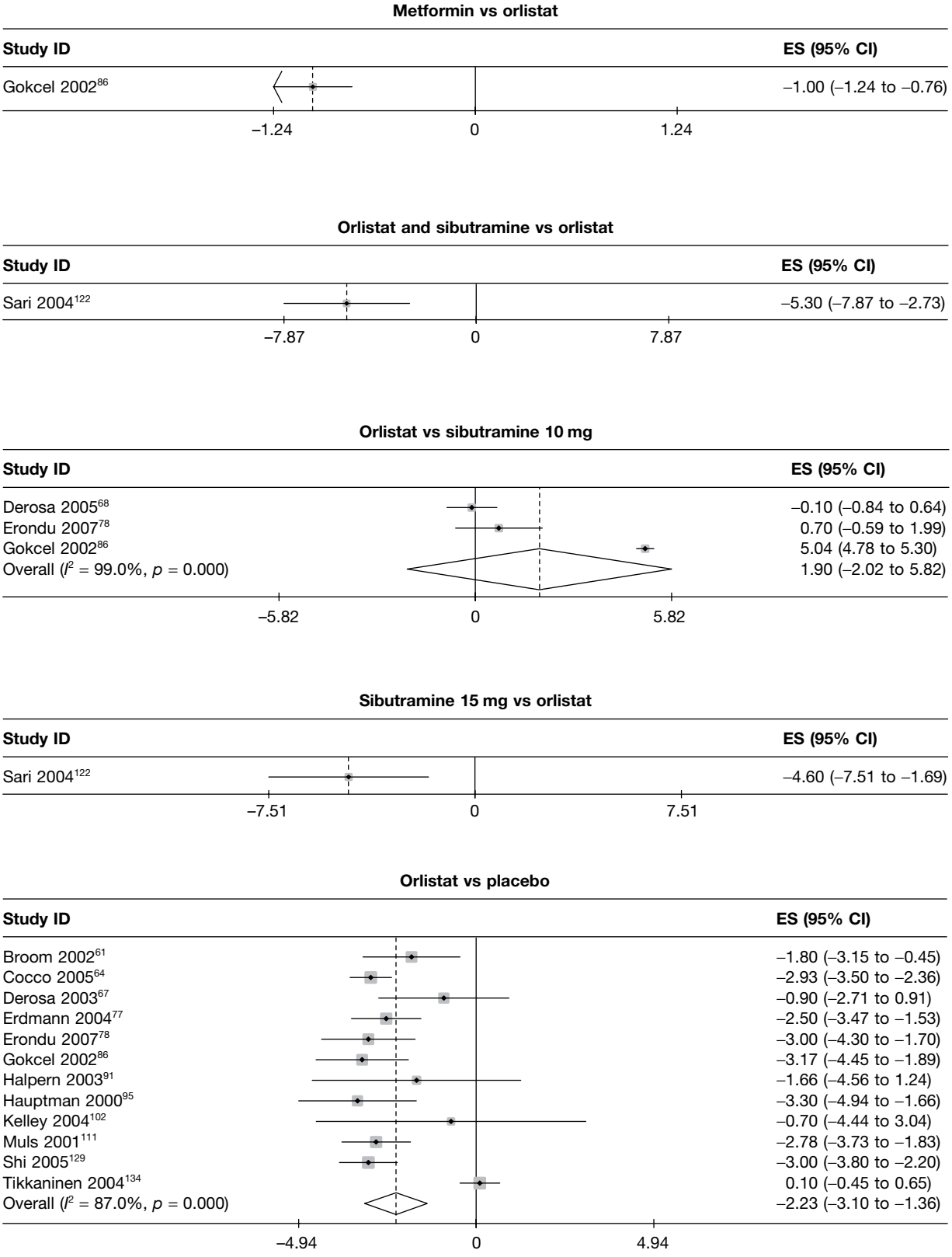
Sibutramine 10 mg vs standard care



Sibutramine 15 mg vs standard care



(h)



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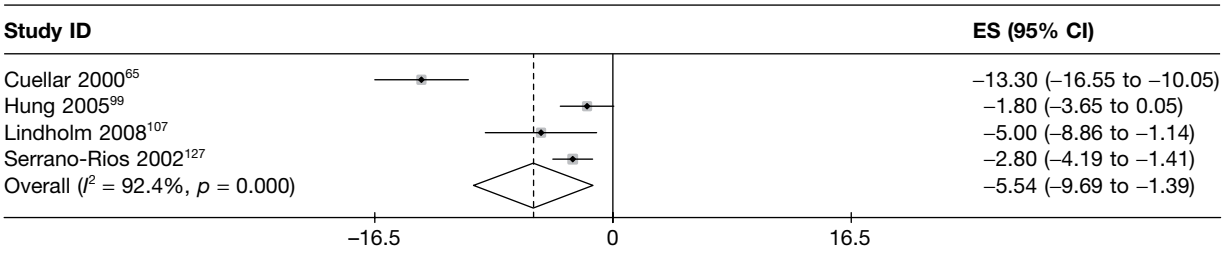
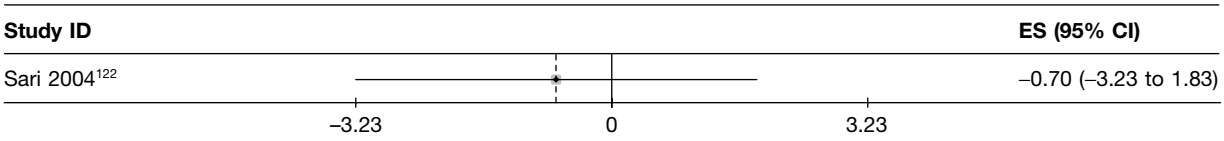
(h) *continued*

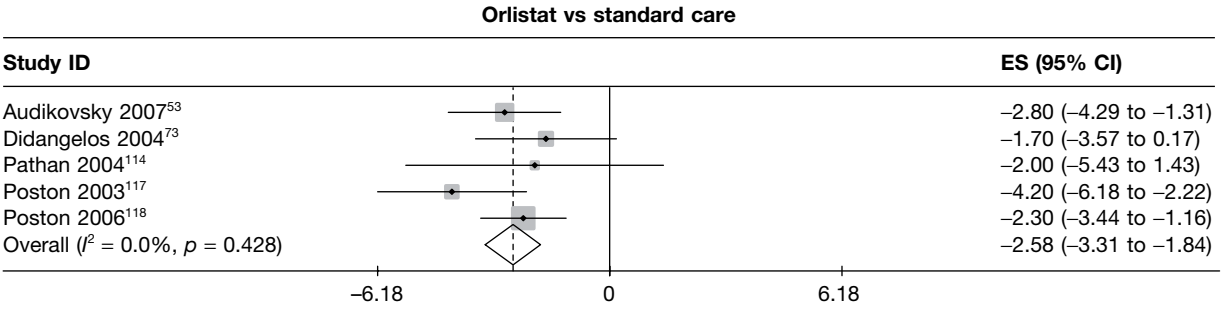
Sibutramine 15 mg vs placebo



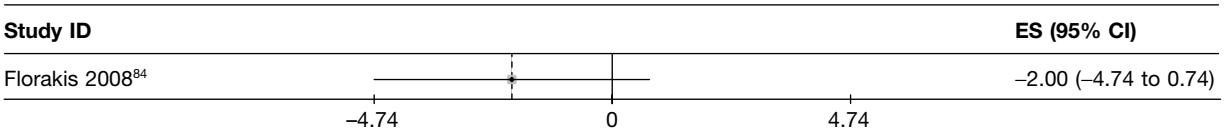
Orlistat and sibutramine vs sibutramine 15 mg



Orlistat vs standard care



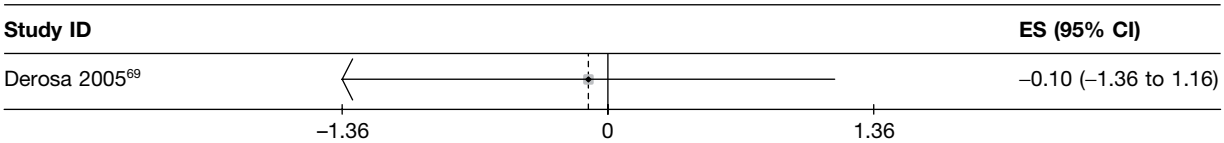
Sibutramine 10 mg vs standard care

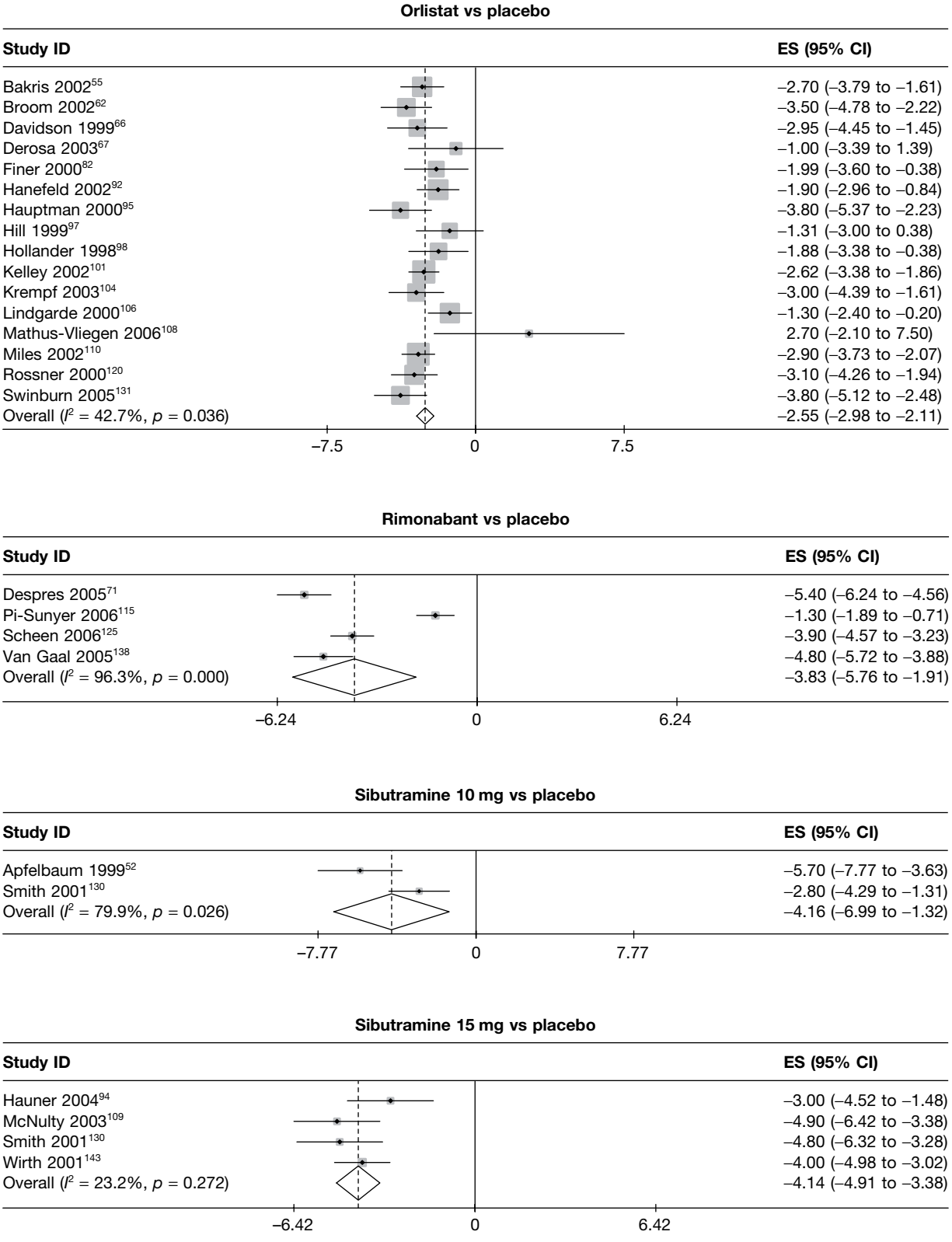


Sibutramine 15 mg vs standard care

(i)

Sibutramine 10 mg vs orlistat





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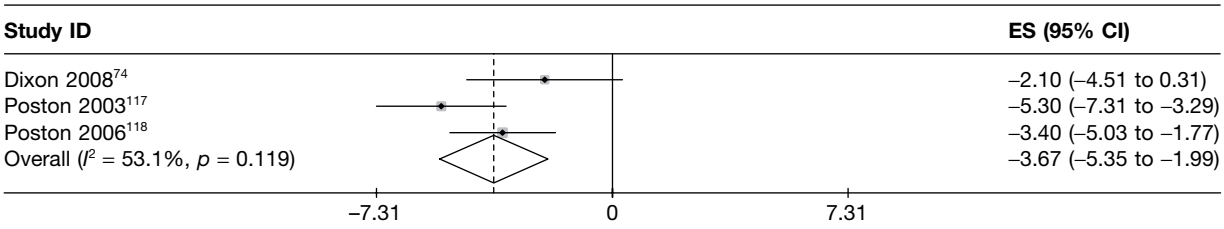
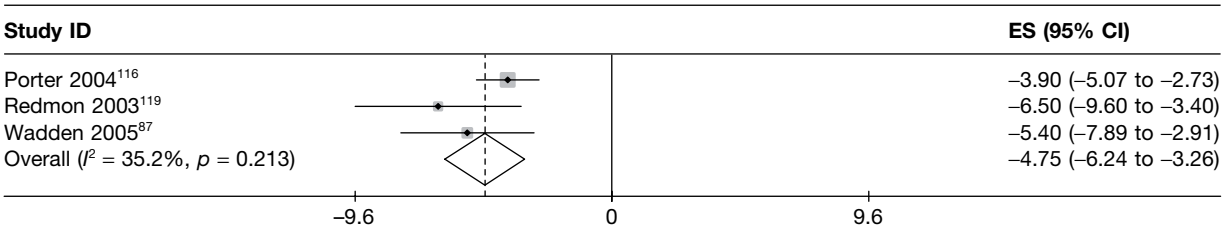
(i) *continued*

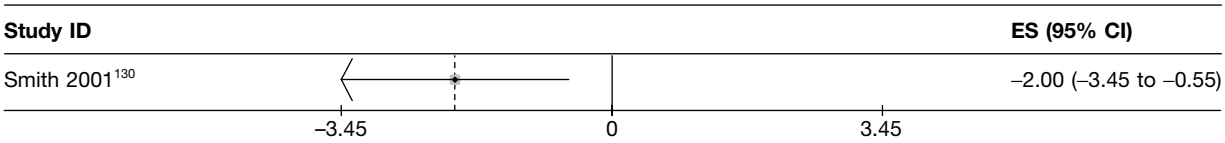
Orlistat vs standard care



Sibutramine 15 mg vs standard care

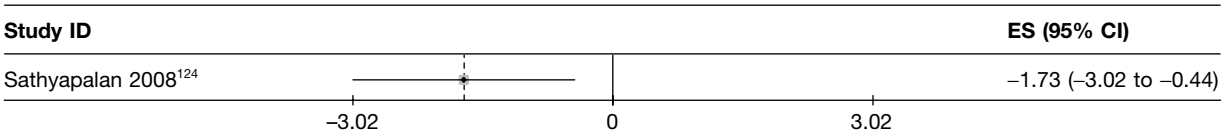


Sibutramine 15 mg vs sibutramine 10 mg

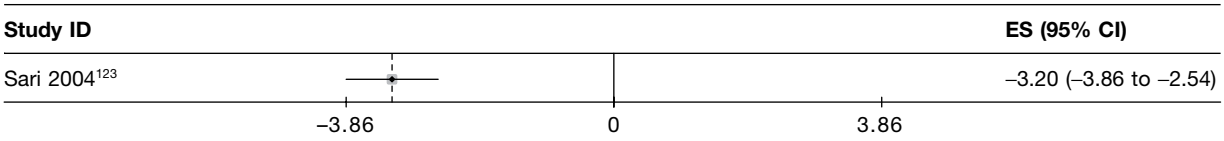


(j)

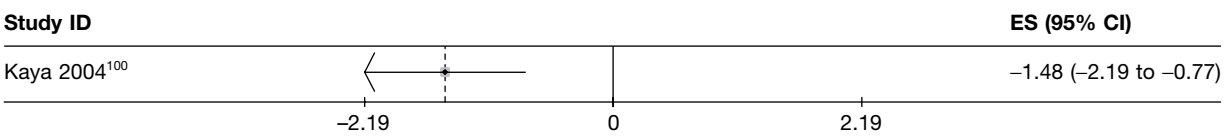
Rimonabant vs metformin



Metformin vs orlistat



Orlistat and sibutramine vs orlistat



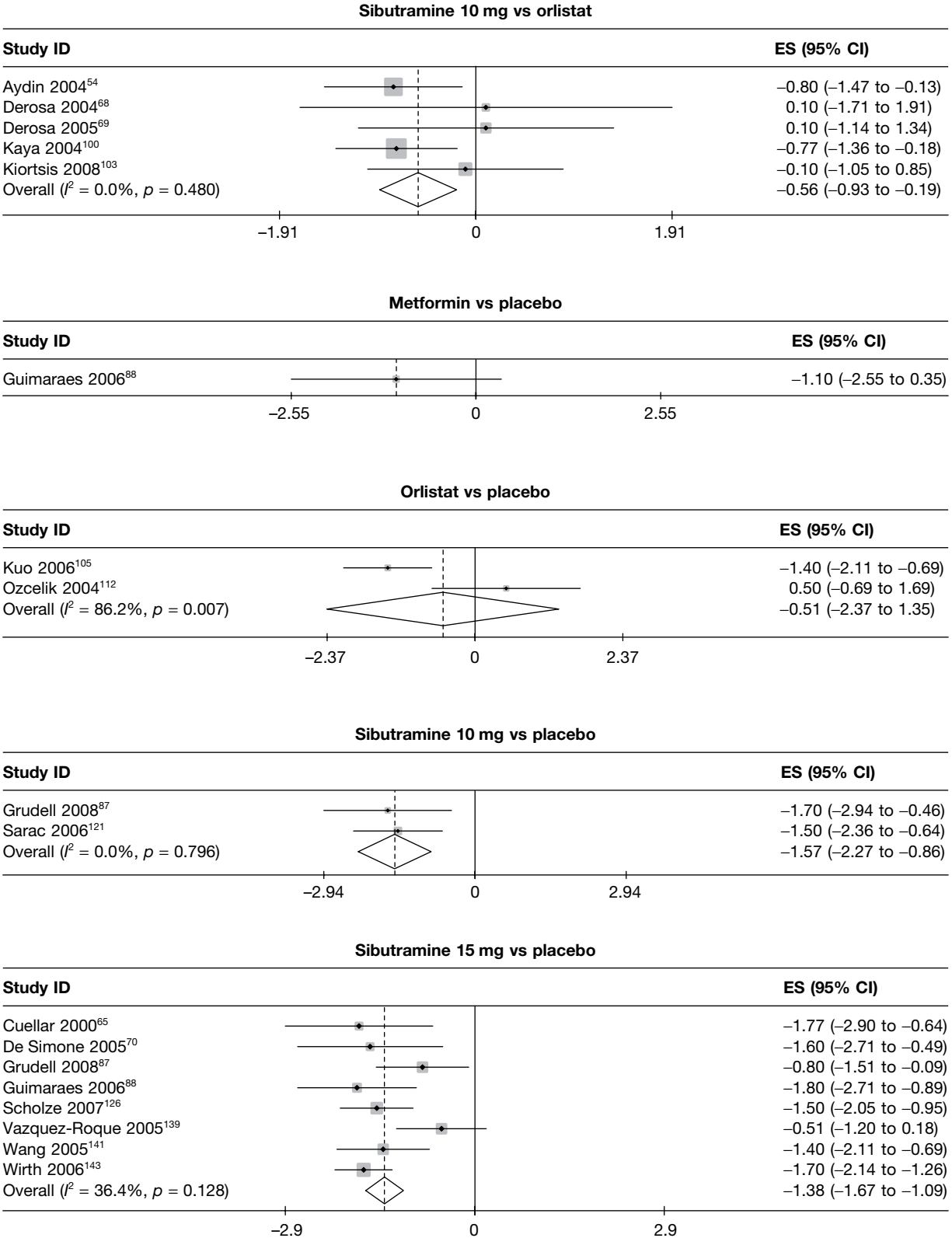
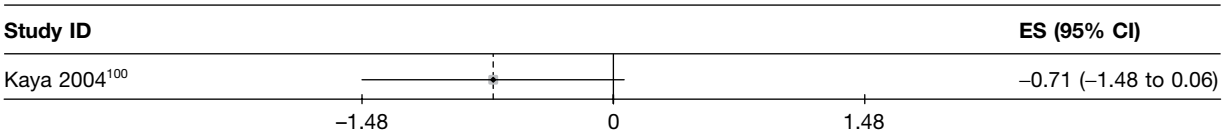


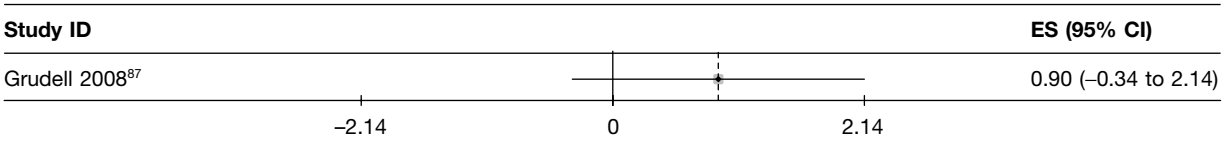
FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weight-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference. (*continued*)

(j) *continued*

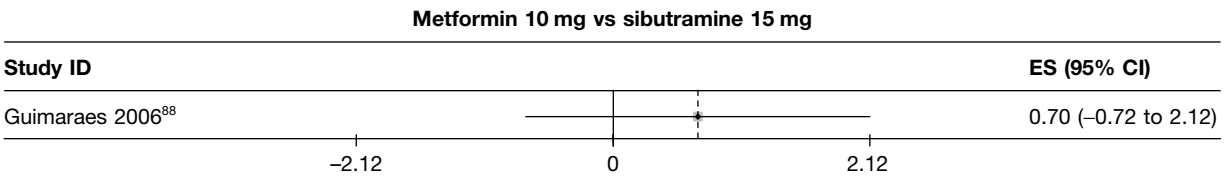
Orlistat and sibutramine vs sibutramine 10 mg



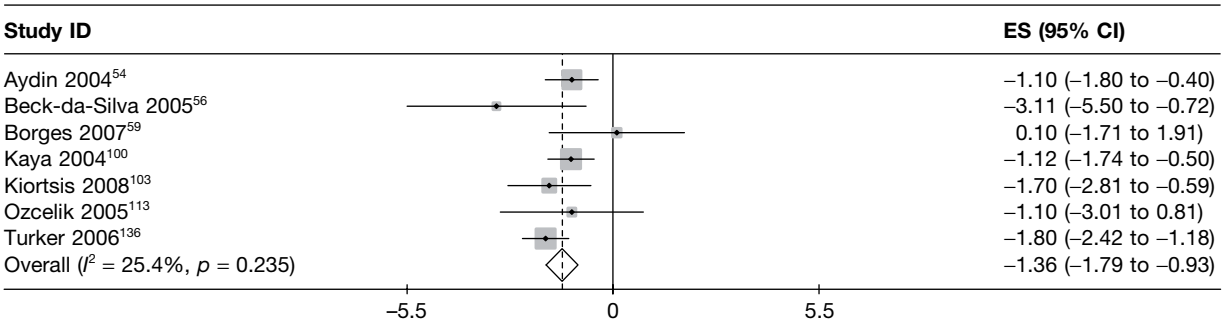
Sibutramine 15 mg vs sibutramine 10 mg



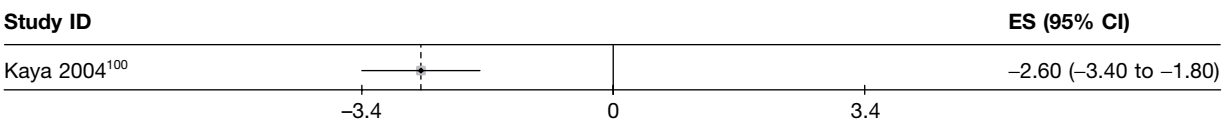
Metformin 10 mg vs sibutramine 15 mg



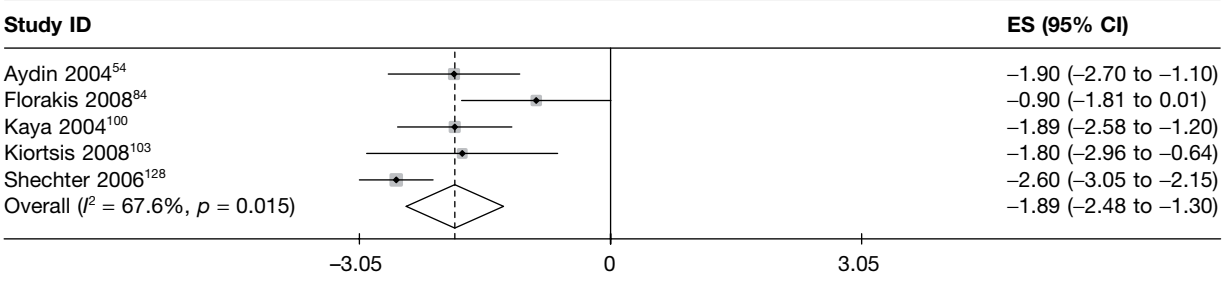
Orlistat vs standard care



Orlistat and sibutramine vs standard care



Sibutramine 10 mg vs standard care



(k)

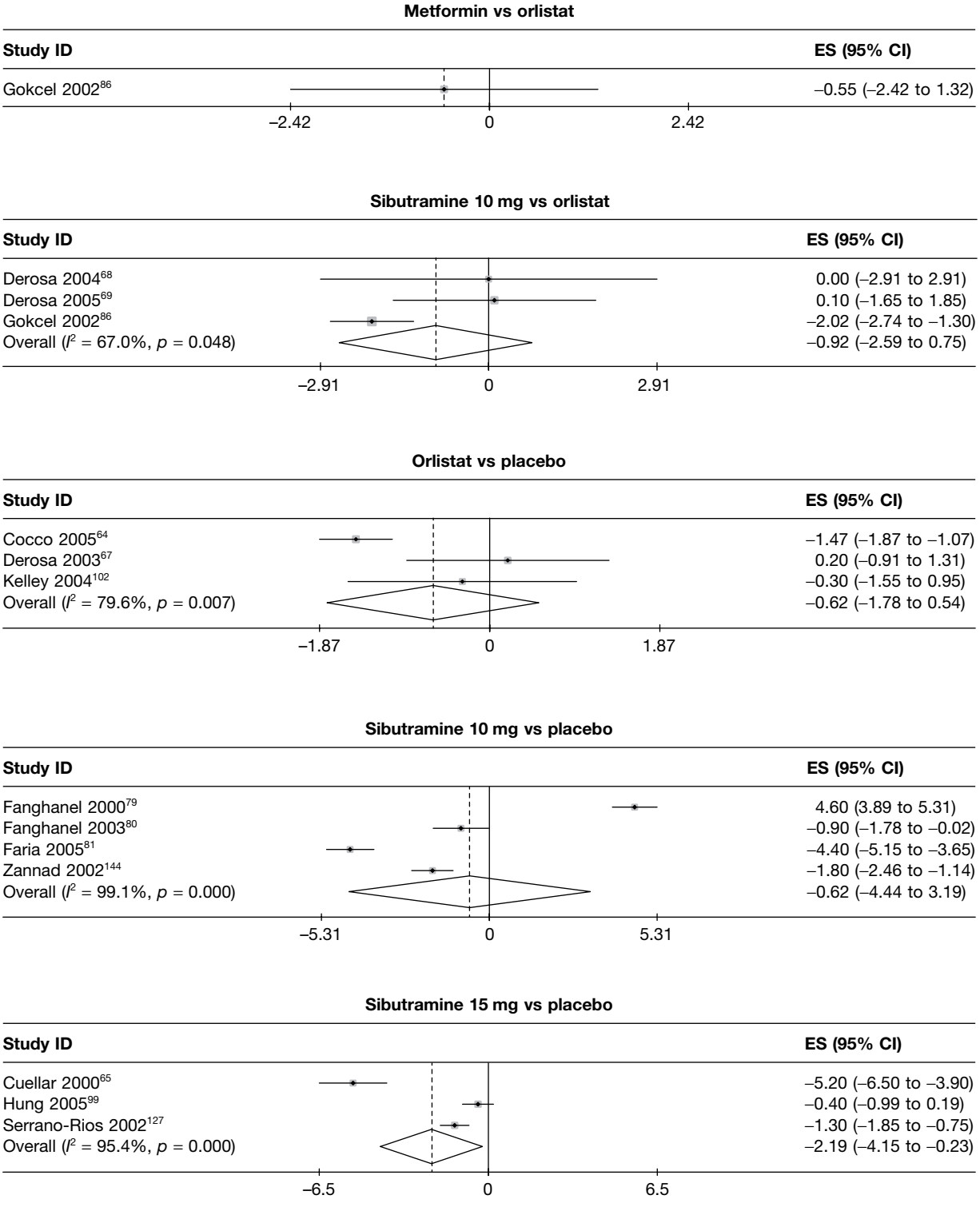
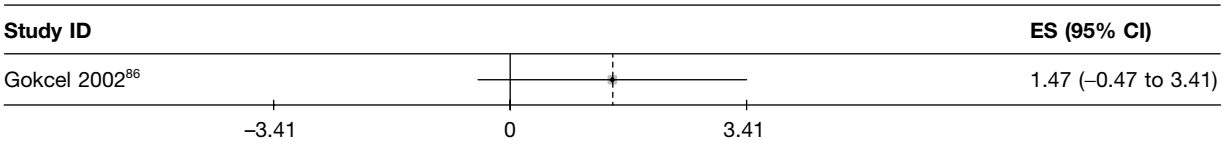


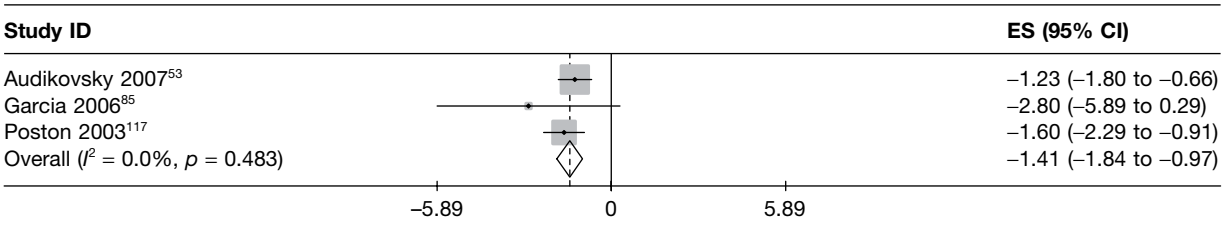
FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weight-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference. (*continued*)

(k) *continued*

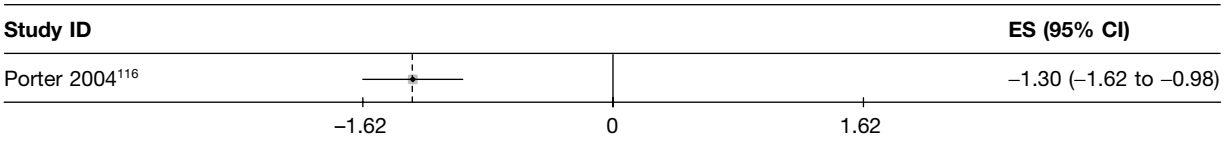
Metformin vs sibutramine 10 mg



Orlistat vs standard care

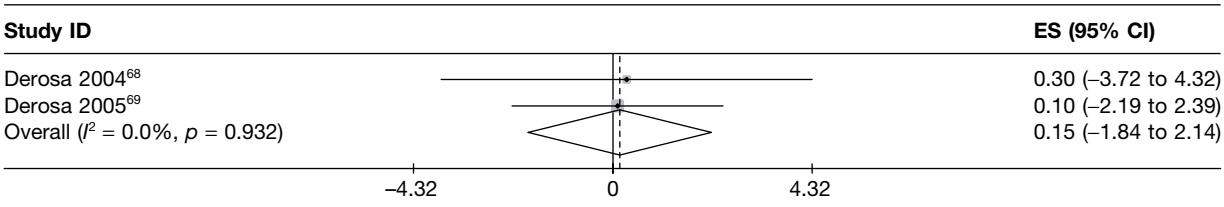


Sibutramine 15 mg vs standard care

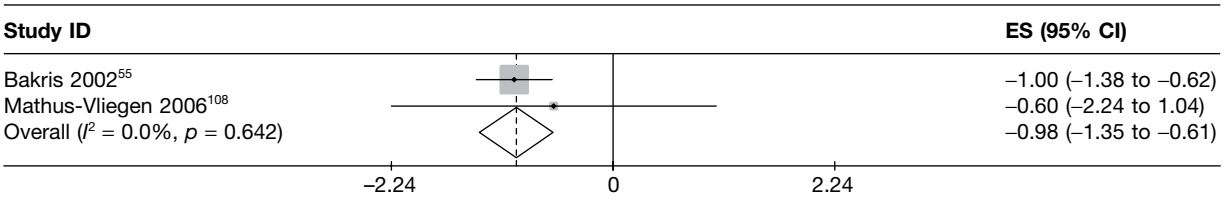


(l)

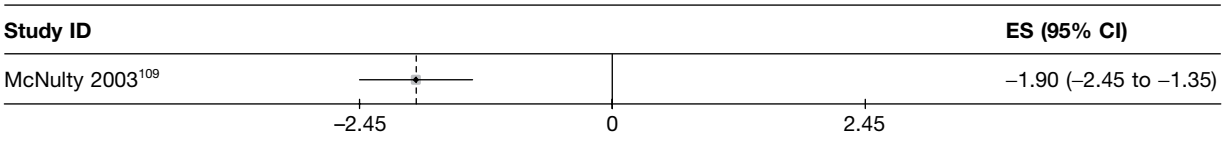
Sibutramine 10 mg vs orlistat



Orlistat vs placebo



Sibutramine 15 mg vs placebo



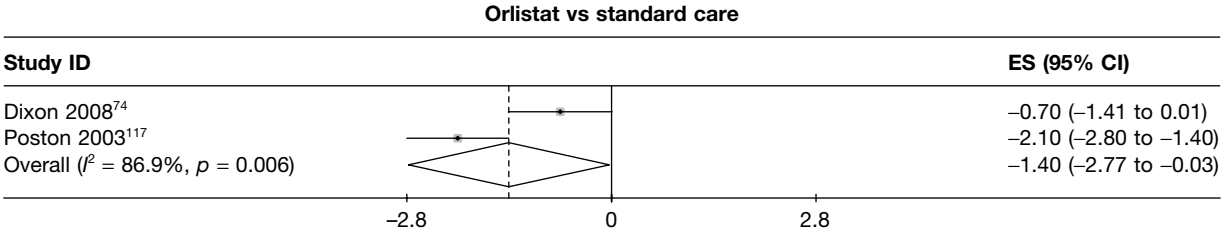
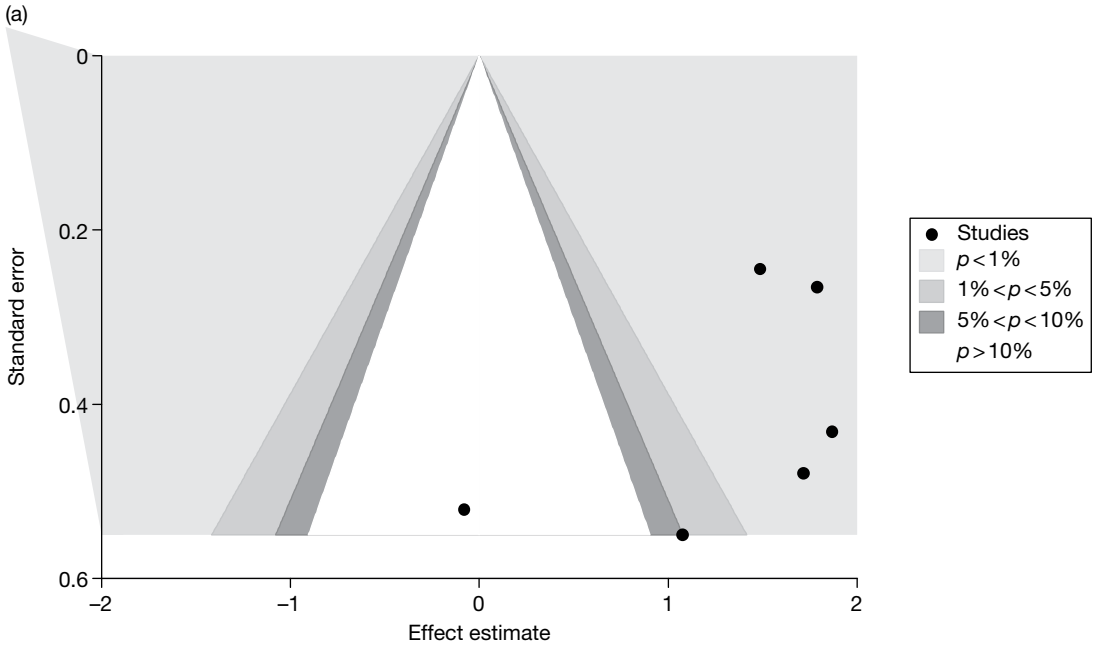
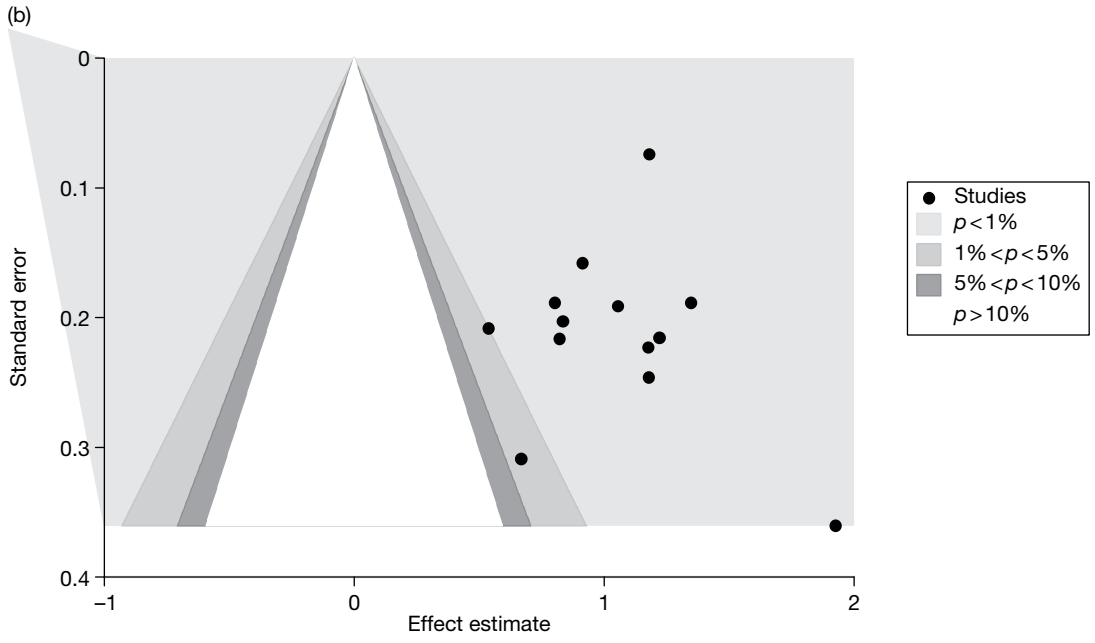


FIGURE 14 Forest plots for pair-wise meta-analysis: (a) 3-month 5% weight-loss data, (b) 6-month 5% weight-loss data, (c) 12-month 5% weight-loss data, (d) 3-month 10% weight-loss data, (e) 6-month 10% weight-loss data, (f) 12-month 10% weight-loss data, (g) 3-month weight change data, (h) 6-month weight change data, (i) 12-month weight change data, (j) 3-month BMI change data, (k) 6-month BMI change data, (l) 12-month BMI change data. Note: weights are from random-effects analysis. ES, estimate of mean difference. (*continued*)


(a)
Standard error
0
0.2
0.4
0.6
−2
−1
0
1
2
Effect estimate
Studies
p<1%
1%<p<5%
5%<p<10%
p>10%


(b)
Standard error
0
0.1
0.2
0.3
0.4
−1
0
1
2
Effect estimate
Studies
p<1%
1%<p<5%
5%<p<10%
p>10%

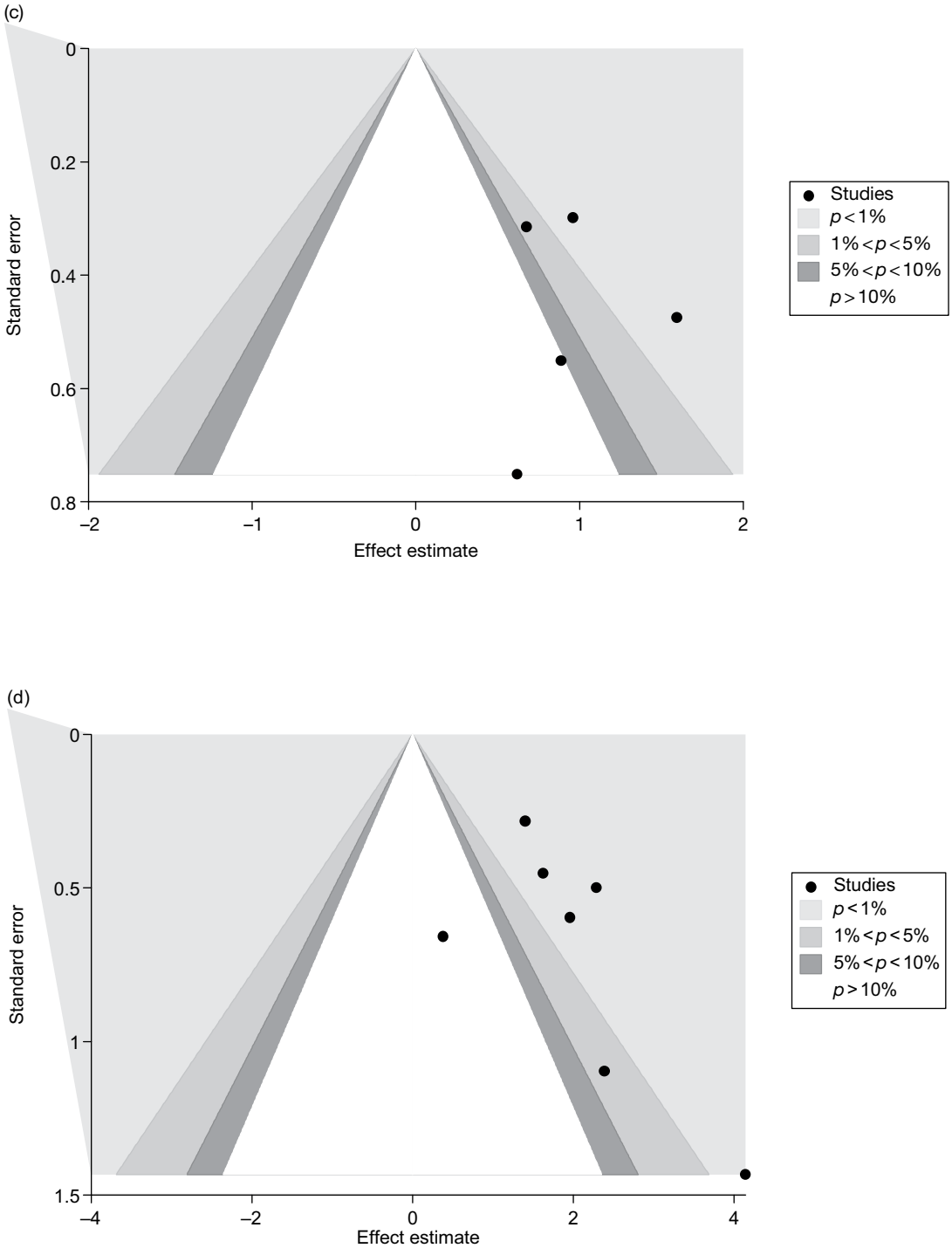
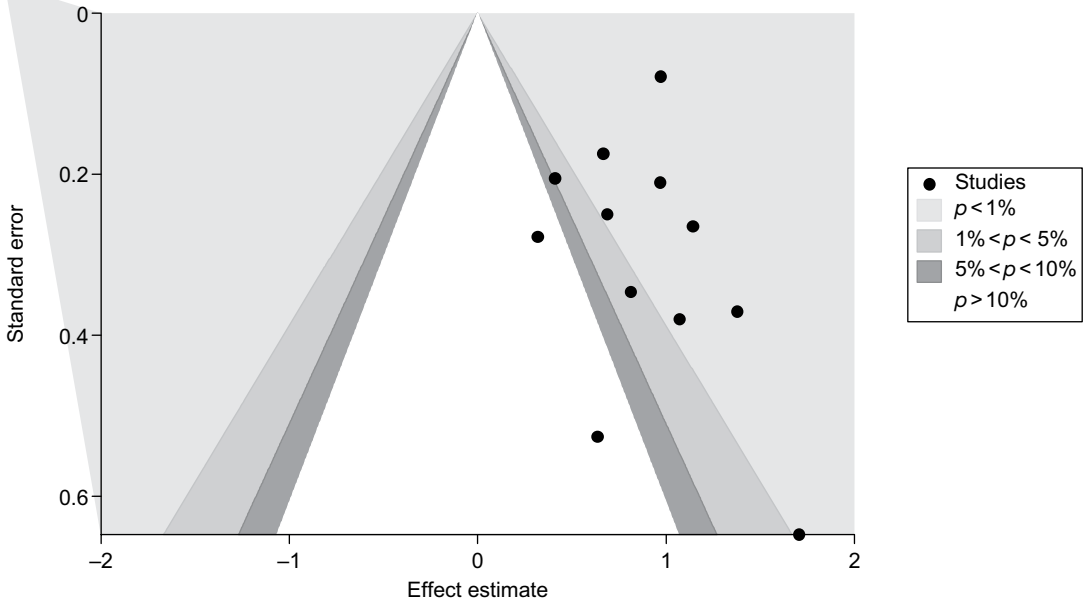
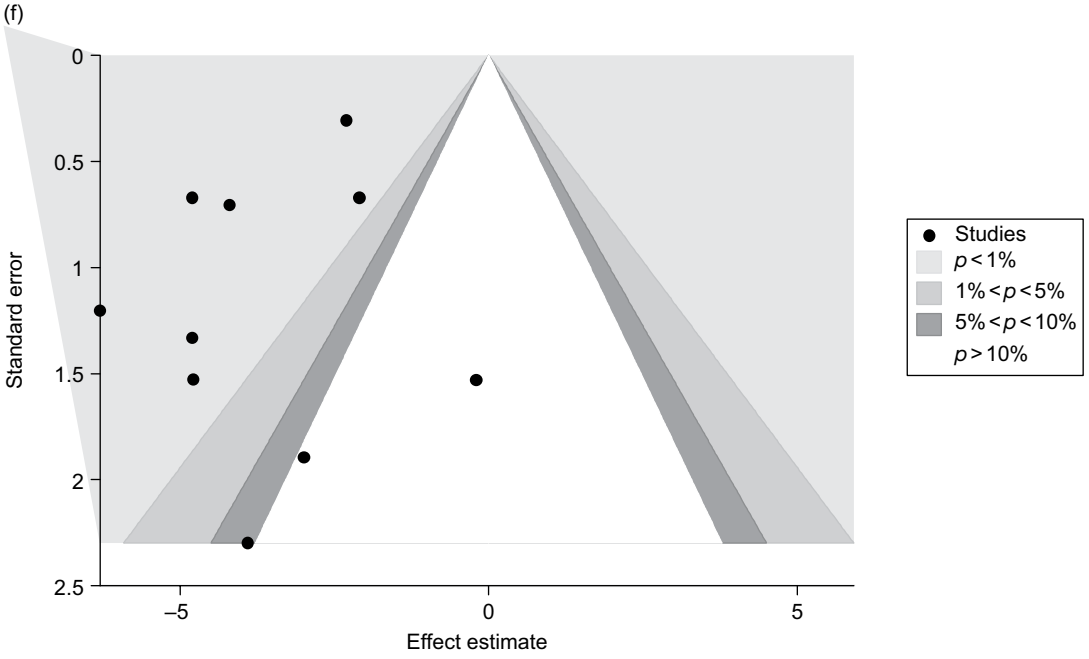


FIGURE 15 Funnel plots. Funnel plots shown only for those comparisons with five or more studies included. (a) Sibutramine vs placebo, 6-month 5% weight loss – log-OR. (b) Orlistat vs placebo, 12-month 5% weight loss – log-OR. (c) Orlistat vs placebo, 6-month 10% weight loss – log-OR. (d) Sibutramine 10 mg vs placebo, 6-month 10% weight loss – log-OR. (e) Orlistat vs placebo, 12-month 10% weight loss – log-OR. (f) Sibutramine 15 mg vs placebo, 3-month weight change. (g) Orlistat vs standard care, 3-month weight change. (h) Orlistat vs placebo, 6-month weight change. (i) Orlistat vs standard care, 6-month weight change. (j) Orlistat vs placebo, 12-month weight change. (k) Sibutramine 10 mg vs orlistat, 3-month BMI change. (l) Sibutramine 15 mg vs placebo, 3-month BMI change. (m) Orlistat vs standard care, 3-month BMI change. (n) Sibutramine 10 mg vs standard care, 3-month BMI change.

(e)


0
0.2
0.4
0.6
Standard error
–2
–1
0
1
2
Effect estimate
Studies
p < 1%
1% < p < 5%
5% < p < 10%
p > 10%

(f)


0
0.5
1
1.5
2
2.5
Standard error
–5
0
5
Effect estimate
Studies
p < 1%
1% < p < 5%
5% < p < 10%
p > 10%

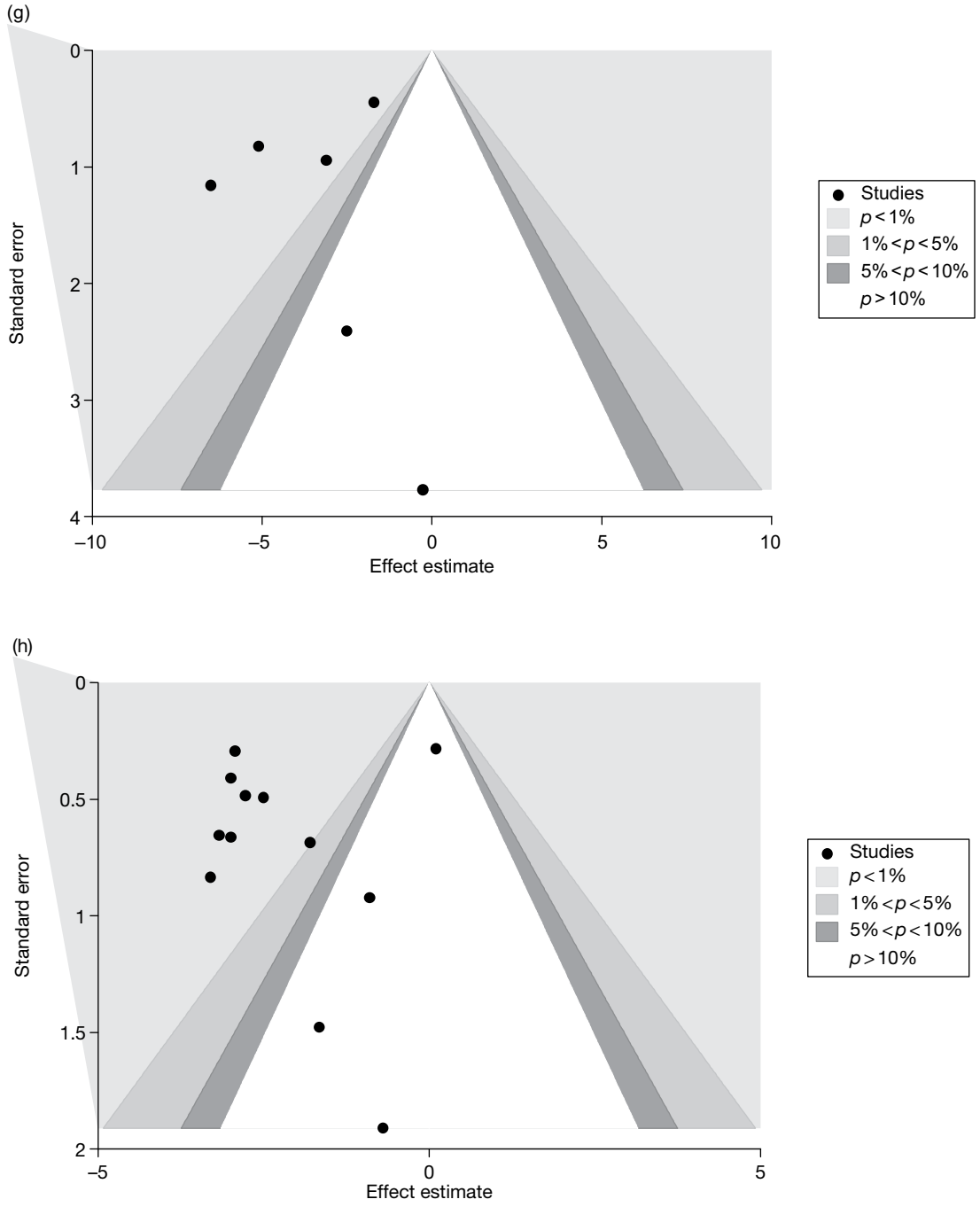
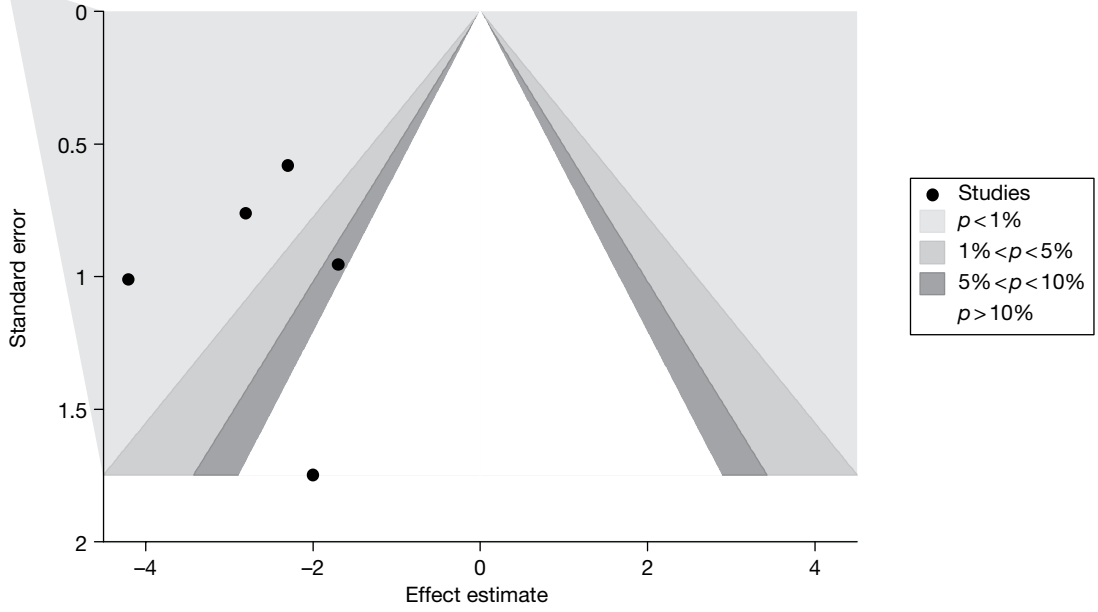
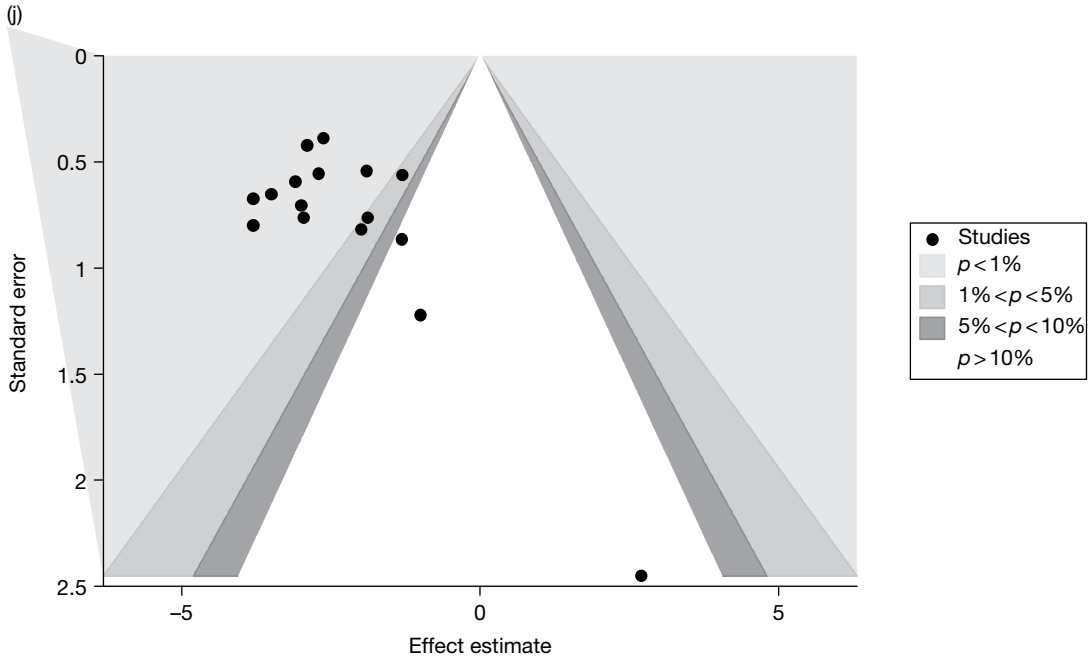


FIGURE 15 Funnel plots. Funnel plots shown only for those comparisons with five or more studies included. (a) Sibutramine vs placebo, 6-month 5% weight loss – log-OR. (b) Orlistat vs placebo, 12-month 5% weight loss – log-OR. (c) Orlistat vs placebo, 6-month 10% weight loss – log-OR. (d) Sibutramine 10 mg vs placebo, 6-month 10% weight loss – log-OR. (e) Orlistat vs placebo, 12-month 10% weight loss – log-OR. (f) Sibutramine 15 mg vs placebo, 3-month weight change. (g) Orlistat vs standard care, 3-month weight change. (h) Orlistat vs placebo, 6-month weight change. (i) Orlistat vs standard care, 6-month weight change. (j) Orlistat vs placebo, 12-month weight change. (k) Sibutramine 10 mg vs orlistat, 3-month BMI change. (l) Sibutramine 15 mg vs placebo, 3-month BMI change. (m) Orlistat vs standard care, 3-month BMI change. (n) Sibutramine 10 mg vs standard care, 3-month BMI change. (*continued*)

(i)


Standard error
0
0.5
1
1.5
2
−4
−2
0
2
4
Effect estimate
Studies
p<1%
1%<p<5%
5%<p<10%
p>10%

(j)


Standard error
0
0.5
1
1.5
2
2.5
−5
0
5
Effect estimate
Studies
p<1%
1%<p<5%
5%<p<10%
p>10%

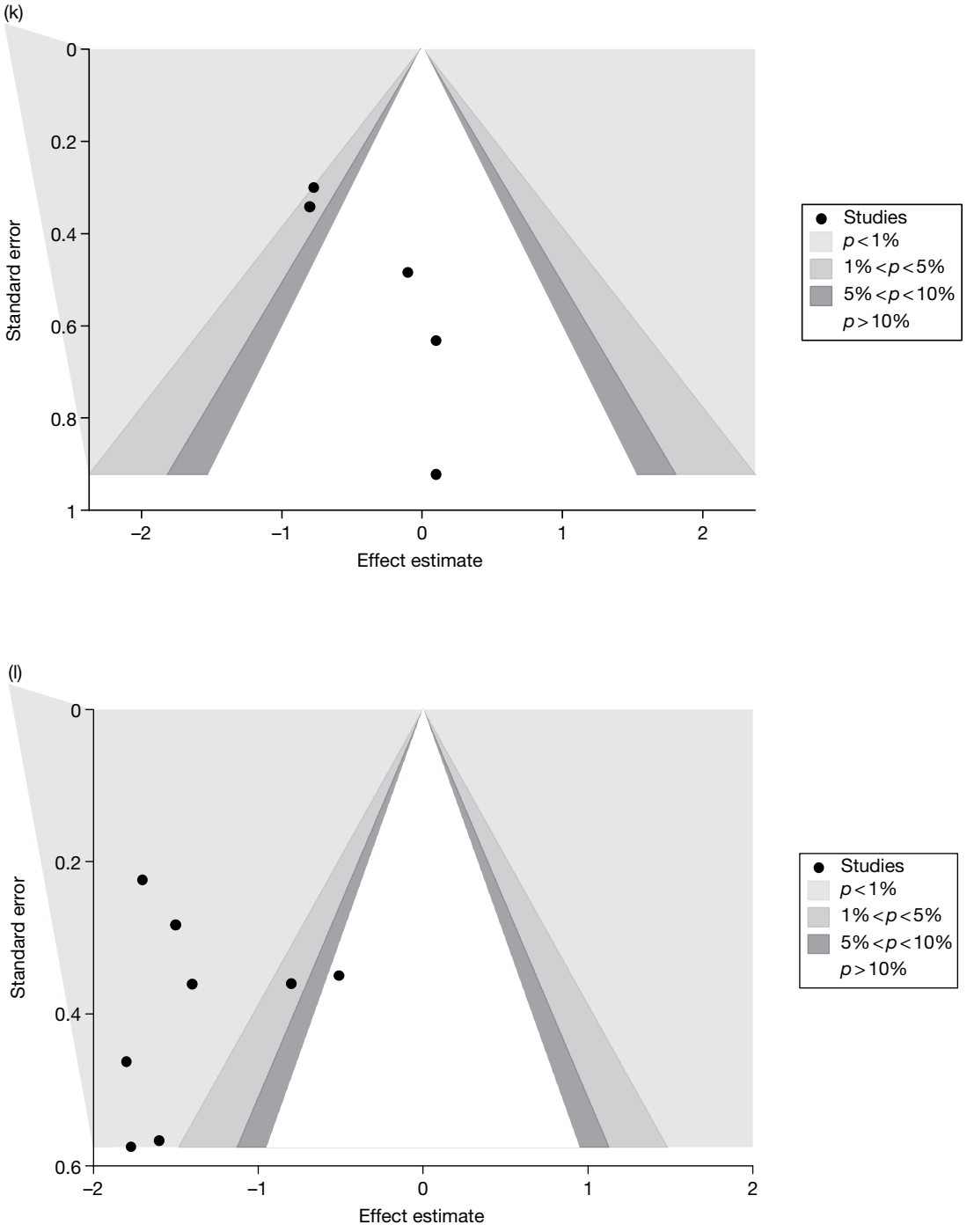


FIGURE 15 Funnel plots. Funnel plots shown only for those comparisons with five or more studies included. (a) Sibutramine vs placebo, 6-month 5% weight loss – log-OR. (b) Orlistat vs placebo, 12-month 5% weight loss – log-OR. (c) Orlistat vs placebo, 6-month 10% weight loss – log-OR. (d) Sibutramine 10 mg vs placebo, 6-month 10% weight loss – log-OR. (e) Orlistat vs placebo, 12-month 10% weight loss – log-OR. (f) Sibutramine 15 mg vs placebo, 3-month weight change. (g) Orlistat vs standard care, 3-month weight change. (h) Orlistat vs placebo, 6-month weight change. (i) Orlistat vs standard care, 6-month weight change. (j) Orlistat vs placebo, 12-month weight change. (k) Sibutramine 10 mg vs orlistat, 3-month BMI change. (l) Sibutramine 15 mg vs placebo, 3-month BMI change. (m) Orlistat vs standard care, 3-month BMI change. (n) Sibutramine 10 mg vs standard care, 3-month BMI change. (*continued*)

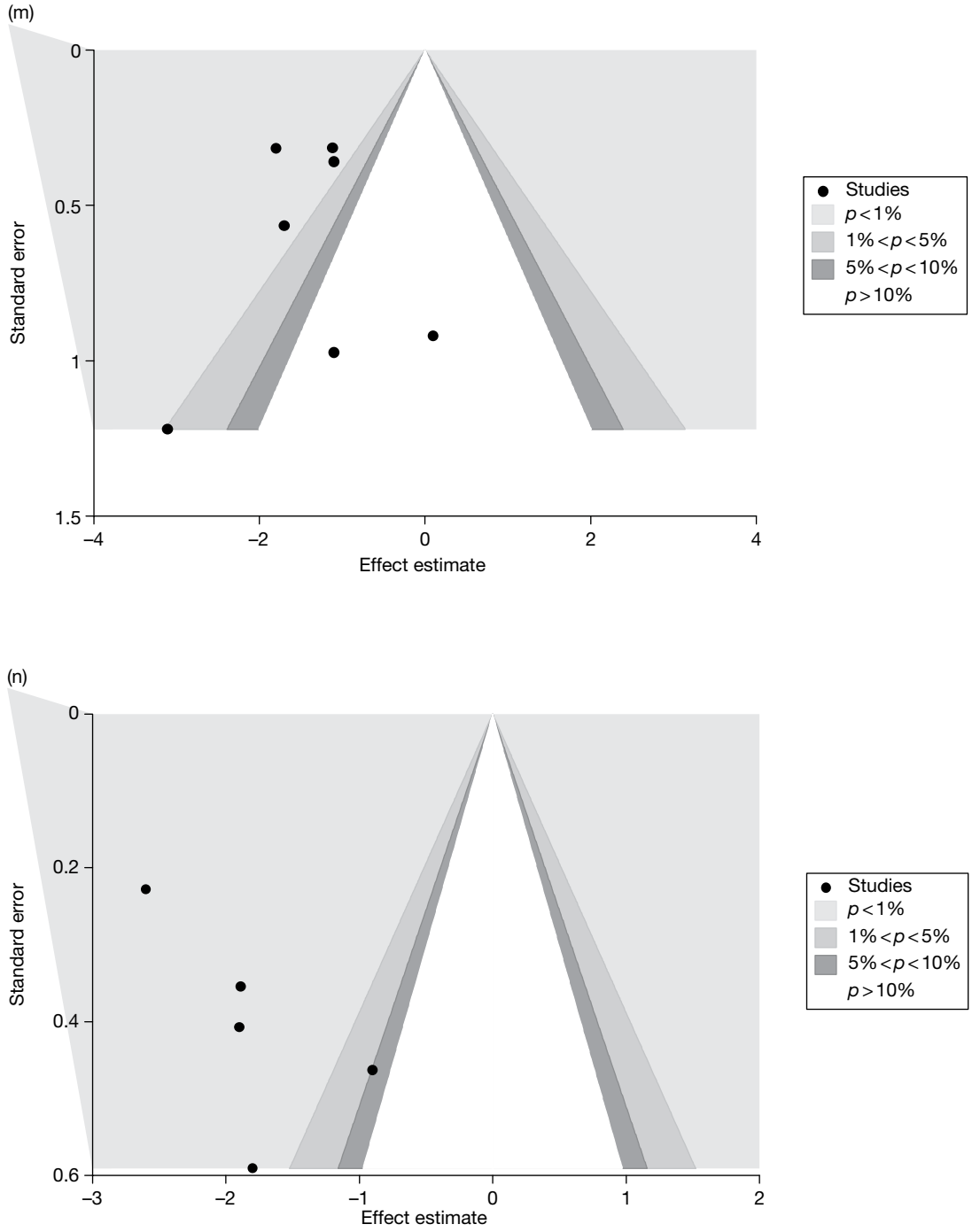


FIGURE 15 Funnel plots. Funnel plots shown only for those comparisons with five or more studies included. (a) Sibutramine vs placebo, 6-month 5% weight loss – log-OR. (b) Orlistat vs placebo, 12-month 5% weight loss – log-OR. (c) Orlistat vs placebo, 6-month 10% weight loss – log-OR. (d) Sibutramine 10 mg vs placebo, 6-month 10% weight loss – log-OR. (e) Orlistat vs placebo, 12-month 10% weight loss – log-OR. (f) Sibutramine 15 mg vs placebo, 3-month weight change. (g) Orlistat vs standard care, 3-month weight change. (h) Orlistat vs placebo, 6-month weight change. (i) Orlistat vs standard care, 6-month weight change. (j) Orlistat vs placebo, 12-month weight change. (k) Sibutramine 10 mg vs orlistat, 3-month BMI change. (l) Sibutramine 15 mg vs placebo, 3-month BMI change. (m) Orlistat vs standard care, 3-month BMI change. (n) Sibutramine 10 mg vs standard care, 3-month BMI change. (*continued*)

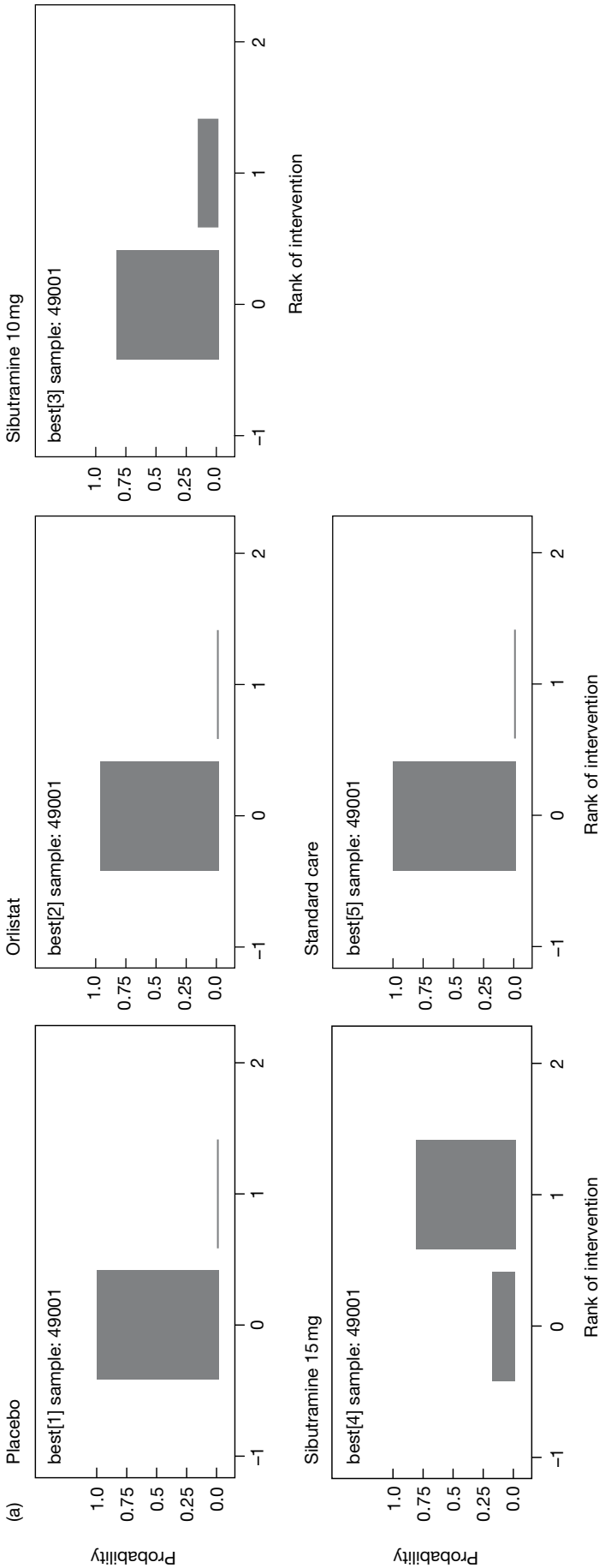


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change.

(b)
Placebo
best[1] sample: 40001
Orlistat
best[2] sample: 40001
Sibutramine 10 mg
best[3] sample: 40001
Sibutramine 15 mg
best[4] sample: 40001
Orlistat and sibutramine
best[5] sample: 40001
Standard care
best[6] sample: 40001
Probability
Rank of intervention

FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

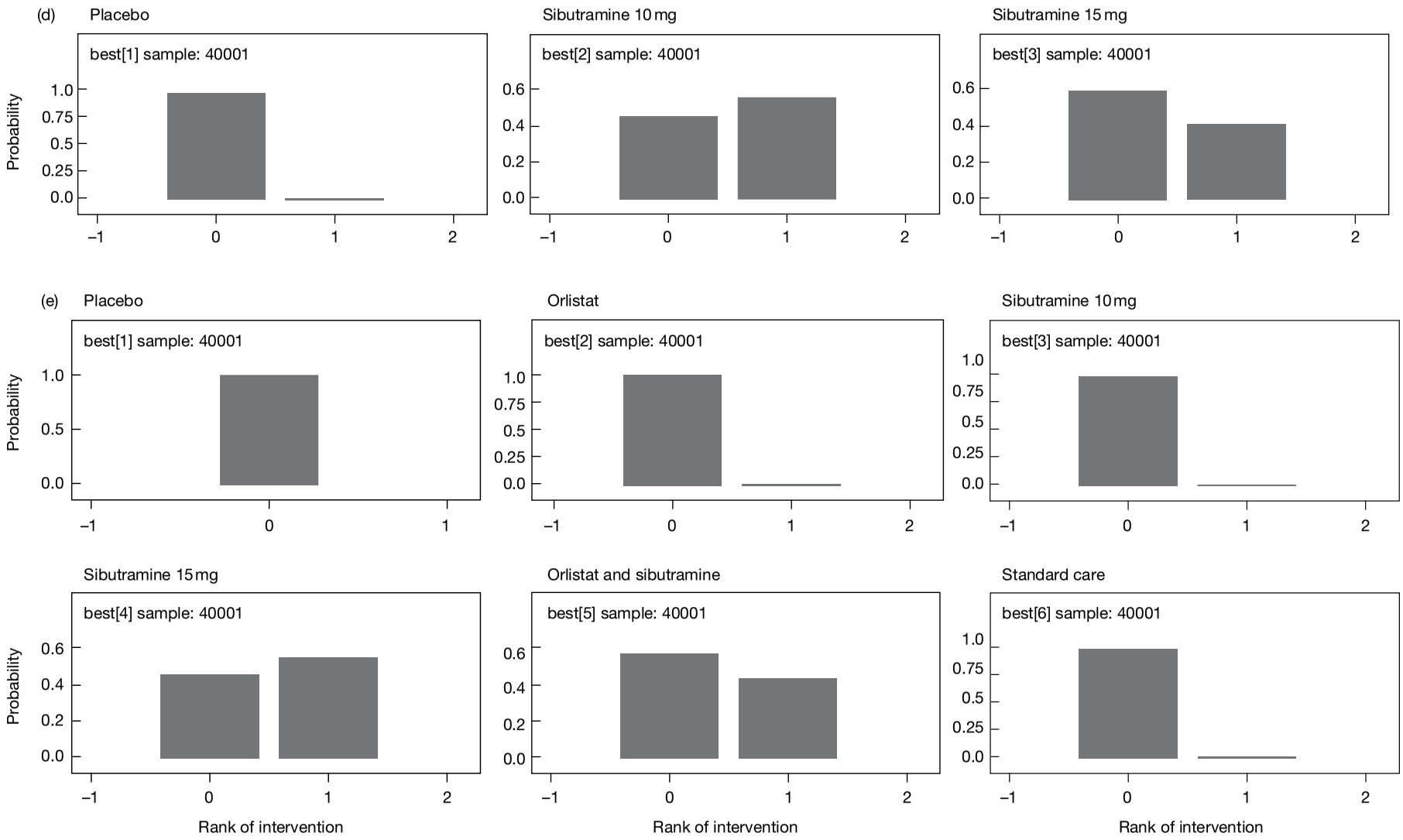
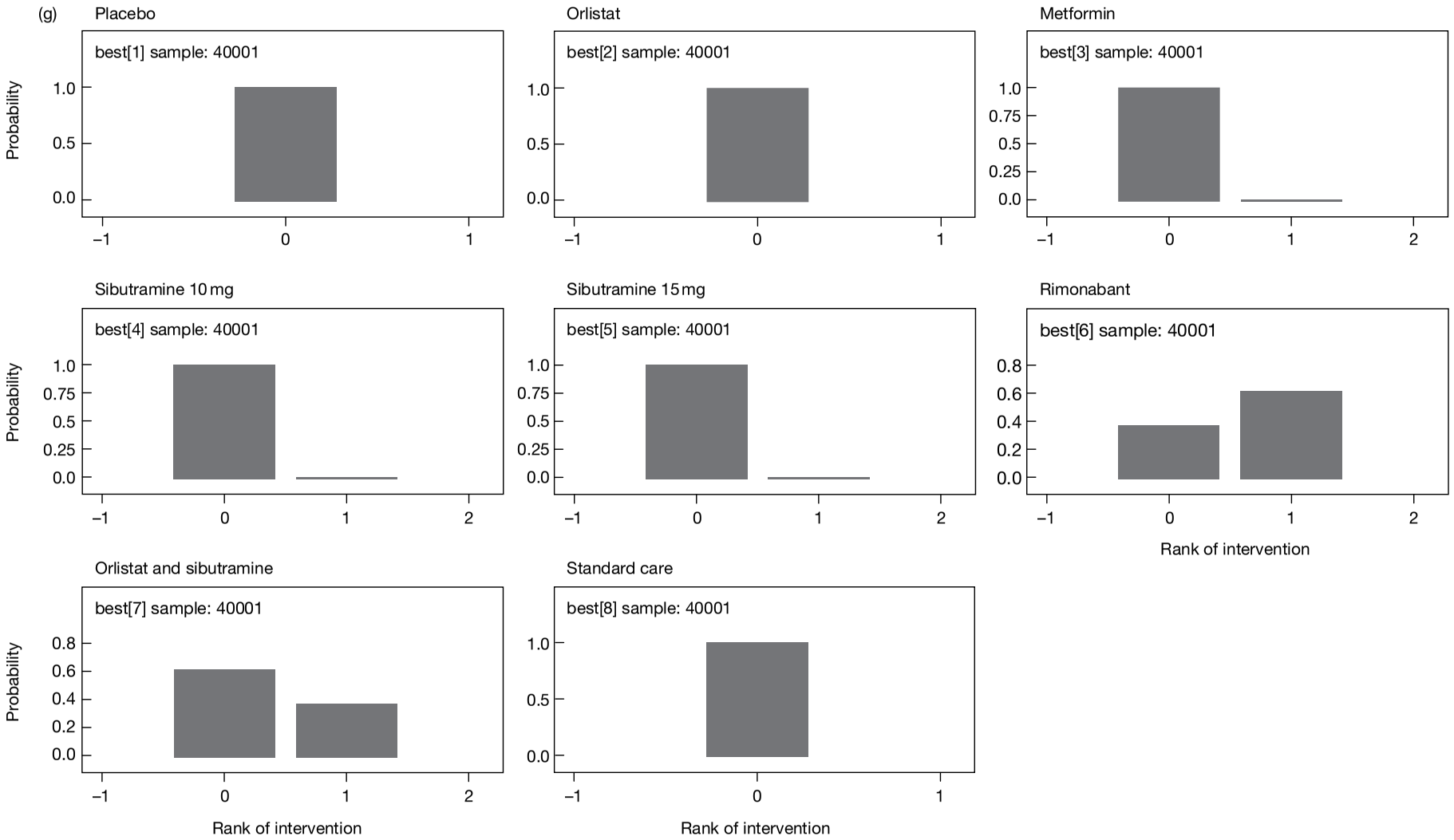

(d)
Placebo
best[1] sample: 40001
Sibutramine 10 mg
best[2] sample: 40001
Sibutramine 15 mg
best[3] sample: 40001
(e)
Placebo
best[1] sample: 40001
Orlistat
best[2] sample: 40001
Sibutramine 10 mg
best[3] sample: 40001
Sibutramine 15 mg
best[4] sample: 40001
Orlistat and sibutramine
best[5] sample: 40001
Standard care
best[6] sample: 40001
Probability
Rank of intervention

FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)


(g)
Placebo
best[1] sample: 40001
Orlistat
best[2] sample: 40001
Metformin
best[3] sample: 40001
Sibutramine 10 mg
best[4] sample: 40001
Sibutramine 15 mg
best[5] sample: 40001
Rimonabant
best[6] sample: 40001
Orlistat and sibutramine
best[7] sample: 40001
Standard care
best[8] sample: 40001
Probability
Rank of intervention

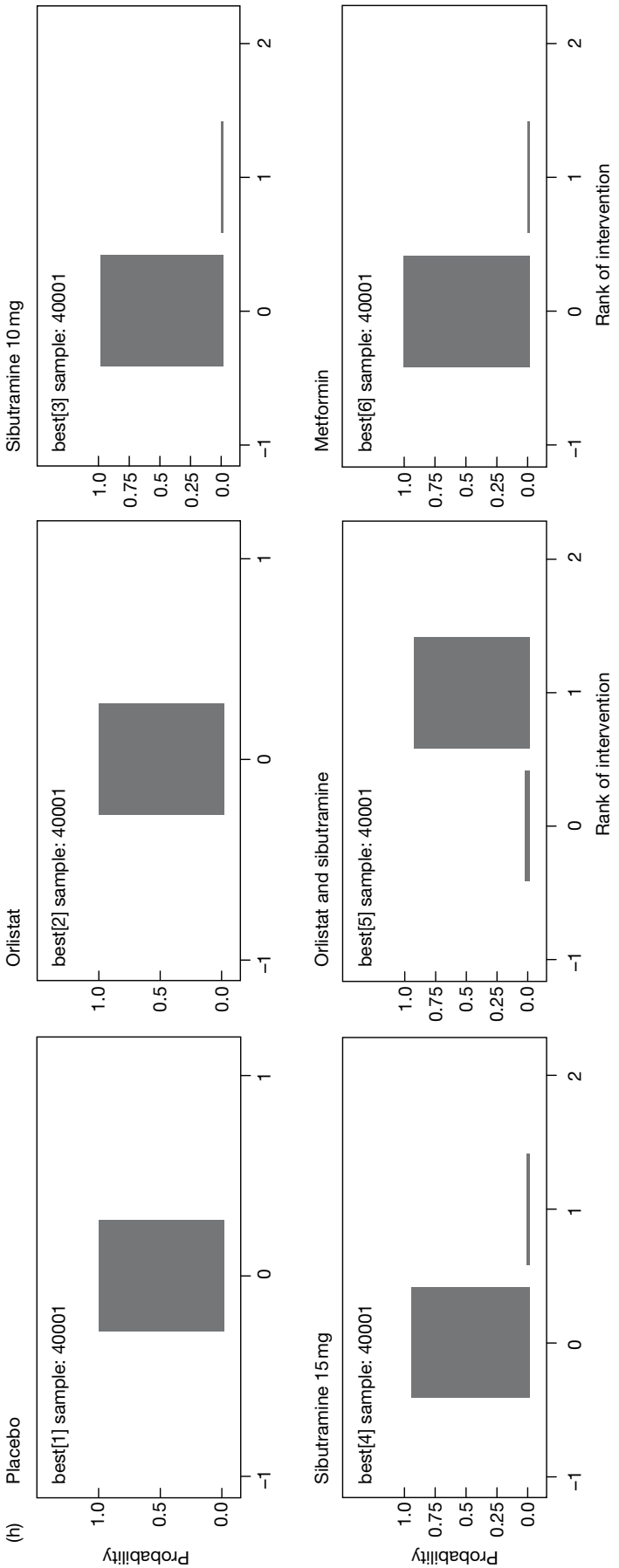


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

(i)
Placebo
best[1] sample: 40001
Orlistat
best[2] sample: 40001
Sibutramine 10 mg
best[3] sample: 40001
Sibutramine 15 mg
best[4] sample: 40001
Rimonabant
best[5] sample: 40001
Standard care
best[6] sample: 40001
Probability
Rank of intervention

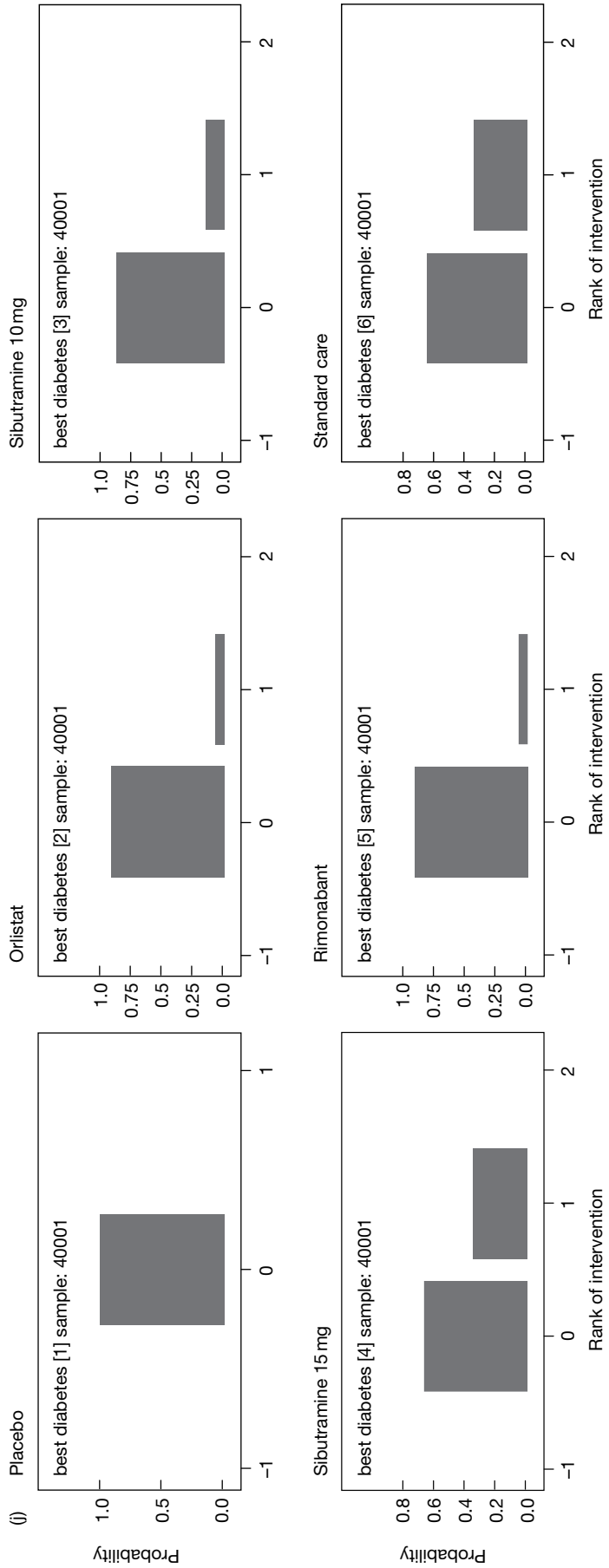


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

(k)
Placebo
Orlistat
Sibutramine 10 mg
Sibutramine 15 mg
Rimonabant
Standard care
best no diabetes [1] sample: 40001
best no diabetes [2] sample: 40001
best no diabetes [3] sample: 40001
best no diabetes [4] sample: 40001
best no diabetes [5] sample: 40001
best no diabetes [6] sample: 40001
Probability
Rank of intervention

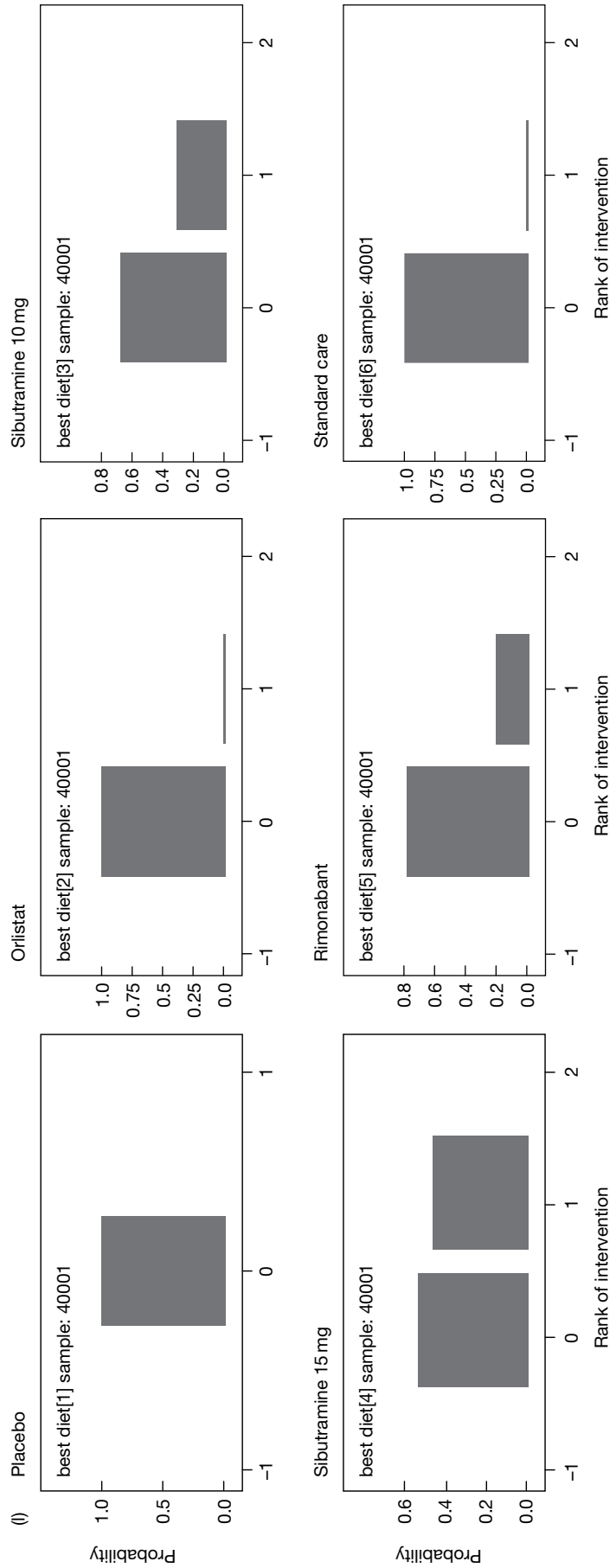


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

(m)
Placebo
best nodiet[1] sample: 40001
Orlistat
best nodiet[2] sample: 40001
Sibutramine 10 mg
best nodiet[3] sample: 40001
Sibutramine 15 mg
best nodiet[4] sample: 40001
Rimonabant
best nodiet[5] sample: 40001
Standard care
best nodiet[6] sample: 40001
Probability
Rank of intervention

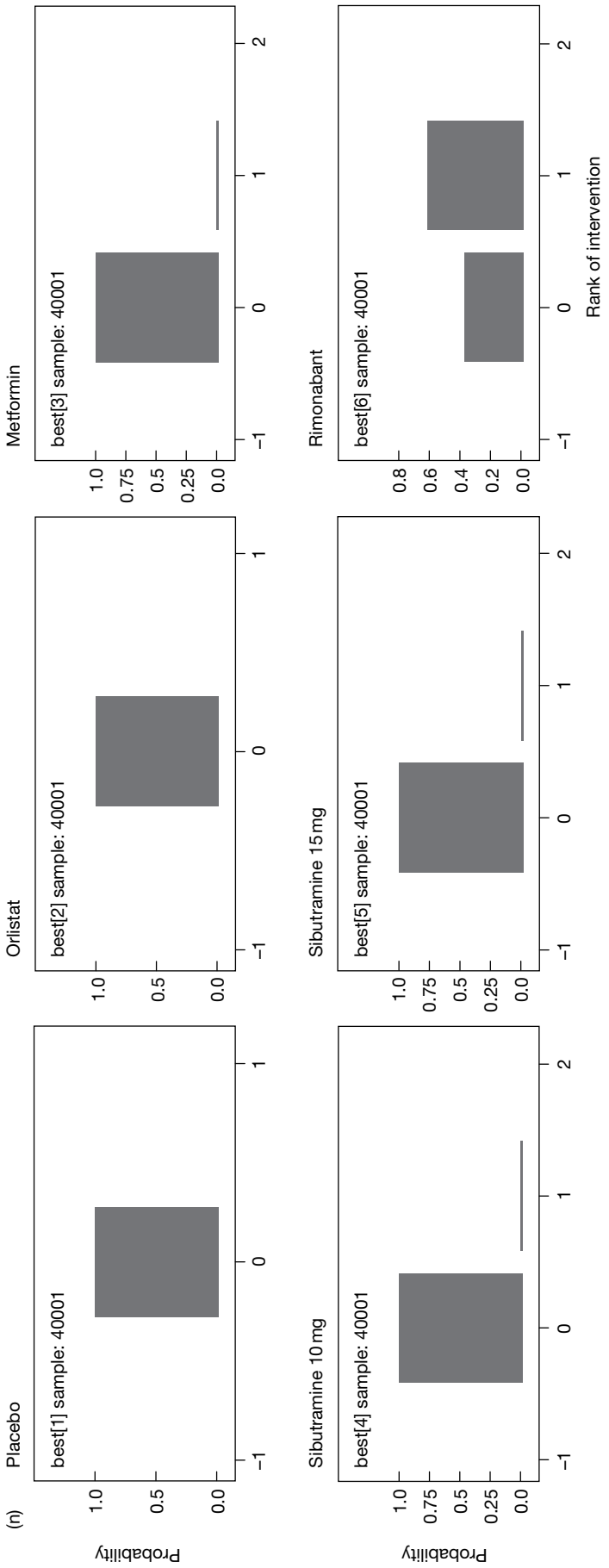


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

(o)
Placebo
best[1] sample: 40001
Orlistat
best[2] sample: 40001
Metformin
best[3] sample: 40001
Sibutramine 10 mg
best[4] sample: 40001
Sibutramine 15 mg
best[5] sample: 40001
Standard care
best[6] sample: 40001
Probability
Rank of intervention

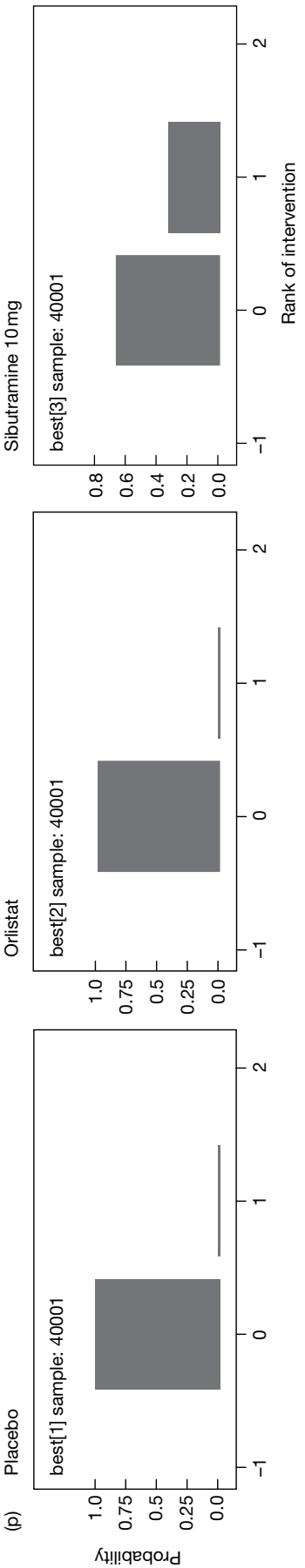


FIGURE 16 Plots showing the probability that each treatment (including placebo) is best (represented by the bar at 1 on the horizontal axis): (a) 3-month 5% weight loss, (b) 6-month 5% weight loss, (c) 12-month 5% weight loss, (d) 3-month 10% weight loss, (e) 6-month 10% weight loss, (f) 12-month 10% weight loss, (g) 3-month weight change, (h) 6-month weight change, (i) 12-month weight change, (j) 12-month weight change – T2DM, (k) 12-month weight change – no T2DM, (l) 12-month weight change – enhanced diet, (m) 12-month weight change – standard diet, (n) 3-month BMI change, (o) 6-month BMI change, (p) 12-month BMI change. (*continued*)

TABLE 27 Sensitivity analysis 12-month weight change

	Treatment	Mean difference	95% CI	% best ranking
All studies	Placebo	Reference		0
	Orlistat	–4.12	–5.07 to –3.15	0.2
	Sibutramine 10 mg	–5.42	–7.36 to –3.42	16.6
	Sibutramine 15 mg	–6.35	–8.06 to –4.63	78.2
	Rimonabant	–4.55	–6.20 to –2.92	5.0
	Standard care	–2.89	–4.90 to –0.84	0
Excluding wash-in studies	Placebo	Reference		0
	Orlistat	–2.79	–3.56 to –2.04	5.0
	Sibutramine 10 mg	–	–	–
	Sibutramine 15 mg	–3.83	–5.06 to –2.68	95.0
	Rimonabant	–	–	–
	Standard care	0.82	–0.40 to 2.06	0
LOCF only	Placebo	Reference		0
	Orlistat	–4.23	–5.52 to –2.92	2.1
	Sibutramine 10 mg	–5.44	–7.67 to –3.13	17.2
	Sibutramine 15 mg	–6.49	–8.89 to –4.09	73.5
	Rimonabant	–3.94	–6.04 to –1.75	3.5
	Standard care	–1.99	–7.73 to 3.67	3.8

Appendix 4

Cost-effectiveness review

Economic literature review inclusion and exclusion criteria

Inclusion criteria

- Cost-effectiveness study with active treatment orlistat, sibutramine or rimonabant compared with diet and exercise or lifestyle advice or no treatment.
- Cost-effectiveness study comparing any of the active treatments.
- Results presented in terms of cost per QALY or cost per life-year.
- Adults aged 18 years or over.
- Full report of modelling methods provided.

Exclusion criterion

- Studies reported in abstract form only.

Cardiovascular events

Of the 13 studies with non-diabetic cohorts at baseline, three[160,161,163] did not model CV events. Eight applied the Framingham Heart Study (FHS) equations to predict coronary[157,158,167,169] or cardiovascular[26,41,159,162] risk for both treatment arms.[19,190,196] One study[169] incorporated BMI changes indirectly into the FHS equations through estimating natural changes in blood pressure and lipids by BMI category. Another[168] estimated CHD risk using changes in waist circumference and one[166] used incidence data from registries for no treatment, applying relative risks per BMI change, obtained from observational studies.

Of the six studies with diabetic cohorts at baseline, two concentrated on just CVD events. They considered MI, stroke, angina and transient ischaemic attack (TIA),[41] and MI, ischaemic heart disease, stroke and congestive heart failure.[159] Three studies[164,165,170] included both micro- and macrovascular events (MI, stroke, peripheral vascular disease, heart failure, cataract extraction), and the sixth[166] included CHD and stroke. Five studies[41,159,164,165,170] used evidence from the UK Prospective Diabetes Study (UKPDS) to predict cardiovascular risk, based on treatment-induced changes in age, gender, lipids, blood pressure, smoking status and glycaemic control.[184,196,197] One study[166] used the same approach as for cardiovascular events, that is, baseline risks of events were obtained from GP registries, national registries and population surveys, and relative risks sourced from observational studies were then applied to the baseline risks. Another study[41] apportioned the risk across event types using prevalence data from Health Outcomes Data Repository (HODAR), and estimated risks of subsequent CHD events using data from Saskatchewan,[198–201] and one[164] increased the baseline risk observed in the UKPDS data by applying a correction factor for obese patients.[184,197]

Incidence of type 2 diabetes mellitus

Obese persons have a higher than average risk of developing T2DM. Of the 13 studies modelling obese cohorts with no comorbidities at baseline, 12[26,41,157–159,161–163,166–169] examined reductions in incidence rates of T2DM, and one used the observed 4-year incidence rates from the treatment

TABLE 28 Articles included in the economic review

Study	Setting	Cost year[a]	Treatment[b]	Comparator[b]	Baseline condition	Model	Horizon treatment	Horizon model	Discount (%), cost (benefit)
Ara 2007[157]	Finland Germany Switzerland UK	2005 €	Sibutramine 10 or 15 mg q.d. + lifestyle	Lifestyle	Obese: BMI ≥ 30 kg/m^2 No comorbidity	Life table	1 year	Lifetime	Finland 5 (5) Germany 5 (5) Switzerland 5 (5) UK 3.5 (3.5)
Brennan 2006[158]	Germany	2004 €	Sibutramine 10 or 15 mg q.d. + lifestyle	Lifestyle	Obese: BMI ≥ 30 kg/m^2 No comorbidity	Life table	1 year	Lifetime	5 (5)
Brown 2006[26]	UK	NR UK£	Orlistat (1 year) ≤ 120 mg t.i.d. + lifestyle	Orlistat (4 years) ≤ 120 mg t.i.d + lifestyle	Obese: mean BMI = 33 kg/m^2	NR	1 year vs 4 years	Lifetime	3.5 (3.5)[c]
Burch 2009[41]	UK	2005 UK£	Rimonabant 20 mg q.d. + diet and exercise	a) Diet and exercise b) Orlistat 120 mg t.i.d. + diet and exercise c) Sibutramine 10–15 mg q.d. + diet and exercise	(a) Obese: BMI ≥ 30 kg/m^2 with or without DM (b) Overweight: BMI ≥ 27 kg/m^2 with treated T2DM (c) Overweight: BMI ≥ 27 kg/m^2 with untreated dyslipidaemia and without T2DM	Markov model	Rimonabant is lifetime Orlistat is lifetime Sibutramine is 1 year	Lifetime	3.5 (3.5)
Caro 2007[159]	UK	2005 UK£	Rimonabant 20 mg q.d.	Diet and exercise advice	Obese: mean, BMI = 36.5 kg/m^2 T2DM: mean, BMI = 33.7 kg/m^2	Markov	1 year	10 years	3.5 (3.5)
Foxcroft 2005[160]	UK	2005 UK£	Orlistat ≤ 120 mg t.i.d. + low-calorie diet	Low-calorie diet	Obese: BMI = 28–47 kg/m^2	EXCEL	1 year	1 year	NA
Hampp 2008[168]	USA	2006 US$	Rimonabant 20 mg q.d. + lifestyle	a) No treatment b) Placebo + lifestyle	Obese: mean BMI = 37.1 kg/m^2	Decision tree	a) 1 year b) 2 years c) 1 year + 1 year placebo	5 years	3 (3)
Hertzman 2005[161]	Sweden	2003 €	Orlistat ≤ 120 mg t.i.d. + low-calorie diet	Low-calorie diet	Obese: mean BMI = 36 kg/m^2 No DM and > 2.5 kg weight loss prior to orlistat	Decision tree	1 year	Lifetime	3 (3)

Study	Setting	Cost year[a]	Treatment[b]	Comparator[b]	Baseline condition	Model	Horizon treatment	Horizon model	Discount (%), cost (benefit)
Iannazzo 2008[162]	Italy	NR €	Orlistat 120 mg t.i.d. + lifestyle	Lifestyle	Obese: BMI ≥ 30 kg/m^2	Markov	4 years	10 years	3.5 (3.5)
Lacey 2005[163]	Ireland	2003 €	Orlistat ≤ 120 mg t.i.d + low-calorie diet	Low-calorie diet	Overweight: BMI ≥ 28 kg/m^2 No T2DM and > 2.5 kg weight loss prior to orlistat		1 year	11 years	3 (3)
Lamotte 2002[164]	Belgium	2000 €	Orlistat, no dose stated + low-calorie diet	Low-calorie diet	Obese: BMI ≥ 30 kg/m^2 with T2DM	Markov state transition	2 years	10-year horizon	3 (0)
Maetzel 2003[170]	Canada	2001 US$	Orlistat 120 mg t.i.d. + diet and exercise + T2DM medication	Diet and exercise + T2DM medication	Overweight or obese with T2DM	Markov state transition	1 year	11 years	3 (3)
Roux 2006[169]	USA	2001 US$	(a) Diet only (b) Diet and orlistat 120 mg t.i.d. (c) Diet and exercise (d) Diet, exercise and behaviour modification	For maintenance orlistat reduced to 50%	Non-pregnant, 35-year-old overweight and obese women	Decision-analytic model	6-month intervention + 6-month maintenance	Lifetime	3 (3)
Ruof 2005[165]	Sweden Switzerland	NR €	Orlistat 120 mg t.i.d. + diet and exercise	Diet and exercise	Overweight or obese with T2DM	Markov model	1 year	11 years	3 (3)
Van Baal 2006[166]	Netherlands	2005 €	Orlistat 120 mg t.i.d. + low-calorie diet	Low-calorie diet (or nothing)	Individuals aged 20–70 years in the Netherlands with BMI ≥ 30 kg/m^2 Not treated for obesity	Population model	1 year	Lifetime	4 (1.5)
Warren 2004[167]	UK USA	2000 €	Sibutramine 10 or 15 mg q.d. + lifestyle	Lifestyle	Obese: BMI > 30 kg/m^2 No comorbidity	Life table	1 year	Lifetime	UK 6 (1.5) USA 3 (3)

DM, diabetes mellitus; NA, not applicable; NR, not reported; q.d., every day; t.i.d., three times a day.

a Direct costs only plus cost of orlistat, which is not reimbursed by Italian NHS.

b Lifestyle = diet and exercise advice.

c Assumed.

TABLE 29 Modelled weight regain and natural history

Study	Description
Ara 2007[157]	No treatment, natural weight increase: 0.08333 kg/month
Warren 2004[167]	Lifestyle regain: 0.36964 kg/month
	Non-responders to active treatment: rebound to trajectory of natural history
	Responders to active treatment regain: 0.38486 kg/month
Brennan 2006[158]	As Ara 2007.[157] Sensitivity analysis: responders maintain weight loss for 6 months after cessation of treatment
Caro 2007[159]	Weight regain for all: linear over 1 year
Foxcroft 2005[160]	NA (1-year horizon)
Brown 2006[26]	NR
Hampp 2008[168]	Weight maintained at 12-month value during second year on rimonabant
	Active treatment regain: linear over 1 year
	Duration modified in sensitivity analyses: 6 months to 3 years
Hertzman 2005[161]	Active treatment regain: linear over 3 years
Iannazzo 2008[162]	Assume 6 years regain to reach placebo level (4 years treatment plus 6 years regain)
Lacey 2005[163]	Weight regain for all: linear over 3 years
Lamotte 2002[164]	Active treatment regain: linear over 5 years
Maetzel 2003[170]	Active treatment: 3-year sustained effect
Roux 2006[169]	No treatment: increase in BMI of +0.26 units/annum
	Active treatment: in the base case 20% of treatment benefit is maintained long term
Ruof 2005[165]	Active treatment: regain is linear over 3 years
Burch 2009[41]	Active treatment: weight is maintained at 12-month level over the full lifetime horizon
Van Baal 2006[166]	Active treatment: in the base case 23% of treatment benefit is maintained long term

NA, not applicable; NR, not reported.

TABLE 30 Comorbidities modelled

Study	Comorbidities modelled
Ara 2007[157]	T2DM, CHD
Brennan 2006[158]	T2DM, CHD
Caro 2007[159]	(a) T2DM, CVD
	(b) CVD
Foxcroft 2005[160]	Not modelled (1-year horizon)
Brown 2006[26]	T2DM, CVD, colorectal cancer
Hampp 2008[168]	T2DM, CHD
Hertzman 2005[161]	T2DM (no CHD)
Iannazzo 2008[162]	T2DM, CVD
Lacey 2005[163]	T2DM (no CHD)
Lamotte 2002[164]	Micro/macro vascular
Maetzel 2003[170]	Micro/macro vascular
Roux 2006[169]	Hypertension, T2DM, hypercholesterolaemia, CHD
Ruof 2005[165]	Micro/macrovascular
Burch 2009[41]	T2DM, CVD
	CVD
	T2DM, CVD
Van Baal 2006[166]	CHD, stroke, T2DM, osteoarthritis, low back pain, cancer
Warren 2004[167]	T2DM, CHD

and control arms of the XENDOS study ($n = 3305$).[162] The remaining studies used incidence rates categorised by BMI level, and two studies[41,159] also included fasting plasma glucose level. These two studies used algorithms from the San Antonio study to predict annual incidence rates, taking into account treatment-induced changes in both BMI and fasting plasma glucose.

Ara and Brennan,[157] Brennan *et al.*[158] and Warren *et al.*[167] used the same evidence to model incidence rates according to one-unit BMI bands, with values ranging from 0.05% for BMI of 23 kg/m^2 to 2.50% for BMI of 42 kg/m^2.[201,202] Roux *et al.*[169] and Brown[26] modelled incidence rates by BMI category using published data,[201,203,204] but neither reported sufficient detail to determine the values used per category. Hampp *et al.*[168] used a baseline annual incidence of 1.1013% for a mean BMI of 37 kg/m^2, and modelled a 0.098% and 0.073% reduction per decrease in unit BMI for men and women respectively.[205,206] Hertzman[161] used a baseline incidence rate of 2.08% for men and 0.85% for women for a BMI of 36 kg/m^2, applying gender- and BMI-specific relative risks from published evidence.[206] Lacey *et al.*[163] assumed that a 10% reduction in BMI was associated with a 30% reduction in T2DM using baseline incidence rates of 0.04% (0.13%) and 1.40% (0.61%) for BMI levels of 25 kg/m^2 and 35 kg/m^2, respectively, for men (women).[20] Finally, van Baal *et al.*[166] used a similar technique to model T2DM rates as employed for the CVD events, using incidence rates from registries, and applying relative risks obtained from observational studies.

Six studies provide sufficient detail to estimate the annual incidence rates of T2DM modelled (*Figure 17*). Lacey *et al.*[163] and Hertzman[161] modelled gender-specific rates while the other four assumed equal rates for men and women. There was a considerable difference in the annual incidence rates for the higher BMI bands (44 kg/m^2), with values ranging from 1.042% for women[163] to 3.20% for men.[161] Ara and Brennan,[157] Brennan *et al.*[158] and Warren *et al.*[167] modelled a non-linear relationship with absolute reduction per unit change in BMI ranging from 0.02% (BMI = 26 kg/m^2) to 0.325% (BMI = 44 kg/m^2). The other three studies[161,163,168] assumed a linear relationship, and reductions ranged from 0.079%[168] to 0.140%[161] per unit change in BMI.

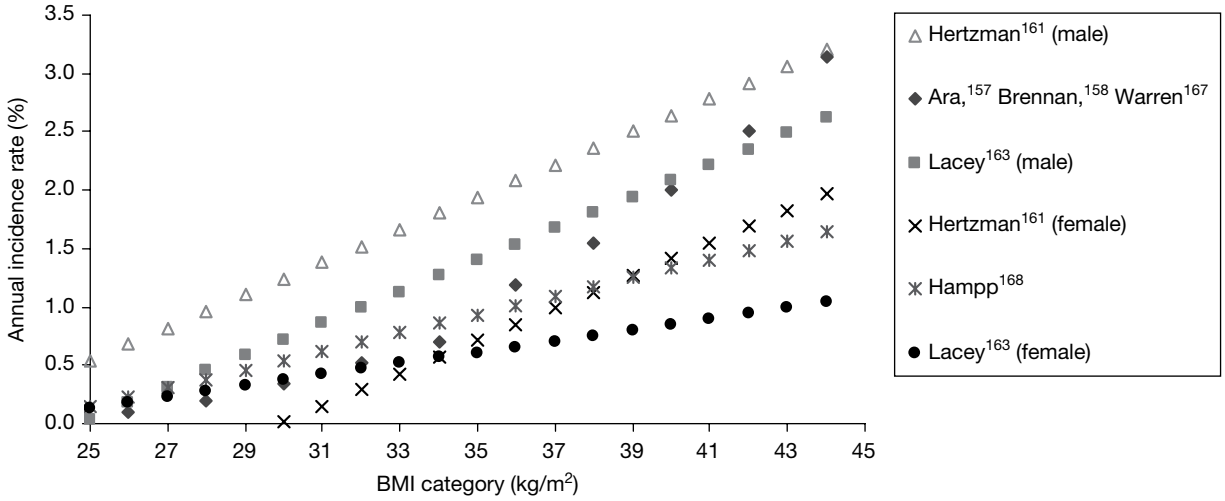


FIGURE 17 Comparing modelled incidence rates by BMI category.

TABLE 31 Health-related quality-of-life data used in models

Study	Baseline	Weight/BMI	T2DM	CVD
Ara 2007[157]	Age adjusted[178]	SF-6D disutility 0.00375/kg[79]	T2DM multiplier = 0.95[207]	EQ-5D CHD multiplier = 0.85[184]
Brennan 2006[158]	Age adjusted[178]	SF-6D disutility 0.00375/kg[174]	T2DM multiplier = 0.95[207]	EQ-5D CHD multiplier = 0.85[184]
Caro 2007[159]	EQ-5D Age adjusted	EQ-5D disutility 0.014/BMI (per unit increase/decrease)[208]	EQ-5D disutility T2DM = –0.041[208]	EQ-5D disutility MI = – 0.072 Stroke = – 0.185 TIA = – 0.088 Angina = – 0.126[208]
Foxcroft 2005[160]	Utility = 1	Disutility 0.017/BMI[209]	Nm	Nm
Hampp 2008[168]	Utility = 1	VAS and Torrance transformation Disutility 0.0179/BMI[209] Increase/decrease equal[210]	Nm	Nm
Hertzman 2005[161]	Utility = 1	VAS and Torrance transformation Disutility 0.01655/BMI, women 0.0264/BMI	Nm	Nm
Iannazzo 2008[162]	Obese men 0.79 Obese women 0.75	Not modelled	T2DM multiplier = 0.79	Multiplier MI = 0.80 Stoke = 0.79
Lacey 2005[163]	Utility = 1	Disutility 0.017/BMI[209]	Nm	Nm
Lamotte 2002[164]	Nm	Nm	Nm	Nm
Maetzel 2003[170]	Nm	Nm	Nm	Nm
Roux 2006[169]	SF-36 Age adjusted[117]	SF-36 Multiplicative Obese = 0.87[211]	SF-36 Multiplicative T2DM = 0.75[211]	SF-36 Multiplicative CHD = 0.75[211]
Ruof 2005[165]	Utility = 1	VAS disutility Obese = 0.017[209]	VAS disutility Obese and T2DM = 0.0285[209]	Disutility MI = –0.08[212] Stroke = –0.30[213] Amputation = –0.11[214] Microvascular = –0.25[215] Heart failure = –0.18 Cataract = –0.04
Burch 2009[41]	EQ-5D Age adjusted Utility[114]	0.014 per unit change in BMI[208]	EQ-5D[208] Additive T2DM = –0.041	EQ-5D[208] Additive Stroke = –0.185 TIA = –0.088 MI = –0.072 Angina = –0.126
Van Baal 2006[166]	Person trade-off Age adjusted[216]	Not modelled explicitly	No values provided	
Warren 2004[167]	EQ-5D Age adjusted[178]		T2DM multiplier = 0.95	CHD multiplier = 0.85[217]

Nm, not modelled; SF-36, Short Form questionnaire-36 items; SF-6D, Short Form questionnaire-6 Dimensions.

Appendix 5

De novo cost-effectiveness model

Subsequent vascular events

UK-specific data are used to ensure that event rates match the likely distribution in the UK. The probabilities of further MIs, strokes and vascular deaths for individuals with a history of MI are derived from patients on the Nottingham Heart Attack Register, whereas the probabilities of subsequent strokes and vascular deaths for patients with a history of a stroke are derived from patients on the South London Stroke Register.[176]

Logistic and multivariate regression analyses were used to estimate the probability of experiencing secondary events within 1 year of a qualifying primary event. First, a logistic regression was used to estimate the probability of experiencing a secondary event of any type, that is, the combined rate of non-fatal MI, non-fatal stroke and vascular death. Multivariate regression analysis was then used to determine the distribution of secondary events between each type, should an event occur. The results confirm the importance of accounting for age in the model. For patients experiencing an MI, the probability of a secondary event within 1 year is strongly correlated with age (mean probability of 14.7% at age 45 years and 29.5% at age 85 years). Similarly, for patients experiencing a stroke, the probability of a secondary event within 1 year increases with age (mean probability of 5.4% at age 45 years and 29.8% at age 85 years), while patients with unstable angina have a mean probability of a secondary event of 8.7% at age 45 years compared with 31.3% at age 85 years.

Similar analyses were performed to estimate the probabilities of subsequent events in subsequent years. In the absence of data from individuals with a history of multiple events, these results are used to inform all subsequent events. This is a conservative approach as the application of these data implies that there is no additive effect on fatal or non-fatal event rates from previous events. Uncertainty in these event rates is explored using multivariate distributions.

List of assumptions used in the economic model

- For individuals in the event-free health state, the Weibull curves derived from the GPRD are used to predict the time to ACM. These curves are valid for up to a maximum of 15 years, after which standard life tables are used.
- Individuals enter the model with the mean characteristics of the patients in the MTC; thus, they have an average age of 45.5 years and a mean BMI of 34.92 kg/m^2, 25.7% are male and 33.2% are diabetic.
- At the end of the active treatment period, BMI reverts to the baseline value in a linear fashion over a 3-year period.[38]
- For rimonabant, as changes in BMI at 6 and 12 months were not available for inclusion in our MTC, we use the average of 1.76 kg/m^2 (relative to placebo change) as reported in a previous economic evaluation.[168]
- For the comparator arm (no active treatment), we assume just one visit with the practice nurse at baseline and no additional monitoring.

TABLE 32 Regressions used for subsequent events (Nottingham Heart Attack Register data)

Logistic regression coefficients – probability of event type given event

	eventype	Coefficient	SE	*z*	*p*>*z*	95% CI
2	Age	0.077705	0.034652	2.242	0.025	0.009789 to 0.145622
	_cons	–7.17201	2.523846	–2.842	0.004	–12.1187 to –2.22536
3	Age	0.047496	0.017134	2.772	0.006	0.013914 to 0.081079
	_cons	–3.24095	1.176916	–2.754	0.006	–5.54767 to –0.93424

		age	_cons	age	_cons
2	age	0.001201			
	_cons	–0.08667	6.3698		
3	age	0.000165	–0.01093	0.000294	
	_cons	–0.01085	0.733099	–0.01993	1.38513

Any event assuming exponential, given survived to end of year 1

	_t	Coefficient	SE	*z*	*p*>*z*	95% CI
	age	0.025344	0.013465	1.882	0.06	–0.00105 to 0.051735
	_cons	–4.95663	0.912665	–5.431	0	–6.74542 to –3.16784

	age	_cons
age	0.000181	
_cons	–0.01213	0.832958

ACS year 1 mlogit

	eventype	Coefficient	SE	*z*	*p*>*z*	95% CI
	age	0.003234	0.012312	0.263	0.793	–0.0209 to 0.027366
	_cons	–3.05907	0.80604	–3.795	0	–4.63888 to –1.47926
	age	0.05624	0.009014	6.239	0	0.038572 to 0.073907
	_cons	–5.71398	0.648273	–8.814	0	–6.98457 to –4.44338

		01:00		02:00	
		age	_cons	age	_cons
1	age	0.000152			
	_cons	–0.00974	0.649701		
2	age	8.50×10^{-6}	–0.00054	0.000081	
	_cons	–0.00054	0.035984	–0.00577	0.420258

ACS exponential post year 1

	_t	Coefficient	SE	*z*	*p*>*z*	95% CI
	age	0.051546	0.006256	8.24	0	0.039285 to 0.063807
	_cons	–5.93184	0.45102	–13.152	0	–6.81582 to –5.04785

_t	age	_cons
age	0.000039	
_cons	–0.00279	0.203419

TABLE 32 Regressions used for subsequent events (Nottingham Heart Attack Register data) (*continued*)

ACS post year 1 mlogit						
		Coefficient	**SE**	***z***	***p*>*z***	**95% CI**
	age	–0.04179	0.017595	–2.375	0.018	–0.07627 to –0.0073
	_cons	1.089838	1.205898	0.904	0.366	–1.27368 to 3.453354
		age	**_cons**			
	age	0.00031				
	_cons	–0.0209	1.45419			

SE, standard error.

TABLE 33 Regressions used for subsequent events (South London Stroke Register data)

Year 1: mlogit all events						
	eventype	**Coefficient**	**SE**	***z***	***p*>*z***	**95% CI**
1	Age	0.008007	0.009213	0.869	0.385	–0.01005 to 0.026063
	_cons	–3.45027	0.651183	–5.298	0	–4.72657 to –2.17398
2	Age	0.08874	0.009097	9.755	0	0.070911 to 0.106569
	_cons	–8.61813	0.717794	–12.006	0	–10.025 to –7.21128
(Outcome eventype==0 is the comparison group)						
		age	**_cons**	**age**	**_cons**	
1	Age	0.000085				
	_cons	–0.00589	0.424039			
2	Age	4.90×10^{-6}	–0.00033	0.000083		
	_cons	–0.00034	0.02368	–0.00648	0.515229	
Year 2: Exponential any event						
	eventype	**Coefficient**	**SE**	***z***	***p*>*z***	**95% CI**
	age2	0.04211	0.00684	6.157	0	0.028705 to 0.055515
	_cons	–5.88035	0.503282	–11.684	0	–6.86676 to –4.89393
		age2	**_cons**			
	age2	0.000047				
	_cons	–0.0034	0.253293			
Mlogit event 1–2						
	evtypey2	**Coefficient**	**SE**	***z***	***p*>*z***	**95% CI**
	age2	–0.05784	0.016193	–3.572	0	–0.08958 to –0.0261
	_cons	3.825288	1.177901	3.248	0.001	1.516645 to 6.133931
(Outcome evtypey2==2 is the comparison group)						
		age2	**_cons**			
	age2	0.000262				
	_cons	–0.01888	1.38745			

SE, standard error.

TABLE 34 Results of ACMM regression

	beta1	beta2	beta3	beta4
BMI/10	0.104753	–0.00471	0.102937	0
$(BMI/10)^2$	–0.02088	–0.00084	–0.01708	0
Female	0.20566	0.068761	0.103689	0
Female*BMI/10	–0.13659	–0.04906	–0.05964	0
$(Female*BMI/10)^2$	0.021341	0.00906	0.008154	0
Age/10	–0.08175	–0.01526	–0.01037	0
$(Age/10)^2$	0.007236	0.001087	0.000396	0
Heart attack	–0.04154	0.009891	–0.03533	0
Stroke	–0.03844	0.005964	–0.0539	0
T2DM	–0.00378	–0.00042	–0.01102	0
Angina	–0.04846	–0.00895	–0.02194	0
Other DM	–0.04612	–0.00347	–0.00403	0
Condition 1	–0.12236	–0.01034	–0.03467	0
Condition 2	–0.16814	–0.01196	–0.05323	0
Condition 3	–0.19991	–0.00558	–0.06245	0
Condition 4	–0.19227	–0.01002	–0.09421	0
Recent angina	–0.02555	0.007781	–0.01335	0
Recent heart attack	0.036931	0.081802	–0.0108	0
Recent stroke	–0.02441	0.011257	0.019356	0
Gamma	0.388339	0.886923	0.669692	15
Var_e	0.02373	0.000681	0.006051	0.1

	delta1	delta2	delta3	delta4
Constant	–5.88849	–2.21162	–3.74868	0
BMI/10	0.428433	0.000379	0.296133	0
Female	0.31338	0.185129	0.438441	0
Age/10	0.040898	0.041858	0.197627	0
Heart attack	1.664323	0.497866	0.949695	0
Stroke	1.978217	0.833343	1.033395	0
T2DM	0.676831	–0.00932	0.523042	0
Angina	0.846194	0.403626	0.762616	0
Other DM	1.131596	0.271272	0.359836	0
Condition 1	2.381369	0.796365	1.42458	0
Condition 2	3.39744	1.235271	2.027874	0
Condition 3	4.503202	1.319402	2.780812	0
Condition 4	4.943372	1.661351	2.994708	0
Recent angina	1.606556	0.532913	0.945333	0
Recent heart attack	8.146078	7.967091	7.593918	0
Recent stroke	1.183494	0.491454	0.921231	0

Delta4 fixed at zero for identification.

TABLE 35 Actual and predicted EQ-5D scores and mean errors in predicted values

	Beta coefficients[a]	Mean EQ-5D		Mean errors			
		Actual	ACMM	ME	MAE	RMSE	< MID (%)
All	24,169	0.8715	0.8707	0.0008	0.1204	0.1806	53
No condition	12,884	0.9514	0.9493	0.0021	0.0752	0.1027	74
At least one condition	11,285	0.7804	0.7811	–0.0007	0.1720	0.2404	29
Angina ≥ 12 months	965	0.6853	0.6832	0.0021	0.1937	0.2578	26
Angina < 12 months	515	0.6151	0.6135	0.0016	0.2184	0.2802	25
MI ≥ 12 months	648	0.6934	0.6900	0.0034	0.1964	0.2603	26
MI < 12 months	64	0.6197	0.6200	–0.0003	0.2156	0.2749	20
Stroke ≥ 12 months	470	0.6857	0.6823	0.0034	0.2090	0.2654	21
Stroke < 12 months	85	0.6482	0.6457	0.0026	0.2138	0.2693	22
T2DM	903	0.7618	0.7603	0.0015	0.1719	0.2351	27
T2DM and angina ≥ 12 months	141	0.6223	0.6282	–0.0059	0.1934	0.2578	29
T2DM and angina < 12 months	78	0.5346	0.5575	–0.0229	0.2195	0.2747	21
T2DM and MI ≥ 12 months	105	0.6456	0.6459	–0.0003	0.1936	0.2551	31
T2DM and MI < 12 months	8	0.5075	0.5665	–0.0590	0.2578	0.3306	13
T2DM and stroke ≥ 12 months	63	0.6240	0.6224	0.0015	0.2195	0.2766	22
T2DM and stroke < 12 months	8	0.5813	0.6813	–0.1000	0.3224	0.3894	25
Age (years)							
< 35	5838	0.9304	0.9289	0.0015	0.0870	0.1371	66
34.9–45.0	5134	0.9014	0.9021	–0.0007	0.1076	0.1661	61
44.9 – 55	4240	0.8678	0.8721	–0.0043	0.1259	0.1878	52
54.9 – 65	4228	0.8333	0.8373	–0.0039	0.1448	0.2102	44
64.9 – 75	2892	0.8239	0.8025	0.0214	0.1454	0.2026	38
75+	1837	0.7727	0.7799	–0.0072	0.1540	0.2110	32

MAE, mean absolute error; ME, mean error; MID, minimum important difference.
a Beta coefficients for the adjusted censored mixture model.

TABLE 36 Ratio of fatal CHD to stroke

	CHD				Stroke			
	Men		Women		Men		Women	
Age (years)	*n*	%	*n*	%	*n*	%	*n*	%
< 35	118	51	23	21	113	49	84	79
35–44	787	78	192	51	223	22	183	49
45–54	2739	83	590	56	570	17	463	44
55–64	6317	84	1742	65	1244	16	949	35
65–74	10,889	78	4861	67	3004	22	2413	33
75+	28,815	65	31,163	63	15,203	35	18,693	37

TABLE 37 Monitoring costs

	1–3 months	4–6 months	7–12 months
Sibutramine	£65.00	£50.00	£105.00
Orlistat	£55.00	£50.00	£100.00
Rimonabant	£55.00	£50.00	£100.00
	Unit	**Total**	**Source**
Sibutramine			
GP 4 × 10 minutes	£35.00	£140.00	Curtis and Netten 2007[180]
Nurse 8 × 15 minutes	£7.50	£60.00	Curtis and Netten 2007[180]
Blood 4 × 10 minutes	£5.00	£20.00	Curtis and Netten 2007[180]
Total		£220.00	
Orlistat and rimonabant			
GP 4 × 10 minutes	£35.00	£140.00	Curtis and Netten 2007[180]
Nurse 8 × 15 minutes	£7.50	£60.00	Curtis and Netten 2007[180]
Blood 1 × 10 minutes	£5.00	£5.00	Curtis and Netten 2007[180]
Total		£205.00	

Cohort size

The number of individuals required to capture the individual patient variation in a typical cohort was determined by examining the average costs and QALYs derived from cohorts of increasing numbers of patients. With a sample size of 200,000, there is still a small amount of variation in the estimated average costs (*Figure 18*) and QALYs (*Figure 19*). These variations have stabilised when using sample size of 400,000.

To ensure that our results represent those of an average cohort, we use a sample size of 1,000,000 for the deterministic analyses. However, because of computational limitations, we use a sample size of 400,000 and 200 Monte Carlo simulations in the stochastic analyses.

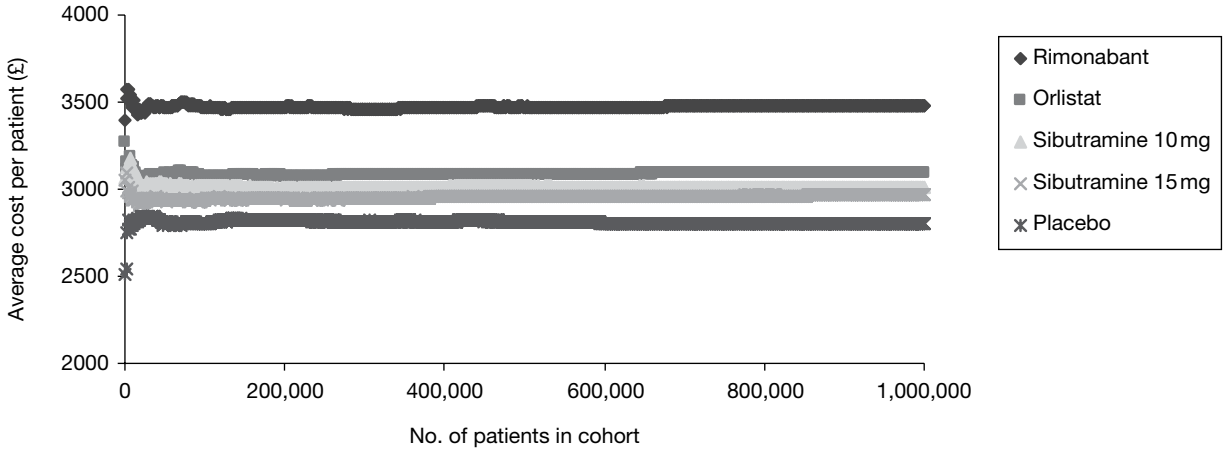


FIGURE 18 Stability analyses for cohort size, average discounted cost per patient.

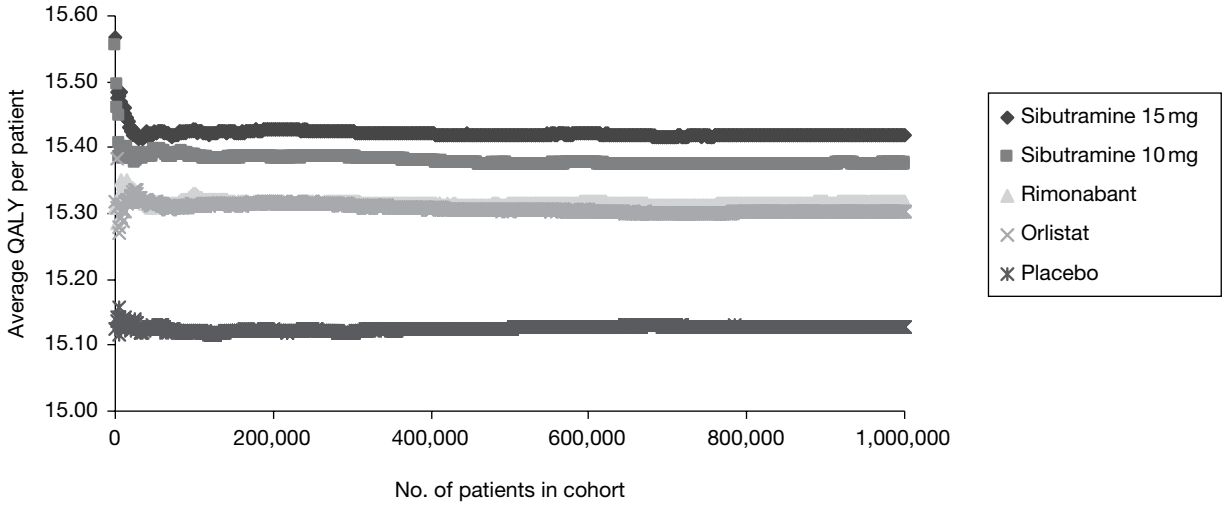


FIGURE 19 Stability analyses for cohort size, average discounted QALYs per patient.

TABLE 38 Percentage of lives needed to be lost for the cost per QALY compared with placebo to be >£20,000: using deterministic results

Treatment	Incremental cost (£)	Incremental QALYs	ICER vs placebo (£)	QALY loss per person to make drug not cost-effective[a]	Percentage of lives needed to be lost to tip cost-effectiveness[b]
Orlistat	291	0.17498	1665	0.16041	1.05
Rimonabant	672	0.18907	3553	0.15548	1.02
Sibutramine 10 mg	205	0.24779	827	0.23754	1.54
Sibutramine 15 mg	161	0.28972	557	0.28165	1.83

a QALY loss per person to make drug not cost effective = incremental QALYs – incremental cost/threshold.
b Percentage of lives needed to be lost to tip cost-effectiveness = QALY loss per person to make drug not cost-effective/discounted QALYs.

TABLE 39 Sensitivity analyses

Sensitivity analysis	Base case	Variable		Life-years	Cost (£)	Discounted cost (£)	QALYs	Discounted QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case			Placebo	75.495	5286	2806	25.12	15.13			
			Orlistat	75.758	5547	3097	25.47	15.30	291	0.1750	1665
SA1	Weight regain period 36 months	Weight regain period 12 months	Placebo	75.163	5373	2942	24.86	14.99			
			Orlistat	75.440	5606	3211	25.14	15.10	269	0.1130	2379
SA2	BMI regain to baseline BMI	BMI regain to trajectory of natural history	Placebo	74.880	6090	3209	22.72	13.82			
			Orlistat	75.115	6406	3530	22.95	13.91	321	0.0927	3466
SA3	Treatment duration 12 months	Treatment duration 24 months	Placebo	75.454	5342	2846	25.09	15.12			
			Orlistat	75.714	5562	3115	25.35	15.21	270	0.0951	2835
SA4	Starting age 45.5 years	Starting age 20 years	Placebo	67.860	10,266	4130	41.74	20.10			
			Orlistat	68.056	10,421	4396	41.95	20.15	266	0.0508	5240
SA4	Starting age 45.5 years	Starting age 60 years	Placebo	79.557	3748	2441	15.89	10.98			
			Orlistat	79.733	4082	2775	16.05	11.07	334	0.0878	3798
SA5	Base case uses a distribution of 74.3% women and 25.7% men	All female	Placebo	73.960	6564	3564	23.77	14.47			
			Orlistat	74.382	6871	3865	24.11	14.60	301	0.1336	2257
SA6	Baseline BMI 34.92 kg/m^2	Baseline BMI 30 kg/m^2	Placebo	79.339	1085	524	29.62	17.11			
			Orlistat	79.343	1436	887	29.65	17.13	363	0.0153	23,720
SA6	Baseline BMI 34.92 kg/m^2	Baseline BMI 40 kg/m^2	Placebo	74.257	6105	3300	23.73	14.54			
			Orlistat	74.440	6368	3599	23.85	14.59	299	0.0485	6155

Appendix 6

Protocol

1) PROJECT TITLE

Evaluating Anti-obesity Treatments (EAT) in primary care

2) PLANNED INVESTIGATION

This project will evaluate the clinical and cost-effectiveness of using drugs in treating obese adults in a primary care setting. The purpose of the study is to apply rigorous methods of systematic reviewing, evidence synthesis and decision analytic modelling to evaluate the comparative clinical and cost-effectiveness of the three pharmaceutical treatments: Orlistat, Sibutramine and Rimonabant.

- **Population**: Clinically obese adults
- **Interventions**: Orlistat, Sibutramine, Rimonabant anti-obesity drugs
- **Comparators**: Orlistat vs. Sibutramine vs. Rimonabant vs. No treatment
- **Outcomes**: Long term weight loss, adverse events, quality of life, cardiovascular risk, lipid profiles, co-morbidity and cost effectiveness
- **Setting**: Primary care
- **Perspective**: NHS and Personal and Social Service (PSS)

2.1 Research aims and objectives

(a) Analyse an existing routine data base of clinical information from primary care to determine the impact of obesity on mortality and morbidity.
(b) Compare the characteristics of patients and effectiveness of anti-obesity agents in the general population with those in clinical trials.
(c) Conduct a full systematic review of the published evidence on the clinical effectiveness of Orlistat, Sibutramine and Rimonabant.
(d) Undertake a full synthesis of the available evidence. This will include the use of a higher-level synthesis of the data using Bayesian methodologies to account for indirect comparison.
(e) Undertake a full systematic review of the published evidence of the cost-effectiveness of the agents. This will include a systematic review of published economic evaluations in the area and identification of other evidence needed to populate an economic model.
(f) Use decision-analytic modelling and probabilistic sensitivity analysis to assess the relative cost-effectiveness of the three agents in terms of the incremental cost per quality adjusted life year (QALY) gained.
(g) Use expected value of information techniques to determine the value of collecting further data on input parameters, and the potential benefits of future head to head trials of the agents.

2.2 Existing research

The authors of the recent NICE obesity clinical guidelines estimate that more than 12 million adults in England will be obese (BMI ≥ 30 kg/m^2) by 2010 if the increasing trend in prevalence continues.{CG43} The guidelines suggest that a large proportion of obese individuals fail to achieve and maintain weight losses without clinical support. The guideline also states that the majority of PCOs did not monitor the effectiveness of drug treatments for obesity and advocated that every necessary step is taken to tackle obesity, recommending that preventing and managing obesity is a priority and that systems should be in place to implement local obesity strategies. The guideline included a full systematic review of the clinical and economic evidence for the two pharmaceutical treatments (i.e. Orlistat and Sibutramine) available on prescription in the UK at the time.

A recently published meta-analysis which included the newer treatment, Rimonabant, found that all three agents modestly reduce weight providing on average less than 5 kg more weight loss compared with placebo.{Rucker, 2007} They found the original weight differential between the placebo and active arms was maintained for up to four years as weight regain was consistent in both groups. A recent retrospective cohort study reported persistence rates to Orlistat or Sibutramine were smaller than 2% at two years; much lower than reported in clinical trials{Padwal, 2007} and the authors suggest that the lack of adherence to treatment is a major factor limiting the efficacy of anti-obesity drugs.

The three agents have unique adverse effects profiles. The evidence on secondary end points suggests they also have differing effects on cardiovascular risk profiles. However, due to absence of data on the effects on mortality or cardiovascular morbidity the exact benefits are uncertain. Of major concern are the generalisability of the results from clinical studies to primary care settings, and as Rucker *et al.* mention, with very high attrition rates, the internal validity of many of the clinical studies is potentially compromised.{Rucker 2007}

There have been a number of UK economic evaluations exploring the cost-effectiveness of Sibutramine and Orlistat compared with placebo.{CG43, TAP 22, TAP 31} An ongoing NICE STA submission on behalf of Sanofi-Aventis includes an economic evaluation of the three interventions within the same modelling framework using pair-wise comparisons of primary outcomes.{ACD Rimonabant} The technology assessment group expressed concerns with discrepancies in the data presented for Orlistat and Sibutramine.{ACD Rimonabant} They also stated a major limitation in the economics is the lack of response hurdles in the clinical pathways modelled for Sibutramine and Orlistat and highlight further research is required on head to head studies and relationships between weight losses and quality of life measurements.

The current proposal describes a study of the clinical benefits and cost-effectiveness of using drugs in treating obese patients in primary care to inform future policy initiatives and primary care clinicians. The study will also identify areas in which further research would be most valuable and in particular the potential net benefits associated with future head to head trials of the three drugs.

2.3 Methods for the systematic identification of evidence

a) Scoping search

A brief scoping literature search combining search terms related to Orlistat, Sibutramine and Rimonabant retrieved the following: 544 citations from MEDLINE 1966–present; 499 citations from EMBASE 1980–present, 99 citations from CINAHL 1982–present, 241 citations from the Cochrane Library various dates–present and 501 from Web of Science 1900–present.

b) Detailed searching techniques

The search strategies will be conducted in separate stages:

i) Search strategy for identification of studies providing information on clinical effectiveness

A search for relevant studies on clinical effectiveness will be conducted by means of electronic searches of key databases including MEDLINE, EMBASE, Science Citation Index and Biological Abstracts.

Searching for clinical information as contained in systematic reviews, meta-analyses or clinical trials. This will focus on the above key databases with the addition of the Cochrane library and specific trials registers. Published methods of searching specifically for systematic reviews and clinical trials as developed by the McMaster University Health Information Research Unit will be used. Specific concepts to be included in the literature searches will include terms relating to obesity (obesity.tw, obese, obesity (subject heading), obesity, morbid (subject heading)), and terms relating to agents (orlistat, sibutramine, rimonabant, anti-obesity agents (subject heading), Tetrahydrolipstatin (subject heading), sibutramine (subject heading), rimonabant (subject heading)). References will also be located through review of references for relevant articles and through citation search facilities via the Web of Science's Science Citation Index and Social Science Citation Index. Where systematic reviews already exist, these will be used to identify relevant studies and to inform subsequent analyses. In addition systematic searches of the Internet using various search engines will be used to identify unpublished materials and work in progress. Key authors and commercial organisations involved in the investigation of pharmaceutical agents will be contacted and asked for unpublished materials.

We will utilise a varied range of sources and search techniques to identify relevant literature. A comprehensive literature search will be undertaken in the major medical, health-related, science and health economic electronic bibliographic databases (i.e. CDSR, NHS DARE, NHS HTA, MEDLINE, EMBASE, CINAHL, Science Citation Index, PreMEDLINE, NHS EED, HEED, CENTRAL, Pascal, ASSIA, Social Care Online, Social Science Citation Index). In addition, various health service research and guideline producing bodies (e.g. SIGN, National Guidelines Clearinghouse, etc.) will be consulted via the internet and key organisations (e.g. National Obesity Forum) will be contacted. We will utilise the expertise within the group and consult with national and international experts in research and practice in obesity. Ongoing and recently completed research in the field will be identified through searching the National Research Register, ReFeR, Current Controlled Trials and its links, HSRProj and Index to Theses. Grey literature will be identified from searches of databases including Dissertation Abstracts and Inside Conferences. Finally, the reference lists of included studies will be examined for additional relevant references and, where appropriate, the citation facility in Web of Science will be used to search for specific papers and authors.

ii) Search strategy for identification of studies providing information on adverse effects

Supplementary searches will be conducted for data on adverse effects. No study restrictions will be utilised. Specific pharmacological databases will be used at this stage of the review. Reference will be made to published work on retrieval of adverse effects literature from the NHS Centre for Reviews and Dissemination.{Golder 2006, Golder 2006} We will also write to the manufacturers of these drugs to obtain any data on file.

iii) Search strategy for identification of studies providing information on adherence to treatment

Given that primary research suggests that lack of adherence to treatment is a major factor limiting the efficacy of anti-obesity drugs it would be valuable in answering the effectiveness-related questions to examine what we know on patients' perceptions of anti-obesity drugs. Ogden and Sidhu (2006) are among the first to examine specifically the qualitative experience of patients on obesity medication. {Ogden 2006} Other qualitative research on perceptions of obesity treatments will also be valuable. We therefore propose to conduct a tightly focused qualitative evidence synthesis using accepted methods of evidence interpretation and integration.{Pope, Mays and Popay, 2007} This review will complement the effectiveness review and modelling work and provide added value by identifying the main variables that can impact on the anticipated effectiveness of anti-obesity medication.

iv) Search strategy for identifying economic evidence

In addition to the search strategies identified above systematic searches will take place of the specialist health economic data sources such as DARE, HTA Database (University of York), NHS EED and the Office for Health Economics HEED database. Economics filters used by the NHS CRD to populate the NHS EED database will be adapted to other databases.

2.4 Epidemiological modelling

A key component of the project is the identification and development of an epidemiological model for the natural history (in terms of diabetes, CVD, colorectal cancer, etc. and their sequelae) of individuals who are obese. Whilst there have been a number of meta-analyses published which have considered the risk of these outcomes in obese individuals, use of Individual Patient Data (IPD) is required so that (a) the risk can be estimated at all levels of BMI, and not just the categorisations often reported, e.g. 25–29.9, 30+ etc., and (b) the risks of specific outcomes may be estimated within a competing risks framework, whilst at the same time taking account of the expected correlation between the various outcomes.

The development of a statistical model relating BMI to clinical outcomes will be undertaken using the General Practice Research Database (GPRD – www.grpd.com). *Figure 1* shows an illustrative model (this may be either Markov or semi-Markov – see section 2.6 below) of a patient pathway for Otherwise Healthy Obese (OHO) individuals, and with the underling transition rates (λ_1,…,λ_5) estimated from GPRD as a function of BMI (and time if semi-Markov).

However, there is also existing evidence (from IPD analyses) available regarding the risk of various clinical events in relationship to BMI (especially CVD and diabetes) {Bogers *et al* 2007} and synthesis of the results from GPRD and reported summary data will also be undertaken {Sutton & Abrams 2001; Sutton *et al* 2007}.

The GPRD will also be used to explore the effect of the three drugs in general practice – both in terms of clinical effectiveness (which will then be compared to the results of the systematic review), but also the effect of patients stopping treatment, i.e. to determine the rate at which they return to their original BMI trajectory or otherwise.

The Health Survey for England (HSE) will be used to establish the distribution of BMI in those individuals who are obese (BMI > 30), and to which the risk models developed via GPRD will be applied in order to populate the initial transitions from an obese state to the various health states (representing the clinical events) in the cost-effectiveness model (see Section 2.6 below), and to which the clinical effectiveness estimates (derived from the systematic review) may then be applied. For example, in *Figure 2*, applying the estimated clinical effect (in terms of reduction in

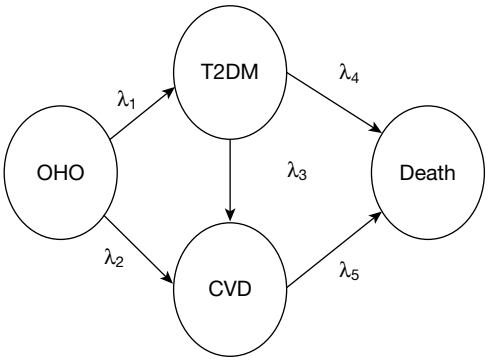


FIGURE 1 Illustrative Markov model for Otherwise Healthy Obese (OHO) individuals.

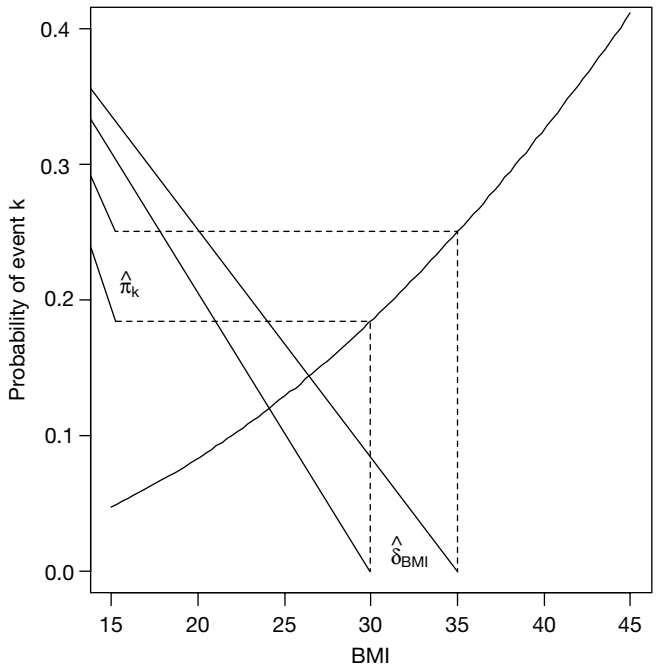


FIGURE 2 Relationships between BMI and probability of an event k.

BMI) δ_{BMI} obtained from the systematic review and meta-analysis to individuals will enable the corresponding change in the risk of the various events being considered to be estimated, i.e. π_k.

2.5 Systematic review methods

A) Clinical data

A key objective of the proposed study is to conduct a systematic review of the published evidence on the pharmacological agents Orlistat, Sibutramine and Rimonabant. This will also include a detailed systematic review of evidence on the adverse event profile of each agent.

The reviews of clinical effectiveness will update those contained in the systematic reviews of Sibutramine and Orlistat {HTA 31, HTA 22} and the industry submission for Rimonabant.{ACD Rimonabant} Obesity impacts on a wide range of health and social care professionals in a wide variety of settings. While the emphasis will be on UK clinical practice, non-UK evidence on effectiveness and outcomes will also be considered.

a) Search strategy (example from EMBASE):

The search strategy will use the following terms:

1, obesity.tw, 2, obese.tw 3, obesity/4, obesity, morbid/5, or/1–4 6, orlistat 7, sibutramine 8, rimonabant 9, anti-obesity agents/10, Tetrahydrolipstatin/11, sibutramine/12, rimonabant/13, or/6–12 14, 5 and 13

Plus methodological filters as described above to locate high quality clinical effectiveness and cost-effectiveness studies. The results of the searches will be stored in a Reference Manager database.

b) Inclusion/exclusion criteria

- *Types of studies:* Randomised controlled trials (RCTs), incorporating any duration of therapy and any length of follow-up will be considered for inclusion in the review.
- *Participants:* i) RCTs recruiting adults (aged 18 years) defined as being overweight or obese. ii) RCTs recruiting adults wishing to maintain weight loss, having been previously overweight or obese. iii) Trials involving specific patient groups such as those with diabetes, hypertension or hyperlipidaemia will be included in the review, provided they meet the above criteria.
- *Interventions*: i) Evaluations of Orlistat, Sibutramine or Rimonabant used to treat overweight/obese patients or to maintain weight loss in previously overweight or obese patients. ii) Orlistat, Sibutramine or Rimonabant may be combined with other strategies such as dietary restriction or behavioural programmes. iii) Participants in control groups may receive placebo, an alternative anti-obesity pharmacological agent or an alternative anti-obesity intervention (e.g. based on dietary regimen, physical activity or behavioural modification).
- Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa will be excluded.
- In trials where overweight/obese participants were recruited as well as those with the above eating disorders, only those where results were presented separately for the overweight/obese participants will be included.

c) Outcomes

The primary outcome of the review will be an assessment of obesity/overweight status as measured by changes in body weight, fat content or fat distribution:

- Measures of weight change include absolute weight change and percentage weight change relative to baseline.
- Measures of fat content include BMI, ponderal index, skinfold thickness, fat-free mass, body percentage and fat change relative to baseline.
- Measures of fat distribution including changes in waist size, waist–hip ratio and girth–height ratio relative to baseline.

Secondary outcomes of the review will be a) physiological changes occurring in association with changes in body weight/fat content/fat distribution such as changes in lipid profiles, glycaemic control among those with diabetes, and blood pressure, b) patient-related quality of life, c) information on adverse effects and d) costs.

d) Review methods

- References identified by the literature searches will be sifted in three stages. They will first be screened for relevance by title. The abstracts of those which are not excluded at this stage will then be read and finally, all manuscripts which seem to be potentially relevant will be

obtained for a more detailed appraisal. Sifting will be undertaken by one reviewer, and to ensure consistency a sample of references will be checked by a second reviewer. All decisions will be coded and recorded in the Reference Manager database.

- Studies will be categorised according to the type of participant (see inclusion criteria). Data extraction will be undertaken by one reviewer, using customised data extraction forms, and checked by a second reviewer. Discrepancies will be discussed, and any which cannot be resolved will be referred for discussion to the study team. Data extraction will cover the design and conduct of trials, characteristics of participants and interventions, and outcomes.
- Quality checklists will be used to appraise each article included. The quality of randomised controlled trials will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination. Non-randomised forms of evidence of clinical effectiveness such as observational studies will be assessed using the Downs and Black checklist.{Tooth 2005} Attrition rates will be assessed and discussed as previous reviews have noted high attrition rates.
- Heterogeneity among the results will be explored with consideration given to the following: patient characteristics, study setting, patient selection, and outcome measures.
- Summary statistics will be derived for each study and a weighted average of the summary statistics will be computed across the studies. Statistical heterogeneity will be assessed using the *I*-squared measurement. The studies will be assessed clinically and methodologically to assess whether it is reasonable to meta-analyse the data. If so, the more conservative random-effects model will be used to account for small clinical and methodological variations between very similar high quality trials. Data from studies that score poorly on the quality assessment; or studies that are found to be statistically heterogeneous will not be combined. In these cases further investigation will be undertaken to identify factors that could potentially explain the heterogeneity. In addition, sensitivity analyses will be conducted to assess the impact of including these studies.

As no 'head-to-head' RCTs are expected (of the three drugs under consideration), a synthesis of the available evidence using indirect meta-analysis methods will be used {Caldwell *et al* 2005}. However, in elaborating the network to include other interventions (used either as a control intervention in pharmacological trials or as additional arms in such trials) Bayesian Mixed Treatment Comparison methods will almost certainly have to be used.{Salanti *et al* 2007;Lu & Ades, 2004} The analysis will incorporate both direct and indirect evidence to enable comparisons to be made between treatments, including not only estimation of all pair-wise comparisons, but also ranking of treatments in terms of clinical effectiveness. As part of the MTC analysis further issues will need to be addressed, including outcomes reported at multiple and different time points,{Lu *et al* 2007}, the fact that there will be heterogeneity in reporting, both in terms of outcome, e.g. BMI, weight change, hip-to-waist ratio {Nam 2007; Riley 2007}, change from baseline or otherwise {Abrams 2005}, extension of the network of evidence to include other comparators that have been evaluated in obese patients {Salanti 2007} and consistency of evidence {Lu & Ades 2006}. In addition there will be an assessment of publication bias (Sutton 2000) and exploration of whether clinical effectiveness varies with baseline obesity, e.g. BMI. The analysis will be done by the Department of Health Sciences at the University of Leicester, using the freely available software WinBUGS {Spiegelhalter, 2002}.

B) Cost-effectiveness data

A systematic review of cost-effectiveness literature will be performed with the objective of identifying and critically reviewing all English language economic evaluations of Orlistat, Sibutramine or Rimonabant. The studies identified will be used to inform assumptions concerning the structure and data sources employed within the decision-analytic model.

a) Search strategy

The search strategy will use the following terms: cost benefit, cost effectiveness, cost utility, cost consequences, cost minimisation, economic evaluation, quality of life, utility, incremental cost effectiveness analysis, incremental cost effectiveness ratio, net present value, incremental net benefit; combined with the search terms used in the effectiveness literature search strategy. Sensitive searching (e.g. economics [ec] as a floating subheading) will be used to pick up costs associated with the health conditions. The results of the searches will be stored in a Reference Manager database.

b) Inclusion criteria

English language papers reporting cost-effectiveness results in terms of cost per QALY or cost per life year gained for the three interventions Orlistat, Sibutramine or Rimonabant.

c) Screening strategy

All abstracts obtained by the computer search will be reviewed for relevance by the two economic analysts. Any disagreement will be resolved by discussion. All papers identified as relevant at the end of the abstract screening process will be obtained and entered into the quality assessment process. The results of the abstract screening will be recorded in the Reference Manager database, including the reason for excluding any paper from the quality assessment stage of the review.

Once papers selected for inclusion in the review have been obtained, a hand search of the reference lists will be undertaken to identify any potentially relevant papers not identified by the search of the literature databases. Any additional papers will be obtained and subjected to the abstract review process prior to inclusion or exclusion from the quality assessment process.

d) Quality assessment

Relevant studies will be critically appraised using the standard economic evaluation and modelling checklists.{Drummond, Eddy 1985} For papers reporting economic evaluations alongside clinical trials, the Drummond checklist will be supplemented with reference to the Good Practice Guidance produced by the ISPOR Task Force on Economic evaluations alongside clinical trials.{Weinstein 2003}

Additional searches will be conducted to identify evidence on quality of life (QoL) in obese individuals, natural history of weight gains, weight regain and relationships between weight changes and co-morbidities such as CHD and diabetes.

2.6 Decision analytic modelling

a) Analyses of an existing database of clinical information from primary care

An existing database of clinical information from primary care will be analysed (SPSS versions 12) using usual statistical techniques. Demographics and clinical characteristics will be discussed using the main descriptive statistics: mean standard deviation, median and range. Correlations and associations between variables will be explored using the Pearson correlation coefficient with significance set at $p < 0.01$. (see Section 2.4 above).

b) Proposed model structure

The aim will be to examine the cost-effectiveness of the three anti-obesity agents currently licensed in the UK in terms of the incremental quality adjusted life years (QALY) gained. The systematic review of published cost-effectiveness studies together with the MTC synthesis and epidemiological modelling will be used to inform the development of a cost-effectiveness model. The form of the model will be determined by the specification of the patient pathway, the

evidence from the literature reviews and the results from the GPRD and HSE evaluations. The exact clinical pathway will be determined through discussions with the clinical experts within the study team. It is likely that a Markov will be appropriate and the model structure and modelling techniques will draw on the team's experience in performing economic evaluations involving populations who are obese, and populations with diabetes and/or CVD.{Galani 2007, Ward 2007, Ara 2007, Ara 2008, Waugh 2007; Whitfield 2006} The results from the GPRD risk models will be integrated within the model structure. Where evidence permits, treatment specific transitions to co-morbidities such as cardiovascular events and diabetes will be incorporated to reflect their differing adverse effect profiles.

i) Parameter estimates: A full list of parameters will be constructed and the clinical and cost-effectiveness literature will be searched for evidence on each parameter. The relationships between changes in BMI and co-morbidities such as CVD and diabetes will be informed by the epidemiological model using the results of the GPRD and the HSE analyses while the results of the Bayesian Mixed Treatment Comparison will inform clinical efficacy. Health related quality of life evidence will be sought for each health state. Data on cost parameters will be obtained from national data sources such as the NHS Reference cost data set and the PSSRU Costs of Health and Social Care.{Netten, Reference costs} Only direct costs relevant to the NHS and PSS will be included in the health economic analysis. All costs and benefits will be discounted at 3.5%. Additional searches will be undertaken for key parameters in addition to those listed above.

ii) Valuation of health outcomes: A recently published review of utility values for obesity found that, while studies showed a negative relationship between Body Mass Index and utility, there was a wide variation in the estimates.{Dixon 2004} Dixon *et al.* concluded the choice of utility measure can be instrumental in whether the cost per quality adjusted life year estimate falls above or below a funding threshold. The scoping search indicated that published studies do not always use the generic preference-based measures of health required to meet the proposed NICE reference case for economic evaluations (the EQ-5D). The utility review will be updated and where possible non EQ-5D quality of life values will be mapped onto the EQ-5D generic preference-based index using published relationships of standard mapping techniques.{Ara 2008} {Brazier 2004}

c) Presentation of model results

The model results will be presented both in terms of the costs and consequences of each individual agent prescribed in conjunction with lifestyle advice such as diet and exercise as currently offered in primary care within the UK. Results will also be presented in terms of incremental cost per life year and incremental cost per QALY for Orlistat vs. Sibutamine vs. Rimonabant.

i) Cost–consequence analyses: The model will be constructed to evaluate the differential impact on clinically relevant outcomes such as cardiovascular events and diabetes incidence rates based on the surrogate trial outcomes such as lipid and glucose profiles and HbA_{1c} levels. The impact of adherence and compliance for each of the treatments will be estimated using the results of the literature searches. The differing adverse event profiles will be quantified using the data from the literature searches supported by the clinical experts in the team.

ii) Uncertainty analyses: Uncertainty surrounding the health effects and costs will be explored. Simple one-way/multi-way sensitivity analysis will be undertaken to identify key determinants of cost-effectiveness. In addition, parameter uncertainty will be examined through probabilistic sensitivity analysis. Uncertainty regarding the value of each parameter in a model will be expressed as a probability distribution, and the impact of this uncertainty will be propagated

through the model using Monte Carlo simulation. The results of the analysis will be presented as incremental cost-effectiveness ratios, scatterplots on the cost-effectiveness plane, and cost-effectiveness acceptability curves.

d) Analysis of value of information

The value of information (or expected value of information EVI) approach describes the costs of the current uncertainty in the results. It can be used to provide information concerning the benefits which may be foregone as a result of withdrawing treatment. The difference between the estimated costs of uncertainty can then be compared to the relevant costs of undertaking primary data collection to estimate the net benefits associated with prospective research. Global and Partial Value of Information will be conducted using the methods described by Felli and Hazen {Felli 1998; Felli 1999} and Brennan and Kharroubi {Brennan 2007} respectively. The analysis will assume lambda = £20,000 based upon the NICE Methods of Health Technology Appraisal.

Project timescales

July 2008
First project team meeting

July 2008 – December 2008
Establish systematic review protocol
Literature searches and document acquisition for systematic reviews
Critical appraisal of literature retrieved from systematic reviews
Data extraction and meta-analysis
Produce reports from systematic reviews and meta-analysis

September 2008
Obtain database of clinical practice from primary care

October 2008 – December 2008
Analyse existing database of clinical practice from primary care
Finalise decision analytic model structure

December 2008
Produce progress report

January 2009 – April 2009
Develop decision analytic model
Assess cost-effectiveness and cost–utility of the three comparators
Undertake expected value of information analyses

April 2009
Produce draft report

May 2009 – June 2009
Peer review and final amendments to report

31st July 2009
Submit final report to NCCHTA
Preliminary findings to be presented at the 17th European Conference on Obesity (May 2009)

EXPERTISE

This is a collaborative project between a wide range of experts, intended to ensure that findings are valid, reliable and feasible in the NHS clinical setting. Our team includes clinical health experts in diabetes and obesity from primary care backgrounds and methodological experts in systematic reviewing, economics, health services research, public health medicine and information retrieval. Many of the team have a strong history of working together on collaborative reviews funded by HTA, NHS Service Delivery and Organisation (SDO) and National Co-ordinating Centre for Research Methodology (NCCRM) programmes. Together they will form a panel to guide study design, literature searching and model development; to provide independent review of articles for the literature review; and to assist in writing up and disseminating the results.

Both the School of Health and Related Research (ScHARR) at the University of Sheffield and the Department of Health Sciences at the University of Leicester are multidisciplinary health services research units carrying out a full range of primary and secondary research for major funding agencies such as the Department of Health, the former NHS Executive Trent, the NHS HTA Programme, the NHS SDO Programme and the Medical Research Council. The ScHARR staff involved in this project will be Roberta Ara (project lead), John Brazier (Health Economics), Michael Gillett (Economic Modeller), and Andrew Booth (Information Resources). The Leicester staff will include: Keith Abrams (Medical Statistics), Alex Sutton (Medical Statistics), Nicola Cooper (Health Economics), Kamlesh Khunti (Clinical expert) and Melanie Davies (Clinical expert).

Team members

Roberta Ara (RA) is a research fellow and has project managed a number of HTA and consultancy studies. She has experience of modelling the cost-effectiveness of an obesity treatment (sibutramine), and several cardiovascular treatments, leading reports for NICE and the HTA. RA will be directly responsible for supervising the project and building the mathematical model and has access to the full range of technical support and experience offered by ScHARR.

John Brazier (JB) is a Professor in Health Economics and is a leading expert in health related quality of life measurements with a particular interest in preference based measures. John has extensive experience in health economics and in particular in the quality of life and has published extensively in this area. He has led and contributed to numerous HTA reviews and lectures worldwide on quality of life evidence used in economic evaluations.

Keith Abrams (KA) is a Professor of Medical Statistics and is a leading expert in the development and use of Bayesian methods in healthcare evaluation (clinical trials, meta-analyses, and comprehensive decision modelling). He has been involved in numerous HTA evidence synthesis/modelling projects, and has published extensively in both the methodological and clinical literature, and has co-authored two books on *Methods for Meta-Analysis in Medical Research* and *Bayesian Approaches to Clinical Trials and Health-care Evaluation*, together with co-editing one of the first texts on *Methods in Evidence-Based Healthcare*.

Alex Sutton (AS) is a Reader in Medical Statistics and a leading expert in meta-analysis with a particular interest in synthesis for decision modelling. Alex has published extensively both methodological and substantive papers on evidence synthesis and is an author on the following two well regarded books: "Meta-analysis in medical research" and "Publication bias in meta-analysis: Prevention, assessment and adjustment".

Nicola Cooper (NC) is a senior research fellow with expertise in both health economics and medical statistics, and her research focuses on the interface of the two. She is currently undertaking an MRC fellowship in 'The use of evidence synthesis and uncertainty modelling in economic evidence-based health related decision models' and has applied these methods in numerous publications. Together with AS and KA, Nicola has developed and delivered many advanced 3- and 5-day courses on evidence synthesis for decision modelling worldwide.

Andrew Booth (AB) is Director of the Information Resources at ScHARR, a specialist information resource designed to support the needs of evidence based healthcare clinical effectiveness and systematic reviews. AB has extensive experience undertaking comprehensive literature searches, and has contributed to numerous systematic reviews, including various HTA reviews and NICE rapid appraisals.

Kamlesh Khunti (KK) and **Melanie Davies (MD)** lead a research group in the Department of Health Sciences and Cardiovascular Sciences undertaking important research into the early identification and intervention in people with diabetes and pre-diabetes. KK and MJD are co-directors of the South East Midlands Diabetes Network and are PIs on several major studies including the Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) Study, one of the world's largest epidemiological cohort studies of diabetes. Data from this study has informed the recent proposals by the Department of Health on Vascular Screening in primary care. They are also PIs on a NIHR funded programme grant on prevention of type 2 diabetes in high risk populations. They will bring clinical expertise in metabolic syndromes (obesity, diabetes and cardiovascular disease).

Michael Gillett (MG) is a research fellow in health economic modelling and has led numerous economic evaluations for both diabetic and cardiovascular populations.

Angie Rees is an up and coming researcher in information studies. She has undertaken the searches for a number of prominent reviews and will work under the supervision of AB.

JUSTIFICATION OF SUPPORT REQUIRED

The budget will be based at a higher education institution and will attract full economic costs, so 80% support is requested. It will support 60% of the Principal Investigator's (RA) time. She will be responsible for day-to-day running of the project, the economic evaluation, writing of reports and dissemination of the findings. Keith Abrams (Medical Statistician) will co-ordinate the research at Leicester and will be involved in advising on the clinical review, the epidemiology model and the synthesis of the evidence (9%). Alex Sutton and Nicola Cooper will be involved advising on the clinical review, the epidemiology model and the synthesis of the evidence from the GPRD database (4%, 4%). A part time researcher will be employed to conduct the clinical review and epidemiological reviews (83%). Kamlesh Khunti (5%) and Melanie Davies (2%) will provide expert clinical advice during the project and will provide access to the GPRD database. Andrew Booth will advise on the design and conduct of searches and the design and conduct of the qualitative elements of the systematic review (1%). John Brazier will advise on quality of life evidence and Michael Gillett (economic modeller) will be involved in the project in an advisory capacity for the diabetes economic components (5%). Angie Rees will design and conduct the literature searches (4%). Clerical support (Andrew Tattersall) is required to co-ordinate inter-library loans (2%). Clerical staff (to be appointed) will provide administration duties (20%).

Office costs comprise of: computing consumables £339; stationary £407; postage £203; photocopying £271. The budget will cover PCs (£1,751); contributions to bibliographic database

subscriptions not currently available through the University of Sheffield (either connection or to pay external providers) £200; and inter-library loans (obtaining articles from other libraries) £1,300. Also included is £15,000 for the GPRD database. The budget will also cover travel and subsistence for members of the team (£1,000) for eight meetings over the project (either in Sheffield or in Leicester). Also included are conference and travel costs for 2 members of the team to present preliminary findings at the 17th European Conference in Amsterdam (£2,400).

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ISSN 1366-5278