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Drug interventions for the treatment of obesity in children and adolescents (Review)

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Drug interventions for the treatment of obesity in children and adolescents.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD012436.
DOI: 10.1002/14651858.CD012436.

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[Intervention Review]

Drug interventions for the treatment of obesity in children and adolescents

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Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: New, published in Issue 11, 2016.
Review content assessed as up-to-date: 15 March 2016.

Citation: Mead E, Atkinson G, Richter B, Metzendorf MI, Baur L, Finer N, Corpeleijn E, O'Malley C, Ells LJ. Drug interventions for the treatment of obesity in children and adolescents. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD012436. DOI: 10.1002/14651858.CD012436.

ABSTRACT

Background

Child and adolescent obesity has increased globally, and can be associated with significant short- and long-term health consequences.

Objectives

To assess the efficacy of drug interventions for the treatment of obesity in children and adolescents.

Search methods

We searched CENTRAL, MEDLINE, Embase, PubMed (subsets not available on Ovid), LILACS as well as the trial registers ICTRP (WHO) and ClinicalTrials.gov. Searches were undertaken from inception to March 2016. We checked references and applied no language restrictions.

Selection criteria

We selected randomised controlled trials (RCTs) of pharmacological interventions for treating obesity (licensed and unlicensed for this indication) in children and adolescents (mean age under 18 years) with or without support of family members, with a minimum of three months' pharmacological intervention and six months' follow-up from baseline. We excluded interventions that specifically dealt with the treatment of eating disorders or type 2 diabetes, or included participants with a secondary or syndromic cause of obesity. In addition, we excluded trials which included growth hormone therapies and pregnant participants.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data following standard Cochrane methodology. Where necessary we contacted authors for additional information.

Main results

We included 21 trials and identified eight ongoing trials. The included trials evaluated metformin (11 trials), sibutramine (six trials), orlistat (four trials), and one trial arm investigated the combination of metformin and fluoxetine. The ongoing trials evaluated metformin (four trials), topiramate (two trials) and exenatide (two trials). A total of 2484 people participated in the included trials, 1478 participants were randomised to drug intervention and 904 to comparator groups (91 participants took part in two cross-over trials; 11 participants not specified). Eighteen trials used a placebo in the comparator group. Two trials had a cross-over design while the remaining 19 trials were parallel RCTs. The length of the intervention period ranged from 12 weeks to 48 weeks, and the length of follow-up from baseline ranged from six months to 100 weeks.

Trials generally had a low risk of bias for random sequence generation, allocation concealment and blinding (participants, personnel and assessors) for subjective and objective outcomes. We judged approximately half of the trials as having a high risk of bias in one or more domain such as selective reporting.

The primary outcomes of this review were change in body mass index (BMI), change in weight and adverse events. All 21 trials measured these outcomes. The secondary outcomes were health-related quality of life (only one trial reported results showing no marked differences; very low certainty evidence), body fat distribution (measured in 18 trials), behaviour change (measured in six trials), participants' views of the intervention (not reported), morbidity associated with the intervention (measured in one orlistat trial only reporting more new gallstones following the intervention; very low certainty evidence), all-cause mortality (one suicide in the orlistat intervention group; low certainty evidence) and socioeconomic effects (not reported).

Intervention versus comparator for mean difference (MD) in BMI change was -1.3 kg/m^2 (95% confidence interval (CI) -1.9 to -0.8; P < 0.00001; 16 trials; 1884 participants; low certainty evidence). When split by drug type, sibutramine, metformin and orlistat all showed reductions in BMI in favour of the intervention.

Intervention versus comparator for change in weight showed a MD of -3.9 kg (95% CI -5.9 to -1.9; P < 0.00001; 11 trials; 1180 participants; low certainty evidence). As with BMI, when the trials were split by drug type, sibutramine, metformin and orlistat all showed reductions in weight in favour of the intervention.

Five trials reported serious adverse events: 24/878 (2.7%) participants in the intervention groups versus 8/469 (1.7%) participants in the comparator groups (risk ratio (RR) 1.43, 95% CI 0.63 to 3.25; 1347 participants; low certainty evidence). A total 52/1043 (5.0%) participants in the intervention groups versus 17/621 (2.7%) in the comparator groups discontinued the trial because of adverse events (RR 1.45, 95% CI 0.83 to 2.52; 10 trials; 1664 participants; low certainty evidence). The most common adverse events in orlistat and metformin trials were gastrointestinal (such as diarrhoea, mild abdominal pain or discomfort, fatty stools). The most frequent adverse events in sibutramine trials included tachycardia, constipation and hypertension. The single fluoxetine trial reported dry mouth and loose stools. No trial investigated drug treatment for overweight children.

Authors' conclusions

This systematic review is part of a series of associated Cochrane reviews on interventions for obese children and adolescents and has shown that pharmacological interventions (metformin, sibutramine, orlistat and fluoxetine) may have small effects in reduction in BMI and bodyweight in obese children and adolescents. However, many of these drugs are not licensed for the treatment of obesity in children and adolescents, or have been withdrawn. Trials were generally of low quality with many having a short or no post-intervention follow-up period and high dropout rates (overall dropout of 25%). Future research should focus on conducting trials with sufficient power and long-term follow-up, to ensure the long-term effects of any pharmacological intervention are comprehensively assessed. Adverse events should be reported in a more standardised manner specifying amongst other things the number of participants experiencing at least one adverse event. The requirement of regulatory authorities (US Food and Drug Administration and European Medicines Agency) for trials of all new medications to be used in children and adolescents should drive an increase in the number of high quality trials.

PLAIN LANGUAGE SUMMARY

Drug interventions for the treatment of obesity in children and adolescents

Review question

Do drug (medicine) interventions reduce weight in obese children and adolescents and are they safe?

Background

Across the world more children and adolescents are becoming overweight and obese. These children and adolescents are more likely to have health problems, both while as children or adolescents and in later life. More information is needed about what works best for treating this problem recognising that so-called lifestyle changes (diet, exercise and counselling) have limited efficacy.

Study characteristics

We found 21 randomised controlled studies (clinical studies where people are randomly put into one of two or more treatment groups) comparing various drugs plus a behaviour changing intervention such as diet, exercise or both (= intervention groups) usually with placebo (a pretend drug) plus a behaviour changing intervention (= control groups). We also identified eight ongoing studies (studies which are currently running but not completed yet). A total of 2484 children and adolescents took part in the included studies. The length of the intervention period ranged from 12 weeks to 48 weeks, and the length of follow-up ranged from six months to 100 weeks.

Key results

The included studies investigated metformin (10 studies), sibutramine (six studies), orlistat (four studies) and one study group evaluated the combination of metformin and fluoxetine. The ongoing studies are investigating metformin (four studies), topiramate (two studies) and exenatide (two studies).

Most studies reported on body mass index (BMI) and bodyweight: BMI is a measure of body fat and is calculated from weight and height measurements (kg/m^2). In children, BMI is often measured in a way that takes into account sex, weight and height as children grow older (BMI z score). The average change in BMI across control groups was between a 1.8 kg/m^2 reduction to a 0.9 kg/m^2 increase, while across all intervention groups the average reduction was more pronounced (1.3 kg/m^2 reduction). The same effect was observed for weight change: on average, children and adolescents in the intervention groups lost 3.9 kg more weight than the children and adolescents in the control groups. Study authors reported an average of serious side effects in 24 per 1000 participants in the intervention groups compared with an average of 17 per 1000 participants in the control groups. The numbers of participants dropping out of the study because of side effects were 40 per 1000 in the intervention groups and 27 per 1000 in the control groups. The most common side effects in the orlistat and metformin studies were gut (such as diarrhoea and mild tummy pain). Common side effects in the sibutramine trials included increased heart rate (tachycardia), constipation and high blood pressure. The fluoxetine study reported dry mouth and loose stools. One study reported health-related quality of life (a measure of physical, mental, emotional and social functioning) and found no marked differences between intervention and control. No study reported the participants' views of the intervention or socioeconomic effects. Only one study reported on morbidity (how often a disease occurs in a specific area) associated with the intervention, where there were more gallstones after the orlistat treatment. Study authors reported one suicide in the orlistat intervention group. However, studies were not long enough to reliably investigate death from any cause. No study investigated drug treatment for children who were only overweight (obese children have a much higher weight, BMI or BMI z score than children being overweight).

This evidence is up to date to March 2016.

Quality of the evidence

The overall certainty of the evidence was low or very low, mainly because there were only a few studies per outcome measurement, the number of included children or adolescents was small, and due to variation in the results of the studies. In addition, many children or adolescents left the studies before the study had finished.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Drug interventions for the treatment of obesity in children and adolescents

Population: obese children and adolescents
Settings: mainly outpatient settings
Intervention: metformin, orlistat, sibutramine usually combined with behaviour changing interventions
Comparison: placebo or no placebo usually with behaviour changing interventions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Comparator	Pharmacological intervention				
a. BMI (kg/m^2) Follow-up: 6 months (14 trials) - 12 months (2 trials) **b. Body weight (kg)** Follow-up: 6 months (10 trials) - 12 months (1 trial)	a. The mean reduction in BMI ranged across control groups from -1.8 to +0.9 b. The mean reduction in weight ranged across control groups from -3.8 kg to +4.9 kg	a. The mean reduction in BMI in the intervention groups was **-1.3 higher** (-1.9 to -0.8 higher) b. The mean reduction in weight in the intervention groups was **-3.9 kg higher** (-5.9 kg to -1.9 kg higher)	-	a. 1884 (16) b. 1180 (11)	a. ⊕⊕◯◯ **Low**[a] b. ⊕⊕◯◯ **Low**[a]	-
Adverse events a. Serious adverse events b. Discontinuation of trial because of adverse events Follow-up: mostly 6 months, maximum 100 weeks (1 trial)	a. **17 per 1000** b. **27 per 1000**	a. **24 per 1000** (11 to 55) b. **40 per 1000** (23 to 69)	a. **RR 1.43** (0.63 to 3.25) b. **RR 1.45** (0.83 to 2.52)	a. 1347 (5) b. 1664 (10)	a. ⊕⊕⊕◯ **Low**[b] b. ⊕⊕⊕◯ **Low**[b]	All trials reported if adverse events occurred; however, only 7/20 trials reported the number of participants who experienced at least 1 adverse event

Health-related quality of life 3 questionnaires (1 trial) and SF-36 (1 trial) Follow-up: 6 months	See comment	See comment	See comment	86 (2)	⊕◯◯◯ **V ery low**[c]	Results were only reported for SF-36 (1 trial on sibutramine, 46 children), there were no marked differences between intervention and comparator groups
All-cause mortality Follow-up: mostly 6 months, maximum 100 weeks (1 trial)	See comment	See comment	See comment	2176 (20)	⊕⊕◯◯ **L ow**[d]	1 suicide in the orlistat intervention group
Morbidity	See comment	See comment	See comment	533 (1)	⊕◯◯◯ **V ery low**[e]	Only 1 trial investigated morbidity defined as illness or harm associated with the intervention (Chanoine 2005). In the orlistat group 6/352 (1.7%) participants developed new gallstones compared with 1/181 (0.6%) in the placebo group
Socioeconomic effects	See comment	See comment	See comment	See comment	See comment	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **RR:** risk ratio; **SF-36:** Short-Form Health Survey 36 items.

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of potential other risk of bias, inconsistency and imprecision (see Appendix 13).
[b]Downgraded by two levels because of potential reporting bias, inconsistency and imprecision (see Appendix 13).
[c]Downgraded by three levels because of one trial only with a small number of participants and imprecision (see Appendix 13).
[d]Downgraded by two levels because of short follow-up periods and no trial was powered to investigate mortality (see Appendix 13).
[e]Downgraded by three levels because of one trial only and imprecision (see Appendix 13).

BACKGROUND

The prevalence of overweight and obese children and adolescents has increased throughout the world, presenting a global public health crisis (Ng 2014; WHO 2015). It is not only a problem in high-income countries, but a high prevalence has also been found in low- and middle-income countries (Wang 2012). Evidence suggests that rates are slowing down or plateauing in high-income countries; however, they are still rising in low- or middle-income countries and prevalence continues to remain high in both (Olds 2011; Rokholm 2010). The Global Burden of Disease Study 2013 reported a mean of 24% of boys and 23% of girls from high-income countries to be overweight or obese, whilst the estimated percentages of boys and girls in low- or middle-income countries who are overweight or obese are 13% each (Ng 2014). This report used the International Obesity Task Force (IOTF) age and sex standardised cut points (Cole 2000). Furthermore, young children also have a high prevalence of being overweight or obese with an estimated 42 million overweight or obese children under five years of age in 2010 (approximately 35 million living in low- or middle-income countries - De Onis 2010); these statistics were based on the World Health Organization (WHO) growth standard (WHO 2006).

An additional concern in some high-income countries, such as the USA (Kelly 2013; Skinner 2014) and England (CMO 2014; Ells 2015a), is the rise in severe paediatric obesity. In England during 2012/2013, 2.9% of girls and 3.9% of boys, aged 10 to 11 years, were classified as severely obese (body mass index (BMI) UK90 99.6th centile or greater - Ells 2015a). In the USA from 2011 to 2012, 2.1% of youths (aged 2 to 19 years) were categorised as class 3 obese (Centers for Disease Control and Prevention growth charts: BMI 140% of greater of the 95th percentile or BMI 40 kg/m^2 or greater - Skinner 2014).

Whilst the IOTF published an international definition for paediatric severe (morbid) obesity in 2012 (Cole 2012), often severe obesity prevalence is reported using country-specific cut points making international comparisons difficult. Data from the USA (Skinner 2014) and England (Ells 2015a) have shown that severe paediatric obesity prevalence varies by socioeconomic status and ethnicity, and may result in greater risk of adverse cardio-metabolic events and severe obesity in adulthood (Kelly 2013).

The prevalence of overweight and obese children is influenced by inequalities, where rates are higher in children from areas of high deprivation in high-income countries (Knai 2012; Shrewsbury 2008), and from more affluent areas in low- or middle-income countries (Lobstein 2004; Wang 2012). Other variables are also likely to influence obesity prevalence including age, sex and ethnicity, with varying rates found in different groups in the USA (Freedman 2006; Skinner 2014), England (HSCIC 2014), and New Zealand (Rajput 2014).

Description of the condition

Being overweight or obese in childhood is associated with many conditions which may affect both physical and psychosocial health. Such conditions include hypertension, insulin resistance and hyperlipidaemia in obese children and adolescents, also including very young children (Bocca 2013; Freedman 1999; Reilly 2003; Weiss 2004). The prevalence of type 2 diabetes has continued to increase in children and adolescents, with recent projections in the USA suggesting a potential quadrupling from 2010 to 2050 in the number of youths (aged less than 20 years old) with type 2 diabetes (Imperatore 2012; Pinhas-Hamiel 2005). Being overweight or obese in early childhood has also been linked to increased cardiovascular risk factors, such as high systolic blood pressure (Falaschetti 2010), with such risks factors also being present in people with type 2 diabetes (Maahs 2014). In addition medical conditions such as sleep apnoea, polycystic ovarian syndrome (PCOS) and poor pulmonary function have also been linked to childhood obesity (Dietz 1998; Ebbeling 2002; Lobstein 2004; Reilly 2003). Furthermore, childhood obesity has been shown to be strongly associated with nonalcoholic fatty liver disease (NAFLD), which is the most common cause of chronic liver disease in children and adolescents (Aggarwal 2014; Berardis 2014).

The condition can also affect the child's mental health and lead to early discrimination, low self-esteem and depression (Dietz 1998; Puhl 2007; Tang-Peronard 2008). There is also evidence that childhood obesity also tracks into adulthood (Parsons 1999; Singh 2008; Whitaker 1997), and hence is associated with an increased risk of ill health in later life (Reilly 2011).

Description of the intervention

Since childhood obesity can potentially have serious consequences on a child's health and well-being, it is very important to identify interventions which can treat obesity in both the short- and long-term. The purposes of such interventions are similar to treatment in adults whereby the primary aims are: to reduce energy intake, increase energy expenditure and decrease sedentary behaviour. However, the child's age and baseline degree of obesity should be taken into consideration before deciding the type, length and intensity of the intervention. This will allow the intervention to be more tailored to the target population and potentially increase the chances of success and reduce the likelihood of adverse events.

In recent years, only three drugs have been licensed for the treatment of adult obesity: rimonabant, sibutramine and orlistat. However, none of these were licensed for use in children (Petkar 2013). Rimonabant was withdrawn from the market due to psychiatric adverse events and sibutramine was suspended by the European Medicine Agency (EMA) and was withdrawn by the US Food and Drug Administration (FDA) in 2010 due to cardiovascular adverse effects; however, sibutramine is still licensed for treatment of obesity in Brazil. Orlistat has been approved by the FDA but only

for people over the age of 12 years (Sherafat-Kazemzadeh 2013). In England, National Institute for Health and Care Excellence (NICE) guidance recommends that orlistat should only be used in children under 12 years old in exceptional circumstances where severe comorbidities exist. Moreover, in children who are 12 years or older, treatment is only recommended if there are physical comorbidities such as sleep apnoea or severe psychological comorbidities (NICE 2014).

Metformin has been approved by the FDA to treat type 2 diabetes mellitus in both adults and children over the age of 10 years but does not have approval for treating obesity in children or adults (McDonagh 2014). However, an analysis of prescribing data in the UK in 2011 showed metformin has regularly been prescribed to treat childhood obesity, the main indication being PCOS (Hsia 2011). Other drugs which have also previously been used off-licence to treat obesity in children and adolescents include antidepressants such as fluoxetine and bupropion (Petkar 2013).

While weight loss alone may be of clinical and psychological benefit, additional health benefits may be achieved by the amelioration of obesity-related disorders, such as hyperglycaemia in type 2 diabetes (Pandey 2015), pain and mobility in osteoarthritis (Widhalm 2016), and improvement in obstructive sleep apnoea (Nespoli 2013). Weight loss may also reduce the risk factors for cardiovascular and metabolic disease (Halpern 2010), or even prevent the development of disease, for example type 2 diabetes (Power 2014). While registration of drugs usually does not require such clinical endpoints, people and health economic considerations increasingly demand evidence on more than just weight or BMI reduction, data that would be more difficult to establish in children and adolescents and have been poorly, if at all, studied.

Adverse effects of the intervention

One systematic review of pharmacological options for managing paediatric obesity stated that the most common adverse events when taking orlistat were gastrointestinal problems related to increased fat excretion (e.g. fatty or oily stools, increased defecation, soft stools, flatus, faecal leakage). Other adverse events included long-term fat-soluble deficiencies, decrease in vitamin D concentrations and asymptomatic gallstones (Boland 2015). The most frequent adverse events associated with metformin are gastrointestinal, some of which can be intolerable (McCreight 2016). A change in dose or duration may resolve these adverse effects (McDonagh 2014). Common adverse effects of sibutramine included dry mouth, headaches, constipation and insomnia (Cheung 2013). However, the drug has also been linked to increased risk of nonfatal stroke or myocardial infarction, as shown in the Sibutramine Cardiovascular Outcomes (SCOUT) trial (James 2010). Consequently, the drug was withdrawn from the market in numerous countries including the UK, USA and Australia.

How the intervention might work

Sibutramine is a serotonin and norepinephrine reuptake inhibitor. It works by reducing hunger and improving satiety leading to decreased food intake (Catoira 2010). Orlistat leads to the excretion of approximately 30% of ingested fat; it works by acting as a gastrointestinal lipase inhibitor (Yanovski 2014). Metformin is a biguanide derivative which activates adenosine monophosphate-activated protein kinase leading to the reduction of glucose production and absorption in the intestines and increasing insulin sensitivity. It is thought to reduce bodyweight by inhibiting fat cell lipogenesis and potentially may decrease food intake by increasing glucagon-like peptide (Matson 2012). Fluoxetine is an antidepressant which works by inhibiting serotonin re-uptake. It can result in weight loss by decreasing appetite and therefore inhibiting energy intake (Ye 2011). Hence, it is important to recognise that any drug that produces aversive taste or gastrointestinal adverse effects could produce weight loss by such adverse effects (Halford 2010).

Why it is important to do this review

In 2003, a systematic Cochrane Review was published entitled "Interventions for treating obesity in children" which assessed the effects of lifestyle interventions (dietary, physical activity, behavioural, or a combination of these) and included the analysis of childhood obesity treatment trials published up to July 2001 (Summerbell 2003). The second version of this Cochrane Review was published in 2009 providing an update to the 2003 review, and assessing the effects of pharmacological and surgical interventions (Oude Luttikhuis 2009).

To reflect the rapid growth in this field, the third update to this review has been split across six reviews focusing on the following treatment approaches: "Surgery for the treatment of obesity in children and adolescents" (Ells 2015b); "Drug interventions for the treatment of obesity in children and adolescents"; "Parent-only interventions for childhood overweight or obesity in children aged 5 to 11 years" (Loveman 2015); "Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in preschool children up to the age of 6 years" (Colquitt 2016); "Diet, physical activity and behavioural interventions for the treatment of overweight or obesity in school children from the age of 6 to 11 years"; and "Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in adolescents aged 12 to 17 years". This review in this series focuses on the efficacy of pharmacological interventions for obese children and adolescents. The review complements the Cochrane Review of "Long-term pharmacotherapy for obesity and overweight" (Padwal 2003), which does not provide randomised controlled trial (RCT) data on pharmacological interventions for children and adolescents.

The results of this current review and other systematic reviews in this series will provide information on which to underpin clinical

guidelines and health policy on the treatment of children and adolescents who are overweight or obese.

OBJECTIVES

To assess the effects of drug interventions for the treatment of obesity in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs where the length of the intervention had to be at least three months and the length of follow-up from baseline had to be a least six months.

Types of participants

We included trials evaluating obese children and adolescents with a mean age of less than 18 years at the commencement of the intervention. We excluded trials with pregnant or critically ill participants. We excluded interventions that specifically dealt with the treatment of eating disorders or type 2 diabetes, or included participants with a secondary or syndromic cause of obesity.

Types of interventions

We investigated any pharmacological intervention which aimed to treat paediatric obesity, using any of the following intervention versus control sequences, where the same letters indicate direct comparisons.

Intervention

- (a) Pharmacological intervention.
- (b) Pharmacological intervention plus other therapy.

Comparator

- (a1) Placebo.
- (a2) Usual care.
- (b1) Placebo plus other therapy.
- (b2) Usual care plus other therapy.

Concomitant therapies were required to be the same in both the intervention and comparator groups.

Summary of specific exclusion criteria

- Trials which included a growth hormone therapy as treatment for obesity.
- Trials which included pregnant participants.
- Trials which included participants who were critically ill.
- Trials where participants had a secondary or syndromic cause of obesity.
- Interventions that specifically dealt with the treatment of eating disorders or type 2 diabetes.
- Trials in which the aim was not to treat obesity in children or adolescents.
- Duration of intervention less than three months.
- Duration of follow-up less than six months.

Types of outcome measures

Primary outcomes

- Body mass index (BMI) and bodyweight.
- Adverse events.

Secondary outcomes

- Health-related quality of life and self-esteem.
- Body fat distribution.
- Behaviour change.
- Participants' views of the intervention.
- Morbidity.
- All-cause mortality.
- Socioeconomic effects.

Timing of outcome measurement

- BMI: defined as weight (kg) divided by height (m) squared, and bodyweight (kg): measured at baseline, 6, 12, 24 and more than 24 months.
- Adverse events: defined as an adverse outcome that occurred during or after the intervention but was not necessarily caused by it, and measured at any time during the trial.
- Health-related quality of life and self-esteem: evaluated by a validated instrument such as the Paediatric Quality of Life Inventory and measured at baseline, 6, 12, 24 and more than 24 months.
- Body fat distribution: defined by validated tools such as dual energy X-ray absorptiometry (DEXA), waist circumference, skin fold thickness, waist-to-hip ratio and bioelectrical impedance analysis and measured at baseline, 6, 12, 24 and more than 24 months.
- Behaviour change: evaluated by a validated instrument and measured at baseline, 6, 12, 24 and more than 24 months.
- Participants' views of the intervention: defined as documented accounts from participant feedback and measured at baseline, 6, 12, 24 and more than 24 months.

- Morbidity: defined as illness or harm associated with the intervention and measured at baseline, 6, 12, 24 and more than 24 months.
- All-cause mortality: defined as any death that occurred during or after the intervention and measured at any time during the trial.
- Socioeconomic effects: defined as a validated measure of socioeconomic status such as parental income or educational status and measured at baseline, 6, 12, 24 and more than 24 months.

'Summary of findings' table

We presented a 'Summary of findings' table to report the following outcomes, listed according to priority.

- BMI and bodyweight.
- Adverse events.
- Health-related quality of life.
- All-cause mortality.
- Morbidity.
- Socioeconomic effects.

Search methods for identification of studies

Electronic searches

We searched the following sources on 15 March 2016 from inception to the specified date.

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (CRSO).
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to 15 March 2016).
- PubMed (subsets not available on Ovid) (15 March 2016).
- Embase 1974 to 2016 Week 11.
- LILACS (15 March 2016).
- ClinicalTrials.gov (15 March 2016).
- WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) (15 March 2016).

For detailed search strategies, see Appendix 1. We continuously applied an email alert service for MEDLINE via OvidSP to identify newly published trials using the search strategy detailed in Appendix 1. If we detected additional relevant key words during any of the electronic or other searches, we modified the electronic search strategies to incorporate these terms and documented the changes. We placed no restrictions on the language of publication when searching the electronic databases or reviewing reference lists of identified trials.

Searching other resources

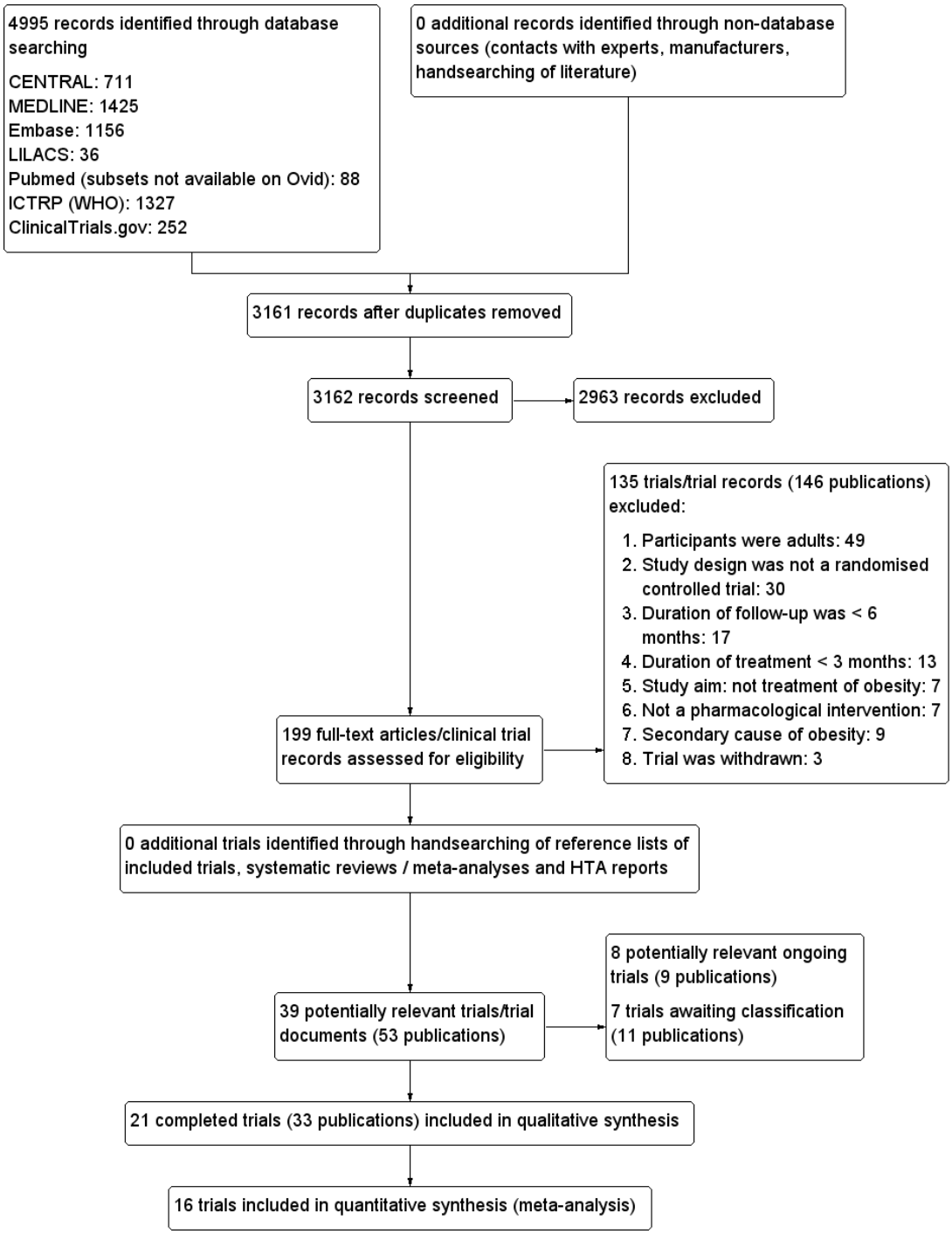
We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews, meta-analyses and health technology assessment reports.

Data collection and analysis

Selection of studies

To determine the trials to be assessed further, two review authors (of EM, LE, CO) independently scanned the abstract, title, or both, of every record retrieved by the searches. We obtained full-text articles of all those trials deemed potentially relevant for inclusion. We resolved any differences in opinion by consultation of a third review author (of GA, EC, LE). If there was an outstanding issue with the trial, we added the article to those 'awaiting assessment' and we contacted trial authors for clarification. We presented an adapted PRISMA flow diagram of trial selection (Figure 1) (Liberati 2009).

Figure 1. Trial flow diagram.



Data extraction and management

For trials that fulfilled the inclusion criteria, two review authors (of EM, LE, GA, NF, EC, LB, CO) independently extracted key participant and intervention characteristics and reported data on efficacy outcomes and adverse events using standard data extraction templates. We resolved any disagreements by discussion, or, if required, by consultation with a third review author (of NF, EC, LB, GA) (for details see Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11).

We provided information, including trial identifier, about potentially relevant ongoing trials in the Characteristics of ongoing studies table and in Appendix 5. We tried to obtain the protocol of each included trial, either in trial registers or in publications of trial designs, or both, and specified the data Appendix 5.

We sent an email to all authors of included trials to enquire whether they were willing to answer questions regarding their trials. Appendix 12 shows the results of this survey. Thereafter, we sought relevant missing information on the trial from the primary author(s) of the article, if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we tried to maximise yield of information by collating all available data and used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (of EM, LE, GA, NF, EC, LB, CO) independently assessed the risk of bias of each included trial. We resolved possible disagreements by consensus, or with consultation of a third party. In cases of disagreement, the rest of the group were consulted and a judgement was made based on consensus.

We assessed risk of bias using Cochrane's 'Risk of bias' tool (Higgins 2011a; Higgins 2011b). We used the following criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment.
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We assessed outcome reporting bias by integrating the results of 'Examination of outcome reporting bias' (Appendix 6), 'Matrix of trial endpoints (publications trial documents)' (Appendix 5), and section 'Outcomes (outcomes reported in abstract of publication)' of the Characteristics of included studies table (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting (reporting bias).

We judged risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We assessed the impact of individual bias domains on trial results at endpoint and trial levels.

For blinding of participants and personnel (performance bias), detection bias (blinding of outcome assessors) and attrition bias (incomplete outcome data), we intended to evaluate risk of bias separately for subjective and objective outcomes (Hróbjartsson 2013). We considered the implications of missing outcome data from individual participants.

We defined the following endpoints as self-reported outcomes.

- All self-reported data such as a self-reported health-related quality of life questionnaires.

We defined the following endpoints as investigator-assessed outcomes.

- All measured data such as assessor measured height and weight.

Measures of treatment effect

We expressed continuous data as mean differences (MD) with 95% confidence intervals (CI). We expressed dichotomous data as odds ratios (ORs) or risk ratios (RRs) with 95% CIs. We used Comprehensive Meta Analysis (CMA) version 3 and Review Manager 5 (RevMan 2014) to conduct the meta-analyses.

Unit of analysis issues

We tried to consider the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data

We obtained relevant missing data from trial authors, if feasible, and evaluated important numerical data such as screened, eligible, randomised participants as well as intention-to-treat (ITT),

as-treated and per-protocol (PP) populations. We investigated attrition rates, for example dropouts, losses to follow-up and withdrawals, and critically appraised issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).
Where standard deviations (SD) for outcomes were not reported, we imputed these values by assuming the SD of the missing outcome to be the mean of the SDs from those trials where this information was reported. We investigated the impact of imputation on meta-analyses by means of sensitivity analyses.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as meta-analytically pooled effect estimates. We identified heterogeneity by visual inspection of the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$, in view of the low power of this test. We examined heterogeneity using the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003), where an I^2 statistic of 75% or more indicates a considerable level of inconsistency (Higgins 2011a). We also calculated Tau^2, another statistic that provides information about heterogeneity.
When we found heterogeneity, we attempted to determine potential reasons for it by examining individual trial and subgroup characteristics.
We expected the following characteristics to introduce clinical heterogeneity.

- Differences in the age of trial population.
- Differences in the trial population demographics.
- Differences in the types of drugs.
- Differences in BMI at baseline.

Assessment of reporting biases

If we included 10 trials or more for a given outcome, we used funnel plots to assess small-trial effects. Due to several explanations for funnel plot asymmetry, we interpreted results carefully (Sterne 2011).

Data synthesis

Unless there was good evidence for homogeneous effects across trials, we primarily summarised low risk of bias data by means of a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). In addition, we performed statistical analyses according to the statistical guidelines referenced in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We presented the overall certainty of the evidence for each outcome specified under 'Types of outcome measures: Summary of findings table' according to the GRADE approach which considers issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results. Two review authors (EM, GA) independently rated the certainty for each outcome. We presented a summary of the evidence in Summary of findings for the main comparison, which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome and the rating of the overall confidence in effect estimates for each outcome. We created the Summary of findings for the main comparison based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).
We presented results on the outcomes as described in Types of outcome measures. If meta-analysis was not possible, we presented results in a narrative form in Summary of findings for the main comparison.
In addition, we established an appendix 'Checklist to aid consistency and reproducibility of GRADE assessments' (Meader 2014) to help with standardisation of 'Summary of findings' tables (Appendix 13).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses and investigated interactions.

- Length of follow-up.
- Impact and nature of maintenance periods.
- The impact of comparator/control: whether concomitant therapy or no treatment (true control).
- The impact of population demographics.

Sensitivity analysis

We planned to performed sensitivity analyses to explore the influence of the following factors on effect size.

- Restricting the analysis to published trials.
- Restricting the analysis considering risk of bias, as specified in the Assessment of risk of bias in included studies section.
- Restricting the analysis to very long or large trials (more than 300 participants in total) to establish how much they dominated the results.
- Restricting the analysis to trials using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We also tested the robustness of the results by repeating the analysis using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

RESULTS

Description of studies

For a detailed description of trials, see the Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies tables.

Results of the search

Our comprehensive literature searches identified 4995 records; from these, 199 full-text papers or clinical trial records were identified for further examination. We excluded trials based on their titles or abstracts because they did not meet the inclusion criteria or were not relevant to the question under trial (see Figure 1 for the amended PRISMA flow diagram). After screening the full text of the selected publications, 21 completed trials (33 publications) met the inclusion criteria and were included in the qualitative synthesis of this review. All trials were published in English apart from Franco 2014 (Portuguese) and Prado 2012 (Spanish). We contacted all trial authors of the included trials and received a reply from all but four authors (Atabek 2008; Berkowitz 2003; Berkowitz 2006; Ozkan 2004). We sought additional information from the authors of all 21 trials, 12 authors responded to these requests and provided further data (Chanoine 2005; Clarson 2009; Franco 2014; Freemark 2001; Godoy-Matos 2005; Maahs 2006; Mauras 2012; NCT00001723; Prado 2012; Rezvanian 2010; Srinivasan 2006; Van Mil 2007). We also identified eight ongoing trials, and an additional seven trials were placed in the 'awaiting classification' section because we could not source the full publication, the trial was completed but there was not yet enough information to include it in this review or the publication was identified when a final draft of the review had been completed (NCT01487993).

Included studies

A detailed description of the characteristics of included trials is presented elsewhere (see Characteristics of included studies; Appendix 2; Appendix 3; Appendix 4). The following is a succinct overview.

Source of data

The literature search identified all 21 included trials in the review and all but one (NCT00001723) were published trials. Ten out of 21 trials were included in the previous review (Oude Luttikhuis 2009), and information relating to these 10 trials was extracted from the 2009 review - two review authors extracted any missing information from the publication. All ongoing trials were found from searching online clinical trial registers.

Comparisons

Of the 21 included trials, 11 used metformin in their intervention arm; four of these trials gave metformin plus a behaviour changing programme to the intervention group and used a placebo plus a behaviour changing programme in the comparator group (Prado 2012; Wiegand 2010; Wilson 2010; Yanovski 2011). Two trials compared metformin plus a behaviour changing programme against a behaviour changing programme alone without using a placebo (Clarson 2009; Mauras 2012). Four trials compared metformin plus a behaviour changing intervention against placebo plus a behaviour changing intervention (Atabek 2008; Kendall 2013; Rezvanian 2010; Srinivasan 2006). Rezvanian 2010 also had two additional intervention arms: metformin plus fluoxetine plus healthy eating plus physical activity advice; and fluoxetine plus healthy eating plus physical activity advice. The remaining trial compared metformin with placebo; hence, there was no lifestyle component included in either arm (Freemark 2001).

Six trials used sibutramine as the pharmacological intervention; three trials compared sibutramine plus a behaviour changing programme with placebo plus a behaviour changing programme (Berkowitz 2003; Berkowitz 2006; Van Mil 2007). The other three trials compared sibutramine plus dietary/exercise advice with placebo plus dietary/exercise advice (Franco 2014; García-Morales 2006; Godoy-Matos 2005).

Four trials investigated orlistat. Chanoine 2005, Maahs 2006, and NCT00001723 examined orlistat plus a behaviour changing intervention versus placebo plus a behaviour changing intervention. Ozkan 2004 did not include a placebo in their comparator group; hence, they compared orlistat plus a behaviour changing intervention with a behaviour changing intervention only.

Overview of trial populations

A total of 2484 children and adolescents participated in the 21 included trials. A total of 1851 participants finished the trial (74.5%) and hence we measured at the study's endpoint. In 10 studies, the dropout rates were higher in the placebo group than the intervention group, potentially showing some dissatisfaction with the control condition. The individual trial sample size ranged from 24 to 539 participants.

The 11 metformin trials included 885 participants. The individual trial sample size ranged from 26 to 155 participants. One metformin trial also included two additional intervention arms of fluoxetine and fluoxetine plus metformin (45 randomised participants in each intervention arm).

The six sibutramine trials included 778 participants. The individual trial sample size ranged from 24 to 498 participants.

The four orlistat trials included 821 participants. The individual trial sample size ranged from 40 to 539 participants.

Trial design

Trials were RCTs. Nineteen trials adopted a parallel group superiority design and two were cross-over trials (Franco 2014; Srinivasan 2006). All but three trials used a placebo comparator (Clarson 2009; Mauras 2012; Ozkan 2004). Five trials were multicentred (Berkowitz 2006; Chanoine 2005; Kendall 2013; Wiegand 2010; Wilson 2010), with the number of centres ranging from two (Wiegand 2010) to 33 (Berkowitz 2006). In terms of blinding, 14 trials were double-blinded for participants and personnel (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Franco 2014; Freemark 2001; Godoy-Matos 2005; Maahs 2006; NCT00001723; Prado 2012; Rezvanian 2010; Srinivasan 2006; Van Mil 2007; Wilson 2010; Yanovski 2011), no trials were single-blinded for participants, and four trials did not define blinding (Atabek 2008; García-Morales 2006; Kendall 2013; Ozkan 2004). Thirteen trials blinded outcome assessors (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Franco 2014; Freemark 2001; Godoy-Matos 2005; Maahs 2006; NCT00001723; Rezvanian 2010; Srinivasan 2006; Van Mil 2007; Wiegand 2010; Wilson 2010; Yanovski 2011). Trials were published between the 2001 and 2014; all but one sibutramine trial were published before the drug was withdrawn by the FDA - Franco 2014 was conducted in Brazil where the drug is still licensed. All metformin trials were published between 2006 and 2012 apart from Freemark 2001. Orlistat trials were published between 2004 and 2006, but one trial did not have any publications available and only posted results on a clinical trial website and in a conference abstract (NCT00001723).

The duration of interventions ranged from 12 weeks to 17 months, with a mean duration of 28 weeks. The duration of follow-up (from end of intervention) ranged from 0 to 52 weeks, with a mean follow-up period of 12 weeks. Participants in nine trials received the intervention/comparator for six months with no additional follow-up; in three trials, participants received the intervention/comparator for six months, which was then followed by an open-label period for six months (Berkowitz 2003; NCT00001723; Yanovski 2011); two trials received the intervention for 12 months with no additional follow-up (Berkowitz 2006; Chanoine 2005); two cross-over trials included a six-month intervention or control condition followed by a washout period, then each participant crossed over into the alternative condition for an additional six months (Franco 2014; Srinivasan 2006); three trials included an intervention/comparator period for three months (or 12 weeks) then a follow-up period for an additional three months (or 12 weeks) (Prado 2012 Rezvanian 2010; Van Mil 2007); one trial gave the intervention or comparator condition for 48 weeks, then included an additional follow-up period for another 48 weeks (Wilson 2010); and finally in one trial the length of the intervention and follow-up varied across participants (Ozkan 2004).

Five trials had a run-in period, of which three included a placebo run-in phase (Chanoine 2005; Godoy-Matos 2005; Wilson 2010), with a duration varying from two to four weeks; Freemark 2001 included 48-hour inpatient tests as their run-in period; two trial gave dietetic advice/counselling (García-Morales 2006; Godoy-Matos 2005); Wilson 2010 also included a lifestyle modification programme in their run-in period. Outcomes were not assessed in these run-in periods. Furthermore, three trials included an open-label phase six months after randomisation where both groups received the drug intervention (Berkowitz 2003; NCT00001723; Yanovski 2011); these open-label phases were not included in our analyses. Participants in one of these trials were also followed up for two years after the open-label phase (NCT00001723). None of the included trials were terminated before regular end; however, two trials that we identified from ClinicalTrials.gov were terminated before enrolment and have been placed in the excluded trials section (see Characteristics of excluded studies table).

Settings

Nine of the 21 trials were conducted in the USA (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Freemark 2001; Maahs 2006; Mauras 2012; NCT00001723; Wilson 2010; Yanovski 2011). The other trials were completed in Turkey (Atabek 2008; Ozkan 2004), Canada (Chanoine 2005; Clarson 2009), Brazil (Franco 2014; Godoy-Matos 2005), Mexico (García-Morales 2006), the UK (Kendall 2013), Australia (Srinivasan 2006), Chile (Prado 2012), Iran (Rezvanian 2010), the Netherlands (Van Mil 2007), Germany (Wiegand 2010), and Switzerland (Wiegand 2010). All trials were performed in an outpatient setting apart from three trials which had both an inpatient and outpatient setting (Freemark 2001; Maahs 2006; Yanovski 2011).

Participants

The participating population consisted of the following: mainly obese children or adolescents (Maahs 2006 also included overweight participants). The mean age of the participants in the trials ranged from 10.1 to 16.3 years with only two trials having a mean age less than 12 years old (Atabek 2008; Yanovski 2011). Two studies required all participants to be postmenarchal (Berkowitz 2003; Prado 2012), while Yanovski 2011 only included children who were prepubertal or early pubertal. Fifteen trials included participants from high-income countries, and six recruited participants from middle-income countries (Atabek 2008; Franco 2014; García-Morales 2006; Godoy-Matos 2005; Ozkan 2004; Rezvanian 2010) - based on the World Bank list of economies July 2015 (World Bank 2015). Ethnic groups were distributed as follows: six trials did not report on ethnic groups (Atabek 2008; Franco 2014; Ozkan 2004; Prado 2012; Rezvanian 2010; Van Mil 2007); one trial reported all their participants were white (Clarson 2009), three trials reported approximately 75% of their population were white (Chanoine 2005; Kendall 2013; Wiegand 2010); five trials reported approximately half of their population were white (Berkowitz 2003; Berkowitz 2006; Freemark 2001; Mauras 2012; Wilson 2010); one trial reported that approximately 60% of their population were Hispanic (Maahs

2006); one trial reported approximately 50% of their population were non-Hispanic (Yanovski 2011); 63% of participants in one trial were non-Hispanic black people while the remaining were non-Hispanic white people (NCT00001723); and one trial reported that 64% of their participants came from ethnic backgrounds with a high prevalence of insulin resistance and metabolic syndrome (Srinivasan 2006). Participants' sex was not distributed evenly in 11 trials (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Freemark 2001; Godoy-Matos 2005; Kendall 2013; Maahs 2006; NCT00001723; Prado 2012; Wiegand 2010; Wilson 2010). Three trials reported glycosylated haemoglobin A1c (HbA1c) at baseline and the mean HbA1c ranged from 5.3% to 5.6% (Freemark 2001; Maahs 2006; Wilson 2010). The mean BMI at baseline for the interventions groups ranged from 26.5 kg/m^2 to 41.5 kg/m^2. The BMI at baseline for the comparator groups ranged from 26.2 kg/m^2 to 41.7 kg/m^2. Thirteen trials reported comorbidities of participants at baseline (Atabek 2008; Berkowitz 2006; Chanoine 2005; Clarson 2009; Freemark 2001; García-Morales 2006; Kendall 2013; Mauras 2012; NCT00001723; Prado 2012; Srinivasan 2006; Wiegand 2010; Yanovski 2011), all but one trial (Freemark 2001) reported cointerventions in participants, and four trials had comedications used by participants (NCT00001723; Ozkan 2004; Wilson 2010; Yanovski 2011). Criteria for entry into the individual trials are outlined in the Characteristics of included studies table. Major trial exclusion criteria were major illnesses such as type 1 or 2 diabetes mellitus or cardiovascular disease; pregnancy; major psychiatric disorders; taking or previously taken medication known to influence body composition or contradiction to the drug therapy; cigarette smoking or alcohol use; obesity associated with genetic disorders; and eating disorders such as bulimia. Adherence/compliance with the intervention was reported in most trials as good (70% or more) and was usually assessed by pill counts.

Diagnosis

All trials included participants who were defined as obese at baseline according to the growth reference they used, apart from one trial (Maahs 2006), which also included overweight children in their inclusion criteria. Seven trials define obesity using the 95th percentile or greater cut-off on the Centers for Disease Control and Prevention (CDC; Kuczmarski 2000) charts (Atabek 2008; Clarson 2009; García-Morales 2006; Mauras 2012; Rezvanian 2010; Wilson 2010; Yanovski 2011), but Wilson 2010 also required their participants to weigh less than 136 kg. One trial used greater than 85th percentile (to include also overweight participants) (Maahs 2006), while Van Mil 2007 used the 97th percentile or greater but also further selected for triceps skinfold thickness 97th percentile or greater for age and sex. NCT00001723 defined obesity by BMI for age and triceps skinfold above the 95th percentile (determined by National Health and Nutrition Examination Survey (NHANES) I age-, sex- and race-specific data) and all participants were required to be over 60 kg in bodyweight. Alternatively two trials used the definition of obesity given by Rosner 1998 of two units more than the US weighted mean of the 95th percentile but no greater than 44 kg/m^2 (Berkowitz 2006; Chanoine 2005). One trial used the IOTF (Cole 2000) definitions for obesity (Srinivasan 2006), while another used the WHO (WHO 1995) growth standards cut-off (Franco 2014). Kendall 2013 used the UK BMI growth charts (Cole 1995), and used the 98th centile as the cut-off for obesity. One trial used German references (Kromeyer-Hausschild 2001) to define obesity using greater than 97th percentile (Wiegand 2010). Three trials used raw BMI to define obesity: BMI greater than 30 kg/m^2 (Freemark 2001); BMI 32 kg/m^2 to 44 kg/m^2 (Berkowitz 2003); and BMI 30 kg/m^2 to 45 kg/m^2 (Godoy-Matos 2005). In two trials, it was unclear which growth reference charts they were referring to (Ozkan 2004; Prado 2012). Participants were diagnosed with type 1 or 2 diabetes mellitus in none of our included trials. However, some trials included additional inclusion criteria other than age and obesity: Atabek 2008 required all participants to have hyperinsulinaemia; Clarson 2009 only included participants who were insulin resistant (defined by homeostasis model assessment (HOMA) for insulin resistance values greater than 3); Godoy-Matos 2005 required all participants to have an adult bone age determined by left hand radiography (Greulich-Pyle method); Kendall 2013 only included participants who had impaired glucose tolerance or hyperinsulinaemia; NCT00001723 only recruited participants who had comorbidities at baseline and these included hypertension, hyperinsulinaemia and hepatic steatosis; Srinivasan 2006 only included participants where there was a suspicion of insulin resistance (fasting insulin to glucose ratio greater than 4.5 or presence of acanthosis nigricans); Prado 2012 required all participants to present with at least one risk factor for type 2 diabetes (e.g. first- or second-degree relative with history of type 2 diabetes); Mauras 2012 only included participants who had normal glucose tolerance but also had elevated highly sensitive C-reactive protein (hsCRP), fibrinogen concentrations or both; Freemark 2001 inclusion criteria included a fasting insulin concentration exceeding 15 IU/mL and at least one first- or second-degree relative with type 2 diabetes; and Yanovski 2011 required all participants to have hyperinsulinaemia (defined as fasting insulin 15 IU/mL or greater). All participants in Wiegand 2010 presented with comorbidities at baseline (features of the metabolic syndrome); however, this did not appear to be an inclusion criterion.

Interventions

Eleven trials used metformin as their pharmacological intervention (Atabek 2008; Clarson 2009; Freemark 2001; Kendall 2013; Mauras 2012; Prado 2012; Rezvanian 2010; Srinivasan 2006; Wiegand 2010; Wilson 2010; Yanovski 2011). The intervention was administered orally and varied between one and four times per day. Between trials, the daily dosage of metformin varied between

500 mg and 2000 mg, with a mean daily dosage of 1364 mg. Four metformin trials reported treatment before the start of the trial (Kendall 2013; Rezvanian 2010; Wiegand 2010; Wilson 2010); this included a healthy 'lifestyle' advice sheet, lifestyle modification treatment and a six-month multiprofessional lifestyle intervention. Seven trials had a titration period, consisting of increasing the number of tablets taken over a period of weeks until the maximum dosage was tolerated (Clarson 2009; Kendall 2013; Mauras 2012; Rezvanian 2010; Srinivasan 2006; Wilson 2010; Yanovski 2011). Two trials did not have a matching placebo in the comparator group - participants received a lifestyle intervention only (Clarson 2009; Mauras 2012). The duration of treatment ranged from 12 weeks/three months to six months with a mean treatment duration of 5.5 months.

Six trials used sibutramine as their intervention (Berkowitz 2003; Berkowitz 2006; Franco 2014; García-Morales 2006; Godoy-Matos 2005; Van Mil 2007). In all six trials, the drug was administered orally once daily. The daily dosage of sibutramine varied between 5 mg and 15 mg, with a mean daily dose of 11 mg. Three trials reported that participants received treatment before the start of the trial (Franco 2014; García-Morales 2006; Godoy-Matos 2005); this included dietetic advice/counselling and a six-month lifestyle intervention. Two trials had a titration period (Berkowitz 2003; Van Mil 2007). All trials had a matching placebo as the comparator intervention. The duration of treatment ranged from 12 weeks to 12 months, with a mean treatment duration of 6.5 months.

Four trials gave orlistat to their intervention group (Chanoine 2005; Maahs 2006; NCT00001723; Ozkan 2004). The drug was administered orally three times per day and the daily dosage of orlistat was 360 mg in all four trials. No trials gave participants any treatment before the trial. One trial did not give a matching placebo to the comparator group - participants received a lifestyle intervention only (Ozkan 2004). The duration of treatment ranged from six months to 12 months, with a mean treatment duration of 8.9 months.

One trial also included two additional intervention arms: metformin plus fluoxetine and fluoxetine only (Rezvanian 2010). The drugs were given by the oral route once daily. The daily dose of fluoxetine was 20 mg. Participants were also given lifestyle modification treatment before the start of the trial. They also had a titration period. The comparator group received a matching placebo. The duration of treatment was 12 weeks.

Outcomes

Fourteen trials explicitly stated a primary endpoint in the publication (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Clarson 2009; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Maahs 2006; Mauras 2012; Prado 2012; Van Mil 2007; Wiegand 2010; Wilson 2010; Yanovski 2011), 10 trials reported 'secondary' endpoints (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Maahs 2006; Wiegand 2010; Wilson 2010; Yanovski 2011). NCT00001723 had no publication attached; however, the trial authors reported both a primary and secondary endpoint on the clinical trials website. The most commonly defined primary outcomes in publications were change in absolute BMI, change in BMI z score/standard deviation score (SDS) and change in bodyweight. The most commonly defined primary outcomes in trial protocols were change in BMI from baseline and per cent change in BMI.

Reporting of endpoints

Twenty-one trials collected a mean of 14 (range four to 25) outcomes. All 21 trials measured raw BMI. Ten trials reported change in BMI z score/SDS (Berkowitz 2003; Clarson 2009; Freemark 2001; Kendall 2013; NCT00001723; Srinivasan 2006; Van Mil 2007; Wiegand 2010; Wilson 2010; Yanovski 2011). All 21 trials reported on whether adverse events occurred. Of those trials which reported adverse events, some reported the total number of adverse events whilst others reported the total number of participants who experienced at least one adverse event. We asked all authors to provide further details on adverse events, such as how many participants experienced severe adverse events and if so, whether they were hospitalised. Two trials measured health-related quality of life with validated questionnaires (García-Morales 2006; Maahs 2006). Seventeen trials reported that they measured body fat distribution. Fifteen trials measured waist circumference, hip circumference, or both (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Clarson 2009; Franco 2014; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Mauras 2012; Prado 2012; Rezvanian 2010; Srinivasan 2006; Wiegand 2010; Wilson 2010; Yanovski 2011). Seven trials measured body fat mass by DEXA (Chanoine 2005; Mauras 2012; NCT00001723; Srinivasan 2006; Van Mil 2007; Wilson 2010; Yanovski 2011). Two trials also measured body fat mass by bioelectrical impedance (Maahs 2006; Wiegand 2010). Six trials measured behaviour change (Atabek 2008; Berkowitz 2003; García-Morales 2006; Kendall 2013; Maahs 2006; Van Mil 2007). Five trials measured food consumption through dietary records or questionnaires (Atabek 2008; García-Morales 2006; Kendall 2013; Maahs 2006; Van Mil 2007), and one trial measured the feeling of hunger (Berkowitz 2003). Two trials measure changes in physical activity: Kendall 2013 used a physical activity questionnaire and Van Mil 2007 measured total energy expenditure which accounts for level of physical activity. Only one trial investigated morbidity defined as illness or harm associated with the intervention (Chanoine 2005). One trial reported a death from suicide (Maahs 2006). Berkowitz 2006 reported two suicide attempts which did not result in death.

No trials assessed participants' views or socioeconomic effects as outcomes. For a summary of all outcomes assessed in each trial, see Appendix 5.

Excluded studies

We excluded 135 trials or trial records after careful evaluation of the full publication. The main reasons for exclusion were the participants were adults or had a mean age of more than 18 years, the trial design was not an RCT, the duration of treatment was less than three months or the duration of follow-up was less than six months. For further details, see Characteristics of excluded studies table.

Risk of bias in included studies

For details on risk of bias of included trials see Characteristics of included studies table. For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials, see Figure 2 and Figure 3. We investigated performance bias, detection bias and attrition bias separately for objective and subjective outcome measures.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

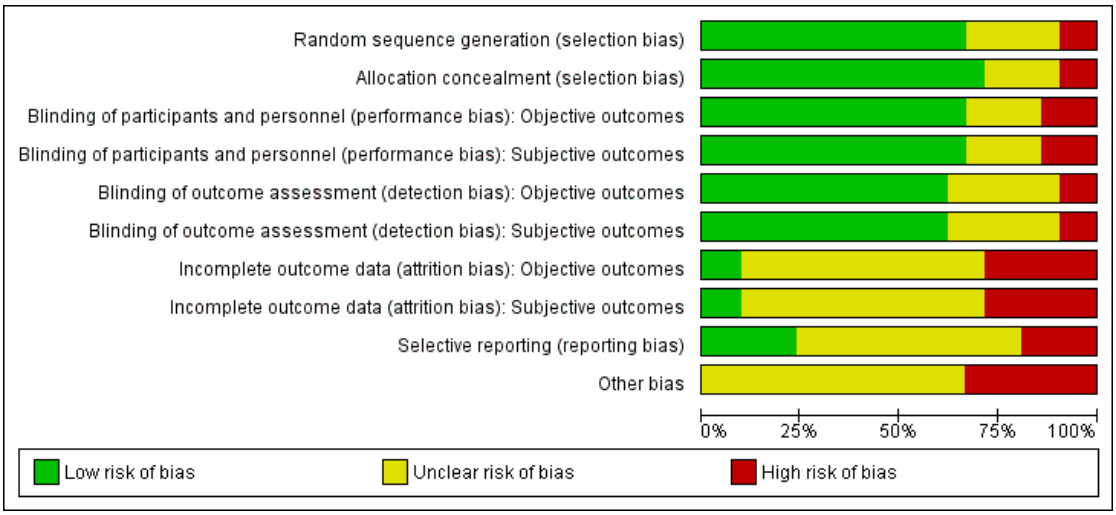
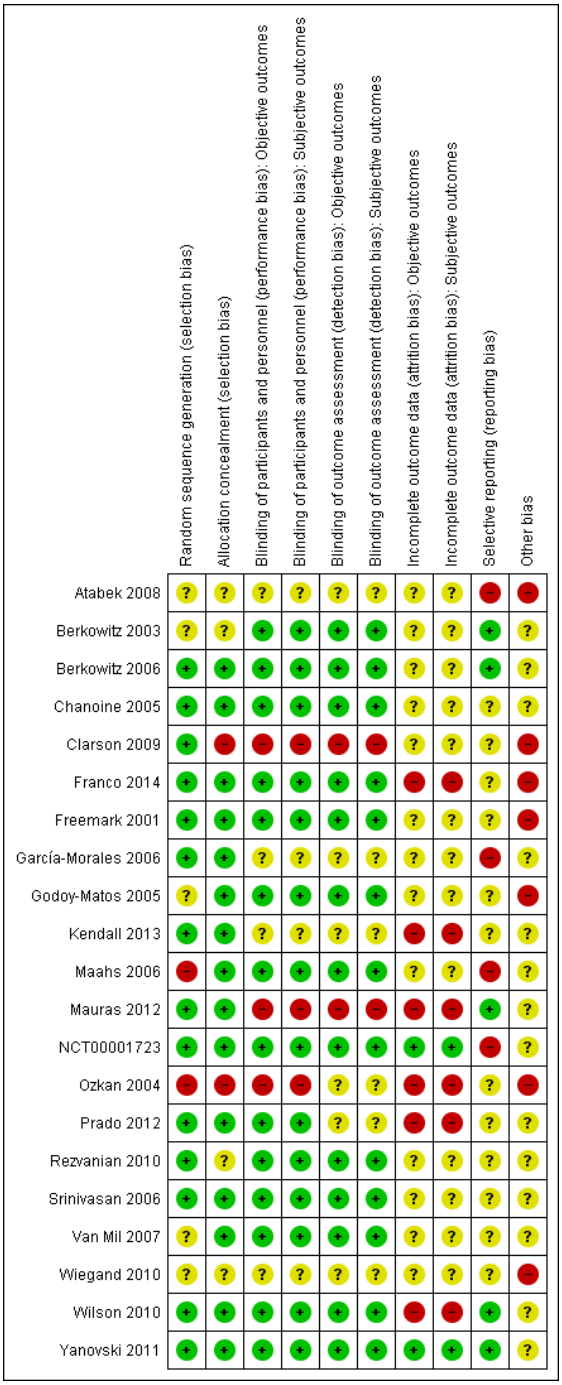


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Allocation

Fifteen trials reported allocation was concealed (Berkowitz 2006; Chanoine 2005; Franco 2014;Freemark 2001; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Mauras 2012; NCT00001723; Prado 2012; Rezvanian 2010; Srinivasan 2006; Wiegand 2010; Wilson 2010; Yanovski 2011); two trials did not conceal allocation (Clarson 2009; Ozkan 2004). It was unclear whether four trials concealed allocation (Atabek 2008; Berkowitz 2003; Rezvanian 2010;Wiegand 2010)). Fourteen trials reported an adequate random sequence generation (Berkowitz 2006; Chanoine 2005; Clarson 2009; Franco 2014; Freemark 2001; García-Morales 2006; Kendall 2013; Mauras 2012; NCT00001723; Prado 2012; Rezvanian 2010; Srinivasan 2006; Wilson 2010; Yanovski 2011). Two trials reported random sequence generation was inadequate; hence, would have likely of introduced bias (Maahs 2006; Ozkan 2004).Five trials did not describe the randomisation process (Atabek 2008; Berkowitz 2003; Godoy-Matos 2005; Van Mil 2007; Wiegand 2010).

Blinding

All 21 trials reported both objective and subjective outcomes. The main objectives outcomes were BMI, weight, waist or hip circumference, blood pressure, cholesterol insulin, glucose and triglycerides, whilst the main subjective outcomes were adverse events, food consumption and health-related quality of life. Subjective outcomes tended to be self-reported (e.g. quality of life and dietary questionnaires), while objective measures usually were investigator-assessed (e.g. BMI, waist circumference). Adverse events could be either self-reported or investigator assessed.

Ten trials explicitly stated that blinding of the participants, personnel and outcome assessors was undertaken (Berkowitz 2003; Berkowitz 2006; Franco 2014; Maahs 2006; NCT00001723; Rezvanian 2010; Srinivasan 2006; Van Mil 2007; Wilson 2010; Yanovski 2011). Seven trials reported that double blinding took place (Atabek 2008; Chanoine 2005; Freemark 2001; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Wiegand 2010), but only three of the trials' authors confirmed this meant blinding was undertaken of participants, personnel and outcomes assessors (Chanoine 2005; Freemark 2001; Godoy-Matos 2005). No trials reported that single blinding was undertaken. Six trials did not provide sufficient information about blinding procedures (Atabek 2008; García-Morales 2006; Kendall 2013; Ozkan 2004; Prado 2012; Wiegand 2010).

Incomplete outcome data

Twenty trials that had losses to follow-up described the number of trial withdrawals (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; Clarson 2009; Franco 2014; Freemark 2001; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Maahs 2006; Mauras 2012; NCT00001723; Ozkan 2004; Prado 2012; Rezvanian 2010; Srinivasan 2006; Van Mil 2007; Wiegand 2010; Wilson 2010; Yanovski 2011). Twelve trials used ITT analyses (Berkowitz 2003; Berkowitz 2006; Chanoine 2005; García-Morales 2006; Godoy-Matos 2005; Kendall 2013; Maahs 2006; NCT00001723; Rezvanian 2010; Van Mil 2007; Wilson 2010; Yanovski 2011). One trial did not report whether there were any losses to follow-up (Atabek 2008). Five trials did not provide detailed descriptions of participants' withdrawals and reasons underpinning them (Atabek 2008; Franco 2014; Freemark 2001; García-Morales 2006; Mauras 2012). Four trials had attrition rates greater than 30% with possible impact on the outcomes(Chanoine 2005; Franco 2014; Mauras 2012; Prado 2012;Wilson 2010).

Selective reporting

Only nine trials provided a clinical trial identifier or reference to a protocol *(*Berkowitz 2003; Berkowitz 2006; Kendall 2013; Mauras 2012; NCT00001723; Srinivasan 2006; Wiegand 2010; Wilson 2010; Yanovski 2011); however, we were unable to source the clinical trial entry of one trial (Wiegand 2010). Three trials had a high risk of reporting bias after failure to report results for one or more outcomes they described as having measured *(*Atabek 2008; García-Morales 2006; Maahs 2006), and a further trial had a high risk due to differences in results reported on the clinical trial website and in a conference abstract (NCT00001723). The remaining trials had unclear risk of reporting bias due to no protocol being available.

Other potential sources of bias

Seven trials were at high risk of other biases. These biases included: the trial not including a power calculation (Atabek 2008; Clarson 2009; Franco 2014; Freemark 2001; Godoy-Matos 2005; Ozkan 2004), the trial lacking methodological detail (Atabek 2008; Franco 2014) and the trial not adjusting for baseline differences (Freemark 2001; Ozkan 2004), The remaining 14 trials were at unclear risk of other potential sources of bias. It is important to note that the trials which do not include a power calculation may not be powered to detect differences in their primary outcome. BMI or weight was the primary outcome in all but two trials (Mauras 2012; Wiegand 2010) that included a power calculation. Mauras 2012 and Wiegand 2010 may not have been adequately powered to detect differences in BMI or weight. With regards to adverse events and the review's secondary outcomes (e.g. morbidity), it is likely that most trials would not have been powered to detect differences in these outcomes. Hence, these results should be interpreted with caution.

Effects of interventions

See: **Summary of findings for the main comparison** Drug interventions for the treatment of obesity in children and adolescents

Baseline characteristics

For details of baseline characteristics, see Appendix 3 and Appendix 4.

Pharmacological intervention versus comparators

We performed the meta-analyses with CMA software version 3 and aligned with the data in the Review Manager 5 (RevMan 2014) meta-analyses. Because the cross-over design did not appear suitable for our research question due to inadequate washout periods and noncomparable baseline measures in the two cross-over periods, we excluded Franco 2014 and Srinivasan 2006 from all meta-analyses. We also excluded Rezvanian 2010 from the meta-analyses because the reported SDs were unreliably small in comparison to all other published SDs of included trials and probably denoted standard errors. We excluded two further trials because of substantial methodological concerns (Ozkan 2004; Prado 2012). In addition, Prado 2012 did not report change in BMI from baseline to follow-up and Ozkan 2004 did not have a consistent follow-up time frame across all participants.

Primary outcomes

Body mass index and bodyweight

We included 16 trials in the meta-analysis of BMI. Most of the BMI data were from the publications, except for Chanoine 2005 and Freemark 2001, where raw BMI, SDs or both were not available; hence, we obtained additional data from the trial authors. We extracted data for NCT00001723 from the ClinicalTrials.gov website. In the meta-analysis, we included trials which had either a six-month or 12-month follow-up from baseline (Berkowitz 2006; Wilson 2010), which was the endpoint in most of the trials. However, even though Chanoine 2005 had a 12-month follow-up, we only had data available at six months from baseline. Wilson 2010 provided data at 100 weeks' follow-up but we did not include these in the meta-analysis.

The summary estimate across all pharmacological interventions versus all comparators (metformin, orlistat or sibutramine mostly versus placebo - usually combined with behaviour changing interventions) showed a MD in BMI change of -1.3 kg/m^2 (95% CI -1.9 to -0.8; P < 0.00001; 16 trials; 1884 participants; low certainty evidence - Analysis 1.1) in favour of the drug interventions. Heterogeneity was considerable (I^2 = 77%).

In Wilson 2010, which reported a BMI change at 100 weeks from baseline (48 weeks of metformin or placebo treatment, then a 48-week drug-free period), the metformin group increased their BMI during the drug-free period (+0.5) while the placebo group decreased their BMI (-0.8), measured as the difference between 52 and 100 weeks from baseline. In the metformin plus fluoxetine trial, the fluoxetine only group had a decrease in BMI of -0.6 (SD 0.1) and the metformin plus fluoxetine group had a decrease in BMI of -0.9 (SD 0.02), compared to an increase of 0.2 (SD 0.04) in the placebo group at 24 weeks from baseline.

Only 11 trials reported weight data at baseline or follow-up (or change from baseline) in their publications; hence, we only included these trials in the meta-analysis. Data were reported at six months from baseline apart from one trial (Berkowitz 2006), which reported the change in weight at 12 months from baseline. The summary estimate across all pharmacological interventions versus comparators (metformin, orlistat or sibutramine mostly versus placebo - usually combined with behaviour changing interventions) showed an MD in change in weight of -3.9 kg (95% CI -5.9 to -1.9; P < 0.00001; 11 trials; 1180 participants; low certainty evidence - Analysis 2.1) in favour of the drug interventions. Heterogeneity was considerable (I^2 = 79%).

Adverse events

Only three trials had sufficiently long exposure times to evaluate adverse events possibly associated with drug interventions for obesity in children and adolescents: one trial with 39 participants randomised to metformin treatment for 100 weeks (Wilson 2010), one trial with 368 participants randomised to sibutramine treatment for 12 months (Berkowitz 2006), and one trial with 357 participants randomised to orlistat treatment for 54 weeks (Chanoine 2005).

Adverse events were reported to have occurred in all 11 metformin trials except from Clarson 2009, which reported that metformin was well tolerated, and the author clarified no adverse events occurred. Gastrointestinal adverse events were most commonly reported with one metformin trial reporting that gastrointestinal adverse events were statistically more prevalent in the intervention group compared to the control group (Yanovski 2011). However, Wiegand 2010 reported such events occurred more frequently in the placebo group. Kendall 2013 reported adverse events were more common in the metformin group and were mainly gastrointestinal. Atabek 2008 reported that two metformin-treated participants experienced diarrhoea, mild abdominal pain/discomfort, or both. Freemark 2001 also reported three participants experienced transient abdominal discomfort or diarrhoea, however so did one placebo participant. Wilson 2010 reported that the most common adverse events included headache, nausea, vomiting, upper respiratory tract infection and musculoskeletal complaints; however, none were statistically different between the metformin and placebo groups. One trial showed the fatigue was more common

in the metformin-treated children (Yanovski 2011). Furthermore, Freemark 2001 reported one case of an exacerbation of migraine and one case of transient nausea in the metformin arm. Nausea was reported in the Srinivasan 2006 trial where two participants were unable to tolerate a higher dose of metformin (1 g); however, they tolerated a lower dose and continued in the trial. Yanovski 2011 also reported that levels of serum vitamin B_{12} were reduced in the metformin group compared with an increase in the placebo group - this difference was statistically significant. Rezvanian 2010 reported two cases of headache, two cases of abdominal pain and three cases of loose stools in the metformin arm but they were all minor and tolerable. Mauras 2012 reported metformin was well tolerated and safe, and the author added that the adverse effects between groups were comparable. Prado 2012 reported metformin was well tolerated by participants and both groups showed a significant increase in alanine transaminase (ALT) and aspartate transaminase (AST), and a reduction in haemoglobin levels, but these were within the normal ranges.

Three of six trials on sibutramine therapy reported on adverse events: one large trial showed tachycardia, dry mouth, constipation, dizziness, insomnia and hypertension were all reported more frequently by sibutramine participants than by placebo participants (Berkowitz 2006). Sibutramine-treated participants also had a higher blood pressure and pulse rate at 12 months' follow-up compared to the placebo-treated participants (Berkowitz 2006). However, another trial reported that there was no statistically significant difference between changes in heart rate or blood pressure between the sibutramine and placebo groups, although abdominal cramps were significantly higher in the sibutramine group (Van Mil 2007). Godoy-Matos 2005 showed constipation was significantly higher in the sibutramine group compared to the placebo group.

All four orlistat trials reported on adverse events: gastrointestinal problems such as fatty stools, oily spotting and fecal urgency, along with headaches and upper respiratory tract infections, were the most common adverse effects. In the NCT00001723 trial, the prevalence of some gastrointestinal problems was higher in the orlistat group compared to the placebo group and this included: fatty-appearing stools, bloating/gas, frequent urge for bowel movement and uncontrolled passage of stool or oil. Chanoine 2005 reported that gastrointestinal tract-related adverse events were more common in the orlistat group compared to the placebo group; however, most were classed as mild to moderate intensity. Maahs 2006 also reported that the orlistat group had significantly increased gastrointestinal adverse events (e.g. soft stools, oily spotting) compared to the placebo group. Mild gastrointestinal complaints (frequent stools) were experienced by all orlistat-receiving participants in the Ozkan 2004 trial. Chanoine 2005 also reported that 10 orlistat and one placebo participant showed abnormalities detected on electrocardiograms; however, an independent cardiologist concluded that none were connected to the treatment; in addition, levels of oestradiol in girls decreased in the orlistat group versus a slight increase in the placebo group (P = 0.05). Symptomatic gallstones were also seen in six orlistat participants which were not seen at baseline (five of these participants had lost large amounts of weight).

In the trial which included a fluoxetine arm, there were five adverse events with regards to the drug which included three cases of dry mouth and two cases of loose stool; these were all considered as minor and tolerable, and reported as transient (Rezvanian 2010).

Serious/severe adverse events were also investigated: most trials did not report how they defined a serious/severe adverse event. It was also unclear in four trials whether a serious/severe adverse event actually occurred (Berkowitz 2003; Ozkan 2004; Van Mil 2007; Wiegand 2010). Only five trials reported that a serious or severe adverse event occurred (Berkowitz 2006; Chanoine 2005; Maahs 2006; NCT00001723; Wilson 2010); the remaining 12 trials reported that there were no serious or severe adverse events. Across all trials the RR for serious adverse events comparing drug interventions with comparators was 1.43 (95% CI 0.63 to 3.25; P = 0.39; 5 trials; 1347 participants; low certainty evidence - Analysis 3.1). Absolute numbers experiencing a serious adverse event were 24/878 (2.7%) participants in the drug intervention groups versus 8/469 (1.7%) participants in the comparator groups.

In the metformin trials, only one trial reported that there were serious adverse events and these included one case of appendectomy and one case of leg vein thrombosis in the metformin group, but these were both seen as unrelated to the drug (Wilson 2010). One sibutramine trial reported that 2.7% of sibutramine-treated participants experienced serious adverse events which included one case of excessive nausea and vomiting, one suicide attempt and five depression cases (Berkowitz 2006). The placebo group had one case of suicide attempt and one case of depression. Chanoine 2005 reported 3% of participants experienced at least one serious adverse event: the five events in the placebo group included acute demyelinating encephalomyelitis, facial palsy, pneumonia, worsening of asthma and pain in the right side; and the 11 events in the orlistat group included pilonidal abscess, depression, asthma attack, seizure, admission for repair of deviated nasal septum, appendicitis, cholelithiasis, gallbladder disorder followed by cholecystectomy, adenoidal hypertrophy and aseptic meningitis. It was only the case of cholelithiasis in the orlistat participant which was seen to be possibly related to the trial medication potentially due to rapid weight loss. Another orlistat trial reported two serious adverse events in the placebo group and these were one case of hypoglycaemia and one case of left lower quadrant pain and vomiting (NCT00001723).

In the sibutramine trials, 32 participants (24 in the intervention groups and eight in the control groups) left the trial because of adverse events. Berkowitz 2006 reported that withdrawals due to tachycardia were similar in both groups but hypertension led to the withdrawal of five participants in the sibutramine group versus none in the placebo group. Two cases of attempted suicide (one intervention and one placebo) also led to discontinuation but were

considered unlikely to be related to the trial drug; one case of excessive nausea and vomiting in the sibutramine group also led to withdrawal and may have been related to the drug. Van Mil 2007 had one withdrawal from the sibutramine group due to symptoms of clinical depression and Berkowitz 2003 had one withdrawal from the placebo group.

In the metformin trials, nine participants withdrew due to adverse events (five in intervention group and four in placebo group). Wilson 2010 reported one participant from the metformin group withdrew due to nausea which was probably related to the drug, and a further two metformin and one placebo participants dropped out of the trial due to elevated levels of ALT. Gastrointestinal symptoms caused 6% of participants (one in metformin group and three in placebo group) to drop out of the Wiegand 2010 trial. In addition, Yanovski 2011 reported one participant dropped out of the metformin group due to medication intolerance.

Across all trials the RR for discontinuing the trial because of adverse events comparing drug interventions with comparators was 1.45 (95% CI 0.83 to 2.52; P = 0.19; 10 trials; 1664 participants; low certainty evidence - Analysis 3.2). Absolute numbers discontinuing the trial because of an adverse event were 52/1043 (5.0%) participants in the drug intervention groups versus 17/621 (2.7%) participants in the comparator groups.

All four orlistat trials had dropouts due to adverse events; 28 participants (23 in the intervention group and five in the placebo group). Chanoine 2005 reported 12 dropouts (3%) in the orlistat group and three dropouts (2%) in the placebo group, mainly due to gastrointestinal adverse events. Ozkan 2004 reported seven participants (32%) dropped out of the orlistat group due to gastrointestinal complaints. Maahs 2006 reported two participants in the orlistat group discontinued due to adverse events (assumed to be gastrointestinal) and one participant in the orlistat group committed suicide. NCT00001723 reported one participant in the orlistat group and two participants in the placebo group dropped out of the trial due to medication intolerance.

For further details, see Appendix 9, Appendix 10, and Appendix 11.

Secondary outcomes

Health-related quality of life

Two trials measured health-related quality of life; the certainty of the evidence was very low. García-Morales 2006 used the 36-Item Short-Form Health Survey (SF-36) questionnaire and found changes in the total score were slightly higher in the sibutramine group compared to the placebo group, but this difference was not statistically significant. Maahs 2006 used three questionnaires to assess health-related quality of life, but found no statistically significant differences between the orlistat and placebo group from baseline to six months. For further details on the health-related quality of life measurements, see Appendix 14.

Body fat distribution

Eighteen trials reported outcomes which measured body fat distribution. Fifteen of these trials measured waist, hip, or both circumferences at baseline and follow-up. In the metformin trials, Mauras 2012 found greater decreases in waist circumference in the metformin plus diet plus exercise group compared with the diet plus exercise group at six months' follow-up. However, this trial was not placebo controlled. In addition, Srinivasan 2006, a cross-over trial, reported a beneficial treatment effect on waist circumference in participants taking metformin for six months, when compared to six months of placebo. However, there was no statistically significant difference in waist circumference between the drug and control groups in Clarson 2009 and Prado 2012 trials at six months' follow-up. Wilson 2010 measured waist circumference but did not report results. Two metformin trials also measured waist-to-hip ratio and found no statistically significant difference between groups at six months' follow-up (Kendall 2013; Wiegand 2010). Yanovski 2011 also measured abdominal and hip circumference at six months' follow-up, and found a statistically significant difference between metformin and placebo, in favour of the intervention. In the metformin plus fluoxetine trial, only the metformin plus fluoxetine arm had a statistically significant between-group difference in waist circumference at 24 weeks from baseline (Rezvanian 2010). In the sibutramine trials, there was a statistically significant difference in waist circumference in favour of the intervention in five trials (Berkowitz 2003; Berkowitz 2006; Franco 2014; García-Morales 2006; Godoy-Matos 2005). Godoy-Matos 2005 also reported a statistically significant reduction in hip circumference in the sibutramine group compared to the placebo group; however, there was no statistically significant difference for waist-to-hip ratio at six months. Only one orlistat trial measured waist circumference and found it increased in the placebo group but decreased in the orlistat group at one year' follow-up (difference statistically significant); this was also seen for hip circumference (Chanoine 2005).

Seven trials measured body composition by DEXA. Four metformin trials and two orlistat trials measured body fat using DEXA. Three metformin trials found no statistically significant difference between groups in the percentage of body fat lost (Mauras 2012; Srinivasan 2006; Wilson 2010). However, one trial observed a statistically significant difference of 1.4 kg between the metformin and placebo groups, in favour of the intervention group at six months' follow-up (Yanovski 2011). One sibutramine trial assessed body composition using underwater weighing and DEXA; however, there was no statistically significant difference in percentage of fat mass between groups. Chanoine 2005 reported they measured fat mass by DEXA in a subgroup of participants as a safety measure and the orlistat group lost more fat mass compared to the placebo group (P = 0.03). NCT00001723 found a slightly greater decrease in body fat (kg) in the orlistat group compared to the placebo group. Two trials estimated fat mass from bioimpedence analysis: one orlistat trial (Maahs 2006) and one met-

formin trial (Wiegand 2010), but they reported no statistically significant difference between intervention and placebo groups. Yanovski 2011 measured fat mass by air displacement plethysmography and found metformin participants had statistically significant decreases in their fat mass compared to placebo participants; they also measured intra-abdominal fat by magnetic resonance imaging but found no statistically significant difference between groups. Srinivasan 2006 also used magnetic resonance imaging and found a beneficial treatment effect of metformin over placebo for subcutaneous abdominal adipose tissue but not visceral abdominal adipose tissue; Mauras 2012 also used this technique and found that intrahepatic fat only decreased in the nonplacebo control group. Wiegand 2010 used abdominal computer tomography (CT) scans to evaluate abdominal fat content but also found no statistically significant difference between metformin and placebo participants in the results.

Behaviour change

Six trials measured behaviour change; however, only two trials reported the results. Participants in three trials all completed a food frequency questionnaire at the beginning and end of the trial; however, no results were presented (Atabek 2008; García-Morales 2006; Maahs 2006). Kendall 2013 assessed dietary habits and exercise levels through three previously validated questionnaires but were unable to analyse the data due to insufficient resources. Van Mil 2007 measured total energy expenditure, using the Maastricht protocol and included data from a seven-day dietary record; however, the difference between the sibutramine and control groups after 12 weeks of intervention was not statistically significant. Physical activity level was also measured using an activity questionnaire, but there was no statistically significant difference between groups at 12 weeks. Changes in total energy expenditure and physical activity levels were not measured at 24-week follow-up due to unavailability of equipment.

Participants' views of the intervention

No trials investigated participants' views of the intervention.

Morbidity

Only one trial investigated morbidity defined as illness or harm associated with the intervention (Chanoine 2005). In the orlistat group, 6/352 (1.7%) participants developed new gallstones compared with 1/181 (0.6%) in the placebo group. The certainty of the evidence was very low.

Some trials investigated various risk indicators, mainly insulin resistance or insulin sensitivity and hyperinsulinaemia (Atabek 2008; Clarson 2009; Freemark 2001; Kendall 2013; Srinivasan 2006; Wiegand 2010; Yanovski 2011). García-Morales 2006 investigated changes in blood pressure, glucose and triglycerides. Prado 2012 investigated glycaemia, insulin resistance and lipid profiles. Mauras 2012 investigated changes in hsCRP and fibrogen concentrations.

All-cause mortality

One trial reported a death from suicide (Maahs 2006); the certainty of evidence was low. The authors reported that quality of life factors were screened extensively and the participant gave negative responses to quality of life questions specific to suicide and was also under the care of a psychiatrist for depression at the time of the trial. Berkowitz 2006 reported two suicide attempts (one in the intervention group and one in the placebo group).

Socioeconomic effects

No trials investigated socioeconomic effects.

For a summary of all outcomes assessed in each trial, see Appendix 5. For further explanation on how trial outcomes were defined, see Appendix 7 and Appendix 8.

Subgroup analyses

We performed subgroup analyses on our primary outcomes of BMI and weight. In our protocol, we specified we would analyse length of follow-up; however, only two trials provided data at a time point greater than six months. There was too much heterogeneity to analyse the maintenance periods and most trials ended on completion of the intervention. In addition, there were only two trials which did not use a placebo; hence, we did not perform subgroup analyses based on type of control given. However, we performed subgroup analyses on BMI for the following factors: drug type (Analysis 1.2), dropout rates (Analysis 1.3), ITT analysis (Analysis 1.4), funding source (Analysis 1.5), publication date (Analysis 1.6), quality of trial (Analysis 1.7), country income (Analysis 1.8), and mean age of participants (Analysis 1.9).

Only two interaction tests for subgroup differences indicated statistically significant differences.

Comparing dropout rates less than 20% showed an MD in BMI change of -1.1 kg/m^2 (95% CI -1.8 to -0.4; 9 trials), with dropout rates 20% or greater showed an MD in BMI change of -1.4 kg/m^2 (95% CI -2.3 to -0.5; 6 trials), and with unclear dropout rates showed an MD in BMI change of -2.7 kg/m^2 (95% CI -3.7 to -1.7; 1 trial). The P value for interaction was 0.03 and heterogeneity was substantial (I^2 = 71%).

Comparing middle-income countries with high-income countries showed an MD in BMI change of -2.4 kg/m^2 (95% CI -3.1 to -1.7; 3 trials) versus -1.1 kg/m^2 (95% CI -1.6 to -0.6; 13 trials). The P value for interaction was 0.004 and heterogeneity was considerable (I^2 = 88%).

For the outcome measure change in weight, only drug type could be used for a subgroup analysis and the interaction test for subgroup differences was not statistically significant (P = 0.52, I^2 = 0%).

We also explored the effects of participant sex on the BMI point estimate, using a meta-regression model in CMA. The proportion of boys at follow-up (or baseline if not reported) in each study was selected as a covariate. We found that the coefficient of determination (r^2) from this model was zero. The 95% CI for the meta-regression slope was extremely wide either side of zero (-6.3 to 4.1). We noted that some study authors only reported the percentage of boys and girls in the total sample at baseline and not at follow-up.

Sensitivity analyses

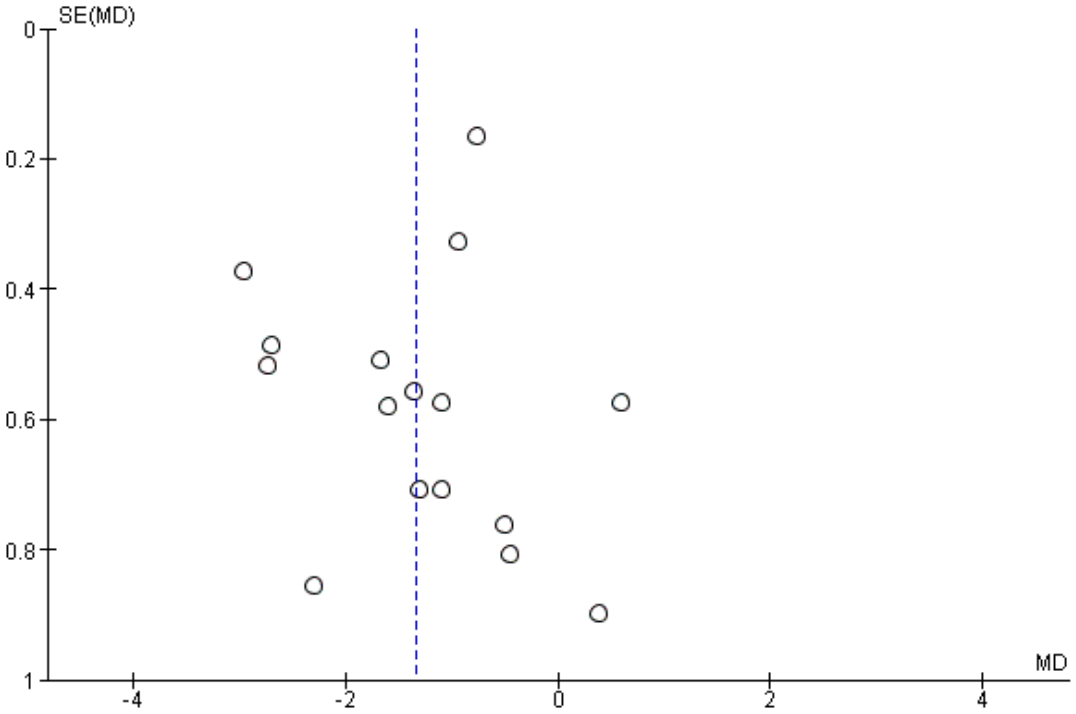
Table 2 shows the sensitivity analyses on BMI change. Our first analysis removed the trials which only reported pre- and post-BMI (not change scores) (Kendall 2013; Wiegand 2010), and hence required the use of a correlation coefficient of 0.78 (Bayer 2011) to predict the point estimates. This made very little difference in the point estimate. Only two trials had larger sample sizes (Berkowitz 2006; Chanoine 2005); however, when we removed these trials from the meta-analysis the point estimate did not change. Furthermore, all trials in the meta-analysis were published and were in English; hence, we could not perform a sensitivity analysis on these criteria. However, we performed a sensitivity analysis with allocation bias, blinding bias (participant and trial personnel, and assessor) and attrition bias by removing the high risk or unclear risk trials, and did not find substantial differences. This was also the case when we removed trials with higher drug dose and 12 months' follow-up, as well as when we removed the trials with an active lifestyle intervention.

We performed similar analyses for weight change (Table 3). We removed trials which did not report change in weight (Atabek 2008; Kendall 2013; Maahs 2006), and this resulted in a slightly greater reduction in the point estimate. We used the same correlation coefficient to calculate the mean change in weight (in the intervention and comparator groups) as we did for the BMI outcome (r = 0.78), although we were able to calculate an exact correlation coefficient in one trial (Maahs 2006) by using their reported BMI at baseline, follow-up and change score (r = 0.975). Reductions in point estimates increased slightly when we removed trials with blinding (participant and trial personnel, and assessor) and attrition bias. This also occurred when we restricted the analysis to trials which also included a high-dose behaviour change intervention. In the sensitivity analyses where we removed trials with high allocation concealment bias, high drug dose, large sample size or follow-up greater than six months, point estimate reductions were slightly less than in the original analysis.

Assessment of reporting bias

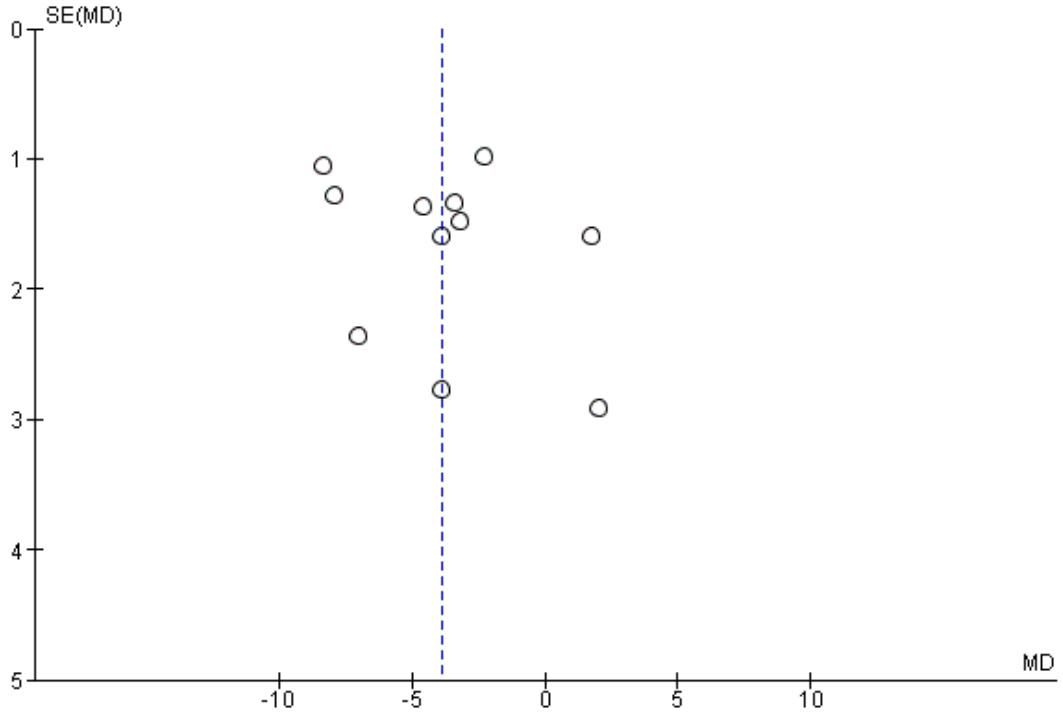
We drew a funnel plot in CMA version 3 and Review Manager 5 for change in BMI as there was a sufficient number of trials (16) (Figure 4). The Egger's regression intercept was -0.75 (95% CI -3.2 to 1.7; P = 0.52); this suggests there was no evidence of reporting bias.

Figure 4. Funnel plot of comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators, outcome: 1.1 Change in BMI (all trials) (kg/m2).



There was a similar finding when we drew a funnel plot for change in weight (11 trials) (Egger's regression intercept 1.7, 95% CI -3.5 to 6.8; P = 0.48) (Figure 5).

Figure 5. Funnel plot of comparison: 2 Weight: pharmacological interventions versus comparators, outcome: 2.1 Change in weight (all trials) (kg).



Ongoing trials

We found eight ongoing RCTs with four receiving metformin in the intervention group (EUCTR2010-023061-21; NCT00889876; NCT01677923; NCT02274948), two receiving topiramate (NCT01859013; NCT02273804), and two receiving exenatide (EUCTR2015-001628-45-SE; NCT02496611). Three trials, originally identified as ongoing, have been moved into the 'awaiting classification' section because the trial has been completed but no results are available on the clinical trial website or through a publication (ISRCTN08063839; NCT00934570; NCT00940628). In addition, one trial which was originally classified as ongoing was moved to the 'awaiting classification' section because during the final stages of conducting the review we identified a new publication (via the MEDLINE email alert service), which included results from 18-month follow-up (van der Aa 2016, see NCT01487993 for a summary of the results). Results from this trial will be incorporated in the next update of the review. For two trials, we were unable to locate the source (Golebiowska 1981; Linquette 1971). In addition, we identified one conference abstract (Pastor 2014a, see EUCTR2010-023061-21) and one conference poster (Smetanina 2015). We attempted to contact both authors but only received a reply from Smetanina 2015, who confirmed the trial had been completed but these data were still being analysed.

DISCUSSION

Summary of main results

We included 21 published RCTs and eight ongoing RCTs in this review. The included trials evaluated metformin (11 trials), sibutramine (six trials), orlistat (four trials), and one trial arm investigating the combination of metformin plus fluoxetine. The ongoing trials included four metformin, two topiramate and two exenatide trials. There were 2484 participants in the included trials, 1478 participants were randomised to drug intervention groups and 904 to comparator groups. All trials but three used a placebo in the comparator group. Two trials had a cross-over design while the remaining 19 trials were parallel RCTs. The length of the intervention period ranged from 12 weeks to 48 weeks, and the length of follow-up from baseline ranged from six months to 100 weeks.

Overall there were small reductions in BMI (MD -1.3, 95% CI -1.9 to -0.8) and bodyweight change (MD -3.9 kg. 95% CI -5.9 to -1.9) in favour of the drug interventions. Five trials reported serious adverse events (24/878 (2.7%) participants in the intervention groups versus 8/469 (1.7%) participants in the comparator groups; RR 1.43, 95% CI 0.63 to 3.25; 1347 participants; low certainty evidence). A total of 52/1043 (5.0%) participants in the intervention groups versus 17/621 (2.7%) in the comparator groups discontinued the trial because of adverse events (RR 1.45, 95% CI 0.83 to 2.52; 10 trials; 1664 participants; low certainty evidence). The most common adverse events in orlistat and metformin trials were gastrointestinal. Common adverse effects in sibutramine trials included tachycardia, constipation and hypertension. The fluoxetine trial reported dry mouth and loose stools. One trials reported health-related quality of life showing no marked differences between intervention and comparator. No trial reported the participants' views of the intervention or socioeconomic effects. Only one trial reported on morbidity associated with the intervention where there were more gallstones after the orlistat treatment. Trial authors reported one suicide in one of the orlistat intervention groups. However, the trials were not sufficiently long to investigate all-cause mortality reliably. No trial investigated drug treatment for overweight children.

Overall completeness and applicability of evidence

We faced problems in meta-analysing BMI as some trials did not report the raw data we required; therefore, we had to try and obtain this from the trial authors. In addition, age and sex are usually taken into account when measuring the weight status of a child because they are growing. However, in this review, we only assessed changes in raw BMI because previous research has shown short-term changes in adiposity are best represented by changes in raw BMI units compared to BMI z scores or BMI centiles (Cole 2005; Kakinami 2014). Furthermore, only 10 trials reported changes in BMI z scores; therefore, we thought it was more appropriate to only meta-analyse raw BMI, then this change could be converted into change in BMI z score (using the desired growth reference) - which we have done in the conclusion section of this review.

All 21 trials measured adverse events; however, some trials reported the total number of participants who experienced at least one adverse event whilst others only reported the number of specific adverse events. Hence, we also had to attempt to obtain this information from the trial authors. Of the six trials which measured behaviour change, only two trials reported the results at follow-up. Only two trials reported health-related quality of life and they used different methods. Hence, more trials are needed to investigate how drugs used to treat obesity affect the participants' health-related quality of life. No trials reported differences in participant views or socioeconomic effects.

Quality of the evidence

Based on the GRADE criteria, we rated the outcomes BMI, body weight, all-cause mortality and adverse events as low. We downgraded the levels of evidence because of potential other risk of bias or reporting bias, inconsistency and imprecision. We rated health-related quality of life and morbidity as very low certainty evidence, mainly because of the small number of participants, one trial only and imprecision.

Potential biases in the review process

We decided to perform unplanned subgroup analyses looking at funding and country as there were enough trials to divide them into groups. We were unable to analyse length of follow-up, impact of maintenance periods and type of control group in the subgroup analyses as there were too few trials or too much heterogeneity. The meta-analyses for BMI and weight included trials which differed in follow-up length, behavioural interventions and drug dose. However, when sensitivity analyses were performed, the changes in point estimates were small.

We did not restrict our search strategy to any date, hence we have sifted through trials ranging back to the 1960s. However, we did not undertake any searches of the grey literature. We had some correspondence with most of trial authors, and some have supplied us with additional information including raw BMI data. Only seven trials gave clinical trial identifiers or protocols available; hence, it was difficult to assess whether reporting bias occurred. However, from the trials where a protocol/clinical trial entry was available, there was little evidence to suggest a source of reporting bias. We excluded a large number of trials because of follow-up times less than six months, especially older trials, and this may have impacted on the overall findings from this review. In addition, we had difficulties calculating the number of adverse events in each trial due to different reporting metrics; for example, some trials reported the total number of adverse events in each group whilst others reported the total number of participants who suffered at least one adverse event. Despite our attempts to contact authors for additional information, we were still unable to meta-analyse most of these findings.

Agreements and disagreements with other studies or reviews

Since the previous review (Oude Luttikhuis 2009), we identified one new orlistat trial; however, the reduction in BMI was similar to what was found previously. The reduction in BMI for the sibutramine trials found in this review was smaller than the change reported in the previous review; however, these data still favour the intervention. This difference is likely to be due to the inclusion of three extra sibutramine trials in the meta-analysis. The previous review did not include a meta-analysis of metformin trials.

Another review and meta-analysis of the effect of orlistat and sibutramine on adolescent weight loss derived a difference in BMI of -2.3 kg/m^2 for sibutramine (95% CI -2.9 to -1.8; 5 trials; 770 participants) and -1.7 kg/m^2 for orlistat (95% CI -3.5 to 0.2; 3 trials; 621 participants) (Czernichow 2010). These point estimates reductions are greater than the ones derived in our review. However, the orlistat point estimate in the Czernichow 2010 review includes the Ozkan 2004 trial with a large BMI weight reduction which we excluded from the meta-analysis in our review for not having a common follow-up time across participants. In addition, the sibutramine analysis included data from a secondary analysis of white and African-American participants from Berkowitz 2003 which may explain why the point estimate was different. In an earlier review, there was an MD of -0.7 kg/m^2 (95% CI -1.2 to -0.3) in orlistat participants compared to placebo, which is consistent with our findings (McGovern 2008). There was a reduction of -2.4 kg/m^2 (95% CI -3.1 to -1.8) in sibutramine trials, which is higher than the reduction we found (McGovern 2008). There were similar findings also found in another meta-analysis where the reduction for sibutramine was an MD of -2.2 kg/m^2 (95% CI -2.8 to -1.6; 4 trials; 686 participants) and the reduction for orlistat was an MD of -0.8 (95% CI -1.2 to -0.5; 2 trials; 573 participants) (Viner 2010).

In metformin trials, McDonagh 2014 determined an effect size of an MD of -1.2 kg/m^2 (95% CI -1.6 to -0.7; 13 trials), which is similar to the point estimate found in this review. In addition, Bouza 2012 found a reduction of a MD of -1.2 kg/m^2 (95% CI -1.8 to -0.5; 7 trials), in favour of metformin. An earlier review found a reduction of -1.4 kg/m^2 (95% CI -2 to -0.8; 5 trials; 320 participants) in metformin trials (Park 2009); however, the review only included five trials and we excluded one of the trials in this review (Love-Osborne 2008).

Overall findings from meta-analyses of metformin, sibutramine and orlistat trials are similar to the ones presented in this review, and reasons for any differences are likely to derive from different inclusion criteria and our inclusion of more recent trials.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review highlights the paucity of both the availability of reliable pharmacotherapy options for the treatment of obese children and adolescents, and the clinical trial evidence to support efficacy and safety. Trial quality and reporting overall was poor, with high dropout and discontinuation rates. Many of the trials assessed the efficacy of drugs which have now been withdrawn (sibutramine) or are not recommended for obesity treatment (metformin) in many countries.

In this review, we found an overall reduction in body mass index (BMI) of 1.3 kg/m^2 in favour of the drug interventions. Using the International Obesity Task Force (IOTF) BMI cut-offs for overweight and obesity (Cole 2012), a 12-year-old boy would have a cut-off of 21.2 kg/m^2 for being overweight, 26.02 kg/m^2 for being obese and 31.21 kg/m^2 for being morbidly obesity. Therefore, it would be possible for a 12-year-old boy who reduces his BMI by 1.3 kg/m^2 to move down a weight status category - but only if they happen to lie just above the cut-off points. This is also similar for girls and older children. In terms of a standardised mean difference (SMD), the reduction in BMI found in this review would equate to a reduction of 0.28 between-individuals standard deviation scores.

Whilst this finding suggests that drug interventions can result in a small BMI and weight reduction over the short term, it is not known whether this is:

- sustainable over the longer term, which is an important consideration given evidence from the pharmacological management of adult obesity demonstrating a need for continued medication to maintain weight loss (Yanovski 2014), that is, drug withdrawal is followed by weight regain, which occurred in Rezvanian 2010, Van Mil 2007, and Wilson 2010 during the drug-free follow-up.

- has any impact on existing or future clinical risk factors or disease. Additionally, though all trials reported adverse events, quantitative data were only available in the minority of the included trials. This is particularly important as none of the included trials collected data on participants' views.

Implications for research

As new pharmacotherapies for the treatment of adult obesity become available (phentermine plus topiramate extended release; liraglutide 3.0 mg; bupropion plus naltrexone; lorcaserin), there may be a demand for an evaluation of their efficacy within an obese paediatric population. The requirement of regulatory authorities (US Food and Drug Administration (FDA) and European Medicines Agency (EMA)) for trials of all new medications to be used in children and adolescents should drive more and better trials. Hence, any future trials should ensure they are evaluated over the longer term (i.e. longer than one year) and collect data on cardiovascular and metabolic parameters, morbidities, health-related quality of life, social and psychological well-being, diet and physical activity behaviours, participant views and socioeconomic effects. It is also important that new trials' protocols reduce all possible sources of bias and provide accurate interpretation of findings, by ensuring power calculations and intention-to-treat analyses are described and conducted, and robust sequence allocation, allocation concealment methods and blinding measures are used and comprehensively described. All new trial protocols should also be registered and published to ensure reporting bias can be assessed. There should also be standardisation in reporting to ensure all trials report a raw BMI score and adverse events

per participant. As evidence from adult weight management indicates the intensity of adjunctive lifestyle interventions can impact on weight loss and associated outcomes, future trials should aim to ensure they maximise and adequately report any concomitant behaviour changing programme. Participant retention is also an issue that needs addressing with improved and novel mechanisms to reduce dropout rates and ensure treatment concordance. Since overweight and obesity is developing at an increasingly early age, future evaluation and trials may need to consider recruiting young, prepubertal participants in whom clearly high levels of safety will need to be established.

ACKNOWLEDGEMENTS

We would like to thank Liane Azevedo (Teesside University), Leanne Mohan (Teesside University), Sarah Smith (Durham University), Katherine Roberts (Public Health England) and Giulia Mainardi (University of Sao Paulo) for their assistance with the data extractions. Also, we would like to thank all of the study authors who provided additional information about their trials, and we also acknowledge the editorial contributions by Gudrun Paletta (Cochrane Metabolic and Endocrine Disorders Group).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Atabek 2008

Methods	Parallel randomised controlled trial, randomisation ratio 3:1 (intervention:control), superiority design
Participants	**Inclusion criteria:** • BMI ≥ 95th percentile for age and sex based on the standards of the CDC **Exclusion criteria:** • children were excluded if they had prior major illness, including type 1 or type 2 diabetes mellitus • took medications or had a condition known to influence body composition, insulin action, or insulin secretion • none of the participants had a history of diabetes mellitus **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + diet and physical activity advice **Comparator:** placebo + diet and physical activity advice **Number of trial centres:** 1 **Treatment before trial:** none **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** BMI, fasting insulin, 120-min insulin levels, FGIR, HOMA-IR, QUICKI
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Funding:** no information given **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To determine whether metformin treatment for 6 months is effective in reducing body weight and hyperinsulinaemia and also ameliorating insulin sensitivity indices in obese adolescents with hyperinsulinaemia"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no description of randomisation process
Allocation concealment (selection bias)	Unclear risk	**Comment:** no description of how allocation was concealed

Atabek 2008 (*Continued*)

Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote:** "a 6 month, randomized, double-blind placebo-controlled, parallel-group, prospective clinical trial" **Comment:** unsure who was blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote:** "a 6 month, randomized, double-blind placebo-controlled, parallel-group, prospective clinical trial" **Comment:** unsure who was blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Quote:** "a 6 month, randomized, double-blind placebo-controlled, parallel-group, prospective clinical trial." **Comment:** unsure who was blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote:** "a 6 month, randomized, double-blind placebo-controlled, parallel-group, prospective clinical trial" **Comment:** unsure who was blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** the trial did not report the number of dropouts, or clarify there were no dropouts
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** the trial did not report the number of dropouts, or clarify there were no dropouts
Selective reporting (reporting bias)	High risk	**Quote:** "A detailed questionnaire on food consumption was completed at the beginning and at the end of the trial medication period" **Comment:** no results shown for food consumption data. Also, very unclear on the number lost to follow-up and what type of analyses were conducted
Other bias	High risk	**Comment:** there was uncertainty to whether this was a randomised controlled trial or a matched controlled trial. Concern arose over a lack of description about randomisation, blinding and allocation. No rationale for the size of intervention group and no calculation of power. They also do not declare who funded the trial

Berkowitz 2003

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • boys and postmenarchal girls aged 13 to 17 years who had a BMI (calculated as weight (kg) divided by height squared (m^2) of 32 to 44 kg/m^2 **Exclusion criteria:** • contraindications to participation included cardiovascular disease (including arrhythmias) • type 1 or 2 diabetes mellitus • major psychiatric disorders • pregnancy • use of a weight-loss medication or a weight loss of ≥ 5 kg in the prior 6 months • use of medications promoting weight gain (e.g. oral steroids) • use of medications contraindicated with use of sibutramine or cigarette smoking **Diagnostic criteria:** see above
Interventions	**Intervention:** behavioural programme + sibutramine **Comparator:** behavioural programme + placebo **Number of trial centres:** 1 **Treatment before trial:** none **Titration period:** in medication-treated participants, sibutramine was increased to 10 mg/day at week 3, and to 15 mg/day at week 7
Outcomes	**Outcomes reported in abstract of publication:** weight (kg), BMI (kg/m^2), reductions in hunger, number of participants who reduced dose or discontinued
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial funding and noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To increase weight loss in obese adolescents by combining a comprehensive behavioral program with pharmacotherapy"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no description of the randomisation process
Allocation concealment (selection bias)	Unclear risk	**Comment:** trial did not describe how allocation was concealed

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "Participants, parents, and all study personnel were blinded to treatment condition during phase 1. Only the research pharmacist was aware of treatment status" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "Participants, parents, and all study personnel were blinded to treatment condition during phase 1. Only the research pharmacist was aware of treatment status" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "Participants, parents, and all study personnel were blinded to treatment condition during phase 1. Only the research pharmacist was aware of treatment status" **Comment:** risk of detection bias likely to be low due to blinding of all trial personnel
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "Participants, parents, and all study personnel were blinded to treatment condition during phase 1. Only the research pharmacist was aware of treatment status" **Comment:** risk of detection bias likely to be low due to blinding of all trial personnel
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** whilst dropout numbers were small, a more appropriate imputation method could have been used to strengthen data analysis. Imputation method only used for primary outcome measures (weight and waist circumference, which were objectively measured)
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** whilst dropout numbers were small, a more appropriate imputation method could have been used to strengthen data analysis. Imputation method only used for primary outcome measures (weight and waist circumference, which were objectively measured)
Selective reporting (reporting bias)	Low risk	**Comment:** no differences found between clinical trial entry and publication

Berkowitz 2003 (*Continued*)

Other bias	Unclear risk	**Comment:** trial was partly funded by 2 pharmaceutical companies. The trial declared these companies had no involvement in the design, analysis or interpretation of the data; however, still could have influenced the reporting of results in some way

Berkowitz 2006

Methods	Parallel randomised controlled clinical trial, randomisation ratio 3:1 (sibutramine: placebo), superiority design
Participants	**Inclusion criteria:** • adolescents 12 to 16 years of age with a BMI (calculated as weight (kg) divided by height squared (m^2)) that was at least 2 units more than the US weighted mean of the 95th percentile based on age and sex and was not more than 44 kg/m^2 • adolescents with stable hypertension who were receiving therapy **Exclusion criteria:** • cardiovascular disease (including arrhythmias) • type 1 or 2 diabetes mellitus • major psychiatric disorders • pregnancy • use of a weight loss medication or participation in structured weight loss programmes for > 2 weeks • medication use promoting weight gain or contraindicated with sibutramine or cigarette smoking • candidates with SBP > 130 mmHg, DBP > 85 mmHg, or pulse rate > 95 beats/min were excluded **Diagnostic criteria:** see above
Interventions	**Intervention:** behaviour therapy programme + sibutramine **Comparator:** behaviour therapy programme + placebo **Number of trial centres:** 33 **Treatment before trial:** no **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** BMI, weight, triglyceride levels, high-density lipoprotein cholesterol levels, insulin levels, insulin sensitivity, rate of tachycardia, completion rate
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial funding** **Publication status:** peer-reviewed journal

Berkowitz 2006 (*Continued*)

Stated aim for study	Quote from publication: "To see whether sibutramine reduced weight more than placebo in obese adolescents who were receiving a behavior therapy program"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The randomization schedule was stratified by center and baseline BMI ($\leq$37 kg/m^2 or >37 kg/m^2) and was computer-generated in blocks of 4 by the sponsor. Each site was responsible for assigning sequential treatments within each stratum" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "The sponsor kept allocation codes sealed and secure until the database was locked before analysis" **Comment:** allocation concealment was sufficient to protect against bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "Participants, their parents, and study personnel were blinded to treatment" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "Participants, their parents, and study personnel were blinded to treatment" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "Participants, their parents, and study personnel were blinded to treatment" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "Participants, their parents, and study personnel were blinded to treatment" **Comment:** risk of performance bias likely to be low due to blinding of participants, parents and trial personnel

Berkowitz 2006 (*Continued*)

Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** LOCF was only used to replace BMI missing data; other objective outcome data were expressed for completers only. Dropout rate was fairly moderate and higher in the placebo group compared to the drug group. Difficult to access level of attrition bias based on these factors
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** LOCF was only used to replace BMI missing data only
Selective reporting (reporting bias)	Low risk	**Comment:** same outcomes reported in both clinical trial register and publication
Other bias	Unclear risk	**Quote:** "the Statistics Department of Abbott Global Pharmaceutical Research and Development (including Ms. Hewkin) was responsible for data management and statistical analysis" **Comment:** potential influence of the funding body (Abbot Global Pharmaceuticals)

Chanoine 2005

Methods	Parallel randomised controlled clinical trial, randomisation ratio 2:1 (orlistat: placebo), superiority design
Participants	**Inclusion criteria:** • adolescents (aged 12 to 16 years) were eligible for enrolment if they: ◦ had a BMI (calculated as weight (kg) divided by height squared (m^2)) ≥ 2 units than the US weighted mean for the 95th percentile based on age and sex ◦ had a parent or guardian prepared to attend trial visits with them ◦ were willing to be actively involved in behavioural modification **Exclusion criteria:** • BMI ≥ 44 (to increase homogeneity of the group) • bodyweight ≥ 130 kg or < 55 kg • weight loss ≥ 3 kg within 3 months prior to screening • diabetes requiring antidiabetic medication • obesity associated with genetic disorders • history or presence of psychiatric disease • use of dexamphetamine or methylphenidate • active gastrointestinal tract disorders • ongoing bulimia or laxative abuse • use of anorexiants or weight-reduction treatments during the 3 months before randomisation **Diagnostic criteria:** see above

Chanoine 2005 (*Continued*)

Interventions	**Intervention:** orlistat + diet + exercise + behaviour therapy **Comparator:** placebo + diet + exercise + behaviour therapy **Number of trial centres:** 32 **Treatment before trial:** no **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** BMI, weight, fat mass (DEXA), waist circumference, adverse events
Study details	**Run-in period:** placebo was given for 2 weeks before treatment began in the intervention group **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To determine the efficacy and safety of orlistat in weight management of adolescents"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were randomized centrally according to a computer-generated randomization schedule prepared by the study's sponsor, with stratification by body weight (<80 kg or ≥80 kg) on day 1 and by weight loss during the lead-in period (<1 kg or ≥1 kg)" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "The allocation process was triple-blind; the allotted treatment group was obtained through an automated telephone system" **Comment:** allocation concealment was sufficient to protect against bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "double-blind study" **Comment:** the author confirmed all participants, trial personnel and outcome assessors were blinded

Chanoine 2005 (*Continued*)

Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "double-blind study" **Comment:** the author confirmed all participants, trial personnel and outcome assessors were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "double-blind study" **Comment:** the author confirmed all participants, trial personnel and outcome assessors were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "double-blind study" **Comment:** the author confirmed all participants, trial personnel and outcome assessors were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** even though an imputation method was used (LOCF), dropout rates were high. Effect on objective outcomes unclear
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** even though an imputation method was used (LOCF), dropout rates were high. Effect on subjective outcomes unclear
Selective reporting (reporting bias)	Unclear risk	**Comment:** unable to assess if all outcomes were reported due to the trial protocol not previously been published
Other bias	Unclear risk	**Quote:** "Hoffmann-La Roche was involved in the study design and conduct and in the analysis and interpretation of the data. All data were independently reanalyzed by an academic statistician" **Comment:** potential influence from the funding body (Hoffmann-La Roche). No rationale to explain the imbalance in the number of participants in the 2 groups

Clarson 2009

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • obese participants aged 10 to 16 years, defined as BMI > 95th percentile for age and sex, and who were also insulin resistant (defined by HOMA > 3.0, calculated as fasting plasma insulin (mU/L) x fasting serum blood glucose (mmol/L)/22.5) were enrolled over a 15-month period between 2005 and 2007. All the participants were

	assessed to be in puberty throughout the trial. HOMA values > 3 in adolescents are indicative of insulin resistance **Exclusion criteria:** • fasting blood glucose > 6.0 mmol/L • contraindications to metformin therapy **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + lifestyle intervention **Comparator:** lifestyle intervention **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** started metformin therapy at 500 mg/day, increasing by 500 mg/day every 7 days to a maximum tolerated dose of 500 mg x 3 per day
Outcomes	**Outcomes reported in abstract of publication:** BMI, HOMA, adiponectin-to-leptin ratio, dyslipidaemic profiles, metabolic risk factors e.g. plasma lipids and adipocytokines
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To access the efficacy of adding metformin to a structured lifestyle intervention in reducing BMI in obese adolescents with insulin resistance"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "subjects were randomized using computer random number generation to lifestyle intervention alone or lifestyle in combination with metformin" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	High risk	**Comment:** author confirmed allocation was not concealed
Blinding of participants and personnel (performance bias) Objective outcomes	High risk	**Quote:** "limitations to this study include the relatively small sample size and the absence of a placebo control group" **Comment:** the absence of a placebo in the control group meant participant and personnel blinding could not have been

Clarson 2009 (*Continued*)

		achieved. Author confirmed participants and personnel were not blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	**Quote:** "limitations to this study include the relatively small sample size and the absence of a placebo control group" **Comment:** the absence of a placebo in the control group meant participant and personnel blinding could not have been achieved. Author confirmed participants and personnel were not blinded
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	**Comment:** outcomes assessment was not blinded as confirmed by the author
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	**Comment:** outcomes assessment was not blinded as confirmed by the author
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** trial dropouts were fairly low; however, no imputation method was used
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** trial dropouts were fairly low; however, no imputation method was used
Selective reporting (reporting bias)	Unclear risk	**Comment:** no previously published protocol; therefore, unable to access reporting bias
Other bias	High risk	**Quote:** "limitations to this study include the relatively small sample size and the absence of a placebo control group" **Comment:** a power calculation was not performed, therefore likely the trial was underpowered. No placebo given to the control group. Unclear whether there were baseline differences

Franco 2014

Methods	Cross-over randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • aged 10 to 18 years • diagnosis of obesity (classification according to the World Health Organization) • ability to understand the guidelines

	• the adolescent's consent and the legal guardian • for initial inclusion, the participant needed to have already carried out some conventional treatments (diet/behavioural) prior, for at least 6 months **Exclusion criteria:** • cardiovascular problems and or arrhythmias • history of anorexia, bulimia and or psychiatric disorders • hypertension • chronic diseases • prior use of any other medication that interfered with the weight change, genetic syndromes, neuropsychomotor development delay, or a combination • glaucoma • use of illicit drugs, tobacco or alcohol • pregnant girls or that they had sexual intercourse without contraceptives **Diagnostic criteria:** see above
Interventions	**Intervention:** sibutramine + dietary guidance **Comparator:** placebo + dietary guidance **Number of trial centres:** 1 **Treatment before trial:** all participants had to have under gone at least 6 months of lifestyle intervention prior to recruitment **Titration period:** none
Outcomes	**Outcomes reported in abstract of publication:** % of participants who lost 10% of initial weight, weight, BMI
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** Portuguese **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "The aim of this study was to evaluate the efficacy and safety of sibutramine in association with a multidisciplinary program for treatment of obesity and check its influence on metabolic laboratory changes"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**From author:** "patients were distributed according to a table of random numbers" **Comment:** randomisation process assessed as low risk

Allocation concealment (selection bias)	Low risk	**From author:** "the study was double-blind placebo-controlled. Patients received placebo or sibutramine for 6 months, 1 month washout and in the next six months who received placebo began receiving sibutramine and vice verse. The researchers had no knowledge who was getting the drug and who was getting the placebo" **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "This study was double blinded placebo controlled cross-over type with duration of 13 months" **Comment:** author confirmed participants, trial personnel and outcome assessors were all blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "This study was double blinded placebo controlled cross-over type with duration of 13 months" **Comment:** author confirmed participants, trial personnel and outcome assessors were all blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "This study was double blinded placebo controlled cross-over type with duration of 13 months" **Comment:** author confirmed participants, trial personnel and outcome assessors were all blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "This study was double blinded placebo controlled cross-over type with duration of 13 months" **Comment:** author confirmed participants, trial personnel and outcome assessors were all blinded
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Quote:** "of the 63 patients who initiated the study only 23 patients completed the study" **Comment:** high attrition rate likely to affect objective outcomes
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Quote:** "of the 63 patients who initiated the study only 23 patients completed the study" **Comment:** high attrition rate likely to affect subjective outcome (i.e. adverse effects)

Franco 2014 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol available so risk was unclear
Other bias	High risk	**Comment:** lacked appropriate methodological detail and the failed to present the results in a meaningful and balanced manner. The cross-over nature of the trial added to the difficulty in deciphering the results with such a high attrition rate. No power calculation performed

Freemark 2001

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design

Participants	**Inclusion criteria:**
	• aged 12 to 19 years and had a BMI > 30 kg/m^2. Criteria for enrolment included:
	  ○ a fasting insulin concentration > 15 mU/mL
	  ○ ≥ 1 first- or second-degree relative (parent, sibling or grandparent) with type 2 diabetes
	Exclusion criteria: -
	Diagnostic criteria: see above

Interventions	**Intervention:** metformin **Comparator:** placebo **Number of trial centres:** 1 **Treatment before trial:** none **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** BMI, serum leptin, fasting blood glucose, fasting insulin levels, insulin sensitivity, glucose effectiveness, haemoglobin A1c, serum lipids, serum lactate, adverse events
Study details	**Run-in period:** 48 hours' inpatient tests **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial funding and noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "We reasoned that drugs that increase glucose tolerance in diabetic patients might prove useful in preventing the progression to glucose intolerance in high-risk patients"
Notes	

Risk of bias

Freemark 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "patients were randomized to the metformin and placebo groups by a research pharmacist using computer-generated randomization tables" **Comment:** an appropriate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "the allocation was made by the research pharmacist at the first medication visit. The pill bottles were coded - thus the pharmacist was blinded to the medication" **Comment:** author confirmed allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "We conducted a double-blind, placebo-controlled study" **Comment:** author confirmed all participants and trial personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "We conducted a double-blind, placebo-controlled study" **Comment:** author confirmed all participants and trial personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "We conducted a double-blind, placebo-controlled study" **Comment:** author confirmed all participants and trial personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "We conducted a double-blind, placebo-controlled study" **Comment:** author confirmed all participants and trial personnel were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** a missing data method was not used; however, dropout rates were fairly low
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** a missing data method was not used; however, dropout rates were fairly low
Selective reporting (reporting bias)	Unclear risk	**Comment:** since no protocol was published before trial was completed, it is unclear whether all outcomes were reported
Other bias	High risk	**Quote:** "the study involved a small number of patients and the results must be con-

Freemark 2001 (*Continued*)

		firmed in a larger sample“ **Comment:** the trial did not perform a power calculation and the sample size was small. It is likely the trial was underpowered. Potential influence of a commercial funding source. Baseline differences identified and not adjusted for in the analysis

García-Morales 2006

Methods	Parallel randomised controlled clinical trial, randomisation ratio: 1:1, superiority design
Participants	**Inclusion criteria:** • all the participants were Mestizo living in the metropolitan area of Mexico City. • male and female participants aged 14 to 18 years with a sex-specific BMI for age and sex > 95th percentile (obesity) to be enrolled in the trial after written informed consent had been obtained from both parents and oral informed consent was obtained from the participants **Exclusion criteria:** • lactating or pregnant females • females who were sexually active without using acceptable contraceptive methods • SBP ≥140 mm Hg or DBP ≥ 90 mm Hg • history of anorexia nervosa or bulimia • received treatment in the previous 30 days with corticosteroids, monoamine oxidase inhibitors, antidepressants, lithium, drugs for weight loss, nasal or respiratory anticongestives, migraine treatment, gastrointestinal prokinetics or antihistaminics • using alcohol or recreational drugs • history of depression or weight loss treatment in the last 6 months • genetic disease associated with obesity, hypothyroidism, cancer, blood disease, gastrointestinal surgery, psychiatric disease, a history of work or school problems, weight loss ≥ 3 kg in the last 3 months, or who were unable to follow the protocol (i.e. they did not attend or were late for visits, or they failed to follow the directions of the investigators) **Diagnostic criteria:** see above
Interventions	**Intervention:** sibutramine + diet + exercise **Comparator:** placebo + diet + exercise **Number of trial centres:** 1 **Treatment before trial:** participants received dietetic advice 15 days before the beginning of the medications. In addition, clinical control visits also occurred before the start of the trial **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** mean weight loss, net weight loss, waist circumference, % BMI loss, SBP, DBP, heart rate, adverse events
Study details	**Run-in period:** yes - dietetic advice **Trial terminated early:** no

García-Morales 2006 (*Continued*)

Publication details	**Language of publication:** English **Commercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "The goal of this article was to assess the efficacy and safety of sibutramine in obese Mexican adolescents"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were block-randomized by using a computer generated list" **Comment:** an appropriate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "Patients were block-randomized by using a computer generated list. All the materials for a patient were identified by the patient number. The placebo and drug capsules were identical in appearance and smell. The trial medications were prepared by one author (A.B.), who did not know the identity of the patients. Another author (L. M.G.-M.) received the trial materials without any knowledge of the procedures or order in the random number list" **Comment:** allocation was appropriately concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote:** "This was a 6 month, randomized, double blind, placebo-controlled, prospective clinical trial of sibutramine QD" **Comment:** unclear who was blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote:** "This was a 6 month, randomized, double blind, placebo-controlled, prospective clinical trial of sibutramine QD" **Comment:** unclear who was blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Quote:** "This was a 6 month, randomized, double blind, placebo-controlled, prospective clinical trial of sibutramine QD" **Comment:** unclear who was blinded

García-Morales 2006 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote:** "This was a 6 month, randomized, double blind, placebo-controlled, prospective clinical trial of sibutramine QD" **Comment:** unclear who was blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Quote:** "the last observation replaced the missing values" **Comment:** LOCF and modified intention-to-treat analysis was used to replace missing data for the primary outcomes. However, the 5 participants who dropped out before the first month were not included
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** baseline and follow-up data for subjective outcomes were not reported in the publication
Selective reporting (reporting bias)	High risk	**Quote:** "A detailed questionnaire on food consumption was completed at the beginning and end of the trial" **Comment:** data on food consumption were not provided in the publication
Other bias	Unclear risk	**Quote:** "This trial was supported by Abbott Laboratories de Mexico, S.A. de C. V., Mexico City, D.F, Mexico. Dr. Berber was the medical manager of sibutramine in Mexico from 1995 to April 2004. The protocol was designed by all the authors; the study was conducted by the non industry authors; and analysis and publication formalities were performed by Drs. Garcia-Morales, Del-Rio-Navarro, and Berber. The non industry authors had access to all the data generated" **Comment:** the trial sponsor (Abbot Laboratories) may have influenced the trial's results

Godoy-Matos 2005

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • boys and girls, aged 14 to 17 years, with a BMI of 30 to 45 (BMI calculated as weight (kg) divided by height squared (m)). To avoid growth variation, all participants were required to have adult bone age, as determined by left hand radiography

	(Greulich- Pyle method) **Exclusion criteria:** • diabetes mellitus • endocrine diseases predisposing to obesity (e.g. Cushing's syndrome) • severe hyperlipidaemia (total cholesterol 300 mg/dL or triglycerides 500 mg/dL) • systemic or major psychiatric disorders • history of bulimia or anorexia • uncontrolled hypertension (DBP 110 mm Hg) or other cardiovascular diseases • weight loss ≥ 3 kg within 2 months or use of weight loss or weight gain drugs within 3 months before recruitment • drug or alcohol abuse • recent tobacco cessation or intention to quit during trial period • pregnancy or lactation **Diagnostic criteria:** see above
Interventions	**Intervention:** sibutramine + hypocaloric diet + exercise **Comparator:** placebo + hypocaloric diet + exercise **Number of trial centres:** 1 **Treatment before trial:** during the run-in period all participants received dietary counselling to achieve an energy deficit of 500 kcal/day. They also all received placebo capsules **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** weight loss, mean BMI reduction, adverse events
Study details	**Run-in period:** a single-blind, 4-week, placebo run-in period **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "The aim of this study was to determine the efficacy and safety of sibutramine in obese adolescents"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were allocated in a random block fashion to placebo or sibutramine" **Comment:** details of the randomisation process was provided by the author - process seems adequate

Allocation concealment (selection bias)	Low risk	**Quote:** "By means of a sealed envelope with a coded number. A container with boxes for each patient displaying the code number were provided. Each box had blisters for each visit with 40 capsules (similar for placebo or active drug). Patients were supplied in each visit with a new box. Adherence was judged by counting used capsules" **Comment:** allocation was concealed as confirmed by the author
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "a randomised, double-blind, placebo-controlled trial" **Comment:** author confirmed all participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "a randomised, double-blind, placebo-controlled trial" **Comment:** author confirmed all participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "a randomised, double-blind, placebo-controlled trial" **Comment:** author confirmed all participants and personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "a randomised, double-blind, placebo-controlled trial" **Comment:** author confirmed all participants and personnel were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** dropout fairly low; however, was higher in the placebo group. Only completers results shown
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** dropout fairly low; however, was higher in the placebo group. Only completers results shown
Selective reporting (reporting bias)	Unclear risk	**Comment:** a protocol was not published before the trial was completed, therefore it is unclear whether all outcomes were reported
Other bias	High risk	**Quote:** "this work was supported by a grant from Abbott Laboratories" **Comment:** the trial did not highlight how involved Abbott Laboratories were the trial

		design, analysis and interpretation of the results **Quote:** "Conclusions regarding treatment group differences are somewhat limited by the small sample size" **Comment:** the trial did not perform a power calculation. Likely the trial was underpowered

Kendall 2013

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • BMI > 98th centile on UK BMI centile charts • impaired glucose tolerance, i.e. OGTT 2-hour plasma glucose value 7.8 to 11.1 mmol/L (with or without impaired fasting glucose 6.1 to 7.0 mmol/L) or hyperinsulinaemia, i.e. fasting insulin > 26 mIU/L or 120-min insulin > 89 mIU/L (pubertal/ postpubertal children); fasting insulin > 15 mIU/L or 120-min insulin > 89 mIU/L (prepubertal children) **Exclusion criteria:** • glycosuria, ketonuria, other chronic illness or chromosomal abnormality or syndrome, e.g. Prader-Willi, renal insufficiency, hepatic dysfunction, raised ALT (> 7.0 IU/L), chronic diarrhoea and a previous episode of lactic acidosis **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + healthy lifestyle advice **Comparator:** placebo + healthy lifestyle advice **Number of trial centres:** 6 **Treatment before trial:** all participants were provided with standardised healthy lifestyle advice at the start in a 1-to-1 session, including a healthy diet advice sheet and increased levels of exercise (available upon request) **Titration period:** participants were instructed to gradually increase the dose by taking 1 pill with breakfast for 1 week and then 1 pill with breakfast and the evening meal the next week and then 2 pills with breakfast and 1 pill with the evening meal thereafter (1.5 g/day)
Outcomes	**Outcomes reported in abstract of publication:** BMI-SDS, fasting glucose, ALT, ALR
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "The objective of the study was to assess the effect of metformin on body mass index SD score (BMI-SDS), metabolic risk factors, and adipokines"

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "Independent pharmacists dispensed either metformin or placebo according to a computer-generated randomization list for each stratification group" **Comment:** an appropriate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "The third party, concealed allocation process ensured that participants and all investigators were unaware of the allocated treatment" **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote:** "This was a prospective, randomized, double-blind, placebo-controlled trial" **Comment:** unclear who was blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote:** "This was a prospective, randomized, double-blind, placebo-controlled trial" **Comment:** unclear who was blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Quote:** "This was a prospective, randomized, double-blind, placebo-controlled trial" **Comment:** unclear who was blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote:** "This was a prospective, randomized, double-blind, placebo-controlled trial" **Comment:** unclear who was blinded
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Quote:** "There were a number of limitations to the MOCA [Metformin in Obese Children and Adolescents] trial including the dropout rate" **Comment:** dropout rate was high and no imputation method was used to replace missing data

Kendall 2013 (*Continued*)

Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Quote:** "There were a number of limitations to the MOCA trial including the dropout rate" **Comment:** dropout rate was high and no imputation method was used to replace missing data
Selective reporting (reporting bias)	Unclear risk	**Quote:** "In the MOCA trial, three previously validated questionnaires (food frequency, diet and eating behavior, and physical activity) were completed by each child at the start and end of the trial. This amounted to a large amount of data, and resources were unfortunately insufficient to allow analysis of these data for inclusion in this paper" **Comment:** behaviour change results were not reported; however, the publication did give a valid reason to why
Other bias	Unclear risk	**Comment:** insufficient information to assess whether an important risk of bias exists

Maahs 2006

Methods	Parallel randomised controlled clinical trial, randomisation ratio: 1:1, superiority design
Participants	**Inclusion criteria:** • aged 14 to 18 years • BMI > 85th percentile for age and sex **Exclusion criteria:** • known secondary causes for obesity (e.g. hypothyroidism, daily corticosteroid exposure > 30 days, history of significant exposure to corticosteroids for chronic illness during the past year and known genetic causes of obesity) **Diagnostic criteria:** see above
Interventions	**Intervention:** orlistat + diet and exercise therapy **Control:** placebo + diet and exercise therapy **Number of trial centres:** 1 **Treatment before trial:** none **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** BMI reduction, adverse effects, laboratory measurements
Study details	**Run-in period:** no **Trial terminated early:** no

Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To evaluate the efficacy of orlistat to enhance weight loss in obese adolescents"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote:** "The GCRC [General Clinical Research Center] statistician generated the randomization sequence before the start of the study" "Two sets of subjects (a sister-sister pair and a girlfriend-boyfriend pair) were assigned to the same cohort, as determined by the order of entry of the first member of the pair; the next paired subject was blocked into the same cohort and given the next available number in that cohort" **Comment:** not all participants were randomised
Allocation concealment (selection bias)	Low risk	**Quote:** "The list of randomization assignments was sealed and sent to the study pharmacist, who had no contact with study subjects" **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "Only the research pharmacist was aware of treatment status" **Comment:** participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "Only the research pharmacist was aware of treatment status" **Comment:** participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "Only the research pharmacist was aware of treatment status" **Comment:** participants and personnel were blinded

Maahs 2006 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "Only the research pharmacist was aware of treatment status" **Comment:** participants and personnel were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** an imputation method was not used to replace missing data; however, dropout was fairly low
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** unable to access effect on subjective outcomes as quality of life results were not reported
Selective reporting (reporting bias)	High risk	**Comment:** results from the quality of life questionnaires were not reported
Other bias	Unclear risk	**Comment:** unclear if any other bias exists

Mauras 2012

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • uncomplicated (exogenous) obesity defined as BMI > 95th percentile for US standards for < 5 years • normal blood pressure, glucose tolerance and total cholesterol **Exclusion criteria:** • chronic illness, medications, alcohol use and smoking **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + diet/exercise intervention **Comparator:** diet/exercise intervention **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** metformin was started at 250 mg orally, twice daily, before meals titrating up to 500 mg twice daily in children < 12 years old and 1000 mg twice daily as tolerated in older children
Outcomes	**Outcomes reported in abstract of publication:** weight loss, hsCRP, fibrinogen, intrahepatic fat
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal

Stated aim for study	Quote from publication: "To determine if metformin improves markers of inflammation, thrombosis, and intrahepatic fat contents in children with uncomplicated obesity"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote (from the author):** "randomisation assignments were balanced for pubertal status. We used sealed envelopes with equal amount of labels organized at random for pubertal and pre-pubertal kids to choose from at their CRC visit (baseline)" **Comment:** adequate randomisation process
Allocation concealment (selection bias)	Low risk	**Comment:** the author of the trial confirmed allocation was concealed via the sealed envelopes
Blinding of participants and personnel (performance bias) Objective outcomes	High risk	**Comment:** no placebo was given to the control group, therefore the participants would not have been blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	**Comment:** no placebo was given to the control group, therefore the participants would not have been blinded
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	**Comment:** author confirmed the outcome assessors were not blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	**Comment:** author confirmed the outcome assessors were not blinded
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Comment:** there was a high number of dropouts and no imputation method was used to replace missing data
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** there was a high number of dropouts and no imputation method was used to replace missing data

Selective reporting (reporting bias)	Low risk	**Quote:** "The study was registered at http://www.clinicaltrials.gov (NCT00139477)" **Comment:** all outcomes reported on the clinical trial register page were reported in the publication
Other bias	Unclear risk	**Comment:** unable to access if any other bias were present

NCT00001723

Methods	**Type of trial:** interventional, randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** • diabetes mellitus • hypertension • metabolic disease • obesity • sleep apnoea syndrome **Enrolment:** 200 **Inclusion criteria:** • good general health. People taking medications for obesity-related comorbid conditions not excluded • obesity: BMI for age and triceps skinfold > 95th percentile (determined by National Health and Nutrition Examination Survey I age-, sex- and race-specific data). All participants > 60 kg in bodyweight • evidence for a quantifiable obesity-related comorbidity. Examples include: systolic or diastolic hypertension (determined by age-specific charts); frank type 2 diabetes, impaired glucose tolerance assessed by OGTT; hyperinsulinaemia (fasting insulin > 15 mIU/mL); significant hyperlipidaemia (total cholesterol > 200 mg/dL, low-density lipoprotein cholesterol > 129 mg/dL or fasting triglycerides > 200 mg/dL); hepatic steatosis (ALT or AST above normal range with negative hepatitis trials) or sleep apnoea documented by a sleep trial • aged 12 to 17 years at the start of the trial • for girls with childbearing potential, a negative pregnancy test before taking and while taking trial medication. Sexually active females used an effective form of contraception, including. total abstinence, oral contraceptives, an intrauterine device, levonorgestrel implants or medroxyprogesterone acetate injections. If one of these could not be used, contraceptive foam with a condom • race of all 4 grandparents self-identified as either all Caucasian or all African-American **Exclusion criteria:** • presence of renal, hepatic (other than obesity-related steatosis), gastrointestinal,

	most endocrinological (e.g. Cushing's syndrome), or pulmonary disorders (other than either asthma not requiring continuous medication or sleep apnoea-related disorders) • pregnancy, breastfeeding or having unprotected intercourse • had, or had parent or guardians who had, current substance abuse or a psychiatric disorder or other condition which, in the opinion of the investigators, would impede competence or compliance or possibly hinder completion of the trial • regularly used prescription medications unrelated to the complications of obesity. Oral contraceptive use permitted, provided the contraceptive was used for at least 2 months before starting trial medication. Use of nonprescription and prescription medications reviewed on a case-by-case basis; depending on the medication, participants who have continued to take prescription medication for at least 3 months prior to trial entry were eligible • recent use (within 6 months) of anorexiant medications for weight reduction • inability to undergo magnetic resonance imaging (e.g. volunteers with metal within their bodies including cardiac pacemakers, neural pacemakers, aneurysmal clips, shrapnel, ocular foreign bodies, cochlear implants, nondetachable electronic or electromechanical devices such as infusion pumps, nerve stimulators, bone growth stimulators, etc. that are contraindications)
Interventions	**Intervention:** orlistat **Comparator:** placebo
Outcomes	**Primary outcome:** change in BMI SDS (baseline to 6 months) **Secondary outcomes:** • change in bodyweight • change in BMI • change in body fat, body fat distribution measures obtained from DEXA • effect of race on change in weight, difference in change of weight according to race (non-Hispanic white participants versus non-Hispanic black participants)
Study details	**NCT number:** NCT00001723 **Other trial ID numbers:** 980111, 98-CH-0111
Publication details	"Safety and Efficacy of Orlistat (Xenical, Hoffmann LaRoche) in African American and Caucasian Children and Adolescents with Obesity-Related Comorbid Conditions"
Stated aim for study	Quote: "Researchers propose to determine the safety, tolerability, and efficacy of Xenical [orlistat] in 12-17 year old severely obese African American and Caucasian children and adolescents who have one or more obesity-related disease (hypertension, hyperlipidemia, sleep apnea, hepatic steatosis, insulin resistance, impaired glucose tolerance, or Type 2 diabetes)"
Notes	The trial was completed when identified. Trial collaborators: • Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) • Roche Pharma AG Results presented on the clinicaltrials.gov website and in a conference abstract Results from ClinicalTrials.gov Results Database: change in BMI SDS orlistat: -0.12 ±

	0.02 and placebo: -0.06 ± 0.02. ANCOVA differences between groups P value = 0.007. Change in bodyweight orlistat: -2.9 ± 0.7 and placebo: -0.6 ± 0.7. No statistical analysis provided. Change in BMI orlistat: -1.44 ± 0.26 and placebo: -0.50 ± 0.20. No statistical analysis provided. 95/100 participants in orlistat and 94/100 in placebo group experienced adverse events with the most common being gastrointestinal disorders. No serious adverse events in orlistat group. In placebo group, 1 participant had hypoglycaemia and 1 participant had left lower quadrant pain and vomiting, and was admitted to hospital overnight

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote from author (via email):** "We randomized participants in a 1:1 fashion to orlistat 120 mg or identical appearing placebo thrice daily with meals plus a daily multivitamin (Centrum, Whitehall-Robins Healthcare, Madison, NJ) containing 5000 IU vitamin A (80% as retinol, 20% as beta carotene), 400 IU vitamin D as ergocalciferol, 30 IU vitamin E (as di-α tocopheryl acetate), and 25 mcg vitamin K (as phytonadione). Investigators assigned consecutive code numbers to participants from pre-specified lists that were stratified by race (Caucasian versus African American), sex (Male, Female), and degree of pubertal development (3 strata for boys: testes <15ml, testes 15-20mL, and testes >20mL; for girls: Breast Tanner stage I-III; Tanner stage IV, and Tanner stage V). The NIH CRC Pharmaceutical Development Section used permuted blocks with stratification to generate allocations that translated code numbers into trial group assignments by using a pseudo-random number program" **Comment:** randomisation process described
Allocation concealment (selection bias)	Low risk	**Quote from author (via email):** "Pharmacy personnel not involved with the conduct of the study, dispensed identical-appearing study capsules in containers that differed only by participant code number. During the trial, no participant, investigator, or other medical or nursing staff interacting with participants was aware of study

NCT00001723 (*Continued*)

		group assignments“ **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** ”Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)“ **Comment:** participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** ”Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)“ **Comment:** participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** ”Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)“ **Comment:** assessors were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** ”Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)“ **Comment:** assessors were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Comment:** according to ClinicalTrials.gov, 87% of orlistat participants completed the trial, 84% completed placebo arm
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Comment:** according to ClinicalTrials.gov, 87% of orlistat participants completed the trial, 84% completed placebo arm
Selective reporting (reporting bias)	High risk	**Comment:** there are differences in the results reported on the ClinicalTrial.gov website and in the conference abstract
Other bias	Unclear risk	**Comment:** unclear as limited information available

Ozkan 2004

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • severe exogenous obesity, described as weight for height index > 140% in otherwise healthy participants, not associated with endocrinopathy, genetic syndromes or medications • adolescents (Tanner stage 2 or higher) aged 10 to 16 years, and informed consent

	for the trial **Exclusion criteria:** - **Diagnostic criteria:** see above
Interventions	**Intervention:** conventional treatment + orlistat **Control:** conventional treatment **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** adverse effects, bodyweight loss, % bodyweight lost, BMI
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To investigate the efficacy and tolerability of orlistat in obese adolescents, a prospective, open-label, randomised, controlled pilot trial was performed"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote:** "Randomisation was done by alternation of successive patients, who met the inclusion criteria, to receive conventional treatment alone or orlistat in addition to conventional treatment" **Comment:** an inappropriate randomisation method was used
Allocation concealment (selection bias)	High risk	**Comment:** allocation was likely not concealed due to the randomisation method used
Blinding of participants and personnel (performance bias) Objective outcomes	High risk	**Quote:** "the true benefit of orlistat versus conventional therapy remains to be determined in a larger placebo-controlled study" **Comment:** the control group did not receive a placebo therefore could not have been blinded

Ozkan 2004 (*Continued*)

Blinding of participants and personnel (performance bias) Subjective outcomes	High risk	**Quote:** "the true benefit of orlistat versus conventional therapy remains to be determined in a larger placebo-controlled study" **Comment:** the control group did not receive a placebo therefore could not have been blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Comment:** unclear if outcome assessors were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Comment:** an imputation method to replace missing data were not performed, and dropout rate was moderate
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** an imputation method to replace missing data were not performed, and dropout rate was moderate
Selective reporting (reporting bias)	Unclear risk	**Comment:** BMI was reported in different formats; median BMI at baseline and mean BMI at follow-up. No protocol published
Other bias	High risk	**Comment:** there were significant differences in baseline BMI between groups which were not accounted for. A power calculation was not performed, therefore trial may have been underpowered

Prado 2012

Methods	Parallel randomised controlled trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • obese adolescents (BMI > 95th percentile for age and sex) • postmenarchal • aged 13 to 19 years • ≥ 1 risk factor for type 2 diabetes **Exclusion criteria:** • diagnosis of diabetes mellitus type 1 or 2 • kidney diseases • liver or respiratory alcoholism • eating disorders • other psychiatric disorders that could diminish adherence to treatment

	• hypersensitivity to metformin • pharmacological treatments by metabolic or nutritional impact during the last 3 months • pregnancy **Diagnostic criteria:** obesity defined as BMI > 95th percentile for age and sex. Risk factors for type 2 diabetes include first- or second-degree relative with a history of type 2 diabetes, or alteration in the results of the following examinations within the past 6 months: glycaemia fasting ≥ 100 mg/dL, postload glucose ≥ 140 mg/dL or HOMA > 3.0
Interventions	**Intervention:** metformin + nutritional guide + exercise programme **Comparator:** placebo + nutritional guide + exercise programme **Number of trial centres:** 1 **Treatment before trial:** none **Titration period:** no
Outcomes	**Outcomes reported in abstract of publication:** weight, BMI, metabolic risk profile
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** Spanish **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To analyze the anthropometric and metabolic impact of metformin in obese adolescents at risk for type 2 diabetes"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Recruited adolescents were randomly assigned into two groups (A and B) through a sequence computational randomization" **Comment:** an appropriate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "An external laboratory was in charge of packing and labelling bottles, keeping content knowledge in confidence until the study ended" **Comment:** there was allocation concealment

Prado 2012 (*Continued*)

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Comment:** author confirmed participants and trial personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Comment:** author confirmed participants and trial personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Comment:** unclear if outcome assessment was blinded and if this would have results in detection bias for the objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Comment:** unclear if outcome assessment was blinded and if this would have results in detection bias for the subjective outcomes
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Comment:** there was no imputation method to replace missing data and dropout rates were fairly high
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Comment:** there was no imputation method to replace missing data and dropout rates were fairly high
Selective reporting (reporting bias)	Unclear risk	**Comment:** do not give follow-up data for some outcomes such as blood pressure
Other bias	Unclear risk	**Comment:** unable to make an assessment on other bias due to lack of information

Rezvanian 2010

Methods	Parallel randomised controlled trial, randomisation ratio: 1:1:1:1, superiority design
Participants	**Inclusion criteria:** • aged 10 to 18 years • failure in weight loss after 3 months of nonpharmacological treatment (by lifestyle modification advised in study author's clinic) • BMI ≥ age- and sex-specific 95th percentile according to the revised CDC growth charts **Exclusion criteria:** • people with syndromal obesity, endocrine disorders, any physical disability, history of chronic medication use, using monoamine oxidase inhibitors, history of mood disorder in parents and first-degree relatives (depression or bipolar), history of any chronic diseases (e.g. kidney disorders, lung diseases, hepatitis or a combination) **Diagnostic criteria:** see above

Interventions	**Intervention 1:** metformin + healthy eating + physical activity advice **Intervention 2:** fluoxetine + healthy eating + physical activity advice **Intervention 3:** metformin + fluoxetine + healthy eating + physical activity advice **Comparator:** placebo + healthy eating + physical activity advice **Number of trial centres:** 1 **Treatment before trial:** 3 months of nonpharmacological treatment (by lifestyle modification advised in study author's clinic) **Titration period:** metformin dosage increased weekly from 500 mg/day to 1500 mg/day. Fluoxetine dosage of 10 mg/day increased to 20 mg/day after 3 weeks
Outcomes	**Outcomes reported in abstract of publication:** BMI, waist circumference, adverse effects
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "We aimed to compare the effects of three types of drug regimens and placebo on generalized and abdominal obesity among obese children and adolescents who did not succeed to lose weight 3 months after lifestyle modification (diet and exercise)"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Sequence was generated by computer generated random number table" **Comment:** randomisation was an adequate method
Allocation concealment (selection bias)	Unclear risk	**Comment:** unclear if allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "triple-masked randomized clinical trial" **Comment:** participants and personnel would have been blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "triple-masked randomized clinical trial" **Comment:** participants and personnel would have been blinded

Rezvanian 2010 (*Continued*)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "triple-masked randomized clinical trial" **Comment:** outcomes assessors would have been blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "triple-masked randomized clinical trial" **Comment:** outcomes assessors would have been blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** an imputation method was not used to replace missing data; however, dropout rate was fairly low
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** an imputation method was not used to replace missing data; however, dropout rate was fairly low
Selective reporting (reporting bias)	Unclear risk	**Comment:** unable to assess if all outcomes were reported due to the unavailability of a protocol
Other bias	Unclear risk	**Comment:** unable to access if any other bias was present

Srinivasan 2006

Methods	Cross-over randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • aged 9 to 18 years referred to the endocrine clinic at The Children's Hospital at Westmead between March 2002 and March 2003 with obesity, as defined by the International Obesity Task Force, and clinical suspicion of insulin resistance, as defined by either a fasting insulin (milliunits per litre) to glucose (millimoles per litre) ratio > 4. 5 (15) or the presence of acanthosis nigricans **Exclusion criteria:** • known type 1 or type 2 diabetes mellitus, • contraindications to metformin therapy or magnetic resonance imaging scanning (or both) and weight > 120 kg due to technical difficulties with DEXA scans **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + "standardised information on healthy eating and exercise" **Comparator:** placebo + "standardised information on healthy eating and exercise" **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** both metformin and placebo doses were gradually built up over a 3-week period to a final dose of 1 g twice daily

Srinivasan 2006 (*Continued*)

Outcomes	**Outcomes reported in abstract of publication:** mean age, median BMI z score, weight, BMI, waist circumference, subcutaneous abdominal adipose tissue, fasting insulin
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "We assessed the effect of metformin on body composition and insulin sensitivity in pediatric subjects with exogenous obesity"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Block randomization (blocks of four) with stratification by pubertal stage (Tanner 1-2 or Tanner 3-5) was performed by computer generated random number allocation" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote (from the author):** "randomisation was performed in the hospital pharmacy by random number generation and only revealed for data analysis" **Comment:** allocation was likely concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "All participants and investigators were blinded to the intervention" **Comment:** participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "All participants and investigators were blinded to the intervention" **Comment:** participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "All participants and investigators were blinded to the intervention" **Comment:** participants and personnel were blinded

Srinivasan 2006 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "All participants and investigators were blinded to the intervention" **Comment:** participants and personnel were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** an imputation method was not used to replace missing data; however, dropout rates were fairly low
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** an imputation method was not used to replace missing data; however, dropout rates were fairly low
Selective reporting (reporting bias)	Unclear risk	**Comment:** the publication did not report raw data for some of the outcomes, but a clinical trial entry was available and there were no differences
Other bias	Unclear risk	**Comment:** no power calculation was performed; therefore, the trial may have been underpowered

Van Mil 2007

Methods	Parallel controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • aged 12 to 18 years, initially selected for BMI ≥ 97th percentile, and further selected for triceps skinfold thickness ≥ 97th percentile for age and sex with persisting obesity despite previous professionally supervised weight loss attempts (97.5th percentile is equivalent to 2 SD) **Exclusion criteria:** • endocrine causes or other secondary causes of obesity • significant physical or medical illness that could influence the results of the trial **Diagnostic criteria:** see above
Interventions	**Intervention:** sibutramine + energy-restricted diet and exercise plan **Comparator:** placebo + energy-restricted diet and exercise plan **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** 5 mg placebo or sibutramine, taken once daily in the morning. After 2 weeks, the dose was increased to 10 mg/day
Outcomes	**Outcomes reported in abstract of publication:** BMI-SDS, BMI, % fat mass, BMRadj, total energy expenditure
Study details	**Run-in period:** no **Trial terminated early:** no

Publication details	**Language of publication:** English **Commercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "The objective of this trial was to examine the effect of treatment with sibutramine (10 mg) on body composition and energy expenditure in obese adolescents"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomisation was performed by Knoll Pharmaceuticals. Boxes with medication for each visit were numbered for each subject. Subjects received their number and the boxes with medication that belonged to that number. The numbers/medication was handed out in order of inclusion in the study" **Comment:** author clarified randomisation process; however, it was unclear if the process would have introduced selection bias
Allocation concealment (selection bias)	Low risk	**Quote:** "Knoll Pharmaceuticals BV [currently Abbott Laboratories (Hoofddorp, The Netherlands)], manufactured and provided code-numbered placebo and sibutramine capsules. Subjects received their trial and medication code according to order of entrance into the study, without stratification" **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Comment:** author confirmed participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Comment:** author confirmed participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment:** author confirmed outcome assessment was blinded

Van Mil 2007 (*Continued*)

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Comment:** author confirmed outcome assessment was blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** an imputation method was used; however, results only shown for completers. Dropout rates fairly low
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** an imputation method was used; however, results only shown for completers. Dropout rates fairly low
Selective reporting (reporting bias)	Unclear risk	**Comment:** unclear whether all outcomes were reported due to no previously published protocol
Other bias	Unclear risk	**Quote:** "E.G.A.H.V.M. was previously employed by Maastricht University, partly on a research grant from Knoll, currently Abbott Pharmaceuticals, The Netherlands" **Comment:** potential influence of funding source

Wiegand 2010

Methods	Parallel randomised controlled trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • obese • aged 10 to 17 years • HOMA IR > 3 or > 95th percentile according to Allard et al • nondiabetic • normal liver and kidney function • already were enrolled in the trial **Exclusion criteria:** • pre-existing diabetes • pregnancy • liver enzymes > 1.5 times the upper limit of normal or elevated creatinine > 1.5 mg/dL • severe chronic or mental illness **Diagnostic criteria:** obesity (not defined)
Interventions	**Intervention:** metformin + multiprofessional lifestyle intervention **Comparator:** placebo + multiprofessional lifestyle intervention **Number of trial centres:** 2 **Treatment before trial:** 6-month multiprofessional lifestyle intervention **Titration period:** no

Wiegand 2010 (*Continued*)

Outcomes	**Outcomes reported in abstract of publication:** BMI, HOMA-IR, fasting insulin, insulin sensitivity index, metabolic syndrome
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial and noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To study whether metformin reduces obesity, homeostasis model assessment for insulin resistance index (HOMA-IR), and the metabolic syndrome (MtS) in obese European adolescents in addition to previous unsuccessful lifestyle intervention"
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no description of the randomisation process
Allocation concealment (selection bias)	Unclear risk	**Comment:** unclear if allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote:** "we performed a double-blind, randomized controlled clinical trial" **Comment:** unclear who was blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote:** "we performed a double-blind, randomized controlled clinical trial" **Comment:** unclear who was blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Quote:** "we performed a double-blind, randomized controlled clinical trial" **Comment:** unclear who was blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote:** "we performed a double-blind, randomized controlled clinical trial" **Comment:** unclear who was blinded
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	**Comment:** no imputation method was used to replace missing data; however, dropout was fairly low

Wiegand 2010 (*Continued*)

Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	**Comment:** no imputation method was used to replace missing data; however, dropout was fairly low
Selective reporting (reporting bias)	Unclear risk	**Comment:** unable to find the clinical trial entry; hence, it is unclear whether selective reporting occurred
Other bias	High risk	**Quote:** "The study was supported in part by BMBF Research grant 01 GS 0825 and by MERCK SANTE S.A.S, Lyon, France (10'000,- Euro)" **Comment:** trial was partly funded by a pharmaceutical company. The authors do not declare their involvement in the design, analysis and interpretation of the results

Wilson 2010

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria**: • BMI ≥ 95th percentile for age and sex but weighed < 136 kg (weight limit for DEXA table) **Exclusion criteria:** • previous diagnosis of diabetes mellitus • had ever used a medication to treat diabetes or insulin resistance or weight loss • were taking any medications known to increase metformin levels • received recent glucocorticoid therapy • had any identified syndrome or medical disorder predisposing to obesity • had surgical therapy of obesity • attended formal weight loss programme in last 6 months • had significant alcohol use in last 6 months • had elevated creatinine or liver enzymes • had untreated disorders of the thyroid • impaired mobility • had ever been pregnant **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + lifestyle intervention programme **Comparator:** placebo + lifestyle intervention programme **Number of trial centres:** 6 **Treatment before trial:** 4-week placebo run-in phase, during which participants were required to attend at least 2 of 3 scheduled lifestyle modification sessions and demonstrate 80% compliance with daily placebo treatment (pill count) for subsequent randomisation **Titration period:** participants either given metformin XR or identical placebo tablets and instructed to take 1 tablet/day (metformin hydrochloride XR 500 mg or placebo) orally before dinner for 2 weeks, then 2 tablets/day for 2 weeks, then 4 tablets/day from

	week 8 to week 52
Outcomes	**Outcomes reported in abstract of publication:** mean adjusted BMI, body compositions, abdominal fat, insulin indices
Study details	**Run-in period:** 4-week placebo run-in phase (see above) **Trial terminated early:** no
Publication details	**Language of publication:** English **Noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "to test the hypothesis that 48 weeks of daily metformin hydrochloride extended release (EX) will reduce body mass index in obese adolescents, as compared with placebo"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Subjects who successfully completed the run-in period were randomized to metformin XR or placebo treatment according to random sequences constructed at the Data Coordinating Center. To ensure balance across major factors, the randomization was stratified by site and sex" "To ensure nonpredictability of assignment, the randomization sequence was grouped in randomly permuted blocks of 2 and 4, and assignments were randomly permuted within block" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "Subjects who successfully completed the run-in period were randomized to metformin XR or placebo treatment according to random sequences constructed at the Data Coordinating Center" **Comment:** adequate allocation concealment
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "Subjects and study personnel were blinded to assignment throughout the entire study" **Comment:** performance bias likely to be

		reduced by blinding participants and trial personnel
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "Subjects and study personnel were blinded to assignment throughout the entire study" "Unblinded data were seen only by the Data and Safety Monitoring Board and study statistician" **Comment:** performance bias likely to be reduced by blinding participants and trial personnel
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "Subjects and study personnel were blinded to assignment throughout the entire study" "Unblinded data were seen only by the Data and Safety Monitoring Board and study statistician" **Comment:** outcomes assessors blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "Subjects and trial personnel were blinded to assignment throughout the entire study" "Unblinded data were seen only by the Data and Safety Monitoring Board and study statistician" **Comment:** outcomes assessors blinded
Incomplete outcome data (attrition bias) Objective outcomes	High risk	**Quote:** "Ninety-two subjects were screened and 77 were randomized, 39 to metformin XR, 38 to placebo; 27 and 19 in each group were measured at weeks 52 and 100, respectively" **Comment:** dropout fairly high in each group and no imputation method was performed to replace missing data
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	**Quote:** "Ninety-two subjects were screened and 77 were randomized, 39 to metformin XR, 38 to placebo; 27 and 19 in each group were measured at weeks 52 and 100, respectively" **Comment:** dropout fairly high in each group and no imputation method was performed to replace missing data
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes reported

Wilson 2010 (*Continued*)

Other bias	Unclear risk	**Comment:** baseline means seemed to be adjusted

Yanovski 2011

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1, superiority design
Participants	**Inclusion criteria:** • BMI ≥ 95th percentile according to the CDC 2000 growth charts for the US • prepubertal or early pubertal (defined as breast Tanner stage I to III for girls; testes < 8 mL for boys) • fasting hyperinsulinaemia, defined as fasting insulin ≥ 15 mU/mL, the 99th percentile for fasting insulin among 224 nonobese 6- to 12-year-old children studied as outpatients at the National Institutes of Health with the same insulin assay **Exclusion criteria:** • impaired fasting glucose • diabetic • diagnosed renal, cardiac, endocrine, pulmonary or hepatic disease that might alter bodyweight • baseline creatinine > 1 mg/dL and for ALT or AST > 1.5 times the upper limit of the laboratory normal range **Diagnostic criteria:** see above
Interventions	**Intervention:** metformin + dietitian-administered weight-reduction programme **Comparator:** placebo + dietitian-administered weight-reduction programme **Number of trial centres:** 1 **Treatment before trial:** no **Titration period:** once baseline assessments were completed, participant's trial medication dose was progressively increased according to a prespecified algorithm over a 3-week period, starting with 500 mg twice daily and increasing to a maximum dose of 1000 mg twice daily
Outcomes	**Outcomes reported in abstract of publication:** BMI, bodyweight, BMI z score, fat mass, fasting plasma glucose, HOMA-IR, adverse events
Study details	**Run-in period:** no **Trial terminated early:** no
Publication details	**Language of publication:** English **Commercial and noncommercial funding** **Publication status:** peer-reviewed journal
Stated aim for study	Quote from publication: "To determine whether metformin treatment causes weight loss and improves obesity related comorbidities in obese children, who are insulin resistant"
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "We randomly assigned participants in a 1:1 randomization ratio to receive metformin hydrochloride or placebo, twice daily with meals. Investigators assigned consecutive code numbers to participants from prespecified lists stratified by race/ethnicity, sex, and degree of pubertal development" **Comment:** an adequate randomisation method was used
Allocation concealment (selection bias)	Low risk	**Quote:** "The CRC Pharmaceutical Development Section used permuted blocks with stratification to generate allocations that translated code numbers into study group assignments by using a pseudo-random number program and prepared identically appearing placebo and metformin capsules" **Comment:** allocation was concealed
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote:** "No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group assignments during the trial" **Comment:** both the participants and personnel were blinded
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote:** "No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group assignments during the trial" **Comment:** both the participants and personnel were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote:** "No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group assignments during the trial" **Comment:** both the participants and personnel were blinded
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote:** "No participant, investigator, or other medical or nursing staff interacting with participants was aware of study group

		assignments during the trial" **Comment:** both the participants and personnel were blinded
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote:** "We assessed efficacy in the intention-to-treat sample of all randomly assigned participants using a multiple imputation model for missing data under a missing-at-random assumption" **Comment:** low risk of attrition bias for objective outcomes
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote:** "We assessed efficacy in the intention-to-treat sample of all randomly assigned participants using a multiple imputation model for missing data under a missing-at-random assumption" **Comment:** low risk of attrition bias for subjective outcomes
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes reported from protocol
Other bias	Unclear risk	**Comment:** unclear if any other bias was present

"-" denotes not reported.
ALR: adiponectin-to-leptin ratio; ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; BMIadj: adjusted body mass index: BMI-SDS: body mass index standardised score; BMRadj: adjusted basal metabolic rate; CDC: Centers for Disease Control and Prevention; DBP: diastolic blood pressure; DEXA: dual energy X-ray absorptiometry; FGIR: fasting glucose insulin ratio; HbA1c: glycosylated haemoglobin A1c; HOMA-IR: homeostasis model assessment for insulin resistance index; hsCRP: highly sensitive C-reactive protein; LOCF: last observation carried forward; min: minute; OGTT: oral glucose tolerance test; QUICKI: quantitative insulin check index; SBP: systolic blood pressure; SD: standard deviation; SDS: standard deviation score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andelman 1967	Duration of treatment only 11 weeks
Ardizzi 1996	Duration of drug treatment only 2 months
Arman 2008	Treatment of schizophrenia or schizoaffective disorder

(*Continued*)

Bacon 1967	Duration of treatment only 2 months
Beyer 1980	Adults
Burgert 2008	Duration of follow-up < 6 months
Canlorbe 1976	Duration of follow-up only 12 weeks
Cannella 1968	Adults
Casteels 2010	Children had neurogenic or myogenic motor deficit
Cayir 2015	Not an RCT
CTRI/2011/10/002081 2011	Duration of follow-up < 6 months
Danielsson 2007	Aim was to treat hypothalamic obesity
Danilovich 2014	Duration of follow-up < 6 months
De Bock 2012	Duration of drug treatment only 6 weeks
Delitala 1977	Adults
Di Natale 1973	Not an RCT
Diaz 2013	Study aim, not all obese at baseline
Doggrell 2006	Not an RCT
EUCTR2009-016921-32-ES	A dietary therapy, intervention not relevant for this review
EUCTR2012-000038-20-DE	Duration of treatment only 6 weeks
Fanghänel 2001	Adults
Faria 2002	Adults
Ferguson 1986	Adults
Ferrara 2013	Duration of follow-up < 6 months
Fox 2015	Not an RCT
Freemark 2007	Not an RCT
Galloway 1975	Adults

(*Continued*)

Gamski 1968	Adults
Garnett 2010	Not a pharmacological intervention
Genova 1967	Study aim not to treat to obesity
Gill 1977	Adults
Giovannini 1990	Duration of treatment only 90 days
Godefroy 1968	Adults
Goldrick 1973	Adults
Goldstein 1993	Adults
González Barranco 1974	Adults
Griboff 1975	Adults
Grube 2014	Adults
Guazzelli 1987	Adults
Gwinup 1967	Duration of follow-up in the placebo group only 13 weeks
Halpern 2006	Adults
Hamilton 2003	Duration of follow-up only 3 months
Hansen 2001	Adults
Haug 1973	Adults
Hawkins 2012	Not an RCT
Honzak 1976	Adults
Hooper 1972	Adults
Huston 1966	Adults
IRCT2013021012421N1	Aim of trial to treat fatty liver disease
IRCT2014020116435N1	Not an RCT
Israsena 1980	Duration of follow-up only 4 months

(*Continued*)

James 2000	Adults
Kasa-Vubu 2008	Not an RCT
Kay 2001	Duration of treatment only 10 weeks
Kelly 2012	1 arm of the cross-over trial was only followed up for 3 months after receiving the drug
Kelly 2013a	Not an RCT
Kelly 2013b	Not an RCT
Kendall 2014	Not an RCT
Klein 2006	Duration of follow-up < 6 months
Kneebone 1968	Adults
Knoll 1975	Not an RCT
Komarnicka 1975	Adults
Komorowski 1982	Duration of treatment only 8 weeks
Kreze 1967	Adults
Lamberto 1993	Not an RCT
Leite 1971	Adults
Lewis 1978	Adults
Libman 2015	Participants had type 1 diabetes - secondary cause of obesity
Liebermeister 1969	Adults
Liu 2013	Adults
Lorber 1966	Duration of treatment only 4 weeks
Love-Osborne 2008	The aim of the study was to treat insulin resistance, not all participants were obese
Maclay 1977	Adults
Malchow-Møller 1980	Duration of follow-up only 12 weeks
Marques 2016	Not an RCT

(*Continued*)

McDuffie 2002	Not an RCT
Molnár 2000	Duration of follow-up only 20 weeks
Muls 2001	Adults
Nadeau 2015	Participants had type 1 diabetes - secondary cause of obesity
Nathan 2016	A description paper of 2 trials which do not meet the inclusion criteria of this review
NCT00076362	Aim of trial to treat hypothalamic obesity
NCT00284557	Not a pharmacological intervention
NCT00775164	Withdrawn prior to enrolment - inadequate enrolment
NCT00845559	Withdrawn prior to enrolment - no reason provided
NCT01023139	Not a pharmacological RCT - all participants were given drugs then randomised to lifestyle intervention or control
NCT01061775	Aim to treat hypothalamic obesity
NCT01107808	Withdrawn prior to enrolment - poor recruitment to the study
NCT01169103	Intervention was a growth hormone therapy
NCT01242241	Aim of the study: not treatment of obesity
NCT01329367	Not a pharmacological intervention
NCT01332448	Not an RCT
NCT01410604	Duration of follow-up only 3 months
NCT01456221	Not a pharmacological intervention
NCT01910246	Not an RCT
NCT02022956	Not an RCT
NCT02063802	Duration of follow-up only 4 months
NCT02186652	Not an RCT
NCT02378259	Surgery intervention
NCT02398669	No control group

(*Continued*)

NCT02438020	Duration of follow-up < 6 months
NCT02515773	Participants had bipolar disorder and were critically ill. They were all treated with anti-psychotics which can cause obesity (potential secondary cause of obesity)
Nwosu 2015	Participants had type 1 diabetes - secondary cause of obesity
O'connor 1995	Adults
Park 2010	Not an RCT
Pedrinola 1994	Not an RCT
Persson 1973	Adults
Plauchu 1967a	Adults
Plauchu 1967b	Adults
Plauchu 1972	Adults
Pugnoli 1978	Adults
Rauh 1968	Duration of follow-up only 12 weeks
Resnick 1967	Adults
Rodos 1969	Adults
Rodriguez 2007	Not an RCT
Roed 1980	Adults
Roginsky 1966	Adults
Sabuncu 2004	Adults
Sainani 1973	Mainly adults
Scavo 1976	Not an RCT
Shutter 1966	Duration of treatment only 6 weeks
Spence 1966	Not an RCT
Spranger 1963	Duration of treatment only 4 weeks
Spranger 1965	Duration of treatment only 4 weeks

(*Continued*)

Sproule 1969	Adults
Stewart 1970	Duration of follow-up only 16 weeks
Sukkari 2010	Not an RCT
TODAY study group 2013	The aim of the study was to treat diabetes, not obesity
Tong 2005	Adults
Toubro 2001	Adults
Tsai 2006	Not an RCT
Van Seters 1982	Adults
Warren-Ulanch 2008	Not an RCT
Weintraub 1984	Adults
Yanovski 2003	Not an RCT
Yu 2013	Duration of drug treatment only 10 weeks

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Golebiowska 1981

Methods	
Participants	
Interventions	
Outcomes	
Study identifier	
Official title	
Stated purpose of study	
Notes	**Unable to source**

ISRCTN08063839

Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** not reported **Primary purpose:** treatment
Participants	**Condition:** adolescent obesity **Enrolment:** target 48 **Inclusion criteria:** • aged 12 to 18 years • BMI > 95th centile for age and sex • pubertal stage ≥ 3 • ability for parent and child to read and understand written instructions in English; parents able to give informed written consent in English; adolescent able to give verbal assent • successfully completed a 6-month lifestyle intervention without a gain in BMI z-score **Exclusion criteria:** • renal disorders, diabetes, diagnosed psychological disorders • taking stimulants or psychotropic medication or drugs known to alter metabolism including insulin sensitisers, glucocorticoids, thyroxine, other weight loss medications • taking any drugs known to be contraindicated with metformin therapy • known adverse reactions to metformin • pregnancy
Interventions	**Intervention:** metformin + lifestyle intervention **Comparator:** placebo + lifestyle intervention
Outcomes	**Primary outcome:** • BMI (pre and post intervention) **Secondary outcomes:** • subjective appetite sensations using a novel electronic appetite rating system (EARS), immediately before and then hourly for 4 hours after a fixed-energy breakfast. Measured at baseline, day 1, week 2, week 4, then monthly. This is a validated technique of measuring appetite which has been used in appetite trials involving obese children • food preferences will be measured using a novel 'liking and wanting' (L&W) experimental procedure. Measured at baseline, day 1, week 2, week 4, then monthly. This method has been validated in several trials. The L&W procedure is sensitive to detect changes in nutrient and taste preferences • we will measure fasting gastrointestinal hormones (at baseline, day 28, 2 months and 6 months) to identify potential biomarkers which could explain any differences in appetite responses between the 2 groups. These will be correlated with fasting and postprandial subjective appetite sensations • in a subset of participants (10 in each group), will measure gastrointestinal hormones and subjective sensations of appetite, pre- and postprandially (by insertion of an intravenous cannula) and pre- and postdosing with metformin (at baseline, each metformin dose increment (day 1, week 2, week 4), 2 months and 6 months) **Other outcomes:** not reported
Study identifier	**ISRCTN number:** ISRCTN08063839 **Trial start date:** 1 July 2010 **Trial completion date:** 30 June 2014

ISRCTN08063839 (*Continued*)

Official title	Investigating the use of pharmacotherapy in adolescents for weight loss maintenance: the role of appetite: a randomised, placebo controlled trial
Stated purpose of study	Quote: "Eat Smart is a novel research study in which 2 dietary approaches to treat childhood obesity are being tested."
Notes	**Trial completed in 2014, no publication available and page not found on website** Trial sponsor: Royal Children's Hospital (Australia) Ethics approved by the Human Research Ethics Committee (HREC) of the Royal Children's Hospital (ref: HREC/10/QRCH/53) Sources of funding are: • Australian Paediatric Endocrine Care (APEC) Research Grant (Pfizer) (Australia) - (ref: E/09) (contact: trudy.snape@pfizer.com) • Royal Children's Hospital (Australia) Further information obtained from trial website: www2.som.uq.edu.au/som/Research/ResearchCentres/cnrc/Pages/CNRCHome.aspx

Linquette 1971

Methods	
Participants	
Interventions	
Outcomes	
Study identifier	
Official title	
Stated purpose of study	
Notes	**Unable to source**

NCT00934570

Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** participants are randomised to metformin medication or placebo, and then randomised to engage in a moderate or vigorous intensity exercise programme for the first 12 weeks of the 2-year programme **Intervention model:** parallel assignment **Masking:** single blind (participant) **Primary purpose:** prevention
Participants	**Condition:** obesity, type 2 diabetes **Enrolment:** estimated 72 **Inclusion criteria:**

	• obese adolescents defined as BMI > 95th percentile for age and sex • metformin-naive participants **Exclusion criteria:** • elevated fasting plasma glucose ≥ 6.0 mmol/L • 2-hour plasma glucose ≥ 11.1 mmol/L after a standard glucose load • HbA1c > 6.0% • medication other than nonprescription drugs, oral contraceptive pill or thyroid hormone replacement • smoking • pregnancy • renal insufficiency (serum creatinine > the upper limit of normal) • hepatic dysfunction (> 1.5 times the upper limit of normal for AST and ALT) • latex allergy • hypersensitivity to metformin or its ingredients • breastfeeding • participants with a history of lactic acidosis • abnormal creatinine clearance • HIV, HBV, and HCV infections • drug and alcohol abuse • severe mental disorders • participants who are planning radiological examinations involving intravenous injection of iodinated contract materials • participation in another clinical trial • significant history or presence of cardiovascular, pulmonary, gastrointestinal, immunological, endocrine, neurological disorders • malignant diseases • previous exposure to any pharmaceutical antidiabetic agent
Interventions	**Interventions:** • metformin + standard exercise • metformin + intensive exercise **Comparators:** • placebo + standard exercise • placebo + intensive exercise
Outcomes	**Primary outcome:** • BMI **Secondary outcomes:** • body composition assessments (fat mass, fat free mass, and % body fat, waist circumference) • metabolic assessments (glycaemic status, serum lipids, plasma adipocytokines) • vascular assessments (blood pressure, endothelial function, vascular properties, heart variability) • programme adherence (attendance, medication) • physical performance assessments (aerobic fitness, strength) • exercise intensity assessments (heart rate, rating of perceived exertion) • physical activity assessments (self-reported physical activity, objective physical activity) • psychosocial function assessments (quality of life, social support, outcome expectations, satisfaction, enjoyment, self-efficacy, task self-efficacy, goal setting self-efficacy, planning self-efficacy, barriers self-efficacy, behavioural intentions, group cohesion, collaboration) • nutrition assessments (diet, 3-day food record)

NCT00934570 (*Continued*)

	Other outcomes: not reported
Study identifier	**NCT number:** NCT00934570 **Other trial ID numbers:** R-08-259, 15590 **Trial start date:** April 2009 **Trial completion date:** May 2012
Official title	Reduction of Adolescent Risk Factors for Type 2 Diabetes and Cardiovascular Disease
Stated purpose of study	Quote: "Assess the sustainability of a two-year intervention aimed at improving body mass index (BMI) and metabolic and vascular health in obese youth."
Notes	**No full publication** Results were presented in a poster (Clarson et al 2013) - "In the MXR [metformin] group, there were significant differences in BMI z score at baseline (2.22 ± 037) and 6 months (2.08 ± 0.48, P < .001), 12 months (2.05 ± 0.49, P = .002) and 24 months (2.10 ± 0.46, P = 0.04)" Author asked for additional results but none were provided **Sponsored by:** Lawson Health Research Institute and Canadian Institutes of Health Research (CIHR) **Protocol:** Wilson et al 2009 Further trial details are provided by Lawson Health Research Institute The health authority associated with this trial: "Canada: Health Canada"

NCT00940628

Methods	**Type of trial:** interventional; randomised control trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** obesity **Enrolment:** 60 **Inclusion criteria:** • adolescent participants, aged 12 to 14 years • overweight or obese **Exclusion criteria:** • aged < 12 or > 14 years; • BMI in normal range
Interventions	**Intervention:** orlistat (Xenical) + diet and exercise programme **Comparator:** diet and exercise programme
Outcomes	**Primary outcome:** • change in BMI (time frame: at each clinic visit, every 4 weeks) **Secondary outcomes:** • adverse events • laboratory parameters (time frame: at each clinic visit, every 4 weeks **Other outcomes:** not reported

NCT00940628 (*Continued*)

Study identifier	**NCT number:** NCT00940628 **Other trial ID number:** ML19569 **Trial start date:** April 2008 **Trial completion date:** September 2010
Official title	Open-label Comparative Randomized Study of the Efficacy and Safety of Orlistat (Xenical) in Complex Therapy of Obesity and Metabolic Disorders in Adolescents
Stated purpose of study	Quote: "This 2 arm study will assess the effect of Xenical on body mass index (BMI) in obese or overweight adolescents"
Notes	**Trial was completed in 2010, no publication is available** The health authority associated with this trial is "Russia: Federal Service on Surveillance in Healthcare and Social Development of RF"

NCT01487993

Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator) **Primary purpose:** treatment
Participants	**Condition:** obesity; insulin resistance **Enrolment:** 127 **Inclusion criteria:** • aged 10 to 16 years at trial entry • white • obesity defined as BMI-SDS > 2.3 • insulin resistance defined as HOMA-IR $\geq$ 3.4 • an obtained informed consent from participants and parents/carers **Exclusion criteria:** • presence of type 2 diabetes (American Diabetes Association criteria) • presence of endocrine disorders with steroid therapy • suspicion of polycystic ovarium syndrome • height < -1.3 SD of target height • syndrome disorders with or without mental retardation • use of anti-hyperglycaemic drugs • pregnancy (pregnancy test will be performed, if applicable) • (history of) alcohol abuse • impaired renal or hepatic function (defined as GFR < 80 mL/min. GFR = 40 x length (cm) / serum creatinine (μmol/L and ALT > 150% of normal value for age), or both • use of ritonavir; use of ACE inhibitors • insufficient knowledge of the Dutch language
Interventions	**Intervention:** metformin + lifestyle intervention **Comparator:** placebo + lifestyle intervention

Outcomes	**Primary outcomes:** • change in BMI from baseline (time frame: 18 months and 36 months). Change in BMI after part 1 (double blind) and part 2 (follow-up) • change in insulin resistance from baseline (time frame: 3, 6, 9, 12, 15, 18, 24, 30 and 36 months). Calculated by the HOMA-IR **Secondary outcomes:** • renal and hepatic function (time frame: 3, 6, 9, 12, 15, 18, 24, 30 and 36 months), creatinine and ALT • tolerability (time frame: 3, 6, 9, 12, 15, 18, 24, 30 and 36 months), number of reported adverse effects, in relation to the achieved dose level • pharmacokinetic parameters: clearance (mL/min) (time frame: 9 months), clearance where applicable expressed per bodyweight, age category, Tanner stage and sex, clearance will be determined with a 2-compartment pharmacokinetic model using nonlinear mixed-effect modelling • % body fat (time frame: 0, 9, 18 and 36 months) • physical fitness (time frame: 0, 9, 18 and 36 months) • quality of life (time frame: 0, 9, 18 and 36 months) • long-term efficacy (time frame: 36 months). Based on BMI and HOMA-IR values • long-term safety (time frame: 36 months). Renal and hepatic function after 36 months of metformin use • long-term tolerability (time frame: 36 months). The amount of adverse effects after 36 months • microvascular complications (time frame: 36 months). Measured as microalbuminuria • macrovascular complications (time frame: 36 months). Measured with pulse wave velocity and augmentation Index • development of type 2 diabetes mellitus (time frame: 36 months) **Other outcomes:** not reported
Study identifier	**NCT number:** NCT01487993 **Other trial ID numbers:** metformin 2011-6, 2010-023980-17
Official title	An Efficacy, Safety and Pharmacokinetic Study on the Short-term and Long-term Use of Metformin in Obese Children and Adolescents
Stated purpose of study	Quote: "The purpose of this study is to determine whether metformin is effective in reducing BMI and insulin resistance in obese children and adolescents"
Notes	The trial was sponsored by St. Antonius Hospital; Jeroen Bosch Ziekenhuis is a collaborator on the trial; the health authority associated to this trial is "Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)" Results of trial are now published (see Van der Aa 2016 - NCT01487993): 62 participants randomised (32 metformin, 30 placebo), 42 analysed (23 metformin, 19 placebo); 18 months' intervention; median change in BMI was +0.2 kg/m^2 (95% CI -2.9 to 1.3) (metformin) versus +1.2 kg/m^2 (95% CI -0.3 to 2.4) kg/m^2 (placebo) (P = 0.02). No serious adverse events reported. 2 out of 9 participants lost to follow-up in the metformin group discontinued treatment because of adverse events. No placebo participants dropped out due to adverse events (13 participants lost to follow-up)

Smetanina 2015

Methods	**Type of** trial**:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** unclear **Primary purpose:** treatment
Participants	**Condition:** overweight and obesity in children and adolescents **Enrolment:** 145 **Inclusion criteria:** • overweight (BMI SDS 1.0 to 2.0) or obese (BMI ≥ 2.0) (IOTF) • children or adolescents **Exclusion criteria:** -
Interventions	**Interventions:** • metformin combined with lifestyle changes • metformin only **Comparators:** • lifestyle changes only • no treatment controls
Outcomes	**Primary outcomes:** • BMI SDS • waist circumference • waist SDS • adverse events • lean mass **Secondary outcomes:** none given **Other outcomes:** none given
Study identifier	-
Official title	-
Stated purpose of study	"To assess the efficacy and safety of Metformin use in combination with lifestyle changes or alone for weight management in OW and OB children and adolescents"
Notes	Project supported by Research Council of Lithuania (grant Nr MIP-039/2013) and Research Foundation of Lithuanian University of Health Sciences (grants 2012 and 2013) **Results:** reduction in BMI, waist circumference and waist circumference SDS adjusted by sex and puberty stages was significantly greater in the metformin + lifestyle changes group compared to the controls no treatment group. Change in BMI after 12 months' intervention: controls = +0.18 kg/m^2, lifestyle changes only = +0.43 kg/m^2, metformin only = -0.59 kg/m^2, metformin + lifestyle changes = -1.07 kg/m^2. Change in waist circumference after 12 months' intervention: controls = -1.8 cm, lifestyle changes only = -2.8 cm, metformin only = -2.3 cm, metformin + lifestyle changes = -4.5 cm. Change in waist circumference SDS after 12 months' intervention: controls = -0.38, lifestyle changes only = -0.58, metformin only = -0.49, metformin + lifestyle changes = -0.85. Initially, there were mild adverse effects with metformin (nausea, diarrhoea) in 21.6% of participants from metformin only group and metformin + lifestyle changes group, which disappeared within 1 week of metformin administration. Adjusted by sex and puberty status, lean mass was significantly increased in lifestyle only group compared to controls no treatment and metformin

	only groups. Change in lean mass after 12 months' intervention: controls = +1.6 kg, lifestyle changes only = +3.98 kg, metformin only = -0.36 kg, metformin + lifestyle changes = -0.37 kg. 12 months' metformin treatment with lifestyle modification was effective and safe method reducing BMI and waist circumference in overweight/obese children and adolescents, superior to that of lifestyle changes alone **Correspondence with author:** the results presented in the poster are only partial results of a larger trial, where these data are currently being analysed. They aim to publish the results in a publication and as part of a PhD thesis

"-" denotes not reported.
ACE: angiotensin converting enzyme; ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; GFR: glomerular filtration rate; HbA1c: haemoglobin A1c; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HOMA-IR: homeostasis model assessment for insulin resistance; IOTF: International Obesity Task Force; min: minute; SD: standard deviation; SDS: standard deviation score.

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2010-023061-21

Trial name or title	Efectos de la metformina en la obesidad infantil: "Effects of metformin on childhood obesity"
Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind **Primary purpose:** treatment
Participants	**Condition:** obesity in prepubertal and pubertal children **Enrolment:** target 160 **Inclusion criteria:** • obese children aged 7 to 14 years prepubertal and pubertal children, boys and girls, with exogenous obesity • basic or history of disease pathology • not received medical treatment or diet (or both) that would interfere with the analytical results 12 months before • inclusion of the same participant more than once not permitted • not participated in a previous trial **Exclusion criteria:** • participants who do not meet the prescribed age • submit or have submitted some underlying disease earlier • receive or have received medication with metabolic adverse effects such as diuretics, beta-blockers, beta-adrenergic agonists, corticosteroids • children undergoing long periods of rest
Interventions	**Intervention:** metformin **Comparator:** placebo

EUCTR2010-023061-21 (*Continued*)

Outcomes	**Primary outcome:** • BMI (baseline, weeks 8, 16 and 24) **Secondary outcomes:** • blood pressure, • blood analysis (lipid profile, hydrocarbon, inflammatory, oxidative) • lifestyle survey (baseline, weeks 8, 16 and 24) **Other outcomes:** not given
Starting date	**Trial start date:** not given **Trial completion date:** not given
Contact information	**Trial sponsor:** Ramón Cañete Estrada **Name of organisation:** Instituto de Salud Carlos III **Country:** Spain **Contact details:** Avda Menendez Pidal s/n, Córdoba, 14004, Spain. Tel: 34957011227. Email: cetico.hrs.sspa@juntadeandalucia.es
Study identifier	**EU clinical trials register number:** EUCTR2010-023061-21
Official title	**Original title:** Ensayo clínico sobre efectos de la metformina en la obesidad pediátrica: efectos en el peso corporal, perfil de biomarcadores inflamatorios y de riesgo cardiovascular, e impacto en factores relacionados con el síndrome metabólico **English title:** Clinical trial on the effect of metformin in pediatric obesity: effects on bodyweight, profile and inflammatory biomarkers of cardiovascular risk, and impact on factors related to metabolic syndrome
Stated purpose of study	To study the clinical and biochemical impact of metformin along with changing lifestyle (diet and exercise) in obese children
Notes	Majority of this online entry is in Spanish; sponsor status: noncommercial; trial was ongoing when identified

EUCTR2015-001628-45-SE

Trial name or title	A study with lifestyle intervention and study medication once weekly or lifestyle intervention and placebo in adolescents with obesity to explore differences between groups with regard to change in BMI
Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind **Primary purpose:** treatment
Participants	**Condition:** obesity in adolescents **Enrolment:** 44 **Inclusion criteria:** • signed informed consent prior to any trial-specific procedures • males or females aged 10 to 18 years and 7 months • obesity (BMI SDS > 2.0 or age-adapted BMI > 30 kg/m^2), according to WHO • not sexually active or usage of adequate contraception. Female participants must also have negative

pregnancy tests. Methods that can achieve a failure rate of less than 1% per year (Pearl index < 1), when used consistently and correctly, are considered as highly effective birth control methods. Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence (if refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the participant)

- ability to understand and comply with the requirements of the trial

Exclusion criteria:

- known syndromal obesity, such as Prader-Willi syndrome, Laurence-Moon syndrome or Bardet-Biedl syndrome
- pregnancy or lactation
- indigestion-causing diseases
- severe gastrointestinal disease
- total or partial gastric or small intestine resection
- type 1 or type 2 diabetes mellitus
- kidney disease (acute or chronic, according to physician (creatinine/urea/cystatin-C for Schwartz calculation)
- hypo-/hyperthyroidism, unless under stable treatment
- severe vitamin D insufficiency, unless under stable treatment
- abnormal QT interval
- clinically significant abnormal laboratory values, e.g. triglycerides > 400 mg/dL (Salzburg) or > 4.5 mmol/L (Uppsala), amylase > 300 U/L (Salzburg) or > 5.1 µkat/L (Uppsala), lipase > 180 U/L (Salzburg) or > 15 µkat/L (Uppsala) or calcitonin > 11.7 pg/mL (Salzburg) or > 3.4 pmol/L (Uppsala) for females and > 17 pg/mL (Salzburg) or > 5.0 pmol/L (Uppsala) for males
- severe depression, severe anxiety or other psychiatric disorder referred to or undergoing special treatment, as judged by the investigator
- severe sleep apnoea (defined clinically)
- chronic diseases, as judged by the investigator
- metformin treatment within 3 months prior to screening or concomitant medication influencing blood glucose (e.g. metformin and acarbose), influencing other parameters of metabolic syndrome (e.g. orlistat) or interfering with the investigational medicinal product
- steroid treatment (oral or injected)
- concomitant medication addressing attention disorders
- antidepressants that can lead to weight gain, as judged by the investigator
- hypersensitivity to exenatide or to any of the excipients
- pacemaker or metal implant that may interfere with MRI
- claustrophobia
- current or prior (within 3 months) participation in another clinical trial involving an investigational medicinal product
- a personal or family history of medullary thyroid carcinoma
- a personal or family history of multiple endocrine neoplasia syndrome type 2

EUCTR2015-001628-45-SE (*Continued*)

Interventions	**Intervention:** exenatide + lifestyle intervention **Comparator:** placebo + lifestyle intervention
Outcomes	**Primary outcome:** • BMI SDS (according to WHO) **Secondary outcomes:** • adverse events, vital signs (blood pressure and pulse), electrocardiogram, tympanic body temperature, glucose, clinical chemistry, haematology and urinalysis • endpoints of insulin secretion and sensitivity derived from oral glucose tolerance test • glucagon levels at specified time points • triglycerides, high-density lipoprotein, low-density lipoprotein, total cholesterol, free fatty acids, apolipoproteins, uric acid and blood pressure • highly sensitive C-reactive protein • bioimpedance assessments to calculate total and regional body composition and MRI assessments of abdominal adipose tissue, organ fat characteristics and morphology (volume of visceral and abdominal subcutaneous adipose tissue and liver fat content) • waist, hip, upper thigh and neck circumference, waist-to-hip ratio, sagittal abdominal diameter and skinfold calipre assessments of body fat • standardised BMI • interdisciplinary adiposity evaluation kit (AD-EVA), sleeping habits questionnaire, self-efficacy and outcome expectations questionnaire, food frequency questionnaire, regular meals questionnaire, portion size questionnaire, walking test (6 min), physical activity questionnaire and physical activity assessed by accelerometry • U-alpha1-microglobulin (protein HC)/creatinine and estimated GFR according to Schwartz formula • AST), ALT), gamma-glutamyl transpeptidase, lactate dehydrogenase and bilirubin
Starting date	**Trial start date:** not given **Trial completion date:** not given
Contact information	**Responsible party/principal investigator:** Peter Bergsten, Department of Medical Cell Biology Uppsala University
Study identifier	**EudraCT Number:** 2015-001628-45
Official title	A parallel, double-blinded, randomized, 6 months, two arms trial with lifestyle intervention and exenatide 2 mg once weekly or lifestyle intervention and placebo in adolescents with obesity to explore differences between groups with regard to change in BMI SDS (according to WHO)
Stated purpose of study	Quote: "To compare the change from baseline to the 6 months visit at the end of treatment, between lifestyle intervention + exenatide 2 mg once weekly and lifestyle intervention + placebo, in BMI SDS (according to WHO) for adolescents with obesity"
Notes	Trial registered on 27 July 2015. Trial status: ongoing (when identified). Trial sponsor: Department of Medical Cell Biology Uppsala University. Monetary or material support provided by: European Commission's Seventh Framework Programme (FP7) project Beta_JUDO (grant 279153). Country: Sweden

NCT00889876

Trial name or title	Effect of exercise or metformin on nocturnal blood pressure and other risk factors for CVD among obese adolescents
Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** factorial assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** CVDs **Enrolment:** 100 **Inclusion criteria:** • aged 13 to 19 years at inclusion date • obesity according to sex- and age-specific BMI (Cole 2000) • reduced nocturnal systolic blood pressure fall (< 10%) • signed informed consent by participant and parents **Exclusion criteria:** • CVD • insulin-dependent diabetes mellitus • participant on medications that are contraindicated during metformin treatment • pregnancy • mental or physical conditions limiting the ability to participate
Interventions	**Intervention:** metformin **Comparator:** exercise
Outcomes	**Primary outcome:** • normalisation of nocturnal blood pressure dipping **Secondary outcome:** • normalisation of insulin metabolism and cardiovascular structure and function
Starting date	**Trial start date:** February 2009 **Trial completion date:** December 2012 (estimated)
Contact information	**Responsible party/principal investigator:** Professor Claude Marcus, Karolinska Institutet, Karolinska Institute
Study identifier	**NCT number:** NCT00889876 **Other trial ID numbers:** 2008-000461-28
Official title	Effect of Exercise or Metformin on Nocturnal Blood Pressure and Other Risk Factors for Cardiovascular Disease (CVD) Among Obese Adolescents
Stated purpose of study	Quote: "The objective is to, among obese adolescents, study impact of regular physical activity or metformin therapy on nocturnal blood pressure and related cardiovascular disease risk factors"
Notes	This trial has not been verified on the clinicaltrials.gov website since February 2011. We have attempted to contact the principal investigator via email; however, have not received a response. Trial sponsor: Karolinska Institutet

NCT01677923

Trial name or title	Obesity in children and adolescents: associated risks and early intervention (OCA)
Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** open label **Primary purpose:** treatment
Participants	**Condition:** obesity **Enrolment:** 400 (estimated) **Inclusion criteria:** • aged 10 to 17 years • weight > 85th percentile for age and sex (by IOTF) • living in Kaunas and its region • no obvious chronic diseases • not on steroid or other long-term treatment • informed consent of the participant and parents (official carers) **Exclusion criteria:** • aged < 10 or > 17 years • diagnosis of type 1 diabetes • chronic illness that may affect physical activity and metabolic profile • insulin treatment • steroid treatment • planning to move from Kaunas or its region in the period of 1 year • protocol refused by the participant or his/her parents
Interventions	**Interventions:** • metformin only • intensive diet and physical activity group + metformin **Comparators:** • intensive diet and physical activity programme • control
Outcomes	**Primary outcome:** • BMI changes (time frame: 12 months) **Secondary outcomes:** • glucose homeostasis (time frame: 12 month), insulin sensitivity increase, HOMA-IR decrease, insulin and glucose concentrations normalisation • lipid profile (time frame: 12 months), lipid profile normalisation • metabolic syndrome (time frame: 12 months), metabolic syndrome prevalence and risks decrease • hepatosteatosis (time frame: 12 months), hepatosteatosis prevalence decrease and liver function improvement, hepatic enzymes normalisation • PCOS and hyperandrogenism in females (time frame: 12 months), PCOS clinical symptoms regression, menstrual cycle normalisation, hirsutism, androgens levels decreasing and oestrogen, sex hormone-binding globulin levels increasing **Other outcomes:** • safety (time frame: 12 months). How many participants will have adverse events and withdraw the metformin due to their intolerance or clinical/biochemical relapse

NCT01677923 (*Continued*)

Starting date	**Trial start date:** May 2013 **Trial completion date:** December 2015
Contact information	**Responsible party/principal investigator:** Rasa Verkauskiene, Lithuanian University of Health Sciences. rasa.verkauskiene@kaunoklinikos.lt. 00370-37-327097
Study identifier	**NCT number:** NCT01677923 **Other trial ID numbers:** BE-2-1
Official title	Phase 3: Effect of Diet, Physical Activity and Insulin Sensitizer Metformin on Obesity and Associated Risks in Children and Adolescents
Stated purpose of study	Quote: "The investigators hypothesize that Metformin decreases weight, normalizes lipid profile and increases insulin sensitivity; the study team hope to get better effect of weight decrease and metabolic processes repair in the intensive treatment group with intervention of physical activity, diet correction and Metformin use"
Notes	The health authorities associated with this trial are Lithuania: Bioethics Committee and Lithuania: State Medicine Control Agency - Ministry of Health; the trial is sponsored by Lithuanian University of Health Sciences; this trial was recruiting participants when identified

NCT01859013

Trial name or title	Topiramate in Adolescents with Severe Obesity
Methods	**Type of trial:** interventional; randomised controlled trial **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** obesity, morbid obesity, weight loss **Enrolment:** estimated 36 **Inclusion criteria:** • BMI $\geq$ 1.2 times the 95th percentile (based on sex and age) or BMI $\geq$ 35 kg/m^2 • aged 12 to 17 years • Tanner stage IV or V by physical examination **Exclusion criteria:** • Tanner stage I, II, or III • BMI $\geq$ 50 kg/m^2 • type 1 or 2 diabetes mellitus • previous (within 6 months) or current use of weight loss medication (participants may undergo washout) • previous (within 6 months) or current use of drugs associated with weight gain (e.g. steroids/anti-psychotics) • previous bariatric surgery • recent initiation (within 3 months) of anti-hypertensive or lipid medication • previous (within 6 months) or current use of medication to treat insulin resistance or

NCT01859013 (*Continued*)

	hyperglycaemia (participants may undergo washout) • major psychiatric disorder • females: pregnant, planning to become pregnant, or unwilling to use ≥ 2 acceptable methods of contraception when engaging in sexual activity throughout the trial • tobacco use • liver/renal dysfunction ALT or AST > 2.5 times the upper limit of normal. Bicarbonate < 18 mmol/L. Creatinine > 1.2 mg/dL • glaucoma • obesity associated with genetic disorder (monogenetic obesity) • hyperthyroidism or uncontrolled hypothyroidism • history of suicidal thought/attempts • history of kidney stones • history of cholelithiasis • current use of other carbonic anhydrase inhibitor
Interventions	**Intervention:** topiramate **Comparator:** placebo
Outcomes	**Primary outcome:** • % change from baseline in BMI at 28 weeks (time frame: baseline and 28 weeks) **Secondary outcomes:** • characterise the safety profile of topiramate for the treatment of adolescent obesity • evaluate the effects of meal replacement therapy followed by topiramate vs meal replacement therapy followed by placebo on risk factors for CVD and type 2 diabetes • evaluate response to topiramate treatment based on baseline eating behaviour phenotype in adolescents with severe obesity **Other outcomes:** not reported
Starting date	**Trial start date:** June 2013 **Trial completion date:** December 2015
Contact information	**Responsible party/principal investigator:** Aaron S Kelly, PhD University of Minnesota - Clinical and Translational Science Institute. Tel: 612-626-3492. Email: kelly105@umn.edu
Study identifier	**NCT number:** NCT01859013 **Other trial ID number:** 1304M31241
Official title	BMI Reduction with Meal Replacements + Topiramate in Adolescents with Severe Obesity
Stated purpose of study	Quote: "the goal of this pilot study is to evaluate the safety and efficacy of 24 weeks of topiramate therapy with a 4-week run-in of meal replacement therapy in adolescents with severe obesity"
Notes	The health authority associated with this trial: "United States: Institutional Review Board"; the trial is sponsored by University of Minnesota - Clinical and Translational Science Institute; the trial was recruiting participants when identified; publication identified for retrospective analysis of participants who received topiramate: Fox et al 2015

NCT02273804

Trial name or title	Topiramate and Severe Obesity (TOBI)
Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** obese children and adolescents **Enrolment:** estimated 160 **Inclusion criteria**: • aged 9 to 17 years • BMI z-score ≥ 4 SD of French reference • weight at enrolment > 50 kg • therapeutic failure > 6 months • for girls of childbearing age, willing to have an acceptable method of contraception (no oestrogens + progestin) • negative pregnancy test for girls of childbearing age • agreeing to participate upon written informed consent • appropriate understanding of the trial **Exclusion criteria:** • syndromic or secondary obesity • major neurological or psychiatric disorder • current or history of suicidal thought/attempts • current or history of breakdown • previous bariatric surgery • severe hypercapnia • renal dysfunction • deformity in the urinary tract or solitary kidney • history of renal lithiasis or glaucoma • poorly controlled diabetic children or adolescents (HbA1c > 10%) and diabetic participants treated with metformin or glibenclamide (or both) • hepatic dysfunction • bicarbonate < 16 mmol/L • known hypersensitivity to the active substance or to 1 of the excipients • intolerance to saccharose • enrolment in another therapeutic trial • high probability to fail to comply with treatment • females: pregnant, planning to become pregnant • no signature on consent form • uncovered by the French national health insurance system (Sécurité sociale)
Interventions	**Intervention:** topiramate **Comparator:** placebo
Outcomes	**Primary outcome:** • % change from baseline in BMI (time frame: 9 months) **Secondary outcomes:** • adverse event outcome (time frame: up to 4.5 years of follow-up)

NCT02273804 (*Continued*)

	• % change from baseline in BMI z-score (time frame: 9 months) • % change from baseline in BMI and BMI z-score (time frame: 1, 3, 6 and 9 months) • eating behaviour (time frame: 9 months). Self-administered questionnaires and scales: Binge Eating Scale; State trait anxiety Inventory for Children; Child depression inventory • physical activity (time frame: 6 and 9 months). Questionnaire from French Ministry of Health • food intake (time frame: 6 and 9 months). High-fat, sugary, salted food intake and beverage other than drinking water • comorbidity outcome (time frame: 6 and 9 months). Comorbidities and metabolic and cardiorespiratory complication **Other outcomes:** none given
Starting date	**Trial start date:** June 2015 **Trial completion date:** December 2020
Contact information	**Responsible party:** Assistance Publique - Hôpitaux de Paris **Principal investigator:** Marie-Laure Frelut, MD
Study identifier	**NCT number:** NCT02273804
Official title	Topiramate and Severe Obesity in Children and Adolescents
Stated purpose of study	The purpose of this trial is to evaluate the efficacy of topiramate on the decrease of BMI compared to placebo at 9 months
Notes	The trial is sponsored by Assistance Publique - Hôpitaux de Paris; recruitment status when identified: not yet recruiting

NCT02274948

Trial name or title	Use of Metformin in Treatment of Childhood Obesity
Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** paediatric obesity **Enrolment:** estimated 120 **Inclusion criteria:** • obese children (based on > +2 SD of BMI to age on WHO 2007 standards) **Exclusion criteria:** • children not of Sri Lankan origin • children who are not planning to live in Sri Lanka during the next year • children with a secondary underlying cause for the overweight/obesity
Interventions	**Intervention:** metformin **Comparator:** placebo

NCT02274948 (*Continued*)

Outcomes	**Primary outcomes:** • improvement in childhood obesity (time frame: 1 year) • improvement of obesity will be measured by reduction in body fat content and BMI **Secondary outcome:** • improvement in obesity-related metabolic derangements including insulin resistance (time frame: 1 year) **Other outcomes:** none given
Starting date	**Trial start date:** July 2014 **Trial completion date:** February 2016
Contact information	**Responsible party/principal investigator:** Pujitha Wickramasinghe, University of Colombo
Study identifier	**NCT number:** NCT02274948
Official title	Effects of Metformin on Body Weight, Composition and Metabolic Derangements in Obese Children. A Randomized Clinical Trial
Stated purpose of study	This study expects to evaluate the use of metformin in the management of obese children. Insulin resistance among obese Sri Lankan children (south Asian origin) is high, which had been shown in the investigators previous work. This study will look at the effect of metformin on changes in insulin resistance, fatty liver state, body fat content, BMI and other metabolic derangement
Notes	Trial sponsored by University of Colombo; recruitment status when identified: this trial is currently recruiting participants; location: Sri Lanka

NCT02496611

Trial name or title	Enhancing Weight Loss Maintenance With GLP-1RA (BYDUREON™) in Adolescents with Severe Obesity
Methods	**Type of trial:** interventional **Allocation:** randomised **Intervention model:** parallel assignment **Masking:** double blind (participant, carer, investigator, outcomes assessor) **Primary purpose:** treatment
Participants	**Condition:** severe obesity **Enrolment:** estimated 100 **Inclusion criteria:** • BMI $\geq$ 1.2 times the 95th percentile (based on sex and age) or BMI $\geq$ 35 kg/m^2 • aged 12 to 17 years **Exclusion criteria:** • type 1 or 2 diabetes mellitus • previous (within 6 months) or current use of medication(s) prescribed primarily for weight loss (refer to appendix material for comprehensive list) • if currently using weight altering drug(s) for nonobesity indication(s) (refer to appendix material for

	comprehensive list), any change in drug(s) or dose within the previous 6 months • previous bariatric surgery • if currently using anti-hypertensive medication(s), lipid medication(s), medication(s) to treat insulin resistance (refer to appendix material for comprehensive list) (or a combination) any change in drug(s) or dose within the previous 6 months • if currently using continuous positive airway pressure/bilevel positive airway pressure (for sleep apnoea), change in frequency of use or settings within the previous 6 months • history of treatment with growth hormone • neurodevelopmental disorder severe enough to impair ability to comply with trial protocol • clinical diagnosis of bipolar illness, schizophrenia, conduct disorder, substance use/abuse, or a combination • females: currently pregnant, planning to become pregnant, or unwilling to use ≥ 2 acceptable methods of contraception when engaging in sexual activity throughout the trial • tobacco use • liver/renal dysfunction • ALT or AST > 2 times the upper limit of normal • bicarbonate < 18 mmol/L • creatinine > 1.2 mg/dL • history of pancreatitis • personal or family history (or both) of medullary thyroid carcinoma • personal or family history (or both) of multiple endocrine neoplasia type 2 • calcitonin level > 50 ng/L • bulimia nervosa • neurological disorder • hypothalamic obesity • obesity associated with genetic disorder (monogenetic obesity) • hyperthyroidism or uncontrolled hypothyroidism • history of suicide attempt • history of suicidal ideation or self-harm within the past year • history of cholelithiasis
Interventions	**Intervention:** exenatide extended-release for injectable suspension (BYDUREON™) **Comparator:** placebo
Outcomes	**Primary outcomes:** • weight loss maintenance (time frame: 52 weeks) • improvement of obesity will be measured by reduction in body fat content and BMI **Secondary outcomes:** • maintenance of body fat changes (time frame: 52 weeks) • maintenance of blood pressure (time frame: 52 weeks) • maintenance of improved insulin sensitivity (time frame: 52 weeks) **Other outcomes:** none given
Starting date	**Trial start date:** December 2015 **Trial completion date:** July 2020
Contact information	**Responsible party/principal investigator:** University of Minnesota - Clinical and Translational Science Institute

NCT02496611 (*Continued*)

Study identifier	**NCT number:** NCT02496611
Official title	Enhancing Weight Loss Maintenance with GLP-1RA (BYDUREON™) in Adolescents with Severe Obesity
Stated purpose of study	Primary objective: evaluate the effect of GLP-1RA treatment on the maintenance of weight loss and durability of cardiometabolic risk factor improvements among adolescents with severe obesity following a meal replacement induction period Secondary objectives: investigate the mechanisms by which glucagon-like peptide-1 receptor agonists treatment facilitates weight loss maintenance and identify predictors of response to treatment
Notes	Trial sponsored by University of Minnesota - Clinical and Translational Science Institute; recruitment status when identified: this trial is currently recruiting participants; location: USA

ACE: angiotensin-converting enzyme; ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CVD: cardiovascular disease; HbA1c: glycated haemoglobin; HOMA-IR: homeostasis model assessment-insulin resistance; IOTF: International Obesity Task Force; SD: standard deviation; GFR: glomerular filtration rate; min: minute; MRI: magnetic resonance imaging; PK: pharmacokinetics; PCOS: polycystic ovary syndrome; SDS: standard deviation score; WHO: World Health Organization.

DATA AND ANALYSES

Comparison 1. Body mass index (BMI): pharmacological interventions versus comparators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in BMI (all trials)	16	1884	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
2 Change in BMI (drug type)	16	1884	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
2.1 Metformin	8	543	Mean Difference (IV, Random, 95% CI)	-1.35 [0.00, -0.69]
2.2 Orlistat	3	773	Mean Difference (IV, Random, 95% CI)	-0.79 [-1.08, -0.51]
2.3 Sibutramine	5	568	Mean Difference (IV, Random, 95% CI)	-1.70 [-2.89, -0.51]
3 Change in BMI (dropout rate)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
3.1 Dropouts < 20%	9	597	Mean Difference (IV, Random, 95% CI)	-1.11 [-1.78, -0.44]
3.2 Dropouts ≥ 20%	6	1145	Mean Difference (IV, Random, 95% CI)	-1.42 [-2.34, -0.50]
3.3 Unclear dropout rate	1	120	Mean Difference (IV, Random, 95% CI)	-2.73 [-3.74, -1.72]
4 Change in BMI (intention-to-treat (ITT) analysis)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
4.1 No ITT	5	282	Mean Difference (IV, Random, 95% CI)	-1.56 [-2.52, -0.60]
4.2 ITT used	11	1580	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.86, -0.65]
5 Change in BMI (funding)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
5.1 Commercial	5	1009	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.69, -0.31]
5.2 Noncommercial	5	271	Mean Difference (IV, Random, 95% CI)	-1.10 [-1.77, -0.44]
5.3 Commercial + noncommercial	4	262	Mean Difference (IV, Random, 95% CI)	-1.17 [-1.86, -0.47]
5.4 Unclear	2	320	Mean Difference (IV, Random, 95% CI)	-1.79 [-3.54, -0.04]
6 Change in BMI (publication date)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
6.1 2007 or before	8	1163	Mean Difference (IV, Random, 95% CI)	-1.41 [-2.21, -0.60]
6.2 After 2007	8	699	Mean Difference (IV, Random, 95% CI)	-1.26 [-1.90, -0.62]
7 Change in BMI (quality of trial)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
7.1 Low	6	322	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.28, -0.52]
7.2 Moderate	10	1540	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.95, -0.67]
8 Change in BMI (country)	16	1862	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
8.1 Middle income	3	216	Mean Difference (IV, Random, 95% CI)	-2.39 [-3.08, -1.69]
8.2 High income	13	1646	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.62, -0.56]
9 Change in BMI (mean age)	16	1884	Mean Difference (IV, Random, 95% CI)	-1.34 [-1.85, -0.83]
9.1 Mean age < 12 years	2	220	Mean Difference (IV, Random, 95% CI)	-1.93 [-3.53, -0.34]
9.2 Mean age ≥ 12 years	14	1664	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.79, -0.71]

Comparison 2. Weight: pharmacological interventions versus comparators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in weight (all trials)	11	1180	Mean Difference (IV, Random, 95% CI)	-3.90 [-5.86, -1.94]
2 Change in weight (drug type)	11	1180	Mean Difference (IV, Random, 95% CI)	-3.90 [-5.86, -1.94]
2.1 Metformin	4	372	Mean Difference (IV, Random, 95% CI)	-3.24 [-5.79, -0.69]
2.2 Sibutramine	5	568	Mean Difference (IV, Random, 95% CI)	-4.71 [-8.10, -1.32]
2.3 Orlistat	2	240	Mean Difference (IV, Random, 95% CI)	-2.48 [-4.31, -0.65]

Comparison 3. Adverse effects: pharmacological interventions versus comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	5	1347	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.63, 3.25]
1.1 Metformin	1	76	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 100.80]
1.2 Orlistat	3	773	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.41, 2.67]
1.3 Sibutramine	1	498	Risk Ratio (M-H, Random, 95% CI)	3.53 [0.46, 27.33]
2 Discontinued trial because of adverse events	10	1664	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.83, 2.52]
2.1 Metformin	3	246	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.26, 5.48]
2.2 Orlistat	4	815	Risk Ratio (M-H, Random, 95% CI)	2.49 [0.74, 8.32]
2.3 Sibutramine	3	603	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.53, 2.46]

Analysis 1.1. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 1 Change in BMI (all trials).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 1 Change in BMI (all trials)

Study or subgroup	Drug intervention N	Mean(SD)[kg/m2]	Comparator N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Freemark 2001	14	-0.485 (1.38)	15	0.88 (1.61)		6.4 %	-1.36 [-2.45, -0.27]
Berkowitz 2003	43	-3.1875 (2.55)	39	-1.52 (2.052)		6.8 %	-1.67 [-2.67, -0.67]
Chanoine 2005	352	-1.08 (2.05)	181	-0.31 (1.68)		8.8 %	-0.77 [-1.10, -0.44]
Godoy-Matos 2005	30	-3.6 (2.5)	30	-0.9 (0.9)		6.9 %	-2.70 [-3.65, -1.75]
Maahs 2006	20	-1.3 (1.6)	20	-0.8 (3)		5.1 %	-0.50 [-1.99, 0.99]
Berkowitz 2006	281	-3.3934 (3.086247)	79	-0.43 (2.871776)		7.7 %	-2.96 [-3.69, -2.23]
Garc a-Morales 2006	23	-3.4 (1.965625)	23	-1.8 (1.965625)		6.3 %	-1.60 [-2.74, -0.46]
Van Mil 2007	11	-0.8 (1.1)	9	-1.4 (1.4)		6.3 %	0.60 [-0.52, 1.72]
Atabek 2008	90	-2.08 (2.32)	30	0.65 (2.5)		6.7 %	-2.73 [-3.74, -1.72]
Clarson 2009	11	-1.8 (2.6533)	14	0.5 (1.122497)		4.6 %	-2.30 [-3.97, -0.63]
Wilson 2010	27	-0.9 (2.5980762)	27	0.2 (2.598076)		5.4 %	-1.10 [-2.49, 0.29]
Wiegand 2010	34	0.07 (3.4111069)	29	-0.31 (3.6619121)		4.4 %	0.38 [-1.38, 2.14]
Yanovski 2011	53	-0.78 (2.7754182)	47	0.32 (2.929046)		6.3 %	-1.10 [-2.22, 0.02]
NCT00001723	100	-1.44 (2.6)	100	-0.5 (2)		8.0 %	-0.94 [-1.58, -0.30]
Mauras 2012	23	-2.4 (2.3979158)	19	-1.1 (2.179449)		5.4 %	-1.30 [-2.69, 0.09]
Kendall 2013	55	-0.25 (4.1901521)	55	0.21 (4.2494817)		4.9 %	-0.46 [-2.04, 1.12]
Total (95% CI)	**1167**		**717**			**100.0 %**	**-1.34 [-1.85, -0.83]**

Heterogeneity: $Tau^2 = 0.74$; $Chi^2 = 65.88$, df = 15 (P<0.00001); $I^2 = 77\%$

Test for overall effect: Z = 5.16 (P < 0.00001)

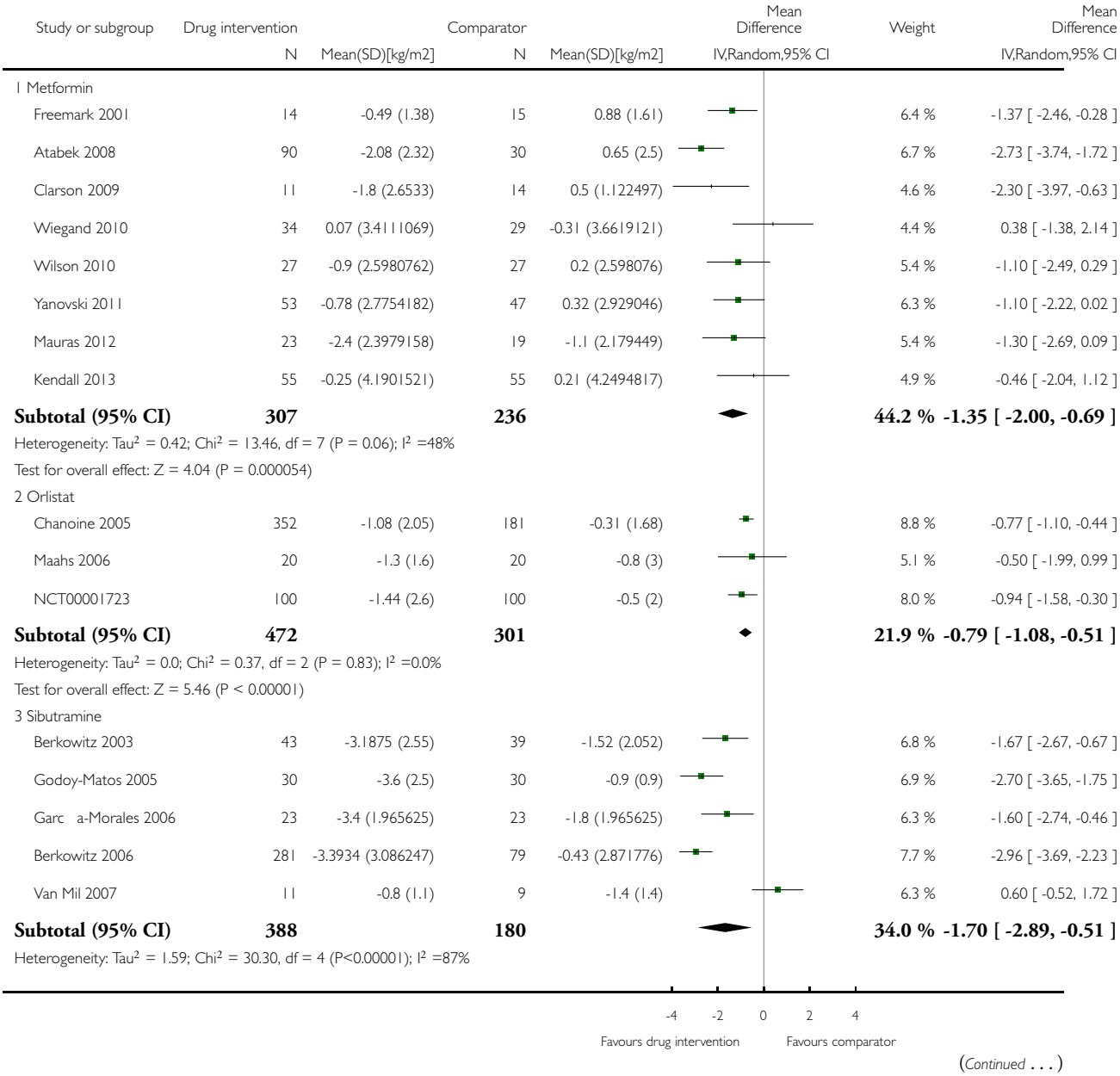
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 2 Change in BMI (drug type).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 2 Change in BMI (drug type)



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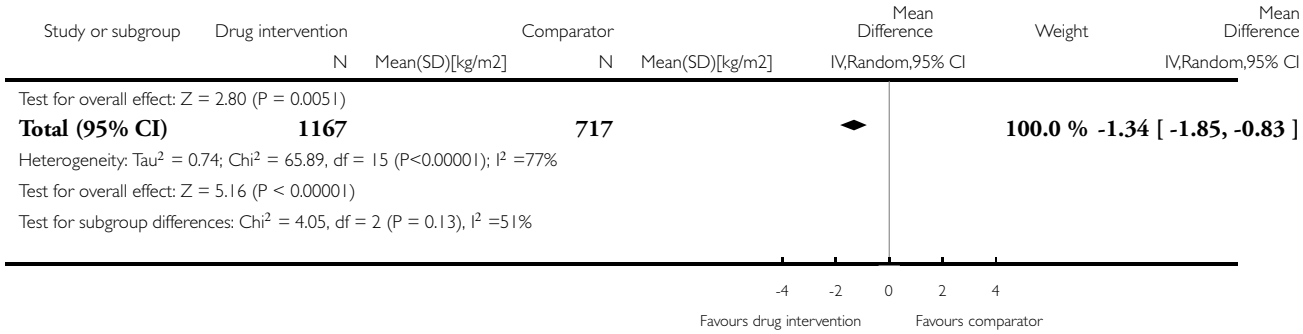
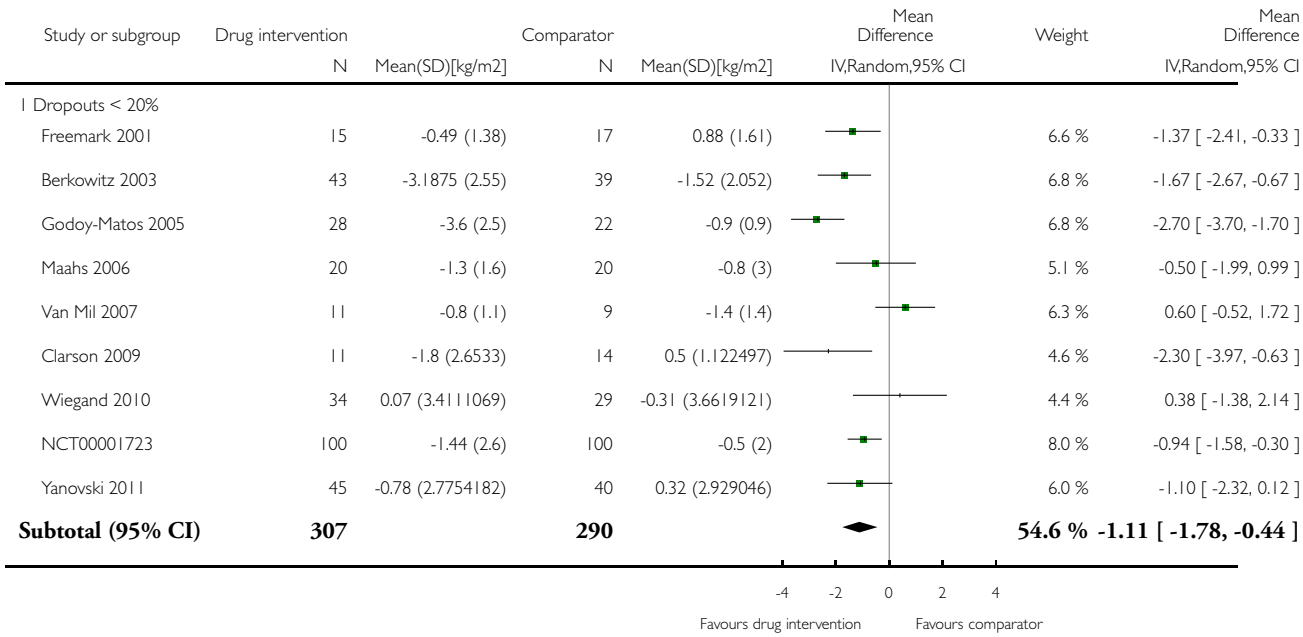


Analysis 1.3. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 3 Change in BMI (dropout rate).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 3 Change in BMI (dropout rate)



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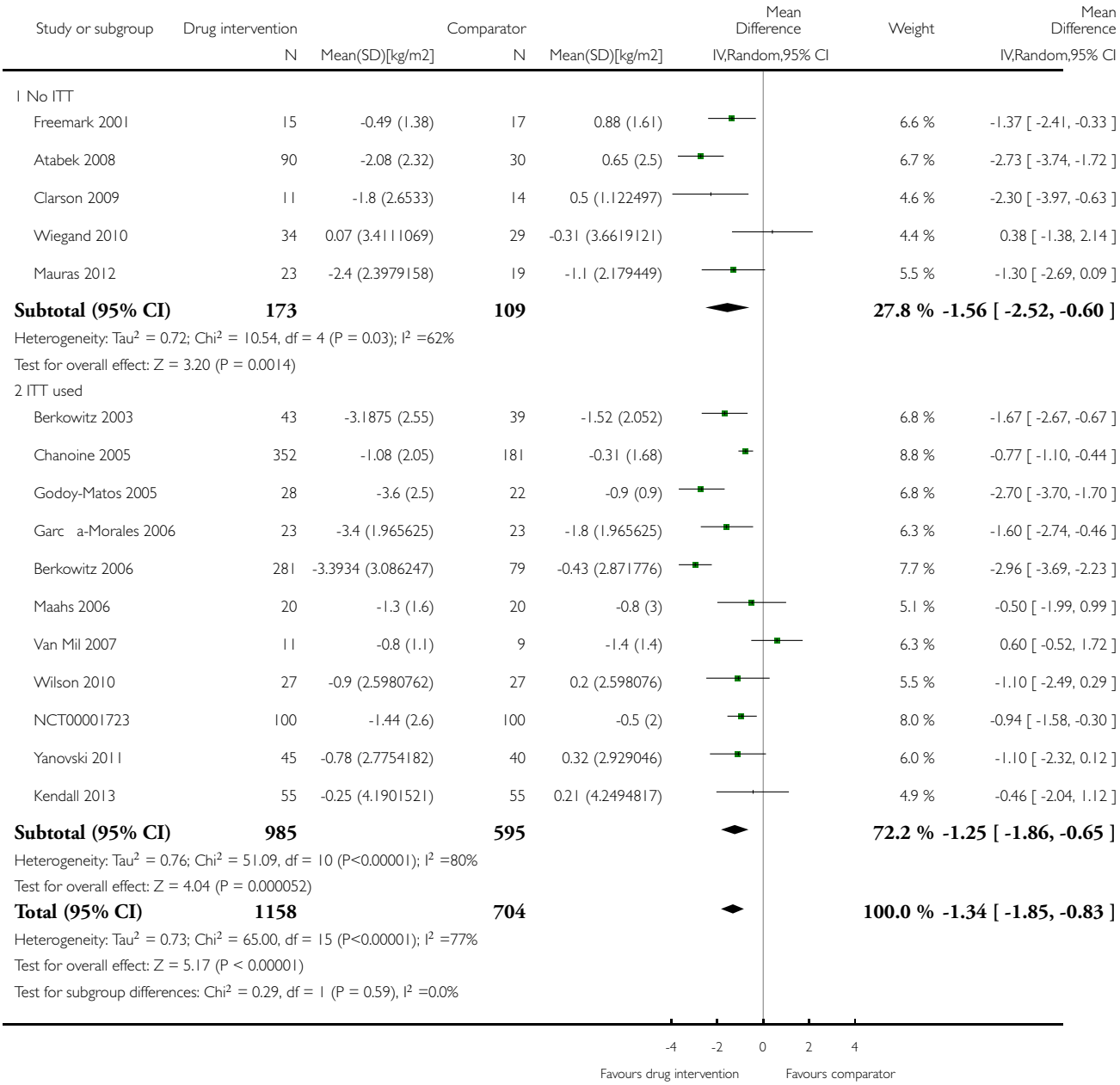
Study or subgroup	Drug intervention N	Mean(SD)[kg/m2]	Comparator N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: Tau^2 = 0.69; Chi^2 = 25.66, df = 8 (P = 0.001); I^2 =69%							
Test for overall effect: Z = 3.23 (P = 0.0013)							
2 Dropouts ≥ 20%							
Chanoine 2005	352	-1.08 (2.05)	181	-0.31 (1.68)		8.8 %	-0.77 [-1.10, -0.44]
Berkowitz 2006	281	-3.3934 (3.086247)	79	-0.43 (2.871776)		7.7 %	-2.96 [-3.69, -2.23]
Garc a-Morales 2006	23	-3.4 (1.965625)	23	-1.8 (1.965625)		6.3 %	-1.60 [-2.74, -0.46]
Wilson 2010	27	-0.9 (2.5980762)	27	0.2 (2.598076)		5.5 %	-1.10 [-2.49, 0.29]
Mauras 2012	23	-2.4 (2.3979158)	19	-1.1 (2.179449)		5.5 %	-1.30 [-2.69, 0.09]
Kendall 2013	55	-0.25 (4.1901521)	55	0.21 (4.2494817)		4.9 %	-0.46 [-2.04, 1.12]
Subtotal (95% CI)	**761**		**384**			**38.6 %**	**-1.42 [-2.34, -0.50]**
Heterogeneity: Tau^2 = 1.00; Chi^2 = 30.39, df = 5 (P = 0.00001); I^2 =84%							
Test for overall effect: Z = 3.02 (P = 0.0026)							
3 Unclear dropout rate							
Atabek 2008	90	-2.08 (2.32)	30	0.65 (2.5)		6.7 %	-2.73 [-3.74, -1.72]
Subtotal (95% CI)	**90**		**30**			**6.7 %**	**-2.73 [-3.74, -1.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.27 (P < 0.00001)							
Total (95% CI)	**1158**		**704**			**100.0 %**	**-1.34 [-1.85, -0.83]**
Heterogeneity: Tau^2 = 0.73; Chi^2 = 65.00, df = 15 (P<0.00001); I^2 =77%							
Test for overall effect: Z = 5.17 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.93, df = 2 (P = 0.03), I^2 =71%							

Analysis 1.4. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 4 Change in BMI (intention-to-treat (ITT) analysis).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 4 Change in BMI (intention-to-treat (ITT) analysis)



Analysis 1.5. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 5 Change in BMI (funding).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 5 Change in BMI (funding)

Study or subgroup	Drug intervention N	Mean(SD)[kg/m2]	Comparator N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Commercial							
Godoy-Matos 2005	28	-3.6 (2.5)	22	-0.9 (0.9)		6.8 %	-2.70 [-3.70, -1.70]
Chanoine 2005	352	-1.08 (2.05)	181	-0.31 (1.68)		8.8 %	-0.77 [-1.10, -0.44]
Berkowitz 2006	281	-3.3934 (3.086247)	79	-0.43 (2.871776)		7.7 %	-2.96 [-3.69, -2.23]
Garc a-Morales 2006	23	-3.4 (1.965625)	23	-1.8 (1.965625)		6.3 %	-1.60 [-2.74, -0.46]
Van Mil 2007	11	-0.8 (1.1)	9	-1.4 (1.4)		6.3 %	0.60 [-0.52, 1.72]
Subtotal (95% CI)	**695**		**314**			**36.0 %**	**-1.50 [-2.69, -0.31]**
Heterogeneity: Tau^2 = 1.63; Chi^2 = 48.16, df = 4 (P<0.00001); I^2 =92%							
Test for overall effect: Z = 2.47 (P = 0.013)							
2 Noncommercial							
Maahs 2006	20	-1.3 (1.6)	20	-0.8 (3)		5.1 %	-0.50 [-1.99, 0.99]
Clarson 2009	11	-1.8 (2.6533)	14	0.5 (1.122497)		4.6 %	-2.30 [-3.97, -0.63]
Wilson 2010	27	-0.9 (2.5980762)	27	0.2 (2.598076)		5.5 %	-1.10 [-2.49, 0.29]
Mauras 2012	23	-2.4 (2.3979158)	19	-1.1 (2.179449)		5.5 %	-1.30 [-2.69, 0.09]
Kendall 2013	55	-0.25 (4.1901521)	55	0.21 (4.2494817)		4.9 %	-0.46 [-2.04, 1.12]
Subtotal (95% CI)	**136**		**135**			**25.5 %**	**-1.10 [-1.77, -0.44]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.31, df = 4 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 3.24 (P = 0.0012)							
3 Commercial + noncommercial							
Freemark 2001	15	-0.49 (1.38)	17	0.88 (1.61)		6.6 %	-1.37 [-2.41, -0.33]
Berkowitz 2003	43	-3.1875 (2.55)	39	-1.52 (2.052)		6.8 %	-1.67 [-2.67, -0.67]
Wiegand 2010	34	0.07 (3.4111069)	29	-0.31 (3.6619121)		4.4 %	0.38 [-1.38, 2.14]
Yanovski 2011	45	-0.78 (2.7754182)	40	0.32 (2.929046)		6.0 %	-1.10 [-2.32, 0.12]
Subtotal (95% CI)	**137**		**125**			**23.8 %**	**-1.17 [-1.86, -0.47]**

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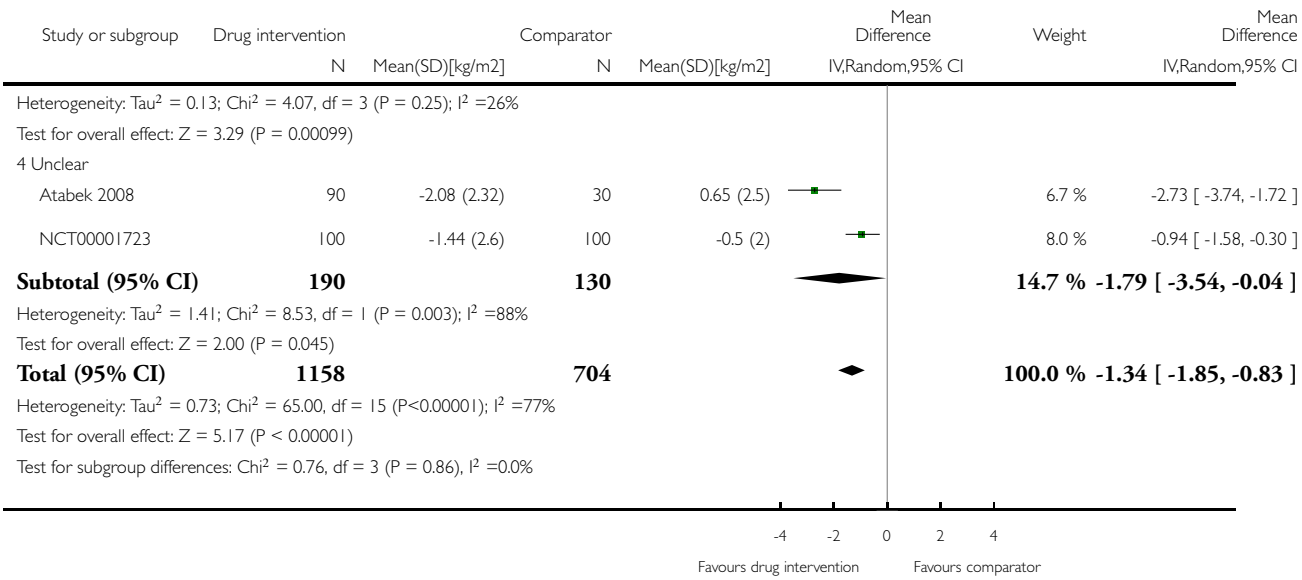


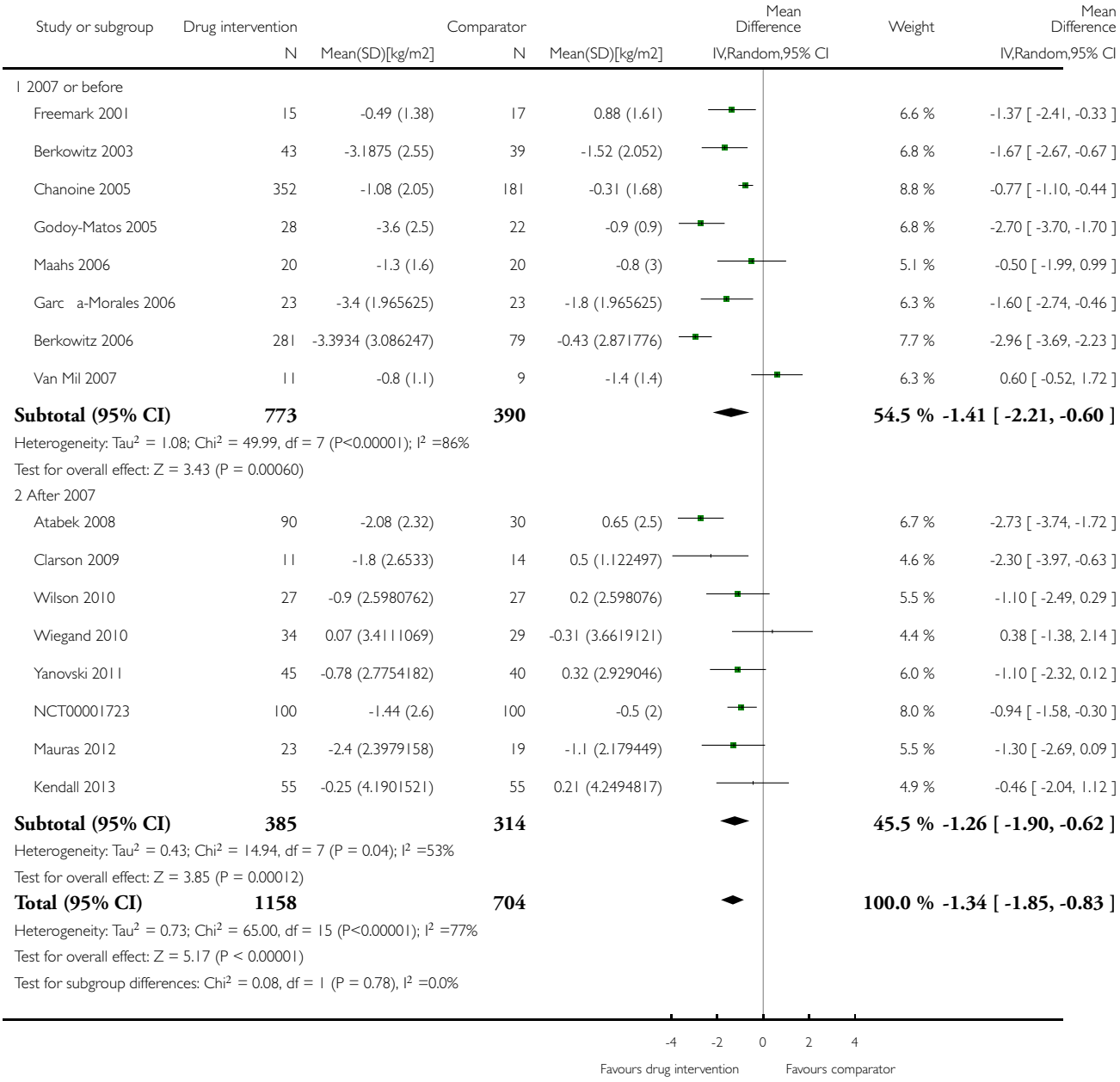
Analysis 1.6. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 6 Change in BMI (publication date).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 6 Change in BMI (publication date)

Study or subgroup	Drug intervention N	Mean(SD)[kg/m2]	Comparator N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 2007 or before							
Freemark 2001	15	-0.49 (1.38)	17	0.88 (1.61)		6.6 %	-1.37 [-2.41, -0.33]
Berkowitz 2003	43	-3.1875 (2.55)	39	-1.52 (2.052)		6.8 %	-1.67 [-2.67, -0.67]
Chanoine 2005	352	-1.08 (2.05)	181	-0.31 (1.68)		8.8 %	-0.77 [-1.10, -0.44]
Godoy-Matos 2005	28	-3.6 (2.5)	22	-0.9 (0.9)		6.8 %	-2.70 [-3.70, -1.70]
Maahs 2006	20	-1.3 (1.6)	20	-0.8 (3)		5.1 %	-0.50 [-1.99, 0.99]
Garc a-Morales 2006	23	-3.4 (1.965625)	23	-1.8 (1.965625)		6.3 %	-1.60 [-2.74, -0.46]
Berkowitz 2006	281	-3.3934 (3.086247)	79	-0.43 (2.871776)		7.7 %	-2.96 [-3.69, -2.23]
Van Mil 2007	11	-0.8 (1.1)	9	-1.4 (1.4)		6.3 %	0.60 [-0.52, 1.72]
Subtotal (95% CI)	**773**		**390**			**54.5 %**	**-1.41 [-2.21, -0.60]**
Heterogeneity: Tau² = 1.08; Chi² = 49.99, df = 7 (P<0.00001); I² =86%							
Test for overall effect: Z = 3.43 (P = 0.00060)							
2 After 2007							
Atabek 2008	90	-2.08 (2.32)	30	0.65 (2.5)		6.7 %	-2.73 [-3.74, -1.72]
Clarson 2009	11	-1.8 (2.6533)	14	0.5 (1.122497)		4.6 %	-2.30 [-3.97, -0.63]
Wilson 2010	27	-0.9 (2.5980762)	27	0.2 (2.598076)		5.5 %	-1.10 [-2.49, 0.29]
Wiegand 2010	34	0.07 (3.4111069)	29	-0.31 (3.6619121)		4.4 %	0.38 [-1.38, 2.14]
Yanovski 2011	45	-0.78 (2.7754182)	40	0.32 (2.929046)		6.0 %	-1.10 [-2.32, 0.12]
NCT00001723	100	-1.44 (2.6)	100	-0.5 (2)		8.0 %	-0.94 [-1.58, -0.30]
Mauras 2012	23	-2.4 (2.3979158)	19	-1.1 (2.179449)		5.5 %	-1.30 [-2.69, 0.09]
Kendall 2013	55	-0.25 (4.1901521)	55	0.21 (4.2494817)		4.9 %	-0.46 [-2.04, 1.12]
Subtotal (95% CI)	**385**		**314**			**45.5 %**	**-1.26 [-1.90, -0.62]**
Heterogeneity: Tau² = 0.43; Chi² = 14.94, df = 7 (P = 0.04); I² =53%							
Test for overall effect: Z = 3.85 (P = 0.00012)							
Total (95% CI)	**1158**		**704**			**100.0 %**	**-1.34 [-1.85, -0.83]**
Heterogeneity: Tau² = 0.73; Chi² = 65.00, df = 15 (P<0.00001); I² =77%							
Test for overall effect: Z = 5.17 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² =0.0%							



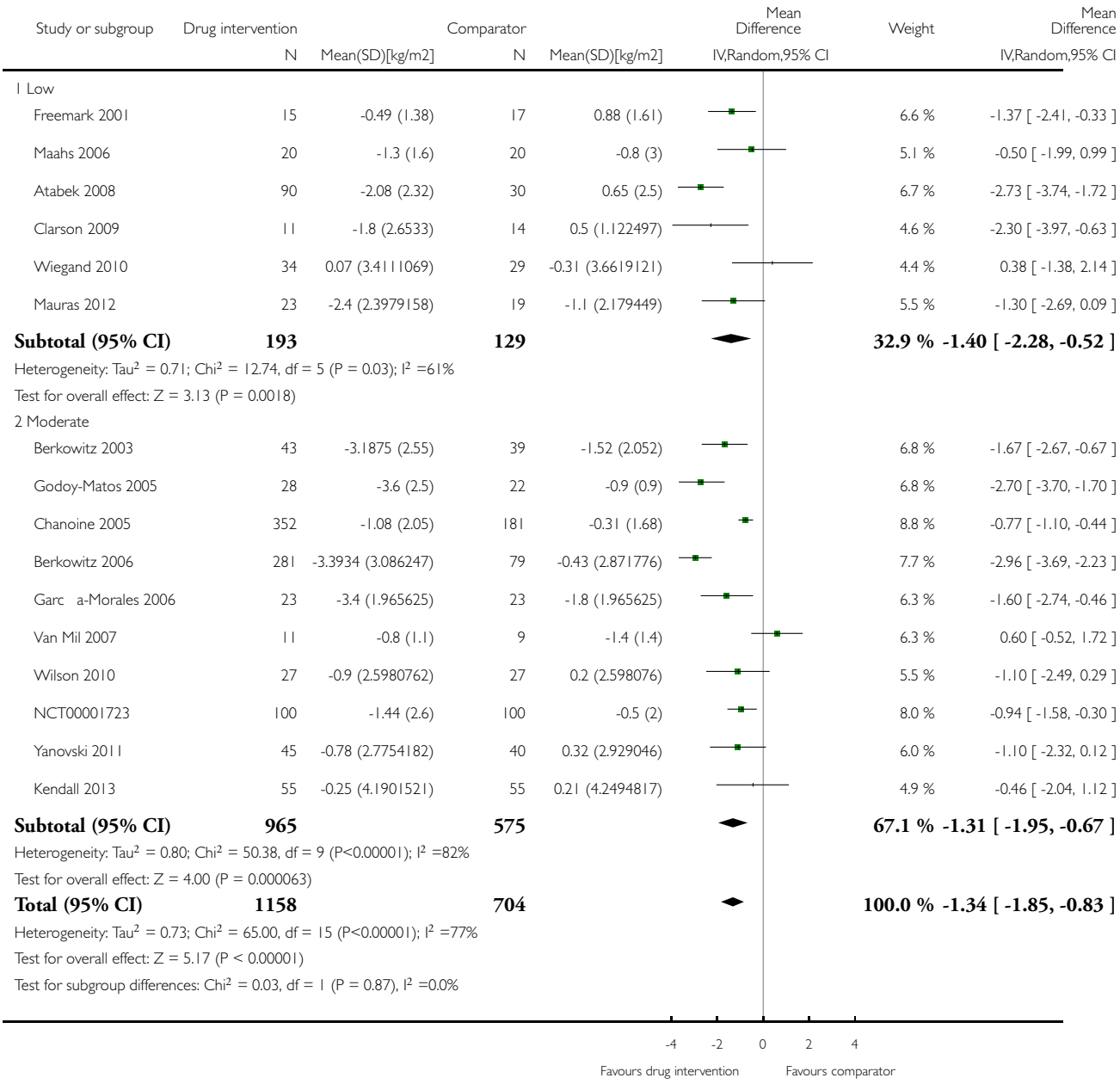
Analysis 1.7. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 7 Change in BMI (quality of trial).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 7 Change in BMI (quality of trial)

Study or subgroup	Drug intervention N	Mean(SD)[kg/m2]	Comparator N	Mean(SD)[kg/m2]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Low							
Freemark 2001	15	-0.49 (1.38)	17	0.88 (1.61)		6.6 %	-1.37 [-2.41, -0.33]
Maahs 2006	20	-1.3 (1.6)	20	-0.8 (3)		5.1 %	-0.50 [-1.99, 0.99]
Atabek 2008	90	-2.08 (2.32)	30	0.65 (2.5)		6.7 %	-2.73 [-3.74, -1.72]
Clarson 2009	11	-1.8 (2.6533)	14	0.5 (1.122497)		4.6 %	-2.30 [-3.97, -0.63]
Wiegand 2010	34	0.07 (3.4111069)	29	-0.31 (3.6619121)		4.4 %	0.38 [-1.38, 2.14]
Mauras 2012	23	-2.4 (2.3979158)	19	-1.1 (2.179449)		5.5 %	-1.30 [-2.69, 0.09]
Subtotal (95% CI)	**193**		**129**			**32.9 %**	**-1.40 [-2.28, -0.52]**
Heterogeneity: $Tau^2 = 0.71$; $Chi^2 = 12.74$, df = 5 (P = 0.03); $I^2 = 61\%$							
Test for overall effect: Z = 3.13 (P = 0.0018)							
2 Moderate							
Berkowitz 2003	43	-3.1875 (2.55)	39	-1.52 (2.052)		6.8 %	-1.67 [-2.67, -0.67]
Godoy-Matos 2005	28	-3.6 (2.5)	22	-0.9 (0.9)		6.8 %	-2.70 [-3.70, -1.70]
Chanoine 2005	352	-1.08 (2.05)	181	-0.31 (1.68)		8.8 %	-0.77 [-1.10, -0.44]
Berkowitz 2006	281	-3.3934 (3.086247)	79	-0.43 (2.871776)		7.7 %	-2.96 [-3.69, -2.23]
Garc a-Morales 2006	23	-3.4 (1.965625)	23	-1.8 (1.965625)		6.3 %	-1.60 [-2.74, -0.46]
Van Mil 2007	11	-0.8 (1.1)	9	-1.4 (1.4)		6.3 %	0.60 [-0.52, 1.72]
Wilson 2010	27	-0.9 (2.5980762)	27	0.2 (2.598076)		5.5 %	-1.10 [-2.49, 0.29]
NCT00001723	100	-1.44 (2.6)	100	-0.5 (2)		8.0 %	-0.94 [-1.58, -0.30]
Yanovski 2011	45	-0.78 (2.7754182)	40	0.32 (2.929046)		6.0 %	-1.10 [-2.32, 0.12]
Kendall 2013	55	-0.25 (4.1901521)	55	0.21 (4.2494817)		4.9 %	-0.46 [-2.04, 1.12]
Subtotal (95% CI)	**965**		**575**			**67.1 %**	**-1.31 [-1.95, -0.67]**
Heterogeneity: $Tau^2 = 0.80$; $Chi^2 = 50.38$, df = 9 (P<0.00001); $I^2 = 82\%$							
Test for overall effect: Z = 4.00 (P = 0.000063)							
Total (95% CI)	**1158**		**704**			**100.0 %**	**-1.34 [-1.85, -0.83]**
Heterogeneity: $Tau^2 = 0.73$; $Chi^2 = 65.00$, df = 15 (P<0.00001); $I^2 = 77\%$							
Test for overall effect: Z = 5.17 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.87), $I^2 = 0.0\%$							

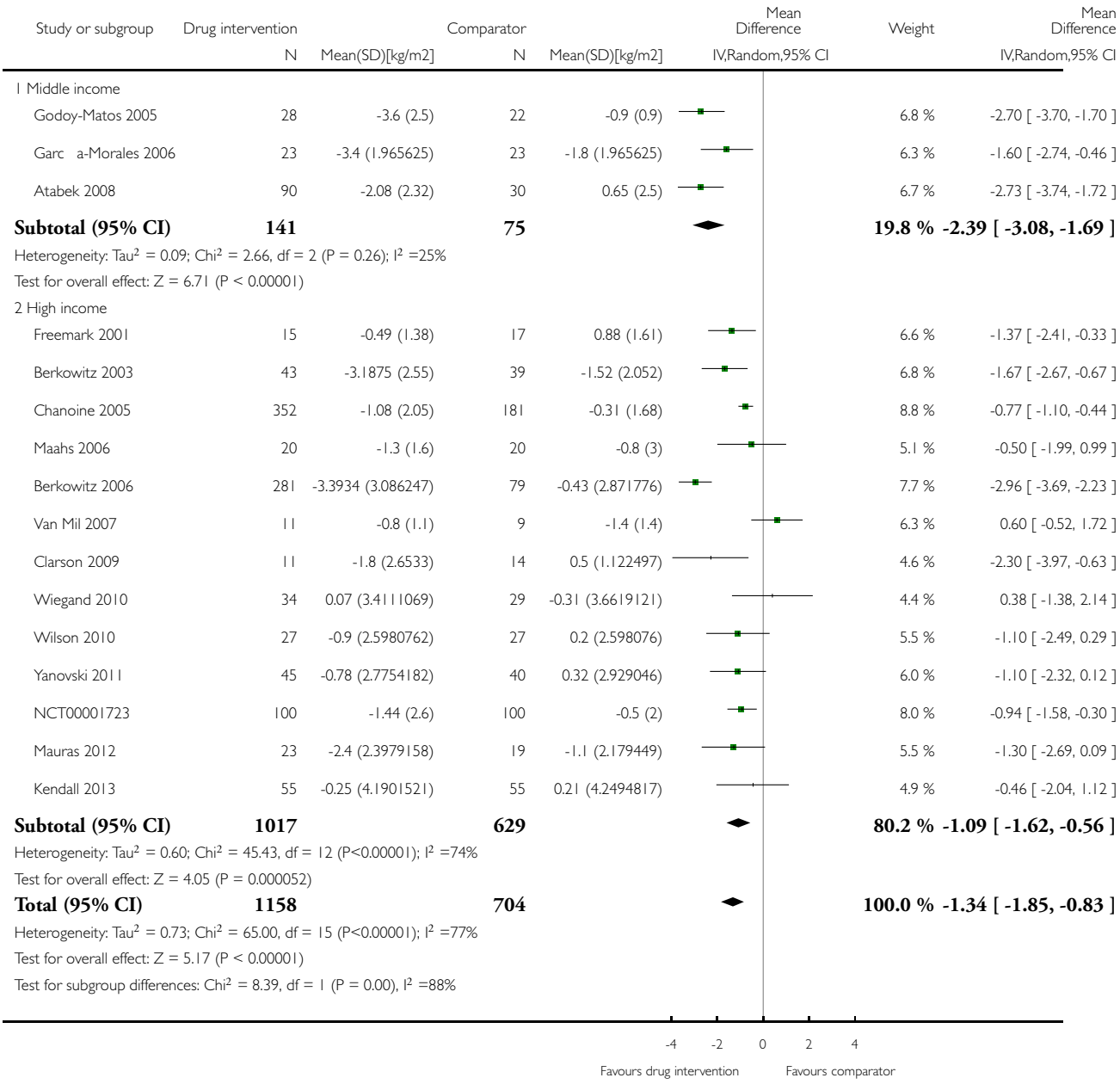


Analysis 1.8. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 8 Change in BMI (country).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 8 Change in BMI (country)

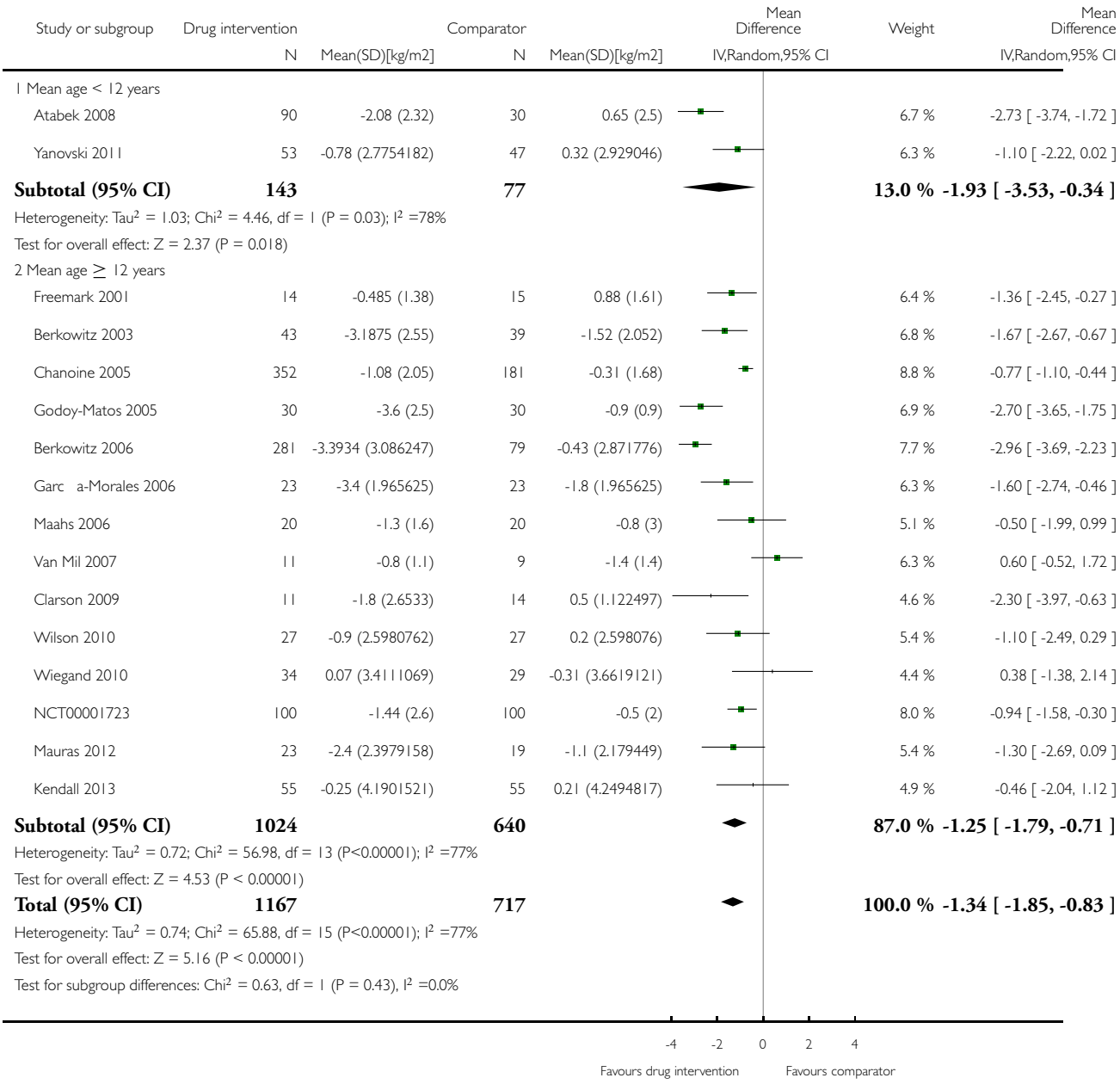


Analysis 1.9. Comparison 1 Body mass index (BMI): pharmacological interventions versus comparators, Outcome 9 Change in BMI (mean age).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 1 Body mass index (BMI): pharmacological interventions versus comparators

Outcome: 9 Change in BMI (mean age)



Analysis 2.1. Comparison 2 Weight: pharmacological interventions versus comparators, Outcome 1 Change in weight (all trials).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 2 Weight: pharmacological interventions versus comparators

Outcome: 1 Change in weight (all trials)

Study or subgroup	Drug intervention N	Mean(SD)[kg]	Comparator N	Mean(SD)[kg]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Berkowitz 2003	43	-7.8 (6.3)	39	-3.2 (6.1)		10.0 %	-4.60 [-7.29, -1.91]
Godoy-Matos 2005	30	-10.3 (6.6)	30	-2.4 (2.5)		10.2 %	-7.90 [-10.43, -5.37]
Garc a-Morales 2006	23	-7.7 (5.78125)	23	-3.8 (4.971875)		9.4 %	-3.90 [-7.02, -0.78]
Berkowitz 2006	281	-6.5593 (8.697846)	79	1.76 (8.171095)		10.8 %	-8.32 [-10.39, -6.25]
Maahs 2006	20	-5.5 (7.47557)	20	-1.6 (9.91254)		6.3 %	-3.90 [-9.34, 1.54]
Van Mil 2007	11	-0.18 (3.11)	9	-1.92 (3.88)		9.3 %	1.74 [-1.39, 4.87]
Atabek 2008	90	-3.46 (11.1774)	30	3.53 (11.1455)		7.3 %	-6.99 [-11.60, -2.38]
Yanovski 2011	53	1.47 (6.439696)	47	4.85 (6.828763)		10.1 %	-3.38 [-5.99, -0.77]
NCT00001723	100	-2.9 (7)	100	-0.6 (7)		11.0 %	-2.30 [-4.24, -0.36]
Mauras 2012	23	-4.9 (4.795832)	19	-1.7 (4.794789)		9.7 %	-3.20 [-6.11, -0.29]
Kendall 2013	55	2.4 (16.2317)	55	0.4 (14.1603)		6.0 %	2.00 [-3.69, 7.69]
Total (95% CI)	**729**		**451**			**100.0 %**	**-3.90 [-5.86, -1.94]**

Heterogeneity: $Tau^2 = 8.15$; $Chi^2 = 47.85$, df = 10 (P<0.00001); $I^2 = 79\%$

Test for overall effect: Z = 3.90 (P = 0.000095)

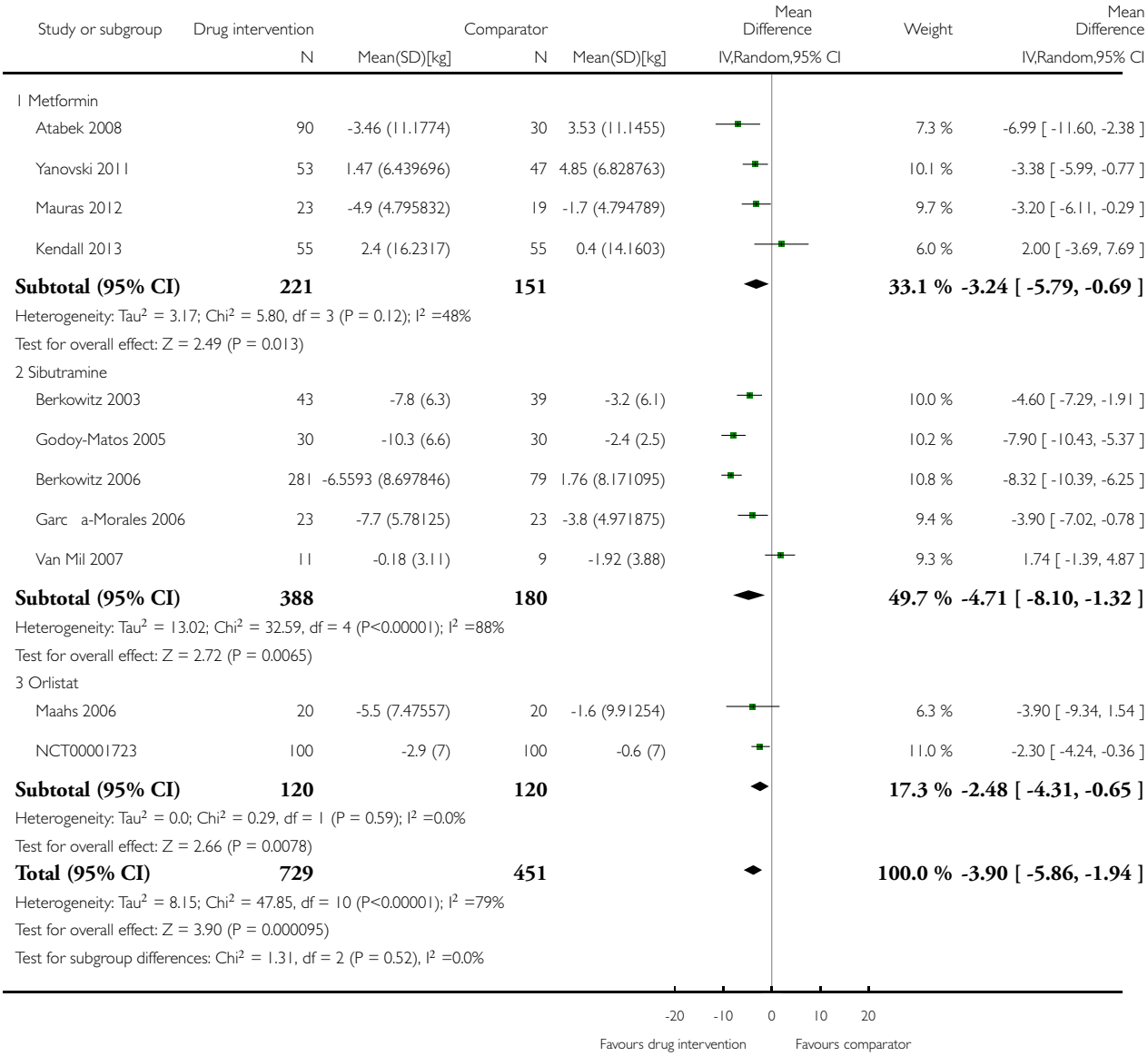
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Weight: pharmacological interventions versus comparators, Outcome 2 Change in weight (drug type).

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 2 Weight: pharmacological interventions versus comparators

Outcome: 2 Change in weight (drug type)

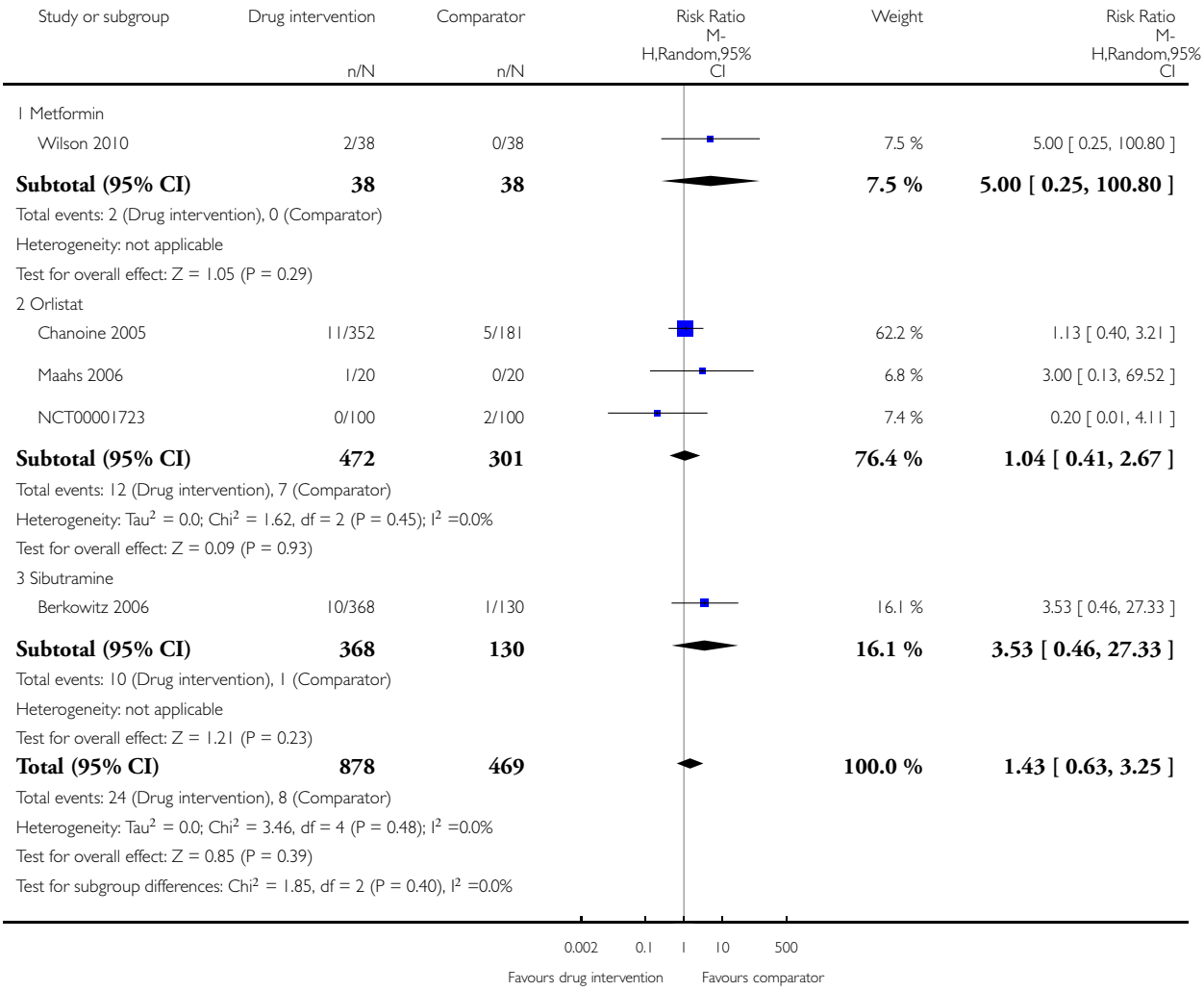


Analysis 3.1. Comparison 3 Adverse effects: pharmacological interventions versus comparator, Outcome 1 Serious adverse events.

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 3 Adverse effects: pharmacological interventions versus comparator

Outcome: 1 Serious adverse events

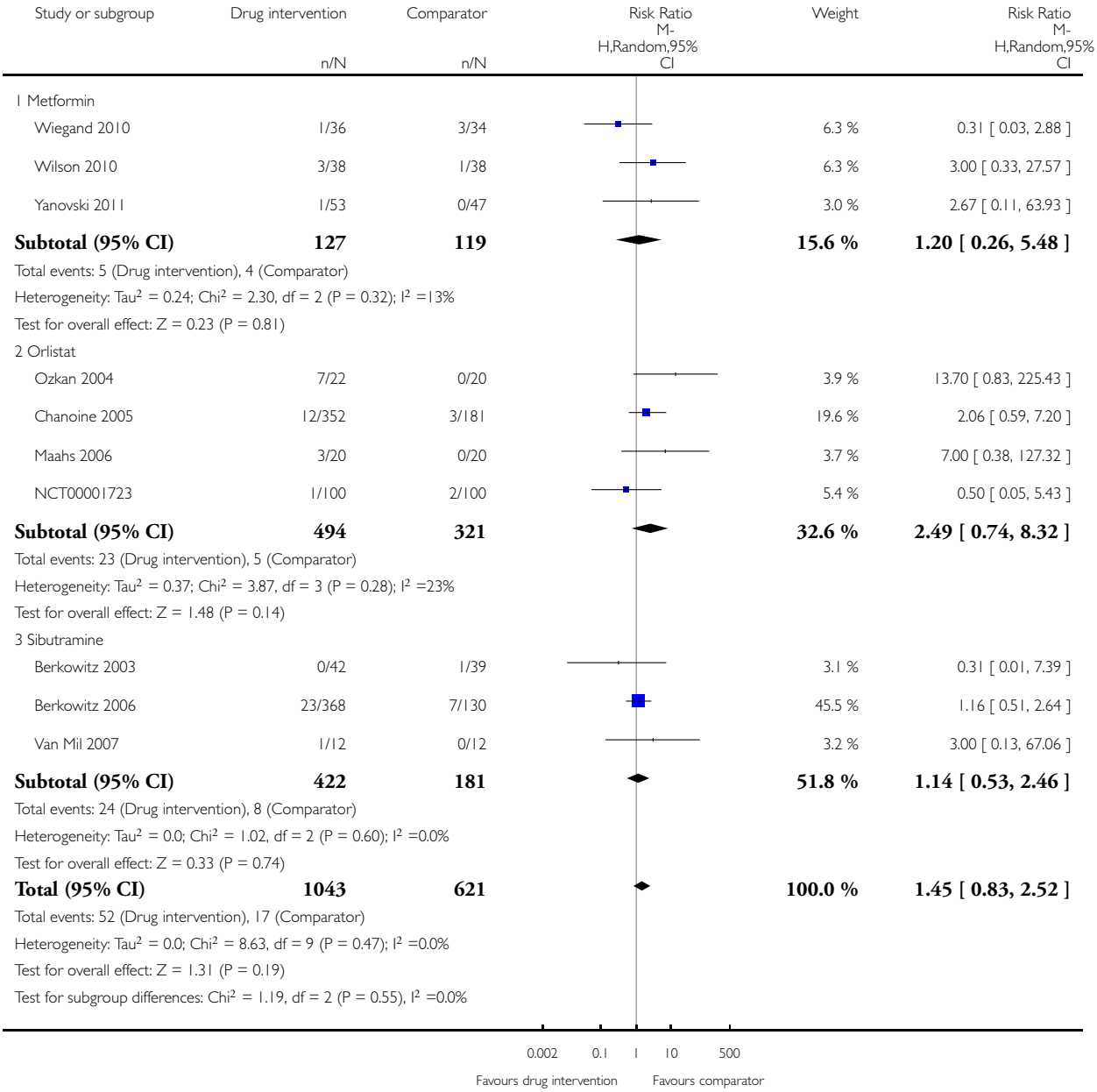


Analysis 3.2. Comparison 3 Adverse effects: pharmacological interventions versus comparator, Outcome 2 Discontinued trial because of adverse events.

Review: Drug interventions for the treatment of obesity in children and adolescents

Comparison: 3 Adverse effects: pharmacological interventions versus comparator

Outcome: 2 Discontinued trial because of adverse events



ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Randomised (N)	Safety (N)	ITT (N)	Finishing trial (N)	Randomised finishing trial (%)	Follow-up time[a]
Atabek 2008[b]	I: metformin + diet and physical activity advice	-	-	90	90	-	90	100	6 months
	C: placebo + diet and physical activity advice			30	30	-	30	100	
	total:			120	120	-	120	100	
Berkowitz 2003	I: behavioural programme + sibutramine	Powered to detect a 4% difference in % change in BMI between the 2 treatment groups with an SD of 5% (α =	146	43	43	43	40	93.0	6 months (not including the 6-month open-label period where all participants received sibutramine)
	C: behavioural programme + placebo			39	39	39	34	87.2	
	total:			82	82	82	62	75.6	
Berkowitz 2006	I: behavioural programme + sibutramine	"Planned sample size was approximately 400 participants with a 3:1 randomization ratio of	-	368	368	-	281	76.4	12 months

Table 1. Overview of trial populations (*Continued*)

		sibutramine to placebo. On the basis of previous 12-month adult trials, we determined that 300 participants in the sibutramine group would be adequate to assess safety and exposure, allowing an overall dropout rate of approximately 50% and a probability that approximately 50% of participants receiving 10 mg of sibutramine would lose 10% or more of initial BMI at 6 months“ ”Although the protocol did not document							

Table 1. Overview of trial populations (*Continued*)

		a formal sample size calculation for efficacy, approximately 132 adolescents (99 in the sibutramine group and 33 in the placebo group) would allow a between-group difference in BMI of 2 kg/m^2, with 90% power (2-sided level of 0.05) to be statistically significant, assuming a common							
	C: behavioural programme + placebo			130	130	-	80	61.5	
	total:			498	498	-	361	72.5	
Chanoine 2005	I: orlistat + diet + exercise + behaviour therapy	"We planned to enroll at least 450 individuals to provide more than 80% power to detect a difference of 1 BMI unit,	588	357	352	348	232	65.0	54 weeks

Table 1. Overview of trial populations (*Continued*)

		assuming a 30% dropout rate“							
	C: placebo + diet + exercise + behaviour therapy			182	181	180	117	64.3	
	total:			539	533	528	349	64.7	
Clarson 2009	I: metformin + lifestyle intervention	-	65	14	-	-	11	78.6	6 months
	C: lifestyle intervention only			17	-	-	14	82.4	
	total:			31	-	-	25	80.6	
Franco 2014 (cross-over trial)	I: sibutramine + dietary guidance	-	73	-	-	-	-	-	13 months
	C: placebo + dietary guidance			–	-	-	-	-	
	total:			63	63	-	23	36.5	
Freemark 2001	I: metformin	-	-	15	-	-	14	93.3	6 months
	C: placebo			17	-	-	15	88.2	
	total:			32	-	-	29	90.6	
Garcia-Morales 2006	I: sibutramine + diet + exercise	13 participants per group (expectations: mean loss of 7.5 kg (SD 5.3)	70	26	26	23	21	80.8	6 months

Table 1. Overview of trial populations (*Continued*)

		in the sibutramine group vs 3.6 kg (SD 4.5) in the placebo group)[e]							
	C: placebo + diet + exercise			25	25	23	19	76.0	
	total:			51	51	46	40	78.4	
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	-	-	30	30	30	28	93.3	24 weeks
	C: placebo + hypocaloric diet + exercise			30	30	30	22	73.3	
	total:			60	60	60	50	83.3	
Kendall 2013	I: metformin + healthy lifestyle advice	"The target recruitment was 140 patients, based on a power calculation using the results of a previous study. A standard power calculation was used to detect a reduction in BMI of 0.15 kg/m^2 (SD 0.3). Sixty-four par-	234	-	74	74	55	-	6 months

Table 1. Overview of trial populations (*Continued*)

		ticipants in each group give a statistical power of 80% for a t test at the 5% significance level. This was rounded up to allow for some loss to follow-up but recognizing that adjustment using multifactorial analysis would likely enhance the trial power by an unpre-							
	C: placebo + healthy lifestyle advice			-	77	77	55	-	
	total:			155	151	151	110	71.0	
Maahs 2006	I: orlistat + diet and exercise therapy	"We determined that a clinically important mean difference in decrease in BMI between the orlistat and placebo groups would be 2.0 kg/m^2 at 6 months	43	20	-	20	18	90.0	6 months

Table 1. Overview of trial populations (*Continued*)

		and used an SD of 1.8. On the basis of this approach, a sample size of 15 subjects per group would be adequate to detect a 2.0 kg/m^2 difference in Student's t test with 80% power and alpha = 0.05. In order to allow for a 25% dropout rate, 20 subjects were randomized							
	C: placebo + diet and exercise therapy			20	-	20	16	80.0	
	total:			40	-	40	34	85.0	
Mauras 2012	I: metformin + diet/ exercise intervention	"Differences in hsCRP and fibrinogen concentrations at 6 months were the primary outcomes. An n = 42 completed subjects provided > 90 %	-	35	35	-	23	65.7	6 months

Table 1. Overview of trial populations (*Continued*)

		power to detect significant changes“							
	C: diet/ exercise intervention			31	31	-	19	61.3	
	total:			66	66	-	42	63.6	
NCT00001	I: orlistat + behavioural weight loss programme	-	-	100	100	100	87	87.0	6 months
	C: placebo + behavioural weight loss programme			100	100	100	84	84.0	
				200	100	100	171	85.5	
Ozkan 2004	I: conventional treatment (nutritional and lifestyle modification programmes) + orlistat	-	-	22	-	-	15	68.2	5 to 15 months
	C: conventional treatment: nutritional and lifestyle modification programmes			20	-	-	15	75.0	
	total:			42	-	-	30	71.4	

Table 1. Overview of trial populations (*Continued*)

Prado 2012	I: metformin + nutritional guide and exercise programme	8 participants were required per intervention group (SD 0.4; difference of 0.6, P < 0.05, power = 90%)	41/26	-	9	-	7	-	6 months
	C: placebo + nutritional guide and exercise programme			-	10	-	6	-	
	total:			26	19	-	13	50	
Rezvanian 2010	I1: metformin + diet and physical activity advice	"By considering alpha = 0.05 and a power level of 0.8, the sample size was calculated as 160, and by considering the attrition during the follow-up, we increased it to 180"	180	45	-	-	41	91.1	24 weeks
	I2: fluoxetine + diet and physical activity advice			45	-	-	40	88.9	
	I3: metformin and fluoxetine + diet and physical activity advice			45	-	-	41	91.1	
	C: placebo + diet and physical activity advice			45	-	-	42	93.3	
	total:			180	-	-	164	91.1	
Srinivasan 2006 (cross-	I: metformin + "standard-	-	34	–	-	-	-	-	12 months

Table 1. Overview of trial populations (*Continued*)

over trial)	ised information on healthy eating and exercise“								
	C: placebo + ”standardised information on healthy eating and exercise“			–	-	-	-	-	
	total:			28	-	-	22	78.6	
Van Mil 2007	I: sibutramine + energy-restricted diet and exercise plan	”The number of patients required per treatment group to detect a difference between treatment groups in mean change in BMI at endpoint intervention of 1.0 kg/m^2, based on an estimate of variance (sd) of 0.65, an overall significance level of 5%, and a power of 90%, was nine.	-	12	12	12	11	91.7	24 weeks

Table 1. Overview of trial populations (*Continued*)

		Allowing a drop-out rate of 25%, the number of patients needed in each group was 12"[h]							
	C: placebo + energy-restricted diet and exercise plan			12	12	12	9	75.0	
	total:			24	24	24	20	83.3	
Wiegand 2010	I: metformin + lifestyle intervention	"Since a clinically significant effect was defined as a decrease in HOMA-IR by -1, two groups of 37 patients had to be included in the study to achieve a power of 0.9 with a	278	36	-	-	34	94.4	6 months
	C: placebo + lifestyle intervention			34	-	-	29	85.3	
	total:			70	-	-	63	90	
Wilson 2010	I: metformin + lifestyle intervention	"Assuming an SD of 1.9 for BMI change, an enrolled sample of 72 provided 80% power to detect a differential	92	39	39	39	19	48.7	100 weeks

Table 1. Overview of trial populations (*Continued*)

		of 1.46 between treatment arms or between sexes and 1.75 between white subjects and							
	C: placebo + lifestyle intervention			38	38	38	19	50.0	
	total:			77	76	76	38	49.4	
Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	"A total sample size of 60 participants would detect a between-group difference of 0.09 BMI SD score units (approximately equivalent to a 2 kg/m^2 difference) with 80% power. Participant accrual was set at 100 participants to allow as much as 40% loss to follow-up"[j]	278	53	-	53	45	84.9	6 months (not including the 6-month open-label phase)
	C: placebo + dietitian-administered weight-			47	-	47	40	85.1	

Table 1. Overview of trial populations (*Continued*)

	reduction programme								
	total:			100	-	100	85	85.0	
Grand total	***All interventions[k]***			***1395***			***1153***		
	All comparators[k]			***817***			***665***		
	All interventions and comparators[k]			***2484***			***1851***		

[a] Duration of intervention and follow-up under randomised conditions until end of trial.
[b] Unclear from the publication on the number which completed the trial and hence number of dropouts.
[c] Actual treatment difference between intervention groups was 4.5% reduction in BMI.
[d] Actual treatment difference between intervention groups at 12 months was 2.9 kg/m^2.
[e] Actual weight loss was 7.3 kg in the sibutramine group vs 4.3 kg in the placebo group.
[f] Actual adjusted treatment difference at 6 months was -1.07 kg/m^2.
[g] Actual treatment difference between intervention groups at 6 months was 0.5 kg/m^2.
[h] Actual treatment difference between intervention groups at end of intervention (12 weeks) was 0.4 kg/m^2 and at end of follow-up (24 weeks) was 1.0 kg/m^2.
[i] Actual treatment difference between intervention groups after 48 weeks was 1.1 kg/m^2.
[j] Actual treatment difference between intervention groups at 6 months for BMI z score was 0.07.
[k] Numbers for interventions and comparators do not add up to 'all interventions and comparators' because several trials did not provide information on randomised participants per intervention/comparator group but only the total number of randomised participants.
"-" denotes not reported.
BMI: body mass index; C: comparator; hsCRP: high sensitivity C-reactive protein; HOMA-IR: homeostasis model assessment for insulin resistance index; I: intervention; ITT: intention-to-treat; n: number of participants; SD: standard deviation.

Table 2. Sensitivity analyses: BMI

Trials with data on mean change only	
Number of trials	14
Point estimate (95% CI) (kg/m^2)	- 1.5 (-2.0 to -0.9) favouring drug intervention
Trials with concealment of allocation	
Number of trials	12
Point estimate (95% CI) (kg/m^2)	-1.3 (-1.8 to -0.7) favouring drug interventions

Table 2. Sensitivity analyses: BMI (*Continued*)

Trials with blinding of participants/personnel	
Number of trials	10
Point estimate (95% CI) (kg/m^2)	-1.3 (-1.9 to -0.7) favouring drug interventions
Trials with blinding of outcome assessors	
Number of trials	10
Point estimate (95% CI) (kg/m^2)	-1.3 (-1.9 to -0.7) favouring drug interventions
Trials without large sample size trials	
Number of trials	14
Point estimate (95% CI) (kg/m^2)	-1.3 (-1.8 to -0.7) favouring drug interventions
Trials with trials with 6 months' follow-up only	
Number of trials	14
Point estimate (95% CI) (kg/m^2)	-1.2 (-1.7 to -0.7) favouring drug interventions
Trials without trials with higher drug dose	
Number of trials	14
Point estimate (95% CI) (kg/m^2)	-1.2 (-1.7 to -0.7) favouring drug interventions
Trials with trials with a high dose/active lifestyle intervention	
Number of trials	10
Point estimate (95% CI) (kg/m^2)	-1.3 (-1.9 to -0.7) favouring drug interventions
Trials without trials with high attrition	
Number of trials	13
Point estimate (95% CI) (kg/m^2)	-1.4 (-2.0 to -0.8) favouring drug interventions

BMI: body mass index; CI: confidence interval.

Table 3. Sensitivity analyses: weight

Trials with data on mean change only	
Number of trials	8
Point estimate (95% CI) (kg)	- 4.1 (-6.3 to -1.8) favouring drug intervention
Trials with concealment of allocation	
Number of trials	9
Point estimate (95% CI) (kg)	-3.5 (-5.8 to -1.2) favouring drug interventions
Trials with blinding of participants/personnel	
Number of trials	7
Point estimate (95% CI) (kg)	-4.2 (-6.8 to -1.5) favouring drug interventions
Trials with blinding of outcome assessors	
Number of trials	7
Point estimate (95% CI) (kg)	-4.2 (-6.8 to -1.5) favouring drug interventions
Trials without large sample size trials	
Number of trials	10
Point estimate (95% CI) (kg)	-3.4 (-5.2 to -1.6) favouring drug interventions
Trials with 6 months' follow-up only	
Number of trials	9
Point estimate (95% CI) (kg)	-3.5 (-5.6 to -1.4) favouring drug interventions
Trials without trials with higher drug dose	
Number of trials	10
Point estimate (95% CI) (kg)	-3.4 (-5.2 to -1.6) favouring drug interventions
Trials with trials with a high dose/active lifestyle intervention	
Number of trials	6
Point estimate (95% CI) (kg)	-4.3 (-6.5 to -2.2) favouring drug interventions

Table 3. Sensitivity analyses: weight (*Continued*)

Trials without trials with high attrition	
Number of trials	9
Point estimate (95% CI) (kg)	-4.4 (-6.6 to -2.2) favouring drug interventions

CI: confidence interval.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies)
Part I: Obesity 1. MESH DESCRIPTOR Obesity 2. MESH DESCRIPTOR Obesity, Morbid 3. MESH DESCRIPTOR Obesity, Abdominal 4. MESH DESCRIPTOR Pediatric Obesity 5. MESH DESCRIPTOR Overweight 6. MESH DESCRIPTOR Weight Loss 7. (adipos* or obes*):TI,AB,KY 8. (overweight* or over weight*):TI,AB,KY 9. (weight adj2 (reduc* or los* or control* or gain*)):TI,AB,KY 10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 *Part II: Anti-obesity drugs* 11. MESH DESCRIPTOR Anti-Obesity Agents 12. MESH DESCRIPTOR Appetite Depressants 13. ((anti obes* or antiobes* or weight loss) adj3 (agent* or drug* or medicine* or pharmac*)):TI,AB,KY 14. (appetite adj3 (suppress* or depress*)):TI,AB,KY 15. ((anorexi* or anorectic*) adj3 (agent* or drug*)):TI,AB,KY 16. anorectics:TI,AB,KY 17. metformin*:TI,AB,KY 18. exenatide*:TI,AB,KY 19. liraglutid*:TI,AB,KY 20. dulaglutid*:TI,AB,KY 21. albiglutid*:TI,AB,KY 22. taspoglutid*:TI,AB,KY 23. lixisenatid*:TI,AB,KY 24. semaglutid*:TI,AB,KY 25. orlistat*:TI,AB,KY

(*Continued*)

26. cetilistat*:TI,AB,KY
27. sibutramin*:TI,AB,KY
28. fluoxetin*:TI,AB,KY
29. rimonabant*:TI,AB,KY
30. lorcaserin*:TI,AB,KY
31. benzphetamin*:TI,AB,KY
32. diethylpropion*:TI,AB,KY
33. phendimetrazin*:TI,AB,KY
34. mazindol*:TI,AB,KY
35. (phentermin* or chlorphentermin* or mephentermin*):TI,AB,KY
36. (phentermin* adj3 topiramat*):TI,AB,KY
37. (bupropion* adj3 naltrexon*):TI,AB,KY
38. (bupropion* adj3 zonisamid*):TI,AB,KY
39. beloranib*:TI,AB,KY
40. velneperit*:TI,AB,KY
41. tesofensin*:TI,AB,KY
42. #11 or #12 or #13 or #14 or #15 or#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41

Part III: Part I + Part II

43. #10 and #42
44. MESH DESCRIPTOR Obesity WITH QUALIFIERS DT
45. MESH DESCRIPTOR Obesity, Morbid WITH QUALIFIERS DT
46. MESH DESCRIPTOR Weight Loss WITH QUALIFIERS DT
47. MESH DESCRIPTOR Overweight WITH QUALIFIERS DT
48. #43 or #44 or #45 or #46 or #47

Part IV: Population

49. MESH DESCRIPTOR Adolescent
50. MESH DESCRIPTOR Child
51. MESH DESCRIPTOR Pediatrics
52. minors:TI,AB,KY
53. (boy or boys or boyhood):TI,AB,KY
54. girl*:TI,AB,KY
55. (kid or kids):TI,AB,KY
56. (child* or schoolchild*):TI,AB,KY
57. adolescen*:TI,AB,KY
58. juvenil*:TI,AB,KY
59. youth*:TI,AB,KY
60. (teen* or preteen*):TI,AB,KY
61. (underage* or under age*):TI,AB,KY
62. pubescen*:TI,AB,KY
63. p?ediatric*:TI,AB,KY
64. #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63

Part V: Part III AND IV

65. #48 and #64
66. MESH DESCRIPTOR Pediatric Obesity WITH QUALIFIERS DT
67. #65 or #66

MEDLINE (OvidSP)

(*Continued*)

Part I: Obesity
1 Obesity/
2 Obesity, Morbid/
3 Obesity, Abdominal/
4 Pediatric Obesity/
5 Overweight/
6 Weight Loss/
7 (adipos* or obes*).tw.
8 (overweight* or over weight*).tw.
9 (weight adj2 (reduc* or los* or control* or gain*)).tw.
10 or/1-9
Part II: Anti-obesity drugs
11 Anti-Obesity Agents/
12 Appetite Depressants/
13 ((anti obes* or antiobes* or weight loss) adj3 (agent* or drug* or medicine* or pharmac*)).tw
14 (appetite adj3 (suppress* or depress*)).mp.
15 ((anorexi* or anorectic*) adj (agent* or drug*)).tw.
16 anorectics.tw.
17 metformin*.mp.
18 exenatide*.mp.
19 liraglutid*.mp.
20 dulaglutid*.mp.
21 albiglutid*.mp.
22 taspoglutid*.mp.
23 lixisenatid*.mp.
24 semaglutid*.mp.
25 orlistat*.mp.
26 cetilistat*.mp.
27 sibutramin*.mp.
28 fluoxetin*.mp.
29 rimonabant*.mp.
30 lorcaserin*.mp.
31 benzphetamin*.mp.
32 diethylpropion*.mp.
33 phendimetrazin*.mp.
34 mazindol*.mp.
35 (phentermin* or chlorphentermin* or mephentermin*).mp.
36 ((phentermin* adj3 topiramat*) or phentermine?topiramat*).mp
37 ((bupropion* adj3 naltrexon*) or bupropion?naltrexon*).mp
38 ((bupropion* adj3 zonisamid*) or bupropion?zonisamid*).mp
39 beloranib*.mp.
40 velneperit*.mp.
41 tesofensin*.mp.
42 or/11-41
Part III: Part I + Part II and additional MeSH/subheading combination
43 10 and 42
44 Obesity/dt [drug therapy]
45 Obesity, Morbid/dt [drug therapy]

(*Continued*)

46 Weight Loss/dt [drug therapy]
47 Overweight/dt [drug therapy]
48 or/43-47
Part IV: Population [based on Leclercq 2013*]*
49 Adolescent/
50 Child/
51 Pediatrics/
52 minors.tw.
53 (boy or boys or boyhood).tw.
54 girl*.tw.
55 (kid or kids).tw.
56 (child* or schoolchild*).tw.
57 adolescen*.tw.
58 juvenil*.tw.
59 youth*.tw.
60 (teen* or preteen*).tw.
61 (underage* or under age*).tw.
62 pubescen*.tw.
63 p?ediatric*.tw.
64 or/49-63
Part V: Part III AND IV and additional MeSH/subheading combination
65 48 and 64
66 Pediatric Obesity/dt
67 65 or 66
Part VI: Study filter [Cochrane Handbook 2008 RCT filter - sensitivity max. version]
68 randomized controlled trial.pt.
69 controlled clinical trial.pt.
70 randomi?ed.ab.
71 placebo.ab.
72 drug therapy.fs.
73 randomly.ab.
74 trial.ab.
75 groups.ab.
76 or/68-75
77 exp animals/ not humans/
78 76 not 77
Part VII: Part V + Part VI
79 67 and 78

Embase (OvidSP)

Part I: Obesity
1 obesity/
2 morbid obesity/
3 abdominal obesity/
4 childhood obesity/
5 weight reduction/
6 (adipos* or obes*).tw.
7 (overweight* or over weight*).tw.
8 (weight adj2 (reduc* or los* or control* or gain*)).tw.

(*Continued*)

9 or/1-8
Part II: Anti-obesity drugs
10 antiobesity agent/
11 anorexigenic agent/
12 ((anti obes* or antiobes* or weight loss) adj3 (agent* or drug* or medicine* or pharmac*)).tw
13 (appetite adj3 (suppress* or depress*)).tw.
14 ((anorexi* or anorectic*) adj (agent* or drug*)).tw.
15 anorectics.tw.
16 metformin*.mp.
17 exenatide*.mp.
18 liraglutid*.mp.
19 dulaglutid*.mp.
20 albiglutid*.mp.
21 taspoglutid*.mp.
22 lixisenatid*.mp.
23 semaglutid*.mp.
24 orlistat*.mp.
25 cetilistat*.mp.
26 sibutramin*.mp.
27 fluoxetin*.mp.
28 rimonabant*.mp.
29 lorcaserin*.mp.
30 benzphetamin*.mp.
31 diethylpropion*.mp.
32 phendimetrazin*.mp.
33 mazindol*.mp.
34 (phentermin* or chlorphentermin* or mephentermin*).mp.
35 ((phentermin* adj3 topiramat*) or phentermine?topiramat*).mp
36 ((bupropion* adj3 naltrexon*) or bupropion?naltrexon*).mp
37 ((bupropion* adj3 zonisamid*) or bupropion?zonisamid*).mp
38 beloranib*.mp.
39 velneperit*.mp.
40 tesofensin*.mp.
41 or/10-40
Part III: Part I + Part II and additional MeSH/subheading combination
42 9 and 41
43 obesity/dt [drug therapy]
44 morbid obesity/dt [drug therapy]
45 weight reduction/dt [drug therapy]
46 or/42-45
Part IV: Population [adapted from Leclercq 2013*]*
47 juvenile/
48 adolescent/
49 child/
50 preschool child/
51 schoolchild/
52 pediatrics/
53 minors.tw.
54 (boy or boys or boyhood).tw.

(*Continued*)

55 girl*.tw.
56 (kid or kids).tw.
57 (child* or schoolchild*).tw.
58 adolescen*.tw.
59 juvenil*.tw.
60 youth*.tw.
61 (teen* or preteen*).tw.
62 (underage* or under age*).tw.
63 pubescen*.tw.
64 p?ediatric*.tw.
65 or/47-64
Part V: Part III AND IV and additional MeSH/subheading combination
66 46 and 65
67 childhood obesity/dt
68 66 or 67
Part VI: Study filter [Wong 2006a*filter - BS version]*
69 random*.tw. or clinical trial*.mp. or exp health care quality/
Part VII: Part V + Part VI
70 68 and 69
71 limit 70 to embase

LILACS (IAHx)

((MH:"Obesity" OR MH:"Obesity, Morbid" OR MH:"Obesity, Abdominal" OR MH:"Pediatric Obesity" OR MH:"Overweight" OR MH:"Weight Loss" OR adipos$ OR obes$ OR overweight$ OR "over weight" OR sobrepes$ OR "exceso de peso" OR "excesso de peso" OR "weight reduction" OR "weight loss" OR "weight control") AND (MH:"Obesity/drug therapy" OR MH:"Obesity, Morbid/drug therapy" OR MH:"Overweight/drug therapy" OR MH:"Weight Loss/drug therapy" OR MH:"Anti-Obesity Agents" OR MH:"Appetite Depressants" OR "farmacos antiobesidad" OR "farmacos antiobesidade" OR "depresores del apetito" OR "depressores do apetite" OR metformin$ OR exenatide$ OR liraglutid$ OR dulaglutid$ OR albiglutid$ OR taspoglutid$ OR lixisenatid$ OR semaglutid$ OR orlistat$ OR cetilistat$ OR sibutramin$ OR fluoxetin$ OR rimonabant$ OR lorcaserin$ OR benzphetamin$ OR diethylpropion$ OR phendimetrazin$ OR mazindol$ OR phentermin$ or chlorphentermin$ or mephentermin$ OR (phentermin$ AND topiramat$) OR (bupropion$ AND (naltrexon$ OR zonisamid$)) OR beloranib$ OR velneperit$ OR tesofensin$) AND (MH:"Adolescent" OR MH:"Child" OR MH:"Pediatrics" OR minors OR boy OR boys OR girl$ OR kid OR kids OR child$ OR schoolchild$ OR escolar$ OR adolescen$ OR preadolescen$ OR juvenil$ OR juventud$ OR youth$ OR teen$ OR preteen$ OR underage$ OR pubescen$ OR paediatri$ OR pediatri$ OR joven$ OR jovem$ OR niños OR niñas OR crianca$ OR menin$ OR "menor de edad" OR "menores de edad" OR "menor de idade" OR "menores de idade") OR MH:"Pediatric Obesity/drug therapy") + Controlled Clinical Trial

PubMed (only subsets not available on Ovid)

#1 Part I: Obesity
adipos*[tw] OR obes*[tw] OR overweight*[tw] OR over weight*[tw] OR weight reduc*[tw] OR weight los*[tw] OR weight control*[tw] OR weight gain*[tw]
#2 Part II: Antiobesity drugs
anti obesity agent*[tw] OR antiobesity agent*[tw] OR anti obesity drug*[tw] OR antiobesity drug*[tw] OR weight loss agent[tw] OR weight loss drug[tw] OR appetite suppress*[tw] OR appetite depress*[tw] OR anorexigenic agent*[tw] OR anorexigenic drug*[tw] OR anorectics[tw] OR metformin*[tw] OR exenatide*[tw] OR liraglutid*[tw] OR dulaglutid*[tw] OR albiglutid*[tw] OR taspoglutid*[tw] OR lixisenatid*[tw] OR semaglutid*[tw] OR orlistat*[tw] OR cetilistat*[tw] OR sibutramin*[tw] OR fluoxetin*[tw] OR rimonabant*[tw] OR lorcaserin*[tw] OR benzphetamin*[tw] OR diethylpropion*[tw] OR phendimetrazin*[tw] OR mazindol*[tw] OR phentermin*[tw] OR chlorphentermin*[tw] OR mephentermin*[tw] OR topiramat*[tw] OR bupropion*[tw] OR naltrexon*[tw]

(*Continued*)

OR zonisamid*[tw] OR beloranib*[tw] OR velneperit*[tw] OR tesofensin*[tw]
#3 Part III: Part I + Part II
#1 AND #2
#4 Part IV: Population
minors[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl*[tw] OR kid[tw] OR kids[tw] OR child*[tw] OR schoolchild*[tw] OR adolescen*[tw] OR juvenil*[tw] OR youth*[tw] OR teen*[tw] OR preteen*[tw] OR underage*[tw] OR under age*[tw] OR pubescen*[tw] OR paediatric*[tw] OR pediatric*[tw]
#5 Part V: Part III AND IV
#3 AND #4
#6 Part VI: Limiting to subsets not available on Ovid
#5 not medline[sb] not pmcbook

ICTRP Search Portal (Standard search)

obes* AND child* OR
obes* AND schoolchild* OR
obes* AND adolesc* OR
obes* AND young* OR
obes* AND pediatric* OR
obes* AND teen* OR
obes* AND preteen* OR
obes* AND juvenil* OR
obes* AND minors OR
obes* AND boy* OR
obes* AND girl* OR
obes* AND kids OR
obes* AND youth* OR
obes* AND underage* OR
obes* AND pube* OR
overweight* AND child* OR
overweight* AND schoolchild* OR
overweight* AND adolesc* OR
overweight* AND young* OR
overweight* AND pediatric* OR
overweight* AND teen* OR
overweight* AND preteen* OR
overweight* AND juvenil* OR
overweight* AND minors OR
overweight* AND boy* OR
overweight* AND girl* OR
overweight* AND kids OR
overweight* AND youth* OR
overweight* AND underage* OR
overweight* AND pube*

ClinicalTrials.gov (Expert search)

(*Continued*)

(obese OR overweight OR obesity) [DISEASE] AND (drug or drugs OR agent OR agents OR appetite OR metformin OR exenatide OR liraglutide OR dulaglutide OR albiglutide OR taspoglutide OR lixisenatide OR semaglutide OR orlistat OR cetilistat OR sibutramine OR fluoxetine OR rimonabant OR lorcaserin OR benzphetamine OR diethylpropion OR phendimetrazine OR mazindol OR phentermine OR chlorphentermine OR mephentermine OR topiramate OR bupropion OR naltrexone OR zonisamide OR beloranib OR velneperit OR tesofensine) [TREATMENT] AND INFLECT EXACT "Child" [AGE-GROUP]

Appendix 2. Description of interventions

Trial	Intervention(s): drug component (route, frequency, total dose/day), behaviour changing component	Comparator(s): drug component (route, frequency, total dose/day), behaviour changing component
Atabek 2008	**Metformin:** oral, twice daily, 500 mg x 2 (1 g)/d, 6 months **Diet and physical activity advice:** individual consultation sessions with a nutritionist, completed food diary at beginning and end of trial, advised to perform 30 min of aerobic physical activity per day, 6 months	**Placebo:** oral, twice daily, 2 tablets/d, 6 months **Diet and physical activity advice:** same as the intervention group
Berkowitz 2003	**Sibutramine:** oral, 1 dose per day, placebo (week 1) 5 mg/d sibutramine (week 2) 10 mg/d (weeks 3 to 6) 15 mg/d (week 7 to month 6), length = 6 months (plus an open-label phase for additional 6 months) **Behavioural programme:** in phase 1 (drug-placebo phase) participants attended 13 weekly group sessions while in phase 2 (drug, open label) group sessions were held biweekly then monthly. Parents met separately from participants. Instructed to consume 1200 kcal/d to 1500 kcal/d and to engage in 120 min of walking or similar activity per week. Eating and activity logs kept daily. Length = 12 months	**Placebo:** oral, 1 dose per day, (months 1 to 6), 6 months **Behavioural programme:** same as intervention group
Berkowitz 2006	**Sibutramine:** oral, 1 dose per day, 10 mg/d (baseline to month 6), 15 mg/d from month 6 in participants who had not lost more than 10% of their initial BMI, 12 months **Behavioural therapy programme:** each individual centre implemented flexible lifestyle modification approaches that were specific to participants' needs. This included self-monitoring of eating habits and physical activity, stress management, stimulus control, problem solving, contingency management, cognitive restructuring and social support. Participants were given counselling at each visit and nutri-	**Placebo:** oral, 1 dose per day, placebo (baseline to month 6), uptitrated after 6 months in participants who had not lost more than 10% of their initial BMI, 12 months **Behavioural therapy programme:** same as intervention group

(*Continued*)

	tional counselling. Length = 12 months	
Chanoine 2005	**Orlistat:** oral, dose 3 times per day, 120 mg x 3 (360 mg)/d, 1 year **Behavioural therapy:** participants were prescribed a nutritionally balanced, hypocaloric diet and at each trial visit the dietitian spoke about compliance. Behavioural modification involved techniques to limit calorie and fat intake, eating more slowly, avoiding snacks and avoiding overeating. Guidelines were given to encourage regular physical activity and reduce sedentary behaviour; compliance was monitored by a behavioural psychologist at each visit. Length = 54 weeks	**Placebo:** oral, dose 3 times per day, 1 year **Behavioural therapy:** same as intervention group
Clarson 2009	**Metformin:** oral, 3 times daily, 500 mg x 3 (1.5 g), 6 months **Behaviour changing intervention:** monthly individual visits and 2 group sessions. Fitness specialist supervised participants in an individual 30-min exercise sessions every 2 months. Diet advice and physical activity advice given. Progress monitored by weekly telephone calls and monthly visits. Length = 6 months	**No placebo** (N/A) **Behaviour changing intervention:** same as intervention group
Franco 2014	**Sibutramine:** oral, once daily, 10 mg, 6 months **Dietary guidance:** the dietary guideline proposal was of a low-calorie diet with restriction of 25% of the total recommended calories for a teenager	**Placebo:** oral, once daily, 10 mg, 6 months **Dietary guidance:** same as intervention group
Freemark 2001	**Metformin:** oral, 2 doses per day, 500 mg x 2 (1g)/d, 6 months No behaviour changing intervention	**Placebo:** oral, 2 doses per day, 6 months No behaviour changing intervention
Garcia-Morales 2006	**Sibutramine:** oral, 1 dose per day, 10 mg/d, 6 months **Diet + exercise:** diet and exercise advice was tailored to each participant. Advice was given on recommended food portions and possible combinations, and all participants were advised to perform at least 30 min of aerobic physical activity per day. Each participant also attended individual consultation sessions with a registered paediatric nutritionist. A detailed food consumption questionnaire was completed at the beginning and end of trial medication period. Length = 6 months	**Placebo:** oral, 1 dose per day, 6 months **Diet + exercise:** same as intervention group

(*Continued*)

Godoy-Matos 2005	**Sibutramine:** oral, 1 dose per day, 10 mg/d, 6 months **Hypocaloric diet + exercise:** participants were given dietary counselling to achieve an energy deficit of 500 kcal/d at the start of the run-in phase (no further visits after). Physical activity instructions were delivered by the attendant doctors in a brief written protocol aimed to obtain mainly aerobic moderate exercises for at least 30 min/d. A lifestyle intervention was not given during 6-month trial	**Placebo:** oral, 1 dose per day, 6 months **Hypocaloric diet + exercise:** same as intervention group
Kendall 2013	**Metformin:** oral, twice daily, 500 mg x 2 + 500 mg (1.5 g), 6 months **Healthy lifestyle advice:** participants provided with a standardised healthy lifestyle advice at the start in a 1-to-1 sessions, including a healthy diet advice sheet and increased levels of exercise (available upon request). A lifestyle intervention was not given during the 6-month trial	**Placebo:** oral, twice daily, 2 + 1 (3) tablets/d, 6 months **Healthy lifestyle advice :** same as intervention group
Maahs 2006	**Orlistat:** oral, 3 doses per day, 120 mg x 3 (360 mg) /d, 6 months **Diet + exercise therapy:** the goal caloric intake was calculated using the Harris-Benedict equation with ambulating activity factor (500 calories was subtracted from the final number to obtain daily calorie level). Participants were instructed to increase activity using a paediatric activity pyramid and encouraged to exercise for at least 30 min, 3 times per week. Monthly follow-up visits with a dietitian reinforced this advice. Log sheets and diet records were also completed. Length = 6 months	**Placebo:** oral, 3 doses per day, 6 months **Diet + exercise therapy:** same as intervention group
Mauras 2012	**Metformin:** oral, twice daily, 500 mg or 1000 mg (dependent on age), 6 months **Diet + exercise intervention:** dietary counselling provided with recommended decrease of 250 calories/d to 500 calories/d. Intense follow-up provided by dietitian. Participants given free membership to YMCA or gym. Encouraged to exercise at least 3 times per week for 30 min per sessions. Activity diary kept and pedometer worn. Length = 6 months	No placebo **Diet + exercise intervention:** same as intervention group
NCT00001723	**Orlistat:** 120 mg 3 times daily for 6 months **Behavioural weight loss programme:** 12-week intensive programme	**Placebo:** 120 mg 3 times daily for 6 months **Behavioural weight loss programme:** same as intervention group

(*Continued*)

Ozkan 2004	**Orlistat:** oral, 3 doses per day, 120 mg x 3 (360 mg) /d, mean 11.7 months - length of treatment was not consistent across participants **Conventional treatment:** the lifestyle modification programme included reducing daily calories. Was administered by a team comprising of a paediatric endocrinologist, paediatrician and a dietitian. Participants seen by dietitian monthly and in the outpatient clinic every 2 months. Length = between 6 and 17 months	No placebo **Conventional treatment:** same as intervention group; length between 6 and 17 months
Prado 2012	**Metformin:** oral, once daily, 500 mg, 3 months **Nutritional guide and exercise programme:** according to pattern 1500 kcal/d. Exercise classes once per week and exercise guide to be practiced twice per week. Length = 3 months	**Placebo:** oral, once daily, 3 months **Nutritional guide and exercise programme:** same as intervention group
Rezvanian 2010	**Metformin:** oral, once daily, 1500 mg/d, 12 weeks **Healthy eating and physical activity advice:** physical activity advice included reducing sedentary time and taking part in 30 min of enjoyable, moderate-intensity physical activity per day. A registered dietitian conducted a nutrition education session with recommendations on diet such as increasing consumption of fruit and vegetables and not using hydrogenated fat	**Placebo:** oral, once daily, 12 weeks **Healthy eating and physical activity advice:** same as intervention group
	Fluoxetine: oral, once daily, 20 mg/d, 12 weeks **Healthy eating and physical activity advice:** same as the other intervention groups	
	Metformin + fluoxetine: oral, once daily, dosage not given, 12 weeks **Healthy eating and physical activity advice:** same as the other intervention groups	
Srinivasan 2006	**Metformin:** oral, 2 doses per day, dose gradually built up to 1g x 2 (2 g)/d, 6 months **"Standardised information on healthy eating and exercise":** no further information given	**Placebo:** oral, 2 doses per day, dose gradually built up to 1 g x 2 (2 g)/d, 6 months **"Standardised information on healthy eating and exercise":** same as intervention group
Van Mil 2007	**Sibutramine:** oral, once daily, 5 mg/d, 12 weeks **Energy-restricted diet and exercise plan:** the energy prescription calculated from measured basal metabolic rate multiplied by an estimated physical activity level minus 500 kcal. Physical activity prescribed based on individual preferences and information obtained by physical activity questionnaire. It contained a daily bout of exercise of at least 30 min.	**Placebo:** oral, once daily, 5 mg/d, 12 weeks **Energy-restricted diet and exercise plan:** same as intervention group

(*Continued*)

	Length = 12 weeks	
Wiegand 2010	**Metformin:** oral, twice daily, 2 x 500 mg (1 g)/d, 6 months **Multiprofessional behaviour changing intervention:** an interview was performed before randomisation to determine 1 to 3 individually chosen tasks (goals). Multiprofessional reinforcement sessions took place every 4 to 8 weeks. Regarding physical activity, participants and their families attended specialised sport classes (2 sport classes per week, 45 min each, was recommended) in addition to regular sport classes at school. Length = 6 months	**Placebo:** oral, twice daily, 6 months **Multiprofessional behaviour changing intervention:** same as intervention group
Wilson 2010	**Metformin:** oral, 4 times daily, 4 x 500 mg (2 g)/d, 48 weeks **Behaviour changing intervention:** used the Weigh of Life LITE programme developed at Texas Children's Hospital, Houston. There were 10 individualised "intensive" sessions at weekly intervals and monthly follow-up sessions for the reminder of the trial. Sessions led by trained health specialist and parent/guardians were invited. Length = 48 weeks	**Placebo:** oral, 4 times daily, 48 weeks **Behaviour changing intervention:** same as intervention group
Yanovski 2011	**Metformin:** oral, twice daily, 2 x 1000 mg (2000 mg) /d, 6 months **Dietitian-administered weight-reduction programme:** each participant and parent/guardian met with a dietitian monthly, who promoted a reduced-energy diet, increased physical activity and decreased inactivity. Participants trained to completed a 7-day food diary which was used to prescribe a "traffic light" style 500 kcal/d deficit diet, and exercise was encouraged for 30 min/d, monitored by pedometers readings. Length = 6 months	**Placebo:** oral, twice daily, 6 months **Dietitian-administered weight-reduction programme:** same as intervention group

"-" denotes not reported.
BMI: body mass index; /d: per day; kcal: kilocalories; min: minute; N/A: not applicable; YMCA: Young Men's Christian Association

Appendix 3. Baseline characteristics (I)

Trial	Intervention(s) and comparator (s)	Duration of intervention (duration of follow-up)	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of obesity (mean years (SD))
Atabek 2008	I: metformin + diet and physical activity advice	6 months (6 months)	Obese adolescents with hyperinsulinaemia	-	Turkey	Hospital in/outpatient clinic/ other based in University School of Medicine	-	-
	C: placebo + diet and physical activity advice							
Berkowitz 2003	I: behavioural programme + sibutramine	6 months (6 months)	Obese adolescent boys and postmenarchal girls	March 1999 to August 2002	USA	University of Pennsylvania School of Medicine	White 49, black 49, other 2	-
	C: behavioural programme + placebo						White 62, black 33, other 5	
Berkowitz 2006	I: behavioural therapy programme + sibutramine	12 months (12 months)	Obese adolescents	July 2000 to February 2002	USA	33 weight loss clinics and outpatient clinic based in a University School of Medicine	White 56, African-American 22, Hispanic or Mexican American 16, other 6	-
	C: behavioural therapy programme + placebo						White 59, African-American 19, Hispanic or Mexican-American 14, other 9	

(*Continued*)

Chanoine 2005	I: orlistat + diet + exercise + behavioural therapy	54 weeks (54 weeks)	Obese adolescents	August 2000 to October 2002	USA and Canada	32 clinical centres	White 75, black 19, other 6	-
	C: placebo + diet + exercise + behavioural therapy						White 78, black 14, other 8	
Clarson 2009	I: metformin + lifestyle intervention	6 months (6 months)	Obese adolescents with insulin resistance	Enrolled 2005 to 2007	Canada	Participants assessed in community clinic and there were monthly visits to clinic during intervention. Intervention carried out in community - at adolescent's home - unclear where group sessions took place	-	-
	C: lifestyle intervention only							
Franco 2014	I: sibutramine + dietary guidance	6 months (6 months)	Obese adolescents	-	Brazil	Paediatric endocrinology outpatient clinic in childhood obesity group of the Instituto da Crianca do Hospital das Clinicas de Faculdade de Medicina de Universidade de Sao Paulo	-	-

(*Continued*)

	C: placebo + dietary guidance							
Freemark 2001	I: metformin	6 months (6 months)	Obese adolescents with fasting hyperinsulinaemia and a family history of type 2 diabetes	-	USA	Inpatient and outpatient clinic of a university	White 64, black 36	-
	C: placebo						White 47, black 53	
Garcia-Morales 2006	I: sibutramine + diet + exercise	6 months (6 months)	Obese Mexican adolescents	August 2001 to August 2003	Mexico	Outpatients attending the endocrinology department of the Federico Gomez Children's Hospital of Mexico	-	-
	C: placebo + diet + exercise							
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	7 months (7 months)	Obese adolescents	January 2002 to April 2003	Brazil	Regular clinical setting	-	-
	C: placebo + hypocaloric diet + exercise							
Kendall 2013	I: metformin + healthy lifestyle advice	6 months (6 months)	Obese children and adolescents with hyperinsulinaemia or impaired fasting glucose or impaired glucose tolerance (or both)	-	UK	UK paediatric endocrine centres	White 80, Asian 19, Afro-Caribbean 11	-

(*Continued*)

	C: placebo + healthy lifestyle advice						White 72, Asian 26, Afro-Caribbean 1	
Maahs 2006	I: orlistat + diet and exercise therapy	26 weeks (26 weeks)	Obese adolescents	December 2002 to September 2003	USA	General clinical research centre at University of New Mexico Hospital	Hispanic 60	-
	C: placebo + diet and exercise therapy						Hispanic 65	
Mauras 2012	I: metformin + diet/exercise intervention	6 months (6 months)	Obese children with normal glucose tolerance but elevated hsCRP or fibrinogen concentrations (or both)	-	USA	-	White 51, African-American 37, other 11	Uncomplicated (exogenous) obesity for < 5 years
	C: diet/exercise intervention						White 39, African-American 42, other 19	
NCT000017	I: orlistat + behavioural weight loss programme	6 months (6 months)	Obese children and adolescents with obesity-related diseases	RCT began in 1999 and ended in 2008	USA	National Institutes of Health Clinical Center	Non-Hispanic black 63, non-Hispanic white 37	-
	C: placebo + behavioural weight loss programme						Non-Hispanic black 60, non-Hispanic whites 40	
Ozkan 2004	I: conventional treatment + orlistat	Intervention group was followed for 5 to 15 months (mean duration of treatment	Adolescents with severe exogenous obesity	-	Turkey	Outpatient clinic	-	-

(*Continued*)

		11.7, SD 3.7 months)						
	C: conventional treatment	Control group was followed for 6 to 17 months (mean 10.2, SD 3.7 months)						
Prado 2012	I: metformin + nutritional guide and exercise programme	3 months (6 months)	Obese female adolescents at risk of developing type 2 diabetes	June 2009 to July 2010	Chile	Conducted at Center of Adolescent Health Serjoven	-	-
	C: placebo + nutritional guide and exercise programme							
Rezvanian 2010	I1: metformin + healthy eating and physical activity advice	12 weeks (24 weeks)	Obese children and adolescents	-	Iran	Pediatric Obesity and Metabolic Syndrome Research Clinic of the Pediatric Preventive Cardiology Department, Isfahan Cardiovascular Research Center	-	-
	I2: fluoxetine + healthy eating and physical activity advice							
	I3: metformin and fluoxetine + healthy eating and physical activity advice							

(*Continued*)

	C: placebo + healthy eating and physical activity advice							
Srinivasan 2006	I: metformin first then placebo + standardised information on healthy eating and exercise	6 months (12 months)	Obese children and adolescents (aged 9 to 18) with suspected insulin resistance	-	Australia	Outpatient clinic of a tertiary paediatric hospital (university teaching hospital)	64% were from ethnic backgrounds with high prevalence of insulin resistance and the metabolic syndrome (e.g. Indian subcontinent, Pacific Islands), 25% were from a northern European background, and 11% were from a mixed background	-
	C: placebo first then metformin + standardised information on healthy eating and exercise							
Van Mil 2007	I: sibutramine + energy-restricted diet and exercise plan	12 weeks (24 weeks)	Obese adolescents	-	The Netherlands	Outpatient clinic	-	-
	C: placebo + energy-restricted diet and exercise plan							
Wiegand 2010	I: metformin + multiprofessional lifestyle intervention	6 months (6 months)	Obese insulin-resistant adolescents	May 2006 to December 2006	Germany and Switzerland	Paediatric obesity centre	White 87, other 13	-

(*Continued*)

	C: placebo + multiprofessional lifestyle intervention						White 92, other 9	
Wilson 2010	I: metformin + lifestyle intervention programme	52 weeks (100 weeks)	Obese adolescents	October 2003 to August 2007	USA	6 Glaser paediatric research centres	White 56, African-American 21, Asian 8, other 15, Hispanic ethnicity 18	-
	C: placebo + lifestyle intervention programme						White 71, African-American 16, Asian 0, other 13, Hispanic ethnicity 29	
Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	6 months (12 months)	Obese insulin-resistant children	September 2000 to August 2008	USA	Trial took place at the NIH clinical research centre	Non-Hispanic white 42, Non-Hispanic black 42, Hispanic white 11, other 5	- -
	C: placebo + dietitian-administered weight-reduction programme						Non-Hispanic white 49, Non-Hispanic black 38, Hispanic white 11, other 2	

"-" denotes not reported.
C: comparator; hsCRP: high sensitivity C-reactive protein; I: intervention; RCT: randomised controlled trial; SD: standard deviation

Appendix 4. Baseline characteristics (II)

Trial	Intervention(s) and comparator(s)	Sex (female %)	Age (mean years (SD))	HbA1c (mean % (SD))	BMI (mean kg/m² (SD))	Bodyweight (mean kg (SD))	Comedications/cointerventions	Comorbidities
Atabek 2008	I: metformin + diet and physical activity advice	50	11.8 (2.8)	-	28.5 (3.4)	67.16 (16.8)	Diet and physical activity advice. Individual consultation sessions with a registered paediatric nutritionist	All participants had hyperinsulinaemia
	C: placebo + diet and physical activity advice	50	11.6 (2.7)	-	28.0 (3.4)	66.27 (16.9)		
Berkowitz 2003	I: behavioural programme + sibutramine	72	14.1 (1.3)	-	37.5 (4.0)	102 (14.7)	Behavioural therapy	-
	C: behavioural programme + placebo	62	14.1 (1.2)	-	38.0 (3.6)	105.3 (16.2)		
Berkowitz 2006	I: behavioural therapy programme + sibutramine	66	13.6 (1.3)	-	35.9 (4.1)	97.9 (14.7)	Behavioural therapy	50.5% had dyslipidaemia, 1.4% had hypertension
	C: behavioural therapy programme + placebo	62	13.7 (1.3)	-	36.1 (3.8)	97.8 (14.6)		57.4% had dyslipidaemia, 2.3% had hypertension
Chanoine 2005	I: orlistat + diet + exercise + behavioural therapy	65	13.6 (1.3)	-	35.7 (4.2)	97.7 (15.0)	Behavioural modification + diet + exercise counselling	In the orlistat group, 14 participants had a baseline abnormality revealed by gallbladder

(*Continued*)

								ultrasound, including 8 participants with fatty liver infiltration or hepatomegaly and 3 participants with gallstones; 25.3% of participants had the metabolic syndrome at baseline
	C: placebo + diet + exercise + behavioural therapy	71	13.5 (1.2)	-	35.4 (4.1)	95.1 (14.2)		-
Clarson 2009	I: metformin + lifestyle intervention	-	13.1	-	36.4 (1.8)	-	Lifestyle intervention	All participants insulin resistant. 15 participants had acanthosis nigricans
	C: lifestyle intervention only	-	13.1	-	33.9 (1.1)	-		
Franco 2014	I: sibutramine + dietary guidance	56	13.3 (1.8)	-	33.9 (7.2)	85.5 (23.2)	Dietary guidance	-
	C: placebo + dietary guidance		12.3 (1.7)	-	32.8 (5.8)	83.1 (19.6)		
Freemark 2001	I: metformin	79	14.4 (0.6)	5.6 (0.1)	41.5 (0.9)	-	-	All participants had fasting hyperinsulinaemia. 8 participants had acan-

(*Continued*)

								thosis nigricans
	C: placebo	46	15.4 (0.5)	5.5 (0.1)	38.7 (1.3)	-		
Garcia-Morales 2006	I: sibutramine + diet + exercise	61	15.2 (1.3)	-	35.1 (5.3)	92.6 (14.6)	Diet and exercise advice	8.7% high blood pressure, 8.7% glucose, 43.5% high triglycerides, 8.7% high cholesterol, 4.3% high LDL, 13% high HDL
	C: placebo + diet + exercise	52	14.7 (1.1)	-	36.6 (5.2)	98.9 (22.7)		30.4% high blood pressure, 8.7% glucose, 52.2% high triglycerides, 34.8% high cholesterol, 17.4% high LDL
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	83	Females: 15.9 (1.1) Males: 16.7 (0.6)	-	Females: 37.5 (3.8) Males: 37.6 (4.3)	Females: 100.5 (14.2) Males: 117.1 (11.7)	Exercise advice	-
	C: placebo + hypocaloric diet + exercise	80	Females: 16.3 (1.2) Males: 16.7 (0.6)	-	Females: 35.8 (4.2) Males: 37.4 (1.9)	Females: 94.0 (13.6) Males: 113.4 (10.0)		-
Kendall 2013	I: metformin + healthy lifestyle advice	66	13.7 (2.3)	-	37.1 (6.4)	100.3 (24.1)	Standardised healthy lifestyle advice	All participants had hyperinsulinaemia or impaired fasting glucose or im-

(*Continued*)

								paired glucose tolerance (or both)
	C: placebo + healthy lifestyle advice	69	13.6 (2.2)	-	36 (6.3)	96.4 (21.8)		
Maahs 2006	I: orlistat + diet and exercise therapy	60	15.8 (1.5)	5.4 (0.1)	39.2 (5.3)	111.1 (22.9)	Dietary and exercise counselling	-
	C: placebo + diet and exercise therapy	75	15.8 (1.4)	5.4 (0.1)	41.7 (11.7)	114.3 (38.4)		-
Mauras 2012	I: metformin + diet/exercise intervention	57	12.3 (0.5)	-	32 (1)	-	Dietary counselling and free membership to a sports club/gym	Elevated hsCRP or fibrinogen (or both) concentrations
	C: diet/exercise intervention	52	12.0 (0.4)	-	33.2 (0.7)	-		
NCT000017	I: orlistat + behavioural weight loss programme	65	14.65 (1.38)	-	41.7 (0.6)	-	Behavioural therapy and a multivitamin for 6 months	All participants had at least 1 of the following: systolic or diastolic hypertension (determined by age-specific charts); frank type 2 diabetes, impaired glucose tolerance assessed by oral glucose tolerance

(*Continued*)

								testing; hyperinsulinaemia (defined as a fasting insulin > 15 IU/mL); significant hyperlipidaemia (total cholesterol > 200 mg/dL, LDL cholesterol > 129 mg/dL or fasting triglycerides > 200 mg/dL); hepatic steatosis (ALT or AST above normal range with negative hepatitis studies) or sleep apnoea documented by a sleep trial
	C: placebo + behavioural weight loss programme	66	14.52 (1.46)	-		-		
Ozkan 2004	I: conventional treatment + orlistat	67	12.9 (2.4)	-	32.5	82.1 (20.9)	Daily oral multivitamin preparation, lifestyle modification programme	-
	C: conventional treatment		12.5 (2.2)	-	31.2	73.9 (15.3)	Lifestyle modification programme	-

(*Continued*)

Prado 2012	I: metformin + nutritional guide and exercise programme	100	15.6 (1.9)	-	33.6	-	Nutritional guide and exercise programme	30% of participants had psychiatric comorbidities
	C: placebo + nutritional guide and exercise programme	100		-	33.3	-		11.1% of participants had psychiatric comorbidities
Rezvanian 2010	I1: metformin + healthy eating and physical activity advice	-	13.1 (1.4)	-	26.4 (0.5)	-	Physical activity advice; nutritional education session and dietary advice	-
	I2: fluoxetine + healthy eating and physical activity advice	-	13.5 (1.2)	-	26.5 (0.7)	-		-
	I3: metformin and fluoxetine + healthy eating and physical activity advice	-	13.7 (1.1)	-	26.6 (0.8)	-		-
	C: placebo + healthy eating and physical activity advice	-	13.4 (1.4)	-	26.2 (0.6)	-		-
Srinivasan 2006	I: metformin first then placebo + standardised information on healthy eating and exer-	54	12.5 (2.2)	-	-	-	Information on healthy eating and exercise	Suspicion of insulin resistance; 89% participants had acanthosis nigricans

(*Continued*)

	cise							
	C: placebo first then metformin + standardised information on healthy eating and exercise			-	-	-		
Van Mil 2007	I: sibutramine + energy-restricted diet and exercise plan	45	14.1 (1.0)	-	30.1 (4.5)	80.8 (15.6)	Diet and exercise plan	-
	C: placebo + energy-restricted diet and exercise plan	58	13.8 (1.5)	-	33.3 (5.0)	89.2 (16.4)		-
Wiegand 2010	I: metformin + multiprofessional lifestyle intervention	72	15.1	-	34.3 (5)	-	Lifestyle intervention	All had risk factors for developing type 2 diabetes: acanthosis nigricans, signs of the metabolic syndrome, impaired fasting glucose, and positive family history of type 2 diabetes, or with impaired glucose tolerance

(*Continued*)

	C: placebo + multiprofessional lifestyle intervention	62	15	-	35.5 (5.8)	-		
Wilson 2010	I: metformin + lifestyle intervention programme	67	14.8 (1.3)	5.4 (0.3)	35.9 (5.7)	95.9 (16.6)	Lifestyle intervention given during run-in period and follow-up sessions provided monthly for the remainder of the trial; a multivitamin tablet and calcium carbonate 1000 mg was taken daily	-
	C: placebo + lifestyle intervention programme	66	15.0 (1.5)	5.3 (0.3)	35.9 (4.7)	101.8 (15.7)		-
Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	57	10.1 (1.6)	-	34.2 (6.8)	76.4 (23.1)	A monthly dietitian administered weight-reduction programme; a daily chewable multivitamin containing cyanocobalamin 6 mg was also prescribed	26.4% had paediatric metabolic syndrome. 64% showed a presence of acanthosis nigricans; all participants had fasting hyperinsulinaemia
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		31.9% had paediatric metabolic syndrome. 68% showed a presence of acanthosis

(*Continued*)

								nigricans; all participants had fasting hyperinsulinaemia

"-" denotes not reported.
ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; C: comparator; HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; HsCRP: high sensitivity C-reactive protein; I: intervention; LDL: low-density lipoprotein; SD: standard deviation

Appendix 5. Matrix of study endpoints (publications and trial documents)

Trial	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a]		Endpoints quoted in publication(s)[b]	Time of measurement
Atabek 2008	N/T		**Primary outcome measures:** -	6 months
			Secondary outcome measures : -	
			Other outcome measures: % change in BMI, DBP, SBP, pulse rate, lipids, triglycerides, serum insulin, serum glucose, HOMA, HDL, BMI z score, LDL, total cholesterol, weight change, adverse events	
Berkowitz 2003	**Source:** NCT00212173 (added 13 September 2005) **Primary outcome measure(s):** BMI, weight	No trial results posted. No link to Berkowitz 2003 publication but links to 2 additional publications. A second protocol for an adolescent lifestyle intervention also included	**Primary outcome measure:** % change in BMI	3, 6, 9, 12 months
	Secondary outcome measure(s): BP, lipids, glucose, insulin		**Secondary outcome measures:** BP, pulse, hunger	

(*Continued*)

	Other outcome measure(s): -		**Other outcome measures:** lipids, triglycerides, serum insulin, serum glucose, HOMA, HDL, BMI z score, LDL, total cholesterol, weight change, waist circumference, adverse events	
Berkowitz 2006	**Source:** NCT00261911 **Primary outcome measure(s):** absolute change in BMI from baseline to endpoint (12 months)	No trial results posted, publications specified	**Primary outcome measures:** absolute change from baseline in BMI	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months
	Secondary outcome measure(s): % change from baseline in BMI, proportions of participants achieving ≥ 5% and ≥ 10% BMI and bodyweight reduction, absolute and % change from baseline in waist circumference, body composition (DEXA), lipid and glycaemic variables (all: 12 months)		**Secondary outcome measures:** % change in BMI, proportion of participants achieving reductions in BMI of ≥ 5% or ≥ 10%, absolute and % changes in bodyweight and lipid and glycaemic variables, absolute change in waist circumference	
	Other outcome measure(s): -		**Other outcome measures:** DBP, SBP, pulse rate, QTc interval, maturation (Tanner staging), adverse events	
Chanoine 2005	N/T		**Primary outcome measures:** change in BMI from baseline to trial end (or trial exit)	-0.5, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12 months
			Secondary outcome measures: change in bodyweight, levels of total, HDL and LDL cholesterol, LDL-to-HDL cholesterol ratio, triglyceride levels, SBP and DBP,	

(*Continued*)

			waist and hip circumference, glucose and insulin responses to an oral glucose challenge, and changes in body composition	
			Other outcome measures: beta carotene, vitamin A, 25-hydroxyvitamin D, vitamin E, Tanner staging, adverse events	
Clarson 2009	N/T		**Primary outcome measures:** change in BMI and modification of metabolic risk factors, including insulin resistance, plasma lipids and adipocytokines, assessment of metformin on the attainment of a target metabolic profile	6 months
			Secondary outcome measures: -	
			Other outcome measures: BMI z score, BP, adverse events, waist circumference	
Franco 2014	N/T		**Primary outcome measures:** -	On average every 40 days for 13 months
			Secondary outcome measures: -	
			Other outcome measures: % of participants loosing 10% of their initial weight, weight, BMI, SBP, DBP, cholesterol, LDL, HDL, triglycerides, leptin, CRP, transaminases, blood glucose, insulin,	

(*Continued*)

			adverse events, waist circumference	
Freemark 2001	N/T		**Primary outcome measures:** -	6 months
			Secondary outcome measures: -	
			Other outcome measures: BMI SDS, insulin, glucose tolerance, leptin, serum lipids, HbA1c, IGF-1, lactate, cholesterol, LDL, HDL, LDL/HDL, triglycerides, adverse events, ALT, AST	
Garcia-Morales 2006	N/T		**Primary outcome measures:** baseline versus endpoint absolute values for bodyweight, BMI, and % of the initial BMI (%BMI)	-15, 30, 60, 90, 120, 150, 180 days
			Secondary outcome measures: waist circumference and % of the initial waist circumference (%waist)	
			Other outcome measures: health-related quality of life, white blood cells, monocytes, eosinophils, glucose, uric acid, creatinine, albumin, chloride, total cholesterol, LDL, AST, alkaline phosphatase, SBP, DBP, heart rate, ST segment, adverse events	
Godoy-Matos 2005	N/T		**Primary outcome measures:** change in weight and BMI	-4, 4, 8, 12, 16, 20, 24 weeks

(*Continued*)

			Secondary outcome measures: change in waist, hip, and waist-to-hip ratio	
			Other outcome measures: SBP, DBP, heart rate, glucose, total cholesterol, triglycerides, HDL, LDL, VLDL, insulin, total cholesterol/ HDL cholesterol, left atrium diameter, left ventricular mass, adverse events, satiety score	
Kendall 2013	**Source:** ISRCTN19517475 **Primary outcome measure:** reduction in BMI SDS	Prior to 16 December 2008: 80 participants aged 9 to 18 years As of 16 December 2008: • pubertal and postpubertal children: fasting insulin > 26 mIU/L • prepubertal children: fasting insulin > 15 mIU/L • 120-minute insulin > 89 mIU/L or impaired glucose tolerance (OGTT 2-hour plasma glucose value ≥ 7.8 to < 11.1 (± impaired fasting glucose ≥ 6.1 to < 7), or both	**Primary outcome measure:** reduction of BMI SDS	3, 6 months
	Secondary outcome measures: Added 16 December 2008: fasting and 2-hour insulin and glucose levels on OGTT, measures of insulin resistance, fasting lipids, CRP, adiponectin, leptin, resistin, BP		**Secondary outcome measures:** BMI and waist-to-hip ratio, fasting and postprandial insulin and glucose levels, metabolic risk factors, adipokines	
	Other outcome measure(s): -		**Other outcome measures:** weight, height, SBP, DBP, cholesterol, HDL, LDL, triglycerides, bilirubin, CRP, lactate, resistin, adverse events	
Maahs 2006	N/T		**Primary outcome measures:** change in BMI from baseline to 6 months	1, 2, 3, 4, 5, 6 months
			Secondary outcome measures: changes in weight, lean body mass, results of	

(*Continued*)

			blood chemistry studies	
			Other outcome measures: health-related quality of life, all-cause mortality, vitamin A, vitamin D, vitamin E, adverse events	
Mauras 2012	**Source:** NCT00139477 **Primary outcome measures:** change from baseline in hsCRP at 6 months, change from baseline in fibrinogen at 6 months, change from baseline in IL-6 at 6 months, change from baseline in PAI-1 at 6 months	Trial results posted, publications specified	**Primary outcome measures:** hsCRP and fibrinogen concentrations at 6 months	3, 6 months
	Secondary outcome measure(s): -		**Secondary outcome measures:** -	
	Other outcome measure(s): -		**Other outcome measures:** weight, BMI percentile, systolic BP, diastolic BP, IL-6, PAI-1, adiponectin, IGF-1, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, free fatty acids, glucose tolerance, resting energy expenditure rates, adverse events, waist circumference	
NCT00001723	**Source:** NCT00001723 **Primary outcome measure:** change in BMI SDS (time frame: baseline to 6 months)	Trial results posted, linked to pilot trial but no link to publication	No publication available	6 months
	Secondary outcome measures: change in bodyweight (time frame: baseline to 6 months), weight, change in BMI			

(*Continued*)

	(time frame: baseline to 6 months), change in body fat (time frame: baseline to 6 months), body fat distribution measures obtained DEXA, effect of race on change in weight (time frame: baseline to 6 months), difference in change of weight according to race (non-Hispanic white versus non-Hispanic black) **Other outcome measure(s):** -			
Ozkan 2004	N/T		**Primary outcome measures:** - **Secondary outcome measures:** - **Other outcome measures:** weight change, % weight change, BMI, adverse events	1 to 15 months
Prado 2012	N/T		**Primary outcome measures:** weight **Secondary outcome measures:** - **Other outcome measures:** BMI, motivational survey results, glycaemia, afterload glucose, HDL, adverse events, waist circumference	1, 2, 3, 4, 5, 6 months
Rezvanian 2010	N/T		**Primary outcome measures:** - **Secondary outcome measures:** -	12, 24 weeks

(*Continued*)

			Other outcome measures: BMI, BMI SDS, waist circumference, waist-to-height ratio, adverse events	
Srinivasan 2006	**Source:** ISRCTN43267711 **Primary outcome measures:** -	No results posted or links to publication Retrospectively registered	**Primary outcome measures:** -	6, 12 months
	Secondary outcome measures: -		**Secondary outcome measures:** -	
	Other outcome measures: -		**Other outcome measures:** BMI, waist circumference z score, fasting insulin, fasting glucose, glucose effectiveness, acute insulin response, disposition index, glucose disposal, acanthosis nigricans neck score, Tanner staging, weight loss, weight z score, BMI z score, adverse events	
Van Mil 2007	N/T		**Primary outcome measure:** change in BMI between the 2 periods (12 weeks' randomised treatment period and 12 weeks' follow-up)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24 weeks
			Secondary outcome measures: -	
			Other outcome measures: height, weight, sleeping metabolic rate, basal metabolic rate, total energy expenditure, physical activity level, basal metabolic rate adjusted, total energy expenditure residuals, adverse events	

(*Continued*)

Wiegand 2010	Found in the references of included trials section: EudraCT Nr. 2004-003816-47 (but currently not available at EU CTR. W ceived the following answ not in the public domain from Ethics Committee you to contact the Natio concerned by this applic by Hübel it is specified "V die Zustimmung der jewe missionen eingeholt (Ch St. Gallen, Schweiz)" - *" proval of the appropriate et (Charité Berlin, Germany;*		**Primary outcome measures:** HOMA-IR **Secondary outcome measures:** anthropometric measurements (BMI and waist-to-hip ratio) , cardiovascular risk parameters (SBP and DBP) , lipid profile (total, LDL, HDL cholesterol and triglycerides), and other metabolic parameters (glucose tolerance and fasting insulin) **Other outcome measures:** adverse events	-6, 3, 6 months
Wilson 2010	**Source:** NCT00209482 and NCT00120146 **Primary outcome measures:** NCT00209482: mean change from baseline in individual BMIs between the 2 groups (compared at 2 time points: at week 52 and week 100) NCT00120146: change in BMI, BMI **Secondary outcome measures:** NCT00209482: - NCT00120146: change in insulin sensitivity; fasting insulin concentrations; characterisation of insulin dynamics and insulin sensitivity; characterisation of fat distribution and fatty infiltration of the liver; use of CT to characterise abdominal fat distribution; use of CT and ALT levels to assess fatty infiltration of the liver;	No trial results posted, publications specified	**Primary outcome measures:** BMI change, BMI z score **Secondary outcome measures:** fat mass, lean mass, fat area, HOMA-IR, area under insulin curve, area under glucose curve, corrected insulin release at glucose peak, LDL cholesterol, HDL cholesterol, triglycerides, triglyceride-to-HDL cholesterol ratio, adverse events	-4, 12, 24, 36, 48, 60, 72, 84, 96 weeks

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	characterisation of body composition; characterisation of dietary amino acids; characterisation of the insulin-to-glucagon ratio; characterisation of the impact of sex on response to metformin XR; characterisation of the impact of race/ethnicity on response to metformin XR; characterisation of health-related quality of life			
	Other outcome measures: NCT00209482: - NCT00120146: -		**Other outcome measures:** waist circumference	
Yanovski 2011	**Source:** NCT00005669 **Primary outcome measures:** changes in bodyweight as determined by BMI SDS (6 months)	Trial results posted, publications specified	**Primary outcome measures:** change in BMI SD score (BMI z score), as determined at the end of the 6-month randomised treatment phase	1, 2, 3, 4, 5, 6 months
	Secondary outcome measures: change in bodyweight as determined by BMI (6 months), change in bodyweight (6 months), change in body fat by DEXA (6 months) , change in body fat by Bod Pod (6 months)		**Secondary outcome measures:** changes in BMI, bodyweight and fat mass at the conclusion of the randomised phase	
	Other outcome measures: -		**Other outcome measures:** changes in skinfold thickness, body circumferences, visceral adipose tissue, insulin resistance and laboratory components of the metabolic syndrome - SBP, DBP, serum insulin, plasma glucose, total cholesterol, HDL cholesterol, LDL choles-	

(*Continued*)

			terol, LDL-to-HDL cholesterol ratio, triglycerides, ALT, AST, hsCRP, vitamin B12, adverse events		

- denotes not reported.
[a] Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).
[b] Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial)
ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; BMI SDS: body mass index standardised deviation score; BP: blood pressure; CDC: Centers for Disease Control and Prevention; CRP: C-reactive protein; CT: computed tomography; DBP: diastolic blood pressure; DEXA: dual-energy X-ray absorptiometry; EMA: European Medicines Agency; EU CTR: European Clinical Trials Register; FDA: Food and Drug Administration (US); HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; HOMA(-IR): homeostasis model assessment (insulin resistance); hsCRP: high sensitivity C-reactive protein; IGF-1: insulin-like growth factor 1; IL-6: interleukin-6; LDL: low-density lipoprotein; N/T: no trial document available; OGTT: oral glucose tolerance test; PAI-1: plasminogen activator inhibitor-1; QTc: heart-rate corrected QT interval; SBP: systolic blood pressure; VLDL: very low density lipoprotein; XR: extended release

Appendix 6. Examination of outcome reporting bias

Trial	Outcome	Clear that outcome was measured and analysed[a] (trial report states that outcome was analysed but only reports that result was not significant)	Clear that outcome was measured and analysed[b] (trial report states that outcome was analysed but no results reported)	Clear that outcome was measured[c] (clear that outcome was measured but not necessarily analysed (judgement says likely to have been analysed but not reported because of nonsignificant results))	Unclear whether the outcome was measured[d] (not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of nonsignificant results)
Atabek 2008	Behaviour change	-	-	Yes	-
Berkowitz 2003	N/A				
Berkowitz 2006	N/A				
Chanoine 2005	N/A				
Clarson 2009	Body fat distribution	Yes	-	-	-

(*Continued*)

Franco 2014	Body fat distribution	-	-	Yes	-
Freemark 2001	N/A				
Garcia-Morales 2006	Behaviour change	-	-	Yes	-
Godoy-Matos 2005	N/A				
Kendall 2013	Behaviour change	-	-	Yes	-
Maahs 2006	Behaviour change	-	-	Yes	-
	Health-related quality of life and self esteem	Yes	-	-	-
Mauras 2012	N/A				
NCT00001723	N/A				
Ozkan 2004	N/A				
Prado 2012	Measured BMI	Yes	-	-	-
	Body fat distribution	Yes	-	-	-
Rezvanian 2010	N/A				
Srinivasan 2006	Measured BMI	-	Yes	-	-
	Body fat distribution	-	Yes	-	-
Van Mil 2007	N/A				
Wiegand 2010	Body fat distribution	Yes	-	-	-
Wilson 2010	Body fat distribution	-	Yes	-	-
Yanovski 2011	N/A				

BMI: body mass index; N/A: not applicable.

Appendix 7. Definition of endpoint measurement[a] (I)

Trial	Measured BMI	Adverse events	Health-related quality of life and self-esteem	All-cause mortality	Morbidity
Atabek 2008	Expressed as BMI (kg/m^2). Obesity defined as ≥ the 95th percentile for age and sex based on the standards of the CDC (IO)	Participants were asked to report any adverse effects every month. Serious adverse events defined as vomiting or lactic acidosis (SO)	N/I	N/I	Hyperinsulinaemia was defined from norms for pubertal stages 2 to 4: mid-puberty > 30 mU/L, and postpubertal hyperinsulinism was defined by adult WHO criteria (> 20 mU/L) . Insulin sensitivity was estimated using FGIR, HOMA-IR and QUICKI (IO)
Berkowitz 2003	The change in raw BMI is not given. Instead it is expressed as % reduction in BMI (kg/m^2). BMI also used to calculate BMI z score (calculated using CDC standards) Obesity defined as BMI 32 to 44 kg/m^2 (IO)	Adverse events were recorded at each medical visit. In addition, blood pressure and heart rate were monitored closely, and any abnormalities were considered as adverse events. A serious adverse event was not defined (AO, IO, SO)	N/I	N/I	N/I
Berkowitz 2006	Expressed as BMI (kg/m^2) in graphical format and % change in BMI in text and tabular format. Used Rosner 1998 to define obesity (IO)	The investigator recorded all adverse events, both observed and volunteered. The only serious event defined as excessive nausea and vomiting. Unclear whether suicide attempt and depression were defined as serious (AO, IO, SO)	N/I	2 suicide attempts - did not result in mortality (AO, IO)	N/I

(*Continued*)

Chanoine 2005	Expressed as BMI (kg/m^2). Used Barlow 1998 to define obesity (IO)	Gastrointestinal tract adverse effects assessed at each visit by a specially designed dictionary of standard terms for defecation patterns for reproducibility and consistency of reporting. Other adverse events were noted and followed by questioning. Serious adverse events included acute demyelinating encephalomyelitis, facial palsy, pneumonia, worsening of asthma, pain in the right side, pilonidal abscess, depression, asthma attack, seizure, admission for repair of deviated nasal septum, appendicitis, cholelithiasis, gallbladder disorder followed by cholecystectomy, adenoidal hypertrophy and aseptic meningitis. The trial also used electrocardiograms to detect abnormalities and measured gallbladder ultrasounds to detect gallstones (AO, IO, SO)	N/I	N/I	Gallstones and fatty liver infiltration or hepatomegaly identified by gallbladder ultrasound (IO)
Clarson 2009	Expressed as BMI (kg/m^2). Obesity defined as BMI > 95th percentile for age and sex (no reference). BMI z scores calculated us-	No adverse events reported, trial highlights that metformin was well tolerated by all participants - unclear how this was assessed	N/I	N/I	Insulin resistance was defined using HOMA > 3 (IO)

(*Continued*)

	ing the CDC reference data (IO)				
Franco 2014	Weight and height used to calculate BMI. Obesity defined by WHO classification (IO)	Adverse effects were investigated on a preset questionnaire and described voluntarily by the participant at each consultation (on average every 40 days) . A serious adverse event was not defined (AO, SO)	N/I	N/I	N/I
Freemark 2001	Expressed change in BMI. Also expressed as BMI SDS. Used Rosner 1998 to adjusting for age, sex and race (IO)	Unclear how and when adverse events were assessed	N/I	N/I	Hyperinsulinaemia defined as fasting insulin concentration exceeding 15 μU/mL. Insulin sensitivity assessed by fasting insulin-to-glucose concentration ratio, QUICKI and HOMA-IR (IO)
Garcia-Morales 2006	Expressed as BMI (kg/m^2). Used CDC growth charts (Kuczmarski 2000) (IO)	Adverse events were reported as they were detected by the participant or investigator. They were also assessed during visits. Severe adverse events defined as life-threatening or those resulting in hospitalisation or producing long-term disabilities (AO, IO, SO)	Health-related quality of life assessed by a 36-item Short-Form Health Survey (SF-36) questionnaire (Alonso 1995) (SO)	N/I	Comorbidities were accessed at baseline and follow-up. These included high blood pressure, high glucose, high triglycerides, high cholesterol, high LDL and high HDL (IO)
Godoy-Matos 2005	Expressed as BMI (kg/m^2). Obesity defined as BMI between 30 and 45 (no reference) (IO)	Adverse events were assessed and recorded at each visit. A significant event was defined as a serious	N/I	N/I	N/I

(*Continued*)

		or rare event - serious event not defined (AO, IO, SO)			
Kendall 2013	Expressed as BMI (kg/m^2). Obesity defined by UK BMI centile charts. No reference for how BMI SDS was calculated (IO)	How and when trial authors assessed adverse events was not described. No explanation to how they defined a severe/series event	N/I	N/I	Participants had hyperinsulinaemia, impaired fasting glucose or impaired glucose tolerance In-sulin resistance/sensitivity was assessed using: HOMA-IR, QUICKI, whole-body insulin sensitivity index, adiponectin-to-leptin ratio (IO)
Maahs 2006	Expressed as BMI (kg/m^2). Obesity defined as BMI that exceeded the 85th percentile for age and sex (assume this from the CDC standards) (IO)	Adverse events assessed at each monthly visit. Serious/severe adverse events not defined (AO, IO, SO)	Health-related quality of life assessed by 4 questionnaires: Brief Symptom Inventory (Derogatis 1983), Parents and Children's KINDL (Ravens-Sieberer 2001), IWQOL-Kids (Kolotkin 1997; Kolotkin 2001), and a global ratings scale (SO)	Defined as suicide - 1 participant in the orlistat group (AO, IO)	N/I
Mauras 2012	Expressed as BMI (kg/m^2). BMI % determined using CDC standards (Kuczmarski 2000) (IO)	Trial authors did not describe how and when adverse events were assessed. Did not report number or type of adverse events	N/I	N/I	Elevated hsCRP and fibrogen concentrations were measured by immuno-nephelometry (IO)
NCT00001723	BMI SDS calculated for age and sex according to CDC standards (IO)	Events were collected by systematic assessment. Trial authors did not define what a serious adverse event was (IO, SO)	N/I	N/I	N/I

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Ozkan 2004	Expressed as BMI (kg/m^2). Severe obesity defined as weight for height index > 140% (no reference) (IO)	Unclear how and when adverse events were assessed. All with mild gastrointestinal complaints apart from 2 (mild diffuse hair loss and another with muscle cramps). A serious/severe event was not defined	N/I	N/I	N/I
Prado 2012	Expressed as BMI (kg/m^2). Obesity defined as BMI > 95th percentile for age and sex (no reference) (IO)	Adverse events monitored by ALT, AST and haemoglobin levels (IO)	N/I	N/I	Risk factors for diabetes mellitus type 2: high glycaemia fasting, high postload glucose or high insulin sensitivity. Insulin sensitivity accessed by HOMA
Rezvanian 2010	Expressed as BMI (kg/m^2). Gave baseline BMI SDS (calculated using revised CDC growth charts: Kuczmarski 2000 but did not give follow-up measurements (IO)	Participants and parents educated on possible signs of symptoms of hypoglycaemia. They were also given a 24-hour mobile phone number to call if any adverse events occurred. No definition of severe/serious adverse events (SO)	N/I	N/I	N/I
Srinivasan 2006	Raw BMI (kg/m^2) data not provided BMI z score (presented only on a graph) was calculated from the CDC reference data 2000. Obesity defined by the International Obesity Task Force (Cole 2000) (IO)	Unclear how and when adverse events were assessed. No definition for serious/severe events	N/I	N/I	Clinical suspicion of insulin resistance defined by fasting insulin-to-glucose ratio or presence of acanthosis nigricans (assessed by severity at the neck by a validated scale) Insulin sen-

(*Continued*)

					sitivity was accessed by SI clamp (minimal model), fasting insulin and fasting glucose (IO)
Van Mil 2007	Expressed as BMI (kg/m^2). BMI SDS was determined using the Dutch age- and sex-adjusted BMI curves (Hansen 1998) . Obesity defined as ≥ 97th percentile (no reference) (IO)	Adverse events were determined at each visit. Heart rate, DBP, SBP were monitored throughout the trial. No definition of a serious/severe event (AO, IO, SO)	N/I	N/I	N/I
Wiegand 2010	Expressed as BMI (kg/m^2) - reference: Park 2009. Also provided BMI SDS, no reference (IO)	Adverse events determined at the 3-month and 6-month visit by a clinical and biochemical assessment. No definition of a serious/severe event (AO, IO, SO)	N/I	N/I	Risk factors for type 2 diabetes: acanthosis nigricans, signs of metabolic syndrome and impaired fasting glucose Insulin sensitivity was assessed by HOMA-IR and insulin sensitivity index (IO)
Wilson 2010	Expressed as BMI (kg/m^2). Used CDC charts to convert BMI to BMI z score (Kuczmarski 2000) (IO)	Adverse events assessed at each visit. An appendectomy was defined as a serious/severe event (AO, IO, SO)	N/I	N/I	N/I
Yanovski 2011	Expressed as BMI (kg/m^2). Also expressed as BMI SDS (no reference) (IO)	Adverse events accessed at each visit and by laboratory analysis. A serious/severe event was not defined (AO, IO, SO)	N/I	N/I	Insulin sensitivity was calculated (from a SI clamp) using the metabolic rate-to-steady-state insulin ratio. Insulin resistance estimated using HOMA-IR (IO)

[a] In addition to definition of endpoint measurement, description who measured the outcome (AO: adjudicated outcome measurement; IO: investigator-assessed outcome measurement; SO: self-reported outcome measurement)
ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; BMI SDS: body mass index standard deviation score;

(*Continued*)

CDC: Centers for Disease Control and Prevention; DBP: diastolic blood pressure; FGIR: fasting insulin concentration/fasting glucose concentration; HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; HOMA(-IR): homeostasis model assessment (insulin resistance); hsCRP: high sensitivity C-reactive protein; IWQOL: Impact of Weight on Quality of Life questionnaire; LDL: low-density lipoprotein; N/I: not investigated; OGTT: oral glucose tolerance test; QUICKI: quantitative insulin check index; SBP: systolic blood pressure; SI clamp: insulin sensitivity clamp; WHO: World Health Organization

Appendix 8. Definition of endpoint measurement[a] (II)

Trial	Body fat distribution	Behaviour change	Participants views of the intervention	Socioeconomic effects
Atabek 2008	N/I	Food consumption was assessed by the completion of a detailed questionnaire at the beginning and end of the trial (no reference or results given) (SO)	N/I	N/I
Berkowitz 2003	Waist circumference measured using reference: Calloway 1988 (IO)	Hunger was evaluated by the Eating Inventory (range 0 to 14) (Stunkard 1985) (SO)	N/I	N/I
Berkowitz 2006	Waist circumference - no description (IO)	N/I	N/I	N/I
Chanoine 2005	Waist circumference - no description on how it was measured. Body composition measured by whole body DEXA (IO)	N/I	N/I	N/I
Clarson 2009	Waist circumference was measured in the standing position at the level of the umbilicus to the nearest 0.1 cm using a constant tension tape (no reference) (IO)	N/I	N/I	N/I
Franco 2014	Waist circumference and hip circumference measured at the smallest and largest diameter. Arm circumference at the middle	N/I	N/I	N/I

(*Continued*)

	third of the left arm (no reference) (IO)			
Freemark 2001	N/I	N/I	N/I	N/I
Garcia-Morales 2006	Waist circumference - measured with a flexible tape between the highest point of the iliac crest and the lowest part of the costal margin at the midaxillary line (no reference) (IO)	A detailed questionnaire on food consumption was completed at the beginning and end of the trial (no reference) (SO)	N/I	N/I
Godoy-Matos 2005	Waist circumference - measured at the minimal circumference between iliac crest and last rib edge. Hip circumference assessed at the greatest circumference through the major trochanters (no reference) (IO)	N/I	N/I	N/I
Kendall 2013	Waist-to-hip ratio (no reference) (IO)	3 previously validated questionnaires (food frequency, diet and eating behaviour, and physical activity) were completed by each child at the start and end of the trial. No results presented (SO)	N/I	N/I
Maahs 2006	BIA	Diet records recorded before enrolment and at 3 and 6 months. No reference or results provided (SO)	N/I	N/I
Mauras 2012	Waist circumference measured at umbilicus (no reference). Intrahepatic fat content measured using fast MRI. References: Fishbein 2001; Fishbein 2003. Body composition was measured DEXA.	N/I	N/I	N/I

(*Continued*)

	Also measured waist-to-height ratio (no reference) (IO)			
NCT00001723	N/I	N/I	N/I	N/I
Ozkan 2004	N/I	N/I	N/I	N/I
Prado 2012	Waist circumference - measured with a central flexible tape, corresponding to the perimeter less between the iliac crest and the bottom edge last rib, then exhale with arms relaxed on both sides (no reference) (IO)	N/I	N/I	N/I
Rezvanian 2010	Waist circumference - measured at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration (no reference) (IO)	N/I	N/I	N/I
Srinivasan 2006	Raw waist circumference data not reported. Waist circumference was calculated from the mean of 3 measures at the level of the umbilicus (no reference). Waist circumference z scores calculated from recent multiracial American reference data (Fernandez 2004). Raw body composition data were not reported. DEXA scans also used. MRI whole-body scans (IO)	N/I	N/I	N/I
Van Mil 2007	Body composition was assessed using a 4-component reference model: total bodyweight = fat mass + total body water + total bone mineral	Physical activity level was estimated using an activity questionnaire. A 7-day dietary record was given to each participant.	N/I	N/I

(*Continued*)

	content and remaining fat-free mass (references: Fuller 1992; Van Marken Lichtenbelt 1999). To calculate this they used densitometry, deuterium dilution (Maastricht protocol) with labelled water test and DEXA (IO)	Only the food quotient used in the assessment (respiratory exchange ratio to calculate TEE). Rest of the data not presented (IO, SO)		
Wiegand 2010	Waist-to-hip ratio and body composition (BIA) were measured but no explanation to how and no results given (apart from saying they were not significant) (IO)	N/I	N/I	N/I
Wilson 2010	Abdominal CT scans evaluated abdominal fat content and distribution (Borkan 1982). Whole body DEXA used to measure % body fat and lean body mass (von Scheven 2006). Waist circumference measured at the smallest circumference below the rib cage and above the umbilicus (Wang 2003) (IO)	N/I	N/I	N/I
Yanovski 2011	Abdominal and hip circumferences (assessed in triplicate) and triceps skinfold thickness. Whole-body fat mass by DEXA and by air displacement plethysmography; and intra-abdominal and subcutaneous abdominal adipose tissue by MRI at L2 to L3 and L4 to L5 (IO)	N/I	N/I	N/I

[a] In addition to definition of endpoint measurement, description who measured the outcome (AO: adjudicated outcome measurement; IO: investigator-assessed outcome measurement; SO: self-reported outcome measurement)
BIA: bioelectrical impedance analysis; CT: computed tomography; DEXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging; n: number of participants; N/I: not investigated; TEE: total energy expenditure

Appendix 9. Adverse events (I)

Trial	Intervention(s) and comparator (s)	Participants included in analysis (N)	Deaths (N)	Deaths (% of participants)	Participants with at least one adverse event (N)	Participants with at least one adverse event (%)	Participants with at least one severe/serious adverse event (N)	Participants with at least one severe/serious adverse event (%)
Atabek 2008	I: metformin + diet and physical activity advice	90	0	0	2	2.2	0	0
	C: placebo + diet and physical activity advice	30	0	0	0	0.0	0	0
Berkowitz 2003	I: behavioural programme + sibutramine	43	0	0	6	14.0	-	-
	C: behavioural programme + placebo	39	0	0	3	7.7	-	-
Berkowitz 2006	I: behavioural therapy programme + sibutramine	368	0	0	327	88.9	10	2.7
	C: behavioural therapy programme + placebo	130	0	0	111	85.4	1	0.8
Chanoine 2005	I: orlistat + diet + exercise + behavioural therapy	352	0	0	341	97	11	3

(*Continued*)

	C: placebo + diet + exercise + behavioural therapy	181	0	0	170	94	5	3
Clarson 2009	I: metformin + lifestyle intervention	14	0	0	0	0	0	0
	C: lifestyle intervention only	17	0	0	0	0	0	0
Franco 2014	I: sibutramine + dietary guidance	63	-	-	8	13.4	0	0
	C: placebo + dietary guidance	63	-	-	3	4.9	0	0
Freemark 2001	I: metformin	15	0	0	4	26.7	0	0
	C: placebo	17	0	0	1	5.9	0	0
Garcia-Morales 2006	I: sibutramine + diet + exercise	23	0	0	10	43.5	0	0
	C: placebo + diet + exercise	23	0	0	10	43.5-	0	0
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	30	0	0	-[a]	-	0	0
	C: placebo + hypocaloric diet + exercise	30	0	0	-[a]	-	0	0

(*Continued*)

Kendall 2013	I: metformin + healthy lifestyle advice	74	0	0	20	27.0	0	0
	C: control + healthy lifestyle advice	77	0	0	8	10.4	0	0
Maahs 2006	I: orlistat + diet and exercise therapy	20	1	5.0	-	-	1	5.0
	C: placebo + diet and exercise therapy	20	0	0	-	-	0	0
Mauras 2012	I: metformin + diet/exercise intervention	35	0	0	-	-	0	0
	C: diet/exercise intervention	31	0	0	-	-	0	0
NCT000017	I: orlistat + behavioural weight loss programme	100	0	0	95	95	0	0
	C: placebo + behavioural weight loss programme	100	0	0	94	94	2	2
Ozkan 2004	I: conventional treatment + orlistat	22	0	0	22	100	-	-
	C: conventional treatment	20	0	0	0	0	-	-

(*Continued*)

Prado 2012	I: metformin + nutritional guide and exercise programme	10	0	0	-	-	0	0
	C: placebo + nutritional guide and exercise programme	9	0	0	-	-	0	0
Rezvanian 2010	I1: metformin + healthy eating and physical activity advice	45	0	0	7	15.6	0	0
	I2: fluoxetine + healthy eating and physical activity advice	45	0	0	-	-	0	0
	I3: metformin and fluoxetine + healthy eating and physical activity advice	45	0	0	-	-	0	0
	C: placebo + healthy eating and physical activity advice	45	0	0	-	-	0	0
Srinivasan 2006	I: metformin first then placebo + "standardised information on healthy eat-	13	0	0	-[b]	-	0	0

(*Continued*)

	ing and exercise“							
	C: placebo first then metformin + ”standardised information on healthy eating and exercise“	15	0	0	-[b]	-	0	0
Van Mil 2007	I: sibutramine + energy-restricted diet and exercise plan	12	0	0	12	100	-	-
	C: placebo + energy-restricted diet and exercise plan	12	0	0	9	75	-	-
Wiegand 2010	I: metformin + multiprofessional lifestyle intervention	36	0	0	8	22.2	-	-
	C: placebo + multiprofessional lifestyle intervention	34	0	0	13	38.2	-	-
Wilson 2010	I: metformin + lifestyle intervention	38	0	0	-[c]	-	2	5.3
	C: placebo + lifestyle intervention	38	0	0	-[c]	-	0	0

(*Continued*)

Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	53	0	0	-[d]	-	0	0
	C: placebo + dietitian-administered weight-reduction programme	47	0	0	-[d]	-	0	0

"-" denotes not reported.
[a]Number of participants with one or multiple adverse events: sibutramine group 47 events in 30 participants; placebo group 45 events in 30 participants.
[b]Two participants were unable to tolerate metformin 1000 mg twice daily because of nausea and were switched to metformin 750 mg twice daily with slower dose increments.
[c]Number of participants with one or multiple adverse events: metformin group: 52 events in 38 participants; placebo group: 43 events in 38 participants.
[d]A total of 9/53 (17%) metformin-treated children were unable to take the highest dose of 2000 mg/d and were prescribed doses ranging from 500 mg/d to 1500 mg/d; number of participants with one or multiple adverse events: metformin group: 64 events in 53 participants; placebo group: 25 events in 47 participants
C: comparator; I: intervention; n: number pf participants.

Appendix 10. Adverse events (II)

Trial	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants discontinuing trial due to an adverse event (N)	Participants discontinuing trial due to an adverse event (%)	Participants with at least one hospitalisation (N)	Participants with at least one hospitalisation (%)	Participants with at least one outpatient treatment (N)	Participants with at least one outpatient treatment (%)
Atabek 2008	I: metformin + diet and physical activity advice	90	0	0	0	0	0	0

(*Continued*)

	C: placebo + diet and physical activity advice	30	0	0	0	0	0	0
Berkowitz 2003	I: behavioural programme + sibutramine	42	0	0	-	-	-	-
	C: behavioural programme + placebo	39	1	2.5	-	-	-	-
Berkowitz 2006	I: behavioural therapy programme + sibutramine	368	23	6	-	-	-	-
	C: behavioural therapy programme + placebo	130	7	5	-	-	-	-
Chanoine 2005	I: orlistat + diet + exercise + behavioural therapy	352	12	3	10	2.8	0	0
	C: placebo + diet + exercise + behavioural therapy	181	3	2	5	2.8	0	0
Clarson 2009	I: metformin + lifestyle intervention	14	0	0	0	0	0	0
	C: lifestyle intervention only	17	0	0	0	0	0	0

(*Continued*)

Franco 2014	I: sibutramine + dietary guidance	63	0	0	0	0	0	0
	C: placebo + dietary guidance	63	0	0	0	0	0	0
Freemark 2001	I: metformin	15	0	0	0	0	0	0
	C: placebo	17	0	0	0	0	0	0
Garcia-Morales 2006	I: sibutramine + diet + exercise	23	0	0	-	-	-	-
	C: placebo + diet + exercise	23	0	0	-	-	-	-
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	30	0	0	0	0	0	0
	C: placebo + hypocaloric diet + exercise	30	0	0	0	0	0	0
Kendall 2013	I: metformin + healthy lifestyle advice	74	0	0	-	-	-	-
	C: control + healthy lifestyle advice	77	0	0	-	-	-	-
Maahs 2006	I: orlistat + diet and exercise therapy	20	3	15	-	-	-	-

(*Continued*)

	C: placebo + diet and exercise therapy	20	0	0	-	-	-	-
Mauras 2012	I: metformin + diet/exercise intervention	35	0	0	0	0	0	0
	C: diet/exercise intervention	31	0	0	0	0	0	0
NCT000017	I: orlistat + behavioural weight loss programme	100	1	1	-	-	-	-
	C: placebo + behavioural weight loss programme	100	2	2	-	-	-	-
Ozkan 2004	I: conventional treatment + orlistat	22	7	32	-	-	-	-
	C: conventional treatment	20	0	0	-	-	-	-
Prado 2012	I: metformin + nutritional guide and exercise programme	10	0	0	0	0	0	0
	C: placebo + nutritional guide and exercise programme	9	0	0	0	0	0	0
Rezvanian 2010	I1: metformin + healthy eat-	45	0	0	0	0	0	0

(*Continued*)

	ing and physical activity advice							
	I2: fluoxetine + healthy eating and physical activity advice	45	0	0	0	0	0	0
	I3: metformin and fluoxetine + healthy eating and physical activity advice	45	0	0	0	0	0	0
	C: placebo + healthy eating and physical activity advice	45	0	0	0	0	0	0
Srinivasan 2006	I: metformin first then placebo + "standardised information on healthy eating and exercise"	13	0	0	0	0	0	0
	C: placebo first then metformin + "standardised information on healthy eating and exercise"	15	0	0	0	0	0	0
Van Mil 2007	I: sibutramine + energy-restricted diet	12	1	8	0	0	0	0

(*Continued*)

	and exercise plan							
	C: placebo + energy-restricted diet and exercise plan	12	0	0	0	0	0	0
Wiegand 2010	I: metformin + multiprofessional lifestyle intervention	36	3	8.3	-	-	-	-
	C: placebo + multiprofessional lifestyle intervention	34	1	2.9	-	-	-	-
Wilson 2010	I: metformin + lifestyle intervention	38	3	7.9	-	-	-	-
	C: placebo + lifestyle intervention	38	1	2.6	-	-	-	-
Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	53	1	1.9	-	-	-	-
	C: placebo + dietitian-administered weight-reduction programme	47	0	0	-	-	-	-

"-" denotes not reported.
C: comparator; I: intervention; n: number of participants.

Appendix 11. Adverse events (III)

Trial	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse events (N)	Participants with at least one specific adverse event (%)
Atabek 2008	I: metformin + diet and physical activity advice	90	**1.** Diarrhoea and mild abdominal pain **2.** Mild discomfort from the abdomen	**1.** 1 **2.** 1	**1.** 1.1 **2.** 1.1
	C: placebo + diet and physical activity advice	30	-	-	-
Berkowitz 2003	I: behavioural programme + sibutramine	42	**1.** High blood pressure and pulse rate **2.** High blood pressure only **3.** High pulse rate only **4.** Knee surgery **5.** Ventricular premature beats **6.** Cholelithiasis/ cholecystectomy **7.** Rash, viral	**1.** 3 **2.** 1 **3.** 1 **4.** 1 **5.** 1 **6.** 1 **7.** 1	**1.** 7.1 **2.** 2.4 **3.** 2.4 **4.** 2.4 **5.** 2.4 **6.** 2.4 **7.** 2.4
	C: behavioural programme + placebo	39	**1.** Elevated blood pressure and pulse rate* **2.** Elevated pulse rate only* **3.** Atrial premature beats **4.** Tonsillectomy **5.** Ventricular premature beats* **6.** Ecchymoses*	**1.** 1 **2.** 1 **3.** 1 **4.** 2 **5.** 1 **6.** 2	**1.** 2.6 **2.** 2.6 **3.** 2.6 **4.** 5.1 **5.** 2.6 **6.** 5.1
Berkowitz 2006	I: behavioural therapy programme + sibutramine	368	**1.** Infection **2.** Headache **3.** Pharyngitis **4.** Tachycardia **5.** Accidental injury **6.** Dry mouth **7.** Pain **8.** Hypertension	**1.** 167 **2.** 113 **3.** 49 **4.** 46 **5.** 41 **6.** 41 **7.** 42 **8.** 39	**1.** 45.3 **2.** 30.7 **3.** 13.3 **4.** 12.5 **5.**11.1 **6.**11.1 **7.** 11.4 **8.** 10.6

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			9. Rhinitis **10.** Abdominal pain **11.** Dysmenorrhoea **12.** Vomiting **13.** Cough increased **14.** Nausea **15.** Dizziness **16.** Rash **17.** Sinusitis **18.** Constipation **19.** Flu syndrome **20.** Insomnia **21.** Viral infection **22.** Allergic reaction **23.** Suicide attempt **24.** Depression **25.** Syncope **26.** Chest pain **27.** Arrhythmia **28.** Extra systoles	**9.** 41 **10.** 37 **11.** 21 **12.** 32 **13.** 28 **14.** 31 **15.** 28 **16.** 25 **17.** 24 **18.** 24 **19.** 23 **20.** 23 **21.** 20 **22.** 18 **23.** 1 **24.** 5 **25.** - **26.** - **27.** - **28.** -	**9.** 11.1 **10.** 10.1 **11.** 5.7 **12.** 8.7 **13.** 7.6 **14.** 8.4 **15.** 7.6 **16.** 6.8 **17.** 6.5 **18.** 6.5 **19.** 6.3 **20.** 6.3 **21.** 5.4 **22.** 4.9 **23.** 0.3 **24.** 1.4 **25.** ≤ 1.5 **26.** ≤ 1.5 **27.** ≤ 1.5 **28.** ≤ 1.5
	C: behavioural therapy programme + placebo	130	**1.** Infection **2.** Headache **3.** Pharyngitis **4.** Tachycardia **5.** Accidental injury **6.** Dry mouth **7.** Pain **8.** Hypertension **9.** Rhinitis **10.** Abdominal pain **11.** Dysmenorrhoea **12.** Vomiting **13.** Cough increased **14.** Nausea **15.** Dizziness **16.** Rash **17.** Sinusitis **18.** Constipation **19.** Flu syndrome **20.** Insomnia **21.** Viral infection **22.** Allergic reaction **23.** Suicide attempt **24.** Depression	**1.** 53 **2.** 39 **3.** 23 **4.** 8 **5.** 8 **6.** 8 **7.** 12 **8.** 11 **9.** 17 **10.** 12 **11.** 13 **12.** 7 **13.** 12 **14.** 12 **15.** 5 **16.** 7 **17.** 6 **18.** 3 **19.** 7 **20.** 4 **21.** 2 **22.** 7 **23.** 1 **24.** 1 **25.** -	**1.** 41 **2.** 30 **3.** 18 **4.** 6.2 **5.** 6.2 **6.** 6.2 **7.** 9.2 **8.** 8.5 **9.** 13.1 **10.** 9.2 **11.** 10 **12.** 5.4 **13.** 9.2 **14.** 9.2 **15.** 3.8 **16.** 5.4 **17.** 4.6 **18.** 2.3 **19.** 5.4 **20.** 3.1 **21.** 1.5 **22.** 5.4 **23.** 0.8 **24.** 0.8 **25.** ≤ 1.5

(*Continued*)

			25. Syncope **26.** Chest pain **27.** Arrhythmia **28.** Extra systoles	**26.** - **27.** - **28.** -	**26.** ≤ 1.5 **27.** ≤ 1.5 **28.** ≤ 1.5
Chanoine 2005	I: orlistat + diet + exercise + behavioural therapy	352	**1.** Fatty/oily stool **2.** Oily spotting **3.** Oily evacuation **4.** Abdominal pain **5.** Fecal urgency **6.** Flatus with discharge **7.** Soft stool **8.** Nausea **9.** Increased defecation **10.** Flatulence **11.** Fecal incontinence **12.** Headache **13.** Upper respiratory tract infection **14.** Nasopharyngitis **15.** Sore throat **16.** Sinusitis **17.** Joint sprain **18.** Nasal congestion **19.** Back pain **20.** Gastroenteritis **21.** Seasonal rhinitis **22.** Limb injury **23.** Asymptomatic gallstones **24.** Pilonidal abscess **25.** Depression **26.** Asthma attack **27.** Seizure **28.** Admission for repair of deviated nasal septum **29.** Appendicitis **30.** Cholelithiasis **31.** Gallbladder disorder followed by	**1.** 177 **2.** 102 **3.** 82 **4.** 77 **5.** 73 **6.** 70 **7.** 53 **8.** 52 **9.** 48 **10.** 32 **11.** 31 **12.** 134 **13.** 114 **14.** 99 **15.** 59 **16.** 40 **17.** 35 **18.** 31 **19.** 28 **20.** 23 **21.** 21 **22.** 18 **23.** 6 **24.** 1 **25.** 2 **26.** 1 **27.** 1 **28.** 1 **29.** 1 **30.** 1 **31.** 1 **32.** 1 **33.** 1 **34.** 10	**1.** 50.3 **2.** 29.0 **3.** 23.3 **4.** 21.9 **5.** 20.7 **6.** 19.9 **7.** 15.1 **8.** 14.8 **9.** 13.6 **10.** 9.1 **11.** 8.8 **12.** 38.1 **13.** 32.4 **14.** 28.1 **15.** 16.8 **16.** 11.4 **17.** 9.9 **18.** 8.8 **19.** 8.0 **20.** 6.5 **21.** 6.0 **22.** 5.1 **23.** 1.7 **24.** 0.3 **25.** 0.6 **26.** 0.3 **27.** 0.3 **28.** 0.3 **29.** 0.3 **30.** 0.3 **31.** 0.3 **32.** 0.3 **33.** 0.3 **34.** 2.8

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			cholecystectomy **32.** Adenoidal hypertrophy **33.** Aseptic meningitis **34.** Electrocardiogram abnormalities		
	C: placebo + diet + exercise + behavioural therapy	181	**1.** Fatty/oily stool **2.** Oily spotting **3.** Oily evacuation **4.** Abdominal pain **5.** Fecal urgency **6.** Flatus with discharge **7.** Soft stool **8.** Nausea **9.** Increased defecation **10.** Flatulence **11.** Fecal incontinence **12.** Headache **13.** Upper respiratory tract infection **14.** Nasopharyngitis **15.** Sore throat **16.** Sinusitis **17.** Joint sprain **18.** Nasal congestion **19.** Back pain **20.** Gastroenteritis **21.** Seasonal rhinitis **22.** Limb injury **23.** Acute demyelinating encephalomyelitis **24.** Facial palsy **25.** Pneumonia **26.** Worsening of asthma **27.** Pain in the right side **28.** Electrocardiogram abnormalities	**1.**15 **2.** 7 **3.** 3 **4.** 20 **5.** 20 **6.** 5 **7.** 19 **8.** 23 **9.** 16 **10.** 8 **11.** 1 **12.** 56 **13.** 48 **14.** 46 **15.** 29 **16.** 19 **17.** 17 **18.** 11 **19.** 11 **20.** 8 **21.** 9 **22.** 5 **23.** 1 **24.** 1 **25.** 1 **26.** 1 **27.** 1 **28.** 1	**1.** 8.3 **2.** 3.9 **3.** 1.7 **4.** 11.0 **5.** 11.0 **6.** 2.8 **7.** 10.5 **8.** 12.7 **9.** 8.8 **10.** 4.4 **11.** 0.6 **12.** 30.9 **13.** 26.5 **14.** 25.4 **15.** 16.0 **16.** 10.5 **17.** 9.4 **18.** 6.1 **19.** 6.1 **20.** 4.4 **21.** 5.0 **22.** 2.8 **23.** 0.6 **24.** 0.6 **25.** 0.6 **26.** 0.6 **27.** 0.6 **28.** 0.6

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Clarson 2009	I: metformin + lifestyle intervention	14	-	-	-
	C: lifestyle intervention only	17	-	-	-
Franco 2014	I: sibutramine + dietary guidance	63	**1.** Anorexia **2.** Dry mouth **3.** Headache **4.** Constipation **5.** Changing the mood **6.** Dyspnoea **7.** Epigastralgia **8.** Hypertension **9.** Insomnia **10.** Nausea **11.** Tachycardia **12.** Dizziness **13.** Tremors **14.** Vomiting	-	**1.** 0.9 **2.** 1.7 **3.** 6.8 **4.** 3.8 **5.** 1.3 **6.** 0.4 **7.** 0.9 **8.** 0.9 **9.** 1.3 **10.** 2.1 **11.** 1.3 **12.** 3.4 **13.** 0.4 **14.** 0.4
	C: placebo + dietary guidance	63	**1.** Change in taste **2.** Headache **3.** Diarrhoea **4.** Hypertension **5.** Irritability **6.** Tachycardia **7.** Dizziness	-	**1.** 0.9 **2.** 3.3 **3.** 2.8 **4.** 0.5 **5.** 1.4 **6.** 0.5 **7.** 0.9
Freemark 2001	I: metformin	15	**1.** Transient abdominal discomfort or diarrhoea **2.** Intermittent nausea	**1.** 3 **2.** 1	**1.** 20 **2.** 6.7
	C: placebo	17	**1.** Transient abdominal discomfort or diarrhoea	**1.** 1	**1.** 5.9
Garcia-Morales 2006	I: sibutramine + diet + exercise	23	**1.** Headache **2.** Dry mouth **3.** Headache with nausea **4.** Headache with weakness **5.** High DBP **6.** High heart rate	**1.** 1 **2.** 1 **3.** 1 **4.** 1 **5.** 1 **6.** 3 **7.** 2 **8.** 2	**1.** 4.3 **2.** 4.3 **3.** 4.3 **4.** 4.3 **5.** 4.3 **6.** 13.0 **7.** 8.7 **8.** 8.7

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			7. High blood pressure (baseline) **8.** High blood pressure (end of trial)		
	C: placebo + diet + exercise	23	**1.** Headache **2.** Headache with somnolence **3.** Headache with dry mouth **4.** High DBP **5.** High heart rate **6.** High blood pressure (baseline) **7.** High blood pressure (end of trial)	**1.** 2 **2.** 1 **3.** 1 **4.** 2 **5.** 2 **6.** 7 **7.** 2	**1.** 8.7 **2.** 4.3 **3.** 4.3 **4.** 8.7 **5.** 8.7 **6.** 30.4 **7.** 8.7
Godoy-Matos 2005	I: sibutramine + hypocaloric diet + exercise	30	**1.** Dry mouth **2.** Headache **3.** Constipation **4.** Abdominal pain **5.** Cold **6.** Dizzy **7.** Tonsillitis **8.** Menstrual cramp **9.** Nausea **10.** Toothache **11.** Otitis **12.** Hair loss **13.** Rhinitis **14.** Sinusitis **15.** Sleepiness **16.** Dry cough **17.** Myalgia **18.** Viral infection **19.** Lumbago	**1.** 7 **2.** 13 **3.** 12 **4.** 3 **5.** 9 **6.** 3 **7.** 2 **8.** 8 **9.** 3 **10.** 3 **11.** 3 **12.** 2 **13.** 1 **14.** 1 **15.** 1 **16.** 1 **17.** 1 **18.** 2 **19.** 2	**1.** 23.3 **2.** 43.3 **3.** 40.0 **4.** 10.0 **5.** 30.0 **6.** 10.0 **7.** 6.7 **8.** 26.7 **9.** 10.0 **10.** 10.0 **11.** 10.0 **12.** 6.7 **13.** 3.3 **14.** 3.3 **15.** 3.3 **16.** 3.3 **17.** 3.3 **18.** 6.7 **19.** 6.7
	C: placebo + hypocaloric diet + exercise	30	**1.** Dry mouth **2.** Headache **3.** Constipation **4.** Abdominal pain **5.** Cold **6.** Dizzy **7.** Tonsillitis **8.** Menstrual cramp **9.** Nausea **10.** Toothache **11.** Otitis	**1.** 3 **2.** 21 **3.** 4 **4.** 4 **5.** 11 **6.** 2 **7.** 2 **8.** 6 **9.** 1 **10.** 1 **11.** 1	**1.** 10.0 **2.** 70.0 **3.** 13.3 **4.** 13.3 **5.** 36.7 **6.** 6.7 **7.** 6.7 **8.** 20.0 **9.** 3.3 **10.** 3.3 **11.** 3.3

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			12. Hair loss **13.** Rhinitis **14.** Sinusitis **15.** Sleepiness **16.** Dry cough **17.** Myalgia **18.** Bronchitis **19.** Inguinal dermatitis **20.** Fever	**12.** 1 **13.** 2 **14.** 2 **15.** 2 **16.** 2 **17.** 2 **18.** 2 **19.** 2 **20.** 2	**12.** 3.3 **13.** 6.7 **14.** 6.7 **15.** 6.7 **16.** 6.7 **17.** 6.7 **18.** 6.7 **19.** 6.7 **20.** 6.7
Kendall 2013	I: metformin + healthy lifestyle advice	74	-	-	-
	C: control + healthy lifestyle advice	77	-	-	-
Maahs 2006	I: orlistat + diet and exercise therapy	20	-	-	-
	C: placebo + diet and exercise therapy	20	-	-	-
	All:	40	**1.** Soft stools **2.** Oily spotting **3.** Fatty or oily stools **4.** Oily evacuation **5.** Liquid stools **6.** Cramping **7.** Flatus with discharge **8.** Fecal incontinence	-	-
Mauras 2012	I: metformin + diet/exercise intervention	35	-	-	-
	C: diet/exercise intervention	31	-	-	-
NCT00001723	I: orlistat + behavioural weight loss programme	100	**1.** Hypoglycaemia **2.** Left lower quadrant pain and vomiting **3.** Ear disorders (otitis, earache, ear pain) **4.** Eye dis-	**1.** 0 **2.** 0 **3.** 7 **4.** 8 **5.**16 **6.** 18 **7.** 6 **8.** 1	**1.** 0 **2.** 0 **3.** 7 **4.** 8 **5.**16 **6.** 18 **7.** 6

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			orders (change in vision, conjunctivitis, styes) **5.** Abdominal pain or cramping **6.** Bloating or gas **7.** Borborygmi **8.** Constipation **9.** Controlled discharge of oil without stool **10.** Decreased frequency of bowel movements **11.** Diarrhoea **12.** Fatty-appearing stools **13.** Flatulence (passage of gas) **14.** Flatus with discharge **15.** Frequent urge for bowel movement **16.** Hiccups **17.** Increased frequency of bowel movements **18.** Nausea **19.** Oily spotting **20.** Rectal bleeding - haemorrhoids **21.** Soft or deliquescent stools **22.** Stomach pain or cramps **23.** Stools almost all liquid with very few solid parts **24.** Stools hard and in the shape of small pellets **25.** Stools mixed with fat or with a separate oily layer **26.** Uncontrolled passage of stool or	**9.** 56 **10.** 25 **11.** 21 **12.** 61 **13.** 60 **14.** 43 **15.** 19 **16.** 1 **17.** 68 **18.** 10 **19.** 6 **20.** 4 **21.** 68 **22.** 8 **23.** 64 **24.** 11 **25.** 83 **26.** 60 **27.** 44 **28.** 7 **29.** 4 **30.** 5 **31.** 5 **32.** 14 **33.** 3 **34.** 5 **35.** 2 **36.** 1 **37.** 6 **38.** 1 **39.** 11 **40.** 16 **41.** 3 **42.** 1 **43.** 1 **44.** 0 **45.** 5 **46.** 0 **47.** 14 **48.** 5	**8.** 1 **9.** 56 **10.** 25 **11.** 21 **12.** 61 **13.** 60 **14.** 43 **15.** 19 **16.** 1 **17.** 68 **18.** 10 **19.** 6 **20.** 4 **21.** 68 **22.** 8 **23.** 64 **24.** 11 **25.** 83 **26.** 60 **27.** 44 **28.** 7 **29.** 4 **30.** 5 **31.** 5 **32.** 14 **33.** 3 **34.** 5 **35.** 2 **36.** 1 **37.** 6 **38.** 1 **39.** 11 **40.** 16 **41.** 3 **42.** 1 **43.** 1 **44.** 0 **45.** 5 **46.** 0 **47.** 14 **48.** 5

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			oil **27.** Urgent, but controlled, need to produce stools **28.** Vomiting **29.** Dizziness **30.** Epistaxis **31.** Feeling cold **32.** Headache **33.** Increased sweating **34.** Increased thirst **35.** Sinusitis, postnasal drip or nasal stuffiness **36.** Unusual tiredness or weakness (fatigue) **37.** Pharyngitis **38.** Sinusitis, postnasal drip or nasal stuffiness **39.** Decrease in appetite **40.** Muscle pain, stiffness, cramps or ache **41.** Migraine headaches **42.** Mental depression **43.** Dysuria or UTI **44.** Nocturia **45.** Asthma symptoms **46.** Cough **47.** Upper respiratory infection **48.** Skin rash		
	C: placebo + behavioural weight loss programme	100	**1.** Hypoglycaemia **2.** Left lower quadrant pain and vomiting **3.** Ear disorders (otitis, earache, ear pain) **4.** Eye dis-	**1.** 1 **2.** 1 **3.** 7 **4.** 9 **5.** 21 **6.** 5 **7.** 2 **8.** 7	**1.** 1 **2.** 1 **3.** 7 **4.** 9 **5.** 21 **6.** 5 **7.** 2 **8.** 7

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			orders (change in vision, conjunctivitis, styes) **5.** Abdominal pain or cramping **6.** Bloating or gas **7.** Borborygmi **8.** Constipation **9.** Controlled discharge of oil without stool **10.** Decreased frequency of bowel movements **11.** Diarrhoea **12.** Fatty-appearing stools **13.** Flatulence (passage of gas) **14.** Flatus with discharge **15.** Frequent urge for bowel movement **16.** Hiccups **17.** Increased frequency of bowel movements **18.** Nausea **19.** Oily spotting **20.** Rectal bleeding - haemorrhoids **21.** Soft or deliquescent stools **22.** Stomach pain or cramps **23.** Stools almost all liquid with very few solid parts **24.** Stools hard and in the shape of small pellets **25.** Stools mixed with fat or with a separate oily layer **26.** Uncontrolled passage of stool or	**9.** 11 **10.** 22 **11.** 8 **12.** 6 **13.** 47 **14.** 11 **15.** 3 **16.** 3 **17.** 45 **18.** 9 **19.** 0 **20.** 2 **21.** 42 **22.** 9 **23.** 34 **24.** 10 **25.** 18 **26.** 11 **27.** 18 **28.** 7 **29.** 4 **30.** 2 **31.**2 **32.** 17 **33.** 4 **34.** 4 **35.** 5 **36.** 5 **37.** 12 **38.** 3 **39.** 9 **40.** 12 **41.** 0 **42.** 3 **43.** 5 **44.** 3 **45.** 3 **46.** 7 **47.** 17 **48.** 2	**9.** 11 **10.** 22 **11.** 8 **12.** 6 **13.** 47 **14.** 11 **15.** 3 **16.** 3 **17.** 45 **18.** 9 **19.** 0 **20.** 2 **21.** 42 **22.** 9 **23.** 34 **24.** 10 **25.** 18 **26.** 11 **27.** 18 **28.** 7 **29.** 4 **30.** 2 **31.**2 **32.** 17 **33.** 4 **34.** 4 **35.** 5 **36.** 5 **37.** 12 **38.** 3 **39.** 9 **40.** 12 **41.** 0 **42.** 3 **43.** 5 **44.** 3 **45.** 3 **46.** 7 **47.** 17 **48.** 2

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			oil **27.** Urgent, but controlled, need to produce stools **28.** Vomiting **29.** Dizziness **30.** Epistaxis **31.** Feeling cold **32.** Headache **33.** Increased sweating **34.** Increased thirst **35.** Sinusitis, postnasal drip or nasal stuffiness **36.** Unusual tiredness or weakness (fatigue) **37.** Pharyngitis **38.** Sinusitis, postnasal drip or nasal stuffiness **39.** Decrease in appetite **40.** Muscle pain, stiffness, cramps, or ache **41.** Migraine headaches **42.** Mental depression **43.** Dysuria or UTI **44.** Nocturia **45.** Asthma symptoms **46.** Cough **47.** Upper respiratory infection **48.** Skin rash		
Ozkan 2004	I: conventional treatment + orlistat	22	**1.** Frequent stools **2.** Soiling, frequent defecation **3.** Mild hair loss **4.** Reported muscle cramps	**1.** 22 **2.** 5 **3.** 1 **4.** 1	**1.** 100 **2.** 22.7 **3.** 4.5 **4.** 4.5
	C: conventional treatment	20	-	-	-

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Prado 2012	I: metformin + nutritional guide and exercise programme	10	**1.** Increase levels of ALT **2.** Increase levels of AST **3.** Reduction in haemoglobin	-	-
	C: placebo + nutritional guide and exercise programme	9	**1.** Increase levels of ALT **2.** Increase levels of AST **3.** Reduction in haemoglobin	-	-
Rezvanian 2010	I1: metformin + healthy eating and physical activity advice	45	**1.** Headache **2.** Abdominal pain **3.** Loose stool	**1.** 2 **2.** 2 **3.** 3	**1.** 4.4 **2.** 4.4 **3.** 6.6
	I2: fluoxetine + healthy eating and physical activity advice	45	**1.** Dry mouth **2.** Loose stool	**1.** 3 **2.** 2	**1.** 6.6 **2.** 4.4
	I3: metformin and fluoxetine + healthy eating and physical activity advice	45	-	-	-
	C: placebo + healthy eating and physical activity advice	45	-	-	-
Srinivasan 2006	I: metformin first then placebo + "standardised information on healthy eating and exercise"	13	-	-	-
	C: placebo first then metformin + "standardised information on healthy eating and exercise"	15	-	-	-
Van Mil 2007	I: sibutramine + energy-restricted diet and exercise plan	12	**1.** Clinical depression **2.** Flu syndrome **3.** Headache	**1.** 1 **2.** 6 **3.** 2 **4.** 7	**1.** 8.3 **2.** 50 **3.** 16.6

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			4. Abdominal complaints **5.** Agitation **6.** Increased appetite **7.** Rash **8.** Dizziness **9.** Dysmenorrhoea **10.** Joint problem **11.** Heart rate > 100 bpm on 2 occasions **12.** DBP > 85 mmHg on 2 occasions	**5.** 3 **6.** 4 **7.** 2 **8.** 3 **9.** 3 **10.** 2 **11.** 4 **12.** 1	**4.** 58.3 **5.** 25 **6.** 33.3 **7.** 16.6 **8.** 25 **9.** 25 **10.** 16.6 **11.** 33.3 **12.** 8.3
	C: placebo + energy-restricted diet and exercise plan	12	**1.** Flu syndrome **2.** Headache **3.** Agitation **4.** Increased appetite **5.** Dizziness **6.** Joint problem **7.** DBP > 85 mmHg on 2 occasions	**1.** 6 **2.** 3 **3.** 1 **4.** 2 **5.** 1 **6.** 2 **7.** 1	**1.** 50 **2.** 25 **3.** 8.3 **4.** 16.6 **5.** 8.3 **6.** 16.6 **7.** 8.3
Wiegand 2010	I: metformin + multiprofessional lifestyle intervention	36	**1.** Gastrointestinal symptoms **2.** Unspecific (e.g. weakness or fatigue)	**1.** 5 **2.** 3	**1.** 13.9 **2.** 8.3
	C: placebo + multiprofessional lifestyle intervention	34	**1.** Gastrointestinal symptoms **2.** Unspecific (e.g. weakness or fatigue)	**1.** 9 **2.** 4	**1.** 26.5 **2.** 11.8
Wilson 2010	I: metformin + lifestyle intervention	38	**1.** Headache **2.** Nausea **3.** Vomiting **4.** Upper respiratory tract infection **5.** Musculoskeletal complaints **6.** Elevated ALT levels **7.** Appendectomy **8.** Leg vein thrombosis	**1.** 18 **2.** 9 **3.** 6 **4.** 18 **5.** 5 **6.** 2 **7.** 1 **8.** 1	**1.** 47 **2.** 24 **3.** 16 **4.** 47 **5.** 13 **6.** 5 **7.** 3 **8.** 3

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	C: placebo + lifestyle intervention	38	**1.** Headache **2.** Nausea **3.** Vomiting **4.** Upper respiratory tract infection **5.** Musculoskeletal complaints **6.** Elevated ALT levels	**1.** 13 **2.** 3 **3.** 1 **4.** 23 **5.** 7 **6.** 1	**1.** 34 **2.** 8 **3.** 3 **4.** 61 **5.** 18 **6.** 3
Yanovski 2011	I: metformin + dietitian-administered weight-reduction programme	53	**1.** Liquid or loose stools **2.** Vomiting **3.** Fatigue **4.** Lost interest in usual pleasurable activities	**1.** 22 **2.** 22 **3.** 20 **4.** 1	**1.** 41.5 **2.** 41.5 **3.** 37.7 **4.** 1.9
	C: placebo + dietitian-administered weight-reduction programme	47	**1.** Liquid or loose stools **2.** Vomiting **3.** Fatigue	**1.** 8 **2.** 10 **3.** 7	**1.** 17 **2.** 21.3 **3.** 14.9

*Berkowitz 2003: these adverse events occurred during the open-label phase where all participants received sibutramine
ALT: alanine transaminase; AST: aspartate transaminase; bpm: beats per minute; DBP: diastolic blood pressure; n: number of participants; UTI: urinary tract infection

Appendix 12. Survey of authors providing information on included trials

Trial	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Atabek 2008	24 January 2014 15 May 2014	No	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details about the trial including funding, allocation concealment, randomisation method, dropout rates and adverse events	N/A

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Berkowitz 2003	20 January 2014 15 May 2014	No	20 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details about the trial including randomisation method, allocation concealment and adverse events	N/A
Berkowitz 2006	20 January 2014 15 May 2014	No	20 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial's adverse events	N/A
Chanoine 2005	20 January 2014 25 March 2014 15 May 2014	20 January 2014 25 March 2014 15 May 2014 03/06/2014	20 January 2014 - asked for additional unpublished data and other ongoing trials 25 March 2014 - asked for raw BMI and SD values at 6 months' follow-up 15 May 2014 - asked for further details about the trial including blinding and adverse events	20 January 2014 - author replied with confirmation the data of the trial was correct and attached an addition paper for the trial 25 March 2014 - author provided the raw data at 6 months 15 May 2014 - provided further details on blinding 3 June 2014 - gave additional results on adverse events
Clarson 2009	24 January 2014 15 May 2014	31 January 2014 19 May 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details about the trial including allocation concealment, blinding and adverse events	31 January 2014 - author confirmed there was no further data for the trial and provided a protocol for an ongoing trial 19 May 2014 - author provided further details about the trial
Franco 2014	24 February 2015	9 March 2015	24 February 2015	9 March 2015 - authors replied with further details on the trial such as funding source, ran-

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				domisation method and blinding
Freemark 2001	20 January 2014 25 March 2014 15 May 2014	16 May 2014	20 January 2014 - asked for additional unpublished data and other ongoing trials 25 March 2014 - asked for BMI raw data and associated SDs 15 May 2014 - asked for further details about the trial including allocation concealment, blinding and adverse events	16 May 2014 - author provided further details about the trial
Garcia-Morales 2006	21 January 2014 15 May 2014	No	21 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details about the trial including the run-in period, blinding and adverse events	N/A
Godoy-Matos 2005	20 January 2014 15 April 2014	17 May 2014	20 January 2014 - asked for additional unpublished data and other ongoing trials 15 April 2014 - asked for further details about the trial including allocation concealment, randomisation method, blinding and adverse events	17 May 2014 - author provided further details about the trial
Kendall 2013	24 January 2014 15 May 2014	29 January 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details about the trial including blinding and adverse events	29 January 2014 - author confirmed no additional data were available for the trial Author did not reply to the follow-up email (15 May 2014)
Maahs 2006	20 January 2014 09 May 2014 15 May 2014	20 January 2014 09 May 2014 15 May 2014	20 January 2014 - asked for additional unpublished data and other on-	20 January 2014 - author confirmed no further data were available

(*Continued*)

			going trials 09 May 2014 - asked to confirmed if the data presented were SDs or SEs 15 May 2014 - asked for further details on the trial's adverse events	for the trial 09 May 2014 - author confirmed the data were SDs 15 May 2014 - author could not provide further information on the adverse events
Mauras 2012	24 January 2014 15 May 2014 16 May 2014	15 May 2014 27 May 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including allocation concealment, randomisation method, number of trial centres, blinding and adverse events 16 May 2014 - asked for further information on adverse events	15 May 2014 - author provided further details on the trial 27 May 2014 - author said she would try to obtain the data; however, we received no further emails
NCT00001723	30 October 2015	30 October 2015	30 October 2015 - asked for further details on the trial: blinding, allocation concealment, randomisation process, funding, publications and lifestyle programme	30 October 2015 - author replied and gave further details
Ozkan 2004	No - was unable to send emails to the address given in the publication	N/A	N/A	N/A
Prado 2012	17 January 2014 24 January 2014 15 May 2014	28 January 2014 18 May 2014	17 January 2014 - asked for raw BMI data 24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including blinding, allocation concealment and adverse events	28 January 2014 - author was unable to provide any unpublished data 18 May 2014 - author provided further information about the trial

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Rezvanian 2010	24 January 2014 15 May 2014	24 January 2014 15 May 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including allocation concealment and adverse events	24 January 2014 - author confirmed there were no further details to give on the trial and provided references to other potentially relevant trials 15 May 2014 - author provided further details about the trial
Srinivasan 2006	20 January 2014 15 May 2014	15 May 2014	20 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including allocation concealment and adverse events	15 May 2014 - author provided further details about the trial
Van Mil 2007	20 January 2014 15 May 2014	20 January 2014 30 May 2014	20 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including randomisation, blinding and adverse events	20 January 2014 - author confirmed findings were correct and highlighted the main finding of their trial 30 May 2014 - author provided further details about the trial
Wiegand 2010	24 January 2014 15/04/2014	27 January 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including allocation concealment, randomisation, blinding and adverse events	27 January 2014 - author confirmed there was no further data available for the trial Author did not reply to the follow-up email
Wilson 2010	24 January 2014 15 May 2014	24 January 2014 15 May 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial including dropouts and adverse events	24 January 2014 - author confirmed there was no unpublished data on the main outcomes of the trial 15 May 2014 - author said he would try to obtain the data; however, I

(*Continued*)

				did not receive any further emails
Yanovski 2011	24 January 2014 15 May 2014	24 January 2014	24 January 2014 - asked for additional unpublished data and other ongoing trials 15 May 2014 - asked for further details on the trial's adverse events	24 January 2014 - author confirmed the trial was over and there is no further information available Author did not reply to the follow-up email

BMI: body mass index; N/A: not applicable; SD: standard deviation; SE: standard error

Appendix 13. Checklist to aid consistency and reproducibility of GRADE assessments

Questions		**BMI**	**Weight**	**Adverse events (serious adverse events / adverse events causing discontinuation of trial)**	**Health-related quality of life**	**All-cause mortality**	**Morbidity**	**Socioeconomic effects**
Trial limitations (risk of bias)[a]	1. Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	Yes / Yes	N/A	N/A	N/A	N/A
	2. Was allocation concealment used (i.e. no potential for selection bias)?	Yes	Yes	Yes / Yes				
	3. Was there blinding of participants and person-	Yes	Yes	Yes / Yes				

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	nel (i.e. no potential for performance bias)?							
	4. Was there blinding of outcome assessment (i.e. no potential for detection bias)?	Yes	Yes	Yes / Yes				
	5. Was an objective outcome used?	Yes	Yes	Yes / Yes				
	6. Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	Yes	Yes / No ()				
	7. Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes	No () / No ()				
	8. No other biases reported (i.e. no potential of other bias)?	No ()	No ()	Unclear / Unclear				

(*Continued*)

	9. Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes / Yes				
Inconsistency[b]	1. Point estimates did not vary widely?	Yes	Yes	Yes / Yes				
	2. To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	Some	Some	Substantial / Substantial				

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	3. Was the direction of effect consistent?	No ()	No ()	No () / No ()				
	4. What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 = 40% to 60%), high (I^2 > 60%)?	High ()	High ()	Low / Low				
	5. Was the test for heterogeneity statistically significant (P < 0.1)?	Statistically significant ()	Statistically significant ()	Not statistically significant / Not statistically significant				
Indirectness[a]	1. Were the populations in included studies applicable to the decision context?	Applicable	Applicable	Applicable / Applicable				
	2. Were the interventions in the included studies applicable to the decision context?	Applicable	Applicable	Applicable / Applicable				
	3. Was the included outcome not a surrogate outcome?	Yes	Yes	Yes / Yes				

(*Continued*)

	4. Was the outcome time frame sufficient?	Sufficient	Sufficient	Sufficient / Sufficient				
	5. Were the conclusions based on direct comparisons?	Yes	Yes	Yes / Yes				
Imprecision[c]	1. Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	Yes	No () / No ()				
	2. What is the magnitude of the median sample size (high: > 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	Low ()	Low ()	Intermediate / Low ()				
	3. What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Large	Large	Moderate / Moderate				

(*Continued*)

	4. Was the outcome a common event (e.g. occurs more than 1/100) ?	N/A	N/A	Yes / Yes				
Publication bias[d]	1. Was a comprehensive search conducted?	Yes	Yes	Yes / Yes				
	2. Was grey literature searched?	No ()	No ()	No () / No ()				
	3. Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes / Yes				
	4. There was no industry influence on studies included in the review?	No ()	No ()	No () / No ()				
	5. There was no evidence of funnel plot asymmetry?	No ()	No ()	Unclear / Unclear				
	6. There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear / Unclear				

(*Continued*)

[a] Questions on risk of bias are answered in relation to most of the aggregated evidence in the meta-analysis rather than to individual studies.
[b] Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2 statistic.
[c] When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful.
[d] Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials.
[e] Depends on the context of the systematic review area.
(): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table
BMI: body mass index; N/A: not applicable.

Appendix 14. Health-related quality of life: instruments

Instrument
Short-Form health survey (SF-36, generic questionnaire) - employed in García-Morales 2006.
Brief Symptom Inventory (BSI, generic questionnaire), parent and children's KINDL (generic questionnaire), Impact of Weight on Quality of Life - Kids (IWQOL-Kids, specific questionnaire) and global ratings scale - all employed in Maahs 2006.

WHAT'S NEW

Last assessed as up-to-date: 15 March 2016.

Date	Event	Description
1 September 2016	New citation required and conclusions have changed	Given the rapid growth in the treatment of child and adolescent obesity, we have split the original review ('Interventions for treating obesity in children and adolescents') into six separate reviews, with a specific intervention and age focus (1) Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in adolescents aged 12 to 17 years. (2) Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in schoolchildren from the age of 6 to 11 years. (3) Diet, physical activity, and behavioural interventions for the treatment of overweight or obesity in

(*Continued*)

		preschool children up to the age of 6 years. (4) Drug interventions for the treatment of obesity in children and adolescents. (5) Parent-only interventions for childhood overweight or obesity in children aged 5 to 11 years. (6) Surgery for the treatment of obesity in children and adolescents
1 September 2016	New search has been performed	This is an update of the former Cochrane review 'Interventions for treating obesity in children and adolescents'

CONTRIBUTIONS OF AUTHORS

EM: search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

GA: data extraction, data analysis, data interpretation, review draft and future review updates.

BR: data analysis, data interpretation and review draft

MIM: search strategy development and review draft.

LB: data extraction, data interpretation, review draft and future review updates.

NF: data extraction, data interpretation, review draft and future review updates.

EC: data extraction, data interpretation, review draft and future review updates.

CO: acquiring trial reports, trial selection, data extraction, data interpretation, review draft and future review updates.

LE: search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

DECLARATIONS OF INTEREST

EM: none known.

GA: none known.

BR: none known.

MIM: none known.

LB: none known.

NF: has provided medical consultancy to several pharmaceutical companies developing and marketing (outside of the UK at present) treatments for obesity. Since March 2016 he is employed by Novo Nordisk, Denmark in Global Medical Affairs.

EC: none known.

CO: none known.

LE: none known.

SOURCES OF SUPPORT

Internal sources

- University Medical Center, Groningen, Netherlands.
- The Children's Hospital at Westmead, Sydney, Australia.
- Centre for Food Physical Activity and Obesity Research, University of Teesside, UK.
- The Wolfson Research Institute, University of Durham, UK.
- Australian National Health & Medical Research Council, Australia.

Postgraduate Research Scholarship for Ms Shrewsbury

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the rapid growth in the treatment of child and adolescent obesity, the original review has now been split into six separate reviews, with a specific intervention and age focus. Whilst the other reviews in this series utilised an updated version of the original search strategy, we developed a new search strategy (see Appendix 1) to reflect advances in pharmacological therapies that may not have been adequately captured in the original search strategy. We decided to exclude trials which included growth hormone therapies to avoid including trials which treated conditions such as Cushing's syndrome. In addition, some subgroup analyses were not possible due to a limited number of trials.

We included only randomised controlled trials that were specifically designed to treat obesity in children and observed participants for a minimum of six months. The rationale for introducing this criterion arose from the belief that many interventions appear to be effective in the short term (up to three months), but not in the long term (Glenny 1997). It seemed to be more important to evaluate the longer-term effects of treatments, as this would provide a more valuable indication of effectiveness, given the chronic nature of obesity.

NOTES

Portions of the methods sections, the appendices, additional tables and figures 1 to 3 of this review are based on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.