Treatment of Overweight/Obesity in Adult Populations: A Systematic Review with Meta-analyses

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Abstract

Background: This report will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to provide guidelines on the treatment of overweight and obesity in adults. The last CTFPHC guideline on the prevention of obesity was conducted in 2006 and published in 2007, while obesity screening was last examined in 1994.

Purpose: To synthesize evidence on behavioural and pharmacological plus behavioural interventions for treating overweight and obesity in adults.

Data Sources: We searched Medline, Cochrane Central Register of Controlled Trials, PsycINFO and EMBASE from September 2010 to April 19, 2013 to update the search conducted for the United States Preventive Services Task Force (USPSTF) 2011 review on this same topic. We also searched for evidence to answer the contextual questions, checked reference lists of included studies and relevant systematic reviews, and conducted a targeted grey literature search.

Study Selection: The titles and abstracts of papers considered for the key question and sub-questions were reviewed in duplicate; any article marked for inclusion by either team member went on to full text screening. Full text review was done independently by two people with consensus required for inclusion or exclusion. For treatment benefits we included randomized controlled trials of behavioural and/or pharmacological (orlistat or metformin) interventions for overweight and obese adults that reported data for at least one weight outcome of interest at a minimum 12 months post baseline assessment. All studies reporting adverse effects of treatments were included, regardless of design, timeframe or outcomes.

Data Abstraction: Review team members extracted data about the population, study design, intervention, analysis and results for outcomes of interest. One team member completed full abstraction, followed by a second team member who verified all extracted data and ratings. We assessed study quality using Cochrane's Risk of Bias tool and the GRADE framework. For the contextual questions, inclusion screening and abstraction were done by one person.

Results: A total of 68 studies were included in this systematic review (39 of behavioural interventions, 27 of pharmacological plus behavioural interventions, and 2 studies with both treatment arms). Thirty-six studies in the 2011 USPSTF review met the inclusion criteria of this review. Using the GRADE system the bodies of evidence used to answer the key question and sub-questions were mostly rated as moderate or low quality. Downgrading occurred primarily as a result of study limitations increasing the risk of bias and concerns regarding reporting bias. No studies on the merits of screening for obesity were identified.

In pooled analyses, intervention participants had significantly greater weight loss [MD (95% CI) -3.02 kg (-3.52, -2.52); I^2=91%], significantly greater waist circumference reduction [MD (95% CI) -2.78 cm (-3.34, -2.22); I^2=91%] and significantly greater reduction in BMI [MD (95% CI) -1.11 kg/m^2 (-1.39, -0.84); I^2=93%], all compared to control participants at the post treatment assessment point. Compared to controls, the RR for weight loss of ≥5% of baseline body weight among intervention participants was 1.77 (95% CI 1.58, 1.99; I^2=69%) with an NNT of 5 (95% CI 4, 7),

and for loss of ≥10% of baseline body weight the RR was 1.91 (95% CI 1.69, 2.16; I^2=16%) with an NNT of 9 (95% CI 7, 12). Behavioural and pharmacological (orlistat or metformin) plus behavioural interventions had similar weight differences. Additional sub-analyses performed on studies reporting weight in kg found only two significant differences; one for type of behavioural intervention (Chi^2=9.32, df=3, P=0.03, I^2=67.8%; exercise programs showed no difference between intervention and control groups while all other types produced significant benefits in favour of the intervention) and the other for behavioural intervention participants' baseline CVD risk status (Chi^2=8.05, df=1 P=0.005, I^2=87.6%; greater weight loss was achieved by participants with low/unknown CVD risk compared to those at high risk). High statistical heterogeneity in most sub-analyses was evident. The long-term sustainability of weight loss benefits could not be assessed.

Pooled effect estimates for all secondary health outcomes showed small but statistically significant benefits in favour of the interventions. At the post intervention point across studies, compared to the control group, intervention participants had reduced their total cholesterol level by an additional 0.21 mmol/L (95% CI -0.29, -0.13; I^2=86%) and their LDL-C level by an additional 0.21 mmol/L (95% CI -0.29, -0.12; I^2=90%), lowered their systolic and diastolic blood pressure by 1.70 mmHg (95% CI -2.23, -1.17; I^2=41%) and 1.42 mmHg more (95% CI -1.88, -0.96; I^2=63%) respectively, and reduced their fasting glucose level by 0.26 mmol/L more (95% CI -0.38, -0.13; I^2=96%). Intervention participants were less likely than controls to be diagnosed with T2D [RR 0.62 (95% CI 0.50, 0.77); I^2=54%; NNT 17 (13, 29)]. There was no evidence that the magnitude of benefits differed for behavioural versus pharmacological plus behavioural interventions on LDL-C, incidence of T2D, or either blood pressure outcome. However, the test for subgroup differences was significant for total cholesterol and fasting glucose levels, with the pharmacological plus behavioural interventions showing greater reductions than behavioural interventions alone. The long-term sustainability of secondary health benefits could not be assessed.

Very few studies of behavioural interventions reported adverse effects, and when they did, the harms were usually injuries associated with physical activity and the number of events was typically quite low. Adverse effects were more commonly experienced by participants in pharmacological plus behavioural studies and were significantly more likely to be reported by those taking the active medications. Compared to control participants, adults who took a 120mg dose of orlistat three times daily had an RR of 1.16 [(95% CI 1.09, 1.23); I^2=75%; NNH 10 (95% CI 7, 17)] for reporting at least one (any) adverse event during the course of the intervention, an RR of 1.58 [(95% CI 1.47, 1.70); I^2=71%; NNH 5 (95% CI 4, 7)] for experiencing at least one gastrointestinal event, and an RR of 1.68 [(95% CI 1.42, 2.00); I^2=15%; NNH 32 (95% CI 22, 47)] for withdrawing from their studies due to adverse events. Only the category of serious adverse events showed no significant difference between those taking the drug and those taking the placebo [RR (95% CI) 1.10 (0.97, 1.25)]. Sub-group analyses found that compared to those with low/unknown CVD risk, pharmacological plus behavioural study participants with high CVD risk at baseline were more likely to report having experienced at least one adverse event and to withdraw from their study due to adverse effects.

Twenty-nine included studies met a point estimate threshold of four kg of weight loss or had a statistically significant effect for loss of ≥5% or ≥10% of baseline body weight. The widely varied interventions in these 29 studies were designated as efficacious. Common features of efficacious behavioural interventions (n=15) included: treatment duration over 12 months, broad or multicomponent scope (lifestyle, diet plus exercise), use of multiple delivery modes (e.g., individual sessions plus technology-based components), and use of weight loss goal setting and self-monitoring. Efficacious pharmacological plus behavioural interventions (n=14) were all more than 12 months in duration and were implemented in conjunction with a diet component; just over half of the studies included a run-in period and in about half of the studies the participants were also encouraged to increase physical activity.

Limitations: Most of the evidence used to answer the key questions was taken from studies that could not reliably be assessed for risk of bias. Potential reporting bias was also identified across a number of outcome/comparison-based study groupings. Using GRADE, the evidence was assessed as moderate and sometimes low quality which reduces confidence in the pooled estimates of effect. Results for secondary health outcomes should be interpreted with caution as our review might have missed trials that reported these outcomes but not our primary weight outcomes. Effect estimates may overestimate adverse events because data were extracted as reported, even when the connection to the intervention was not clear and even if the data included events that occurred during a run-in period. We searched only for papers in English or French.

Conclusion: There is moderate quality evidence that behavioural and pharmacological plus behavioural interventions for treating overweight and obesity in adults lead to clinically important reductions in weight and a substantial reduction in the incidence of T2D. Benefits of drug treatments should be considered in light of significant adverse effects also experienced by those taking these medications.

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Table of Contents

List of Acronyms

ARI	Absolute Risk Increase
ARR	Absolute Risk Reduction
BMI	Body Mass Index
CCHS	Canadian Community Health Survey
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
cm	Centimeters
CQ	Contextual Question(s)
CTFPHC	Canadian Task Force on Preventive Health Care
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DPP	Diabetes Prevention Program
EOSS	Edmonton Obesity Staging System
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IV	Inverse Variance
kg	Kilograms
KQ	Key Question(s)
LDL-C	Low-Density Lipoprotein Cholesterol
MD	Mean Difference
mg/dL	Milligrams per Decilitre
mmol/L	Millimoles per Litre
NNH	Number Needed to Harm
NNT	Number Needed to Treat
RCT	Randomized Controlled Trial
RR	Relative Risk / Risk Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SES	Socioeconomic Status
SIGN	Scottish Intercollegiate Guidelines Network
SQ	Supplemental Questions
T2D	Type 2 Diabetes
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
WC	Waist Circumference
WHO	World Health Organization

Chapter 1: Introduction

Purpose and Background

This review will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to provide guidelines on the treatment of overweight and obesity in adults. The last CTFPHC guideline on the management and prevention of obesity was conducted in 2006 and published in 2007,[1] while obesity screening was last examined in 1994.[2] Since this time, other Canadian and international groups have provided guidance on obesity screening, management and prevention, including the Obesity Canada Clinical Guidelines Expert Panel (2006),[3] the Scottish Intercollegiate Guidelines Network (SIGN) (2010),[4] and the United States Preventive Services Task Force (USPSTF) (2011).[5] The lack of updated Canadian guidelines on this topic, the availability of new evidence and the growing burden of obesity were key reasons why this topic was chosen by the CTFPHC.

Definition

Obesity is characterized by an increase in total body fat and is defined by a body mass index (BMI, measured in kg/m^2) $\geq$30, based on the definition used by the World Health Organization (WHO) and adopted by the Canadian Guidelines for Body Weight Classification in Adults.[6] Canadian adults ($\geq$18 years) with BMIs of 25 to 29.9 are currently considered overweight and at risk of becoming obese, whereas those with BMIs of 18.5 to 24.9 are considered normal weight.[7] Studies used to develop the classification system were mainly based on Caucasians and more recently studies world-wide continue to explore the complex associations between body weight and total mortality, with increasing emphasis on determining key characteristics and metabolic profiles associated with excess total and cause-specific mortality.[8-11] More recent studies have also shown that physically fit obese individuals may not be at increased mortality risk, compared to their lower weight peers.[12] Other lines of work have explored the associations among the metabolically healthy versus unhealthy and mortality.[13,14] In the meantime, the current BMI classification system provides one useful indicator of body composition.

Prevalence and Burden of Obesity

Obesity has become a worldwide issue. According to the WHO report on the global epidemic, an estimated one billion adults are overweight and at least 300 million are clinically obese.[15] Obesity occurs across all ages and ethnic groups, and is associated with socioeconomic status (SES). According to a review by McLaren, the effect of SES differs by the Human Development Index; negative associations (i.e., lower SES associated with larger body size) for women in highly developed countries were most common with education and occupation, while positive associations for women in medium- and low-development countries were most common with income and material possessions.[16] For the first time in history, obesity is more prevalent world-wide than under-nutrition.[17]

In 1980, the prevalence of obesity in Canadian adults was approximately 8%. Since then, the number of obese adults in Canada has tripled.[18] According to results of the 2007-2009 Canadian Health Measures Survey (CHMS), based on measured height and weight the prevalence of obesity in adults was estimated at 24.1%.[19] From 1978/1979 to 2004, the proportion of adults falling into obese Class I (BMI 30 to 34.9 increased from 10.5 to 15.2%, the proportion in Class II (BMI 35.0 to 39.9) doubled from 2.3 to 5.1%, and the proportion in Class III (BMI ≥40) tripled from 0.9 to 2.7%.[16,20] Obesity is more prevalent among men than women; the average BMI was estimated at 27.5 (27 to 28.0) for men and 26.7 (26 to 27.4) for women,[21] however, females are more likely to fall into obese Class II and Class III than males.[21] In Canada, obesity does not appear to be associated with lower SES status, instead it is more prevalent in rural-dwelling adults and among people in Eastern and Northern Canada.[22] Based on the 2008/2009 Canadian Community Health Survey (CCHS) measured data, regional, provincial and territorial variation were observed; obesity varied across provinces and territories, from a low of 12.8% in British Columbia to a high of 25.4% in Labrador. The prevalence of obesity tends to be lower in urban regions and higher in rural areas; obesity ranged from 5.3% in urban/suburban Richmond British Columbia to a high of 35.9% in the Northern Region of Saskatchewan.[16,20] Consistent with these statistics, a recently available report citing data from the CCHS indicated the estimated prevalence of obesity in the Canadian adult population in 2011 was 25.3%.[23]

Etiology, Risk Factors and the Natural History of Obesity

The etiology of weight gain and obesity is multi-faceted, encompassing hereditary, environmental, metabolic, lifestyle, psychological and medical or drug-related conditions (see Table 1). The principal cause of obesity is an imbalance between calories consumed and calories expended; many factors can be responsible for this imbalance. The rapid rise in obesity prevalence since 1980 suggests metabolic, environmental and lifestyle factors are prominent, including an increased intake of energy-dense foods coupled with a decrease in physical activity due to increasing sedentary lifestyles.[21,24,24-27] Metabolic factors include a low baseline metabolic rate, increased carbohydrate oxidation, insulin resistance, and sympathetic activity. However, these factors are not easily measured and are less strongly linked to obesity than are lifestyle factors. Sedentary behaviours, such as prolonged screen time appears to contribute to weight gain.[28] Similarly, among many lifestyle behaviours that predispose people to obesity, sleep deprivation and smoking cessation have also been associated with weight gain.[29,30] Among dietary factors, certain patterns of eating increase the risk for weight gain; these include consuming energy-dense foods, social norms for mealtimes and portion size, fast-food consumption, and frequent snacking, especially during the evening hours.[31] In recent years there has been increasing interest in determining the role of genetic factors in the pathogenesis of obesity. In general, genetic factors are considered to have a role in determining inter-individual variability in body weight. However, in adults with more severe obesity, less than 5% will have recognized obesity-associated mutations such as those that cause leptin (a hormone that affects energy intake and expenditure) deficiency or leptin receptor dysfunction.[25] Obesity can develop at any age but

prevalence is highest in middle age and typically declines in the elderly, partly due to increased mortality and a multi-factorial age-related decline in BMI, with loss of both lean and fat mass.[32]

Health Consequences of Obesity

Some obese adults, especially those who are sedentary and with an adverse metabolic profile or other risk factors are at increased risk for developing major diseases that include type 2 diabetes, coronary artery disease, stroke, depression, and certain cancers (see Table 2)[33-35] and weight loss can reduce the severity or incidence of some conditions, especially diabetes.[36] Obesity can also exacerbate the severity of gastrointestinal, muscular and skeletal conditions or make medical management more difficult. Weight loss with exercise and pain management can improve mobility and functional ability in some cases, but evidence is still limited.[37] It is also estimated that one in 10 premature deaths in adults, aged 20 to 64 years, is directly attributable to overweight and obesity.[38,39] Declines in total mortality after lifestyle interventions for diabetes prevention have not yet been demonstrated.

Once excess weight has been added, it is very difficult for many people to lose body weight, recognizing that there is substantial interplay and variation in individuals' neurological, physiological and behavioural systems. Thus, weight loss as a therapy for increased health risk in the overweight and obese has been controversial. Modest weight loss and increased physical fitness both appear to have modest beneficial effects on health. Weight loss in the range of 5% has often been quoted as being clinically relevant and is a more easily measured clinical indicator than physical fitness in most primary care settings.[40]

Rationale for Screening for Overweight and Obesity

Screening directly for overweight and obesity may help guide clinical practice to improve patients' health.

Potential Benefits of Screening

Screening for overweight and obesity can improve patients' health in three ways:

- In adults found to be obese and who have obesity-related diseases, modest weight loss (5% to 10% of total body weight) has been shown to improve control of such diseases and related symptoms and can reduce drug therapy requirements.[3,41]
- In adults found to be obese but who do not have obesity-related diseases, lifestyle interventions such as starting a regular exercise program can reduce the risk of developing such diseases or can curtail their progression (e.g., prevention of diabetes in adults with impaired glucose tolerance).[3,41]
- In adults found to be overweight but who are otherwise healthy, promoting healthy lifestyle practices may prevent the development of obesity.[3,41]

Screening to Guide Clinical Practice

In clinical practice, an intervention relating to obesity could have two main goals:[3]

- *Prevention of obesity*. Prevention can be considered in individual adults who are overweight and at risk for developing obesity, through interventions aimed at attaining a healthy weight or preventing weight gain.
- *Treatment of obesity*. Treatment interventions can be aimed to achieve weight loss in people who are already obese, thus reducing associated symptoms or burden of comorbidities. An example of this is a weight loss intervention for an obese adult with diabetes that aims to reduce hyperglycemia-related symptoms and reduce the need for glucose-lowering drugs.

Detection of Overweight and Obesity

There are several screening methods for assessing obesity and overweight. Methods include waist to hip and waist to height ratios; however the two main measures used in everyday practice are BMI and waist circumference (WC).

- BMI is strongly correlated with direct measures of body fat, such as magnetic resonance imaging, and is a reliable determinant of adiposity-related health risks in adult men and women.[42]
- WC measures abdominal (or central) body fat, which is strongly correlated with an increased risk for type 2 diabetes (T2D), hypertension, dyslipidemia, and the metabolic syndrome, the latter combining all three former conditions.[42]

Practical Considerations when Using BMI and WC in Clinical Practice

Combining BMI and WC to assess health risk. Although BMI and WC are correlated, WC provides an additional independent estimate of health risk beyond that provided by BMI.[43,44] Considering both BMI and WC may be especially useful in adults with normal BMI as this can identify adults with an abdominal fat distribution who are at increased health risk despite normal BMI.[42]

BMI and WC as part of an overall health risk assessment. The classification schemes for BMI and WC were originally derived based on health risk assessments from large, heterogeneous population studies. Consequently, the value of using BMI and WC only to assess health risk in individual adults is limited. BMI and WC are useful however, as part of an overall risk assessment:

- BMI and WC should be combined with other determinants of individual health risk, which include smoking, concomitant disease, diet, physical activity, and personal and family weight history. However, what may be under-appreciated is the importance of BMI and WC on health risk compared to other, more traditional, risk factors. For example, until recently obesity was considered to increase the risk of coronary artery disease through its association with hypertension, dyslipidemia, and diabetes. However, BMIs ≥30 appear to independently confer an increased risk for coronary artery disease which is comparable to the effect of hypertension.[35] A similar effect also occurs with WC, as adults with increased WC were more likely to develop hypertension, type 2 diabetes and dyslipidemia.
- The Edmonton Obesity Staging System (EOSS)[45] contributes to our ability to assess obesity-related comorbidity. Applied to those with a BMI ≥25, data from interview, exam or

laboratory testing are used to assign a rating of 0 (no apparent comorbidity) to 4 (severe obesity-related comorbidities or functional disability).[45] Using data from the National Health and Nutrition Examination Survey 1999-2004, the scale independently predicts increased mortality.[46]

- Because BMI and WC reflect an individual's risk at a single time point, longitudinal changes in BMI and WC may provide additional information on health risk. For example, an upward trend in BMI and WC in adults with impaired glucose tolerance places such individuals at increased risk for clinically overt T2D.[47] Conversely, a downward trend in BMI and WC with unintentional weight loss may indicate increased health risk due to the development of underlying disease.

Current Clinical Practice: Prevention and Treatment of Obesity

Prevention of Obesity

A variety of individually-focused preventive interventions exist, mostly focusing on healthy living guidelines (e.g., Canada's Food Guide and Physical Activities Guidelines) with recommendations to maintain a healthy weight. There is some information on the use of such interventions in primary care.[48] See recommendation according to 2006 Canadian clinical practice guideline below.[3]

Treatment of Obesity

Many therapeutic interventions aimed at weight loss to treat obesity and obesity-related complications exist and can be broadly categorized by main focus as: dietary, physical exercise, behaviour, psychological, pharmacologic therapy and bariatric surgery. Non-pharmacologic, non-surgical approaches can result in modest three to five kilograms (kg) weight loss.[49] Such losses may have health benefits, but rarely achieve individuals' weight loss goals. The addition of pharmacologic agents adds modestly to such weight loss (e.g., a further reduction of approximately 2.8 to 4.5 kg).[50]

Bariatric surgery, typically with Roux-en-Y gastric bypass, can result in considerable weight loss of 50 to 70 kg but is reserved for adults with severe obesity (BMI >40) or those with less severe obesity (BMI >35) that is associated with significant obesity-related comorbidities.[51] Although bariatric surgery has been shown to be effective in severely obese patients, it is excluded from this review because the CTFPHC Working Group considered populations with extreme BMIs for whom surgery would be indicated to be out of scope; the same exclusion was applied in the 2011 USPSTF review.[5] Pharmacological and behavioural therapies, on the other hand, may be considered in primary care of overweight and obese patients (i.e., not limited to those who are very obese) and as such remain within our scope.

Previous Review and Recommendations

The 2006 CTFPHC guidelines for the management and prevention of obesity made the following recommendations:[1]

- There is insufficient evidence to recommend for or against community-wide cardiovascular disease preventive programs to prevent obesity (I recommendation).
- There is fair evidence to recommend intensive individual and small group counselling for a reduced calorie or low fat diet to prevent obesity (B recommendation).
- There is fair evidence to recommend an intensive individual or structured group program of endurance exercise to prevent obesity (B recommendation).
- There is insufficient evidence to recommend a program of strength training exercise to prevent obesity (I recommendation).
- There is fair evidence to recommend an intensive individual or small group program of a combined low fat/reduced calorie diet and endurance exercise intervention to prevent obesity (B recommendation).
- There is fair evidence to recommend against low intensity interventions employing telephone or mail support, or financial incentives to promote a low fat/reduced calorie diet and endurance exercise as a means to prevent obesity (D recommendation).

The 2011 CTFPHC Adult Obesity Working Group reviewed other relevant guidelines. The Australian[52] and New Zealand[53] guidelines only considered evidence from treatment of overweight and obesity. Neither the Obesity Canada Clinical Guidelines Expert Panel[3] or the National Institute for Health and Care Excellence[54] considered mortality or morbidity outcomes of screening, but both made recommendations about treatment. The review for the SIGN[4] guidelines searched for studies on the effectiveness of screening but found none. The SIGN group also made recommendations for obesity management. The USPSTF conducted a review[5] and released guideline recommending that clinicians screen adults for obesity and offer or refer patients with a BMI $\geq$30 to intensive, multicomponent behavioural interventions (B recommendation).[55]

Chapter 2: Methods

Review Approach

At the outset of the review process the CTFPHC Working Group conceptualized an "ideal approach," considering the analytic framework and key questions for both screening and prevention of obesity in adults that they believed were most important for clinicians. An evidence based analysis on screening and prevention of obesity was planned to address key questions about the effectiveness of screening and preventive efforts for normal weight, overweight or obese adults in primary care on mortality, morbidity, various anthropometric measures of weight reduction or stabilization, costs, and harms. However, our preliminary search found recent reviews by the USPSTF[5] and SIGN[4] that asked similar questions and identified no evidence on screening. To avoid duplication of effort, our protocol was designed as an update of the USPSTF search. We removed the key question related to screening and instead added a series of supplemental questions. These questions were examined through a condensed review process that searched for evidence on screening for obesity published since the 2011 USPSTF review. The USPSTF[5] also examined interventions for preventing obesity in overweight and obese populations.

Based on the acquired knowledge and newly available products, the CTFPHC Working Group adopted a pragmatic approach to select the review questions, focusing on areas which the scoping review indicated there would be sufficient evidence upon which to formulate recommendations. In addition, to avoid duplication of work already completed, the Working Group directed the McMaster Evidence Review and Synthesis Centre team to:

- update the USPSTF search[5] to examine treatment interventions for those who are already overweight and obese, and,
- conduct a de novo review to address the effectiveness of weight gain prevention interventions for those who are currently of normal weight.

The protocol was registered with PROSPERO (#CRD42012002753).

Analytic Framework and Key Questions

The analytic framework, presented in Figure 1, includes both prevention and treatment of adult overweight/obesity. This review focuses only on the aspects related to treatment; a separate review was conducted to examine prevention (available on the CTFPHC website http://canadiantaskforce.ca/).

The key question (KQ) and sub-questions considered for this treatment focused review are:

KQ1. Do primary care relevant treatment interventions (behavioural and/or pharmacotherapy) in overweight/obese adults lead to improved health outcomes, short-term or sustained weight loss, or weight gain prevention, with or without improved physiological measures?

a. Are there differences in efficacy between patient subgroups [e.g., age 65 years or older, sex, baseline cardiovascular disease (CVD) risk status]?

b. What are the adverse effects of primary care relevant treatment interventions in overweight/obese adults [i.e., any adverse events, serious adverse events (requiring hospitalization or urgent medical care), gastrointestinal events, withdrawal from study due to adverse events]?
c. Are there differences in adverse effects between patient subgroups (e.g., age 65 years or older, sex, baseline CVD risk status)?
d. How well is weight loss or health outcomes maintained after an intervention is completed?
e. What are common elements of efficacious interventions?

The contextual questions (CQ) considered for both the prevention and the treatment reviews are:

CQ1. Is there evidence that the burden of disease, the risk/benefit ratio of prevention or treatment, the optimal prevention or treatment method/access, and implementation differ in any ethnic subgroups or by age, rural and remote populations, or lower SES populations?
CQ2. What are the resource implications and cost effectiveness of overweight and obesity prevention/treatment in Canada?
CQ3. What are patients' and practitioners' values and screening preferences regarding overweight and obesity prevention/treatment?
CQ4. What are the most effective (accurate and reliable) risk assessment tools identified in the literature to assess future health risk as a result of obesity?

The supplemental questions (SQ) on obesity screening considered for both the prevention and the treatment reviews are:

SQ1. Is there direct evidence that primary care screening programs for adult overweight or obesity improve health outcomes or result in short-term (12 month) or sustained (>12 month) weight loss or improved physiological measures?
a. How well is weight loss maintained after a screening intervention is completed?
b. What is the most effective method of screening for overweight and obesity in adults in primary care?
c. What is the optimal interval/frequency for screening for overweight and obesity in adults in primary care?
d. What is the most effective type of screening (opportunistic vs. organized/systematic) for overweight and obesity in adults in primary care?
e. What are the harms associated with screening for overweight and obesity in adults in primary care?

Search Strategy

For this review we updated the search conducted for the 2011 USPSTF review.[5] For the key and supplemental questions we searched Medline, Cochrane Central Register of Controlled Trials, PsycINFO and EMBASE from September 2010 (the date of the last USPSTF search) to April 19, 2013, using terms such as *overweight, obesity, diet, exercise, behavioural, counseling, lifestyle, orlistat,* and *metformin*. Reference lists of the included studies of this review and the included studies of other on topic reviews were searched for any relevant studies that were not captured by

our search. A separate search was conducted to look for evidence that would answer the contextual questions; this strategy included three databases (Medline, EMBASE, PsycINFO) and covered the period between January 2007 and August 16, 2013. The full search strategies are provided in Appendix 1. In addition, a focused grey literature search of Canadian sources was undertaken for recent reports on obesity in Canada. All citations were uploaded to a web-based systematic review software program[56] for screening and data extraction.

Study Selection

Titles and abstracts of papers considered for the key question and sub questions were reviewed in duplicate; articles marked for inclusion by either team member went on to full text screening. Full text inclusion was done independently by two people. All disagreements were resolved through discussions rather than relying on a particular level of kappa score to indicate when discussions were no longer necessary. The inclusion results were reviewed by a third person. For papers located in the contextual questions search, title and abstract screening was done by one person.

Inclusion and Exclusion Criteria

Language

The published results of studies had to be available in either English or French.

Populations

Eligible studies included adults ≥18 years of age who were overweight (BMI ≥25) or obese (BMI ≥30), but not morbidly obese (BMI ≥40). Studies were excluded if the mean BMI minus one standard deviation fell below 25 (studies that fell below this threshold were considered for inclusion in the companion review on adult overweight/obesity prevention). The sample populations were unselected, selected for low CVD risk, or selected for increased risk for specified conditions (CVD, hypertension, dyslipidemia, or T2D). Trials limited to participants with CVD were excluded, but trials with some participants with CVD were included. Studies were excluded if they specifically enrolled participants who were pregnant, had an eating disorder, or had a condition for which weight gain is a cardinal manifestation (e.g., metabolic syndrome, polycystic ovarian disease).

Interventions

The focus of the intervention had to be weight loss treatment or management. Interventions considered for inclusion were behavioural and/or pharmacological (orlistat or metformin). Behavioural interventions could include diet, exercise, diet plus exercise, or lifestyle strategies. Lifestyle interventions were typically referred to as such by the study authors and often included counseling, education or support and environmental changes, in addition to diet and/or exercise.

We excluded behavioural interventions that did not focus primarily on weight loss, surgical interventions, primary prevention programs that did not involve a weight loss goal for all participants, and trials focusing on pharmacological agents other than orlistat or metformin.

Settings

Trials were conducted in settings generalizable to Canadian primary care, feasible for conducting in primary care or feasible for referral from primary care. Studies conducted in in-patient hospital settings, institutional settings, school-based programs, occupational settings, faith-based programs, and other settings deemed not generalizable to primary care, such as those with existing social networks among participants or the ability to offer intervention elements that could not be replicated in a health care setting were excluded. Commercial weight loss programs were eligible for inclusion.

Comparator and Study Design

To answer the questions about the benefits of treatment interventions, only randomized controlled trials (RCTs) with true comparison groups were considered for inclusion. More specifically, an acceptable control group could not receive a personalized intervention, at-home workbook materials, and/or advice more frequently than annually, or participate in frequent weigh-ins (<3 months). Provision of healthy lifestyle messages was considered too close to weight loss messages, thus was not considered a valid control group condition. Case reports, case series and chart reviews were excluded.

Any study design (with or without comparison groups) was considered acceptable to answer the questions about adverse events and the contextual questions.

Outcomes

To answer the questions about the benefits of treatment interventions, only studies that reported data for one or more specified weight outcomes were included (i.e., weight change in kg, loss of ≥5% baseline body weight, loss of ≥10% baseline body weight, change in waist circumference, change in BMI). There was no weight outcome requirement if a study reported data for adverse events of interest [i.e., any adverse events, serious adverse events (necessitating hospitalization or urgent medical care), gastrointestinal symptoms, study withdrawal due to adverse events]. Secondary outcomes of interest included: total cholesterol, low density lipoprotein cholesterol (LDL-C), fasting glucose, incidence of type 2 diabetes (T2D), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Timeframe

There was no intervention duration criterion. However, for the questions regarding treatment effectiveness, studies were only included if they provided outcome data for a minimum of 12 months post baseline assessment.

There was no intervention duration requirement or 12 month minimum expectation for outcome measurements in studies that reported adverse events or for inclusion of studies to address the contextual questions.

Data Abstraction

For each study used to answer the KQ, review team members extracted data about the population, study design, intervention, analysis and results for outcomes of interest. For each study one team member completed full abstraction (study characteristics, risk of bias assessment, outcome data) using electronic forms housed in a web-based systematic review software program.[56] A second team member verified all extracted data and ratings; disagreements were resolved through discussion and/or third party consultation when consensus could not be reached. Prior to performing meta-analyses, tables were produced for each outcome and all data were checked in a third round of verification.

Unadjusted immediate post assessment data was extracted for most studies. However, for a small number of studies the immediate post intervention data did not meet our minimum 12 months post baseline assessment criterion; in these cases we extracted data at the point closest to the end of the intervention that was ≥12 months post baseline (e.g., intervention duration six months, follow up six months later). Another small group of studies reported 12 month interim results for longer term interventions. Since there was no condition that interventions must be completed to be included in this review, we extracted this interim data.

To answer the adverse effects KQ we selected the more inclusive option and extracted data for all reported adverse events of interest, regardless of whether they were attributed to study participation. In addition, for the meta-analyses we only included mutually exclusive adverse events data, that is, we selected results that reported the number of participants who experienced at least one event in the respective overall adverse effects category. The results from studies that reported the total number of adverse events experienced across all study group participants are captured only in the narrative results of this review.

Assessing Risk of Bias

Arriving at a Grading of Recommendations Assessment, Development and Evaluation or GRADE rating for a body of evidence (see next section) requires a preliminary assessment of the risk of bias or study limitations for the individual studies. The two observational studies with no control groups that were included to help answer the adverse effects KQ (narrative results only) were not assessed for methodological quality.[57,58] However, all RCTs included to answer the KQ of this review were assessed using the Cochrane Risk of Bias tool.[59]

This rating tool covers six domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome reporting; selective outcome reporting; and other risk of bias. A few adjustments were made for the purpose of this review: we separated our assessment of blinding of participants and personnel from our assessment of blinding of outcome assessors; we considered objective (total cholesterol, LDL-C, fasting blood glucose, incidence of T2D) subjective (weight, blood pressure, adverse effects) and self-report (weight, adverse effects) outcomes separately under the domains of blinding of outcome assessors and incomplete outcome reporting; we selected study power/sample size and funding

as the two main sources of other risk of bias; and we added an overall risk of bias rating specific to outcome group (objective, subjective, self-report).

Information to determine risk of bias was abstracted from the primary methodology paper for each study and any other relevant published papers. For each study, one team member completed the initial ratings which were then verified by a second person; disagreements were resolved through discussion and/or third party consultation when consensus could not be reached. To assign a high or low risk of bias rating for a particular domain we looked for explicit statements or other clear indications that the relevant methodological procedures were or were not followed. In the absence of such details we assigned unclear ratings to the applicable risk of bias domains. To determine the overall risk of bias rating for an outcome group we considered all domains, however greater emphasis was placed on the assessments of first three areas of randomization, allocation and blinding.

Table 3 summarizes the risk of bias ratings applied to the RCTs included in this review.

Assessing Strength or Quality of the Evidence

The strength of the evidence was determined based on the GRADE system of rating the quality of evidence using GRADEPro software.[60,61] This system of assessing evidence is widely used and is endorsed by over 40 major organizations including WHO, Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.[62,62] The GRADE system rates the quality of a body of evidence as high, moderate, low or very low; each of the four levels reflects a different assessment of the likelihood that further research will impact the estimate of effect (i.e., high quality: further research is unlikely to change confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; very low quality: the estimate of effect is very uncertain).[62]

A GRADE quality rating is based on an assessment of five conditions: (1) risk of bias (limitations in study designs), (2) inconsistency (heterogeneity) in the direction and/or size of the estimates of effect, (3) indirectness of the body of evidence to the populations, interventions, comparators and/or outcomes of interest, (4) imprecision of results (few participants/events/observations, wide confidence intervals), and (5) indications of reporting or publication bias. Grouped RCTs begin with a high quality rating which may be downgraded if there are serious or very serious concerns across the studies related to one or more of the five conditions. For this review, key data were entered into the GRADEPro software along with the quality assessment ratings to produce two analytic products for each outcome and the comparisons of interest: (1) a GRADE Evidence Profile Table and (2) a GRADE Summary of Findings Table (presented in Evidence Sets 1 to 15).

There was no assessment of the quality of the evidence used to answer the contextual questions.

Data Analysis

To perform meta-analyses, immediate post treatment data (means, standard deviations) were utilized for continuous outcomes such as change in weight in kg, BMI and waist circumference; while number of events data were utilized for binary outcomes such as loss of ≥5% baseline body weight and incidence of T2D. The DerSimonian and Laird random effects model with inverse variance (IV) method was utilized to generate the summary measures of effect in the form of mean difference (MD) for continous outcomes and risk ratio (RR) for binary outcomes.[63] The random effects model assumes the studies are a sample of all potential studies and incorporates an additional between-study component to the estimate of variability.

MD were calculated using change from baseline data [i.e., mean difference between pre-treatment (baseline) and post treatment (final/end-point) values along with its standard deviation (SD) for both intervention and control groups]. For studies that did not report SD, we calculated this value from the reported standard error (SE) of the mean, or from the 95% confidence intervals (CI) using equations provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions.*[64] For studies that provided neither SD or SE for the follow-up data, we imputed the SD from either the baseline values or other included studies of similar sample size and for the same outcome. The units of measurement for total cholesterol, LDL-C and fasting glucose, if reported in mg/dL, were converted to Canadian standard units (i.e., mmol/L).

For studies that recruited a single gender or for mixed gender studies that reported results for men and for women, we entered this data separately into the meta-analyses, using alphabetical extensions to identify gender (e.g., Ross 2012-M, Ross 2012-F). For studies with more than one intervention arm, we took different approaches depending on how similar the interventions were to one another. When groups were similar (e.g., two arms evaluating the benefits of a lifestyle intervention, one using phone contact and one using in-person support) we the pooled the intervention group data to do a pair-wise comparison with the control group. Alternatively, if the intervention groups were substantially different from each other (e.g., a low calorie diet group and a high intensity aerobic exercise group) we included the data for each intervention arm compared with the control group but split the sample size for the control group in half to avoid a unit-of-analysis error and double counting. In the meta-analyses, multiple intervention arms within a single study are differentiated by alphabetical extensions for mixed gender studies (e.g., Andrews 2011-A, Andrews 2011-B) and by numerical extensions when data were also entered separately for men (M) and women (F) (e.g., Wood 1991-1F, Wood 1991-2F). For orlistat studies with multiple treatment arms based on different doses of the medication, we selected the intervention data only for groups taking 120mg three times daily (the most common dose used across studies) to include in the meta-analyses.

We used I^2 statistic to quantify statistical heterogeneity between studies, where $P<0.05$ indicates high statistical heterogenity between studies. There are no strict rules for interpreting I^2 but a value >50% may represent substantial heterogeneity.[64]

Sensitivity analyses were performed to evaluate statistical stability and effect on statistical heterogeneity. The sub-group analyses were based on primary focus of intervention (behavioural, pharmacological plus behavioural) for all outcomes and comparisons (except gender for weight in kg and gastrointestinal side effects which included studies in a single group). Additional sub-group analyses were based on type of intervention (behavioural: diet, exercise, diet plus exericse, lifestyle; pharmacological plus behavioural: metformin, orlistat), length of intervention (≤12 or >12 months), gender, and participants' baseline CVD risk status (high risk: CVD risk factors and/or diagnosed with T2D, hypertension, dyslipidemia; low CVD risk or unselected population or not specified) only for weight in kg because this was the outcome that most of the studies reported. A sensitivity analysis was planned using study risk of bias rating for the sub-groups but was not performed because almost all of the evidence fell into the unclear risk of bias group.

Meta-analyses were performed using Review Manager version 5.1.[59] Publication bias for each outcome (with sufficient studies) was assessed with the Egger's test[65] using STATA version 12.[66]

For two primary outcomes (loss of ≥5% and ≥10% baseline body weight) and one secondary outcome (incidence of T2D), if the effect was significant we added the estimate of absolute risk reduction (ARR) and number needed to treat (NNT) to the GRADE tables. NNTs were calculated using the absolute numbers presented in the GRADE tables. GRADE estimates the absolute number per million using the control group event rate and risk ratio with the 95% CI obtained from the meta-analysis.

For harms based on binary data (any adverse events, serious adverse events, gastrointestinal events, study withdrawal due to adverse events), when effects were significant, we added the estimate of absolute risk increase (ARI) and number needed to harm (NNH) to the GRADE tables. The NNHs were calculated using the absolute numbers presented in the GRADE tables. GRADE estimates the absolute number per million using the control group event rate and risk ratio with the 95% CI obtained from the meta-analysis.

For studies that provided data that could not be pooled, findings are reported narratively.

Results presented throughout the body of this review are rounded and/or reported to the second decimal. However, at the request of the CTFPHC, we used four decimals in our calculations and in the presentation of results in the Evidence Sets.

To answer the sub-question about common elements of efficacious interventions it was necessary to first to identify the efficacious interventions. For this review we identified efficacious interventions from studies included in the meta-analyses that showed a statistically significant effect size for any or all of the clinically significant outcomes of loss of ≥5% baseline body weight, loss of ≥10% baseline body weight, and at least four kg of weight loss.[67] Some of the elements we examined in these interventions were adapted from the features list presented in the 2011 USPSTF review.[5] We also included intervention duration, focus and setting as we believe primary care physicians would want to take such features into consideration when making program recommendations to their patients.

Chapter 3: Results

Summary of the Literature Search for Key Questions

The search and selection process for relevant literature occurred in three stages. Initially we conducted a combined search that included children and adults; prevention and treatment. We believed that some efficiency would be gained in the screening stage if we started with a comprehensive search strategy.

The initial comprehensive search (including both adults and children) located 30,196 unique citations (see Figure 2). These citations were reviewed for title and abstract relevance and were filtered for population (adult or child) and intervention focus (prevention or treatment). A total of 10,914 were excluded at this first level of relevance screening. There were 11,183 citations streamed for adult populations and 8,099 citations streamed for children (further information regarding child-related citations is reported in the child obesity treatment and child obesity prevention reviews available on the CTFPHC website http://canadiantaskforce.ca/).

The second stage involved another round of title and abstract screening and streaming of the 11,183 citations related to adults. At this level 6,711 citations were excluded and 3,320 citations remained for consideration as prevention interventions (these results are further delineated in the adult obesity prevention review available on the CTFPHC website http://canadiantaskforce.ca/) and 1,152 citations remained for consideration as treatment interventions.

Finally, the literature search was updated in April 2013. This updated search was adapted from the original search and any terms referring to children were removed. That search added an additional 2,348 citations for possible inclusion. Another round of title and abstract screening was undertaken where an additional 3,226 citations were excluded. To the remaining search yield we added all studies included in the meta-analyses in the 2011 USPSTF review[5] (50 studies with 70 papers) as well as 14 citations located by hand search for consideration. Full text screening took place on 358 citations and 141 were excluded (see list of excluded studies available on the CTFPHC website http://canadiantaskforce.ca/).

One hundred systematic reviews were identified by our team. The reference lists of on topic systematic reviews were searched to ensure that we had not missed any relevant studies. No additional studies were located in those reference lists.

At the end of the search and selection process, 68 studies with 117 papers met the inclusion criteria for this review. This total includes 36 studies brought forward from the 2011 USPSTF review that met our inclusion criteria,[5] and 32 studies found in the more recent literature.

Summary of the Included Studies

A total of 68 studies (117 papers) were included to answer the key question and sub-questions in this review.[57,58,68-95,96-133] Of these, only 56 studies reported weight outcome data that also met the study design (RCT), comparison group (usual care or no intervention) and minimum 12

month post baseline assessment requirements. Two of these 56 RCTs[101,105] provided eligible weight change (kg) data and one[101] also reported data for fasting blood glucose, but the results of these studies could not be pooled with the other evidence available for these outcomes and thus are captured narratively. The 12 studies that were excluded from pooled analyses of the weight outcomes, which included two single-group pre-post designs,[57,58] one study with a more active comparison group[75] and nine studies reporting outcomes at <12 months,[107,113,125-130,132] were included in analyses of adverse events which did not stipulate inclusion criteria related to design, comparison group or timing of assessment. Almost all (90%) of the RCT evidence was rated as having an unclear risk of bias, primarily due to the lack of information about or lack of procedures to ensure random sequence generation, allocation concealment and blinding of participants, personnel and/or outcome assessment. Behavioural treatments (diet, exercise, diet plus exercise, lifestyle) were examined in 39 studies.[57,68-105] Pharmacological plus behavioural interventions using orlistat or metformin were the focus in 27 studies: 23 studies used 120 mg of orlistat three times daily;[106-128] two studies used 60 mg of orlistat three times daily (included only for adverse events)[58,129] one study used 500 mg of metformin once daily;[130] and one study used 850 mg of metformin once daily.[131] Two studies included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily or 1,500 mg once daily) plus behavioural intervention arms.[132,133] All studies targeted overweight (BMI 25 to 29.9) and/or obese (BMI 30 to 39.9) individuals. Only two studies[96,103] specifically recruited seniors (≥ 65 years); the rest of the interventions included younger adults or participants of any age, with mean age falling between 18 and 64 years. All but five studies included mixed gender samples; three interventions targeted only women[89,99,132] and two were limited to male participants.[69,92] Just over one-third of the studies were directed at participants with high CVD risk (i.e., screened/identified as high CVD risk and/or diagnosed with T2D, hypertension and/or dyslipidemia).[57,70-73,76,78,81,83-85,88,94,106,108,109,111,113,115,117,118,121,123,124,127,130] The median length of intervention was 12 months, ranging from four to 38 months. Intervention duration was one year or less in almost three-quarters of the studies (n=49); in the remaining 19 studies the duration ranged from 13 to 60 months, with most of these interventions (n=13) running for two years or less. Most studies included to answer the treatment effectiveness questions reported outcomes at the immediate post treatment point; although a few were included that reported one year interim results from two or three year interventions,[110,114,133] and four studies were included that reported data for assessments conducted six to 18 months after completion of treatment programs lasting four or six months.[68,77,84,89] Only two studies were situated in or had at least one research site in Canada.[79,118] Almost half of the studies (n=31) were conducted in European countries, many (n=26) were located in the US, one was co-located in Europe and the US, several studies (n=6) were conducted in Australia and/or New Zealand, and one study took place in each of Japan and China. The evidence base for this review is fairly recent, with over half of the studies (n=35) published in the last five years (2009-2013); the remaining studies appeared in the literature between 1985 and 2008. The characteristics of the 68 included studies are reported individually in Table 4.

Results for Key Questions

KQ1: Do primary care relevant treatment interventions (behavioural and/or pharmacotherapy) in overweight/obese adults lead to improved health outcomes, short-term or sustained weight loss, or weight gain prevention, with or without improved physiological measures?

High level summaries of the included studies and key findings across outcomes with pooled estimates of effect are provided in Tables 5 through 8. Detailed results for each outcome are presented below.

Primary Outcome: Weight

Change in Weight in KG

Evidence Set 1 provides the GRADE Evidence Profile Table (1.1), the GRADE Summary of Findings Table (1.1), the forest plots (1.1 to 1.8), the funnel plots (1.1 to 1.8) and the Egger's test results (for publication bias) generated for the outcome of weight change in kg for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 49 of the 51 studies that reported weight change in kg; findings from the two remaining studies could not be pooled and thus are reported narratively below. Eight sub-analyses were conducted to look more closely at this comparison: (1) by primary focus of intervention (behavioural, pharmacological plus behavioural), (2) by type of behavioural intervention (diet, exercise, diet plus exercise, lifestyle), (3) by type of pharmacological plus behavioural intervention (orlistat, metformin), (4) by duration of behavioural intervention (≤12 months, >12 months), (5) by duration of pharmacological plus behavioural intervention (≤12 months, >12 months), (6) by behavioural intervention participants' baseline CVD risk status (high risk, low/unknown risk); (7) by pharmacological plus behavioural intervention participants' baseline CVD risk status (high risk, low/unknown risk); and (8) by gender in behavioural interventions.

1.1 Overall and by Primary Focus of Intervention

Overall

Forty-nine RCTs (n=22,615) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis on weight change in kg.[68-74,76-79,81,83-97,99,100,102-104,106,109-111,114-124,131,133] Across the 49 studies, 47 included adults aged 18-64 years, and two included adults 65 years and older. Most studies (n=45) included mixed gender samples; two included only women and two included only men. In 21 studies (43%) the participants had a high risk of CVD. Of the 49 RCTs, 32 studied behavioural interventions (some studies included more than one type of intervention; eight included a diet arm, four included an exercise arm, 10 included a diet plus exercise arm, 16 included a lifestyle arm), 16 studied pharmacological [15 orlistat (120 mg three times daily), one metformin (850 mg once daily)] plus behavioural interventions, and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus

behavioural arms. Intervention duration was 12 months or less in 32 studies and more than 12 months in 17 studies. One study was conducted in Canada, one in Canada and the US, 22 in the US, 19 in European countries, five in Australia and/or New Zealand, and one in Japan. About half of the studies (n=23) were published in the last five years; the remaining 26 studies were published between 1985 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.02 kg (-3.52, -2.52); I^2=91%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.25, df=1 (P=0.62), I^2=0%].

Behavioural Interventions

Thirty-three behavioural RCTs (n=10,829) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[68-74,76-79,81,83-97,99,100,102-104,133] Across the 33 studies, 31 included adults aged 18-64 years, and two included adults 65 years and older. Most studies (n=29) included mixed gender samples; two included only women and two included only men. In 12 studies (36%) the participants had a high risk of CVD. Eight studies included a diet intervention arm, four included an exercise intervention arm, nine included a combined diet plus exercise intervention arm, and in 17 studies lifestyle programs were provided (the total number is >33 because some studies included more than one type of intervention). Control participants received usual care from their physicians or no intervention; in seven studies they also received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 21 studies and more than 12 months in 12 studies. One study was conducted in Canada, 17 in the US, 10 in European countries, four in Australia and/or New Zealand, and one in Japan. More than half of the studies (n=22) were published in the last five years; the remaining 11 studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.13 kg (-3.88, -2.38); I^2=92%].

Two additional behavioural RCTs met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[101,105] A recent study of a 12 month community-based lifestyle intervention with Caribbean Latinos in the US provided a median change score from baseline to 12 months of -2.5 pounds (95% CI -4.0, -1.5) for intervention participants and a significantly different median change score of 0.63 pounds (95% CI -1.05, 2.00) for control participants.[101] A fairly recent UK-based diabetes prevention study with a focus on healthy lifestyle behaviours reported a non-significant weight change between control and intervention group but did not provide the actual data.[105]

Pharmacological plus Behavioural Interventions

Seventeen pharmacological plus behavioural RCTs (n=11,786) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[106,109-111,114-124,131,133] All 17 studies included adults aged 18-64 years, and mixed gender samples. In nine studies (53%) the participants had a high risk of CVD. In 15 studies the pharmacological intervention was orlistat (120 mg three times daily) and in two studies it was

metformin (850 mg once daily; 850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 11 studies and more than 12 months in six studies. One study was conducted in Canada and the US, six in the US, nine in European countries, and one in Australia. Only one study was published in the last five years; the remaining 16 studies were published between 1996 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.89 kg (-3.49, -2.29); I^2=87%].

1.2 Type of Behavioural Intervention

The test for subgroup differences was significant [Chi^2=9.32, df=3 (P=0.03), I^2=67.8%] suggesting that the amount of weight change depended on the type of behavioural intervention (diet, exercise, diet plus exercise, lifestyle). Interventions of exercise alone did not lead to significant reductions in weight; whereas diet alone had the largest impact on weight.

Diet

Eight diet focused RCTs (n=913) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[73,77,81,85,88,92,93,99] All eight studies included adults aged 18-64 years, and most studies (n=6) included mixed gender samples; one included only women and one included only men. In three studies (38%) the participants had a high risk of CVD. In all eight studies at least one intervention arm was focused on diet. Control participants received usual care from their physicians or no intervention. Intervention duration was 12 months or less in six studies and more than 12 months in two studies. Five studies were conducted in the US, two in European countries and one in Australia. Half of the studies (n=4) were published in the last five years; the remaining four studies were published between 1985 and 1991. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -4.71 kg (-6.22, -3.21); I^2=72%].

Exercise

Four exercise focused RCTs (n=598) of low GRADE quality (downgraded for risk of bias and imprecision) were included in the meta-analysis assessing weight change in kg.[76,92,96,99] Across the four studies, three included adults aged 18-64 years, and one included adults 65 years and older. Two studies included mixed gender samples, one included only women and one included only men. In only one study (25%) the participants had a high risk of CVD. In all four studies one behavioural intervention arm was exercise. Control participants received usual care from their physicians or no intervention. Intervention duration was 12 months or less in all four studies. Three studies were conducted in the US and one in Italy. Three of the studies were published in the last five years; the remaining study was published in 1988. There was no difference in weight change between the intervention and control groups [MD (95% CI) -1.49 kg (-3.32, 0.35); I^2=85%].

Diet plus Exercise

Ten diet plus exercise focused RCTs (n=2,382) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing weight change in kg.[69,73,74,77,79,83,86,93,99,100] All 10 studies included adults aged 18-64 years. Two studies included mixed gender samples, one included only women and one included only men. In two studies (20%) the participants had a high risk of CVD. In all 10 studies one behavioural intervention arm was diet plus exercise. Control participants received usual care from their physicians or no intervention; in one study control participants received a minimal component (e.g., printed health education materials). Intervention duration was 12 months or less in nine studies and more than 12 months in one study. One study was conducted in Canada, four in the US, and five in European countries. Most of the studies (n=8) were published in the last five years; the remaining two studies were published in 1991 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.83 kg (-5.49, -2.16); I^2=90%].

Lifestyle

Seventeen lifestyle focused RCTs (n=6,936) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing weight change in kg.[68,70-72,78,84,87,89-91,94,95,97,102-104,133] Across the 17 studies, 16 included adults aged 18-64 years, and one included adults 65 years and older. Most studies (n=16) included mixed gender samples; one included only women. In six studies (35%) the participants had a high risk of CVD. In terms of intervention focus, all 17 studies had at least one lifestyle intervention arm. Control participants received usual care from their physicians or no intervention; in six of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in nine studies and more than 12 months in eight studies. Ten studies were conducted in the US, three in European countries, three in Australia, and one in Japan. Most of the studies (n=11) were published in the last five years; the remaining six studies were published between 1993 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.52 kg (-3.54, -1.49); I^2=93%].

1.3 Type of Pharmacological plus Behavioural Intervention

There was no evidence that the effect of treatment differed based on type of pharmacological (metformin, orlistat) plus behavioural intervention [Chi^2=3.20, df=1 (P=0.07), I^2=68.8%].

Metformin

Two pharmacological plus behavioural RCTs (n=1,938) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[131,133] Both studies included adults aged 18-64 years, and mixed gender samples. Neither study included participants with a high risk of CVD. In both studies the pharmacological intervention was metformin (850 mg once daily; 850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months in one study and 38 months in the other study (although we

extracted 12 month interim data for this study). One study was conducted in the US and the other study was conducted in France. Neither study was published in the last five years; one was published in 1996 and the other in 1999. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -1.92 kg (-2.94, -0.89); I^2=60%].

Orlistat

Fifteen pharmacological plus behavioural RCTs (n=9,848) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[106,109-111,114-124] All 15 studies included adults aged 18-64 years, and mixed gender samples. In nine studies (60%) the participants had a high risk of CVD. In all studies the pharmacological intervention was orlistat at a dose of 120 mg three times daily. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in 10 studies and more than 12 months in five studies. One study was conducted in Canada and the US, five in the US, eight in European countries, and one in Australia. Only one study was published in the last five years; the remaining 14 studies were published between 1996 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.05 kg (-3.75, -2.35); I^2=88%].

1.4 Duration of Behavioural Intervention

There was no evidence that the effect of treatment differed based on duration of behavioural intervention (≤12 months, >12 months) [Chi^2=1.31, df=1 (P=0.25), I^2=23.4%].

Intervention Duration ≤12 Months

Twenty-one behavioural RCTs (n=4,780) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing weight change in kg.[68,69,73,74,76,77,83-87,89,92-96,99,102-104] Across the 21 studies, 19 included adults aged 18-64 years, and two included adults 65 years and older. Most studies (n=17) included mixed gender samples; two included only women and two included only men. In six studies (29%) the participants had a high risk of CVD. In seven studies at least one intervention arm was diet, in four there was at least one exercise arm, in seven it was a combination of diet and exercise, and in nine studies lifestyle programs were provided. Control participants received usual care from their physicians or no intervention; in five studies they also received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in all studies. One study was conducted in Canada and the US, nine in the US, eight in European countries and three in Australia. More than half of the studies (n=14) were published in the last five years; the remaining seven studies were published between 1991 and 2005. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.43 kg (-4.32, -2.55); I^2=88%].

Intervention Duration >12 Months

Twelve behavioural RCTs (n=6,049) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing weight change in kg.[70-72,78,79,81,88,90,91,97,100,133] All 12 studies included adults aged 18-64 years, and mixed gender samples. In six studies (50%) the participants had a high risk of CVD. In terms of intervention focus, two were diet, two were diet plus exercise, and eight were lifestyle. Control participants received usual care from their physicians or no intervention; in two of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was more than 12 months in all 12 studies. One study was conducted in Canada, seven in the US, three in European countries, and one in Australia. Two-thirds of the studies (n=8) were published in the last five years; the remaining four studies were published between 1985 and 2003. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.53 kg (-3.81, -1.24); I^2=95%].

1.5 Duration of Pharmacological plus Behavioural Intervention

There was no evidence that the effect of treatment differed based on duration of pharmacological plus behavioural intervention (≤12 months, >12 months) [Chi^2=0.13, df=1 (P=0.72), I^2=0%].

Intervention Duration ≤12 Months

Eleven pharmacological plus behavioural RCTs (n=4,418) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[106,109,111,115,117,118,120,121,123,124,131] All 11 studies included adults aged 18-64 years, and mixed gender samples. In nine studies the participants had a high risk of CVD. In 10 studies the intervention drug was orlistat (120 mg three times daily) and in one study it was metformin (850 mg once daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in all 11 studies. One study was conducted in Canada, one in Canada and the US, three in the US, five in European countries, and one in Australia and New Zealand. Only one study was published in the last five years; the remaining 10 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.89 kg (-3.90, -1.88); I^2=91%].

Intervention Duration >12 Months

Six pharmacological plus behavioural RCTs (n=7,368) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[110,114,116,119,122,133] All six studies included adults aged 18-64 years, and mixed gender samples. None of the studies included participants with a high risk of CVD. In five studies the intervention drug was orlistat (120 mg three times daily) and in one study it was metformin (850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was more than 12 months in all six studies. Three studies were conducted in the US and three in

European countries. None of the studies was published in the last five years; the six studies were published between 1999 and 2004. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.69 kg (-3.00, -2.38); I^2=9%].

1.6 Participants' Baseline CVD Risk Status in Behavioural Interventions

The test for subgroup differences was significant [Chi^2=8.05, df=1 (P=0.005), I^2=87.6%] suggesting that, as compared to the control group, changes in weight were greater for participants with low/unknown baseline CVD risk status than those with high baseline CVD risk status.

High CVD Risk

Twelve behavioural RCTs (n=2,951) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing weight change in kg.[70-73,76,78,81,83-85,88,94] All 12 studies included adults aged 18-64 years, mixed gender samples, and participants with a high risk of CVD. In terms of intervention focus three were diet, one was exercise, two were diet plus exercise, and six were lifestyle. Control participants received usual care from their physicians or no intervention; in five of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in six studies and more than 12 months in six studies. Six studies were conducted in the US, three in European countries, and three in Australia. About half of the studies (n=7) were published in the last five years; the remaining five studies were published between 1985 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -1.89 kg (-2.69, -1.08); I^2=75%].

Low/Unknown CVD Risk

Twenty-one behavioural RCTs (n=7,878) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[68,69,74,77,79,86,87,89-91,93-97,99,100,102-104,133] Across the 21 studies, 19 included adults aged 18-64 years, and two included adults 65 years and older. Most studies (n=17) included mixed gender samples; two included only women and two included only men. In all 21 studies participants were unselected for or had a low risk of CVD. In terms of intervention focus, two were diet, one was exercise, seven were diet plus exercise, and 11 were lifestyle. Control participants received usual care from their physicians or no intervention; in two of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 15 studies and more than 12 months in six studies. One study was conducted in Canada, 11 in the US, seven in European countries, one in Australia, and one in Japan. About two-thirds of the studies (n=15) were published in the last five years; the remaining six studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.66 kg (-4.59, -2.74); I^2=92%].

1.7 Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions

There was no evidence that the effect of treatment differed based on participants' baseline CVD risk status (high, low/unknown) [Chi^2=0.06, df=1 (P=0.80), I^2=0%].

High CVD Risk

Nine pharmacologial plus behavioural RCTs (n=3,411) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[106,109,111,115,117,118,121,123,124] All nine studies included adults aged 18-64 years, mixed gender samples and participants at high risk for CVD. The pharmacological intervention in all nine studies was orlistat (120 mg three times daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in all studies. One study was conducted in Canada and the US, three in the US, four in European countries, and one in Australia and New Zealand. Only one study was published in the last five years; the remaining eight studies were published between 1996 and 2004. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.93 kg (-4.08, -1.79); I^2=92%].

Low/Unknown CVD Risk

Eight pharmacological plus behavioural RCTs (n=8,375) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[110,114,116,119,120,122,131,133] All eight studies included adults aged 18-64 years, mixed gender samples, and participants with low/unknown risk of CVD. The pharmacological plus behavioural intervention in six studies was orlistat (120 mg three times daily) and in two studies it was metformin (850 mg once daily; 850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in two studies and more than 12 months in six studies. Three studies were conducted in the US and five in European countries. None of the studies were published in the last five years; all eight studies were published between 1996 and 2004. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -2.77 kg (-3.27, -2.28); I^2=54%].

1.8 Gender

Ten behavioural RCTs provided data for weight in kg that was separated by gender. Eight of the studies provided results for female participants and another grouping of eight studies provided results for male participants. There is no evidence that the treatment effect differed based on gender [Chi^2=1.46, df=1 (P=0.23), I^2=31.5%].

Female Only

Eight behavioural RCTs (n=1,800) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[79,84,89-91,93,99,102] All eight studies included adults aged 18-64 years. Most studies (n=6) included mixed gender samples; two

included only women. Only one study included participants with a high risk of CVD. All interventions were behavioural (one diet, two diet plus exercise, five lifestyle). Control participants received usual care from their physicians or no intervention; in one study control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in five studies and more than 12 months in three studies. One study was conducted in Canada, five in the US, one in Australia, and one in Japan. Three studies were published in the last five years; the remaining five studies were published between 1991 and 2008. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -3.33 kg (-4.80, -1.86); I^2=87%].

Male Only

Eight behavioural RCTs (n=2,131) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing weight change in kg.[69,79,84,90,91,93,94,102] All eight studies included adults aged 18-64 years. Most studies (n=6) included mixed gender samples; two included only men. Only one study included participants with a high risk of CVD. All interventions were behavioural (one diet, three diet plus exercise, four lifestyle). Control participants received usual care from their physicians or no intervention; in one study control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in five studies and more than 12 months in three studies. One study was conducted in Canada, five in the US, one in Australia, and one in Japan. Three studies were published in the last five years; the remaining five studies were published between 1988 and 2005. Intervention participants had a significantly greater reduction in weight as compared to the control group [MD (95% CI) -4.65 kg (-6.20, -3.09); I^2=89%].

Loss of ≥5% of Baseline Body Weight

Evidence Set 2 provides the GRADE Evidence Profile Table (2.1), the GRADE Summary of Findings Table (2.1), the forest plot (2.1), the funnel plot (2.1) and the Egger's test results (for publication bias) generated for the outcome of loss of ≥5% of baseline body weight for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including all 24 studies that reported loss of ≥5% body weight and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural).

Overall

Twenty-four RCTs (n=9,857) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing loss of ≥5% of baseline body weight.[68,70,71,78,83,86,88,89,95,103,104,108-110,112,114-118,120,122-124] Across the studies, 23 included adults aged 18-64 years and one included adults 65 years and older. Most studies (n=23) included mixed gender samples; one included only women. In 12 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 11 were behavioural (one diet, two diet plus exercise, eight lifestyle) and 13 were pharmacological (all 120 mg of orlistat taken three times

daily) plus behavioural. Intervention duration was 12 months or less in 16 studies and more than 12 months in eight studies. One study was conducted in Canada and the US, 12 in the US, 10 in European countries, and one in Australia. One-third of the studies (n=8) were published in the last five years; the remaining 16 studies were published between 1985 and 2008. Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to control participants [RR (95% CI) 1.77 (1.58, 1.99); I^2=69%; absolute value per million 204,152 more, range from 153,226 more to 261,352 more]. The absolute risk reduction (ARR) is 20.42%. The number needed to treat (NNT) to achieve one participant with ≥5% total body weight loss from baseline is 5 (95% CI 4, 7). There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.02, df=1 (P=0.88), I^2=0%].

Behavioural Interventions

Eleven behavioural RCTs (n=2,841) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing loss of ≥5% of baseline body weight.[68,70,71,78,83,86,88,89,95,103,104] Across the 11 studies, 10 included adults aged 18-64 years and one included adults 65 years and older. Most studies (n=10) included mixed gender samples; one included only women. In five studies (45%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, two were diet plus exercise, and eight were lifestyle. Control participants received usual care from their physicians or no intervention; in four of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in seven studies and more than 12 months in four studies. Seven studies were conducted in the US, three in European countries, and one in Australia. Most of the studies (n=8) were published in the last five years; the remaining three studies were published in 1985 and 2008. Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to control participants [RR (95% CI) 1.75 (1.35, 2.27); I^2=57%; absolute value per million 116,728 more, range from 54,551 more to 197,346 more]. The ARR is 11.67%. The NNT to achieve one participant with ≥5% total body weight loss from baseline is 9 (95% CI 5, 18).

Pharmacological plus Behavioural Interventions

Thirteen pharmacological plus behavioural RCTs (n=7,016) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing loss of ≥5% of baseline body weight.[108-110,112,114-118,120,122-124] All 13 studies included adults aged 18-64 years, and mixed gender samples. In seven studies (54%) the participants had a high risk of CVD. The pharmaceutical intervention in all studies was orlistat (120 mg three times daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in nine studies and more than 12 months in four studies. One study was conducted in Canada and the US, five in the US, and seven in European countries. None of the studies were published in the last five years; all 13 studies were published between 1985 and

2005. Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to control participants [RR (95% CI) 1.79 (1.57, 2.04); I^2=76%; absolute value per million 242,612 more, range from 174,934 more to 319,779 more]. The ARR is 24.26%.The NNT to achieve one participant with ≥5% total body weight loss from baseline is 4 (95% CI 3, 6).

Loss of ≥10% of Baseline Body Weight

Evidence Set 3 provides the GRADE Evidence Profile Table (3.1), the GRADE Summary of Findings Table (3.1), the forest plot (3.1), the funnel plot (3.1) and the Egger's test results (for publication bias) generated for the outcome of loss of ≥10% of baseline body weight for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including all 16 studies that reported loss of ≥10% of baseline body weight and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural).

Overall

Sixteen RCTs (n=7,523) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing loss of ≥10% of baseline body weight.[70,71,86,108-110,112,114-120,122,124] All 16 studies included adults aged 18-64 years, and mixed gender samples. In eight studies (50%) the participants had a high risk of CVD. In terms of intervention focus, three were behavioural (one diet plus exercise, two lifestyle) and 13 were pharmacological plus behavioural (all 120 mg of orlistat taken three times daily). Intervention duration was 12 months or less in nine studies and more than 12 months in seven studies. One study was conducted in Canada and the US, six in the US, and nine in European countries. Three studies were published in the last five years; the remaining 13 studies were published between 1998 and 2005. Intervention participants were significantly more likely to lose ≥10% of their baseline body weight as compared to control participants [RR (95% CI) 1.91 (1.69, 2.16); I^2=16%; absolute value per million 112,366 more, range from 85,561 more to 142,666 more]. The ARR is 11.24%. The NNT to achieve one participant with ≥10% weight loss from baseline is 9 (95% CI 7, 12). There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.06, df=1 (P=0.81), I^2=0%].

Behavioural Interventions

Three behavioural RCTs (n=744) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing loss of ≥10% of baseline body weight.[70,71,86] All three studies included adults aged 18-64 years, and mixed gender samples. In two studies (67%) the participants had a high risk of CVD. In terms of intervention focus, one was diet plus exercise and two were lifestyle. Control participants received usual care from their physicians or no intervention; in one of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in one study and more than 12 months in two studies. Two studies were conducted in the US and one in Finland. All three studies were published in the last five years. Intervention participants

were significantly more likely to lose ≥10% of their baseline body weight as compared to control participants [RR (95% CI) 2.04 (1.30, 3.21); I^2=0%; absolute value per million 80,085 more, range from 22,954 more to 169,900 more]. The ARR is 8.01%. The NNT to achieve one participant with ≥10% weight loss from baseline is 12 (95% CI 6, 44).

Pharmacological plus Behavioural Interventions

Thirteen pharmacological plus behavioural RCTs (n=6,779) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing loss of ≥10% of baseline body weight.[108-110,112,114-120,122,124] All 13 studies included adults aged 18-64 years, and mixed gender samples. In six studies (46%) the participants had a high risk of CVD. In all studies the pharmacological intervention was orlistat (120 mg taken three times daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in eight studies and more than 12 months in five studies. One study was conducted in Canada and the US, four in the US, and eight in European countries. None of the studies was published in the last five years; all 13 studies were published between 1998 and 2005. Intervention participants were significantly more likely to lose ≥10% of their baseline body weight as compared to control participants [RR (95% CI) 1.92 (1.67, 2.21); I^2=31%; absolute value per million 118,115 more, range from 86,093 more to 154,942 more]. The ARR is 11.81%. The NNT to achieve one participant with ≥10% weight loss from baseline is 8 (95% CI 6, 12).

Change in Body Mass Index

Evidence Set 4 provides the GRADE Evidence Profile Table (4.1), the GRADE Summary of Findings Table (4.1), the forest plot (4.1), the funnel plot (4.1) and the Egger's test results (for publication bias) generated for the outcome of change in BMI for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 26 of the 27 studies that reported BMI and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural). Findings from the one remaining study could not be pooled and thus are reported narratively below.

Overall

Twenty-six RCTs (n=10,611) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in BMI from baseline.[69-74,76-80,82,87,96-100,102-104,106,111,116,123,133] Across these 26 studies, 24 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=24) included mixed gender samples; one included only women and one included only men. In nine studies (35%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (one diet, four exercise, seven diet plus exercise, nine lifestyle), four were pharmacological plus behavioural (all 120 mg of orlistat taken three times daily), and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or

less in 16 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, 13 in European countries, one in Australia, and one in Japan. Most of the studies (n=21) were published in the last five years; the remaining five studies were published between 1995 and 2003. Intervention participants had a significantly greater reduction in BMI as compared to the control group [MD (95% CI) -1.11 kg/m^2 (-1.39, -0.84); I^2=93%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.30, df=1 (P=0.59), I^2=0%].

Behavioural Interventions

Twenty-two behavioural RCTs (n=7,487) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in BMI from baseline.[69-74,76-80,82,87,96-100,102-104,133] Across these 22 studies, 20 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=20) included mixed gender samples; one included only women and one included only men. In six studies (27%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, four were exercise, seven were diet plus exercise, and 10 were lifestyle. Control participants received usual care from their physicians or no intervention; in four of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 13 studies and more than 12 months in nine studies. One study was conducted in Canada, nine in the US, 10 in European countries, one in Australia, and one in Japan. Most of the studies (n=20) were published in the last five years; the remaining two studies were published in 1995 and 1999. Intervention participants had a significantly greater reduction in BMI as compared to the control group [MD (95% CI) -1.09 kg/m^2 (-1.43, -0.75); I^2=93%].

One additional behavioural RCT met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[94] This older study, assessed as having unclear risk of bias, involved a 12 month general practice-based intervention using nurse counselors with patients at high CVD risk in Australia. In contrast to the pooled estimate, the immediate post results of this study showed BMI had increased in the intervention and control groups with no significant between-group differences (P=0.9899).[94]

Pharmacological plus Behavioural Interventions

Five pharmacological plus behavioural RCTs (n=3,124) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in BMI from baseline.[106,111,116,123,133] All five studies included adults aged 18-64 years, and mixed gender samples. In three studies (60%) the participants had a high risk of CVD. Four studies included orlistat (120 mg three times daily) as the pharmacological intervention and one used metformin (850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in three studies and more than 12 months in two studies. Two studies were conducted in the US and three in European countries. One study was published in the last five years; the remaining four studies were published between 1999 and

2003. Intervention participants had a significantly greater reduction in BMI as compared to the control group [MD (95% CI) -1.27 kg/m^2 (-1.82, -0.72); I^2=93%].

Change in Waist Circumference

Evidence Set 5 provides the GRADE Evidence Profile Table (5.1), the GRADE Summary of Findings Table (5.1), the forest plot (5.1), the funnel plot (5.1) and the Egger's test results (for publication bias) generated for the outcome of change in waist circumference in centimeters (cm) for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including all 33 studies that reported waist circumference and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural).

Overall

Thirty-three RCTs (n=16,565) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in waist circumference from baseline.[68-73,76,77,79,83,84,86,87,95-97,99,100,102-104,106,108,109,111,115,116,119,121-124,133] Across these studies, 31 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=31) included mixed gender samples; one included only women and one included only men. In 15 studies (45%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (one diet, two exercise, seven diet plus exercise, 11 lifestyle), 11 were pharmacological (all 120 mg of orlistat taken three times daily), and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) arms. Intervention duration was 12 months or less in 23 studies and more than 12 months in 10 studies. One study was conducted in Canada, 12 in the US, 16 in European countries, three in Australia and/or New Zealand, and one in Japan. About two-thirds of the studies (n=20) were published in the last five years; the remaining 13 studies were published between 1998 and 2008. Intervention participants had a significantly greater reduction in waist circumference as compared to the control group [MD (95% CI) -2.78 cm (-3.34, -2.22); I^2=91%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=1.80, df=1 (P=0.18), I^2=44.4%].

Behavioural Interventions

Twenty-two behavioural RCTs (n=7,770) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in waist circumference from baseline.[68-73,76,77,79,83,84,86,87,95-97,99,100,102-104,133] Across the 22 studies, 20 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=20) included mixed gender samples; one included only women and one included only men. In seven studies (32%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, two were exercise, seven were diet plus exercise, and 11 were lifestyle. Control participants received usual care from their physicians or no intervention; in five of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or

less in 15 studies and more than 12 months in seven studies. One study was conducted in Canada, nine in the US, nine in European countries, two in Australia, and one in Japan. Most of the studies (n=19) were published in the last five years; the remaining three studies were published between 1999 and 2008. Intervention participants had a significantly greater reduction in waist circumference as compared to the control group [MD (95% CI) -3.05 cm (-3.86, -2.24); I^2=90%].

Pharmacological plus Behavioural Interventions

Twelve pharmacological plus behavioural RCTs (n=8,795) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in waist circumference from baseline.[106,108,109,111,115,116,119,121-124,133] All 12 studies included adults aged 18-64 years, and mixed gender samples. In eight studies (67%) the participants had a high risk of CVD. In 11 studies the pharmacological intervention was orlistat (120 mg three times daily); in one study it was metformin (850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in eight studies and more than 12 months in four studies. Four studies were conducted in the US, seven in European countries, and one in Australia. Only one study was published in the last five years; the remaining 11 studies were published between 1998 and 2005. Intervention participants had a significantly greater reduction in waist circumference as compared to the control group [MD (95% CI) -2.29 cm (-3.04, -1.55); I^2=91%].

Secondary Outcomes: Lipids

Change in Total Cholesterol

Evidence Set 6 provides the GRADE Evidence Profile Table (6.1), the GRADE Summary of Findings Table (6.1), the forest plot (6.1), the funnel plot (6.1) and the Egger's test results (for publication bias) generated for the outcome of change in total cholesterol for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 33 of the 34 studies that reported total cholesterol and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural). Findings from the one remaining study could not be pooled and thus are reported narratively below.

Overall

Thirty-three RCTs (n=10,039) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in total cholesterol level.[68,70-74,76,79,81,83,87,92,93,96-98,100,103,106,108,109,111,112,114,115,117-121,123,124,131] Across these studies, 31 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=32) included mixed gender samples; one included only men. In 17 studies (52%) the participants had a high risk of CVD. In terms of intervention focus, 18 were behavioural (two diet, three exercise, six diet plus exercise, seven lifestyle) and 15 were pharmacological [14 orlistat (120 mg taken three times daily), one metformin (850 mg once daily)] plus behavioural. Intervention duration was 12 months or less in

24 studies and more than 12 months in nine studies. One study was conducted in Canada, one in Canada and the US, 11 in the US, 17 in European countries, and three in Australia and/or New Zealand. Half of the studies (n=16) were published in the last five years; the remaining 17 studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in total cholesterol level as compared to the control group [MD (95% CI) -0.21 mmol/L (-0.29, -0.13); I^2=86%]. The test for subgroup differences was significant [Chi^2=14.57, df=1 (P=0.0001), I^2=93.1%] suggesting that, as compared to the control group, changes in total cholesterol level were greater for pharmacological plus behavioural interventions than behavioural interventions alone.

Behavioural Interventions

Eighteen behavioural RCTs (n=4,282) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing change in total cholesterol level.[68,70-74,76,79,81,83,87,92,93,96-98,100,103] Across these studies, 16 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=15) included mixed gender samples; one included only men. In seven studies (39%) the participants had a high risk of CVD. In terms of intervention focus, two were diet, three were exercise, six were diet plus exercise, and seven were lifestyle. Control participants received usual care from their physicians or no intervention; in four of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 11 studies and more than 12 months in seven studies. One study was conducted in Canada, seven in the US, eight in European countries, and two in Australia. Most of the studies (n=15) were published in the last five years; the remaining three studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in total cholesterol level as compared to the control group [MD (95% CI) -0.10 mmol/L (-0.18, -0.03); I^2=63%].

One additional behavioural RCT met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[94] This older study, assessed as having unclear risk of bias, involved a 12 month general practice-based intervention using nurse counselors with patients at high CVD risk in Australia. The immediate post results of this study showed total cholesterol level fell by 3% in the intervention group and by 2% in the control group. The authors note that explanation of changes in lipid levels is challenged by a baseline imbalance in treatment with lipid-lowering drugs between groups that occurred despite randomization. However, lipid-lowering drug treatment was included as a covariate in analyses.

Pharmacological plus Behavioural Interventions

Fifteen pharmacological plus behavioural RCTs (n=5,757) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in total cholesterol level.[106,108,109,111,112,114,115,117-121,123,124,131] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 10 studies (67%) the participants had a high risk of CVD. In terms of intervention focus, 14 were orlistat (120 mg three times daily) and one was metformin (850 mg once daily). Control participants followed the same diet and exercise instructions as the

intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 13 studies and more than 12 months in two studies. One study was conducted in Canada and the US, four in the US, nine in European countries, and one in Australia and New Zealand. Only one study was published in the last five years; the remaining 14 studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in total cholesterol level as compared to the control group [MD (95% CI) -0.33 mmol/L (-0.42, -0.24); I^2=81%].

Change in Low Density Lipoprotein Cholesterol

Evidence Set 7 provides the GRADE Evidence Profile Table (7.1), the GRADE Summary of Findings Table (7.1), the forest plot (7.1), the funnel plot (7.1) and the Egger's test results (for publication bias) generated for the outcome of change in LDL-C for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 30 of the 32 studies that reported LDL-C and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural). Findings from the two remaining studies could not be pooled and thus are reported narratively below.

Overall

Thirty RCTs (n=9,313) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing change in LDL-C level.[70-74,76,79,81,83,92,93,95-97,103,106,108,109,111,112,114,115,117-121,123,124,131] Across these studies, 28 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=29) included mixed gender samples; one included only men. In 17 studies (57%) the participants had a high risk of CVD. In terms of intervention focus, half of the studies (n=15) were behavioural (two diet, two exercise, five diet plus exercise, six lifestyle), and the other half (n=15) were pharmacological [14 orlistat (120 mg taken three times daily), one metformin (850 mg once daily)] plus behavioural. Intervention duration was 12 months or less in 22 studies and more than 12 months in eight studies. One study was conducted in Canada, one in Canada and the US, 12 in the US, 13 in European countries, and three in Australia and/or New Zealand. About half of the studies (n=13) were published in the last five years; the remaining 17 studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in LDL-C level as compared to the control group [MD (95% CI) -0.21 mmol/L (-0.29, -0.12); I^2=90%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=2.51, df=1 (P=0.11), I^2=60.1%].

Behavioural Interventions

Fifteen behavioural RCTs (n=3,556) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in LDL-C level.[70-74,76,79,81,83,92,93,95-97,103] Across these studies, 13 included adults aged 18-64 years and two included adults 65 years and older. Most studies (n=14) included mixed gender samples; one included only men. In seven

studies (47%) the participants had a high risk of CVD. In terms of intervention focus, two were diet, two were exercise, five were diet plus exercise, and six were lifestyle. Control participants received usual care from their physicians or no intervention; in two of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in nine studies and more than 12 months in six studies. One study was conducted in Canada, eight in the US, four in European countries, and two in Australia. Most of the studies (n=12) were published in the last five years; the remaining three studies were published between 1988 and 2008. Intervention participants had a significantly greater reduction in LDL-C level as compared to the control group [MD (95% CI) -0.14 mmol/L (-0.29, -0.002); I^2=90%].

Two additional behavioural RCTs met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[94,98] The older study, assessed as having unclear risk of bias, involved a 12 month general practice-based intervention using nurse counselors with patients at high CVD risk in Australia. At 12 months post baseline, LDL-C levels had improved in all groups (no data provided). The authors note that explanation of changes in lipid levels is challenged by a baseline imbalance in treatment with lipid-lowering drugs between groups that occurred despite randomization. However, lipid-lowering drug treatment was included as a covariate in analyses. The more recent study examined the effects of a supervised 12 month exercise program on cardiovascular risk factors in pre-diabetic patients in Austria.[98] The results of this study, which was rated as having unclear risk of bias, reported no significant between- or within-subject effects for LDL-C (no data provided).

Pharmacological plus Behavioural Interventions

Fifteen pharmacological plus behavioural RCTs (n=5,757) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in LDL-C level.[106,108,109,111,112,114,115,117-121,123,124,131] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 10 studies (67%) the participants had a high risk of CVD. In terms of intervention focus, 14 were orlistat (120 mg three times daily) and one was metformin (850 mg once daily). Control participants followed the same diet and exercise instructions as the intervention participants but received placebos instead of the active medications. Intervention duration was 12 months or less in 13 studies and more than 12 months in two studies. One study was conducted in Canada and the US, four in the US, nine in European countries, and one in Australia and New Zealand. Only one study was published in the last five years; the remaining 14 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in LDL-C level as compared to the control group [MD (95% CI) -0.28 mmol/L (-0.38, -0.19); I^2=89%].

Secondary Outcomes: Diabetes

Change in Fasting Glucose

Evidence Set 8 provides the GRADE Evidence Profile Table (8.1), the GRADE Summary of Findings Table (8.1), the forest plot (8.1), the funnel plot (8.1) and the Egger's test results (for

publication bias) generated for the outcome of change in fasting glucose for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 28 of the 29 studies that reported fasting glucose and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural). Findings from the one remaining study could not be pooled and thus are reported narratively below.

Overall

Twenty-eight RCTs (n=12,646) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in fasting glucose level.[70-73,77,79,81,87,95-98,100,103,106,108,114-122,124,131,133] Across the 28 studies, 26 included adults aged 18-64 years and two included adults 65 years and older. All 28 studies included mixed gender samples. In 12 studies (43%) the participants had a high risk of CVD. In terms of intervention focus, half of the studies (n=14) were behavioural (one diet, two exercise, four diet plus exercise, seven lifestyle), 13 were pharmacological [12 orlistat (120 mg taken three times daily), one metformin (850 mg once daily)] plus behavioural and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or less in 16 studies and more than 12 months in 12 studies. One study was conducted in Canada, one in Canada and the US, nine in the US, 14 in European countries, and three in Australia and/or New Zealand. About half of the studies (n=15) were published in the last five years; the remaining 17 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in fasting glucose level as compared to the control group [MD (95% CI) -0.26 mmol/L (-0.38, -0.13); I^2=96%]. The test for subgroup differences was significant [Chi^2=5.17, df=1 (P=0.02), I^2=80.7%] suggesting that, as compared to the control group, changes in fasting glucose level were greater for pharmacological plus behavioural interventions than behavioural interventions alone.

Behavioural Interventions

Fifteen behavioural RCTs (n=5,106) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in fasting glucose level.[70-73,77,79,81,87,95-98,100,103,133] Across these studies, 13 included adults aged 18-64 years and two included adults 65 years and older. All 15 studies included mixed gender samples. In five studies (33%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, two were exercise, four were diet plus exercise, and eight were lifestyle. Control participants received usual care from their physicians or no intervention; in two of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in seven studies and more than 12 months in eight studies. One study was conducted in Canada, six in the US, six in European countries, and two in Australia. Almost all of the studies (n=14) were published in the last five years; only one study was published more than five years ago. Intervention participants had a significantly greater

reduction in fasting glucose level as compared to the control group [MD (95% CI) -0.14 mmol/L (-0.23, -0.05); I^2=81%].

One additional behavioural RCT met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[101] For fasting glucose, this recent study of a 12 month community-based lifestyle intervention with Caribbean Latinos in the US provided a median change score from baseline to 12 months of 0.03 mmol/L (95% CI -0.05, 0.16) for intervention participants and a non-significantly different median change score of -0.08 mmol/L (95% CI -0.17, 0.12) for control participants.

Pharmacological plus Behavioural Interventions

Fourteen pharmacological plus behavioural RCTs (n=7,540) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in fasting glucose level.[106,108,114-122,124,131,133] All 14 studies included adults aged 18-64 years and mixed gender samples. In seven studies (50%) the participants had a high risk of CVD. Most studies (n=12) used orlistat (120 mg three times daily) as the pharmacological intervention, two used metformin (850 mg once daily; 850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in nine studies and more than 12 months in five studies. One study was conducted in Canada and the US, four in the US, eight in European countries, and one in Australia and New Zealand. Only one study was published in the last five years; the remaining 13 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in fasting glucose level as compared to the control group [MD (95% CI) -0.43 mmol/L (-0.66, -0.20); I^2=98%].

Incidence of Type 2 Diabetes

Evidence Set 9 provides the GRADE Evidence Profile Table (9.1), the GRADE Summary of Findings Table (9.1), the forest plot (9.1), the funnel plot (9.1) and the Egger's test results (for publication bias) generated for the outcome of incidence of T2D for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including all nine studies that reported T2D incidence and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural).

Overall

Nine RCTs (n=8,624) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of T2D.[95-97,100,101,105,122,131,133] Across the nine studies, eight included adults aged 18-64 years and one included adults 65 years and older. All nine studies included mixed gender samples. None of the studies selected participants with a high risk of CVD. In terms of intervention focus, six studies were behavioural (one diet, one exercise, one diet plus exercise, three lifestyle), two were pharmacological [one orlistat (120 mg three times daily), one metformin (850 mg once daily)] plus behavioural, and one included both behavioural

(lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or less in four studies and more than 12 months in five studies. Five studies were conducted in the US and four in European countries. Two-thirds of the studies (n=6) were published in the last five years; the remaining three studies were published between 1996 and 2004. Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.62 (0.50, 0.77); I^2=54%; absolute value per million 57,457 fewer, range from 34,265 fewer to 76,059 fewer]. The ARR is 5.75%. The NNT to achieve one less new case of T2D is 17 (95% CI 13, 29). There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=2.50, df=1 (P=0.11), I^2=60.0%].

Behavioural Interventions

Seven behavioural RCTs (n=3,198) of moderate GRADE quality (downgraded for risk of bias) T2D.[95-97,100,101,105,133] Across the seven studies, six included adults aged 18-64 years and one included adults 65 years and older. All seven studies included mixed gender samples. None of the studies selected participants with a high risk of CVD. In terms of intervention focus, one was diet, one was exercise, one was diet plus exercise and four were lifestyle. Control participants received usual care from their physicians or no intervention; in one of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in three studies and more than 12 months in four studies. Four studies were conducted in the US and two in European countries. All of the studies were published in the last five years. Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.55 (0.42, 0.72); I^2=23%; absolute value per million 88,849 fewer, range from 55,323 fewer to 114,477 fewer]. The ARR is 8.88%. The NNT to achieve one less new case of T2D is 11 (95% CI 9, 18).

Pharmacological plus Behavioural Interventions

Three pharmacological plus behavioural RCTs (n=5,426) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of T2D.[122,131,133] All three studies included adults aged 18-64 years and mixed gender samples. None of the studies selected participants with a high risk of CVD. One study used orlistat (120 mg three times daily) as the pharmacological intervention and two studies used metformin (850 mg once daily; 850 mg twice daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in one study and more than 12 months in two studies. One study was conducted in the US and two in European countries. All three studies were published more than five years ago. Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.72 (0.59, 0.87); I^2=27%; absolute value per million 36,035 fewer, range from 16,586 fewer to 52,071 fewer]. The ARR is 3.60%. The NNT to achieve one less new case of T2D is 28 (95% CI 19, 60).

Secondary Outcomes: Hypertension

Change in Systolic Blood Pressure

Evidence Set 10 provides the GRADE Evidence Profile Table (10.1), the GRADE Summary of Findings Table (10.1), the forest plot (10.1), the funnel plot (10.1) and the Egger's test results (for publication bias) generated for the outcome of change in SBP for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including all 37 studies that reported SBP and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural).

Overall

Thirty-seven RCTs (n=16,668) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in SBP.[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,108-111,114,116-124,131,133] Across these studies, 36 included adults aged 18-64 years and one included adults 65 years and older. All studies included mixed gender samples. In 17 studies (46%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (one diet, one exercise, six diet plus exercise, 13 lifestyle), 15 were pharmacological [14 orlistat (120 mg three times daily), one metformin (850 mg once daily)] plus behavioural, and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or less in 22 studies and more than 12 months in 15 studies. One study was conducted in Canada, one in Canada and the US, 14 in the US, 17 in European countries, and four in Australia and/or New Zealand. Less than half of the studies (n=15) were published in the last five years; the remaining 22 studies were published between 1991 and 2008. Intervention participants had a significantly greater reduction in SBP as compared to the control group [MD (95% CI) -1.70 mmHg (-2.23, -1.17); I^2=41%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.01, df=1 (P=0.91), I^2=0%].

Behavioural Interventions

Twenty-two behavioural RCTs (n=7,644) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in SBP.[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,133] Across these studies, 21 included adults aged 18-64 years and one included adults 65 years and older. All studies included mixed gender samples. In nine studies (41%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, one was exercise, six were diet plus exercise, and 14 were lifestyle. Control participants received usual care from their physicians or no intervention; in six of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 12 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, eight in European countries, and three in Australia. Most of the studies (n=15) were published in the last five years; the remaining seven studies were

published between 1991 and 2008. Intervention participants had a significantly greater reduction in SBP as compared to the control group [MD (95% CI) -1.76 mmHg (-2.61, -0.91); I^2=50%].

Pharmacological plus Behavioural Interventions

Sixteen pharmacological plus behavioural RCTs (n=9,024) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in SBP.[108-111,114,116-124,131,133] All 16 studies included adults aged 18-64 years, and mixed gender samples. In eight studies (50%) the participants had a high risk of CVD. Orlistat (120 mg three times daily) was the pharmacological agent used in 14 studies and metformin (850 mg once daily; 850 mg twice daily) was used in two studies. Control participants followed the same diet and exercise instructions as the intervention participants but received placebos instead of the active medications. Intervention duration was 12 months or less in 10 studies and more than 12 months in six studies. One study was conducted in Canada and the US, five in the US, nine in European countries, and one in Australia and New Zealand. None of the studies were published in the last five years; all 16 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in SBP as compared to the control group [MD (95% CI) -1.70 mmHg (-2.28, -1.13); I^2=19%].

Change in Diastolic Blood Pressure

Evidence Set 11 provides the GRADE Evidence Profile Table (11.1), the GRADE Summary of Findings Table (11.1), the forest plot (11.1), the funnel plot (11.1) and the Egger's test results (for publication bias) generated for the outcome of change in DBP for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 36 of the 37 studies that reported DBP and a sub-analysis was conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural). Findings from the one remaining study could not be pooled and thus are reported narratively below.

Overall

Thirty-six RCTs (n=16,158) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in DBP.[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,108-111,114,116,117,119-124,131,133] Across the 36 studies, 35 included adults aged 18-64 years and one included adults 65 years and older. All studies included mixed gender samples. In 16 studies (44%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (one diet, one exercise, six diet plus exercise, 13 lifestyle), 14 were pharmacological [13 orlistat (120 mg three times daily), one metformin (850 mg once daily)] plus behavioural, and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or less in 21 studies and more than 12 months in 15 studies. One study was conducted in Canada, 14 in the US, 17 in European countries, and four in Australia and/or New Zealand. Less than half of the studies (n=15) were published in the last five years; the remaining 21 studies were published between 1991 and 2008. Intervention participants had a significantly greater reduction in DBP as compared to the control

group [MD (95% CI) -1.42 mmHg (-1.88, -0.96); I^2=63%]. There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.57, df=1 (P=0.45), I^2=0%].

Behavioural Interventions

Twenty-two behavioural RCTs (n=7,690) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in DBP.[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,133] Across these studies, 21 included adults aged 18-64 years and one included adults 65 years and older. All studies included mixed gender samples. In nine studies (41%) the participants had a high risk of CVD. In terms of intervention focus, one was diet, one was exercise, six were diet plus exercise, and 14 were lifestyle. Control participants received usual care from their physicians or no intervention; in six of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 12 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, eight in European countries, and three in Australia. Most of the studies (n=15) were published in the last five years; the remaining seven studies were published between 1991 and 2008. Intervention participants had a significantly greater reduction in DBP as compared to the control group [MD (95% CI) -1.60 mmHg (-2.27, -0.93); I^2=63%].

Pharmacological plus Behavioural Interventions

Fifteen pharmacological plus behavioural RCTs (n=8,468) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing change in DBP.[108-111,114,116,117,119-124,131,133] All of these studies included adults aged 18-64 years and mixed gender samples. In seven studies (47%) the participants had a high risk of CVD. Orlistat (120 mg three times daily) was the pharmacological intervention used in 13 studies and metformin (850 mg once daily; 850 mg twice daily) was used in two studies. Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in nine studies and more than 12 months in six studies. Five studies were conducted in the US, nine in European countries, and one in Australia and New Zealand. None of the studies were published in the last five years; all 15 studies were published between 1996 and 2005. Intervention participants had a significantly greater reduction in DBP as compared to the control group [MD (95% CI) -1.24 mmHg (-1.88, -0.61); I^2=65%].

One additional pharmacological plus behavioural RCT met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[118] This older study, conducted in both Canada and the US assessed the effect of orlistat (120 mg three times daily) on body weight, glycemic control, and cardiovascular risk factors in metformin treated type 2 diabetic patients. In contrast to the pooled effect of the meta-analysis for this review, the results of this study narratively reported a non-significant difference between the orlistat and placebo groups for DBP (no data provided).

KQ1a: Are there differences in efficacy between patient subgroups (e.g., age 65 years or older, sex, baseline cardiovascular risk status)?

Patient subgroup analyses were conducted only for the weight in kg outcome and only for baseline CVD risk status in behavioural and pharmacological plus behavioural intervention studies and for gender in behavioural intervention studies. Results of these sub-analyses are presented above (see sections 1.6, 1.7 and 1.8) and in Evidence Set 1 (see forest plots 1.6, 1.7 and 1.8). None of the included drug studies provided data for weight in kg by gender and there were only two behavioural intervention studies (one exercise and one lifestyle) that targeted older adults; conducting analyses for these patient subgroups was therefore not possible or not reasonable.

KQ1b: What are the adverse effects of primary care-relevant treatment interventions in overweight/obese adults [e.g., any adverse events, serious adverse events (requiring hospitalization or urgent medical care), gastrointestinal events, study withdrawal due to adverse events]?

A total of 30 studies included in this review provided data for at least one of the four categories of adverse effects: (1) any adverse events, (2) serious adverse events (requiring hospitalization or urgent medical care), (3) gastrointestinal events, and (4) study withdrawal due to adverse events.

Any Adverse Events

The category of any adverse events includes any and all types of harms experienced by study participants, whether mild, moderate or severe.

Evidence Set 12 provides the GRADE Evidence Profile Table (12.1), the GRADE Summary of Findings Table (12.1), the forest plots (12.1, 12.2), the funnel plot (12.1) and the Egger's test results (for publication bias) generated for the outcome of any adverse events for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 17 of the 20 studies that reported any adverse events and sub-analyses were conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural) and by participants' baseline CVD risk status (high, low/unknown; only for the pharmacological plus behavioural studies). Findings from the three remaining studies could not be pooled and thus are reported narratively below.

Overall

Seventeen RCTs (n=5,512) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of any adverse events.[108-111,114,116,117,119-124,131,133] All these studies included adults aged 18-64 years, and most studies (n=16) included mixed gender samples; one included only women. In eight studies (47%) the participants had a high risk of CVD. In terms of intervention focus, two were behavioural (both lifestyle), 14 were pharmacological [12 orlistat (11 studies used 120 mg three times daily; 1 study used 60 mg three times daily), two metformin (500 mg once daily; 850 mg once daily)] plus behavioural, and one

included both behavioural (lifestyle) and pharmacological (metformin: 1,500 mg once daily) plus behavioural arms. Intervention duration was 12 months or less in 15 studies and more than 12 months in two studies. One study was conducted in Europe and the US, three in the US, 10 in European countries, two in Australia and/or New Zealand, and one in China. About one-third of the studies (n=6) were published in the last five years; the remaining 11 studies were published between 1996 and 2005. Intervention participants were significantly more likely to experience adverse events as compared to the control group [RR (95% CI) 1.16 (1.09, 1.23); I^2=73%; absolute value per million 93,095 more, range from 52,756 more to 135,929 more] (forest plot 12.1). The absolute risk increase (ARI) is 9.31%. The number of patients who need to be treated before any adverse events occur [number needed to harm (NNH)] is 11 (95% CI 7, 19). The test for subgroup differences was significant [Chi^2=3.84, df=1 (P=0.05), I^2=74.0%] suggesting that, as compared to the control group, the risk of adverse events was higher in pharmacological plus behavioural interventions than in behavioural only interventions.

Behavioural Interventions

Three behavioural RCTs (n=561) of low GRADE quality (downgraded for risk of bias and imprecision) were included in the meta-analysis assessing the risk of any adverse events.[75,78,132] All three studies included adults aged 18-64 years. Two studies included mixed gender samples; one included only women. In one study (33%) the participants had a high risk of CVD. All three studies used lifestyle interventions. Control participants received usual care from their physicians or no intervention; in two of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in two studies and more than 12 months in one study. Two studies were conducted in the US and one in Australia. All three studies were published in the last five years (2010-2012). Across all three studies, only one of 301 intervention participants reported an adverse event (musculoskeletal injury that could not be conclusively related to participation). There was no difference in adverse events between the intervention and control groups [RR (95% CI) 0.19 (0.03, 1.16); absolute value per million 18,616 fewer, range from 22,332 fewer to 3,637 more] (forest plot 12.1).

Two additional behavioural intervention studies, both recently conducted in the US and both assessed as having unclear risk of bias, met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[80,96] During an 18 month exercise intervention study at least one injury or illness was experienced by 46% of the 397 participants (the seven most commonly reported injuries/illnesses were: lower body musculoskeletal, cold/flu/respiratory, back pain/injury, allergies, surgery, upper body musculoskeletal, and GI condition) and 32% of participants attributed at least one injury to exercise; percentages were not provided for intervention and control groups separately, however the authors indicated no significant differences were found between groups.[80] Results of another exercise intervention study lasting 12 months and targeting older (aged 60 to 89) adults (intervention n=180, usual care n=122), indicated 691 adverse events were reported across all participants, most of which were classified as not serious in nature and not attributed to increased

physical activity.[96] The 36 non-serious adverse events attributed to study participation included exacerbation of pre-existing joint or back pain (n=20), minor injury cause by a fall (n=5), pulled or sore muscle (n=4), heat exhaustion (n=3), knee, finger or head injury (n=3) and blisters (n=1). Only four of the 41 reported serious adverse events were or were possibly attributed to increased physical activity: radiating shoulder pain while walking on treadmill prompting hospitalization, a broken femur from a treadmill fall, a transient ischemic attack resulting in hospitalization, and shortness of breath which was later diagnosed as a myocardial infarction.

Pharmacological plus Behavioural Interventions

Fifteen pharmacological plus behavioural RCTs (n=4,951) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of any adverse events.[107,108,111,113,116,120,121,123,125-127,129-132] All 15 studies included adults aged 18-64 years, and mixed gender samples. In seven studies (47%) the participants had a high risk of CVD. In terms of pharmacological agents, 12 studies used orlistat (11 studies used 120 mg taken three times daily; one study used 60 mg three times daily), and three studies used metformin (500 mg once daily, 850 mg once daily, 1,500 mg once daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 14 studies and more than 12 months in one study. One study was conducted in Europe and the US, one in the US, 10 in European countries, two in Australia and/or New Zealand, and one in China. Four of the studies were published in the last five years; the remaining 11 studies were published between 1996 and 2005. Intervention participants were significantly more likely to experience adverse events as compared to the control group [RR (95% CI) 1.16 (1.09, 1.23); I^2=75%; absolute value per million 103,638 more, range from 59,970 more to 149,925 more] (forest plot 12.1). The ARI is 10.36%. The NNH is 10 (95% CI 7, 17). Most (about 80%) of the reported adverse events across orlistat studies fell into the category of mild to moderate gastrointestinal disturbance (see below for examples). The exact nature of the non-gastrointestinal injuries and illnesses were not always elaborated in the papers and few of these adverse events were considered to be related to the study medication; a couple studies indicated a small number of treatment participants experienced episodes of hypoglycemia or bronchitis. Comparatively fewer gastrointestinal symptoms were reported in the two studies involving metformin (three of six adverse events in the treatment group of one study and five of 34 events in the second study); the other complaints included rash (n=1), dizziness (n=9), headache (n=9) and acute upper respiratory tract infection (n=9). Sub-group analysis examining baseline CVD risk status (forest plot 12.2) showed that intervention participants at both high and low/unknown CVD risk were significantly more likely to experience adverse events as compared to high and low/unknown risk control participants [RR (95% CI) high risk: 1.09 (1.01, 1.18); P=0.03; I^2=70%; low/unknown risk 1.22 (1.13, 1.31), P<0.00001; I^2=60%]. The test for subgroup differences was significant [Chi^2=4.38, df=1 (P=0.04), I^2=77.1%] suggesting that, as compared to the control group, the risk of adverse events was higher for those with a low/unknown CVD risk at baseline than those with a high CVD risk at baseline.

One additional orlistat (60 mg three times daily) study recently conducted in the UK met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[58] Results of this three month, single group, pre-post design study indicated that 10 of the 26 participants (38%) experienced adverse events which were not described by the authors other than they were mild and most often gastrointestinal in nature (e.g., diarrhea).

Serious Adverse Events

Serious adverse events were categorized or described as such by study authors or there was an indication that the events resulted in hospitalization or required urgent medical care.

Evidence Set 13 provides the GRADE Evidence Profile Table (13.1), the GRADE Summary of Findings Table (13.1), the forest plots (13.1, 13.2), the funnel plot (13.1) and the Egger's test results (for publication bias) generated for the outcome of serious adverse events for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 14 of the 21 studies that reported serious adverse events and sub-analyses were conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural) and by participants' baseline CVD risk status (high, low/unknown; only for the pharmacological plus behavioural studies). Findings from the seven remaining studies could not be pooled and thus are reported narratively below.

Overall

Fourteen RCTs (n=10,811) of low GRADE quality (downgraded for risk of bias and imprecision) were included in the meta-analysis assessing the risk of serious adverse events.[71,78,107,109,111,116,117,120-123,127,129,133] All 14 studies included adults aged 18-64 years, and mixed gender samples. In eight studies (57%) the participants had a high risk of CVD. In terms of intervention focus, two were behavioural (both lifestyle), 11 were pharmacological (10 studies used 120 mg of orlistat three times daily; 1 study used 60 mg orlistat three times daily) plus behavioural, and one included both behavioural (lifestyle) and pharmacological (metformin: 850 mg twice daily) plus behavioural arms. Intervention duration was 12 months or less in nine studies and more than 12 months in five studies. One study was conducted in Europe and the US, four in the US, eight in European countries, and one in Australia and New Zealand. Less than one-third of the studies (n=4) were published in the last five years; the remaining 10 studies were published between 1998 and 2005. There was no difference between groups in the risk of serious adverse events [RR (95% CI) 1.07 (0.96, 1.20); I^2=0%; absolute value per million 7,382 more, range from 3,706 fewer to 19,730 more] (forest plot 13.1). There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.60, df=1 (P=0.44), I^2=0%].

Behavioural Interventions

Three behavioural RCTs (n=2,174) of low GRADE quality (downgraded for risk of bias and imprecision) were included in the meta-analysis that assessed the risk of serious adverse events.[71,78,133] All three studies included adults aged 18-64 years, and mixed gender samples. In

two studies (67%) the participants had a high risk of CVD. All three studies used lifestyle interventions. Control participants received usual care from their physicians or no intervention; in one of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was more than 12 months in all three studies. All studies were conducted in the US. Two were published in the last five years; the third was published in 1999. There was no difference between groups in terms of the risk of experiencing serious adverse events [RR (95% CI) 0.99 (0.80, 1.24); I^2=0%; absolute value per million 644 fewer, range from 24,989 fewer to 29,707 more] (forest plot 13.1).

Four additional behavioural intervention studies, all recently conducted in the US, met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[57,70,96,97] A pilot study investigating a the effects of a non-nutritive sweetener over 12 months with a very small sample of obese T2D participants (12 recruited; eight completed) and no control group reported a single uncomplicated myocardial infarction which was not attributed to consumption of the sweetener.[57] Participants (n=415) taking part in a lifestyle study for obese participants with at least one CVD risk factor reported 48 hospitalizations during the course of the 24 month intervention (15 in control arm, 15 in remote support arm, 18 in in-person support arm – no reasons given); in addition one participant in the in-person support arm was assaulted while exercising and suffered musculoskeletal injuries as a result.[70] Results of an exercise intervention study lasting 12 months and targeting older adults (intervention n=180, usual care n=122), indicated 41 serious adverse events were reported across all participants, only four of which were or may possibly be attributed to increased physical activity (i.e., radiating shoulder pain while walking on treadmill prompting hospitalization, a broken femur from a treadmill fall, a transient ischemic attack resulting in hospitalization, and shortness of breath which was later diagnosed as a myocardial infarction).[96] Finally the results of a 15 month lifestyle intervention assessed as having an unclear risk of bias indicated that serious adverse events attributed to study participation were experienced by four people in the coach-led intervention arm (three fractures, one case of chronic subdural hematoma); six additional hospitalizations not attributed to participation (no reasons given) were reported (three in coach-led intervention arm, one in self-directed intervention arm, two in usual care arm) but it was not clear if these events were experienced by six different individuals or if one or more individuals experienced more than one event.[97]

Pharmacological plus Behavioural Interventions

Twelve pharmacological plus behavioural RCTs (n=8,637) of low GRADE quality (downgraded for risk of bias and imprecision) were included in the meta-analysis assessing the risk of serious adverse events.[107,109,111,116,117,120-123,127,129,133] All 12 studies included adults aged 18-64 years, and mixed gender samples. In six studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 11 studies used orlistat (10 studied used 120 mg three times daily; one study used 60 mg three times daily) and one study used metformin (850 mg twice daily). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active

medications. Intervention duration was 12 months or less in nine studies and more than 12 months in three studies. One study was conducted in Europe and the US, two in the US, eight in European countries, and one in Australia and New Zealand. Two studies were published in the last five years; the remaining 10 studies were published between 1998 and 2005. There was no difference between groups in the risk of serious adverse events [RR (95% CI) 1.10 (0.97, 1.25); I^2=0%; absolute value per million 9,534 more, range from 2,779 fewer to 23,475 more] (forest plot 13.1). Descriptions were not usually given of the adverse events, often because they were not attributed to study participation (one study[127] reported four serious adverse events in the orlistat group including elective cystoscopy and hydrodistension, stroke, sleep disorder and benign fluid filled breast cyst). Sub-group analysis examining baseline CVD risk status (forest plot 13.2) showed no difference between intervention and control groups at both high and low/unknown CVD risk on the outcome of serious adverse events [RR (95% CI) high risk: 1.13 (0.70, 1.82); P=0.61; I^2=40%; low/unknown risk 1.10 (0.96, 1.25); P=0.17; I^2=0%]. There was no evidence that the effect of treatment differed based on baseline CVD risk (high, low/unknown) [Chi^2=0.02, df=1 (P=0.90), I^2=0%].

Three older orlistat studies conducted in the US and Europe, all moderately sized (n>600) and assessed as having unclear risk of bias, also met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[114,119,125] One study indicated that over the 24 months of the intervention only two serious adverse events occurred that might have been connected to orlistat treatment (one case of cholelithiasis and one case of diverticulitis); however it was not clear whether these events happened to the same individual or to two different participants and it was not clear which dose of the drug was being taken by the affected participant(s).[119] Another two year study reported that one participant died of acute myocardial infarction after 301 days of treatment with the 120 mg dose of orlistat; however the authors do not indicate if any other serious adverse events occurred in the 120 mg or the 60 mg dose groups.[114] Finally, the results of a six month trial investigating different doses of orlistat (30 mg, 60 mg, 120 mg and 240 mg) reported serious adverse events were experienced by two participants in the placebo group and by 12 participants across the four orlistat groups. Only four events were considered as remotely, possibly or probably related to treatment (fecal incontinence, diverticulitis, and two episodes of abdominal pain) and no data were provided specifically for the 120 mg dose participants.[125]

Gastrointestinal Events

Gastrointestinal events were described as such by study authors or the reported disturbances clearly fell within this category (e.g., fecal incontinence, flatulence, soft stools).

Evidence Set 14 provides the GRADE Evidence Profile Table (14.1), the GRADE Summary of Findings Table (14.1), the forest plots (14.1, 14.2), the funnel plot (14.1) and the Egger's test results (for publication bias) generated for the outcome of gastrointestinal events for the comparison between intervention participation and usual care or no intervention. The available evidence was limited to pharmacological plus behavioural studies. An analysis was performed including 23 of the 28 studies that reported gastrointestinal events and a sub-analysis was

conducted to look more closely at this comparison by participants' baseline CVD risk status. Findings from the five remaining studies could not be pooled and thus are reported narratively below.

Pharmacological plus Behavioural Interventions

Twenty-three pharmacological plus behavioural RCTs (n=12,954) of low GRADE quality (downgraded for risk of bias and reporting bias) were included in the meta-analysis assessing the risk of gastrointestinal events.[107,109,111-119,121-127,129-133] All 23 studies included adults aged 18-64 years and most (n=22) included mixed gender samples; one study included only women. In 11 studies (48%) the participants had a high risk of CVD. In terms of intervention focus, most studies (n=21) were pharmacological [19 orlistat (18 using 120 mg three times daily; one using 60 mg three times daily), two metformin (500 mg once daily; 850 mg once daily)] plus behavioural, and two included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg twice daily; 1,500 once daily) plus behavioural arms. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 18 studies and more than 12 months in five studies. One study was conducted in Canada and the US, one in Europe and the US, five in the US, 13 in European countries, two in Australia and/or New Zealand, and one in China. Only four studies were published in the last five years; the remaining 19 studies were published between 1996 and 2005. Intervention participants were significantly more likely to experience gastrointestinal events as compared to the control group [RR (95% CI) 1.58 (1.47, 1.70); I^2=71%; absolute value per million 187,235 more, range from 150,343 more to 226,998 more] (forest plot 14.1). The ARI is 18.72%. The NNH is 5 (95% CI 4, 7). Most (about 80%) of the adverse events experienced by participants in the orlistat trials (and some in the metformin trials) were gastrointestinal disturbances. Commonly reported symptoms across studies were fatty/oily stool, increased defecation, increased urgency, abdominal pain, soft stools, oily spotting, and flatulence. Most studies reported that the gastrointestinal events were typically mild or moderate in intensity and were experienced by participants only once or twice, usually near the beginning of treatment. Sub-group analysis examining baseline CVD risk status (forest plot 14.2) showed that intervention participants at both high CVD risk and at low/unknown CVD risk were significantly more likely to experience gastrointestinal events as compared to high and low/unknown risk control participants [RR (95% CI) high risk: 1.51 (1.36, 1.67); P<0.00001; I^2=70%; low/unknown risk 1.66 (1.48, 1.85); P<0.00001; I^2=70%]. There was no evidence that the effect of treatment differed based on baseline CVD risk (high, low/unknown) [Chi^2=1.57, df=1 (P=0.21), I^2=36.3%].

Four additional pharmacological plus behavioural studies (one metformin, three orlistat), all conducted in Europe, also met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[106,108,120,128] Results of one recent study indicated that 24 of the participants treated with 1,500 to 2,500 mg of metformin per day (15%) reported experiencing a variety of gastrointestinal side effects (e.g., diarrhea, bloating, abdominal pain); no corresponding data were provided for patients in the untreated control group.[128] An older study investigating orlistat (120 mg three times daily) as a treatment for obese patients with T2D

reported that 103 gastrointestinal events (no examples provided) occurred across the 111 participants who received the active medication and 48 gastrointestinal events occurred across the 109 participants who took the placebo.[108] An older 12 month orlistat (120 mg three times daily) trial provided data on the number of participants in each study group (intervention n=343, control n=340) that experienced various forms of gastrointestinal events (e.g., fatty/oily stool, increased defecation, oily spotting, soft or liquid stool, fecal urgency, flatulence, abdominal pain); except for abdominal pain which was slightly higher in the placebo group (9% vs. 7%), the overall frequency of experiencing each type of gastrointestinal event was higher in the orlistat group than in the placebo group.[120] Finally, a recent 12 month study with a low risk of bias indicated more mild to moderate gastrointestinal events (e.g., flatulence, constipation, abdominal pain, fatty/oily stool, increased defecation, increased urgency) were reported by the obese T2D participants who took orlistat (120 mg three times daily) than were reported by the control participants who took the placebo; however the difference between groups was not statistically significant.[106]

Withdrawals from Studies due to Adverse Events

This outcome captures the number of participants who reportedly withdrew their participation from studies as a direct result of experiencing adverse events.

Evidence Set 15 provides the GRADE Evidence Profile Table (15.1), the GRADE Summary of Findings Table (15.1), the forest plots (15.1, 15.2), the funnel plot (15.1) and the Egger's test results (for publication bias) generated for the outcome of withdrawal from studies due to adverse events for the comparison between intervention participation and usual care or no intervention. An overall analysis was performed including 26 of the 27 studies that reported withdrawals due to adverse events and sub-analyses were conducted to look more closely at this comparison by primary focus of intervention (behavioural, pharmacological plus behavioural) and by participants' baseline CVD risk status (high, low/unknown; only for pharmacological plus behavioural studies). Findings from the remaining study could not be pooled and thus are reported narratively below.

Overall

Twenty-six RCTs (n=12,987) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of withdrawal from studies due to adverse effects.[96,106,108-127,129-131] Across the 26 studies, 25 included adults aged 18-64 years and one included adults 65 years and older. All studies included mixed gender samples. In 13 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, one was behavioural (exercise) and 25 were pharmacological [23 orlistat (22 studies used 120 mg taken three times daily; one study used 60 mg three times daily), two metformin (500 mg once daily; 850 mg once daily)] plus behavioural. Control participants in the behavioural intervention study received usual care from their physicians. Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 21 studies and more than 12 months in five studies. One study was conducted in Canada and the US, one in the US and Sweden, six in the US, 16 in European countries, one in Australia and New Zealand, and

one in China. Less than one-fifth of the studies (n=5) were published in the last five years; the remaining 21 studies were published between 1996 and 2005. Intervention participants were significantly more likely to withdraw from their study due to adverse events as compared to the control group [RR (95% CI) 1.69 (1.43, 2.00); I^2=15%; absolute value per million 30,547 more, range from 18,892 more to 44,348 more] (forest plot 15.1). The ARI is 3.05%. The NNH is 33 (95% CI 23, 53). There was no evidence that the effect of treatment differed based on primary focus of intervention (behavioural, pharmacological plus behavioural) [Chi^2=0.21, df=1 (P=0.65), I^2=0%].

Behavioural Interventions

Only one behavioural RCT (n=302) of low GRADE quality (downgraded for risk of bias) provided data on withdrawals from the study due to adverse effects (forest plot 15.1).[96] This recently published, US-based, 12 month exercise intervention study included adults 65 years and older and a mixed gender sample that was not selected for high risk of CVD. Control participants received usual care from physicians. Study results showed no difference between groups in terms of withdrawing from the study due to adverse events [RR (95% CI) 3.40 (0.16, 70.16); no absolute value calculated]. The reason for withdrawal for both intervention group participants was severe pain.

One additional behavioural study recently conducted in the US with T2D participants met the inclusion criteria of this review but the data provided for this outcome could not be incorporated in the meta-analysis.[57] Two of the 12 participants initially recruited for this 12 month, single group, pre-post design, diet (non-nutritive sweetener) intervention withdrew in the first week of the study due to gastrointestinal symptoms (diarrhea, flatulence, bloating) and another participant with pre-existing asthma withdrew after two months due to a persistent dry cough that cleared after discontinuing the study.

Pharmacological plus Behavioural Interventions

Twenty-five pharmacological plus behavioural RCTs (n=12,685) of moderate GRADE quality (downgraded for risk of bias) were included in the meta-analysis assessing the risk of study withdrawal due to adverse effects.[106,108-127,129-131] All 25 studies included adults aged 18-64 years, and mixed gender samples. In 13 studies (52%) the participants had a high risk of CVD. Most studies used orlistat (22 used 120 mg three times daily; one used 60 mg three times daily) as the pharmacological intervention (n=23) while two studies used metformin (500 mg once daily; 850 mg once daily). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 20 studies and more than 12 months in five studies. One study was conducted in Canada and the US, one in the US and Sweden, five in the US, 16 in European countries, one in Australia and New Zealand, and one in China. Only four studies were published in the last five years; the remaining 21 studies were published between 1996 and 2005. Intervention participants were significantly more likely to withdraw from their study due to adverse events as compared to the control group [RR (95% CI) 1.68 (1.42, 2.00); I^2=18%; absolute value per million 30,930 more, range from 21,078 more to 45,300 more] (forest plot 15.1). The ARI is 3.09%. The NNH is 32 (95% CI 22, 47). Few studies elaborated on the adverse events that prompted

premature withdrawal; those that did primarily implicated unpleasant gastrointestinal side effects of the study medications. Sub-group analysis examining baseline CVD risk status (forest plot 15.2) showed that intervention participants at both high and low/unknown CVD risk were significantly more likely to withdraw from their study due to adverse events as compared to high and low/unknown risk control participants [RR (95% CI) high risk: 1.40 (1.06, 1.84); P=0.02; I^2=29%; low/unknown risk 2.02 (1.67, 2.45); P<0.00001; I^2=0%]. The test for subgroup differences was significant [Chi^2=4.63, df=1 (P=0.03), I^2=78.4%] suggesting that, as compared to the control group, the risk of study withdrawal was higher for participants with low/unknown CVD risk at baseline than those with a high CVD risk at baseline.

KQ1c: Are there differences in adverse effects between patient subgroups (e.g., age 65 years or older, sex, baseline cardiovascular risk status)?

Participant subgroup analyses were conducted only for baseline CVD risk status. Results of these sub-analyses are presented above (KQ1b) and in Evidence Sets 12 to 15 see forest plots 12.2, 13.2, 14.2 and 15.2. There was insufficient data to run additional subgroup analyses based on age or gender.

KQ1d: How well is weight loss or health outcomes maintained after an intervention is completed?

For sub-question KQ1d, we did not find any studies that examined how well weight loss or health outcomes are maintained after an intervention is completed that met the inclusion criteria. However the search for the full review located 10 papers eight studies concerning weight maintenance interventions following weight loss. In every instance, participants had been through an active weight loss phase then were assigned to an intervention or control group for a different strategy aimed at maintaining their weight loss. This body of evidence is summarized in a supplementary weight maintenance report available on the CTFPHC website http://canadiantaskforce.ca/.

KQ1e: What are common elements of efficacious interventions (behavioural and/or pharmacotherapy)?

Efficacious interventions were identified from studies included in the meta-analyses that showed a statistically significant effect size for any or all of the clinically significant outcomes of loss of ≥5% baseline body weight and loss of ≥10% baseline body weight, and at least four kilograms of weight loss,[67] (see Evidence Sets 1 to 3). A total of 29 studies included interventions or intervention arms that resulted in statistically significant effects for 5% and/or 10% weight loss and/or satisfied the four kg condition.

Behavioural Interventions

Fifteen behavioural studies showed statistically significant effect sizes for 5% and/or 10% weight loss and/or satisfied the four kg condition.[68,70,77,83,86,88,90,92,93,95,99,102-104,133] Some of the components we examined in these efficacious interventions were adapted from the features list presented in the 2011 USPSTF review.[5] We also included intervention duration, focus and setting as we believe

primary care physicians would want to take such features into consideration when making program recommendations to their patients. Table 9 offers a summary of the common features of the 15 efficacious behavioural interventions identified in this review. Our examination revealed that most of the interventions (n=13) were over 12 months in duration although the number of sessions and the primary setting varied across studies. Many (n=13) of the studies interventions were broad in scope (e.g., lifestyle) or included more than one approach (e.g., diet plus exercise). Another common feature of efficacious interventions (n=12) was the use of multiple modes of delivery such as group sessions combined with individual sessions or individual sessions combined with technology-based components. Finally, about half of the interventions applied weight loss goal setting (n=7) and/or encouraged active use of self-monitoring (n=8).

Pharmacological plus Behavioural Interventions

Fourteen pharmacological plus behavioural studies showed statistically significant effect sizes for 5% and/or 10% weight loss and/or satisfied the four kg condition.[106,108-110,112,114-118,120,122-124] The drug treatment in all of these studies was orlistat. We only included studies that administered a 120 mg dose three times daily in our meta-analyses for weight outcomes. All efficacious drug interventions were more than 12 months in duration and just over half of the studies included a run-in period ranging from two to five weeks. All of the studies incorporated a diet component (e.g., mildly hypocaloric, reduced calorie or low energy) that was followed by both the intervention and control arms. Participants in more than half of these studies were also encouraged to increase physical activity.

Results for Contextual Questions

We searched Medline, EMBASE and PsycINFO from January 2007 to August 2013 for any papers, with any study design, that might answer the Contextual Questions (CQ).

CQ1: Is there evidence that the burden of disease, the risk-benefit ratio of prevention or treatment, the optimal prevention or treatment method/access, and implementation differ in any ethnic subgroups or by age, rural and remote populations, or lower SES populations?

Summary of Findings

A total of 79 articles were screened for evidence relating to this question and 20[20,134-152] were included. All 20 reports were based on Canadian data. International studies were not reported here as relevant Canadian data were available. No evidence relating to prevention (Canadian or international) was identified. With regard to burden of disease, eight papers[20,136-138,141,142,146,147] considered variation by ethnic group. Two analyses reported estimates of the prevalence of obesity by age,[20,141] four reports discussed disease burden in rural and remote areas,[140,150-152] and 11 papers[20,134,135,139,141-144,148,149,151] considered the impact of socioeconomic status (SES). One paper[145] discussed optimal treatment in relation to aboriginal populations and to age. There was no information (Canadian or international) regarding optimal treatment method/access and

implementation in rural or remote areas, or in relation to SES. Finally, no evidence (Canadian or international) relating to the risk-benefit ratio of treatment was identified.

Burden of Disease

Ethnic Subgroups

Three studies[20,136,137] reported a relatively high prevalence of overweight and obesity among Canada's Aboriginal communities. A diabetes screening study of Manitoba First-Nations adults[136] concluded that the prevalence of obesity in this group was among the highest reported for a Canadian First Nation community living on a reserve (approximately 50% of men and 65% of women as defined by BMI), and substantially higher than off-reserve Aboriginal populations or the Canadian population in general. A cross-sectional survey of three Aboriginal communities in the Northwest Territories[137] reported that 65% of participants were classified as being overweight or obese. A 2011 joint report from the Public Health Agency of Canada and the Canadian Institute for Health Information[20] used data from several surveys to provide a summary of the prevalence of obesity among all First Nations, Inuit and Métis people in Canada. With the exception of Nunavut, the self-reported prevalence of obesity among Aboriginal peoples aged 18 years and older is higher than that of the general Canadian population in all Provinces and Territories. This difference is statistically significant in Québec, Ontario, Manitoba, Alberta and in Canada overall. Almost 26% of Aboriginal adults (excluding First Nations on-reserve) were estimated to be obese, with estimates being similar for Inuit (23.9%), Metis (26.4%) and off-reserve First-Nations populations (26.1%). Over one-third (36.0%) of on-reserve First-Nations were estimated to be obese.

Four studies used data from the National Population Health Survey (NPHS) and the Canadian Community Health Survey (CCHS) to assess differences in disease risk factors (obesity included) among immigrant groups to Canada.[138,141,142,147] Chiu et al.[138] examined the age- and sex-standardized prevalence rates of eight cardiovascular risk factors among white, South Asian, Chinese, and black persons living in Ontario, and reported variation in obesity rates among the racial subgroups (Chinese 2.5%, South Asian 8.1%, black 14.1%, white 14.8%). Based on data obtained from the 2005 CCHS, Slater et al.[141] reported a significantly higher relative risk of obesity among white Canadians compared with visible minorities [RR 1.45 (95% CI 1.26, 1.66); P<0.002] and among non-immigrants compared with immigrants who have been in Canada less than 10 years [RR 2.04 (95% CI 1.44, 2.89) P<0.002]. The relative risk estimates for overweight and obesity combined were also higher in white Canadians [RR 1.25 (95% CI 1.17, 1.33); P<0.002] and non-immigrants [RR 1.33 (95% CI 1.19, 1.49); P<0.002]. Similar findings were reported by Bergeron et al.[147] who also used the 2005 CCHS data, looking specifically at persons living in three Canadian metropolitan areas (Toronto, Montréal and Vancouver). Setia et al.[142] assessed whether the BMI of different immigrant groups to Canada converged to Canadian population levels over a 12-year period (1994-2006). They found that the mean BMI of non-white immigrants (male and female) was lower than that of Canadian-born individuals, while the BMI of white immigrant males was similar to that of Canadian-born males at the time of immigration. The

BMI of white immigrant females ranged between that of Canadian-born women and non-white immigrant women. After 12 years of follow-up, the mean BMI of all groups increased, however between-group differences (and similarities) remained constant, suggesting that convergence of BMI to Canadian levels may not occur over time in certain immigrant groups. A summary of the data reported in this study are provided in Table 10. Using a joint USA-Canada health survey to explore racial inequities in health,[146] Siddiqi et al. reported significantly higher odds of obesity among native-born American whites versus Canadian whites [OR 1.31 (95% CI 1.12, 1.55); P<0.05] and native-born American non-whites versus native-born Canadian non-whites [OR 2.80 (95% CI 1.75, 4.48); P<0.05], while the USA-Canada comparison of foreign-born whites and non-whites showed inter-country differences were not as pronounced or statistically significant.

Age

A paper by Slater et al.[141] reported age and sex-specific rates of obesity and obesity plus overweight combined, in Canadian adults aged 25-64. The data for this analysis were obtained from the 2005 CCHS and are provided in Table 11. A later analysis that also used data from the CCHS (2007-08)[20] reported that the prevalence of obesity in Canadian adults increases with age in both males and females, and peaks in the 55-64 age group for both sexes. The reported prevalence estimates are provided in Table 12.

Rural and Remote Populations

A provincial report on obesity[151] used data from seven cycles of the NPHS/CCHS to assess differences in obesity between rural and urban areas of Manitoba. Data from 2004 to 2008 showed obesity was lowest in urban areas (24.8-28.5% for males and 21.7-28.3% for females), higher in rural areas (28.5-38.0% for males and 26.0-38.7% for females), and highest in northern regions (39.8-42.6% for males and 31.7-40.9% for females).

An analysis that used data from the CCHS (2003) to study geography and overweight in Québec[140] reported significantly increased odds of overweight among men living in rural areas [OR 1.17 (95% CI 1.02, 1.33); P<0.05], after adjusting for demographic, socio-economic, and lifestyle characteristics.

A report on the health of rural Canadians[152] used data from four national data sources including the CCHS (2000-01) and found an increased odds of overweight and obesity in rural versus metropolitan regions in Canada (ORs ranged from 1.20 to 1.41 depending on Metropolitan Influence Zone (MIZ) category and gender, and were all statistically significant at P<0.05). At the same time, healthy dietary practices such as eating at least five servings of fruits and vegetables per day were lower than in urban areas (31.1-36.5% depending on MIZ category versus 38.2% in urban areas).

Using data from the 2003 CCHS and the 2001 Census, a national study on healthy weights[150] reported that adult Canadians living in locations outside an urban core (i.e., urban fringe, urban area outside census metropolitan area, secondary urban core, rural fringe, and rural areas outside census metropolitan areas) are significantly more likely to report a BMI of 25 and greater (55-57%

depending on location compared with 48% in an urban core; all comparisons between various locations and urban core were significant at P<0.05 level). One explanation provided was that people living in a city core are more likely to walk or bike, while those living in outer-areas may be more car-dependent.

Socioeconomic Status

Several Canadian studies relating obesity and SES have been conducted using data from the NPHS and the CCHS.[20,134,135,139,141-144,148,151]

An analysis conducted by Slater et al.[141] reported higher odds of obesity among Canadians with lower levels of education (ORs ranged from 1.32 to 1.40 depending on education level, compared with post-secondary graduates, and all comparisons were statistically significant at the P<0.002 level), and lower household incomes (ORs ranged from 1.20 to 1.33 depending on income level, compared with ≥$80,000/year, and all comparisons were statistically significant at the P<0.002 level). Analyses were adjusted for age and sex.

The authors of one study[134] reported variation across provinces in the relationship between income and BMI, and suggested that a possible contributing factor may be access to fresh produce which can be affected by regional availability, food prices, as well as by differing purchasing power due to variability in taxation rates.

One report[20] of an analysis conducted with data from the 2007-08 CCHS found that obesity tends to decrease as income increases among females, however this pattern was not seen in males, in whom obesity was relatively constant regardless of income. This trend was observed in the general population as well as in Aboriginal peoples. An inverse relationship between education and obesity in Canadian men and women was also reported, in both the general population as well as in Aboriginal peoples.

Godley et al.[135] explored the relationship between BMI and SES as measured by income and education after controlling for sociodemographic variables, and that found their results differed by the measure of SES used and by gender. Education was strongly and consistently inversely related to BMI for both men and women. The relationship between income and BMI was also consistently inverse in women; however men in the highest quartile of income had a higher BMI than men in the lowest income quartile. The authors suggested that cultural factors, as represented by educational attainment, may be more important than material factors, as represented by income, in explaining social class disparities in BMI.

McLaren et al.[139] studied the association between SES and BMI among Canadian men and women in 1978 and 2005. The 1978 data were obtained from the Canada Health Survey. They found an inverse relationship between BMI and education for both genders and at both time points, with no narrowing of this relationship over time. The observed association was stronger among women [ordinary least square regression coefficients for having at least a bachelor's degree versus less than a complete bachelor's degree were -0.78 (95% CI -1.4, -0.17) in 1978 and -0.57 (95% CI -1.05, -0.09) in 2005 among men; for women these coefficients were -0.96

(95% CI -1.8, -0.14) in 1978 and -1.3 (95% CI: -1.9, -0.67) in 2005]. There was no clear relationship between BMI and income for men, while this association for women was inverse and changed between the two time periods, with women in the middle income category being heavier according to the 2005 data. The authors suggested that this may be due to changes in women's participation in the workforce between the two time periods.

An analysis that assessed the BMI of adult (aged 18-54 years) immigrant men and women over a 12-year period[142] showed an inverse but not significant relationship between income and BMI, and reported a significantly lower BMI among all higher levels of education (at least secondary education), after adjusting for age, sex, visible minority status, marital status, and other factors.

In another study by McLaren et al.[143] the relationship between BMI and occupational prestige was studied. After adjusting for income and education, the authors found that women in higher-ranking positions tended to have lower BMI scores; however this relationship was not maintained after adjusting for education. Men in supervisory/managerial positions tended to be heavier than men in lower-ranking positions. The authors suggested that males in supervisory roles may benefit from a larger body size.

Combining data from the CCHS (2000-2004) and 2001 Census tract-level neighbourhood data, Matheson et al.[144] explored the relationship between neighbourhood material deprivation and BMI. While they found a positive relationship between these two factors in general [a one-unit increase in the neighbourhood material deprivation scale (scale range: -2 to 6) was associated with an increased BMI score of 0.12 kg/m^2], the effect for men and women was different, with higher mean BMIs reported among men living in more affluent neighbourhoods (1.0 point higher than men in more disadvantaged areas), and women living in poorer neighbourhoods (1.8 points higher compared with less deprived areas).

A study by Lee et al.[148] reported that the prevalence of obesity increased for all levels of income (between 2.8-4.1%, depending on income quartile) between 1993 and 2005.

An analysis of the Manitoba population[151] found decreased odds of obesity among people with at least a high-school education [OR 0.74 (95% CI 0.72, 0.76); $P<1E^{-10}$], and decreased but less pronounced odds of obesity among persons with higher household income (i.e., >$60,000 per year) [OR 0.9988 (95% CI 0.9977, 09988); P<0.01].

Using data from the Ontario Food Survey (1997-98), Ward et al.[149] explored the relationship between socioeconomic variation in lifestyle factors and overweight and obesity. The authors found a significant inverse relationship between high risk adiposity and income (β=-0.22, P<0.05) and education (β=-0.19, P<0.05) for women, but this relationship did not hold for men. Other potential contributing factors considered in the model included fruit and vegetable intake, long-term physical activity, and smoking status. Only fruit and vegetable intake was a mediator in the inverse relationship between high risk adiposity and education in women.

Optimal Treatment Method/Access and Implementation

Ethnic Subgroups and Age

A study by Schaefer et al.[145] assessed dietary intake and adequacy among Inuit women of childbearing age living in three communities in Nunavut. The authors reported that the prevalence of overweight and obesity among women living in these communities was >70%. There was inadequate consumption of dietary fiber and nutrients in general, and non-nutrient dense foods contributed to more than 30% of energy intake. The authors recommended that strategies be adopted to target the replacement of non-nutrient-dense foods with traditional foods and other nutrient-rich foods such as fruits, vegetables and grains.

CQ2: What are the resource implications and cost-effectiveness of overweight and obesity prevention/treatment in Canada?

Summary of Findings

Twenty-nine articles were screened for evidence relating to the resource implications of obesity and the cost-effectiveness of its treatment in Canada. Five articles relating to the resource implications of obesity treatment in a Canadian context were identified.[20,151,153-155] With regard to cost-effectiveness, no full Canadian economic evaluations were identified. The only economic assessment found was for a lifestyle modification program[156] and it did not report cost-effectiveness ratios. Seven systematic reviews of economic evaluations[157-163] were also identified. Two of the reviews[160,162] also conducted *de novo* economic evaluations; however the vast majority of the studies included in the seven systematic reviews were not conducted from a Canadian perspective. It is difficult to draw conclusions regarding the cost-effectiveness of interventions because assessments were conducted from the perspective of other jurisdictions; however the findings of the reviews have been summarized below for informative purposes.

Resource Implications

Several Canadian studies have used population-attributable fractions obtained from surveys and the literature, together with data from a national burden of illness study (*Economic Burden of Illness in Canada*) to estimate the economic costs attributable to obesity and overweight.[20,153,154] Moffat et al.[153] estimated the cost of obesity and overweight in Alberta in 2005. They estimated the total direct and indirect costs for that year to be $1.092B, and caregiver costs to be $181.8M, for an annual total of $1.274B. Anis et al.[154] estimated the economic burden of overweight and obesity at the national level, reporting total direct costs of $6.0B in 2006. An analysis done for a national report on obesity[20] also used this methodology to examine the change in the economic burden of obesity between 2000 and 2008; costs were estimated to have increased from $3.9B ($1.55B direct and $2.33B indirect costs) to $4.6B ($1.98B direct and $2.63B indirect costs) over that time period.

Tarride et al.[155] reported the economic burden associated with BMI in Ontario for 2000-01. Linking data from the CCHS to three administrative databases and using multivariate analyses,

the authors found that >50% of adults were overweight or obese, and that hospitalization costs were 40% higher and physician costs were 22% higher among the overweight and obese, compared with the normal weight population.

A Manitoba report[151] examined health care resource use among the adult overweight and obese. The authors considered the use of physician services, prescription drug use, hospitalization rates, inpatient days, rates of specific procedures (i.e., joint replacement, cholecystectomy, cardiac catheterization and revascularization), and home care. The authors reported that the obese group typically had the highest rates of health service use, and any differences between the normal and overweight groups tended to be small. This was the case for most health services examined, with the exception of cholecystectomy rates (similarly high in overweight and obese females), cardiac catheterization and revascularization rates (high in overweight and obese males, and comparatively low in females for all levels of BMI), homecare services (relatively similar across gender and BMI levels), and personal homecare (highest in the normal weight category).

Cost-effectiveness

Gagnon et al.[156] compared the effectiveness and costs of one year of an interdisciplinary intervention consisting of individual counselling every six weeks and 25 group seminars, to group seminars alone. Participants included men and women with a BMI of $\geq$27 kg/m^2. Participants in the intervention group had clinically and statistically significant changes in average weight (4.9 kg) and waist circumference (5 cm), while no significant changes were observed in the group seminar arm. The estimated cost of the combined intervention was CDN$733.06/year, while that of the seminar alone was CDN$81.36/year. The authors concluded that participation in low-cost, moderate-intensity interdisciplinary approaches combined with group seminars leads to clinically important weight loss.

Wieland et al.'s systematic review of computer-based interventions for weight-loss or weight maintenance in the overweight or obese[157] included three American economic evaluations on weight loss, however the authors considered two of the studies to be technologically outdated, and the third was conducted among military personnel and its broader applicability was questioned by the authors. Therefore the details of this review are not reported here.

A systematic review of economic evaluations of adult weight management interventions[158] included 44 articles; 21 of behavioural interventions, 12 of surgical interventions, and 11 of pharmacological plus behavioural interventions. The reviewed studies originated in the United States (n=22), Australia (n=4), the Netherlands (n=4), and various other countries (n=10). The objective of the review was to assess the methods used in each of the studies, and to determine whether methodology affected the results of the evaluations. While quality of life is an important outcome in assessing the impact of obesity interventions, only 12 studies considered this outcome. Among these 12 studies, the intervention was more cost-effective than standard of care in only three of these analyses, however it is unclear to what extent modelling methods could explain this finding. The authors found that many of the models used in the evaluations were not suitable for chronic diseases with changing health risks, and called for methodological

improvements in terms of using recommended practices in economic modelling and a better assessment of the long-term consequences of obesity.

Lehnert et al.[159] conducted a systematic review of the long-term cost-effectiveness (defined as ≥40 years) of obesity prevention interventions. The authors identified 18 cost-utility analyses of 41 interventions (21 behavioural, 12 community, and eight environmental) that originated in the US, Australia, Mexico, the Netherlands, the UK, New Zealand, and Switzerland. They reported that 24 interventions were shown to be cost-effective. Ten interventions (six community-based and four behavioural) had cost-utility ratios of >$50,000US (generally considered to be not cost-effective). Finally, seven environmentally-targeted interventions were reported to be cost-saving.

Loveman et al.[161] published a systematic review of the clinical and cost-effectiveness of long-term weight management schemes for adults. The authors identified 419 studies in their cost-effectiveness searches, but none met their full inclusion criteria. They included two of these studies in the review, nonetheless, with a cautionary note as to their failure to meet all inclusion criteria (i.e., one study used prescription anti-obesity drugs in some participants, and the other study had a follow-up of less than 18 months). One study was conducted from a US perspective, and the other in the UK. The studies used lifetime chronic disease models and included both the costs and benefits of avoiding chronic illnesses. Both studies used some combination of diet, exercise, pharmacotherapy and behavioural interventions as comparators, and found all the interventions to be cost-effective. The most cost-effective and efficient strategy was a combined intervention of diet, exercise and behavioural modification with a cost per QALY gained of $12,640US. The diet-only strategy was less effective and more costly than routine care, the diet and pharmacotherapy and diet and exercise strategies were less effective and less costly than the triple intervention.

Neovius and Narbro[163] published a systematic review of cost-effectiveness studies of pharmacological plus behavioural anti-obesity treatments. They identified 14 studies (11 cost-utility and three cost-effectiveness analyses), nine of which were on orlistat, four on sibutramine (withdrawn from the Canadian market due to side effects), and one on rimonabant (not approved by the FDA or Health Canada and eventually withdrawn from the UK market). All analyses were conducted in western European countries or the United States. The authors found that all the economic evaluations reported the interventions to be cost-effective, but noted that uncertainty remained regarding weight loss sustainability and long-term health benefits and utility gains associated with weight loss.

A systematic review of the clinical and cost-effectiveness of using drugs to treat obese patients in primary care was conducted by Ara et al.[160] The authors identified 14 published articles on the cost-effectiveness of orlistat, sibutramine, and rimonabant and found that the studies generally reported cost-effective results. The authors then conducted an independent economic evaluation of all three drugs from a UK perspective, which modelled diet and exercise plus one of the pharmacological plus behavioural alternatives or placebo, on changes in body mass and the occurrence of various obesity-related health events and states (e.g., stroke, myocardial infarction,

diabetes). All treatment alternatives were found to be highly cost-effective versus placebo (range: £557-£3553 per QALY). Given the dangers subsequently found to be associated with sibutramine and rimonabant, the authors acknowledged that apart from the clinical implications, accounting for the adverse effects later associated with these treatments in the economic analyses would have likely rendered these two treatments not cost-effective.

Bogers et al.[162] explored the relationship between the costs of lifestyle interventions and weight loss in overweight adults. After examining 14 reviews as well as the results of a systematic MEDLINE search, the authors identified and selected 19 randomized trials that described 31 interventions (countries of origin not provided). The regression model that they constructed to explore the relationship between intervention costs and weight loss explained 47% of the variance in weight loss, and reported that clinically-relevant loss of at least 5% of baseline body weight was seen for interventions which cost as little as €110. However the effects on weight loss seemed to level off at about 6%, even with growing costs.

CQ3: What are patients' and practitioners' values and screening preferences regarding overweight and obesity prevention and/or treatment?

Summary of Findings

Six articles were screened and three[164-166] were found to contain relevant information relating to this question.

Patients' Values and Preferences

Garip and Yardley[165] synthesized the findings of 17 qualitative studies (eight from the USA and Canada, five from the UK, three from Europe, and one from Australia) of the views and experiences of overweight and obese persons who participated in weight management programs. A total of 290 people participated in these studies, and the majority (at least 224) were women. The authors derived 11 themes from the reviewed studies, specifically: 1. *Health concerns related to excess weight* were a motivating factor for participation in weight management programs; 2. *Expectations of weight management* varied and may influence weight management attempts; 3. *Attributions for weight gain and the maintenance of excess weight* were often made when people were not trying to manage their weight; 4. *Psychological facilitators* included mental preparedness or understanding one's eating patterns; 5. *Psychological barriers* included lack of will-power, lack of knowledge or skills, psychological problems, or reverting to old dietary habits; 6. *Self-perception and body image* (both negative and positive) were important factors in motivation; 7. *Stigmatizing experiences relating to excess weight* may hinder some people from taking up public activities to manage their weight; 8. *Socio-cultural factors* (e.g., support vs. pressure from family and friends) may facilitate or hinder weight loss; 9. *Environmental factors* such as barriers to healthy foods and safety (i.e., for physical activity in one's neighbourhood); 10. *Experiences with weight management programs* including support and contact with health professionals and peers, as well as the structure provided by the program, may have a positive influence on outcome; and 11. *Positive outcomes of participating in a*

weight management program, such as weight loss, psychosocial benefits, improved mobility, self-acceptance, and relationships with others, may encourage individuals to adhere to weight management efforts.

No evidence on patients' values or preferences for screening was identified. The lack of available evidence may be due to the fact that our search for the contextual questions was limited to the past five years; therefore earlier studies which looked at patient preferences for screening for obesity would not appear in our results.

Practitioners' Values and Preferences

Piccinini-Vallis et al.[164] conducted a survey of practitioners' awareness of and familiarity with the *2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children,* including the frequency with which practitioners measured weight, calculated BMI, and measured waist circumference in overweight and obese patients. A random sample of 425 general practitioners were selected to complete a mailed questionnaire, and 36.9% (n=157) responded. Almost 38% of the respondents reported being aware of the guidelines, and had a mean familiarity rating of 2.72 (1=not at all familiar, 5=very familiar). Physicians who were aware of the guidelines were more likely to calculate BMI. Other factors that predicted the likelihood of calculating BMI were physician's own BMI and access to an electronic medical record (EMR). Measurement of waist circumference was more likely if the physician was in a group (vs. solo) practice. Physicians in urban practices were significantly more likely to be aware of the guidelines than those in rural practices.

In the *2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children,*[166] Dent et al. discuss physician-related barriers to weight management and physicians' attitudes toward overweight and obesity. Based on a literature search, they concluded that only 40% of obese people receive recommendations from their physicians regarding weight loss and weight management, even when they have related comorbidities. Based on comparison of surveys conducted before and after 1999, obese people may be subject to negative bias by the medical community, which may in turn be a barrier to the care of these individuals. A tendency to blame patients for their obesity was a consistent view reported across physicians, nurses, medical students, and dieticians.

General Summary of Evidence for CQ1, CQ2 and CQ3

Data Gaps

- Studies relating to the risk-benefit ratio of prevention interventions were not identified;
- Studies regarding optimal prevention method, access, and implementation were not identified, and only limited information was found on treatment (one study);
- Canadian economic evaluations of overweight and obesity interventions are lacking

Findings

- Higher rates of obesity have been observed among Canada's Aboriginal peoples compared with the general Canadian population;
- The rate of overweight and obesity among Inuit women of childbearing age is substantial, and nutritional deficits are common;
- Visible minority immigrants tend to have lower BMIs than the general Canadian population, both at the time of immigration and over time, while the BMIs of non-visible minority immigrants are more similar to those of native-born Canadians;
- Average Canadian overweight and obesity rates increase with age and peak between the ages of 55 and 64, after which time they decline;
- Obesity tends to be higher in rural areas (compared with urban areas) and may be even higher in northern regions. Possible explanations may be differences in dietary practices, food access and physical activity;
- There is a general inverse relationship between obesity and socioeconomic status, however, this relationship has been found to differ by gender and by measure of socioeconomic status, and may be mediated by factors such as regional taxation rates, dietary practices and food access, type of profession, and other societal factors;
- Recent estimates of the economic burden of overweight and obesity in Canada are significant and vary between $4.6B (2008 direct and indirect costs) and $6.0B (2006 direct costs only) per year;
- Costs of healthcare among the overweight and obese combined are higher than those of the general Canadian population; however one provincial study found that obese persons have higher rates of use of some health care services compared with overweight and normal-weight individuals, which tend to be similar;
- A large proportion of international economic evaluations of the prevention and treatment of obesity report these interventions as cost-effective;
- Patients' preferences and values regarding overweight and obesity prevention and treatment are based on multiple and sometimes complex internal and external factors. Practitioners' attitudes towards obesity may influence patients' decisions to seek or access treatment;
- Physicians' measurement of weight or BMI is greatly influenced by awareness of guidelines. Other influences include physicians' personal BMI, access to electronic medical records, whether the practice is based in an urban or rural area, and whether physicians are in group versus solo practice.

CQ4: What are the most effective (accurate and reliable) risk assessment tools identified in the literature to assess future health risk as a result of obesity?

One study was found that examined a risk assessment tool for obesity[167] and one study was found that looked at assessing mortality risks in already obese adults.[168]

A study conducted with French people assessed the relationship between dietary quality and the development of obesity.[167] The study assessed and compared the predictive value of six different dietary scores on relative weight change and risk of obesity after 13 years of follow-up. The six dietary scores were the French Programme National Nutrition Santé-Guideline Scores (PNNS-GS), the Dietary Guidelines for Americans Index (DGAI), the Diet Quality Index-International (DQI-I), the Mediterranean Diet Scale (MDS), the relative Mediterranean Diet Score (rMED) and the Mediterranean Style Dietary Pattern Score (MSDPS).This study included participants aged 45-60 years at baseline who provided 24-hour dietary records for two years with no missing dietary, anthropometric or covariate data (n=3,151). Among the non-obese men at baseline, 123 became obese and among the 1,385 non-obese women, 84 became obese. For men the odds ratios (OR) of becoming obese after 13 years associated with one standard deviation increase in dietary score values ranged from 0.63 (95% CI 0.51, 0.78) for DGAI to 0.72 (95% CI 0.59, 0.88) for MDS (fully adjusted models), while the MSDPS displayed non-significant associations. In women, no association between the dietary scores and obesity risk were found. A non-significant risk reduction was found for one standard deviation increase of rMED [OR 0.82 (95% CI 0.65, 1.03)], DGAI [OR 0.86 (95% CI 0.68, 1.08)] and PNNS–GS [OR 0.94 (95% CI 0.73, 1.21)].

A study in Texas examined whether the Edmonton Obesity Staging System (EOSS), was helpful to identify obese individuals who are at greater mortality risk.[168] Data from the Aerobics Center Longitudinal Study (n=29,533) were used to assess mortality risk in obese individuals by EOSS stage [follow-up (SD), 16.2 (7.5) years]. The effect of weight history and lifestyle factors on EOSS classification was explored. Obese participants were categorized, using a modified EOSS definition, as stages 0 to 3, based on the severity of their risk profile and conditions (stage 0, no risk factors or comorbidities; stage 1, mild conditions; and stages 2 and 3, moderate to severe conditions). Compared with normal-weight individuals, obese individuals in stage 2 or 3 had a greater risk of all-cause mortality [stage 2 hazard ratio (HR) (95% CI), 1.6 (1.3, 2.0); stage 3 HR, 1.7 (1.4, 2.0)] and cardiovascular-related mortality [stage 2 HR, 2.1 (1.6, 2.8); stage 3 HR. 2.1 (1.6, 2.8)]. Stage 0/1 was not associated with higher mortality risk. Lower self-ascribed preferred weight, weight at age 21, cardiorespiratory fitness, reported dieting, and fruit and vegetable intake were each associated with an elevated risk for stage 2 or 3. The authors suggest that given the health risk associated with the weight cycling that many obese people experience, physicians should consider promoting weight maintenance as opposed to weight loss especially for patients who score an EOSS stage 0 and 1.

Results for Supplemental Questions

SQ1: Is there direct evidence that primary care screening programs for adult overweight or obesity improve health outcomes or result in short-term (12 month) or sustained (>12 month) weight loss or improved physiological measures?

For the supplemental questions, we did not find any studies that examined primary care screening programs for adult overweight or obesity that met the inclusion criteria for this review.

Chapter 4: Discussion, Limitations and Conclusion

Discussion

To address the questions of interest, this review used a systematic review process and the quality of the included evidence was evaluated using the GRADE system.[61] A substantial body of high level (RCT) and direct evidence was found to answer most of the key questions.

In this review we considered five measures of weight loss: weight loss in kg, loss of ≥5% of baseline body weight, loss of ≥10% of baseline body weight, reduction in waist circumference, and reduction in BMI. Pooled effect estimates for all weight outcomes were statistically significant in favour of the interventions. Intervention participants had 3.02 kg greater weight loss, 2.78 cm greater reduction in waist circumference, 1.11 kg/m^2 greater reduction in BMI, and were more likely to lose ≥5% (RR 1.77) and ≥10% (RR 1.91) of their baseline body weight as compared to control participants at post treatment assessment. While statistically precise reductions in weight measures were observed, the clinical significance of these modest benefits should be considered. In terms of absolute weight loss, across the 49 studies (55 intervention arms) experimental participants lost just over three kg by the end of the active phase of intervention which is not considered clinically or personally meaningful. In only 16 arms across nine studies (seven behavioural, two pharmacological plus behavioural) was the reduction more than four kg[65] and only men in one treatment arm of an older behavioural study showed a decrease of more than 10 kg. Fewer studies provided data for the conventionally applied indicators of clinically significant weight loss. Across the 24 studies that reported on loss of ≥5% baseline body weight, 21 interventions (eight of 11 behavioural, 13 pharmacological plus behavioural) showed a significant effect. The smaller body of evidence that looked at the greater loss of ≥10% baseline body weight showed a significant effect for only one of three behavioural interventions and 11 of 13 pharmacological plus behavioural interventions. However the overall findings for achievement of ≥5% or 10% weight loss, with NNTs of 5 and 9 respectively, are very important clinical findings. Offering these interventions in primary care could provide important benefits to the population of patients. Based on the evidence available for this review, we are unable to comment on the long-term sustainability of weight loss benefits (although a supplemental report was prepared to consider the evidence provided by eight studies of weight maintenance interventions initiated following active weight loss, available on the CTFPHC website http://canadiantaskforce.ca/).

There was no significant difference between behavioural and pharmacological plus behavioural interventions on any weight outcome. Additional sub-analyses performed on studies providing weight change in kg data found only two significant differences. First, across the four types of behavioural interventions (diet, exercise, diet plus exercise, lifestyle), exercise alone was the only approach that showed no statistically significant effect on weight loss in the intervention group as compared to the control group [test for subgroup differences P=0.03, I^2=67.8%; exercise MD (95% CI) -1.49 kg (-3.32, -0.35); I^2=85%]. Second, across the behavioural interventions, participants' baseline CVD risk status (high, low/unknown) was associated with a statistically significant

difference in the intervention effect on weight loss (test for subgroup differences P=0.005, I2=87.6%). While both sub-groups of intervention participants lost significantly more weight than control participants [MD (95% CI) low/unknown CVD risk -3.66 kg (-4.59, -2.74), I^2=92%; high CVD risk -1.89 kg (-2.69, -1.08), I^2=75%], the difference between groups was significantly greater in studies that included adults with low/unknown CVD risk. Other than these two explanations, the high statistical heterogeneity across studies in most sub-analyses is most likely due to small versus large treatment effects observed across studies.

In addition to the primary weight outcomes we examined the available evidence for six secondary health outcomes: total cholesterol, LDL-C, SBP, DBP, fasting glucose, and incidence of T2D. Pooled effect estimates for all these outcomes were statistically significant in favour of the interventions. Intervention participants had small but significantly greater reductions in LDL-C level (0.21 mmol/l), SBP (1.7 mmHg), DBP (1.4 mmHg) and fasting blood glucose level (0.26 mmol/L) compared to control participants at the post treatment assessment. These findings are of questionable clinical significance for individuals, but may be important at the population level. Modest weight reduction, corresponding to loss of ≥5% or ≥10% of baseline body weight (NNTs of 5 and 9 respectively) had clinically important effects, most notably a 38% reduction (NNT 17) in the incidence of T2D. With prevalence rates for T2D in the US and European Union[169] of 9.3% and 10% respectively, coupled with its increasing prevalence, a 38% reduction in the incidence of T2D could have a significant benefit on population health. Based on the evidence available for this review, we are unable to comment on the long-term sustainability of any secondary health benefits.

The benefits of treatment must be considered in light of any harm induced by or associated with the interventions. For this review we looked at the available evidence for harms data in four categories: any adverse effects, serious adverse effects (requiring hospitalization or urgent medical care), gastrointestinal effects, and withdrawal from studies due to adverse effects. As expected, very few behavioural studies reported adverse events, and when they did, the harms were usually injuries associated with physical activity and the number of events was typically quite low. Furthermore, no significant differences were found between behavioural intervention and control groups across adverse effects categories. Adverse effects were more commonly experienced by participants in pharmacological plus behavioural studies and were significantly more likely to be reported by those taking the active medications. Compared to control participants, adults who took a 120 mg dose of orlistat three times daily were more likely to report having experienced at least one (any) adverse event during the course of the intervention (RR 1.16), they were more likely to have experienced at least one gastrointestinal event (RR 1.58), and they were more likely to have withdrawn from their study due to adverse events (RR 1.68). Only the category of serious adverse events showed no significant difference between those taking the drug and those taking the placebo [RR (95% CI) 1.10 (0.97, 1.25); I^2=0%]. Sub-group analysis on the adverse effects data was only possible using the baseline CVD risk status comparison (high, low/unknown). Significant sub-group differences were found for two categories of harm. As compared to the control group, those with low/unknown CVD risk at

baseline were more likely to report having experienced at least one adverse event and to withdraw from the study due to adverse effects than those with high CVD risk at baseline.

To answer the sub-question about features of efficacious interventions we used a point estimate threshold of four kg of weight loss or a statistically significant effect for loss of ≥5% or loss of ≥10% of baseline body weight to identify relevant interventions (or intervention arms). Fifty-one studies were included across the three meta-analyses for the outcomes of weight change in kg, ≥5% weight loss and ≥10% weight loss. Just over half (n=29, 57%) of these studies either met the four kg cut point and/or showed significant results for the percentage weight loss outcomes; this included about an equal number of behavioural interventions (n=15) and pharmacological plus behavioural interventions (n=14). The common features of efficacious behavioural interventions included: duration over 12 months, broad scope (lifestyle, diet plus exercise), use of multiple delivery modes (e.g., individual sessions plus technology-based components); about half of these interventions also used weight loss goal setting and self-monitoring. Efficacious pharmacological plus behavioural interventions were all more than 12 months in duration and were implemented in conjunction with a diet component; just over half of these studies included a run-in period and in about half the participants were also encouraged to increase physical activity.

Our review of the literature for the contextual questions provided important information for understanding the unique nature and extent of the obesity problem in Canada. In this country, rates of obesity are higher in Aboriginal people, rural areas and northern regions. Conversely, recent and newly established (in Canada for up to 12 years) visible minority immigrants tend to have lower BMIs than the general Canadian population. In Canada the economic burden of overweight and obesity is significant and ranges between $4.6B and $6.0B per year. The costs of healthcare among overweight and obese populations combined are higher than the general population. On the positive side, international economic evaluations have reported that treatment interventions are cost-effective. Despite the fiscal arguments supporting these interventions, overweight and obese adults' values and preferences regarding treatment are based on a complex combination of internal and external factors and whether they choose to seek/access treatments is a decision that can be influenced by their primary care providers' attitudes about obesity. Physicians' decisions to assess patients' weight status are influenced by a number of factors including their awareness of the guidelines, personal BMI score, access to electronic medical records, and the size and location of their practice. Except for the Edmonton Obesity Staging System which was identified as a helpful strategy for identifying obese individuals at greater mortality risk, the contextual questions search found little evidence about effective risk assessment tools.

The findings for the primary weight outcomes in this review are consistent with the findings reported in the recent USPSTF review.[5] Extending the timeframe of the USPSTF search by 36 months garnered an additional 32 studies, but the expanded pool of evidence did not point to changes in any important outcomes. We were able to conduct some additional analyses. Future research could benefit from longer term follow-up to examine weight loss maintenance, to study the effects of repeated weight loss and regain, and to determine if improvements in health

outcomes are related to the interventions apart from weight loss.[5] However, the volume of and consistency in the evidence suggest we no longer need to study the same treatments; new research on weight loss interventions should test novel approaches. Furthermore, given the apparent lack of evidence in this area, future research should also be conducted to provide clarity on the question of the most appropriate primary care screening measure(s) for adult overweight/obesity.

Limitations

Limitations of this review may affect the validity and generalizability of the findings.

Almost all of the evidence used to answer the key questions was taken from studies that could not be comprehensively assessed for risk of bias, primarily due to the lack of information about or lack of procedures to ensure random sequence generation, allocation concealment and blinding of participants, personnel and/or outcome assessment. All of the drug studies were funded by pharmaceutical companies. In addition 65% of the drug studies included in the analysis of treatment benefits had pre-randomization run-in periods lasting two to four weeks that involved very low calorie diets and/or placebo, which may have exaggerated the potential benefits of treatment. Potential reporting bias was also identified across a number of outcome/comparison-based study groupings. The relatively high attrition rates observed in many of the included studies leads to further risk of bias. Taken together, these methodological limitations reduced the strength of the evidence, resulting in moderate and sometimes low quality GRADE ratings which reduce confidence in the pooled estimates of observed effect.

Studies were categorized as diet, exercise, diet and exercise or lifestyle, yet each category represents a wide range of treatment approaches. A high degree of heterogeneity was noted in all groups of studies and a review of efficacious interventions revealed many differences, thus providing limited guidance on key components to include in practice.

Most studies were of relatively short duration (≤12 months), and we were unable to address the question of whether (and for how long) weight loss is maintained after interventions are complete.

Results presented for secondary outcomes (total cholesterol, LDL-C, fasting glucose, blood pressure, incidence of T2D) should be interpreted with caution as we only included interventions that had a focus on weight loss; we did not include studies of, for example, effectiveness of behavioural interventions on cholesterol if the paper did not report weight outcomes.

Adverse events data were extracted as reported, even when the connection to the intervention was not clear and even if the data included events that occurred during a run-in period; this approach may have led to an overestimation of adverse events.

No studies were found that examined primary care screening programs for adult overweight or obesity that met the inclusion criteria; thus none of the supplemental questions could be answered.

Finally, we restricted our search to papers in English or French, thus we may have missed the opportunity to analyze data from papers written in other languages.

Conclusion

The obesity epidemic has become a global phenomenon and is an important health issue in Canada. The best solution to this problem is to prevent people from becoming overweight or obese in the first place. When this does not happen there are treatment options available to help people lose weight. The evidence in this systematic review supports the conclusion that behavioural and pharmacological plus behavioural interventions are associated with statistically significant reductions in weight as well as improvements in other health outcomes, although the benefits of drug treatments should be considered in light of the significant adverse effects that are also experienced by those who take these medications. It is a novel and clinically important finding that these interventions appear to lead to at least a 5% weight reduction (NNT 5) which in turn may confer important health benefits including reduced risk of T2D (NNT 17) and reduced need for drug treatments for blood pressure and glycemic control.

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Figures

Figure 1: Analytic Framework

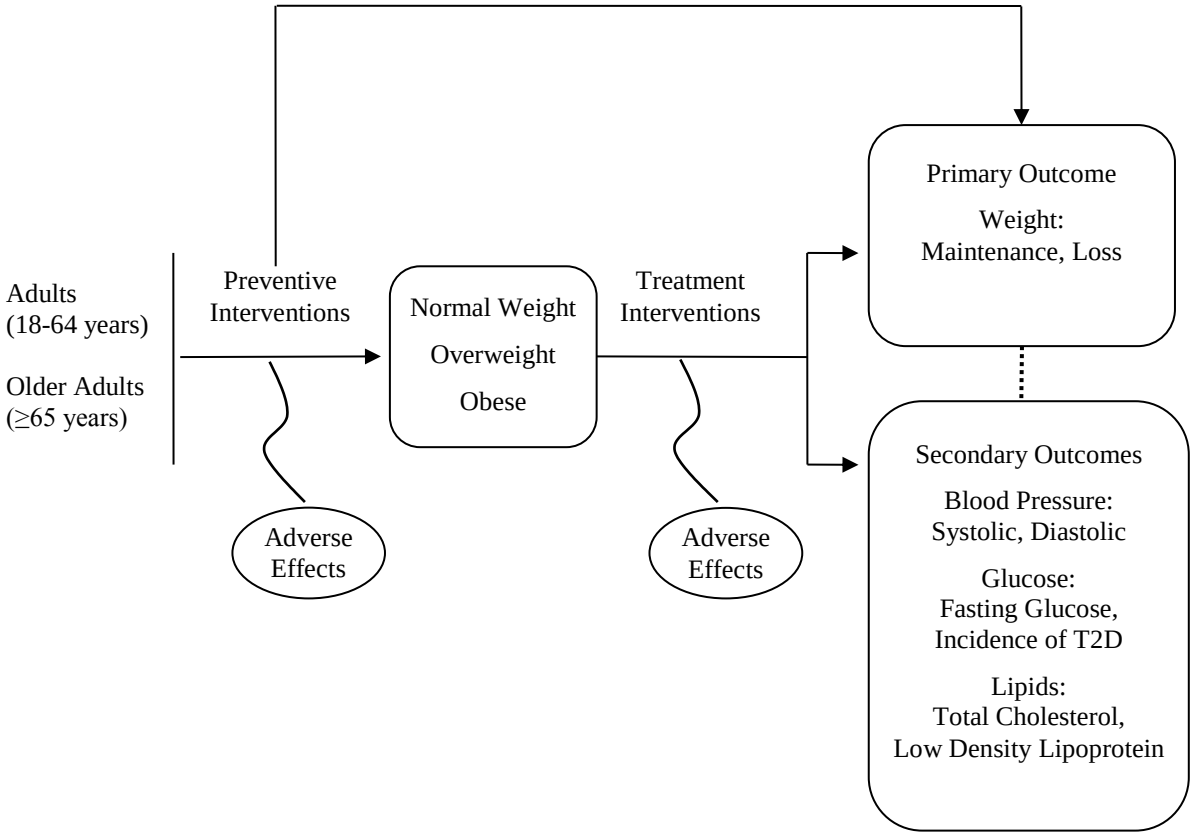
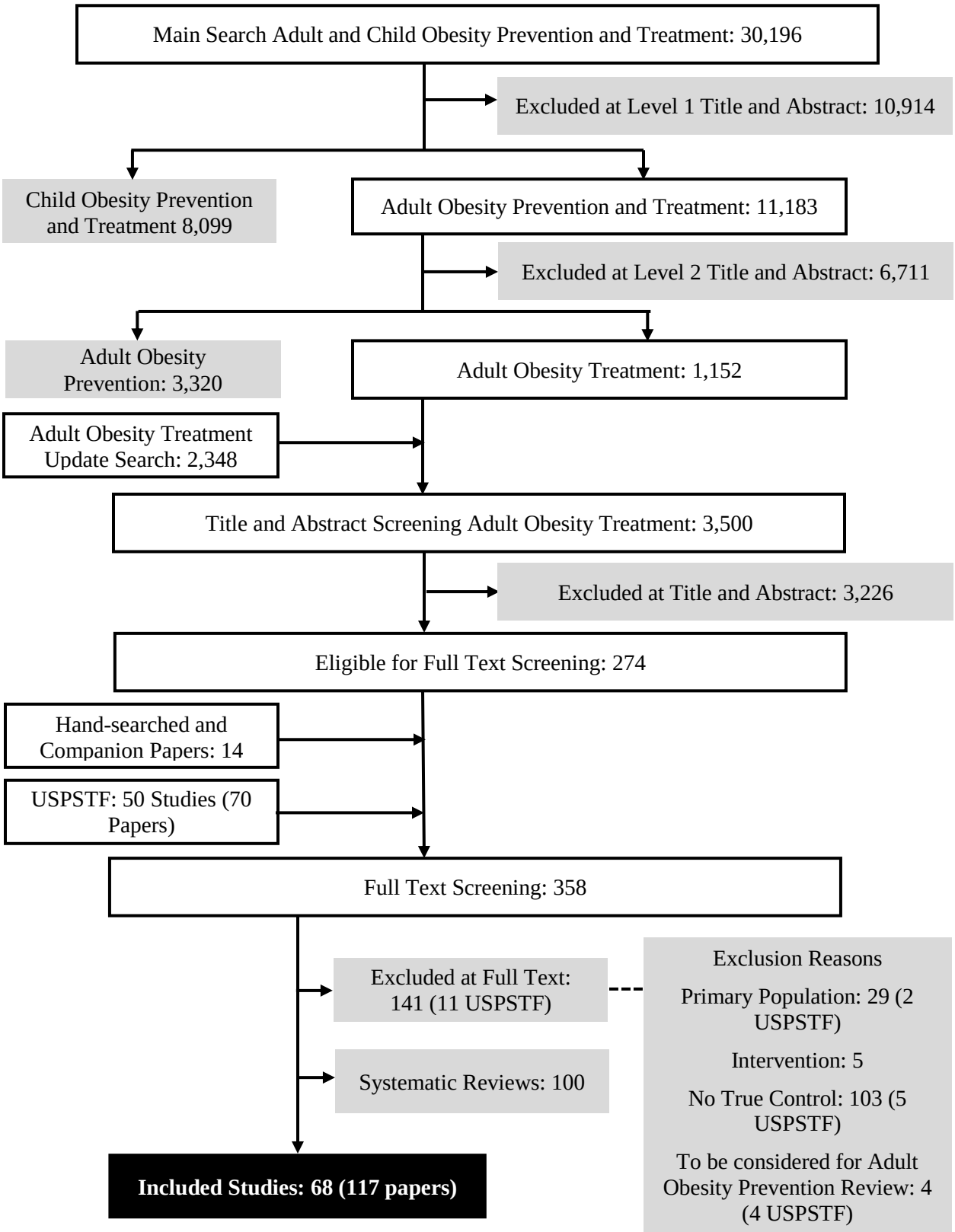


Figure 2: Search Results



Tables

Table 1: Factors Associated with Weight Gain and/or Obesity

Category	Condition/Disease
Neuroendocrine	• Cushing's syndrome[170] • hypothalamic obesity[171] • hypothyroidism[172] • polycystic ovary syndrome[173] • growth hormone deficiency[174] • weight cycling[175]
Congenital	• Prader-Willi syndrome[176] • Lawrence-Moon-Biedle syndrome[177]
Dietary	• overeating relative to energy expenditure[178] • increased dietary fat intake[179] • frequent fast-food consumption[180] • night-eating syndrome[181,182]
Lifestyle	• sedentary lifestyle[28] • decreased physical activity[183] • sleep deprivation[30] • smoking cessation[184] • pregnancy/post-pregnancy[185] • poor diet[186] • skipping meals[186] • snacking[187] • consuming sugary soft drinks[188]
Psychiatric/Psychological/ Psychosocial	• binge eating and other eating disorders[178] • seasonal affective disorder[189] • depression/anxiety[190,191] • boredom[192] • stress[193]
Drugs	• antipsychotics[194] • antidepressants[195] • anticonvulsants[196] • corticosteroids[197]
Biochemical	• genetics[27] • metabolism[27] • injury[198] • mobility issues[199] • intrauterine growth[200]
Socio-Economic Determinants	• education[201] • income[201]

Table 2: Health Consequences of Obesity

Organ System	Condition/Disease
Cardiovascular	• coronary artery disease • hypertension • venous thromboembolism • varicose veins and venous hypertension
Respiratory	• obstructive sleep apnea • hypoventilation syndrome • cor pulmonale
Neurologic	• stroke • intracranial hypertension • meralgia paresthetica
Gastrointestinal	• cholelithiasis • gastroesophageal reflux disease • hepatic steatosis • non-alcoholic steatohepatitis • abdominal and inguinal hernias • colon cancer
Genitourinary	• urinary stress incontinence • hypogonadism • amenorrhea • prostate cancer • breast cancer • uterine cancer
Endocrine/Metabolic	• dyslipidemia • impaired glucose tolerance • type 2 diabetes • metabolic syndrome • infertility • polycystic ovarian syndrome • hypothyroidism • renal disease
Musculoskeletal	• degenerative osteoarthritis • low back strain
Skin	• cellulitis • intertrigo
Psychological	• depression • social and work-related discrimination

Table 3: Summary of Risk of Bias Assessment of Included RCTs

Study	Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessors			Incomplete Reporting			Selective Reporting	Other Bias
				OBJ	SUB	S-R	OBJ	SUB	S-R		
Anderssen 1995[82]	U	L	H	L	U		L	L		L	L
Andrews 2011[73]	L	L	H	L	H		L	L		L	U
Appel 2011[70]	L	U	H	L	L	H	L	L	L	L	L
Balducci 2010[76]	U	U	U	L	U		L	L		L	H
Bakris 1992[123]	U	U	U	L	U	U	H	H	H	L	U
Bennett 2012[78]	L	U	H	L	U	H	L	L	L	L	L
Berne 2004[108]	L	U	U	L	U	U	L	L	L	L	H
Broom 2002a[109]	L	U	U	L	U	U	H	H	H	L	H
Broom 2002b[127]	U	U	U			U			H	L	H
Burke 2005[84]	L	U	H		U			H		L	L
Burtscher 2012[98]	U	U	H	L	U		L	L		L	H
Christian 2008[83]	L	L	H	L	U		L	L		L	L
Cohen 1991[85]	U	U	H		U			L		L	H
Davidson 1999[110]	U	U	U	L	U	U	H	H	H	L	H
Dekkers 2011[68]	L	L	H	L	U		H	H		L	L
de Mello 2012[100]	U	U	H	L	L		L	L		L	L
Derosa 2003[111]	L	L	L	L	L	L	L	L	L	L	H
Derosa 2012[106]	L	L	L	L	L	L	L	L	L	L	L
DPP 1999[133]	L	U	H	L	U	H	U	U	U	L	H
Finer 2000[112]	L	L	U	L	L	L	H	H	H	L	H
Fontbonne 1996[131]	U	U	U	L	U	U	L	L	L	L	H
Foster-Schubert 2012[99]	L	U	H	L	L		L	L		L	L
Haapala 2009[86]	U	U	U		U			H		L	H
Hanefeld 2002[113]	U	U	U			U			H	L	H
Hauptman 2000[114]	U	U	U	L	U	U	H	H	H	H	U
He 2012[130]	L	L	L			L			L	L	L
Hollander 1998[115]	U	U	U	L	U	L	L	L	L	L	H
Janney 2010[80]	U	U	H		U	U		H	H	L	L
Janus 2012[103]	L	L	H	L	U		L	L		L	L
Kelley 2002[124]	U	U	U	L	U	U	H	H	H	U	H
Krempf 2003[116]	U	U	U	L	U	U	H	H	H	L	H
Kirby 2011[74]	U	U	H	L	U		H	H		L	L
Kopelman 2010[107]	U	U	U	L	U	L	L	L	L	L	H
Kulzer 2009[87]	U	U	H	L	L		L	L		L	H

Study	Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessors			Incomplete Reporting			Selective Reporting	Other Bias
				OBJ	SUB	S-R	OBJ	SUB	S-R		
Langford 1985[88]	U	U	H		U			U		L	H
Lim 2010[81]	U	U	U	L	U		H	H		L	H
Lim 2011[132]	L	L	U			L			H	U	L
Lindgarde 2000[117]	U	U	U	L	U	U	L	L	L	L	H
Ma 2013[97]	L	U	H	L	L	H	L	L	L	L	L
Martin 2008[89]	U	U	H		U			H		L	H
Miles 2002[118]	U	U	U	L	U	U	H	H	H	U	H
Morey 2012[96]	U	L	H	L	L	U	L	L	L	L	L
Muls 2001[126]	U	U	U	L	U	U	L	L	L	L	H
Nakade 2012[102]	U	U	H		U			L		H	L
Nanchahal 2012[104]	L	U	H		L			H		L	L
Ockene 2012[101]	U	U	H	L	U		L	L		H	L
Parikh 2010[95]	L	U	H	L	U		L	L		H	L
Patrick 2011[69]	L	U	H		L			H		L	H
Penn 2009[105]	L	U	H	L	U		H	L		L	H
Ross 2012[79]	L	U	H	L	L		L	L		L	L
Rossner 2000[119]	U	U	U	L	U	U	H	H	H	L	H
Seifarth 2013[128]	H	H	H			H			L	L	U
Sjostrom 1998[120]	L	U	U	L	U	U	L	L	L	L	H
Smith 2011[129]	U	U	U			U			L	L	H
Stevens 1993[90]	U	L	U		L	U		L	L	L	L
Stevens 2001[91]	U	U	H	L	L		L	L		L	L
Swinburn 2005[121]	L	U	U	L	U	L	L	L	L	H	H
ter Bogt 2011[72]	L	U	H	L	U		L	L		L	L
Torgerson 2004[122]	L	L	L	L	L	L	L	L	L	U	H
Tsai 2010[75]	L	L	H	L	H	H	L	L	L	U	H
Van Gaal 1998[125]	U	U	U			U			L	L	H
Vissers 2010[77]	U	U	H	L	U		L	L		L	H
Wadden 2011[71]	L	U	H	L	U	U	L	L	L	L	L
Wood 1988[92]	L	L	H	L	U		L	L		L	L
Wood 1991[93]	U	U	H	L	U		L	L		L	L
Woollard 2003[94]	L	U	H	L	H		L	L		L	L

L (green) = Low Risk; U (yellow) = Unclear Risk; H (red) = High Risk; OBJ = Objective Outcome; SUB = Subjective Outcome; S-R = Self-Reported Outcome

Table 4: Characteristics of Included Studies

Study	Anderssen 1995[82]; Companion paper: ODES Investigators[202]
Comments	See USPSTF Review[5] for details

Study/Location	Andrews 2001[73] England
Objective	To investigate whether increased physical activity has effects on glycaemia, blood pressure, lipid profile, insulin resistance, and insulin secretion in addition to those yielded by intensified dietary intervention or usual care in individuals with newly diagnosed T2D
Methods	Design: RCT Selection: searching records databases of 217 general practices in southwest England, and of community-based education programs, and by direct advertising Inclusion criteria: diagnosed with diabetes in past 5-8 months; >30 years at diagnosis Exclusion criteria: >80 years; HbA1c >10%; blood pressure >180/100 mmHg; LDL-C >4 mmol/L; BMI <25; weight >180 kg; use of weight-loss drugs; taking sulphonylurea at maximum dose; unstable angina; myocardial infarction in previous 3 months; inability to increase physical activity; pregnant or planning to become pregnant
Participants	Sample: 593 Intervention 1 (diet) n=248; Intervention 2 (diet + exercise) n=246; Control n=99 Age, Mean (SD) years: Intervention 1: 60.1 (10.2); Intervention 2: 60.0 (9.7); Control: 59.5 (11.1) Gender [Female n (%)]: Intervention 1 n=90 (36%); Intervention 2 n=81 (33%); Control n=37 (37%) Race/Ethnicity: 94-97% of participants (by group) were white Co-morbidities: Diabetes Loss to follow-up: Intervention 1 n=2; Intervention 2 n=6; Control n=6
Intervention	Description of intervention 1 (diet): intensive, goal-oriented/motivation-based, non-prescriptive diet with dietary advice and goal setting reinforcement provided by regular sessions with dietitians and study nurses Description of intervention 2 (diet + exercise): same diet conditions plus 5 days/week 30 minutes of brisk walking in addition to current physical activities, also given pedometers and written materials (motivating literature and exercise diaries) Description of control: standard dietary and exercise advice Duration of intervention: 12 months Length of follow-up: immediate post

Study/Location	Appel 2011[70] US
Objective	To examine the effects of two behavioural weight-loss interventions in obese patients with at least one cardiovascular risk factor
Methods	Design: RCT Selection: recruited from 8 primary care practices in Baltimore metropolitan area physician referral, brochures, and targeted mailing Inclusion criteria: obese adults belonging to one of the included practices; ≥21 years of age; ≥1 cardiovascular risk factors (hypertension, hyper-cholesterolemia, or diabetes); regular access to a computer; basic computer skills Exclusion: lost ≥5% body weight recently; medication that causes/prevents weight loss
Participants	Sample: 415 Intervention 1 (remote) n=139; Intervention 2 (in-person) n=138; Control n=138 Age, Mean (SD) years: Overall: 54.0 (10.2); Intervention 1: 55.8 (9.7); Intervention 2: 53.3 (10.5); Control: 52.9 (10.1) Gender [Female n (%)]: Intervention 1 n=88 (63.3%); Intervention 2 n=88 (63.85); Control n=88 (63.8%) Race/Ethnicity [White n (%)]: Intervention 1: 83 (59.7%); Intervention 2: 78 (56.5%); Control: 72 (52.2%) SES [College graduate n (%)]: Intervention 1: 81 (58.3%); Intervention 2: 90 (65.2%); Control: 75 (54.3%) Co-morbidities: high risk for CVD Loss to follow-up: n=23
Intervention	Description of intervention 1 (remote): provided patients with weight-loss support remotely via telephone, a study-specific Website, and e-mail Description of intervention 2 (in-person): provided in-person support during group and individual sessions, along with the 3 remote means of support Description of control: met with weight-loss coach at the time of randomization and, if desired, after final data-collection visit, at 24 months; received brochures and a list of recommended Web sites promoting weight loss Duration of intervention: 24 months Length of follow-up: immediate post

Study	Bakris 2002[123]
Comments	See USPSTF Review[5] for details

Study/Location	Balducci 2010[76] Italy
Objective	To investigate effect of exercise modalities on high sensitivity-C reactive protein and other inflammatory markers in patients with T2D and metabolic syndrome (MS)
Methods	Design: RCT Inclusion: T2D and MS; no known CVD; aged 40-75; diabetes duration >1 year; BMI 27-40; ability to walk without assistance; eligibility after cardiovascular evaluation
Participants	Sample: 82 Intervention 1 n=20; Intervention 2 n=20; Intervention 3 n=22; Control n=20 Age, Mean (SD) years: Intervention 1: 62.5 (7.1); Intervention 2: 64.3(8.1); Intervention 3: 60.6(9.3); Control: 61.1(7.1) Gender [Female n (%)]: Intervention 1 n=9 (45%); Intervention 2 n=8 (40%); Intervention 3 n=8 (36%); Control n=9 (45%) Co-morbidities: Diabetes Loss to follow-up: 6.1%
Intervention	Description of intervention 1: structured exercise counseling Description of intervention 2: prescribed and supervised aerobic activity only Description of intervention 3: aerobic and resistance exercise Description of control: remain sedentary Duration of intervention: 12 months Length of follow-up: immediate post

Study/Location	Bennett 2012[78] US; Companion paper: Greaney[203]
Objective	To evaluate the effectiveness of a behavioural intervention that emphasized weight loss and hypertension medication adherence among primary care patients
Methods	Design: RCT Selection: urban community health centers serving racial/ethnic minority patient populations, using electronic medical record or automated scheduling system Inclusion: BMI of 30–50 (and weighing <400 pounds); being treated for hypertension; ≥21 years of age; a patient at one of the participating CHC; read and speak English or Spanish; provide informed consent; willing to change diet, physical activity and weight
Participants	Sample: 365 Intervention n=180; Control n=185 Age, Mean (SD) years: Intervention: 54.58 (10.77); Control: 54.67 (11.03) Gender [Female n (%)]: Intervention n=128 (71.1%); Control n=122 (65.9%)

	Race/Ethnicity: Intervention: non-Hispanic Black 71.7%; Control: non-Hispanic Black 70.8% SES (High school or less): Intervention: 58.9%; Control: 66.5% Co-morbidities: Hypertension Loss to follow-up: Intervention 10.3%; Control 17.8%
Intervention	Description of intervention: health educators delivered monthly counseling (year 1) and bimonthly (year 2) group sessions; primary care provider delivered ≥1 brief standard messages about importance of the intervention and tailored behavioural skills training materials, walking kits with pedometers Description of control: standard of care offered by the CHC; received the Aim for a Healthy Weight self-help booklet at baseline and 12 months later; providers used usual prevention, weight management, and CVD management strategies Length of intervention: 104 weeks Length of follow-up: immediate post

Study	Berne 2005[108]
Comments	See USPSTF Review[5] for details

Study	Broom 2002a[109]
Comments	See USPSTF Review[5] for details

Study	Broom 2002b[127]
Comments	See USPSTF Review[5] for details

Study	Burke 2005[84]
Comments	See USPSTF Review[5] for details

Study/Location	Burtscher 2012[98] Austria; Companion paper: Burtscher[204]
Objective	To study the effects of a supervised exercise program on serum gamma-glutamyl transferase, glycemic control and cardiovascular risk factors in pre-diabetic patients with isolated impaired fasting glucose and those with IFG + impaired glucose tolerance
Methods	Design: RCT

	Selection: recruited by family physicians primarily through screening for high-risk groups, such as first-degree relatives of patients with T2D and overweight individuals (BMI >25) aged 40-65 years. Inclusion criteria: impaired fasting glucose (IFG - fasting plasma glucose concentration of 100–125 mg/dL) and/or impaired glucose tolerance (IGT - plasma glucose concentration of 140–199 mg/dL after 2h of a 75 g glucose load) Exclusion criteria: diagnosis of diabetes mellitus; any indication of alcohol abuse; the presence of chronic disease rendering 3-year survival unlikely, and cardiopulmonary or musculoskeletal diseases not compatible with the planned exercise program.
Participants	Sample: 60 Intervention 1 (IFG) n=12; Intervention 2 (IFG+IGT) n=12; Control (IFG) n=18; Control (IFG+IGT) n=18 Age, Mean (SD) years: Intervention 1: 57.8 (6.5); Intervention 2: 54.0 (8.0); Control 1: 57.8 (7.9); Control 2: 57.6 (5.8) Gender [Female n (%)]: Intervention n=16 (66.7%); Control n=18 (50%) Loss to follow-up: no loss
Intervention	Description of interventions: participants informed about their risk for developing T2D and associated health problems by family physicians; instructed about preventive effectiveness of changing lifestyle, especially losing weight and regular physical activity by health promotion and exercise physiology specialists; exercise group offered progressive, individually tailored aerobic exercise programs and circuit-type resistance-training sessions for 1 h twice a week Description of controls: participants informed about their risk for developing T2D and associated health problems by family physicians; instructed about preventive effectiveness of changing lifestyle, especially losing weight and regular physical activity by health promotion and exercise physiology specialists Length of intervention: 12 months Length of follow-up: immediate post

Study	Christian 2008[83]
Comments	See USPSTF Review[5] for details

Study	Cohen 1991[85]
Comments	See USPSTF Review[5] for details

Study	Davidson 1999[110]
Comments	See USPSTF Review[5] for details

Study/Location	Dekkers 2011[68] The Netherlands; Companion papers: van Wier[205,206]
Objective	To investigate lifestyle intervention effects on cardiovascular risk factors in healthy overweight employees
Methods	Design: RCT Selection: recruited from 7 service-sector companies in the Netherlands Inclusion criteria: ≥18 years old; BMI ≥ 25; access to Internet and know how to use it; paid employment for at least 8 hours a week; able to read and write Dutch Exclusion criteria: pregnancy; disorders that make physical activity difficult
Participants	Sample: 1,386 Intervention 1 n=462; Intervention 2 n=464; Control n=460 Age, Mean (SD) years: Overall: 43 (8.6); Intervention 1: 43 (8.8); Intervention 2: 43 (8.4); Control: 43 (8.7) Gender [Female n (%)]: Intervention 1 n=141 (31%); Intervention 2 n=162 (35%); Control n=154 (33%) SES [highly educated (≥5 years secondary education)]: Intervention 1 n=271 (60.1%); Intervention 2 n=281 (62.2%); Control n=255 (58.8%) Co-morbidities: Diabetes, Hypertension Loss to follow-up: Intervention 1 n=199; Intervention 2 n=217; Control n=214
Intervention	Description of intervention 1 (phone): self-help materials on overweight, physical activity and healthy diet; access to a lifestyle intervention program consisting of 10 workbook based modules on nutrition, physical activity and behavior modification; phone contact with personal counselor Intervention 2 (internet): self-help materials on overweight, physical activity and healthy diet; access to a lifestyle intervention program consisting of 10 modules on nutrition, physical activity and behavior modification strategies provided through an interactive Web site composed of personalized Web pages; contact by e-mail with personal counselor Description of control: self-help materials on overweight, physical activity and healthy diet Duration of intervention: 6 months Length of follow-up: 18 months
Comments	Patients also took medication for angina

Study	de Mello 2012[100]; Companion papers: Eriksson,[207] Lindstrom,[208] Ruusunen,[209] Tuomilehto 2001,[210] Uusitupa[211]
Comments	See USPSTF Review[5] (Tuomilehto[210] main paper) for details

Study	Derosa 2003[111]
Comments	See USPSTF Review[5] for details

Study/Location	Derosa 2012[106] Italy; Companion paper: Derosa[212]
Objective	To compare the effects of orlistat and placebo on body weight, glycaemic and lipid profile and insulin resistance in patients with T2D
Methods	Design: RCT Selection: patients identified from review of case notes and/or computerized clinic registers, contacted by investigators in person or by telephone Inclusion criteria: Caucasian patients with T2D aged ≥18, obese (BMI) ≥30, uncontrolled T2D on therapy with different oral hypoglycaemic agents or insulin Exclusion criteria: history of ketoacidosis or unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function [defined as plasma aminotransferase and/or gamma-glutamyltransferase level higher than the upper limit of normal (ULN) for age and sex], impaired renal function (defined as serum creatinine level higher than the ULN for age and sex) or severe anaemia; serious CVD (e.g. New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions in past 6 months; GI disorders or major abdominal surgery in past 6 months; women who were pregnant or breast-feeding or of child-bearing potential and not taking adequate contraceptive precautions
Participants	Sample: 254 Intervention n=126; Control n=128 Age, Mean (SD) years: Intervention: 53 (6); Control: 52 (5) Gender (Female): Intervention: n=64; Control: n=62 Race/Ethnicity: Caucasian only Comorbidities: Diabetes Loss to follow-up: 7.9%
Intervention	Description of intervention: Orlistat 360 mg Description of control: placebo Duration of intervention: 52 weeks Length of follow-up: immediate post

Study/Location	Donner 2010[57] US
Objective	To explore the metabolic effects of D-tag given daily to people with T2D
Methods	Design: One group pre/post Selection: T2D for at least 1 year in duration
Participants	Sample: 8 Age, Mean (SD) years: Overall: 50.7 (10.9) Gender (Female): 50% Co-Morbidities: Diabetes Loss to follow-up: see comments
Intervention	Description of intervention: after 2-month run-in, given 15-g packages of D-tag to be taken 3/day with nonstandardized meals; dissolved in liquids, used in baking, or added to prepared foods; encouraged not to otherwise alter diet; remained physically inactive Description of control: NA Duration of intervention: 52 weeks Length of follow-up: immediate post
Comments	Four of the 12 initially screened subjects were excluded from analysis because they did not complete the study; analysis performed on the 8 subjects who completed study

Study	The Diabetes Prevention Program (DPP) 1999[133]; Companion papers: Ackermann,[213] Crandall,[214] Diabetes Prevention Program Research Group,[215] Florez,[216] Goldberg,[217] Haffner,[218] Knowler,[219] Krakoff,[220] Orchard,[221] Price,[222] Ratner,[223] Rubin,[224] West[225]
Comments	See USPSTF Review[5] for details

Study	Finer 2000[112]
Comments	See USPSTF Review[5] for details

Study	Fontbonne 1996[131]
Comments	See USPSTF Review[5] for details

Study/Location	Foster-Schubert 2012[99] US; Companion papers: Mason,[226-228] Imayama,[229,230] Campbell,[231] Kong[232]
Objective	To determine the effects of a calorie-reduced, low-fat diet, a moderate-intensity, facility-based aerobic exercise program, or the combination of both interventions vs. a no-lifestyle-change control on change in body weight and composition

Methods	Design: RCT Selection: mass mailings, media publicity and community outreach Inclusion criteria: age 50-75; BMI≥25 (Asian-American ≥23); <100 minutes/week of moderate or vigorous intensity physical activity; post-menopausal; not taking hormone replacement therapy for past 3 months; no history of breast cancer, heart disease, diabetes or other serious medical conditions; fasting glucose <126 mg/dL; not smoking; alcohol intake <2 drinks/day; able to attend sessions; normal exercise tolerance test
Participants	Sample: 439 Intervention 1 (calorie-reduced diet) n=118; Intervention 2 (aerobic exercise) n=117; Intervention 3 (aerobic exercise + calorie-reduced diet) n=17; Control n=87 Age, Mean (SD) years: Overall: 58.0 (5.0); Intervention 1: 58.1 (6.0); Intervention 2: 58.1 (5.0); Intervention 3: 58.0 (4.5); Control: 57.4 (4.4) Gender (Female): 100% Race/Ethnicity [non-Hispanic white n (%)]: Intervention 1: 101 (85.5%); Intervention 2: 98 (83.8); Intervention 3: 100 (85.5%); Control: 74 (85.1) SES [college graduate n (%)]: Intervention 1: 76 (64.4%); Intervention 2: 70 (59.9); Intervention 3: 82 (70.1); Control: 59 (67.8%) Loss to follow-up: 9%
Intervention	Description of intervention 1: diet only, calorie-reduced, low-fat. Description of intervention 2: exercise only (moderate-intensity, aerobic exercise) Description of intervention 3: exercise and diet combined Description of control: no lifestyle change. Length of intervention: 12 months Length of follow-up: immediate post

Study	Haapala 2009[86]
Comments	See USPSTF Review[5] for details

Study	Hanefeld 2002[113]
Comments	See USPSTF Review[5] for details

Study	Hauptman 2000[114]
Comments	See USPSTF Review[5] for details

Study/Location	He 2012[130] China
Objective	To explore whether metformin-based treatment could benefit obesity-related hypertension without diabetes
Methods	Design: RCT Selection: recruited via flyer at a hospital in Chongqing, China Inclusion criteria: aged 30–70 years; elevated BP; waist circumference >90cm in men or 80cm in women Exclusion criteria: diabetes (known history or confirmed by oral glucose tolerance test at baseline); known allergy or hypersensitivity to trial drugs; heart failure, myocardial infarction or cerebro-vascular accident in past year; acute infections; tumor; severe arrhythmia, mental disease, drug or alcohol abuse; history of hepatitis or cirrhosis or severe kidney disease; pregnant or lactating; enrolled in other trials in past 3 months
Participants	Sample: 360 Intervention n=180; Control n=180 Age, Mean (SD) years: Intervention: 58 (7.0); Control: 57 (7.0) Gender [Female n (%)]: Intervention 118 (65.7%); Control 108 (60.0%) Co-morbidities: Hypertension Loss to follow-up: Intervention 16.7%; Control 13.9%
Intervention	Description of intervention: low-dose metformin (500 mg/day) and simultaneously one of the three antihypertensive drugs: candesartan 8 mg/day, telmisartan 80 mg/day, or amlodipine 5 mg/day; provided with general lifestyle guidelines Description of control: placebo and simultaneously one of the three antihypertensive drugs; provided with general lifestyle guidelines Length of intervention: 24 weeks Length of follow-up: immediate post

Study	Hollander 1998[115]
Comments	See USPSTF Review[5] for details

Study/Location	Janney 2010[80] USA
Objective	To assess the effects of exercise and BMI on the pattern of injuries/illnesses attributed to exercise over time and to identify predictors of time to first injury/illness
Methods	Design: RCT Selection: participants enrolled in one of two randomized clinical trials that emphasized exercise as part of a weight loss or weight gain prevention program

	Inclusion criteria: BMI 25-39.9 weight loss study; 25-29.9 weight gain prevention study Exclusion criteria: history of myocardial infarction; medications that alter heart rate or blood pressure during exercise (e.g. b-blockers) or affect metabolism or weight loss (e.g. thyroid medication); treatment for psychological conditions; pregnant, pregnant in past 6 months, planning to become pregnant; medical conditions that could affect metabolism or body weight (e.g. diabetes); reported weight loss >5% or participated in weight loss or physical activity study during the previous 12 months; reported exercising regularly for ≥20 minutes/day on ≥3 days/week over past 3 months
Participants	Sample: 397 Intervention 1 n=64; Intervention 2 n=172; Intervention 3 n=84; Control n=77 Age, Mean (SD) years: Intervention 1: 44.2 (8.4); Intervention 2: 44.0 (8.3); Intervention 3: 45.3 (8.3); Control: 44.4 (8.0) Gender [Female n (%)]: Intervention 1: 59 (92%); Intervention 2: 134 (78%); Intervention 3: 77 (92%); Control: 70 (91%) Race/Ethnicity [White n (%)]: Intervention 1: 50 (79%); Intervention 2: 117 (68%); Intervention 3: 67 (80%); Control: 58 (75%) Loss to follow-up: NR
Intervention	Description of intervention 1 and 2 (weight gain prevention intervention): increasing exercise and modifying eating behaviours; gradually progress to 150 or 300 minutes/week of moderate-intensity exercise Description of intervention 3 (weight loss intervention): increasing exercise and modifying eating behaviours; gradually progress to 200 min/week of moderate-intensity exercise and reduce energy intake to 1200-1500 kcal/day, reduce dietary fat intake to 20-30% of total energy intake Both the weight gain prevention and weight loss studies recommended brisk walking for exercise, 5 days/week; duration (150, 200 or 300 minutes/week) but not intensity of the recommended exercise differed among exercise groups Description of control: self-help manual related to exercise adoption and maintenance, printed materials related to healthy eating and exercise, and a monthly newsletter Duration of intervention: 18 months Length of follow-up: immediate post
Comments	The two interventions are reported together with outcomes reported by duration of exercise (group 1: 150 min/week; group 2: 200 min/week; group 3: 300 min/week)

Study/Location	Janus 2012[103] Australia
Objective	To report results from the preliminary phase of an evaluation of the Greater Green Triangle Diabetes Prevention Program.
Methods	Design: RCT Selection: sources included primary healthcare practices; patients with impaired glucose tolerance or impaired fasting glucose identified and contacted, others screened

	opportunistically in waiting rooms; additional recruitment at community events Inclusion criteria: 50-75 years at high T2D risk (15 or above on AUSDRISK tool) Exclusion criteria: diabetes; cancer; severe mental illness; substance abuse; recent myocardial infarction; pregnancy; difficulty with English; belong to cultural group for whom AUSDRISK not calibrated, another household member involved in study
Participants	Sample: 92 Intervention n=49; Control n=43 Age, Mean (SD) years: Intervention: 64.2 (7.5); Control: 65.0 (6.0) Gender [Female n (%)]: Intervention n=21 (55.3%); Control n=32 (76.2%) SES [reported as income level, n(%)]: Intervention: low 20 (54.1%); medium 15 (40.5%); high 2 (5.4%); Control: low 29 (74.4%); medium 9 (23.1%); high 1 (2.6%) Loss to follow-up: Intervention 22.4%; Control 2.3%
Intervention	Description of intervention: 6 structured group based lifestyle sessions Description of control: usual care provided by general practitioner Length of intervention: 12 months Length of follow-up: immediate post

Study	Kelley 2002[124]
Comments	See USPSTF Review[5] for details

Study/Location	Kirby 2011[74] Ireland
Objective	To investigate whether weight loss is associated with changes in serum concentrations of lutein and zeaxanthin and/or macular pigment optical density
Methods	Design: RCT Inclusion criteria: BMI ≥ 28; age ≥ 18 years; no known family history of AMD; no ocular pathology Exclusion criteria: pregnancy; planning pregnancy; currently in a weight loss program; ocular pathology; positive family history of AMD (given the previously established comprised relationship between serum carotenoids and MPOD in this subgroup)
Participants	Sample: 104 Intervention n=54; Control n=50 Age, Mean (SD) years: Overall: 46 (11); Intervention: 47 (10); Control: 44 (11) Gender [Female n (%)]: Intervention n=44 (81%); Control n=34 (68%) Loss to follow-up: Intervention n=20; Control n=16

Intervention	Description of intervention: Customized weight loss plan: dietary intervention, exercise intervention, motivational lectures, weekly weight checks Description of control: any steps necessary to achieve weight loss in a personal capacity; did not actively encourage or discourage weight loss in these subjects Duration of intervention: 12 months Length of follow-up: immediate post

Study/Location	Kopelman 2010[107] UK
Objective	To determine the efficacy and safety of cetilistat and orlistat relative to placebo in obese patients with type 2 diabetes, on metformin
Methods	Design: RCT Selection: NR Inclusion criteria: aged 18-65; T2D (diagnosis >3 months previously, controlled by stable dose of metformin for ≥3 months); BMI 28-45; HbA1c >6 and <10%
Participants	Sample: 250 Intervention n=124; Control n=126 Age, Mean (SD) years: Intervention: 54.3 (7.8); Control: 54.4 (7.6) Gender [Female n (%)]: Intervention n=55 (45.5%); Control n=72 (57.6%) Co-morbidities: Diabetes Loss to follow-up: Intervention n=23; Control n=22
Intervention	Description of intervention and control: treatment with orlistat (120 mg t.i.d.) or matching placebo, stratified on the basis of the dose of metformin (≤ or >1,500 mg/day), medication taken three times daily with meals Duration of intervention: 12 weeks Length of follow-up: immediate post

Study	Krempf 2003[116]
Comments	See USPSTF Review[5] for details

Study	Kulzer 2009[87]
Comments	See USPSTF Review[5] for details

Study	Langford 1985[88]; Companion paper: Wassertheil-Smoller[233]
Comments	See USPSTF Review[5] for details

Study/Location	Lim 2010[81] Australia
Objective	To compare changes in weight and other cardiovascular risk factors in 3 isocaloric energy-restricted diets to no-intervention control after 1 year
Methods	Design: RCT Selection: public advertisement Inclusion criteria: aged 20-65; ≥1CVD risk factor other than obesity; BMI 28-40 Exclusion criteria: hypoglycemic medication that affects insulin sensitivity; history of heavy alcohol consumption; history of metabolic or coronary heart disease; diabetes; fluctuating exercise patterns and frequent dining out (>2/week and unable to cease)
Participants	Sample: 113 Intervention 1 n=30; Intervention 2 n=30; Intervention 3 n=30; Control n=23 Age, Mean (SD) years: Overall: 47 (10) Gender [Female n (%)]: 93 (82%) Co-morbidities: CVD Loss to follow-up: Intervention 1 n=13; Intervention 2 n=12; Intervention 3 n=15; Control n=4
Intervention	Description of interventions: first 3 months diet groups (i.e. VLC, VLF, HUF) received intensive support to maximize dietary compliance; provided with prescriptive meal plans and foods contributing to 65% energy of the meal plans; received individual dietary counseling every 2 weeks from qualified dietitian to monitor; advised to maintain allocated energy-restricted diet for an additional 12 months Description of control: attended clinic for measurements but received no intervention Duration of intervention: 15 months Length of follow-up: immediate post

Study/Location	Lim 2011[132] Australia
Objective	To determine the effect of metformin on body weight, body composition, metabolic risk factors and reproductive hormone levels in overweight or obese young women compared to placebo and comprehensive lifestyle intervention
Methods	Design: RCT Selection: public advertisement Inclusion: women 17-37 years; BMI 25.1-44; access to internet; ability to attend clinic Exclusion: significant illnesses, including kidney disease, liver disease, malignancy, uncontrolled hypertension, self-reported diabetes or thyroid disease; pregnancy or lactation; current rapid weight loss (0.5 kg/week)

Participants	Sample: 297 Intervention 1 n=98; Intervention 2 n=99; Control n=100 Age, Mean (SD) years: Overall: 28 (0.3) Gender (Female): 100% SES (university degree): 40% Loss to follow-up: 35%
Intervention	Description of intervention 1: metformin (gradually increased to 1,500 mg/day) Description of intervention 2: comprehensive lifestyle program including hypocaloric high protein diet, structured exercise program and supports for behaviour modification Description of control: placebo Duration of intervention: 12 weeks Length of follow-up: immediate post

Study	Lindgärde 2000[117]; Companion paper: Lindgärde[234]
Comments	See USPSTF Review[5] for details

Study/Location	Ma 2013[97] US
Objective	To evaluate two adapted Diabetes Prevention Program (DPP) lifestyle interventions
Methods	Design: RCT Selection: recruited from single primary care clinic that is part of a large multispecialty group practice Inclusion criteria: ≥18 years; BMI ≥25; presence of pre-DM (defined by impaired fasting plasma glucose level of 100 to 125 mg/dL) or metabolic syndrome Exclusion criteria: serious medical or psychiatric conditions (e.g., stroke, psychotic disorder) or special life circumstances (e.g., pregnancy, planned move)
Participants	Sample: 241 Intervention 1 n=79; Intervention 2 n=81; Control n=81 Age, Mean (SD) years: Overall: 52.9 (10.6); Intervention 1: 54.6 (11.0); Intervention 2: 51.8 (9.9); Control: 52.5 (10.9) Gender [Female n (%)]: Intervention 1: 38 (48.1%); Intervention 2: 37 (45.7%); Control: 37 (45.7%) Race/Ethnicity (White): Intervention 1: 77.2%; Intervention 2: 79.0%; Control: 77.8%

	SES [income ≥150,000]: Intervention 1: 37.7%; Intervention 2: 52.6%; Control: 53.9% SES [≥college]: Intervention 1: 93.5%; Intervention 2: 100%; Control: 97.9% Loss to follow-up: 19.5%
Intervention	Description of interventions (coach-led vs. self-directed intervention 3-month intensive intervention and 12-month maintenance; during intensive intervention received adapted, 12-session DPP lifestyle intervention; curriculum delivered in-person in 12-weekly classes to coach-led intervention participants or via a home-based DVD to self-directed intervention participants Description of control: usual care from primary care providers Length of intervention: 15 months Length of follow-up: immediate post
Comments	During the trial period, 15 of 81 participants in the usual care group reported joining a weight-loss program outside the study (12 used commercial programs, 2 used nutrition classes offered by the care delivery system, and 1 used a personal trainer), compared with 5 of 79 in the coach-led group (4 used personal trainers, and 1 used a commercial program) and 3 of 81 in the self-directed group (2 used personal trainers, and 1 used a commercial program).

Study	Martin 2008[89]; Companion paper: Davis-Martin[235]
Comments	See USPSTF Review[5] for details

Study	Miles 2002[118]
Comments	See USPSTF Review[5] for details

Study/Location	Morey 2012[96] US
Objective	To determine whether a home-based lifestyle physical activity counseling intervention is effective in reducing glycemic measures in older outpatients with prediabetes
Methods	Design: RCT Selection: prescreened age-eligible VA clinic patients were sent recruitment packages followed by phone contact Inclusion criteria: ≥60 years; impaired glucose tolerance (fasting glucose 100-125 mg/dl, but no diabetes diagnosis; HbA1c <7%; BMI 25-45
Participants	Sample: 302 Intervention n=180; Control n=122

	Age, Mean (SD) years: Intervention: 67.1 (6.3); Control: 67.7 (6.2) Gender [Female n (%)]: Intervention n=7 (3.9%); Control n=3 (2.5%) Race/Ethnicity [White n (%)]: Intervention: 129 (71.7%); Control: 83 (68.0%) SES [Some college or trade school, n (%)]: Intervention: 107 (59.4); Control: 65 (53.3%) Loss to follow-up: 13.2%
Intervention	Description of intervention: in-person baseline counseling consultation with a trained health counselor, handouts on exercising and regular telephone counseling bi-weekly for 6 weeks and monthly until end of 1 year with regular encouragement by automated phone system and quarterly individualized feedback report that summarized progress toward each long-term goal of endurance and strengthening exercise Description of control: standard of care as provided in usual VA primary, women's health, or geriatrics clinic Length of intervention: 12 months Length of follow-up: immediate post

Study	Muls 2001[126]
Comments	See USPSTF Review[5] for details

Study/Location	Nakade 2012[102] Japan
Objective	To evaluate the effects of a behavioural approach which placed emphasis on tailored behavior counseling, diet, weight loss and weight maintenance
Methods	Design: RCT Selection: recruitment by the Saku Health Dock Center; letter to potential participants Inclusion criteria: aged 40-64, visited Saku Health Dock Center from 2000 on and were in the top 5% ($\geq$28.4 kg/m^2) in terms of the result of the latest BMI screening Exclusion criteria: psychiatric conditions or physical conditions that would preclude full participation (e.g., significant hepatic or renal dysfunction, cardiovascular diseases); current treatment for obesity, current treatments known to affect eating or weight
Participants	Sample: 235 Intervention n=119; Control n=116 Age, Mean (SD) years: Intervention: males: 53.6 (6.7), females: 55.1 (6.4); Control: males: 53.7 (6.3), females: 54.2 (6.2) Gender [Female n (%)]: Intervention n=57 (49.6%); Control n=56 (50.5%) Race/Ethnicity: Japanese

	Co-morbidities: hypertension, dyslipidemia Loss to follow-up: Intervention 3.4%; Control 4.3%
Intervention	Description of intervention: 1 year behavioural lifestyle intervention for weight loss Description of control: no support Length of intervention: 12 months Length of follow-up: immediate post

Study/Location	Nanchahal 2012[104] England
Objective	To evaluate effectiveness of a structured one-to-one behaviour change program on weight loss in obese and overweight individuals.
Methods	Design: RCT Selection: 23 of 39 general practices wrote to sample of patients meeting criteria, GPs and nurses given referral pads with study information and contact details, posters, flyers, and text messages Inclusion criteria: age ≥18 years; BMI ≥25; attending participating practice; willing to attend visits with CAMWELL advisor over 12 months Exclusion criteria: pregnancy; lactation; diagnosis of renal failure; use of pacemaker; recent diagnosis of cancer; participation in another weight management study
Participants	Sample: 381 Intervention n=190; Control n=191 Age, Mean (SD) years: Overall: 48.8 (14.8); Intervention: 48.2 (14.1); Control: 49.4 (15.5) Gender [Female n (%)]: Intervention n=137 (71.7%); Control n=138 (72.6%) Race/Ethnicity (White): Intervention: 74.3%; Control: 70.6% SES (university degree): Intervention: 44.7%; Control: 48.7% SES: participants spread evenly across area deprivation quartiles (approximately 25% in each group) Loss to follow-up: Intervention 46%; Control 40%
Intervention	Description of intervention: lifestyle intervention; evidence based components for behaviour change and weight loss: healthier eating, regular physical activity, goal setting, food/activity diaries, self-monitoring, positive reinforcement, coping, support, advisors, motivational interviewing, weight management software, 100-calorie portions, pedometers, handouts Description of control: routine clinical practice Length of intervention: 12 months Length of follow-up: immediate post

Study/Location	Ockene 2012[101] US
Objective	To test the effectiveness of a community-based, literacy sensitive, and culturally tailored lifestyle intervention on weight loss and diabetes risk reduction among low-income, Spanish-speaking Latinos at increased diabetes risk
Methods	Design: RCT Selection: recruited Latino participants (60% of Dominican origin and 40% Puerto Rican) from Lawrence, Massachusetts, who were at high risk for type 2 diabetes Inclusion criteria: self-reported Latino/Hispanic; ≥25 years; BMI>24; ≥30% likelihood of being diagnosed with diabetes in next 7.5 years (risk calculated using validated predictive algorithm based on age, gender, ethnicity, fasting blood glucose, systolic blood pressure, high-density lipoprotein cholesterol, BMI, and family history of diabetes) Exclusion criteria: inability to walk 5 city blocks (one quarter mile); life-limiting medical conditions; taking a medication or having a medical condition that interfered with the assessment of diabetes risk
Participants	Sample: 312 Intervention n=162; Control n=150 Age, Mean (SD) years: Intervention: 51.37 (10.9); Control: 52.37 (11.6) Gender [Female n (%)]: Intervention 117 (72.2%); Control 115 (76.7%) Race/Ethnicity: 100% Latino SES (<high school education): Intervention: 97 (60.6%); Control: 85 (57.1%) Loss to follow-up: 6%
Intervention	Description of intervention: 3 individual and 13 group sessions Description of control: usual care Length of intervention: 12 months Length of follow-up: immediate post

Study	Parikh 2010[95]
Comments	See USPSTF Review[5] for details

Study/Location	Patrick 2011[69] US
Objective	To assess the effect of a 1-year internet-based weight loss intervention for men
Methods	Design: RCT Selection: recruited from community through printed and radio advertisements, a TV

	news story, and flyers Inclusion/Exclusion criteria: NR
Participants	Sample: 441 Intervention n=224; Control n=217 Age, Mean (SD) years: Overall: 43.9 (8.0); Intervention: 44.9 (7.8); Control: 42.8 (8.0) Gender: 100% male Race/Ethnicity (White non-Hispanic): Intervention: 72.8%; Control: 69.1% SES [some post-secondary education]: Intervention: 90%; Control: 94% Loss to follow-up: Intervention n=70; Control n=62
Intervention	Description of intervention: initial computerized assessment to tailor recommendations for behavioural targets, weekly Web-based learning activities, individualized feedback Description of control: wait-list Duration of intervention: 6 months Length of follow-up: 6 months

Study/Location	Penn 2009[105] UK
Objective	To test the hypothesis that T2D can be prevented by lifestyle intervention and to explore secondary outcomes in relation to diabetes incidence
Methods	Design: RCT Selection: referral by primary care physician Inclusion criteria: >40 years, BMI >25, established IGT defined as a mean 2-hour plasma glucose value ≥7.8 mmol/l and <11.1 mmol/l from 2 consecutive standard OGTTs (glucose load 75 g) conducted 12 weeks apart Exclusion criteria: previous diagnosis of diabetes, chronic illness that would make moderate physical activity impossible, a special diet for medical reasons
Participants	Sample: 102 Intervention n=51; Control n=51 Age, Mean years: Intervention: 56.8; Control: 57.4 Gender [Female n (%)]: Intervention 30 (58.8%); Control 31 (60.8%) Loss to follow-up: 58.8% in each arm at year 5
Intervention	Description of intervention: regular individual advice from dietician and physiotherapist trained in motivational interviewing; invited to group sessions, notably 'cook and eat' events; received a quarterly newsletter Description of control: standard health promotion advice including widely available

	contemporary written leaflets on healthy eating and physical activity Length of intervention: 60 months Length of follow-up: immediate post

Study/Location	Ross 2012[79] Canada; Companion papers: Ross[236]
Objective	To assess the effectiveness of a 2-year behaviourally based physical activity and diet program implemented entirely within clinical practices to reduce obesity
Methods	Design: RCT Selection: 12 physicians supplied patient lists to the project coordinator, who created an information letter for each potential participant; physicians reviewed letters addressed removed those known to be ineligible or unable to participate for other reasons Inclusion criteria: 25-74 years; sedentary (planned activity for purpose of health ≤1 day/week); waist circumference ≥102 or 88 cm for men and women, respectively; ± 2 kg for 6 months before start study; BMI 25-39.9; informed consent Exclusion criteria: significant CVD including history of myocardial infarction, stroke, coronary bypass surgery or angioplasty in past 6 months, peripheral artery disease, unstable angina or ischaemia; insulin-dependent diabetes; pregnancy; physical impairment; plans to move from area; participating in another research study; clinically judged unsuitable for participation or adherence
Participants	Sample: 490 Intervention n=249; Control n=241 Age, Mean (SD) years: Intervention: 51.3 (11.0); Control: 52.4 (11.8) Gender [Female n (%)]: Intervention: 175 (70%); Control: 169 (70%) Loss to follow-up: Intervention 14.5%; Control 23.7%
Intervention	Description of intervention: individually tailored counselling based on transtheoretical model and social cognitive theory; Phase 1: health educator works one-on-one with participants (20 weeks, 15 sessions); Phase 2 (when lose 5% in waist circumference): encouraged by health educator to continue program (45-60 minutes of activity/day and health eating patterns); Phase 3: contact with health educator continues, duration of sessions based on waist circumference values and adoption of physical activity, those achieving targets meet health educator bimonthly for 30-minute session, those who have not achieved goals see health educator monthly for 60-minute sessions Description of control: advice from physicians regarding lifestyle as a strategy for obesity reduction, continue to meet with physician according to usual schedule; physicians asked not to change routine counseling approach Duration of intervention: 24 months Length of follow-up: immediate post

Study	Rossner 2000[119]
Comments	See USPSTF Review[5] for details

Study/Location	Seifarth 2013[128] Germany
Objective	To examine the effectiveness of metformin as a weight reducing drug in obese and overweight patients with regard to their degree of insulin resistance
Methods	Design: CCT Selection: patients screened at endocrinology practice Inclusion criteria: BMI≥ 27 Exclusion criteria: overt diabetes, impaired glucose tolerance or already taking anti-diabetic drugs (including metformin); on steroid or antipsychotic medication; depression; drug addiction; pregnant and nursing women
Participants	Sample: 199 Intervention n=154; Control n=45 Age, Mean (SD) years: Intervention: 37.8 (12.9); Control: 40.3 (11.4) Gender (Female): Intervention n=138; Control n=41 Loss to follow-up: no loss
Intervention	Description of interventions: metformin, dosage slowly uptitrated starting with 500 mg per day during the first week, then weekly increased by 500 mg daily to final dose; patients with BMI <30 received 1,500 mg final dose per day, patients with a BMI ≥30 but <35 received 2,000 mg and patients with a BMI ≥35 received 2,500 mg Description of control: untreated patients Length of intervention: 6 months Length of follow-up: immediate post

Study	Sjostrom 1998[120]
Comments	See USPSTF Review[5] for details

Study/Location	Smith 2011[129] US and Sweden
Objective	To determine if a 24 week weight loss program with orlistat 60 mg in overweight subjects would produce a greater change in visceral adipose tissue compared to placebo
Methods	Design: RCT

	Inclusion criteria: 18–60 years; normal eating habits; BMI 25–34.9; waist circumference for females >88 cm (35 inches) or for males >102 cm (40 inches) Exclusion criteria: pregnancy; recent weight loss; prescription drugs that could interfere with weight or intestinal transit time; taking cyclosporine, warfarin, or amiodarone HCL; history of GI diseases, diabetes, uncontrolled hypertension, or heart disease
Participants	Sample: 131 Intervention n=65; Control n=66 Age, Mean (SD) years: Overall: 43.4 (10.40); Intervention: 42.9 (9.03); Control: 43.8 (11.68) Gender [Female n (%)]: Intervention: 51 (82.3%); Control: 51 (83.6%) Race/Ethnicity [White n (%)]: Intervention: 43 (69.4%); Control: 51 (83.6%) Loss to follow-up: Intervention 16.9%; Control 19.7%
Intervention	Description of intervention: met with registered dietitian for nutrition counseling and instructed to consume a hypocaloric, low-fat diet containing 50% carbohydrate, 30% fat and 20% protein; encouraged to exercise (e.g., a 30-45 min walk, five/week); received educational material; one capsule with each main meal three times a day and a multivitamin daily at least 2 h before or after taking the study medication. Description of control: Same as intervention group but with placebo. Duration of intervention: 24 weeks Length of follow-up: immediate post

Study	Stevens 1993[90]; Companion papers: Whelton,[90] Hypertension Prevention Collaborative Research Group,[237] Satterfield[238]
Comments	See USPSTF Review[5] for details

Study	Stevens 2001[91]; Companion papers: Hypertension Prevention Collaborative Research Group,[239] Hollis[240]
Comments	See USPSTF Review[5] for details

Study	Swinburn 2005[121]
Comments	See USPSTF Review[5] for details

Study/Location	ter Bogt 2011[72] The Netherlands; Companion papers: ter Bogt,[241-243] Driehuis[244]
Objective	To examine the 1-year effects of lifestyle counselling by nurse practitioner on physical activity and diet, compared with usual care from general practitioner
Methods	Design: RCT

	Selection: 12 general practice locations (varying from one to seven general practitioners and one to three nurse practitioners in the northern part of the Netherlands) Inclusion criteria: BMI 25-40; either hypertension or dyslipidaemia, or both Exclusion criteria: diabetes; hypothyroidism; pregnancy; liver or kidney disease; current treatment for malignancy; severely shortened life expectancy; mental illness; addiction to alcohol or drugs
Participants	Sample: 457 Intervention n=225; Control n=232 Age Mean (SD) years: Intervention: 55.2 (7.7); Control: 57.1 (7.7) Gender [Female n (%]): Intervention n=87 (51.5%); Control n=94 (54.7%) Co-morbidities: hypertension; dyslipidemia Loss to follow-up: Intervention n=54; Control n=36
Intervention	Description of intervention: in first year, the lifestyle intervention of the Nurse Practitioner consisted of 4 individual visits (at 1, 2, 3 and 8 months after baseline) and one feedback session by telephone (5 months after baseline) Description of control: offered one visit with GP to discuss results from screening and thereafter received usual GP care Duration of intervention: 36 months Length of follow-up: immediate post

Study/Location	Thomas 2011[58] UK
Objective	To determine whether 60 mg orlistat is effective as a weight loss option in a free-living community population with minimal professional input.
Methods	Design: Pre/Post Selection: poster advertising in local area and Clinical Imaging Centre volunteer panel Inclusion criteria: Aged 18-60 years; BMI 25-34.9; WC >88 cm (female), >102 (male) Exclusion criteria: recent history of weight loss or taking prescription drugs that affect body weight or metabolism
Participants	Sample: 27 Age, Mean (SD) years: Overall: 39.8 (8.7) Gender [Female n (%)]: 7 (26%) Race/Ethnicity (Caucasian): n=17 Loss to follow-up: 3
Intervention	Description of intervention: 4-week supply of alli (60 mg orlistat), educational materials included in the US starter kit and access to the US alli web site

	Description of Control: NA Duration of intervention: 12 weeks Length of follow-up: immediate post

Study	Torgerson 2004[122]; Companion paper: Torgerson[245]
Comments	See USPSTF Review[5] for details

Study/Location	Tsai 2010[75] US
Objective	To evaluate the effect of using medical assistants (MAs) as weight loss counselors
Methods	Design: RCT Selection: recruited through flyers, direct referrals from PCPs, and word-of-mouth Inclusion criteria: BMI 27-50; willingness to keep food and activity records Exclusion criteria: medical conditions that contraindicated weight loss; use of medications associated with weight gain or loss of ≥5% (e.g., systemic steroids, weight loss medications); substance abuse; or serious psychiatric illness including bipolar disorder, schizophrenia, or severe depression (score of ≥29 on the Beck Depression Inventory)
Participants	Sample: 50 Intervention n=24; Control group n=26 Age, Mean (SD) years: Intervention: 51.3 (2.3); Control: 47.6 (2.5) Gender (Female): 88% Race/Ethnicity (African American): Intervention: 79%; Control: 81% SES [education years (SD)]: Intervention: 14.4 (0.5); Control: 13.3 (0.4) Loss to follow-up: 6.0%
Intervention	Description of intervention: same schedule of Primary Care Practitioner visits, same materials as control participants; series of 8 brief (15–20 min) individual visits with a MA at weeks 0, 2, 4, 8, 12, 16, 20, and 24. Visits conducted by MAs using handouts adapted from the Diabetes Prevention Program Description of control: quarterly meetings with PCPs during study; provided 1–2 page handouts developed by the Weight-Control Information Network of the National Institutes of Health, a calorie counter, a pedometer, and a sample meal plan; weight management component of visit lasted about 2–3 min; PCPs instructed to encourage patients to lose weight, using materials provided, but did not give specific behavioural strategies for weight management Duration of intervention: 52 weeks Length of follow-up: immediate post

Study	Van Gaal 1998[125]
Comments	See USPSTF Review[5] for details

Study/Location	Vissers 2010[77] Belgium
Objective	To determine the effect of whole body vibration combined with caloric restriction on weight
Methods	Design: RCT Selection: recruited in outpatient clinics and through media advertising Exclusion criteria: diabetes; pregnancy; treatment with tricyclic antidepressants; joint replacement surgery; use of weight loss drugs; BMI >40, weight loss >5% in past 6 weeks; unable to swallow or unable/unwilling to participate in physical activity
Participants	Sample: 58 Intervention1 (Diet) n=2; Intervention 2 (Fitness) n=20; Intervention 3 (Vibration) n=18; Control n=21 Age, Mean (SD) years: Intervention 1: 45.5 (13.1); Intervention 2: 44.7 (13.0); Intervention 3: 43.3 (9.6); Control: 44.8 (11.4) Gender (Female): 74.7% Loss to follow-up: Intervention 1 n=8; Intervention 2 n=1; Intervention 3 n=5; Control n=4
Intervention	Description of intervention 1: diet only Description of intervention 2: diet and aerobic exercise Description of intervention 3: diet and non-aerobic exercise Description of control: NR Duration of intervention: 6 months Length of follow-up: 6 months

Study/Location	Wadden 2011[71] US
Objective	To compare weight loss during a 2-year period in response to three lifestyle interventions, all delivered by PCPs in collaboration with auxiliary health professionals (lifestyle coaches) in their practices
Methods	Design: RCT Selection: multiple methods of recruitment, including PCP referral and self-referral in response to in-clinic advertisements at six primary care practices selected from a total of 27 on the basis of providing care to 2,000 or more adults and having at least two

	physicians and two auxiliary health providers on staff Inclusion: age ≥21 years; BMI 30-50; at least two of five components of the metabolic syndrome to increase likelihood of having cardiovascular risk factors Exclusion: recent CVD; other medical conditions contraindicating weight loss; blood pressure ≥ 160/100 mmHg, medications that substantially affect body weight, substance abuse, severe psychiatric illness that could affect adherence; bariatric surgery; loss of ≥5% of body weight in the previous 6 months; pregnancy or lactation
Participants	Sample: 390 Intervention 1 (brief lifestyle counseling) n=131; Intervention 2 (enhanced lifestyle counseling) n=129*; Control n=130 Age, Mean (SD) years: Intervention: 52.0 (12.2); Control: 51.7 (12.1) Gender [Female n (%)]: Intervention: 110 (84.0%); Control: 98 (75.4%) Race/Ethnicity [White n (%)]: Intervention: 75 (57.3%); Control: 81 (62.3%) SES (post-secondary education): Intervention n=99 (76%); Control n=95 (73%) Loss to follow-up: Intervention n=19; Control n=20
Intervention	Description of intervention: quarterly visits with primary care provider, brief lifestyle counseling including 10 to 15 minutes each month with auxiliary health care provider (medical assistant), referred to as a lifestyle coach, who delivered treatment by following abbreviated lessons from the Diabetes Prevention Program Description of control: usual care (quarterly visits with primary care provider) Duration of Intervention: 24 months Length of follow-up: immediate post
Comments	*There was a second intervention group that was enhanced brief counseling. The enhanced component involved participants choosing to take sibutramine, orlistat or meal replacements. Outcomes were not reported by what enhanced option participants chose. Also, there was no placebo group for comparison. As a result, data was not extracted for this group.

Study	Wood 1988[92]; Companion papers: Frey-Hewitt[246]
Comments	See USPSTF Review[5] for details

Study	Wood 1991[93]; Companion paper: Kiernan[247]
Comments	See USPSTF Review[5] for details

Study	Woollard 2003[94]
Comments	See USPSTF Review[5] for details

Table 5: Broad Features of the Available Evidence

Designs	• 68 studies (66 RCTs, 2 single group pre-post designs included for harms outcomes only)
Populations	• All studies included overweight (BMI 25-29.9) and/or obese (BMI 30-39.9) adults • 2 interventions targeted seniors (≥65 years) • 61 studies included men and women; 3 included only women; 2 included only men (or reported data only for men) • 26 studies (38%) were directed at high CVD risk populations
Interventions	• 41 behavioural intervention arms (8 diet, 4 exercise, 10 diet + exercise, 19 lifestyle) • 29 pharmacological [25 orlistat (dose: 23 studies 120mg 3x/day; 2 studies 60mg 3x/day); 4 metformin (dose: 500mg 1x/day, 850mg 1x/day, 850mg 2x/day, 1,500 mg 1x/day)] plus behavioural arms • 49 interventions (72%) were 12 months or less in duration
Quality Assessment	• 62 RCTs (94%) rated as having unclear or high risk of bias for the weight outcomes • Most outcomes received moderate GRADE ratings (downgraded for risk of bias); occasional low GRADE ratings applied due to added concerns primarily regarding reporting bias
Study Locations	• 2 studies in Canada, 27 in the US, 32 in European countries, 6 in Australia or New Zealand, 1 in Japan, 1 in China
Publication Dates	• 35 studies (51%) were published in the last 5 years; 33 were published between 1985 and 2008

Table 6: Key Findings of Overall and Sub-group Analyses for Continuous Outcomes (Weight in KG, BMI, Waist Circumference, Total Cholesterol, LDL-C, Fasting Glucose, SBP, DBP)

Group or Sub-group	Meta-analysis, Mean Difference (95% CI)	Statistical Heterogeneity (Within Group) P-Value, I^2-Value	Test for Between Group Differences P-Value, I^2-Value	No. Participants	No. Studies	GRADE Rating
Outcome: Weight Change in KG						
Overall	-3.02 (-3.52 to -2.52)	<0.00001, 91%	na	22,615	49	Moderate
Behavioural	-3.13 (-3.88 to -2.38)	<0.00001, 92%	0.62, 0%	10,829	33	Moderate
Pharmacological + Behavioural	-2.89 (-3.49 to -2.29)	<0.00001, 87%		11,786	17	Moderate
Behavioural – Diet	-4.71 (-6.22 to -3.21)	0.0003, 72%	0.03, 67.8%	913	8	Moderate
Behavioural – Exercise	-1.49 (-3.32 to 0.35)	0.0002, 85%		598	4	Low
Behavioural – Diet + Exercise	-3.83 (-5.49 to -2.16)	<0.00001, 90%		2,382	10	Low
Behavioural – Lifestyle	-2.52 (-3.54 to -1.49)	<0.00001, 93%		6,936	17	Low
Behavioural ≤12 Months	-3.43 (-4.32 to -2.55)	<0.00001, 88%	0.07, 23.4%	4,780	21	Low
Behavioural >12 Months	-2.53 (-3.81 to -1.24)	<0.00001, 95%		6,049	12	Low
Behavioural – Male	-4.65 (-6.20 to -3.09)	<0.00001, 89%	0.23, 31.5%	2,131	8	Moderate
Behavioural – Female	-3.33 (-4.80 to -1.86)	<0.00001, 87%		1,800	8	Moderate
Behavioural – High CVD Risk	-1.89 (-2.69 to -1.08)	<0.00001, 75%	0.005, 87.6%	2,951	12	Low
Behavioural – Low CVD Risk	-3.66 (-4.59 to -2.74)	<0.00001, 92%		7,878	21	Moderate
Pharmacological + Behavioural – Metformin	-1.92 (-2.94 to -0.89)	0.11, 60%	0.07, 68.8%	1,938	2	Moderate
Pharmacological + Behavioural – Orlistat	-3.05 (-3.75 to -2.35)	<0.00001, 88%		9,848	15	Moderate
Pharmacological + Behavioural ≤12 Months	-2.89 (-3.90 to -1.88)	<0.00001, 91%	0.72, 0%	4,418	11	Moderate
Pharmacological + Behavioural >12 Months	-2.69 (-3.00 to -2.38)	0.36, 9%		7,368	6	Moderate
Pharmacological + Behavioural – High CVD Risk	-2.93 (-4.08 to -1.79)	<0.00001, 92%	0.80, 0%	3,411	9	Moderate
Pharmacological + Behavioural – Low CVD Risk	-2.77 (-3.27 to -2.28)	0.03, 54%		8,375	8	Moderate
Outcome: Change in BMI (kg/m^2)						
Overall	-1.11 (-1.39 to -0.84)	<0.00001, 93%	na	10,611	26	Moderate
Behavioural	-1.09 (-1.43 to -0.75)	<0.00001, 93%	0.59, 0%	7,487	22	Moderate
Pharmacological + Behavioural	-1.27 (-1.82 to -0.72)	<0.00001, 93%		3,124	5	Moderate
Outcome: Change in Waist Circumference (cm)						
Overall	-2.78 (-3.34 to -2.22)	<0.00001, 91%	na	16,565	33	Moderate
Behavioural	-3.05 (-3.86 to -2.24)	<0.00001, 90%	0.18, 44.4%	7,770	22	Moderate
Pharmacological + Behavioural	-2.29 (-3.04 to -1.55)	<0.00001, 91%		8,795	12	Moderate

Group or Sub-group	Meta-analysis, Mean Difference (95% CI)	Statistical Heterogeneity (Within Group) P-Value, I^2-Value	Test for Between Group Differences P-Value, I^2-Value	No. Participants	No. Studies	GRADE Rating
Outcome: Change in Total Cholesterol (mmol/L)						
Overall	-0.21 (-0.29 to -0.13)	<0.00001, 86%	na	10,039	33	Moderate
Behavioural	-0.10 (-0.18 to -0.03)	<0.0001, 63%	0.0001, 93.1%	4,282	18	Low
Pharmacological + Behavioural	-0.33 (-0.42 to -0.24)	<0.00001, 81%		5,757	15	Moderate
Outcome: Change in LDL-C (mmol/L)						
Overall	-0.21 (-0.29 to -0.12)	<0.00001, 90%	na	9,313	30	Low
Behavioural	-0.14 (-0.29 to -0.002)	<0.00001, 90%	0.11, 60.1%	3,556	15	Moderate
Pharmacological + Behavioural	-0.28 (-0.38 to -0.19)	<0.00001, 89%		5,757	15	Moderate
Outcome: Change in Fasting Glucose (mmol/L)						
Overall	-0.26 (-0.38 to -0.13)	<0.00001, 96%	na	12,646	28	Moderate
Behavioural	-0.14 (-0.23 to -0.05)	<0.00001, 81%	0.02, 80.7%	5,106	15	Moderate
Pharmacological + Behavioural	-0.43 (-0.66 to -0.20)	<0.00001, 98%		7,540	14	Moderate
Outcome: Change in SBP (mmHg)						
Overall	-1.70 (-2.23 to -1.17)	0.002, 41%	na	16,668	37	Moderate
Behavioural	-1.76 (-2.61 to -0.91)	0.0009, 50%	0.91, 0%	7,644	22	Moderate
Pharmacological + Behavioural	-1.70 (-2.28 to -1.13)	0.24, 19%		9,024	16	Moderate
Outcome: Change in DBP (mmHg)						
Overall	-1.42 (-1.88 to -0.96)	<0.00001, 63%	na	16,158	36	Moderate
Behavioural	-1.60 (-2.27 to -0.93)	<0.00001, 63%	0.45, 0%	7,690	22	Moderate
Pharmacological + Behavioural	-1.24 (-1.88 to -0.61)	0.0002, 65%		8,468	15	Moderate

Table 7: Key Findings of Overall and Sub-group Analyses for Dichotomous Outcomes (Loss of ≥5% Baseline Body Weight, Loss of ≥10% Baseline Body Weight, Incidence T2D)

Group or Sub-group	Effect				Statistical Heterogeneity (Within Group) P-Value, I^2-Value	Test for Between Group Differences P-Value, I^2-Value	No. Participants	No. Studies	GRADE Rating
	RR (95% CI)	Absolute Number per Million (Range)	ARR	NNT (95% CI)					
Outcome: Loss of ≥5% Baseline Body Weight									
Overall	1.77 (1.58 to 1.99)	204,152 more (153,226 to 261,352 more)	20.42%	5 (4, 7)	<0.00001, 69%	na	9,857	24	Low
Behavioural	1.75 (1.35 to 2.27)	116,728 more (54,551 to 197,346 more)	11.67%	9 (5, 18)	0.01, 57%	0.88, 0%	2,841	11	Low
Pharmacological+Behavioural	1.79 (1.57 to 2.04)	242,612 more (174,934 to 319,779 more)	24.26%	4 (3, 6)	<0.00001, 76%		7,016	13	Low
Outcome: Loss of ≥10% Baseline Body Weight									
Overall	1.91 (1.69 to 2.16)	112,366 more (85,516 to 142,666 more)	11.24%	9 (7, 12)	0.27, 16%	na	7,523	16	Low
Behavioural	2.04 (1.30 to 3.21)	80,085 more (22,954 to 169,900 more)	8.01%	12 (6, 44)	0.81, 0%	0.81, 0%	744	3	Moderate
Pharmacological+Behavioural	1.92 (1.67 to 2.21)	118,115 more (86,093 to 154,942 more)	11.81%	8 (6, 12)	0.14, 31%		6,779	13	Low
Outcome: Incidence of T2D									
Overall	0.62 (0.50 to 0.77)	57,457 fewer (34,265 to 76,059 fewer)	5.75%	17 (13, 29)	0.02, 54%	na	8,624	9	Moderate
Behavioural	0.55 (0.42 to 0.72)	88,849 fewer (55,323 to 114,477 fewer)	8.88%	11 (9, 18)	0.25, 23%	0.11, 60%	3,198	7	Moderate
Pharmacological+Behavioural	0.72 (0.59 to 0.87)	36,035 fewer (16,586 to 52,071 fewer)	3.60%	28 (19, 60)	0.26, 27%		5,426	3	Moderate

Table 8: Key Findings of Overall and Sub-group Analyses for Harms (Any Adverse Events, Serious Adverse Events, Gastrointestinal Events, Withdrawal from Study due to Adverse Events)

Group or Sub-group	Effect		ARI	NNH (95% CI)	Statistical Heterogeneity (Within Group) P-Value, I^2-Value	Test for Between Group Differences P-Value, I^2-Value	No. Participants	No. Studies	GRADE Rating
	RR (95% CI)	Absolute Number per Million (Range)							
Outcome: Any Adverse Events									
Overall	1.16 (1.09 to 1.23)	93,095 more (52,756 to 135,929 more)	9.31%	11 (7, 19)	<0.00001, 73%	na	5,512	17	Moderate
Behavioural	0.19 (0.03 to 1.16)	18,616 fewer (22,332 fewer to 3,637 more)	-	-	0.41, 0%	0.05, 74%	561	3	Low
Pharmacological+Behavioural	1.16 (1.09 to 1.23)	103,638 more (59,970 to 149,925 more)	10.36%	10 (7, 17)	<0.00001, 75%		4,951	15	Moderate
Outcome: Serious Adverse Events									
Overall	1.07 (0.96 to 1.20)	7,382 more (3,706 fewer to 19,730 more)	-	-	0.74, 0%	na	10,811	14	Low
Behavioural	0.995 (0.80 to 1.24)	644 fewer (24,989 fewer to 29,707 more)	-	-	0.68, 0%	0.44, 0%	2,174	3	Low
Pharmacological+Behavioural	1.10 (0.97 to 1.25)	9,534 more (2,779 fewer to 23,475 more)	-	-	0.62, 0%		8,637	12	Low
Outcome: Gastrointestinal Events									
Pharmacological+Behavioural	1.58 (1.47 to 1.70)	187,235 more 150,343 to 226,998 more)	18.72%	5 (4, 7)	<0.00001, 71%	na	12,954	23	Low
Outcome: Study Withdrawal due to Adverse Events									
Overall	1.69 (1.43 to 2.00)	30,547 more (18,892 to 44,348 more)	3.05%	33 (23, 53)	0.65, 0%	na	12,987	26	Moderate
Behavioural	3.40 (0.16 to 70.16)	-	-		-	0.65, 0%	302	1	Low
Pharmacological+Behavioural	1.68 (1.42 to 2.00)	30,930 more (21,078 to 45,3000 more)	3.09%	32 (22, 47)	0.25, 15%		12,685	25	Moderate

Table 9: Summary of Features of Efficacious Behavioural Interventions

Study	Intervention Duration (months)	Intervention Focus	Intervention Setting	Estimated Number of Sessions	Includes Group Sessions	Includes Individual Sessions	Technology-based	Weight Loss Goal Set	Active Use of Self-monitoring
Appel 2011[70]	24 m	Lifestyle (Remote Support Group or In-person Support Group)	Primary Care	9 Group and 3 Individual Sessions for In-person Support 12 Weekly Calls for Remote Support	Yes (In-person Support Group)	Yes (Remote Support and In-person Support Groups)	Yes (Remote Support and In-person Support Groups)	Yes	Yes
Christian 2008[83]	12 m	Diet + Exercise	Clinic	4		Yes	Yes		
Dekkers 2011[68]	6 m	Lifestyle (Internet Group or Phone Group)	Multi-setting	Unclear		Yes (Internet and Phone Groups)	Yes (Internet Group)		
DPP 1999[133]	38 m	Lifestyle	Community	23	Yes	Yes		Yes	Yes
Foster-Schubert 2012[99]	12 m	Diet Diet + Exercise	Community	32 for Diet 188 for Diet + Exercise	Yes	Yes	Yes	Yes (Both Groups)	Yes
Haapala 2009[86]	12 m	Diet + Exercise	Home	0			Yes	Yes	Yes
Janus 2012[103]	12 m	Lifestyle	Primary Care	6	Yes				
Langford 1985[88]	13 m	Diet	Clinic	18	Yes	Yes		Yes	Yes
Nakade 2012[102]	12 m	Lifestyle	Clinic	5	Yes	Yes		Yes	
Nanchanhal 2012[104]	12 m	Lifestyle	Primary Care	14		Yes		Yes	Yes
Parkih 2010[95]	12 m	Lifestyle	Community	8	Yes				
Stevens 1993[90]	18 m	Lifestyle	Clinic	23	Yes	Yes			Yes
Wood 1988[92]	12 m	Diet	Community	23	Yes	Yes			
Wood 1991[93]	12 m	Diet Diet + Exercise	Community	25	Yes				Yes
Vissers 2010[77]	6 m	Diet Diet + Exercise (Fitness Group or Vibration Group)	Multi-setting	15 for Diet 42 for Diet + Fitness Unclear for Diet + Vibration	Yes (Diet + Exercise Groups)	Yes (Diet Group)			

Table 10: Mean BMI by Immigrant Status and Sex, Canada 1994 and 2006[142]

Immigrant Status	1994		2006	
	Males n=2,504	**Females** n=2,906	**Males** n=2,386	**Females** n=2,865
Canadian-born	26.2 (3.9)	24.9 (5.2)	27.9 (4.3)	26.9 (5.9)
White immigrants	26.3 (4.0)	24.3 (4.7)	28.0 (4.8)	26.2 (5.7)
Non-white immigrants	24.3 (3.4)	23.2 (4.1)	25.7 (3.8)	24.5 (3.9)

Estimates in brackets are standard deviation units

Table 11: Prevalence of Self-Reported Obesity, and Obesity and Overweight in Canada, by Age and Sex, 2005[141]

Gender	Age Group				
	25-34	35-44	45-54	55-64	All Ages
Obese					
Males	15.42	17.76	20.36	21.98	18.77
Females	12.81	13.83	17.55	19.42	15.79
Overweight and Obese Combined					
Males	53.78	62.11	64.83	67.10	61.92
Females	33.63	38.76	46.25	55.65	43.17

Table 12: Prevalence of Self-Reported Obesity in Canada, by Age and Sex, 2007-08[20]

Gender	Age Group							
	18-19	20-24	25-34	35-44	45-54	55-64	65-74	75+
Males	7.2	11.1	15.9	19.4	20.6	23.3	21.2	12.0
Females	5.5	8.4	13.3	16.0	17.5	21.4	20.2	14.3

EVIDENCE SETS

- **Evidence Set 1: Weight Change in KG**
- **Evidence Set 2: Loss of ≥5% Baseline Body Weight**
- **Evidence Set 3: Loss of ≥10% Baseline Body Weight**
- **Evidence Set 4: Weight – Change in BMI**
- **Evidence Set 5: Weight – Change in Waist Circumference**
- **Evidence Set 6: Health/Physiological Outcomes – Change in Total Cholesterol**
- **Evidence Set 7: Health/Physiological Outcomes – Change in LDL-C**
- **Evidence Set 8: Health/Physiological Outcomes – Change in Fasting Glucose**
- **Evidence Set 9: Health/Physiological Outcomes – Incidence of T2D**
- **Evidence Set 10: Health/Physiological Outcomes – Change in SBP**
- **Evidence Set 11: Health/Physiological Outcomes – Change in DBP**
- **Evidence Set 12: Adverse Effects – Any Adverse Events**
- **Evidence Set 13: Adverse Effects – Serious Adverse Events**
- **Evidence Set 14: Adverse Effects – Gastrointestinal Events**
- **Evidence Set 15: Adverse Effects – Withdrawal from Study Due to Adverse Events**

Evidence Set 1: Do primary care relevant treatment interventions in overweight/obese adults lead to weight loss (kg)?

- Summary of Weight Change in KG Evidence
- GRADE Evidence Profile Table 1.1: Effect of Treatment Interventions on Weight in KG
- GRADE Summary of Findings Table 1.1: Effect of Treatment Interventions on Weight in KG
- Forest Plots 1.1 to 1.8: Effect of Treatment Interventions on Weight in KG
  - 1.1: Overall and by Primary Focus of Intervention – Behavioural and Pharmacological plus Behavioural
  - 1.2: Type of Behavioural Intervention (Diet, Exercise, Diet plus Exercise, Lifestyle)
  - 1.3: Type of Pharmacological plus Behavioural Intervention (Metformin, Orlistat)
  - 1.4: Duration of Behavioural Intervention (≤12 Months, >12 Months)
  - 1.5: Duration of Pharmacological plus Behavioural Intervention (≤12, >12 Months)
  - 1.6: Participants' Baseline CVD Risk Status in Behavioural Interventions (High Risk, Low/Unknown Risk)
  - 1.7: Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions (High Risk, Low/Unknown Risk)
  - 1.8: Gender (Female, Male)
- Funnel Plots 1.1 to 1.8: Effect of Treatment Interventions on Weight in KG
  - Same as bulleted list above
- Egger's Test Results (for Publication Bias)

Summary of Weight Change in KG Evidence

<u>1.1 Overall and by Primary Focus of Intervention</u>

Overall
- 49 studies; 22,615 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.02 kg (-3.52, -2.52)]
- High heterogeneity across studies [Chi^2=685.01, df=62 (P<0.00001), I^2=91%]

Test for subgroup differences is not significant [Chi^2=0.25, df=1 (P=0.62), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions
- 33 studies; 10,829 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.13 kg (-3.88, -2.38)]
- High heterogeneity across studies [Chi^2=556.46, df=45 (P<0.00001), I^2=92%]

Pharmacological plus Behavioural Interventions
- 17 studies; 11,786 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.89 kg (-3.49, -2.29)]
- High heterogeneity across studies [Chi^2=122.66, df=16 (P<0.00001), I^2=87%]

1.2 Type of Behavioural Intervention

Test for subgroup differences is significant [Chi^2=9.32, df=3 (P=0.03), I^2=67.8%]; type of intervention does explain some of the variation across behavioural studies

Diet
- 8 studies; 913 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -4.71 kg (-6.22, -3.21)]
- High heterogeneity across studies [Chi^2=29.05, df=8 (P=0.0003), I^2=72%]

Exercise
- 4 studies; 598 participants
- No statistically significant effect on weight in the intervention group as compared to the control group [MD (95% CI) -1.49 kg (-3.32, 0.35)]
- High heterogeneity across studies [Chi^2=20.08, df=3 (P=0.0002), I^2=85%]

Diet plus Exercise
- 10 studies; 2,382 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.83 kg (-5.49, -2.16)]
- High heterogeneity across studies [Chi^2=109.41, df=11 (P<0.00001), I^2=90%]

Lifestyle
- 17 studies; 6,936 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.52 kg (-3.54, -1.49)]
- High heterogeneity across studies [Chi^2=301.45, df=20 (P<0.00001), I^2=93%]

1.3 Type of Pharmacological plus Behavioural Intervention

Test for subgroup differences is not significant [Chi^2=3.20, df=1 (P=0.07), I^2=68.8%]; type of drug does not explain variation across pharmacological plus behavioural studies

Metformin
- 2 studies; 1,938 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -1.92 kg (-2.94, -0.89)]
- Moderate heterogeneity across studies [Chi^2=2.51, df=1 (P=0.11), I^2=60%]

Orlistat
- 15 studies; 9,848 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.05 kg (-3.75, -2.35)]
- High heterogeneity across studies [Chi^2=117.05, df=14 (P<0.00001), I^2=88%]

1.4 Duration of Behavioural Intervention

Test for subgroup differences is not significant [Chi^2=1.31, df=1 (P=0.25), I^2=23.4%]; duration of intervention does not explain variation across behavioural studies

≤12 Months
- 21 studies; 4,780 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.43 kg (-4.32, -2.55)]
- High heterogeneity across studies [Chi^2=249.88, df=30 (P<0.00001), I^2=88%]

>12 Months
- 12 studies; 6,049 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.53 kg (-3.81, -1.24)]
- High heterogeneity across studies [Chi^2=256.18, df=14 (P<0.00001), I^2=95%]

1.5 Duration of Pharmacological plus Behavioural Intervention

Test for subgroup differences is not significant [Chi^2=0.13, df=1 (P=0.72), I^2=0%]; duration of intervention does not explain variation across pharmacological plus behavioural studies

≤12 Months
- 11 studies; 4,418 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.89 kg (-3.90, -1.88)]
- High heterogeneity across studies [Chi^2=114.47, df=10 (P<0.00001), I^2=91%]

>12 Months
- 6 studies; 7,368 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.69 kg (-3.00, -2.38)]
- Low heterogeneity across studies [Chi^2=5.47, df=5 (P=0.36), I^2=9%]

1.6 Participants' Baseline CVD Risk Status in Behavioural Interventions

Test for subgroup differences is significant [Chi^2=8.05, df=1 (P=0.005), I^2=87.6%]; participants' baseline CVD risk status does explain some of the variation across behavioural studies

High Risk
- 12 studies; 2,951 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -1.89 kg (-2.69, -1.08)]
- High heterogeneity across studies [Chi^2=52.70, df=13 (P<0.00001), I^2=75%]

Low/Unknown Risk
- 21 studies; 7,878 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.66 kg (-4.59, -2.74)]
- High heterogeneity across studies [Chi^2=400.02, df=31 (P<0.00001), I^2=92%]

1.7 Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions

Test for subgroup differences is not significant [Chi^2=0.06, df=1 (P=0.80), I^2=0%]; participants' baseline CVD risk status does not explain variation across pharmacological plus behavioural studies

High Risk

- 9 studies; 3,411 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.93 kg (-4.08, -1.79)]
- High heterogeneity across studies [Chi^2=104.58, df=8 (P<0.00001), I^2=92%]

Low/Unknown Risk

- 8 studies; 8,375 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -2.77 kg (-3.27, -2.28)]
- Moderate heterogeneity across studies [Chi^2=15.20, df=7 (P=0.03), I^2=54%]

1.8 Gender

Ten behavioural intervention studies provided results separated by gender. Test for subgroup differences is not significant [Chi^2=1.46, df=1 (P=0.23), I^2=31.5%]; gender does not explain variation across behavioural studies

Female

- 8 behavioural intervention studies; 1,800 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -3.33 kg (-4.80, -1.86)]
- High heterogeneity across studies [Chi^2=75.52, df=10 (P<0.00001), I^2=87%]

Male

- 8 behavioural intervention studies; 2,131 participants
- Statistically significant reduction in weight in the intervention group as compared to the control group [MD (95% CI) -4.65 kg (-6.20, -3.09)]
- High heterogeneity across studies [Chi^2=82.06, df=9 (P<0.00001), I^2=89%]

GRADE Evidence Profile Table 1.1: Effect of Treatment Interventions on Weight in KG *

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Weight Change in KG: Overall (Better indicated by lower values)											
49	randomized trials[1]	serious risk [2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	12,840	9,775	3.0180 lower (3.5188 to 2.5171 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
33	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	6,463	4,366	3.1301 lower (3.8754 to 2.3848 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
17	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	6,377	5,409	2.8874 lower (3.4850 to 2.2898 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Type of Behavioural Intervention - Diet (Better indicated by lower values)											
8	randomized trials[19]	serious risk[20]	no serious inconsistency[21]	no serious indirectness[22]	no serious imprecision[23]	none[24]	653	260	4.7125 lower (6.2188 to 3.2062 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Type of Behavioural Intervention - Exercise (Better indicated by lower values)											
4	randomized trials[25]	serious risk[26]	no serious inconsistency[27]	no serious indirectness[28]	serious imprecision[29]	none[30]	406	192	1.4874 lower (3.3231 lower to 0.3484 higher)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by Type of Behavioural Intervention - Diet plus Exercise (Better indicated by lower values)											
10	randomized trials[31]	serious risk[32]	no serious inconsistency[33]	no serious indirectness[34]	no serious imprecision[35]	reporting bias[36]	1,390	992	3.8257 lower (5.4935 to 2.1579 lower)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by Type of Behavioural Intervention - Lifestyle (Better indicated by lower values)											
17	randomized trials[37]	serious risk[38]	no serious inconsistency[39]	no serious indirectness[40]	no serious imprecision[41]	reporting bias[42]	4,014	2,922	2.5174 lower (3.5443 to 1.4904 lower)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by Type of Pharmacological plus Behavioural Intervention - Metformin (Better indicated by lower values)											
2	randomized trials[43]	serious risk[44]	no serious inconsistency[45]	no serious indirectness[46]	no serious imprecision[47]	none[48]	1,237	701	1.9163 lower (2.9438 to 0.8887 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Type of Pharmacological plus Behavioural Intervention - Orlistat (Better indicated by lower values)											
15	randomized trials[49]	serious risk[50]	no serious inconsistency[51]	no serious indirectness[52]	no serious imprecision[53]	none[54]	5,140	4,708	3.0513 lower (3.7510 to 2.3517 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Length of Behavioural Interventions ≤12 Months (Better indicated by lower values)											

21	randomized trials[55]	serious risk[56]	no serious inconsistency[57]	no serious indirectness[58]	no serious imprecision[59]	reporting bias[60]	2,999	1,781	3.4339 lower (4.3163 to 2.5515 lower)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by Length of Behavioural Interventions >12 Months (Better indicated by lower values)											
12	randomized trials[61]	serious risk[62]	no serious inconsistency[63]	no serious indirectness[64]	no serious imprecision[65]	reporting bias[66]	3,464	2,585	2.5266 lower (3.8089 to 1.2444 lower)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by Length of Pharmacological plus Behavioural Interventions ≤12 Months (Better indicated by lower values)											
11	randomized trials[67]	serious risk[68]	no serious inconsistency[69]	no serious indirectness[70]	no serious imprecision[71]	none[72]	2,209	2,209	2.8889 lower (3.9017 to 1.8762 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Length of Pharmacological plus Behavioural Interventions >12 Months (Better indicated by lower values)											
6	randomized trials[73]	serious risk[74]	no serious inconsistency[75]	no serious indirectness[76]	no serious imprecision[77]	none[78]	4,168	3,200	2.6938 lower (3.0035 to 2.3841 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by CVD Risk in Behavioural Interventions - High Risk (Better indicated by lower values)											
12	randomized trials[79]	serious risk[80]	no serious inconsistency[81]	no serious indirectness[82]	no serious imprecision[83]	reporting bias[84]	1,810	1,141	1.8862 lower (2.6932 to 1.0793 lower)	⊕⊕OO LOW	CRITICAL
Weight Change in KG: by CVD Risk in Behavioural Interventions - Low/Unknown Risk (Better indicated by lower values)											
21	randomized trials[85]	serious risk[86]	no serious inconsistency[87]	no serious indirectness[88]	no serious imprecision[89]	none[90]	4,653	3,225	3.6629 lower (4.5878 to 2.7379 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by CVD Risk in Pharmacological plus Behavioural Interventions - High Risk (Better indicated by lower values)											
9	randomized trials[91]	serious risk[92]	no serious inconsistency[93]	no serious indirectness[94]	no serious imprecision[95]	none[96]	1,702	1,709	2.9342 lower (4.0750 to 1.7933 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by CVD Risk in Pharmacological plus Behavioural Interventions - Low/Unknown Risk (Better indicated by lower values)											
8	randomized trials[97]	serious risk[98]	no serious inconsistency[99]	no serious indirectness[100]	no serious imprecision[101]	none[102]	4,675	3,700	2.7737 lower (3.2683 to 2.2792 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Gender in Behavioural Interventions - Female (Better indicated by lower values)											
8	randomized trials[103]	serious risk[104]	no serious inconsistency[105]	no serious indirectness[106]	no serious imprecision[107]	none[108]	1,070	730	3.3278 lower (4.7950 to 1.8607 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight Change in KG: by Gender in Behavioural Interventions - Male (Better indicated by lower values)											
8	randomized trials[109]	serious risk[110]	no serious inconsistency[111]	no serious indirectness[112]	no serious imprecision[113]	none[114]	1,126	1,005	4.6451 lower (6.1986 to 3.0917 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 1.1: Effect of Treatment Interventions on Weight in KG

Outcome: Weight Change in KG	Compared to the control group, the mean weight in kg (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**3.0180 lower** (3.5188 to 2.5171 lower)	22,615 (49 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**3.1301 lower** (3.8754 to 2.3848 lower)	10,829 (33 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**2.8874 lower** (3.4850 to 2.2898 lower)	11,786 (17 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]
By Type of Behavioural Intervention - Diet	**4.7125 lower** (6.2188 to 3.2062 lower)	913 (8 studies[19])	⊕⊕⊕⊖ **moderate**[20,21,22,23,24]
By Type of Behavioural Intervention - Exercise	**1.4874 lower (**3.3231 lower to 0.3484 higher)	598 (4 studies[25])	⊕⊕⊖⊖ **low**[26,27,28,29,30]
By Type of Behavioural Intervention - Diet plus Exercise	**3.8257 lower** (5.4935 to 2.1579 lower)	2,382 (10 studies[31])	⊕⊕⊖⊖ **low**[32,33,34,35,36]
By Type of Behavioural Intervention - Lifestyle	**2.5174 lower** (3.5443 to 1.4904 lower)	6,936 (17 studies[37])	⊕⊕⊖⊖ **low**[38,39,40,41,42]
By Type of Pharmacological plus Behavioural Intervention - Metformin	**1.9163 lower** (2.9438 to 0.8887 lower)	1,938 (2 studies[43])	⊕⊕⊕⊖ **moderate**[44,45,46,47,48]
By Type of Pharmacological plus Behavioural Intervention - Orlistat	**3.0513 lower** (3.7510 to 2.3517 lower)	9,848 (15 studies[49])	⊕⊕⊕⊖ **moderate**[50,51,52,53,54]
By Length of Behavioural Interventions ≤12 Months	**3.4339 lower** (4.3163 to 2.5515 lower)	4,780 (21 studies[55])	⊕⊕⊖⊖ **low**[56,57,58,59,60]
By Length of Behavioural Interventions >12 Months	**2.5266 lower** (3.8089 to 1.2444 lower)	6,049 (12 studies[61])	⊕⊕⊖⊖ **low**[62,63,64,65,66]
By Length of Pharmacological plus Behavioural Interventions ≤12 Months	**2.8889 lower** (3.9017 to 1.8762 lower)	4,418 (11 studies[67])	⊕⊕⊕⊖ **moderate**[68,69,70,71,72]
By Length of Pharmacological plus Behavioural Interventions >12 Months	**2.6938 lower** (3.0035 to 2.3841 lower)	7,368 (6 studies[73])	⊕⊕⊕⊖ **moderate**[74,75,76,77,78]
Weight Loss (kg): by CVD Risk in Behavioural Interventions - High Risk	**1.8862 lower** (2.6932 to 1.0793 lower)	2,951 (12 studies[79])	⊕⊕⊖⊖ **low**[80,81,82,83,84]
By CVD Risk in Behavioural Interventions - Low/Unknown Risk	**3.6629 lower** (4.5878 to 2.7379 lower)	7,878 (21 studies[85])	⊕⊕⊕⊖ **moderate**[86,87,88,89,90]

By CVD Risk in Pharmacological plus Behavioural Interventions - High Risk	**2.9342 lower** (4.0750 to 1.7933 lower)	3,411 (9 studies[91])	⊕⊕⊕⊖ **moderate**[92,93,94,95,96]
By CVD Risk in Pharmacological plus Behavioural Interventions - Low/Unknown Risk	**2.7737 lower** (3.2683 to 2.2792 lower)	8,375 (8 studies[97])	⊕⊕⊕⊖ **moderate**[98,99,100,101,102]
By Gender in Behavioural Interventions - Female	**3.3278 lower** (4.7950 to 1.8607 lower)	1,800 (8 studies[103])	⊕⊕⊕⊖ **moderate**[104,105,106,107,108]
By Gender in Behavioural Interventions - Male	**4.6451 lower** (6.1986 to 3.0917 lower)	2,131 (8 studies[109])	⊕⊕⊕⊖ **moderate**[110,111,112,113,114]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Weight in KG

[1] The 49 studies are:[68-74,76-79,81,83-97,99,100,102-104,106,109-111,114-124,131,133] Immediate post assessment for all but 7 studies; for these 7 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] and Martin[89] provide 6 month follow-up data post completion of 6 month interventions; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 46 studies (94%) were rated as unclear risk and 3 studies (6%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (51%), allocation concealment (39%), blinding of participants and/or personnel (35%), and blinding of outcome assessors (67%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (59%; behavioural studies), incomplete reporting (33%), and other sources of bias (47%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=685.01, df=62 (p<0.00001); I^2=91%] the direction of the effect is consistent across studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.25, df=1 (p=0.62), I^2=0%). The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 49 studies, 47 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=45) included mixed gender samples; 2 included only women and 2 included only men. In 21 studies (43%) the participants had a high risk of CVD. In terms of intervention focus, 32 were behavioural (some studies included more than one type of intervention; eight included a diet arm, four included an exercise arm, 10 included a diet plus exercise arm, 16 included a lifestyle arm), 16 were pharmacological plus behavioural [15 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)], and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 7 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 32 studies and more than 12 months in 17 studies. One study was conducted in Canada, 1 in Canada and the US, 22 in the US, 19 in European countries, 5 in Australia and/or New Zealand, and 1 in Japan. About half of the studies (n=23) were published in the last 5 years (2009-2013); the remaining 26 studies were published between 1985 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (12,840 intervention arm, 9,775 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.0180 (-3.5188, -2.5171)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.354). This body of evidence was not downgraded for suspected publication bias.

[7] The 33 studies are:[68-74,76-79,81,83-97,99,100,102-104,133] Immediate post assessment for all but 5 studies; for these 5 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] and Martin[89] provide 6 month follow-up data post completion of 6 month interventions; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 33 studies with a behavioural intervention (100%) were rated as unclear risk. Across studies, there was a lack of certainty regarding risk of bias associated with sequence generation (45%), allocation concealment (79%), blinding of participants and/or personnel (12%), and blinding of outcome assessors (61%); identified risks were primarily located in the domains of blinding of participants and personnel (88%), incomplete reporting (24%), and other sources of bias (30%; i.e., industry funding and/or insufficient power). Given that all the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is high [Chi^2=556.46, df=45 (p<0.00001); I^2=92%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 33 studies, 31 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=29) included mixed gender samples; 2 included only women and 2 included only men. In 12 studies (36%) the participants had a high risk of CVD. Eight studies included a diet intervention arm, four included an exercise intervention arm, nine included a combined diet plus exercise intervention arm, and in 17 studies lifestyle programs were provided (the total number is >33 because some studies included more than one type of intervention). Control participants received usual care from their physicians or no intervention; in 7 studies they also received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 21 studies and more than 12 months in 12 studies. One study was conducted in Canada, 17 in the US, 10 in European countries, 4 in Australia and/or New Zealand, and 1 in Japan. More than half of the studies (n=22) were published in the last 5 years (2009-2013); the remaining 11 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (6,463 intervention arm, 4,366 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.1301 (-3.8754, -2.3848)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.941). This body of evidence was not downgraded for suspected publication bias.

[13] The 17 studies are:[106,109-111,114-124,131,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 14 (82%) of the studies with a pharmacological plus behavioural intervention were rated as unclear risk and 3 (18%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (59%), allocation concealment (82%), blinding of participants and/or personnel (76%), and blinding of outcome assessors (82%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (47%) and other sources of bias (82%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[15] Although the statistical heterogeneity is high [Chi^2=122.66, df=16 (p<0.00001); I^2=87%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 17 studies included adults aged 18-64 years, and mixed gender samples. In 9 studies (53%) the participants had a high risk of CVD. In 15 studies the pharmacological plus behavioural intervention was orlistat (120 mg 3x/day) and in 2 studies it was metformin (850 mg 1x/day; 850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 11 studies and more than 12 months in 6 studies. One study was conducted in Canada and the US, 6 in the US, 9 in European countries, and 1 in Australia. Only 1 study was published in the last 5 years (2012); the remaining 16 studies were published between 1996 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[17] The sample size is adequate (6,377 intervention arm, 5,409 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.8874 (-3.4850, -2.2898)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.165). This body of evidence was not downgraded for suspected publication bias.

[19] The 8 studies are:[73,77,81,85,88,92,93,99] Immediate post assessment for all but 1 study; for this 1 study the data point closest to the immediate post and ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention).

[20] Using Cochrane's Risk of Bias tool, for this outcome all 8 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (63%), allocation concealment (75%), and blinding of outcome assessors (75%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (88%) and other sources of bias (50%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[21] Although the statistical heterogeneity is high [Chi^2=29.05, df=8 (p=0.0003); I^2=72%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[22] All 8 studies included adults aged 18-64 years, and most studies (n=6) included mixed gender samples; 1 included only women and 1 included only men. In 3 studies (38%) the participants had a high risk of CVD. In all 8 studies at least one intervention arm was focused on diet. Control participants received usual care from their physicians or no intervention. Intervention duration was 12 months or less in 6 studies and more than 12 months in 2 studies. Five studies were conducted in the US, 2 in European countries and 1 in Australia. Half of the studies (n=4) were published in the last 5 years (2010-2012); the remaining 4 studies were published between 1985 and 1991. There were no serious concerns regarding indirectness for this body of evidence.

[23] The sample size is adequate (653 intervention arm, 260 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-4.7125 (-6.2188, -3.2062)]. This body of evidence was not downgraded for imprecision.

[24] There were too few studies (n<10) to assess publication bias.

[25] The 4 studies are:[76,92,96,99] Immediate post assessment for all 4 studies.

[26] Using Cochrane's Risk of Bias tool, for this outcome all 4 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (50%), allocation concealment (50%), blinding of participants and/or personnel (25%), and blinding of outcome assessors (50%); identified risks (high ratings) were primarily located in the domain of blinding of participants and personnel (75%). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[27] Although the statistical heterogeneity is high [Chi^2=20.08, df=3 (p=0.0002); I^2=85%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[28] Across the 4 studies, 3 included adults aged 18-64 years, and 1 included adults 65 years and older. Two studies included mixed gender samples, 1 included only women and 1 included only men. In only 1 study (25%) the participants had a high risk of CVD. In all 4 studies the behavioural intervention was exercise. Control participants received usual care from their physicians or no intervention. Intervention duration was 12 months or less in all 4 studies. Three studies were conducted in the US and 1 in Italy. Three of the studies were published in the last 5 years (2010-2012); the remaining study was published in 1988. There were no serious concerns regarding indirectness for this body of evidence.

[29] The sample size is adequate in the intervention arm (n=406) but of some concern in the control arm (n=192) and the pooled effect estimate is not precise with a confidence interval that includes the no effect value [-1.4874 (-3.3231, 0.3484)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[30] There were too few studies (n<10) to assess publication bias.

[31] The 10 studies are:[69,73,74,77,79,83,86,93,99,100] Immediate post assessment for all but 1 study; for this study the data point closest to the immediate post and ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention).

[32] Using Cochrane's Risk of Bias tool, for this outcome all 10 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (50%), allocation concealment (80%), and blinding of outcome assessors (50%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (90%), incomplete reporting (30%), and other sources of bias (30%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[33] Although the statistical heterogeneity is high [Chi^2=109.41, df=11 (p<0.00001); I^2=90%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[34] All 10 studies included adults aged 18-64 years. Two studies included mixed gender samples, 1 included only women and 1 included only men. In 2 studies (20%) the participants had a high risk of CVD. In all 10 studies one behavioural intervention arm was diet plus exercise. Control participants received usual care from their physicians or no intervention; in 1 study control participants received a minimal component (e.g., printed health education materials). Intervention duration was 12 months or less in 9 studies and more than 12 months in 1 study. One study was conducted in Canada, 4 in the US, and 5 in European countries. Most of the studies (n=8) were published in the last 5 years (2009-2012); the remaining 2 studies were published in 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[35] The sample size is adequate (1,390 intervention arm, 992 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.8257 (-5.4935, -2.1579)]. This body of evidence was not downgraded for imprecision.

[36] The Egger's test was conducted to detect publication bias; results were significant (p=0.029). This body of evidence was downgraded for strongly suspected publication bias.

[37] The 17 studies are:[68,70-72,78,84,87,89-91,94,95,97,102-104,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Martin[89] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[38] Using Cochrane's Risk of Bias tool, for this outcome all 17 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (29%), allocation concealment (82%), and blinding of outcome assessors (59%); identified risks (high ratings) were primarily located

in the domains of blinding of participants and personnel (94%), incomplete outcome reporting (24%) and other sources of bias (18%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[39] Although the statistical heterogeneity is high [Chi^2=301.45, df=20 (p<0.00001); I^2=93%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[40] Across the 17 studies, 16 included adults aged 18-64 years, and 1 included adults 65 years and older. Most studies (n=16) included mixed gender samples; 1 included only women. In 6 studies (35%) the participants had a high risk of CVD. In terms of intervention focus, all 17 studies had at least one lifestyle intervention arm. Control participants received usual care from their physicians or no intervention; in 6 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 9 studies and more than 12 months in 8 studies. Ten studies were conducted in the US, 3 in European countries, 3 in Australia, and 1 in Japan. Most of the studies (n=11) were published in the last 5 years (2009-2013); the remaining 6 studies were published between 1993 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[41] The sample size is adequate (4,014 intervention arm, 2,922 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.5174 (-3.5443, -1.4904)]. This body of evidence was not downgraded for imprecision.

[42] The Egger's test was conducted to detect publication bias; results were significant (p=0.015). This body of evidence was downgraded for strongly suspected publication bias.

[43] The 2 studies are:[131,133] Immediate post assessment for 1 study and for the other study the data point ≥ 12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[44] Using Cochrane's Risk of Bias tool, for this outcome both of the metformin studies (n=2) were rated as unclear risk. There was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (n=1), allocation concealment (n=2), blinding of participants and/or personnel (n=1), blinding of outcome assessors (n=2), and incomplete outcome reporting (n=1); identified risks (high ratings) were located in the domains of blinding of participants and/or personnel (n=1) and other sources of bias (n=2; i.e., industry funding and/or insufficient power). Given that information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[45] Statistical heterogeneity is moderate and not significant [Chi^2=2.51, df=1 (p=0.11); I^2=60%]. The direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[46] Both studies included adults aged 18-64 years, and mixed gender samples. Neither study included participants with a high risk of CVD. In both studies the pharmacological plus behavioural intervention was metformin (850 mg 1x/day; 850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months in 1 study and 38 months in the other study (although we extracted 12 month interim data for this study). One study was conducted in the US and the other study was conducted in France. Neither study was published in the last 5 years; one was published in 1996 and the other in 1999. There were no serious concerns regarding indirectness for this body of evidence.

[47] The sample size is adequate (1,237 intervention arm, 701 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.9163 (-2.9438, -0.8887)]. This body of evidence was not downgraded for imprecision.

[48] There were too few studies (n<10) to assess publication bias.

[49] The 15 studies are:[106,109-111,114-124] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions).

[50] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (80%) were rated as unclear risk and 3 studies (20%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (60%), allocation concealment (80%), blinding of participants and/or personnel (80%), and blinding of outcome assessors (80%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (53%) and other sources of bias (80%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[51] Although the statistical heterogeneity is high [Chi^2=117.05, df=14 (p<0.00001); I^2=88%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[52] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 9 studies (60%) the participants had a high risk of CVD. In all studies the pharmacological plus behavioural intervention was orlistat (120 mg 3x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in 10 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 5 in the US, 8 in European countries, and 1 in Australia. Only 1 study was published in the last 5 years (2012); the remaining 14 studies were published between 1996 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[53] The sample size is adequate (5,140 intervention arm, 4,708 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.0513 (-3.7510, -2.3517)]. This body of evidence was not downgraded for imprecision.

[54] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.138). This body of evidence was not downgraded for suspected publication bias.

[55] The 21 studies are:[68,69,73,74,76,77,83-87,89,92-96,99,102-104] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] and Martin[89] provide 6 month follow-up data post completion of 6 month interventions; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention).

[56] Using Cochrane's Risk of Bias tool, for this outcome all 21 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty regarding risk of bias associated with sequence generation (48%), allocation concealment (71%), and blinding of outcome assessors (67%); identified risks were primarily located in the domains of blinding of participants and personnel (90%), incomplete reporting (33%), and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that all the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[57] Although the statistical heterogeneity is high [Chi^2=249.88, df=30 (p<0.00001); I^2=88%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[58] Across the 21 studies, 19 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=17) included mixed gender samples; 2 included only women and 2 included only men. In 6 studies (29%) the participants had a high risk of CVD. In 7 studies at least one intervention arm was diet, in 4 there was at least one exercise arm, in7 it was a combination of diet and exercise, and in 9 studies lifestyle programs were provided. Control participants received usual care from their physicians or no intervention; in 5 studies they also received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in all studies. One study was conducted in Canada and the US, 9 in the US, 8 in European countries and 3 in Australia. More than half of the studies (n=14) were published in the last 5 years (2009-2012); the remaining 7 studies were published between 1991 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[59] The sample size is adequate (2,999 intervention arm, 1,781 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.4339 (-4.3163, -2.5515)]. This body of evidence was not downgraded for imprecision.

[60] The Egger's test was conducted to detect publication bias; results were significant (p=0.000). This body of evidence was downgraded for strongly suspected publication bias.

[61] The 12 studies are:[70-72,78,79,81,88,90,91,97,100,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[62] Using Cochrane's Risk of Bias tool, for this outcome all 12 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (42%), allocation concealment (92%), and blinding of outcome assessors (50%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (83%) and other sources of bias (25%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[63] Although the statistical heterogeneity is high [Chi^2=256.18, df=14 (p<0.00001); I^2=95%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[64] Across the 12 studies, all included adults aged 18-64 years, and mixed gender samples. In 6 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 2 were diet, 2 were diet plus exercise, and 8 were lifestyle, Control participants received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was more than 12 months in all 12 studies. One study was conducted in Canada, 7 in the US, 3 in European countries, and 1 in Australia. Two-thirds of the studies (n=8) were published in the last 5 years (2010-2012); the remaining 4 studies were published between 1985 and 2003. There were no serious concerns regarding indirectness for this body of evidence.

[65] The sample size is adequate (3,464 intervention arm, 2,585 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.5266 (-3.8089, -1.2444)]. This body of evidence was not downgraded for imprecision.

[66] The Egger's test was conducted to detect publication bias; results were significant (p=0.013). This body of evidence was downgraded for strongly suspected publication bias.

[67] The 11 studies are:[106,109,111,115,117,118,120,121,123,124,131] Immediate post assessment for all 11 studies.

[68] Using Cochrane's Risk of Bias tool, for this outcome 9 studies (82%) were rated as unclear risk and 2 studies (18%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (55%), allocation concealment (82%), blinding of participants and/or personnel (82%), and blinding of outcome assessors (82%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (36%), and other sources of bias (82%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[69] Although the statistical heterogeneity is high [Chi^2=114.47, df=10 (p<0.00001); I^2=91%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[70] All 11 studies included adults aged 18-64 years, and mixed gender samples. In 9 studies the participants had a high risk of CVD. In 10 studies the intervention drug was orlistat (120 mg 3x/day) and in 1 study it was metformin (850 mg 1x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in all 11 studies. One study was conducted in Canada, 1 in Canada and the US, 3

in the US, 5 in European countries, and 1 in Australia and New Zealand. Only 1 study was published in the last 5 years (2012); the remaining 10 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[71] The sample size is adequate (2,209 intervention arm, 2,209 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.8889 (-3.9017, -1.8762)]. This body of evidence was not downgraded for imprecision.

[72] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.073). This body of evidence was not downgraded for suspected publication bias.

[73] The 6 studies are:[110,114,116,119,122,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[74] Using Cochrane's Risk of Bias tool, for this outcome 5 studies (83%) were rated as unclear risk and 1 study (17%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (67%), allocation concealment (83%), blinding of participants and/or personnel (67%), and blinding of outcome assessors (83%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (67%), and other sources of bias (83%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[75] Statistical heterogeneity is low and not significant [Chi^2=5.47, df=5 (p=0.36); I^2=9%]. The direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[76] All 6 studies included adults aged 18-64 years, and mixed gender samples. None of the studies included participants with a high risk of CVD. In 5 studies the intervention drug was orlistat (120 mg 3x/day) and in 1 study it was metformin (850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was more than 12 months in all 6 studies. Three studies were conducted in the US and 3 in European countries. None of the studies was published in the last 5 years; the 6 studies were published between 1999 and 2004. There were no serious concerns regarding indirectness for this body of evidence.

[77] The sample size is adequate (4,168 intervention arm, 3,200 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.6938 (-3.0035, -2.3841)]. This body of evidence was not downgraded for imprecision.

[78] There were too few studies (n<10) to assess publication bias.

[79] The 12 studies are:[70-73,76,78,81,83-85,88,94] Immediate post assessment for all but 1 study; for this one exception the data point closest to the immediate post and ≥ 12 months post baseline was selected (Burke[84] provides 12 month follow-up data post completion of a 4 month intervention).

[80] Using Cochrane's Risk of Bias tool, for this outcome all 12 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (33%), allocation concealment (83%), blinding of participants and/or personnel (17%), and blinding of outcome assessors (75%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (83%), incomplete reporting (17%), and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[81] Although the statistical heterogeneity is high [Chi^2=52.70, df=13 (p<0.00001); I^2=75%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[82] All12 studies included adults aged 18-64 years, mixed gender samples, and participants with a high risk of CVD. In terms of intervention focus 3 were diet, 1 was exercise, 2 were diet plus exercise, and 6 were lifestyle. Control participants received usual care from their physicians or no intervention; in 5 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 6 studies and more than 12 months in 6 studies. Six studies were conducted in the US, 3 in European countries, and 3 in Australia. About half of the studies (n=7) were published in the last 5 years (2010-2012); the remaining 5 studies were published between 1985 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[83] The sample size is adequate (1,810 intervention arm, 1,141 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.8862 (-2.6932, -1.0793)]. This body of evidence was not downgraded for imprecision.

[84] The Egger's test was conducted to detect publication bias; results were significant (p=0.006). This body of evidence was downgraded for strongly suspected publication bias.

[85] The 21 studies are:[68,69,74,77,79,86,87,89-91,93-97,99,100,102-104,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] and Martin[89] provide 6 month follow-up data post completion of 6 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[86] Using Cochrane's Risk of Bias tool, for this outcome all 21 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (52%), allocation concealment (76%), and blinding of outcome assessors (52%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (90%), incomplete reporting (29%), and other sources of bias (29%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[87] Although the statistical heterogeneity is high [Chi^2=400.02, df=31 (p<0.00001); I^2=92%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[88] Across the 21 studies, 19 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=17) included mixed gender samples; 2 included only women and 2 included only men. In all 21 studies participants were unselected for or had a low risk of CVD. In terms of intervention focus, 2 were diet, 1 was exercise, 7 were diet plus exercise, and 11 were lifestyle. Control participants received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 15 studies and more than 12 months in 6 studies. One study was conducted in Canada, 11 in the US, 7 in European countries, 1 in Australia, and 1 in Japan. About two-thirds of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 6 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[89] The sample size is adequate (4,653 intervention arm, 3,225 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.6629 (-4.5878, -2.7379)]. This body of evidence was not downgraded for imprecision.

[90] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.619). This body of evidence was not downgraded for suspected publication bias.

[91] The 9 studies are:[106,109,111,115,117,118,121,123,124] Immediate post assessment for all 9 studies.

[92] Using Cochrane's Risk of Bias tool, for this outcome 7 studies (78%) were rated as unclear risk and 2 studies (22%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (56%), allocation concealment (78%), blinding of participants and/or personnel (78%), and

blinding of outcome assessors (78%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (44%), and other sources of bias (78%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[93] Although the statistical heterogeneity is high [Chi^2=104.58, df=8 (p<0.00001); I^2=92%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[94] All 9 studies included adults aged 18-64 years, mixed gender samples and participants at high risk for CVD. The pharmacological plus behavioural intervention in all 9 studies was orlistat. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in all 9 studies. One study was conducted in Canada and the US, 3 in the US, 4 in European countries, and 1 in Australia and New Zealand. Only 1 study was published in the last 5 years (2012); the remaining 8 studies were published between 1996 and 2004. There were no serious concerns regarding indirectness for this body of evidence.

[95] The sample size is adequate (1,702 intervention arm, 1,709 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.9342 (-4.0750, -1.7933)]. This body of evidence was not downgraded for imprecision.

[96] There were too few studies (n<10) to assess publication bias.

[97] The 8 studies are:[110,114,116,119,120,122,131,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[98] Using Cochrane's Risk of Bias tool, for this outcome 7 studies (88%) were rated as unclear risk and 1 study (12%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (63%), allocation concealment (88%), blinding of participants and/or personnel (75%), and blinding of outcome assessors (88%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (50%), and other sources of bias (88%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[99] Although the statistical heterogeneity is moderate [Chi^2=15.20, df=7 (p=0.03); I^2=54%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[100] All 8 studies included adults aged 18-64 years, mixed gender samples, and participants with low/unknown risk of CVD. The pharmacological plus behavioural intervention in 6 studies was orlistat (120 mg 3x/day) and in 2 studies it was metformin (850 mg 1x/day; 850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 2 studies and more than 12 months in 6 studies. Three studies were conducted in the US and 5 in European countries. None of the studies were published in the last 5 years (2009-2013); all 8 studies were published between 1996 and 2004. There were no serious concerns regarding indirectness for this body of evidence.

[101] The sample size is adequate (4,675 intervention arm, 3,700 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.7737 (-3.2683, -2.2792)]. This body of evidence was not downgraded for imprecision.

[102] There were too few studies (n<10) to assess publication bias.

[103] The 8 studies are:[79,84,89-91,93,99,102] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and ≥ 12 months post baseline was selected (Martin[89] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention).

[104] Using Cochrane's Risk of Bias tool, for this outcome all 8 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (63%), allocation concealment (88%), and blinding of outcome assessors (50%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (88%) and incomplete reporting (25%). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[105] Although the statistical heterogeneity is high [Chi^2=75.52, df=10 (p<0.00001); I^2=87%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[106] All 8 studies included adults aged 18-64 years. Most studies (n=6) included mixed gender samples; 2 included only women. Only 1 study included participants with a high risk of CVD. All interventions were behavioural (1 diet, 2 diet plus exercise, 5 lifestyle). Control participants received usual care from their physicians or no intervention; in 1 study control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 5 studies and more than 12 months in 3 studies. One study was conducted in Canada, 5 in the US, 1 in Australia, and 1 in Japan. Three studies were published in the last 5 years (2011-2012); the remaining 5 studies were published between 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[107] The sample size is adequate (1,070 intervention arm, 730 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.3278 (-4.7950, -1.8607)]. This body of evidence was not downgraded for imprecision.

[108] There were too few studies (n<10) to assess publication bias.

[109] The 8 studies are:[69,79,84,90,91,93,94,102] Immediate post assessment for all but 1 study; for this one exception the data point closest to the immediate post and ≥ 12 months post baseline was selected (Burke[84] provides 12 month follow-up data post completion of a 4 month intervention).

[110] Using Cochrane's Risk of Bias tool, for this outcome all 8 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (50%), allocation concealment (75%), and blinding of outcome assessors (50%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (88%) and incomplete reporting (25%). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

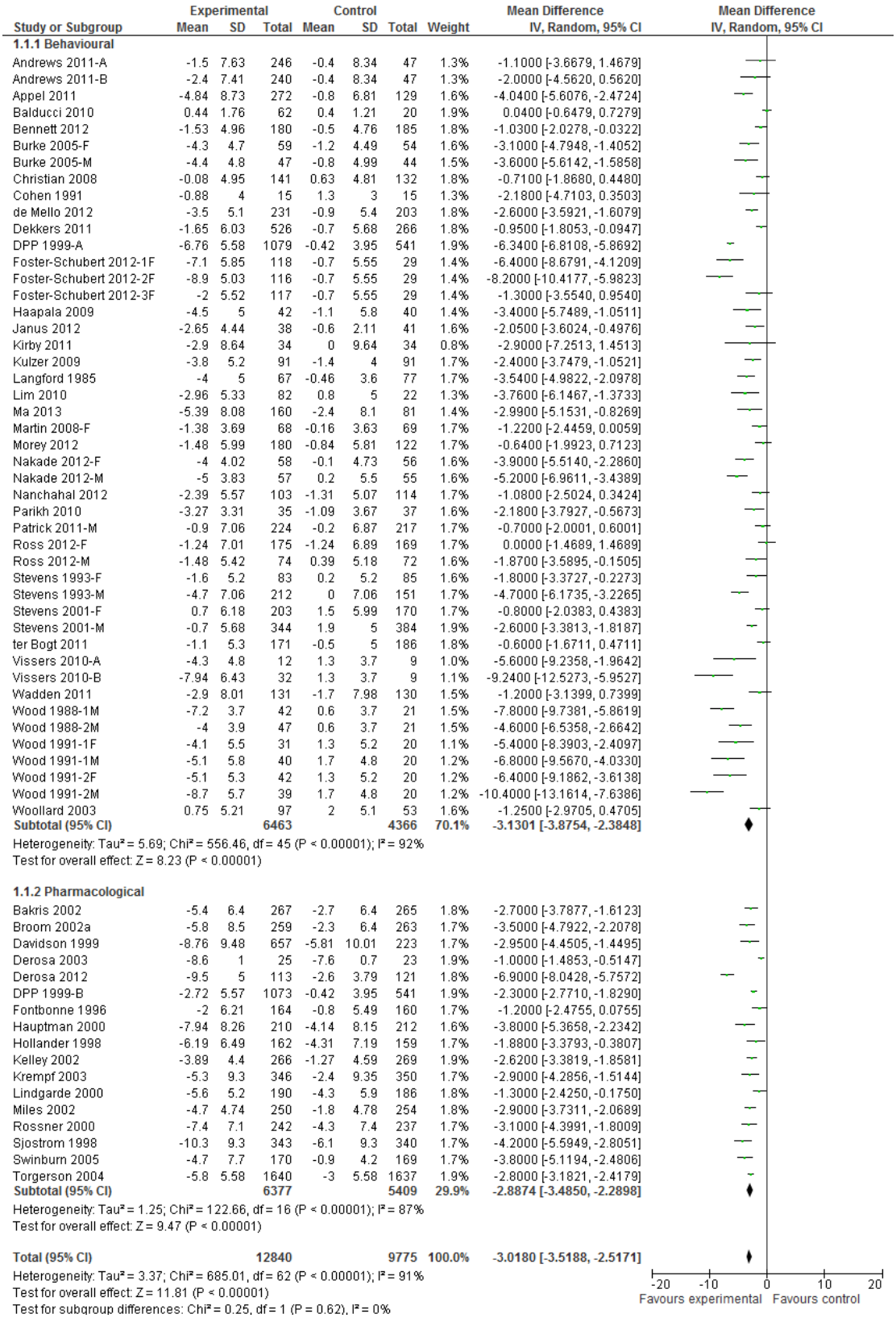
[111] Although the statistical heterogeneity is high [Chi^2=82.06, df=9 (p<0.00001); I^2=89%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[112] All 8 studies included adults aged 18-64 years. Most studies (n=6) included mixed gender samples; 2 included only men. Only 1 study included participants with a high risk of CVD. All interventions were behavioural (1 diet, 3 diet plus exercise, 4 lifestyle). Control participants received usual care from their physicians or no intervention; in 1 study control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 5 studies and more than 12 months in 3 studies. One study was conducted in Canada, 5 in the US, 1 in Australia, and 1 in Japan. Three studies were published in the last 5 years (2011-2012); the remaining 5 studies were published between 1988 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

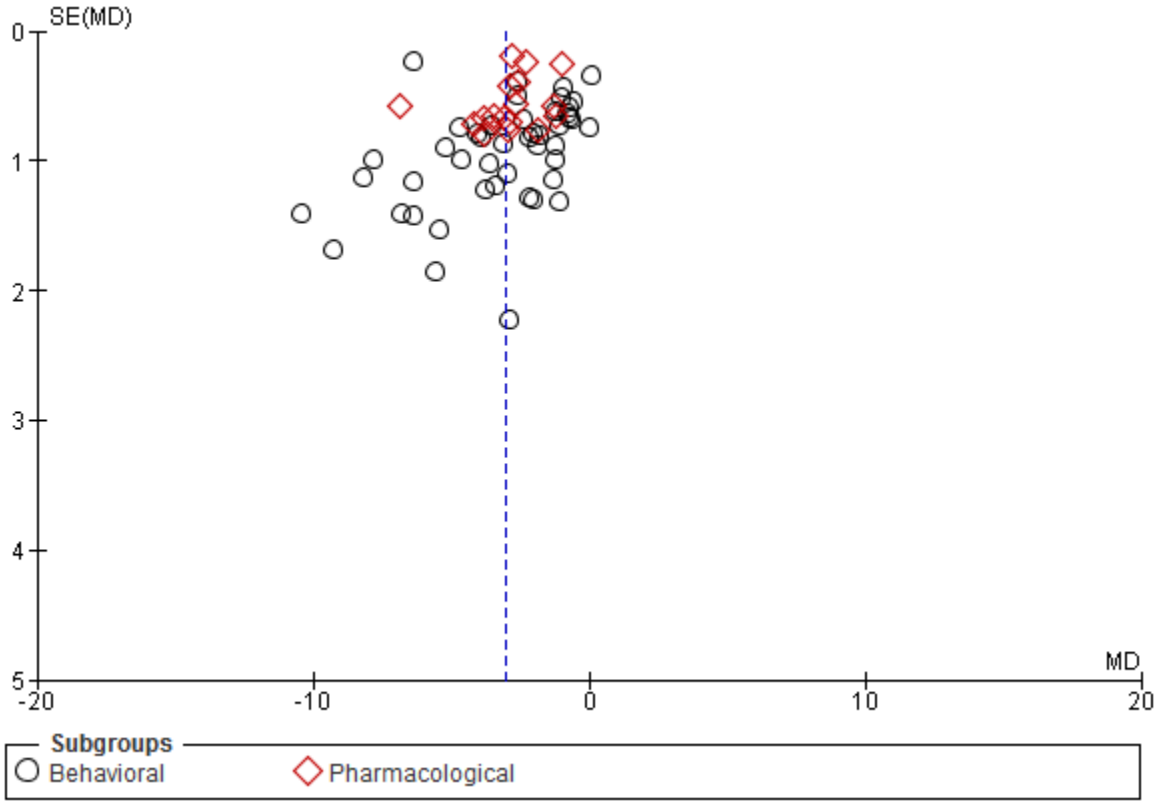
[113] The sample size is adequate (1,126 intervention arm, 1,005 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-4.6451 (-6.1986, -3.0917)]. This body of evidence was not downgraded for imprecision.

[114] There were too few studies (n<10) to assess publication bias.

Forest Plot 1.1: Effect of Treatment Interventions on Weight in KG – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



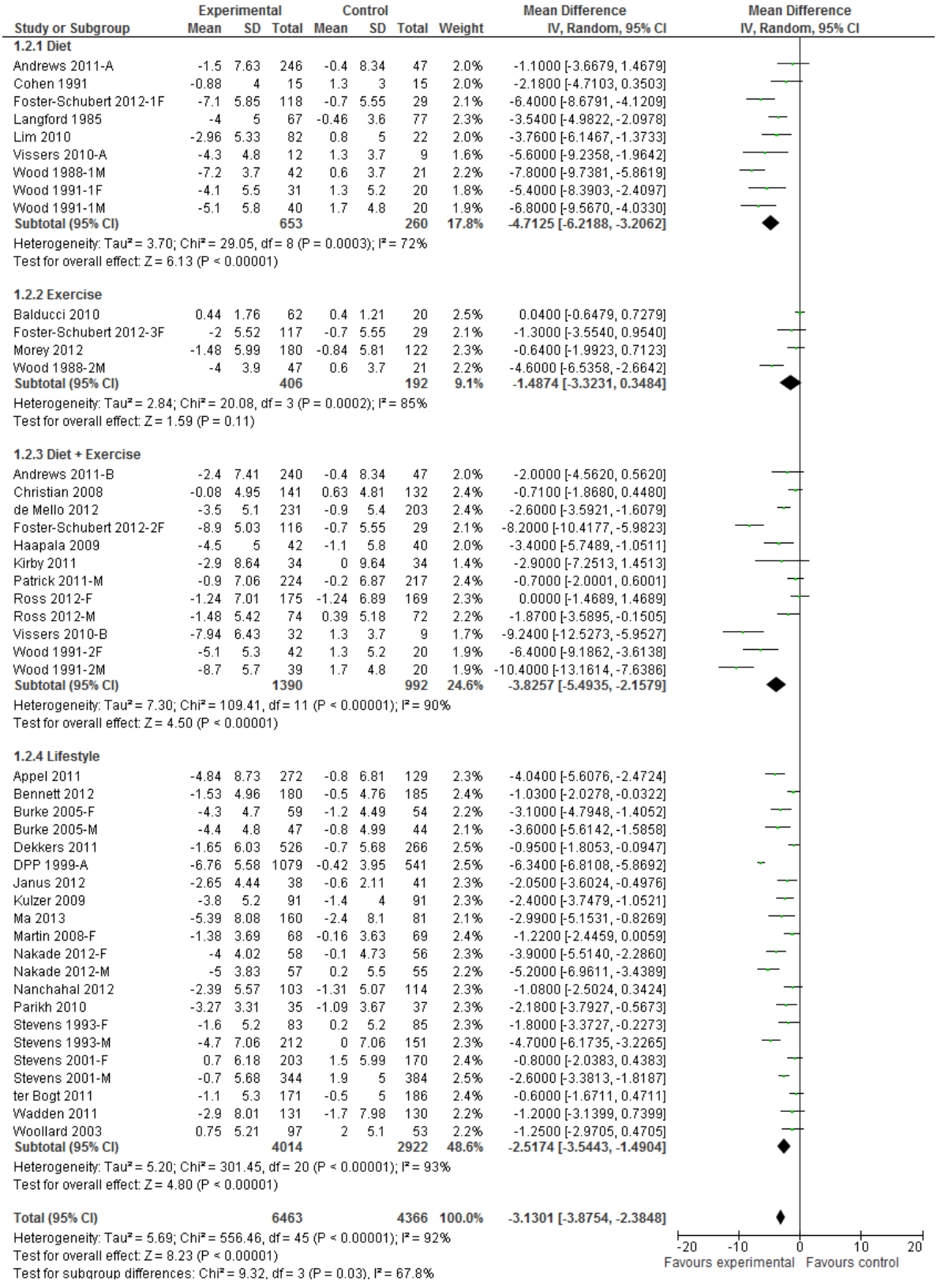
Funnel Plot 1.1: Effect of Treatment Interventions on Weight in KG – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



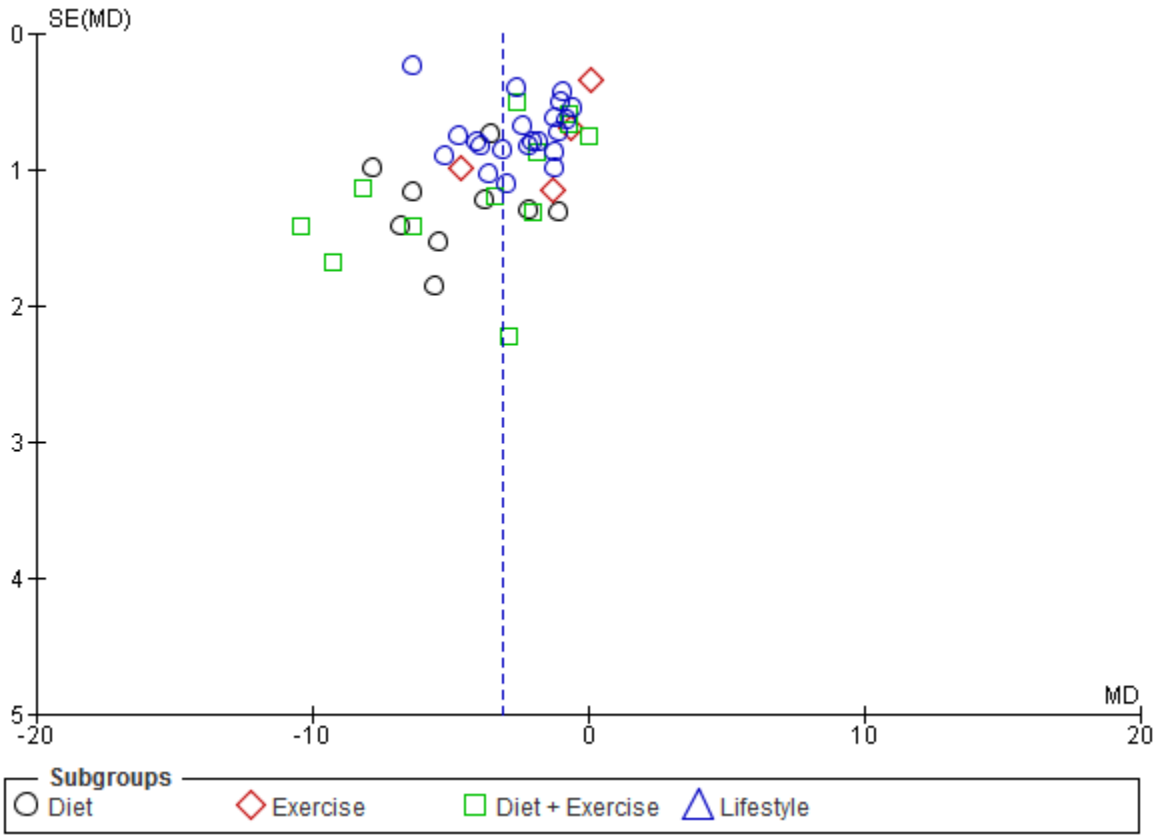
Egger's Test to Detect Publication Bias: Weight Change in KG – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall / All	0.354
Behavioural Interventions	0.941
Pharmacological plus Behavioural Interventions	0.165

Forest Plot 1.2: Effect of Treatment Interventions on Weight in KG – by Type of Behavioural Intervention (Diet, Exercise, Diet plus Exercise, Lifestyle)



Funnel Plot 1.2: Effect of Treatment Interventions on Weight in KG – by Type of Behavioural Intervention (Diet, Exercise, Diet plus Exercise, Lifestyle)



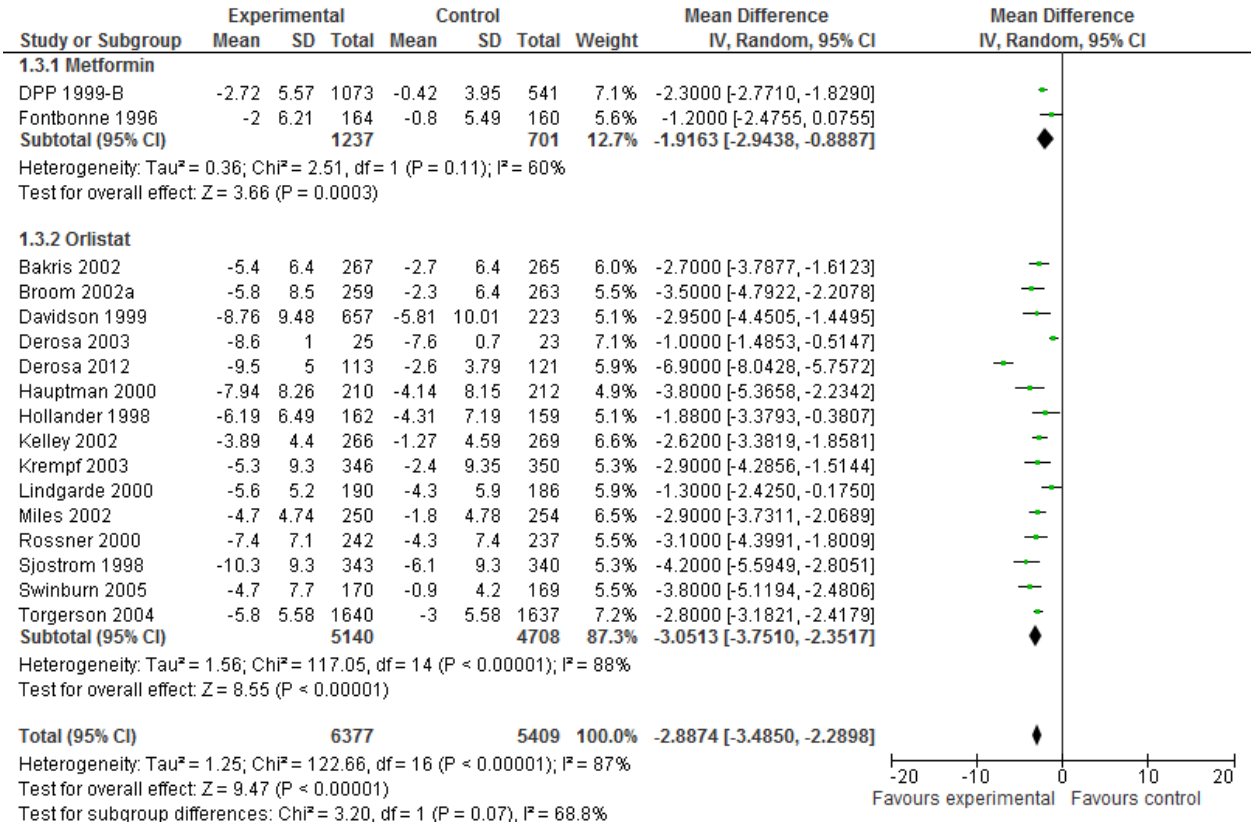
Egger's Test to Detect Publication Bias: Weight Change in KG – by Type of Behavioural Intervention (Diet, Exercise, Diet plus Exercise, Lifestyle)

Included Studies	P-value
Behavioural Interventions – Diet	**
Behavioural Interventions – Exercise	**
Pharmacological plus Behavioural Interventions – Diet plus Exercise	0.029*
Behavioural Interventions – Lifestyle	0.015*

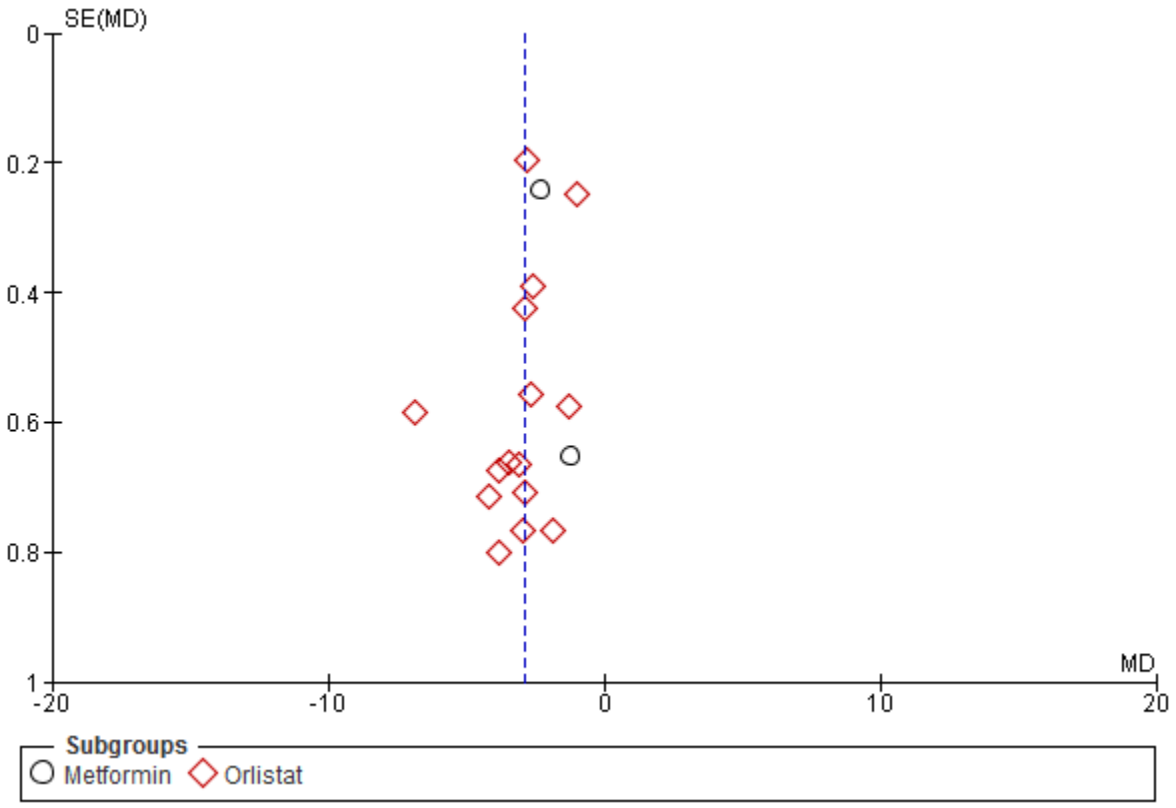
* Significant $p \leq 0.05$

** Too few studies ($n < 10$) to assess

Forest Plot 1.3: Effect of Treatment Interventions on Weight in KG – by Type of Pharmacological plus Behavioural Intervention (Metformin, Orlistat)



Funnel Plot 1.3: Effect of Treatment Interventions on Weight in KG – by Type of Pharmacological plus Behavioural Intervention (Metformin, Orlistat)

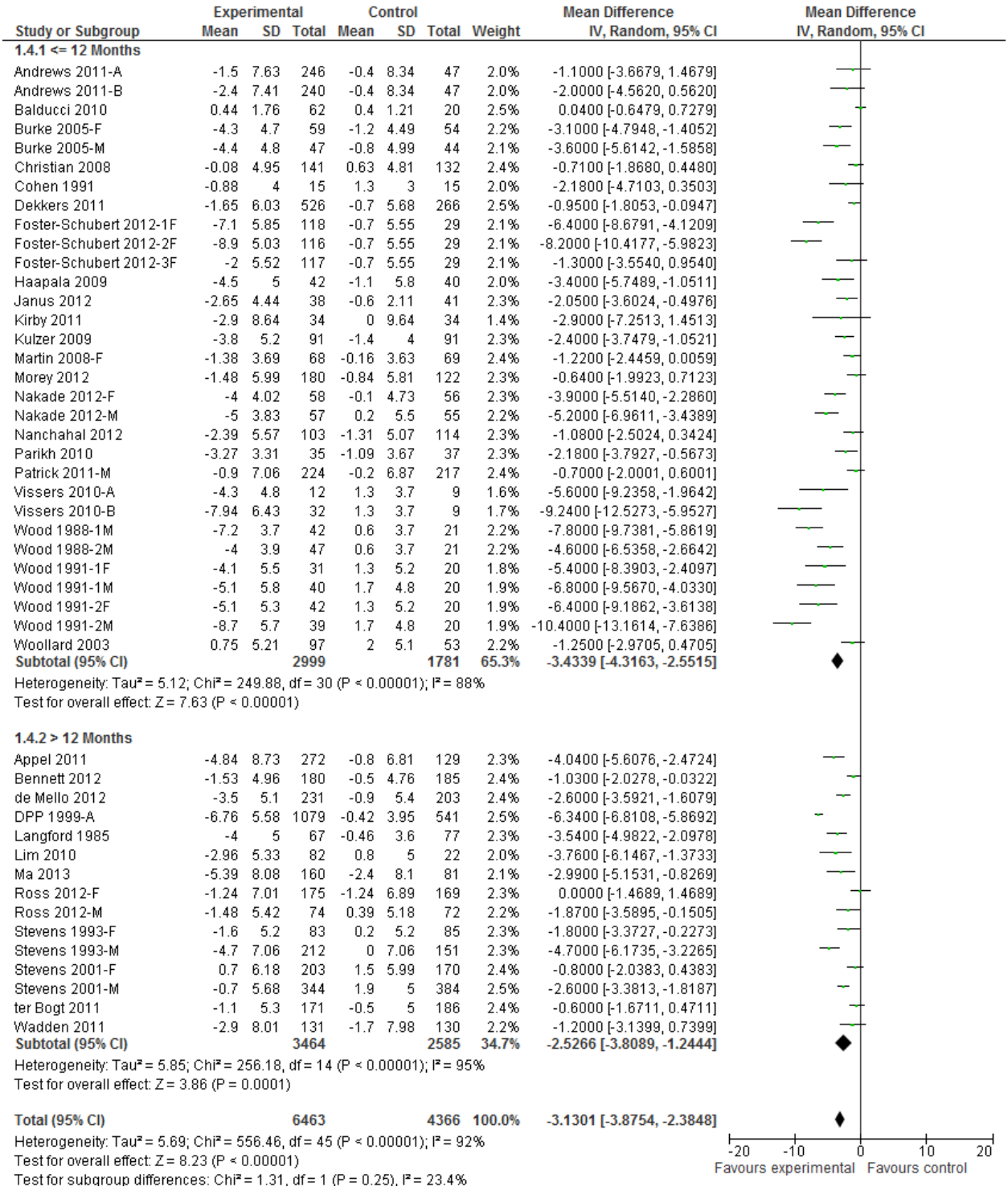


Egger's Test to Detect Publication Bias: Weight Change in KG – by Type of Pharmacological plus Behavioural Intervention (Metformin, Orlistat)

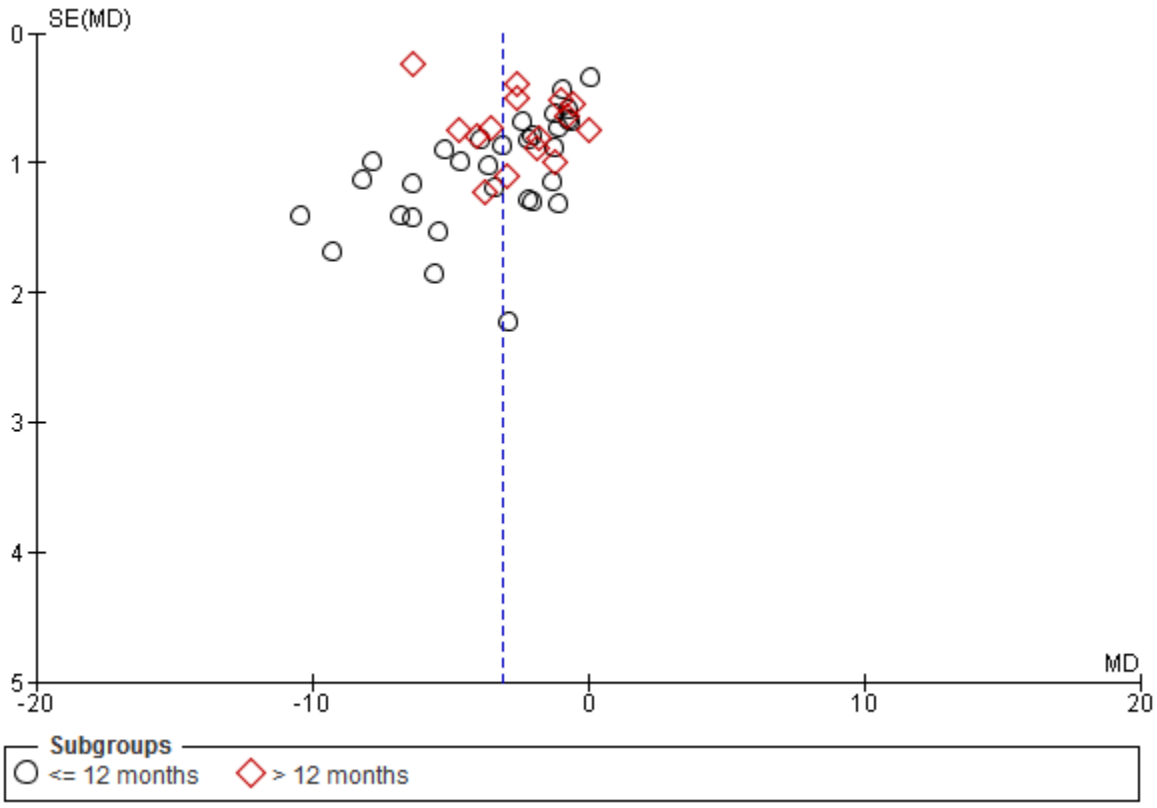
Included Studies	P-value
Pharmacological plus Behavioural Interventions – Metformin	**
Pharmacological plus Behavioural Interventions – Orlistat	0.138

** Too few studies (n<10) to assess

Forest Plot 1.4: Effect of Treatment Interventions on Weight in KG – by Duration of Behavioural Intervention (≤12 Months, >12 Months)



Funnel Plot 1.4: Effect of Treatment Interventions on Weight in KG – by Duration of Behavioural Intervention (≤12 Months, >12 Months)

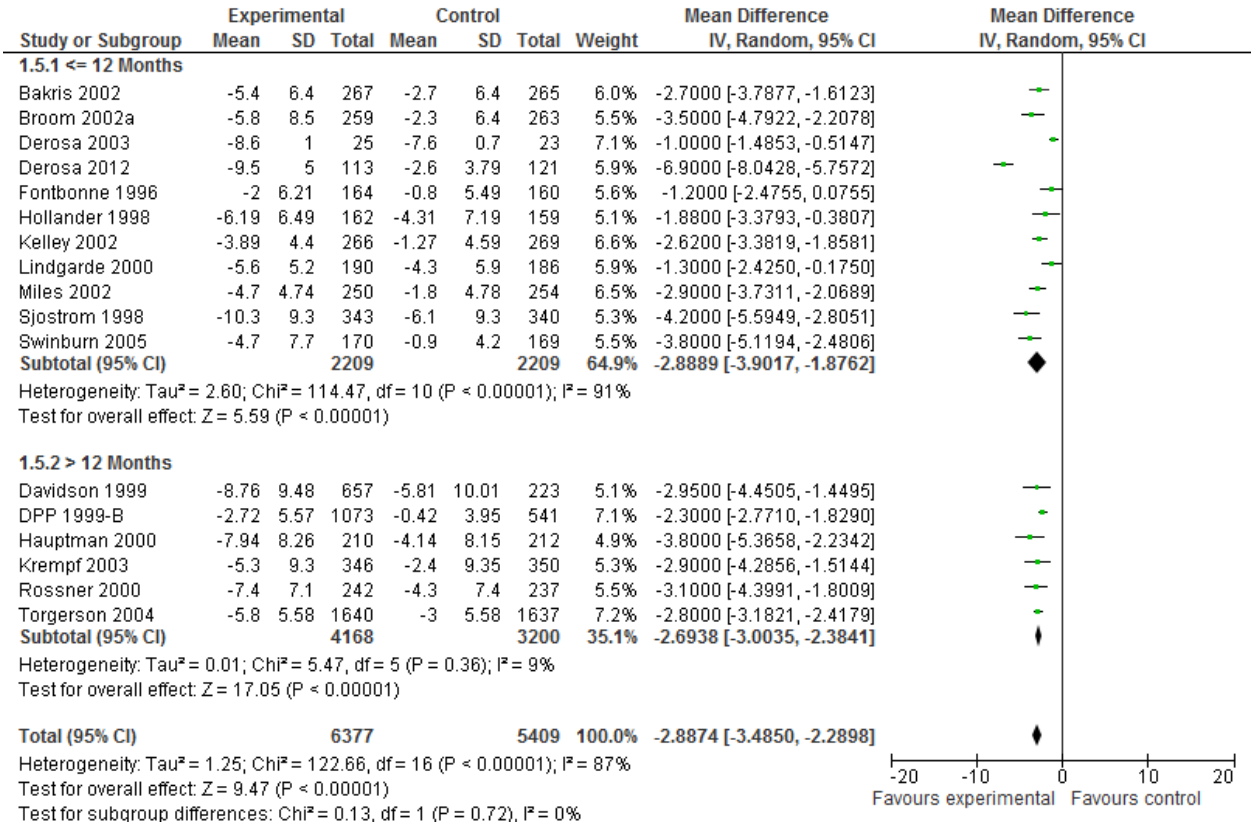


Egger's Test to Detect Publication Bias: Weight Change in KG – by Duration of Behavioural Intervention (≤12 Months, >12 Months)

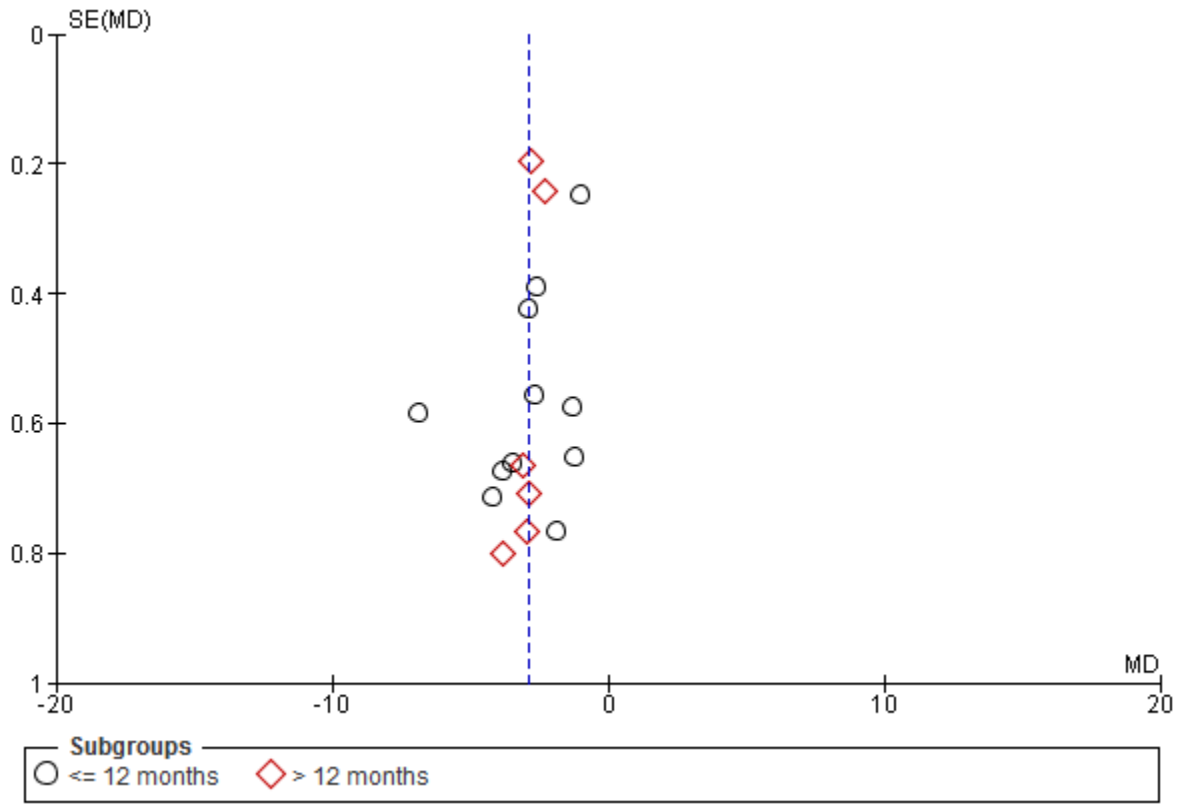
Included Studies	P-value
Behavioural Interventions ≤12 Months	0.000*
Behavioural Interventions >12 Months	0.013*

* Significant p≤0.05

Forest Plot 1.5: Effect of Treatment Interventions on Weight in KG – by Duration of Pharmacological plus Behavioural Intervention (≤12 Months, >12 Months)



Funnel Plot 1.5: Effect of Treatment Interventions on Weight in KG – by Duration of Pharmacological plus Behavioural Intervention (≤12 Months, >12 Months)

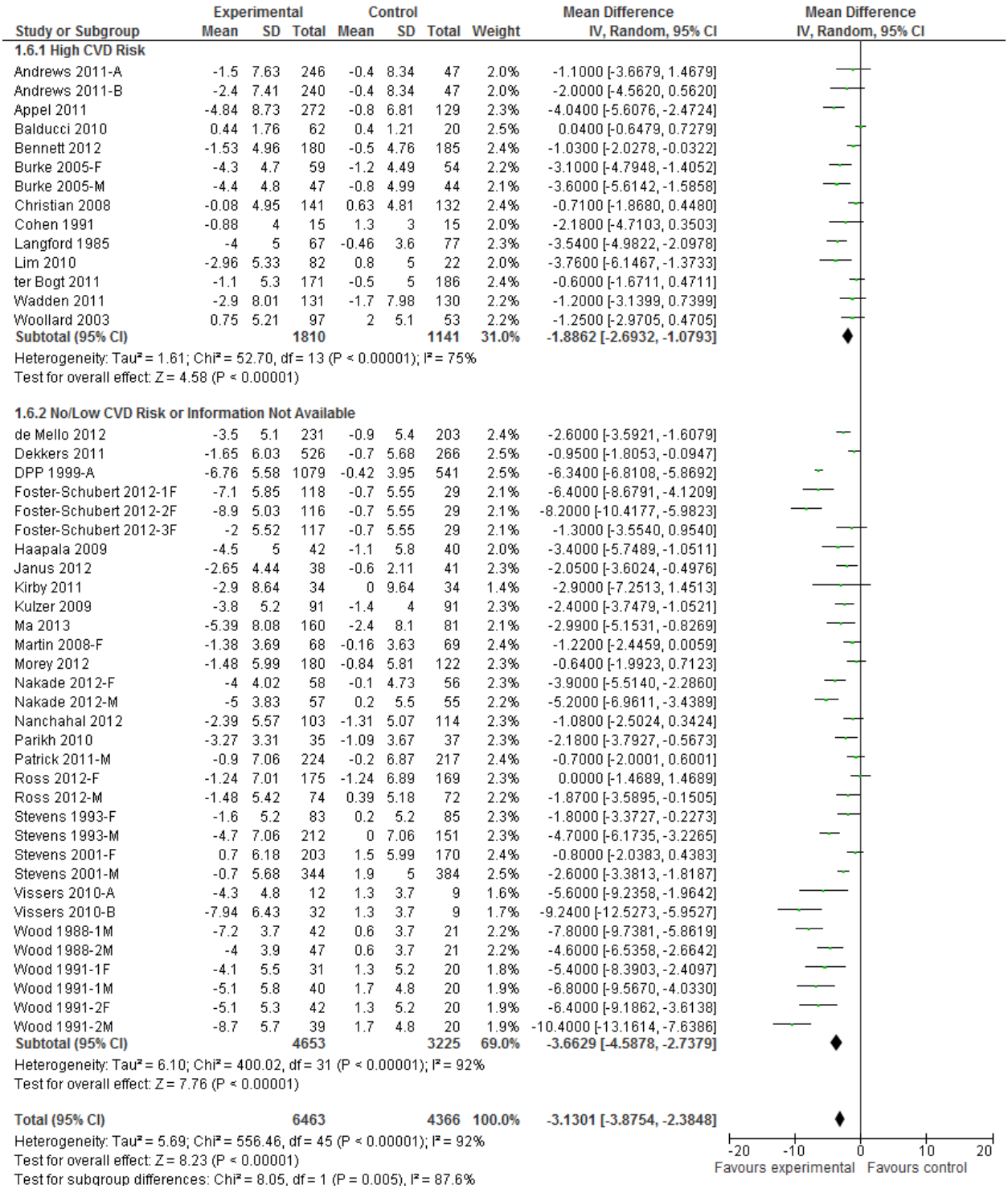


Egger's Test to Detect Publication Bias: Weight Change in KG – by Duration of Pharmacological plus Behavioural Intervention (≤12 Months, >12 Months)

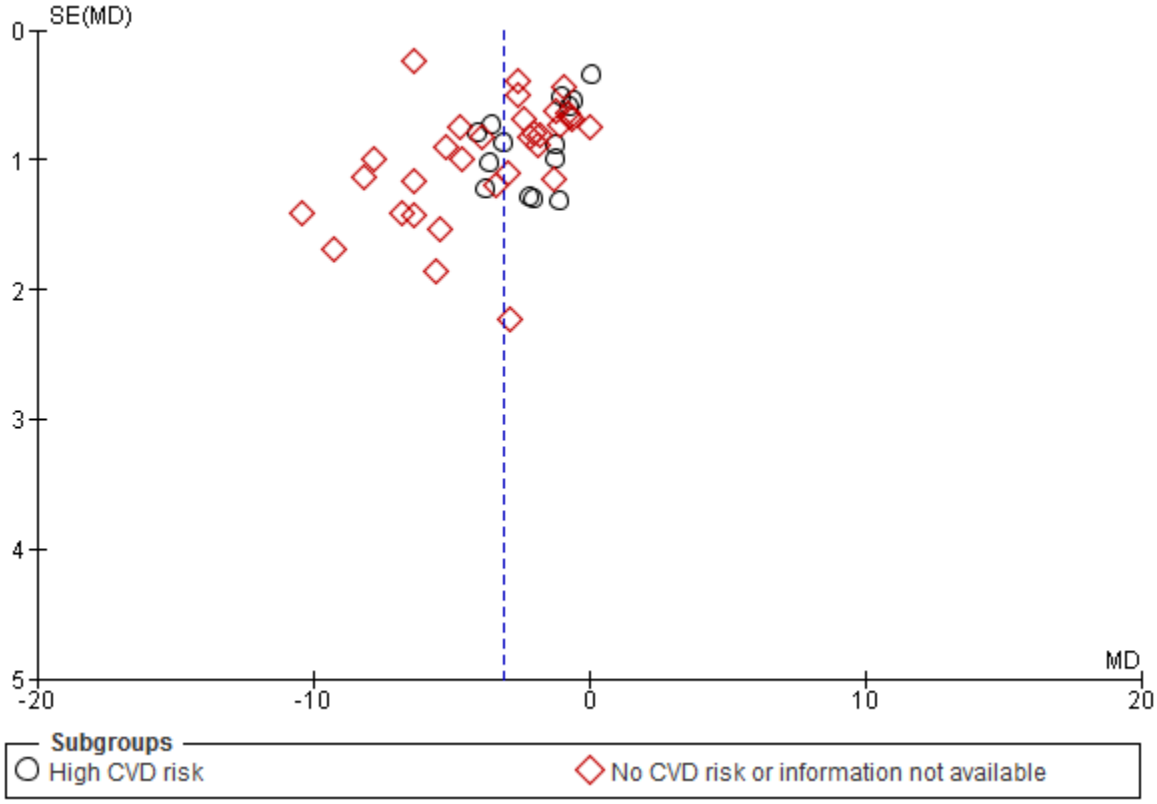
Included Studies	P-value
Pharmacological plus Behavioural Interventions ≤12 Months	0.073
Pharmacological plus Behavioural Interventions >12 Months	**

** Too few studies (n<10) to assess

Forest Plot 1.6: Effect of Treatment Interventions on Weight in KG – by Participants' Baseline CVD Risk Status in Behavioural Interventions (High Risk, Low/Unknown Risk)



Funnel Plot 1.6: Effect of Treatment Interventions on Weight in KG – by Participants' Baseline CVD Risk Status in Behavioural Interventions (High Risk, Low/Unknown Risk)

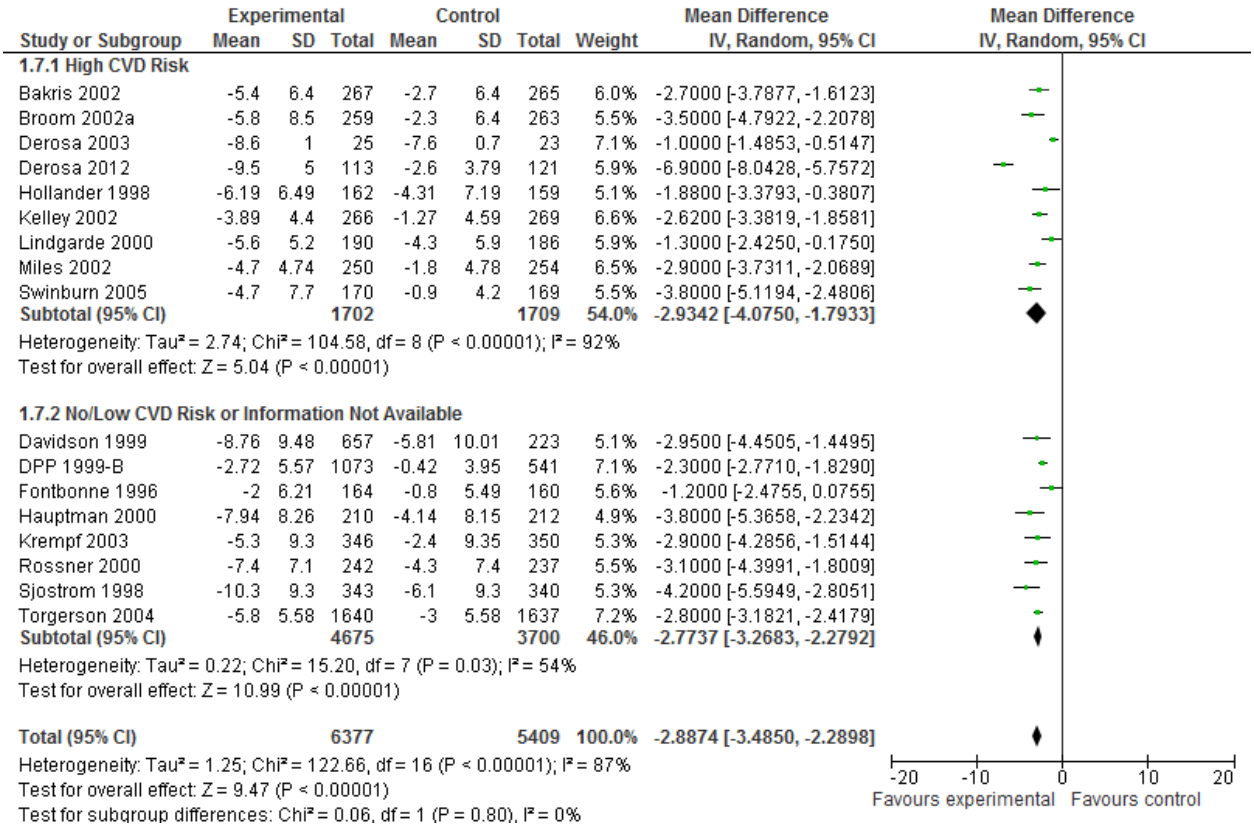


Egger's Test to Detect Publication Bias: Weight Change in KG – by Participants' Baseline CVD Risk Status in Behavioural Interventions (High Risk, Low/Unknown Risk)

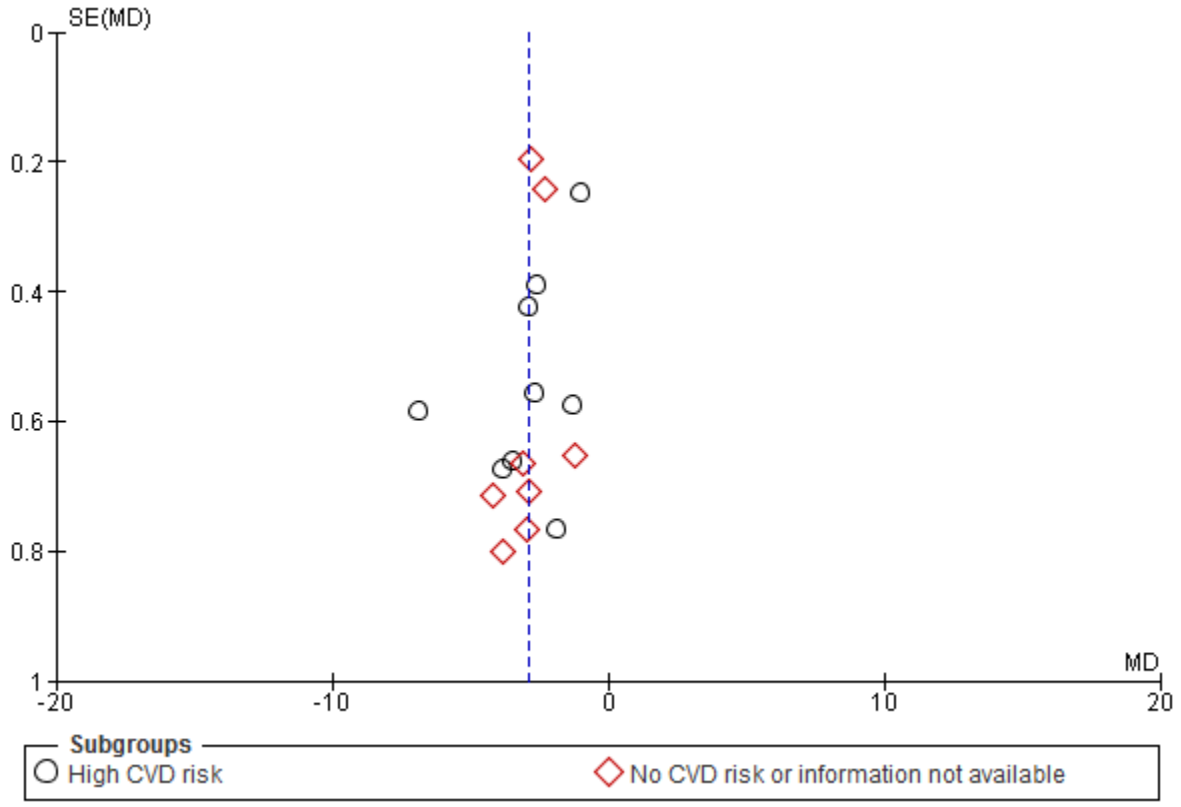
Included Studies	P-value
Behavioural Interventions – High Risk	0.006*
Behavioural Interventions – Low/Unknown Risk	0.619

* Significant p≤0.05

Forest Plot 1.7: Effect of Treatment Interventions on Weight in KG – by Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions (High Risk, Low/Unknown Risk)



Funnel Plot 1.7: Effect of Treatment Interventions on Weight in KG – by Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions (High Risk, Low/Unknown Risk)

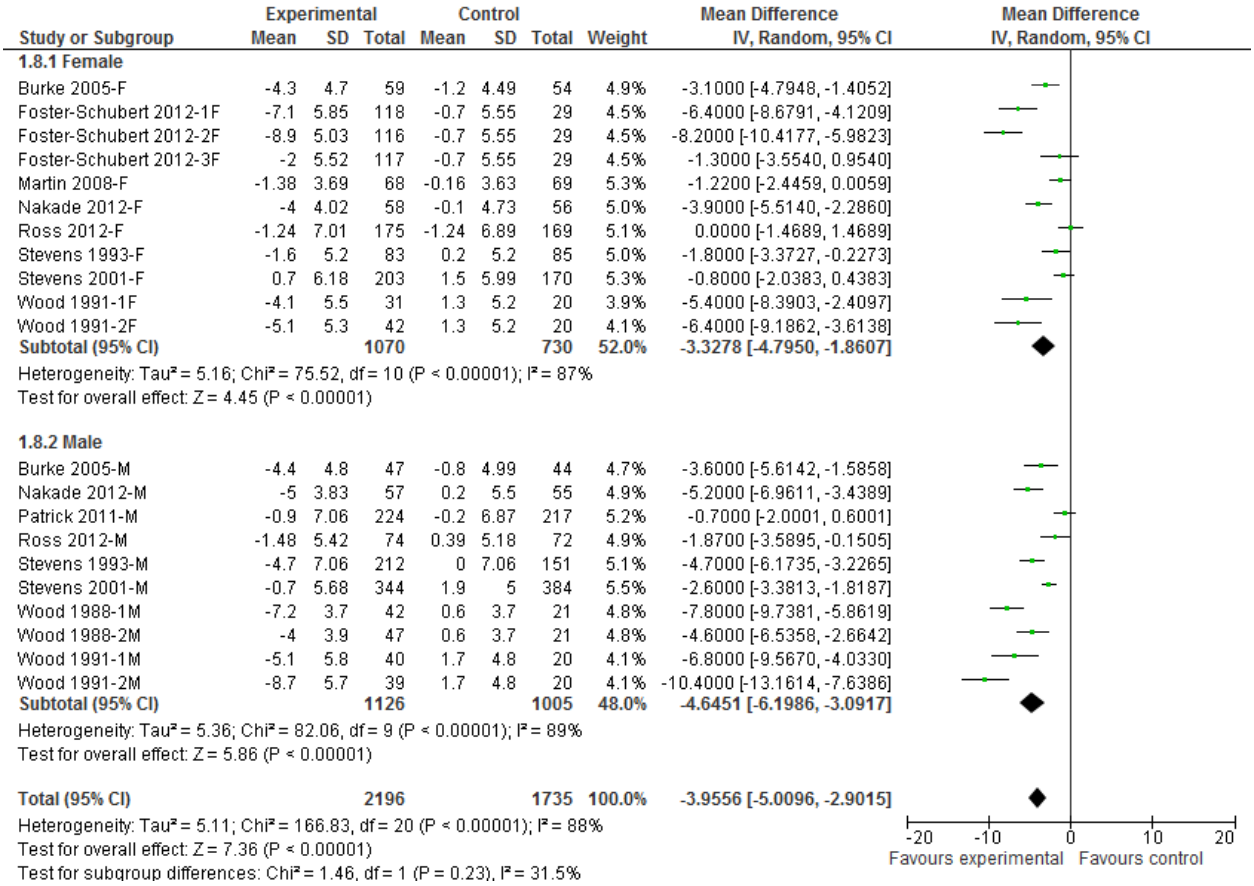


Egger's Test to Detect Publication Bias: Weight Change in KG – by Participants' Baseline CVD Risk Status in Pharmacological plus Behavioural Interventions (High Risk, Low/Unknown Risk)

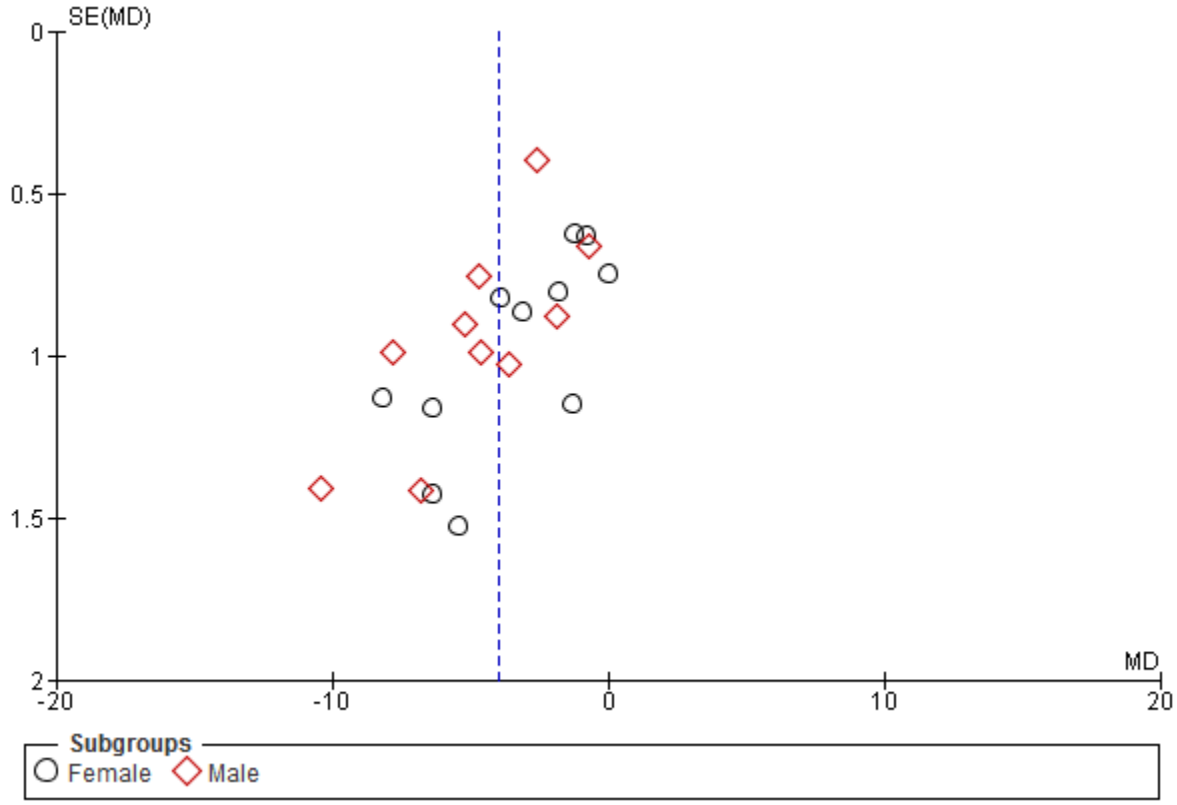
Included Studies	P-value
Behavioural Interventions – High Risk	**
Behavioural Interventions – Low/Unknown Risk	**

** Too few studies (n<10) to assess

Forest Plot 1.8: Effect of Treatment Interventions on Weight in KG – by Gender Only for Behavioural Studies that Reported Outcome Data by Gender (Female, Male)



Funnel Plot 1.8: Effect of Treatment Interventions on Weight in KG – by Gender Only for Behavioural Studies that Reported Outcome Data by Gender (Female, Male)



Egger's Test to Detect Publication Bias: Weight Change in KG – by Gender Only for Behavioural Studies that Reported Outcome Data by Gender (Female, Male)

Included Studies	P-value
Behavioural with Gendered Analysis – Female	**
Behavioural with Gendered Analysis – Male	**

** Too few studies (n<10) to assess

Evidence Set 2: Do primary care relevant treatment interventions in overweight/obese adults lead to weight loss (≥5% baseline body weight)?

- Summary of Loss of ≥5% Baseline Body Weight Evidence
- GRADE Evidence Profile Table 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight
- GRADE Summary of Findings Table 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight
- Forest Plot 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Loss of ≥5% Baseline Body Weight Evidence

Overall

- 24 studies; 9,857 participants
- Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to the control group [RR (95% CI) 1.77 (1.58, 1.99)]
- Absolute risk reduction is 20.42%
- Number needed to treat is 5 (95% CI 4, 7)
- Moderate heterogeneity across studies [Chi^2=73.91, df=23 (P<0.00001), I^2=69%]

Test for subgroup differences is not significant [Chi^2=0.02, df=1 (P=0.88), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 11 studies; 2,841 participants
- Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to the control group [RR (95% CI) 1.75 (1.35, 2.27)]
- Absolute risk reduction is 11.67%
- Number needed to treat is 9 (95% CI 5, 18)
- Moderate heterogeneity across studies [Chi^2=23.01, df=10 (P=0.01), I^2=57%]

Pharmacological plus Behavioural Interventions

- 13 studies; 7,016 participants
- Intervention participants were significantly more likely to lose ≥5% of their baseline body weight as compared to the control group [RR (95% CI) 1.79 (1.57, 2.04)]
- Absolute risk reduction is 24.26%
- Number needed to treat is 4 (95% CI 3, 6)
- High heterogeneity across studies [Chi^2=50.77, df=12 (P<0.00001), I^2=76%]

GRADE Evidence Profile Table 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight *

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARR	NNT (95% CI)		
≥5% Weight Loss: Overall														
24	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	reporting bias[6]	2,506/5,498 (45.5802%)	1,149/4,359 (26.3593%)	RR 1.7745 (1.5813 to 1.9915)	204,152 more (from 153,226 to 261,352 more)	20.42%	5 (4, 7)	⊕⊕OO LOW	CRITICAL
≥5% Weight Loss: by Primary Focus of Intervention – Behavioural														
11	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	reporting bias[12]	431/1,615 (26.6873%)	190/1,226 (15.4976%)	RR 1.7532 (1.3520 to 2.2734)	116,728 more (from 54,551 to 197,346 more)	11.67%	9 (5, 18)	⊕⊕OO LOW	CRITICAL
≥5% Weight Loss: by Primary Focus of Intervention – Pharmacological plus Behavioural														
13	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	reporting bias[18]	2,075/3,883 (53.4381%)	959/3,133 (30.6096%)	RR 1.7926 (1.5715 to 2.0447)	242,612 more (from 174,934 to 319,779 more)	24.26%	4 (3, 6)	⊕⊕OO LOW	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight

Outcome: Loss of ≥5% Baseline Body Weight	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**263,593**	**467,745** (416,819 to 524,945)	**RR 1.7745** (1.5813 to 1.9915)	9,857 (24 studies[1])	⊕⊕⊖⊖ **low**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**154,976**	**271,703** (209,527 to 352,321)	**RR 1.7532** (1.3520 to 2.2734)	2,841 (11 studies[7])	⊕⊕⊖⊖ **low**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**306,096**	**548,708** (481,030 to 625,875)	**RR 1.7926** (1.5715 to 2.0447)	7,016 (13 studies[13])	⊕⊕⊖⊖ **low**[14,15,16,17,18]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Loss ≥5% Baseline Body Weight

[1] The 24 studies are:[68,70,71,78,83,86,88,89,95,103,104,108-110,112,114-118,120,122-124] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Martin[89] provides 6 month follow-up data post completion of a 6 month intervention; Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions).

[2] Using Cochrane's Risk of Bias tool, for this outcome 23 studies (96%) were rated as unclear risk and 1 study (4%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (46%), allocation concealment (79%), blinding of participants and/or personnel (54%), and blinding of outcome assessors (83%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (42%), incomplete reporting (50%), and other sources of bias (58%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is moderate [Chi^2=73.91, df=23 (p<0.00001); I^2=69%] the direction of the effect is consistent across studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.02, df=1 (p=0.88), I^2=0%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 24 studies, 23 included adults aged 18-64 years and 1 included adults 65 years and older. Most studies (n=23) included mixed gender samples; 1 included only women. In 12 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 11 were behavioural (1 diet, 2 diet plus exercise, 8 lifestyle), 13 were pharmacological plus behavioural (all 120 mg orlistat 3x/day). Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 16 studies and more than 12 months in 8 studies. One study was conducted in Canada and the US, 12 in the US, 10 in European countries, and 1 in Australia. One-third of the studies (n=8) were published in the last 5 years (2009-2012); the remaining 16 studies were published between 1985 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (5,498 intervention arm, 4,359 control arm), the number of events is sufficient (2,506 intervention arm, 1,149 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.7745 (1.5813, 1.9915)]. This body of evidence was not downgraded for imprecision.

[6] The Egger's test was conducted to detect publication bias; results were significant (p=0.002). This body of evidence was downgraded for suspected publication bias.

[7] The 11 studies are:[68,70,71,78,83,86,88,89,95,103,104] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Martin[89] provides 6 month follow-up data post completion of a 6 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 11 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (27%), allocation concealment (73%), and blinding of outcome assessors (82%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (91%), incomplete reporting (36%), and other sources of bias (27%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is moderate [Chi^2=23.01, df=10 (p=0.01); I^2=57%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 11 studies, 10 included adults aged 18-64 years and 1 included adults 65 years and older. Most studies (n=10) included mixed gender samples; 1 included only women. In 5 studies (45%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 2 were diet plus exercise, and 8 were lifestyle. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 7 studies and more than 12 months in 4 studies. Seven studies were conducted in the US, 3 in European countries, and 1 in Australia. Most of the studies (n=8) were published in the last 5 years (2009-2012); the remaining 3 studies were published in 1985 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (1,615 intervention arm, 1,226 control arm), the number of events is sufficient, though a bit low in the control arm (431 intervention arm, 190 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.7532 (1.3520, 2.2734)]. This body of evidence was not downgraded for imprecision.

[12] The Egger's test was conducted to detect publication bias; results were significant (p=0.012). This body of evidence was downgraded for suspected publication bias.

[13] The 13 studies are:[108-110,112,114-118,120,122-124] Immediate post assessment for all but 2 studies; for these 2 studies the data point at 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions).

[14] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (92%) were rated as unclear risk and 1 study (8%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (62%), allocation concealment (85%), blinding of participants and/or personnel (92%), and blinding of outcome assessors (85%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (62%), and other sources of bias (85%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

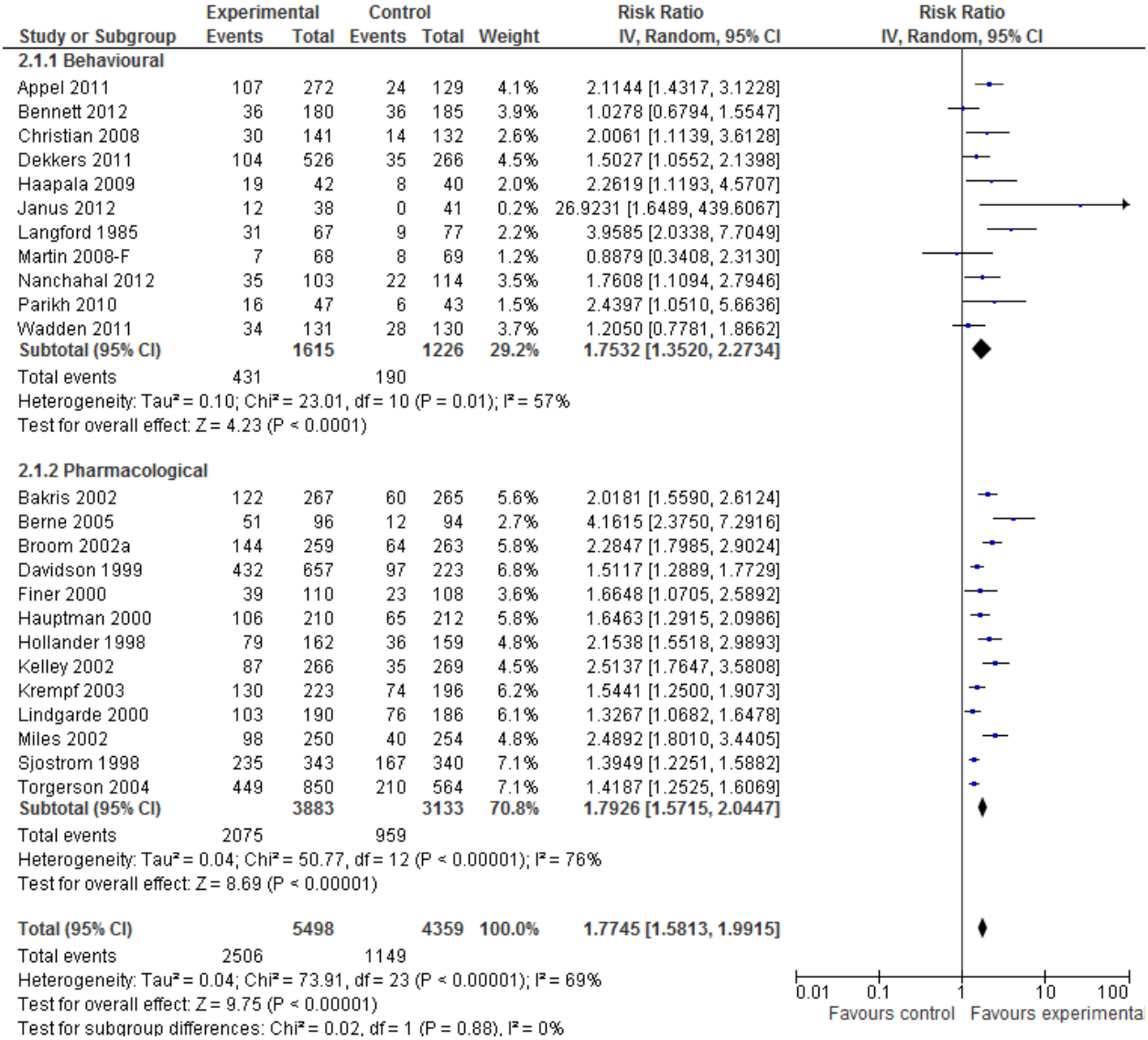
[15] Although the statistical heterogeneity is high [Chi^2=50.77, df=12 (p<0.00001); I^2=76%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 13 studies included adults aged 18-64 years, and mixed gender samples. In 7 studies (54%) the participants had a high risk of CVD. The pharmaceutical intervention in all studies was orlistat (120 mg 3x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medication. Intervention duration was 12 months or less in 9 studies and more than 12 months in 4 studies. One study was conducted in Canada and the US, 5 in the US, and 7 in European countries. None of the studies were published in the last 5 years; all 13 studies were published between 1985 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

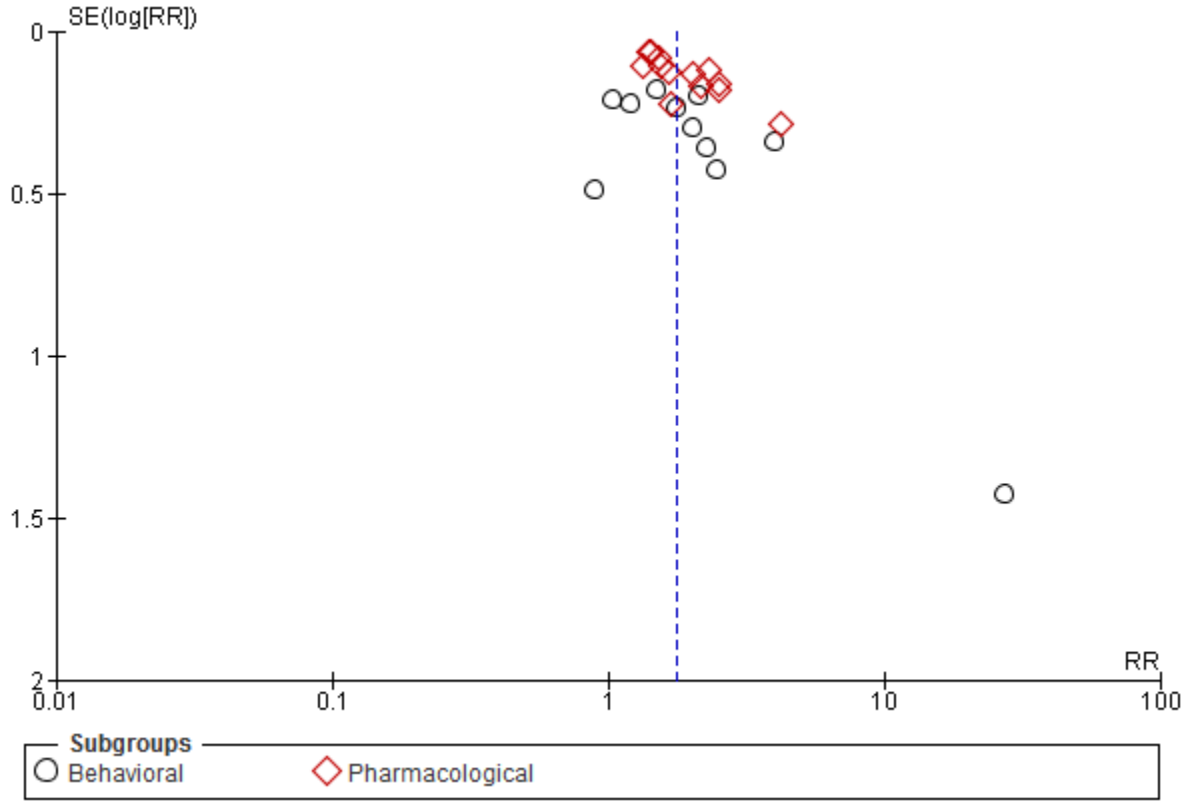
[17] The sample size is adequate (3,883 intervention arm, 3,133 control arm), the number of events is sufficient (2,075 intervention arm, 959 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.7926 (1.5715, 2.0447)]. This body of evidence was not downgraded for imprecision.

[18] The Egger's test was conducted to detect publication bias; results were significant (p=0.001). This body of evidence was downgraded for suspected publication bias.

Forest Plot 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 2.1: Effect of Treatment Interventions on Loss of ≥5% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Loss of ≥5% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.002*
Behavioural Interventions	0.012*
Pharmacological plus Behavioural Interventions	0.001*

* Significant p≤0.05

Evidence Set 3: Do primary care relevant treatment interventions in overweight/obese adults lead to weight loss (≥10% baseline body weight)?

- Summary of Loss of ≥10% Baseline Body Weight Evidence
- GRADE Evidence Profile Table 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight
- GRADE Summary of Findings Table 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight
- Forest Plot 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Loss of ≥10% Baseline Body Weight Evidence

Overall

- 16 studies; 7,523 participants
- Intervention participants were significantly more likely to lose ≥10% of their baseline body weight as compared to the control group [RR (95% CI) 1.91 (1.69, 2.16)]
- Absolute risk reduction is 11.24%
- Number needed to treat is 9 (95% CI 7, 12)
- Low heterogeneity across studies [Chi^2=17.87, df=15 (P=0.27), I^2=16%]

Test for subgroup differences is not significant [Chi^2=0.06, df=1 (P=0.81), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 3 studies; 744 participants
- Intervention participants were significantly more likely to lose ≥10% of their baseline body weight as compared to the control group [RR (95% CI) 2.04 (1.30, 3.21)]
- Absolute risk reduction is 8.01%
- Number needed to treat is 12 (95% CI 6, 44)
- Low heterogeneity across studies [Chi^2=0.43, df=2 (P=0.81), I^2=0%]

Pharmacological plus Behavioural Interventions

- 13 studies; 6,779 participants
- Intervention participants were significantly more likely to lose ≥10% of their baseline body weight as compared to the control group [RR (95% CI) 1.92 (1.67, 2.21)]
- Absolute risk reduction is 11.81%
- Number needed to treat is 8 (95% CI 6, 12)
- Low heterogeneity across studies [Chi^2=17.30, df=12 (P=0.14), I^2=31%]

GRADE Evidence Profile Table 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight *

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARR	NNT (95% CI)		
Loss of ≥10% Baseline Body Weight: Overall														
16	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	reporting bias[6]	1,077/4,220 (25.5213%)	407/3,303 (12.3221%)	RR 1.9119 (1.6940 to 2.1578)	112,366 more (from 85,516 to 142,666 more)	11.24%	9 (7, 12)	⊕⊕OO LOW	CRITICAL
Loss of ≥10% Baseline Body Weight: by Primary Focus of Intervention – Behavioural														
3	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	74/445 (16.6292%)	23/299 (7.6923%)	RR 2.0411 (1.2984 to 3.2087)	80,085 more (from 22,954 to 169,900 more)	8.01%	12 (6, 44)	⊕⊕⊕O MODERATE	CRITICAL
Loss of ≥10% Baseline Body Weight: by Primary Focus of Intervention – Pharmacological plus Behavioural														
13	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	reporting bias[18]	1,003/3,775 (26.5695%)	384/3,004 (12.7830%)	RR 1.9240 (1.6735 to 2.2121)	118,115 more (from 86,093 to 154,942 more)	11.81%	8 (6, 12)	⊕⊕OO LOW	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight

Outcome: Loss of ≥10% Baseline Body Weight	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**123,221**	**235,587** (208,737 to 265,887)	**RR 1.9119** (1.6940 to 2.1578)	7,523 (16 studies[1])	⊕⊕⊖⊖ **low**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**76,923**	**157,008** (99,877 to 246,823)	**RR 2.0411** (1.2984 to 3.2087)	744 (3 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**127,830**	**245,944** (213,923 to 282,772)	**RR 1.9240** (1.6735 to 2.2121)	6,779 (13 studies[13])	⊕⊕⊖⊖ **low**[14,15,16,17,18]

* The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight

[1] The 16 studies are:[70,71,86,108-110,112,114-120,122,124] Immediate post assessment for all but 2 studies; for these 2 studies the data point at 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions).

[2] Using Cochrane's Risk of Bias tool, for this outcome 15 studies (94%) were rated as unclear risk and 1 study (6%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (56%), allocation concealment (88%), blinding of participants and/or personnel (81%), and blinding of outcome assessors (81%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (13%), incomplete reporting (56%), and other sources of bias (81%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is low [Chi^2=17.87, df=15 (p=0.27); I^2=16%], the direction of the effect is consistent across studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.06, df=1 (p=0.81), I^2=0%]. This body of evidence was not downgraded for inconsistency.

[4] All 16 studies included adults aged 18-64 years, and mixed gender samples. In 8 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 3 were behavioural (1 diet plus exercise, 2 lifestyle) and 13 were pharmacological plus behavioural (all 120 mg orlistat 3x/day). Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 9 studies and more than 12 months in 7 studies. One study was conducted in Canada and the US, 6 in the US, and 9 in European countries. Three studies were published in the last 5 years (2009, 2011); the remaining 13 studies were published between 1998 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (4,220 intervention arm, 3,303 control arm), the number of events is sufficient (1,077 intervention arm, 407 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.9119 (1.6940, 2.1578)]. This body of evidence was not downgraded for imprecision.

[6] The Egger's test was conducted to detect publication bias; results were significant (p=0.018). This body of evidence was downgraded for suspected publication bias.

[7] The 3 studies are:[70,71,86] Immediate post assessment for all 3 studies.

[8] Using Cochrane's Risk of Bias tool, for this outcome all 3 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (33%), allocation concealment (100%), blinding of participants and/or personnel (33%), and blinding of outcome assessors (67%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (67%), incomplete reporting (33%), and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is low [Chi^2=0.43, df=2 (p=0.81); I^2=0%], the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[10] All 3 studies included adults aged 18-64 years, and mixed gender samples. In 2 studies (67%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet plus exercise and 2 were lifestyle. Control participants received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 1 study and more than 12 months in 2 studies. Two studies were conducted in the US and 1 in Finland. All 3 studies were published in the last 5 years (2009, 2011). There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (445 intervention arm, 299 control arm) but the number of events is low in both arms (74 intervention, 23 control). The pooled effect estimate is precise with a narrow confidence interval [RR=2.0411 (1.2984, 3.2087)]. This body of evidence was not downgraded for imprecision.

[12] There were too few studies (n<10) to assess publication bias.

[13] The 13 studies are:[108-110,112,114-120,122,124] Immediate post assessment for all but 2 studies; for these 2 studies the data point at 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions).

[14] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (92%) were rated as unclear risk and 1 study (8%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (62%), allocation concealment (88%), blinding of participants and/or personnel (94%), and blinding of outcome assessors (88%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (50%), and other sources of bias (94%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

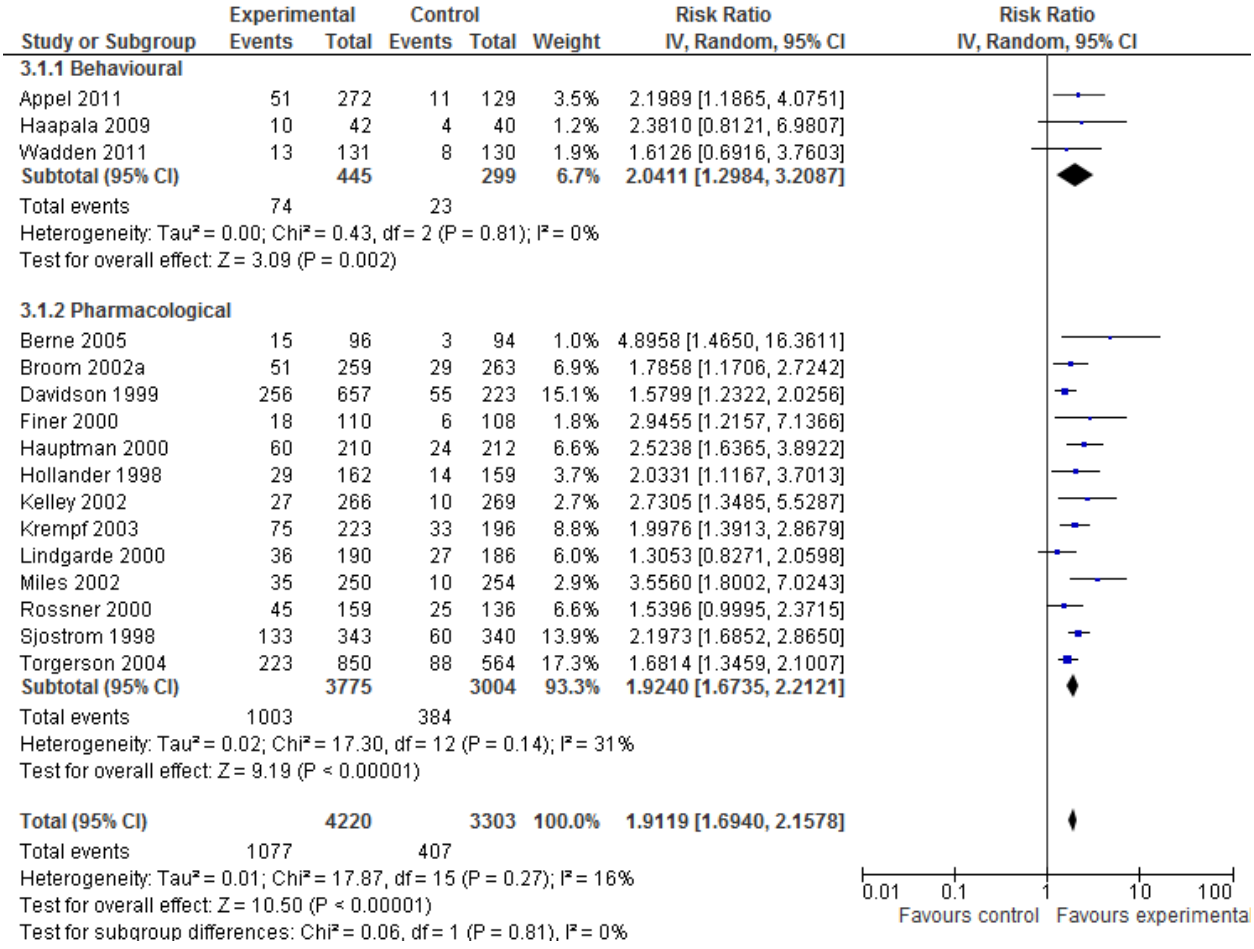
[15] Statistical heterogeneity is low [Chi^2=17.30, df=12 (p=0.14); I^2=31%], the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[16] All 13 studies included adults aged 18-64, years and mixed gender samples. In 6 studies (46%) the participants had a high risk of CVD. In all studies the pharmacological plus behavioural intervention was orlistat (120 mg 3x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 8 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 4 in the US, and 8 in European countries. None of the studies was published in the last five years; all 13 studies were published between 1998 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

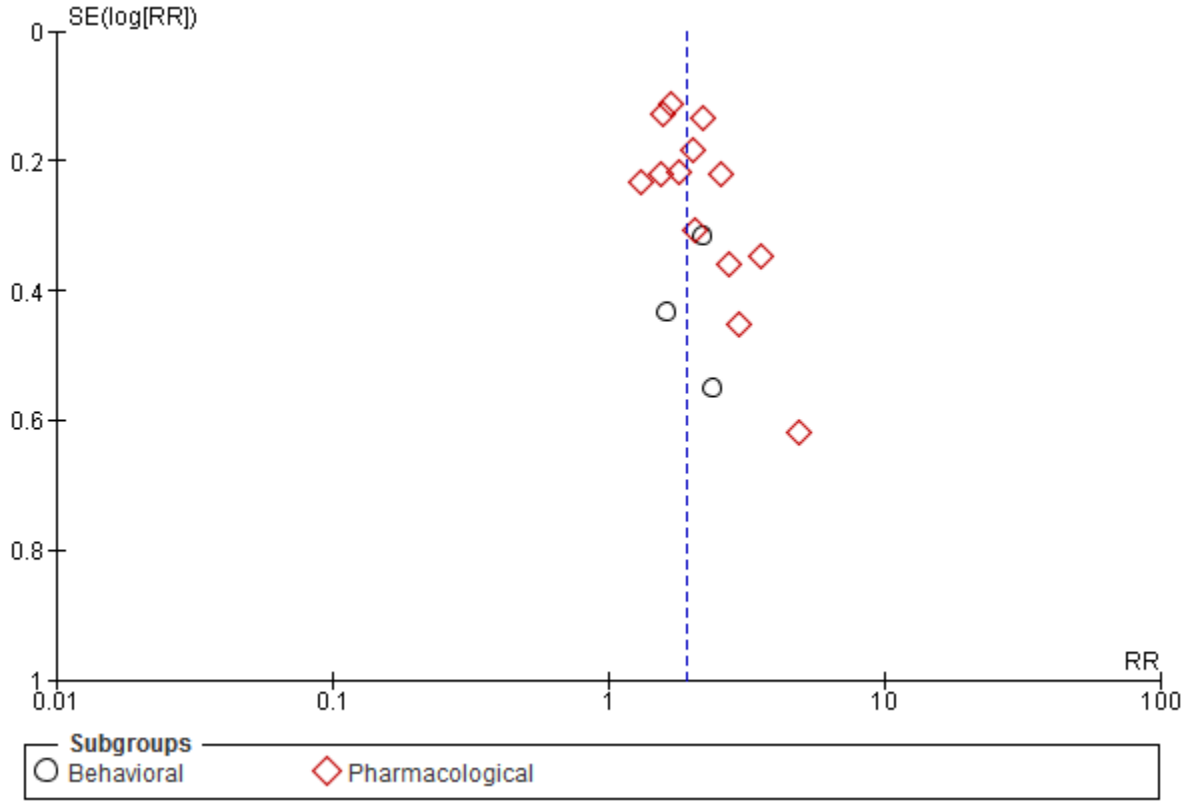
[17] The sample size is adequate (3,775 intervention arm, 3,004 control arm), the number of events is sufficient (1,003 intervention arm, 384 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.9240 (1.6735, 2.2121)]. This body of evidence was not downgraded for imprecision.

[18] The Egger's test was conducted to detect publication bias; results were significant (p=0.013). This body of evidence was downgraded for suspected publication bias.

Forest Plot 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 3.1: Effect of Treatment Interventions on Loss of ≥10% Baseline Body Weight - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Loss of ≥10% Baseline Body Weight – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.018*
Behavioural Interventions	**
Pharmacological plus Behavioural Interventions	0.013*

* Significant p≤0.05

** Too few studies (n<10) to assess

Evidence Set 4: Do primary care relevant treatment interventions in overweight/obese adults lead to weight loss (reduction in BMI)?

- Summary of Change in BMI Evidence
- GRADE Evidence Profile Table 4.1: Effect of Treatment Interventions on BMI
- GRADE Summary of Findings Table 4.1: Effect of Treatment Interventions on BMI
- Forest Plot 4.1: Effect of Treatment Interventions on BMI – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 4.1: Effect of Treatment Interventions on BMI – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in BMI Evidence

Overall

- 26 studies; 10,611 participants
- Statistically significant reduction in BMI in the intervention group as compared to the control group [MD (95% CI) -1.11 kg/m^2 (-1.39, -0.84)]
- High heterogeneity across studies [Chi^2=490.88, df=34 (P<0.00001), I^2=93%]

Test for subgroup differences is not significant [Chi^2=0.30, df=1 (P=0.59), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 22 studies; 7,487 participants
- Statistically significant reduction in BMI in the intervention group as compared to the control group [MD (95% CI) -1.09 kg/m^2 (-1.43, -0.75)]
- High heterogeneity across studies [Chi^2=435.15, df=29 (P<0.00001), I^2=93%]

Pharmacological plus Behavioural Interventions

- 5 studies; 3,124 participants
- Statistically significant reduction in BMI in the intervention group as compared to the control group [MD (95% CI) -1.27 kg/m^2 (-1.82, -0.72)]
- High heterogeneity across studies [Chi^2=53.55, df=4 (P<0.00001), I^2=93%]

GRADE Evidence Profile Table 4.1: Effect of Treatment Interventions on BMI *

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in BMI: Overall (Better indicated by lower values)											
26	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	6,529	4,082	1.1136 lower (1.3922 to 0.8350 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in BMI: by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
22	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	4,705	2,782	1.0908 lower (1.4273 to 0.7542 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in BMI: by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
5	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	1,824	1,300	1.2698 lower (1.8182 to 0.7214 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 4.1: Effect of Treatment Interventions on BMI

Outcome: Change in BMI	Compared to the control group, the mean change in BMI (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**1.1136 lower** (1.3922 to 0.835 lower)	10,611 (26 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**1.0908 lower** (1.4273 to 0.7542 lower)	7,487 (22 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**1.2698 lower** (1.8182 to 0.7214 lower)	3,124 (5 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on BMI

[1] The 26 studies are:[69-74,76-80,82,87,96-100,102-104,106,111,116,123,133] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 24 studies (92%) were rated as unclear risk and 2 studies (8%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (46%), allocation concealment (77%), and blinding of outcome assessors (54%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (81%), incomplete reporting (23%), and other sources of bias (31%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=490.88, df=34 (p<0.00001); I^2=93%] the direction of the effect is consistent across studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.30, df=1 (p=0.59), I^2=0%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 26 studies, 24 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=24) included mixed gender samples; 1 included only women and 1 included only men. In 9 studies (35%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (1 diet, 4 exercise, 7 diet plus exercise, 9 lifestyle), 4 were pharmacological plus behavioural (all 120 mg orlistat 3x/day), and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 1x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 16 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, 13 in European countries, 1 in Australia, and 1 in Japan. Most of the studies (n=21) were published in the last 5 years (2009-2013); the remaining 5 studies were published between 1995 and 2003. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (6,529 intervention arm, 4,082 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.1136 (-1.3922, -0.8350)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.721). This body of evidence was not downgraded for suspected publication bias.

[7] The 22 studies are:[69-74,76-80,82,87,96-100,102-104,133] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 22 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (45%), allocation concealment (82%), and blinding of outcome assessors (55%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (95%), incomplete reporting (18%), and other sources of bias (27%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is high [Chi^2=435.15, df=29 (p<0.00001); I^2=93%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 22 studies, 20 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=20) included mixed gender samples; 1 included only women and 1 included only men. In 6 studies (27%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 4 were exercise, 7 were diet plus exercise, and 10 were lifestyle. Control participants received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 13 studies and more than 12 months in 9 studies. One study was conducted in Canada, 9 in the US, 10 in European countries, 1 in Australia, and 1 in Japan. Most of the studies (n=20) were published in the last 5 years (2009-2013); the remaining 2 studies were published in 1995 and 1999. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (4,705 intervention arm, 2,782 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.0908 (-1.4273, -0.7542)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.342). This body of evidence was not downgraded for suspected publication bias.

[13] The 5 studies are:[106,111,116,123,133] Immediate post assessment for all but 1 study; for this exception the data point at 12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 3 studies (60%) were rated as unclear risk and 2 studies (40%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (40%), allocation concealment (60%), blinding of participants and personnel (40%), and blinding of outcome assessors (60%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (40%), and other sources of bias (60%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

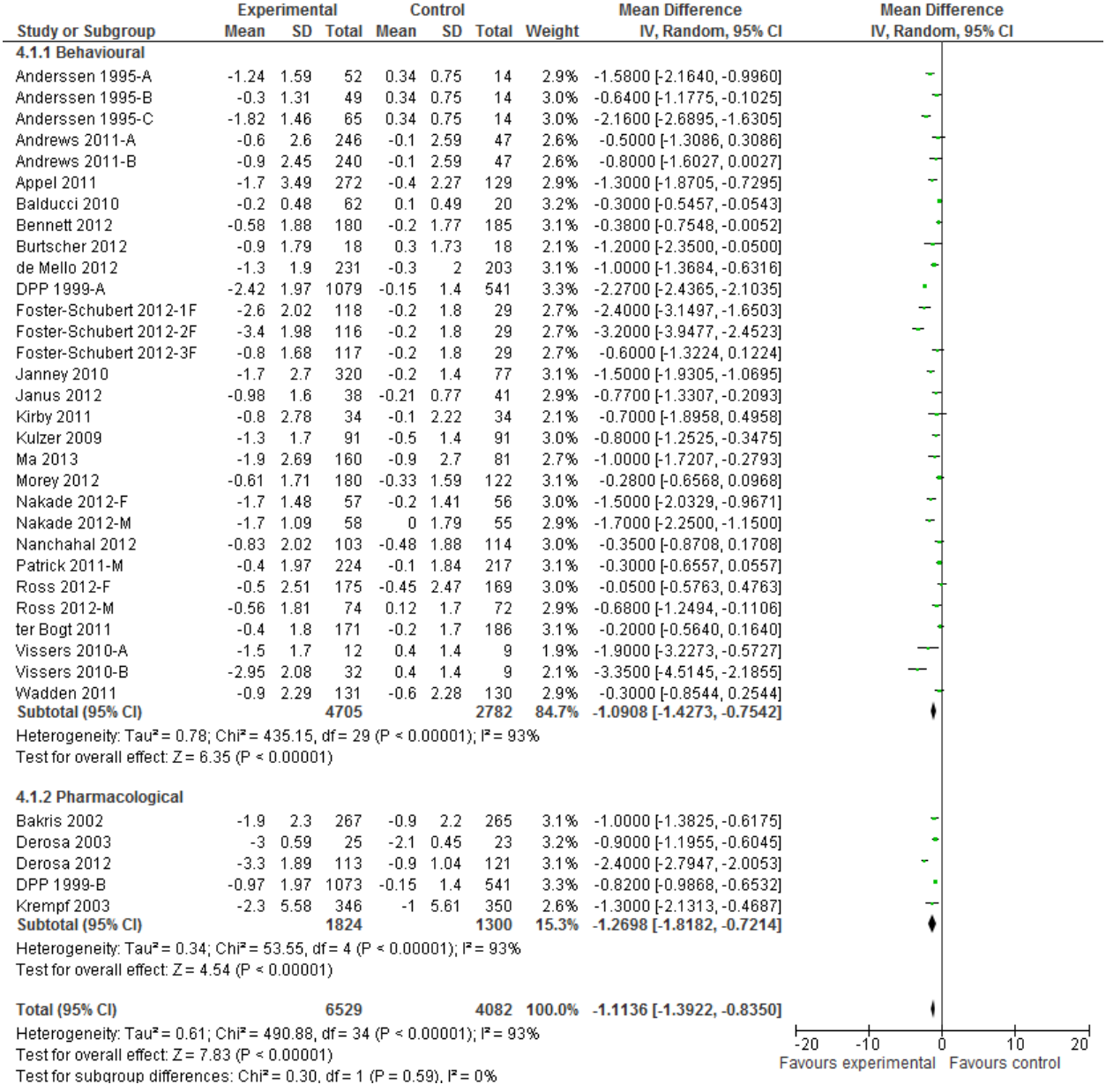
[15] Although the statistical heterogeneity is high [Chi^2=53.55, df=4 (p<0.00001); I^2=93%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 5 studies included adults aged 18-64 years, and mixed gender samples. In 3 studies (60%) the participants had a high risk of CVD. Four studies included orlistat (120 mg 3x/day) as the pharmacological plus behavioural intervention, 1 used metformin (850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 3 studies and more than 12 months in 2 studies. Two studies were conducted in the US and 3 in European countries. One study was published in the last 5 years (2012); the remaining 4 studies were published between 1999 and 2003. There were no serious concerns regarding indirectness for this body of evidence.

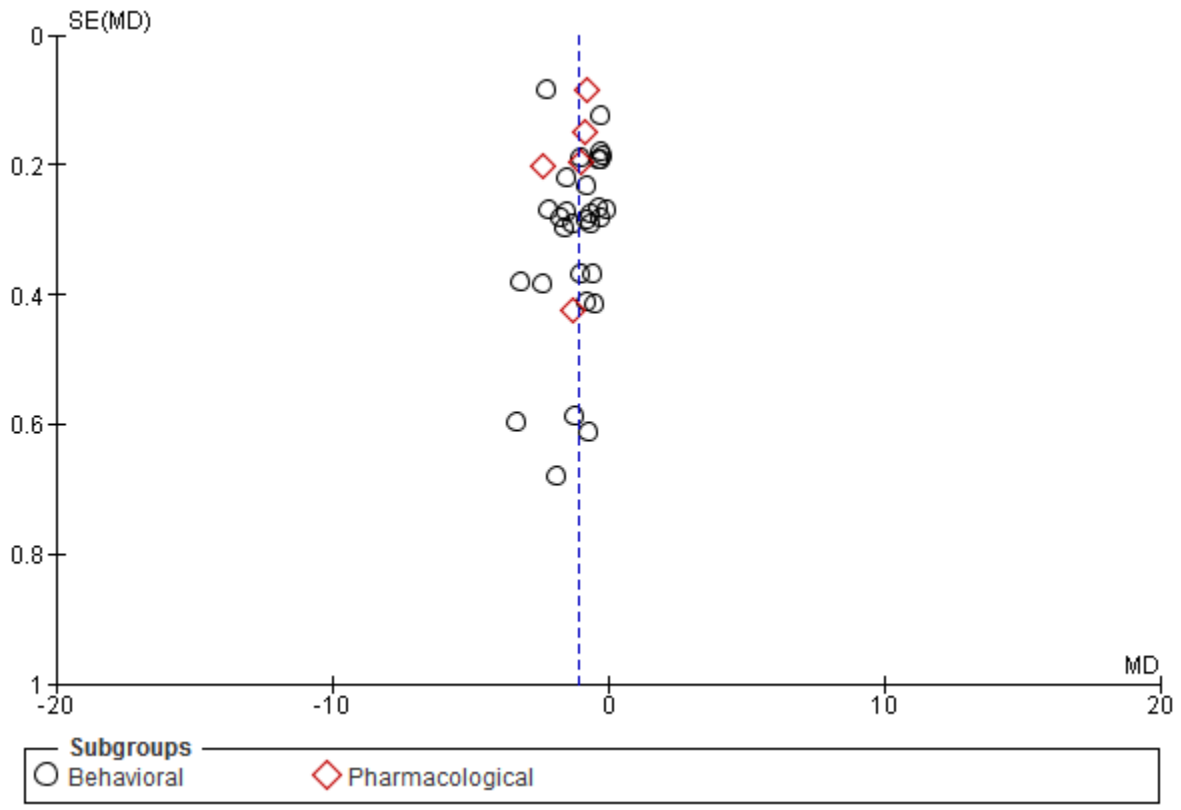
[17] The sample size is adequate (1,824 intervention arm, 1,300 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.2698 (-1.8182, -0.7214)]. This body of evidence was not downgraded for imprecision.

[18] There were too few studies (n<10) to assess publication bias.

Forest Plot 4.1: Effect of Treatment Interventions on BMI - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 4.1: Effect of Treatment Interventions on BMI - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in BMI - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.721
Behavioural Interventions	0.342
Pharmacological plus Behavioural Interventions	**

** Too few studies (n<10) to assess

Evidence Set 5: Do primary care relevant treatment interventions in overweight/obese adults lead to weight loss (reduction in waist circumference)?

- Summary of Change in Waist Circumference Evidence
- GRADE Evidence Profile Table 5.1: Effect of Treatment Interventions on Waist Circumference
- GRADE Summary of Findings Table 5.1: Effect of Treatment Interventions on Waist Circumference
- Forest Plot 5.1: Effect of Treatment Interventions on Waist Circumference – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 5.1: Effect of Treatment Interventions on Waist Circumference – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in Waist Circumference Evidence

Overall

- 33 studies; 16,565 participants
- Statistically significant reduction in waist circumference in the intervention group as compared to the control group [MD (95% CI) -2.78 cm (-3.34, -2.22)]
- High heterogeneity across studies [Chi^2=450.50, df=40 (P<0.00001), I^2=91%]

Test for subgroup differences is not significant [Chi^2=1.80, df=1 (P=0.18), I^2=44.4%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 22 studies; 7,770 participants
- Statistically significant reduction in waist circumference in the intervention group as compared to the control group [MD (95% CI) -3.05 cm (-3.86, -2.24)]
- High heterogeneity across studies [Chi^2=284.19, df=28 (P<0.00001), I^2=90%]

Pharmacological plus Behavioural Interventions

- 12 studies; 8,795 participants
- Statistically significant reduction in waist circumference in the intervention group as compared to the control group [MD (95% CI) -2.29 cm (-3.04, -1.55)]
- High heterogeneity across studies [Chi^2=120.50, df=11 (P<0.00001), I^2=91%]

GRADE Evidence Profile Table 5.1: Effect of Treatment Interventions on Waist Circumference *

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in Waist Circumference (cm): Overall (Better indicated by lower values)											
33	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	9,460	7,105	2.7822 lower (3.3420 to 2.2223 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in Waist Circumference (cm): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
22	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	4,799	2,971	3.0467 lower (3.8564 to 2.2369 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in Waist Circumference (cm): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
12	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	4,661	4,134	2.2941 lower (3.0390 to 1.5491 lower)	⊕⊕⊕O MODERATE	CRITICAL

***** Footnotes appear after Summary of Findings Table

GRADE Summary of Findings Table 5.1: Effect of Treatment Interventions on Waist Circumference

Outcome: Change in Waist Circumference (cm)	Compared to the control group, the mean change in waist circumference (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**2.7822 lower** (3.3420 to 2.2223 lower)	16,565 (33 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**3.0467 lower** (3.8564 to 2.2369 lower)	7,770 (22 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**2.2941 lower** (3.0390 to 1.5491 lower)	8,795 (12 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Reduction of Waist Circumference

[1] The 33 studies are:[68-73,76,77,79,83,84,86,87,95-97,99,100,102-104,106,108,109,111,115,116,119,121-124,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 30 studies (91%) were rated as unclear risk and 3 studies (9%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (36%), allocation concealment (76%), blinding of participants and/or personnel (30%), and blinding of outcome assessors (61%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (61%), incomplete reporting (30%), and other sources of bias (45%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=450.50, df=40 (p<0.00001); I^2=91%] the direction of the effect is consistent across studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=1.80, df=1 (p=0.18), I^2=44.4%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 33 studies, 31 included adult aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=31) included mixed gender samples; 1 included only women and 1 included only men. In 15 studies (45%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (1 diet, 2 exercise, 7 diet plus exercise, 11 lifestyle), 11 were pharmacological plus behavioural (all 120 mg orlistat 3x/day), and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 5 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 23 studies and more than 12 months in 10 studies. One study was conducted in Canada, 12 in the US, 16 in European countries, 3 in Australia and/or New Zealand, and 1 in Japan. About two-thirds of the studies (n=20) were published in the last 5 years (2009-2013); the remaining 13 studies were published between 1998 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (9,460 intervention arm, 7,105 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.7822 (-3.3420, -2.2223)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.130). This body of evidence was not downgraded for suspected publication bias.

[7] The 22 studies are:[68-73,76,77,79,83,84,86,87,95-97,99,100,102-104,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 22 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (32%), allocation concealment (77%), and blinding of outcome assessors (55%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (91%), incomplete reporting (23%), and other sources of bias (27%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is high [Chi^2=284.19, df=28 (p<0.00001); I^2=90%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 22 studies, 20 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=20) included mixed gender samples; 1 included only women and 1 included only men. In 7 studies (32%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 2 were exercise, 7 were diet plus exercise, and 11 were lifestyle. Control participants received usual care from their physicians or no intervention; in 5 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 15 studies and more than 12 months in 7 studies. One study was conducted in Canada, 9 in the US, 9 in European countries, 2 in Australia, and 1 in Japan. Most of the studies (n=19) were published in the last 5 years (2009-2013); the remaining 3 studies were published between 1999 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (4,799 intervention arm, 2,971 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-3.0467 (-3.8564, -2.2369)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.967). This body of evidence was not downgraded for suspected publication bias.

[13] The 12 studies are:[106,108,109,111,115,116,119,121-124,133] Immediate post assessment for all but 1 study; for this exception the data point at 12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 9 studies (75%) were rated as unclear risk and 3 studies (25%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (42%), allocation concealment (75%), blinding of participants and/or personnel (67%), and blinding of outcome assessors (75%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (42%), and other sources of bias (83%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

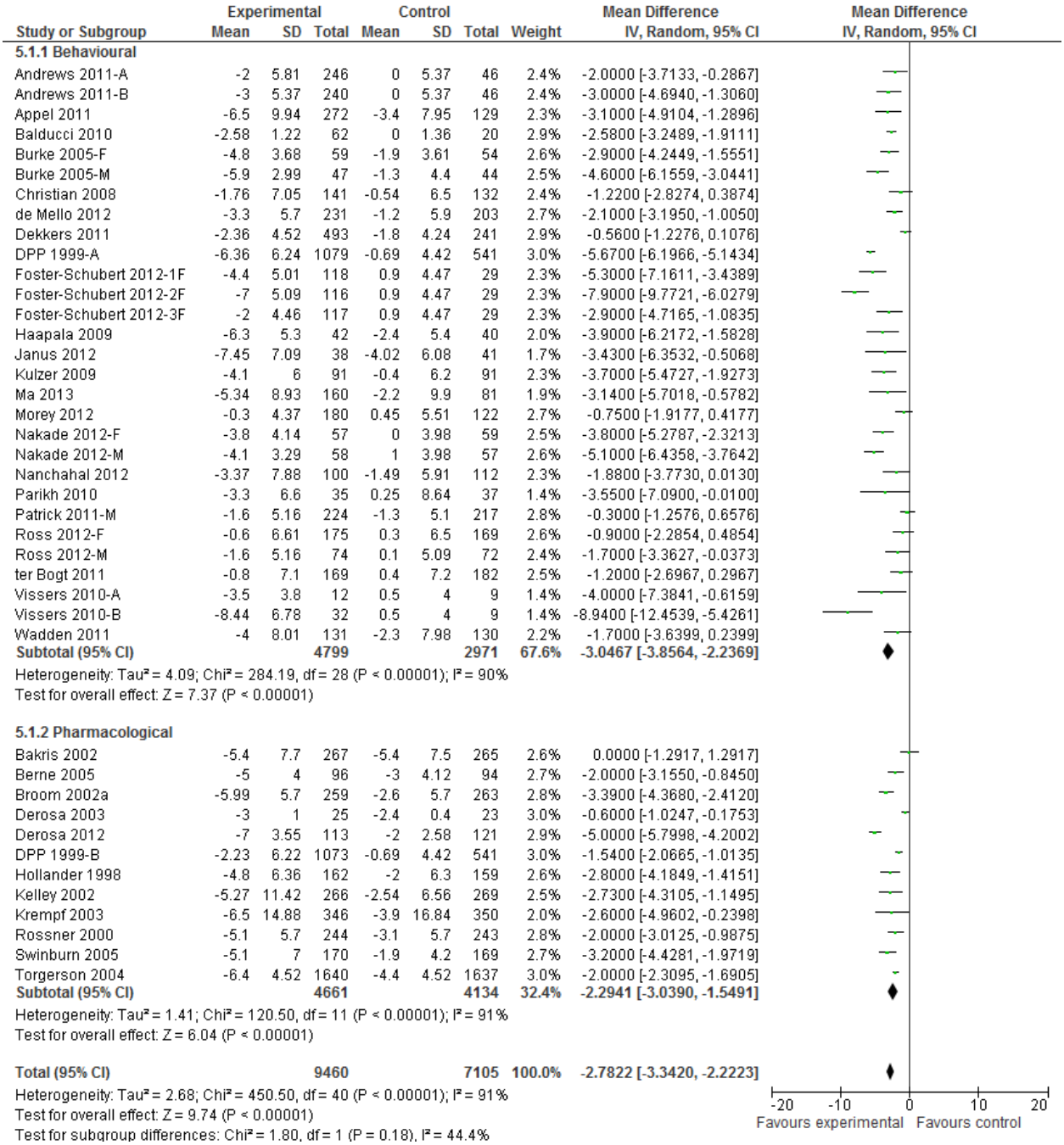
[15] Although the statistical heterogeneity is high [Chi^2=120.50, df=11 (p<0.00001); I^2=91%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 12 studies included adults aged 18-64 years, and mixed gender samples. In 8 studies (67%) the participants had a high risk of CVD. In 11 studies the pharmacological plus behavioural intervention was orlistat (120mg 3x/day), in 1 study it was metformin (850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 8 studies and more than 12 months in 4 studies. Four studies were conducted in the US, 7 in European countries, and 1 in Australia. Only 1 study was published in the last 5 years (2012); the remaining 11 studies were published between 1998 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

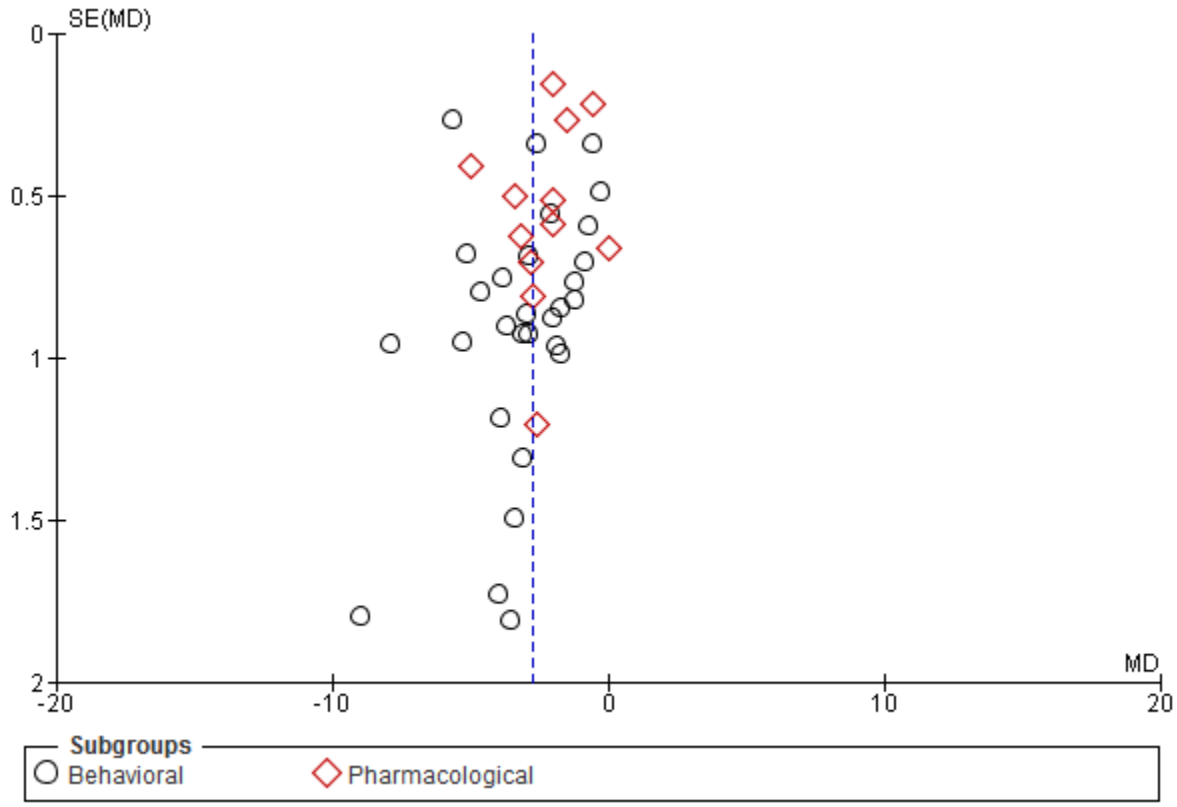
[17] The sample size is adequate (4,661 intervention arm, 4,134 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-2.2941 (-3.0390, -1.5491)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.308). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 5.1: Effect of Treatment Interventions on Waist Circumference – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 5.1: Effect of Treatment Interventions on Waist Circumference – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in Waist Circumference – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.130
Behavioural Interventions	0.967
Pharmacological plus Behavioural Interventions	0.308

Evidence Set 6: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in total cholesterol)?

- Summary of Change in Total Cholesterol Evidence
- GRADE Evidence Profile Table 6.1: Effect of Treatment Interventions on Total Cholesterol
- GRADE Summary of Findings Table 6.1: Effect of Treatment Interventions on Total Cholesterol
- Forest Plot 6.1: Effect of Treatment Interventions on Total Cholesterol - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 6.1: Effect of Treatment Interventions on Total Cholesterol - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in Total Cholesterol Evidence

Overall

- 33 studies; 10,039 participants
- Statistically significant reduction in total cholesterol level in the intervention group as compared to the control group [MD (95% CI) -0.21 mmol/L (-0.29, -0.13)]
- High heterogeneity across studies [Chi^2=263.86, df=38 (P<0.00001), I^2=86%]

Test for subgroup differences is significant [Chi^2=14.57, df=1 (P=0.0001), I^2=93.1%]; primary focus of intervention does explain some of the variation across all studies

Behavioural Interventions

- 18 studies; 4,282 participants
- Statistically significant reduction in total cholesterol level in the intervention group as compared to the control group [MD (95% CI) -0.10 mmol/L (-0.18, -0.03)]
- Moderate heterogeneity across studies [Chi^2=61.67, df=23 (P<0.0001), I^2=63%]

Pharmacological plus Behavioural Interventions

- 15 studies; 5,757 participants
- Statistically significant reduction in total cholesterol level in the intervention group as compared to the control group [MD (95% CI) -0.33 mmol/L (-0.42, -0.24)]
- High heterogeneity across studies [Chi^2=72.47, df=14 (P<0.00001), I^2=81%]

GRADE Evidence Profile Table 6.1: Effect of Treatment Interventions on Total Cholesterol *

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in Total Cholesterol (mmol/L): Overall (Better indicated by lower values)											
33	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	5,495	4,544	0.2119 lower (0.2892 to 0.1346 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in Total Cholesterol (mmol/L): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
18	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	reporting bias[12]	2,613	1,669	0.1047 lower (0.1824 to 0.0270 lower)	⊕⊕OO LOW	CRITICAL
Change in Total Cholesterol (mmol/L): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
15	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	2,882	2,875	0.3310 lower (0.4174 to 0.2446 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 6.1: Effect of Treatment Interventions on Total Cholesterol

Outcome: Change in Total Cholesterol (mmol/L)	Compared to the control group, the mean reduction in total cholesterol level (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**0.2119 lower** (0.2892 to 0.1346 lower)	10,039 (33 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**0.1047 lower** (0.1824 to 0.0270 lower)	4,282 (18 studies[7])	⊕⊕⊖⊖ **low**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**0.3310 lower** (0.4174 to 0.2446 lower)	5,757 (15 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Total Cholesterol

[1] The 33 studies are:[68,70-74,76,79,81,83,87,92,93,96-98,100,103,106,108,109,111,112,114,115,117-121,123,124,131] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Hauptman[114] presents 12 month interim outcomes for a 24 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 28 studies (85%) were rated as unclear risk and 5 studies (15%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (48%), allocation concealment (73%), and blinding of participants and/or personnel (45%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (30%), and other sources of bias (48%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=263.86, df=38 (p<0.00001); I^2=86%] the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was significant [Chi^2=14.57, df=1 (p=0.0001), I^2=93%]. This body of evidence was not downgraded for inconsistency.

[4] Across the 33 studies, 31 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=32) included mixed gender samples; 1 included only men. In 17 studies (52%) the participants had a high risk of CVD. In terms of intervention focus, 18 were behavioural (2 diet, 3 exercise, 6 diet plus exercise, 7 lifestyle) and 15 were pharmacological plus behavioural [14 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)]. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 24 studies and more than 12 months in 9 studies. One study was conducted in Canada, 1 in Canada and the US, 11 in the US, 17 in European countries, and 3 in Australia and/or New Zealand. Half of the studies (n=16) were published in the last 5 years (2009-2013); the remaining 17 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (5,495 intervention arm, 4,544 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.2119 (-0.2892, -0.1346)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.993). This body of evidence was not downgraded for suspected publication bias.

[7] The 18 studies are:[68,70-74,76,79,81,83,87,92,93,96-98,100,103] Immediate post assessment for all but 1 study; for this one exception the data point closest to the immediate post and ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome 15 studies (83%) were rated as unclear risk and 3 studies (17%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (44%), allocation concealment (67%), and blinding of participants and/or personnel (11%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (89%), incomplete reporting (17%), and other sources of bias (22%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is moderate [Chi^2=61.67, df=23 (p<0.00001); I^2=63%] the direction of the effect is consistent across most studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[10] Across the 18 studies, 16 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=15) included mixed gender samples; 1 included only men. In 7 studies (39%) the participants had a high risk of CVD. In terms of intervention focus, 2 were diet, 3 were exercise, 6 were diet plus exercise, and 7 were lifestyle. Control

participants received usual care from their physicians or no intervention; in 4 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 11 studies and more than 12 months in 7 studies. One study was conducted in Canada, 7 in the US, 8 in European countries, and 2 in Australia. Most of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 3 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (2,613 intervention arm, 1,669 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.1047 (-0.1824, -0.270)]. This body of evidence was not downgraded for imprecision.

[12] The Egger's test was conducted to detect publication bias; results were significant (p=0.000). This body of evidence was downgraded for strongly suspected publication bias.

[13] The 15 studies are:[106,108,109,111,112,114,115,117-121,123,124,131] Immediate post assessment for all but 1 study; for this one exception the data point at 12 months post baseline was selected (Hauptman[114] presents 12 month interim outcomes for a 24 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 13 studies (87%) were rated as unclear risk and 2 studies (13%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (53%), allocation concealment (80%), and blinding of participants and/or personnel (87%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (47%), and other sources of bias (80%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

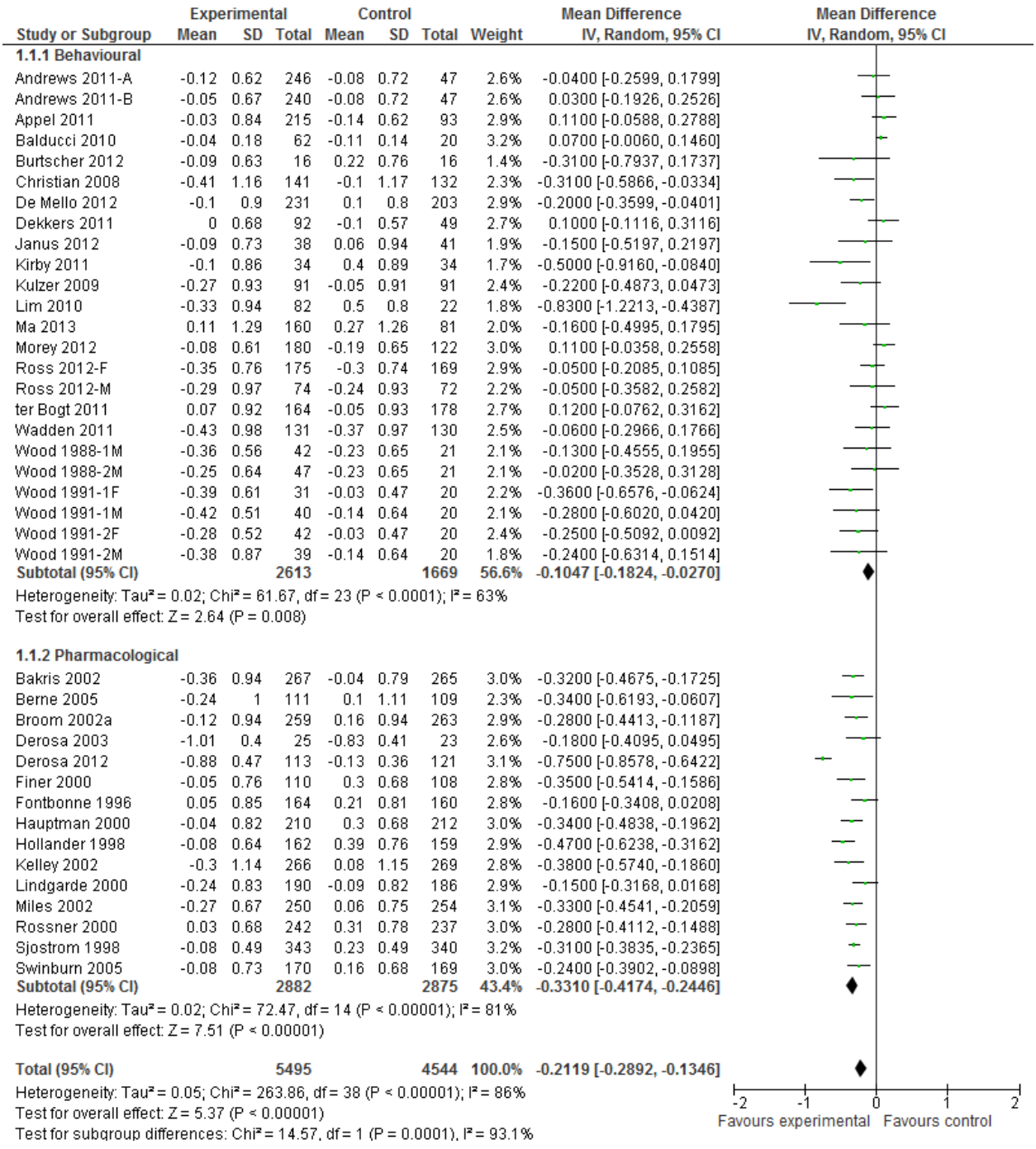
[15] Although the statistical heterogeneity is high [Chi^2=72.47, df=14 (p<0.00001); I^2=81%] the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[16] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 10 studies (67%) the participants had a high risk of CVD. In terms of intervention focus, 14 were orlistat (120 mg 3x/day) and 1 was metformin (850 mg 1x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 13 studies and more than 12 months in 2 studies. One study was conducted in Canada and the US, 4 in the US, 9 in European countries, and 1 in Australia and New Zealand. Only 1 study was published in the last 5 years (2012); the remaining 14 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

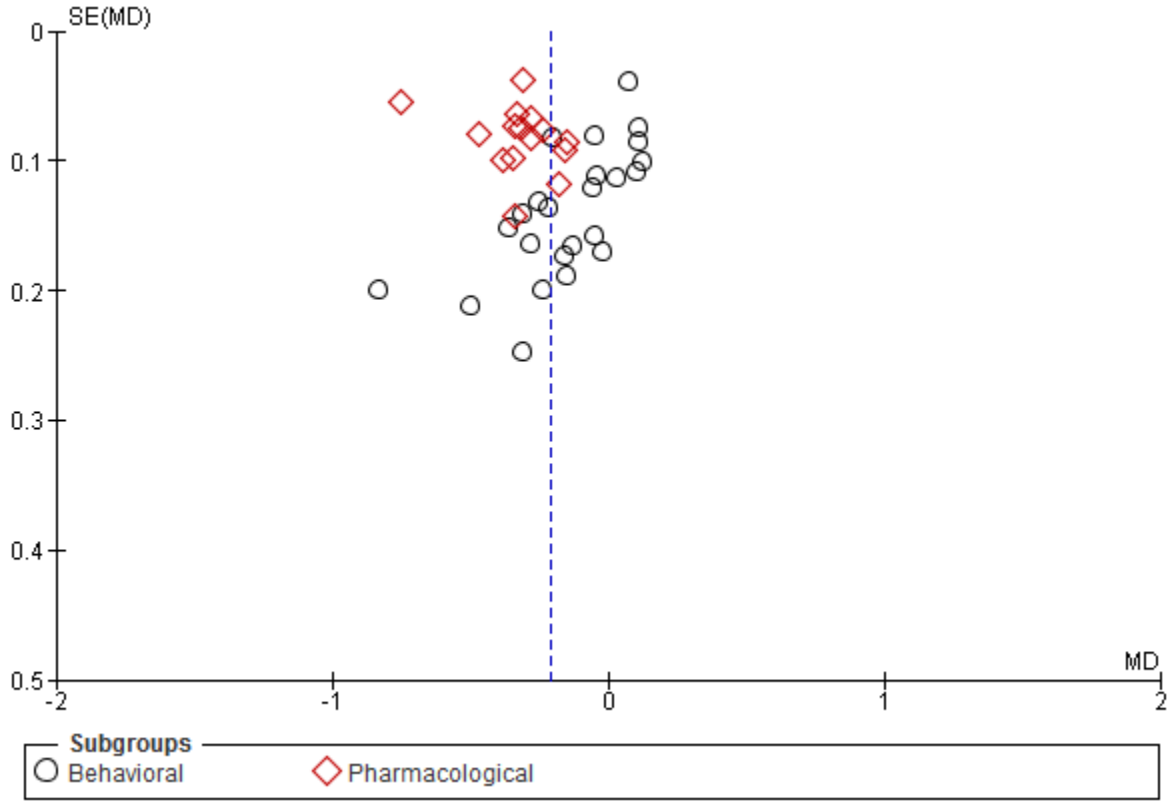
[17] The sample size is adequate (2,882 intervention arm, 2,875 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.3310 (-0.4174, -0.2446)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.401). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 6.1: Effect of Treatment Interventions on Total Cholesterol – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 6.1: Effect of Treatment Interventions on Total Cholesterol – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in Total Cholesterol - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.993
Behavioural Interventions	0.000*
Pharmacological plus Behavioural Interventions	0.401

* Significant $p \leq 0.05$

Evidence Set 7: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in LDL-C)?

- Summary of Change in LDL-C Evidence
- GRADE Evidence Profile Table 7.1: Effect of Treatment Interventions on LDL-C
- GRADE Summary of Findings Table 7.1: Effect of Treatment Interventions on LDL-C
- Forest Plot 7.1: Effect of Treatment Interventions on LDL-C – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 7.1: Effect of Treatment Interventions on LDL-C – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in LDL-C Evidence

Overall

- 30 studies; 9,313 participants
- Statistically significant reduction in LDL-C level in the intervention group as compared to the control group [MD (95% CI) -0.21 mmol/L (-0.29, -0.12)]
- High heterogeneity across studies [Chi^2=350.80, df=35 (P<0.00001), I^2=90%]

Test for subgroup differences is not significant [Chi^2=2.51, df=1 (P=0.11), I^2=60.1%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 15 studies; 3,556 participants
- Statistically significant reduction in LDL-C level in the intervention group as compared to the control group [MD (95% CI) -0.14 mmol/L (-0.29, -0.00)]
- High heterogeneity across studies [Chi^2=195.76, df=20 (P<0.00001), I^2=90%]

Pharmacological plus Behavioural Interventions

- 15 studies; 5,757 participants
- Statistically significant reduction in LDL-C level in the intervention group as compared to the control group [MD (95% CI) -0.28 mmol/L (-0.38, -0.19)]
- High heterogeneity across studies [Chi^2=130.12, df=14 (P<0.00001), I^2=89%]

GRADE Evidence Profile Table 7.1: Effect of Treatment Interventions on LDL-C

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in LDL-C (mmol/L): Overall (Better indicated by lower values)											
30	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	reporting bias[6]	5,095	4,218	0.2052 lower (0.2881 to 0.1224 lower)	⊕⊕OO LOW	CRITICAL
Change in LDL-C (mmol/L): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
15	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	2,213	1,343	0.1442 lower (0.2860 to 0.0023 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in LDL-C (mmol/L): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
15	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	2,882	2,875	0.2829 lower (0.3796 to 0.1862 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 7.1: Effect of Treatment Interventions on LDL-C

Outcome: Change in LDL–C (mmol/L)	Compared to the control group, the mean reduction in LDL-C level (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**0.2052 lower** (0.2881 to 0.1224 lower)	9,313 (30 studies[1])	⊕⊕⊖⊖ **low**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**0.1442 lower** (0.2860 to 0.0023 lower)	3,556 (15 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**0.2829 lower** (0.3796 to 0.1862 lower)	5,757 (15 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on LDL-C

[1] The 30 studies are:[70-74,76,79,81,83,92,93,95-97,103,106,108,109,111,112,114,115,117-121,123,124,131] Immediate post assessment for all but 1 study; for this one exception the data point at 12 months post baseline was selected (Hauptman[114] presents 12 month interim outcomes for a 24 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 25 studies (83%) were rated as unclear risk and 5 studies (17%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (43%), allocation concealment (73%), and blinding of participants and/or personnel (50%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (43%), incomplete reporting (30%), and other sources of bias (47%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=350.80, df=35 (p<0.00001); I^2=90%] the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=2.51, df=1 (p=0.11), I^2=60%). The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 30 studies, 28 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=29) included mixed gender samples; 1 included only men. In 17 studies (57%) the participants had a high risk of CVD. In terms of intervention focus, half of the studies (n=15) were behavioural (2 diet, 2 exercise, 5 diet plus exercise, 6 lifestyle), and the other half (n=15) were pharmacological plus behavioural [14 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)]. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 22 studies and more than 12 months in 8 studies. One study was conducted in Canada, 1 in Canada and the US, 12 in the US, 13 in European countries, and 3 in Australia and/or New Zealand. About half of the studies (n=13) were published in the last 5 years (2010-2013); the remaining 17 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (5,095 intervention arm, 4,218 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.2052 (-0.2881, -0.1224)]. This body of evidence was not downgraded for imprecision.

[6] The Egger's test was conducted to detect publication bias; results were significant (p=0.017). This body of evidence was downgraded for strongly suspected publication bias.

[7] The 15 studies are:[70-74,76,79,81,83,92,93,95-97,103] Immediate post assessment for all studies.

[8] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (80%) were rated as unclear risk and 3 studies (20%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (33%), allocation concealment (67%), and blinding of participants and/or personnel (13%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (87%), incomplete reporting (13%), and other sources of bias (13%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is high [Chi^2=195.76, df=20 (p<0.00001); I^2=90%] the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 15 studies, 13 included adults aged 18-64 years, and 2 included adults 65 years and older. Most studies (n=14) included mixed gender samples; 1 included only men. In 7 studies (47%) the participants had a high risk of CVD. In terms of intervention focus, 2 were diet, 2 were exercise, 5 were diet plus exercise, and 6 were lifestyle. Control

participants received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 9 studies and more than 12 months in 6 studies. One study was conducted in Canada, 8 in the US, 4 in European countries, and 2 in Australia. Most of the studies (n=12) were published in the last 5 years (2010-2013); the remaining 3 studies were published between 1988 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (2,213 intervention arm, 1,343 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.1442 (-0.2860, -0.0023)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.165). This body of evidence was not downgraded for suspected publication bias.

[13] The 15 studies are:[106,108,109,111,112,114,115,117-121,123,124,131] Immediate post assessment for all but 1 study; for this one exception the data point at 12 months post baseline was selected (Hauptman[114] presents 12 month interim outcomes for a 24 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 13 studies (87%) were rated as unclear risk and 2 studies (13%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (53%), allocation concealment (80%), and blinding of participants and/or personnel (87%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (47%), and other sources of bias (80%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

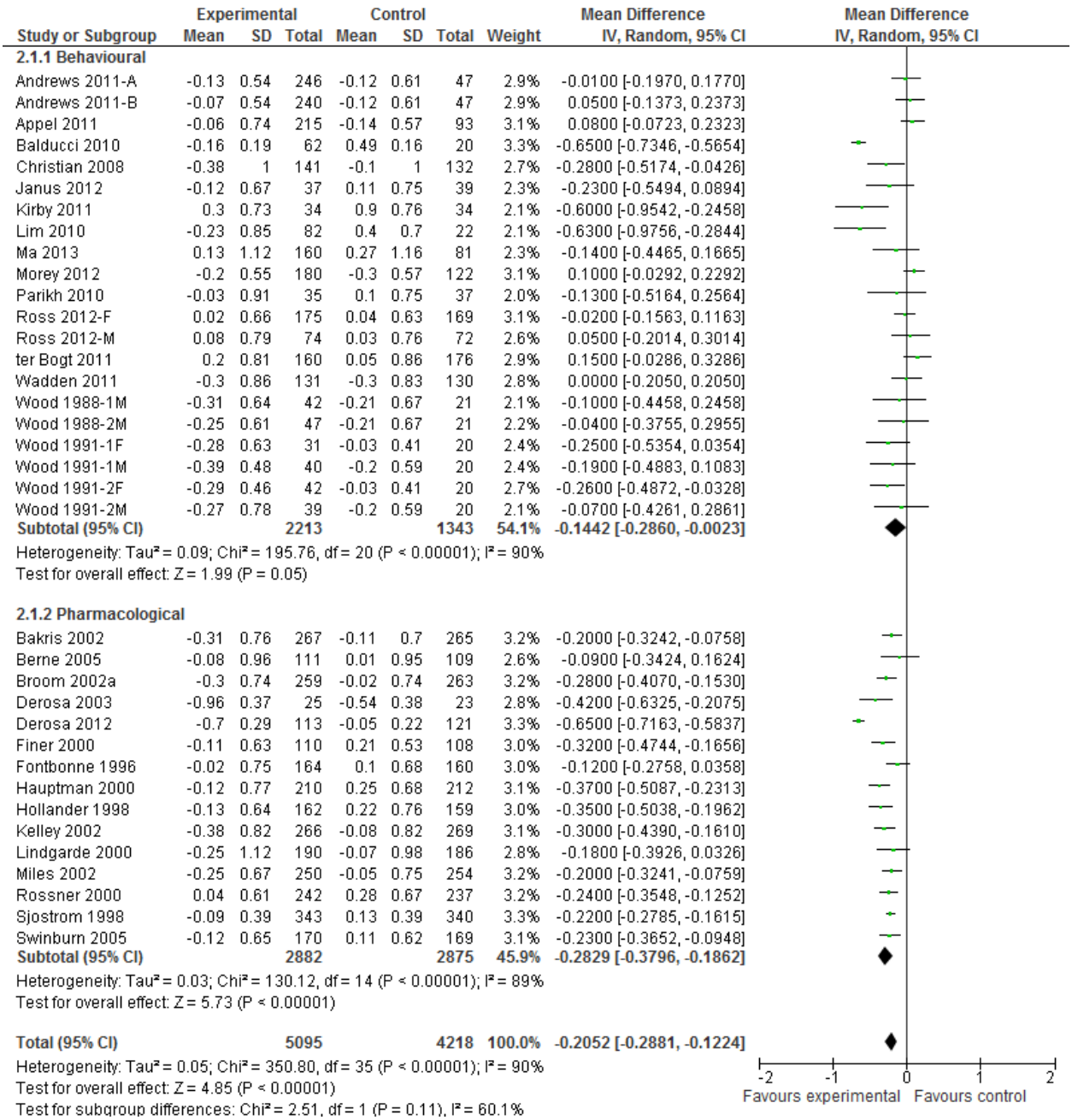
[15] Although the statistical heterogeneity is high [Chi^2=130.12, df=14 (p<0.00001); I^2=89%] the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 10 studies (67%) the participants had a high risk of CVD. In terms of intervention focus, 14 were orlistat (120 mg 3x/day) and 1 was metformin (850 mg 1x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 13 studies and more than 12 months in 2 studies. One study was conducted in Canada and the US, 4 in the US, 9 in European countries, and 1 in Australia and New Zealand. Only 1 study was published in the last 5 years (2012); the remaining 14 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

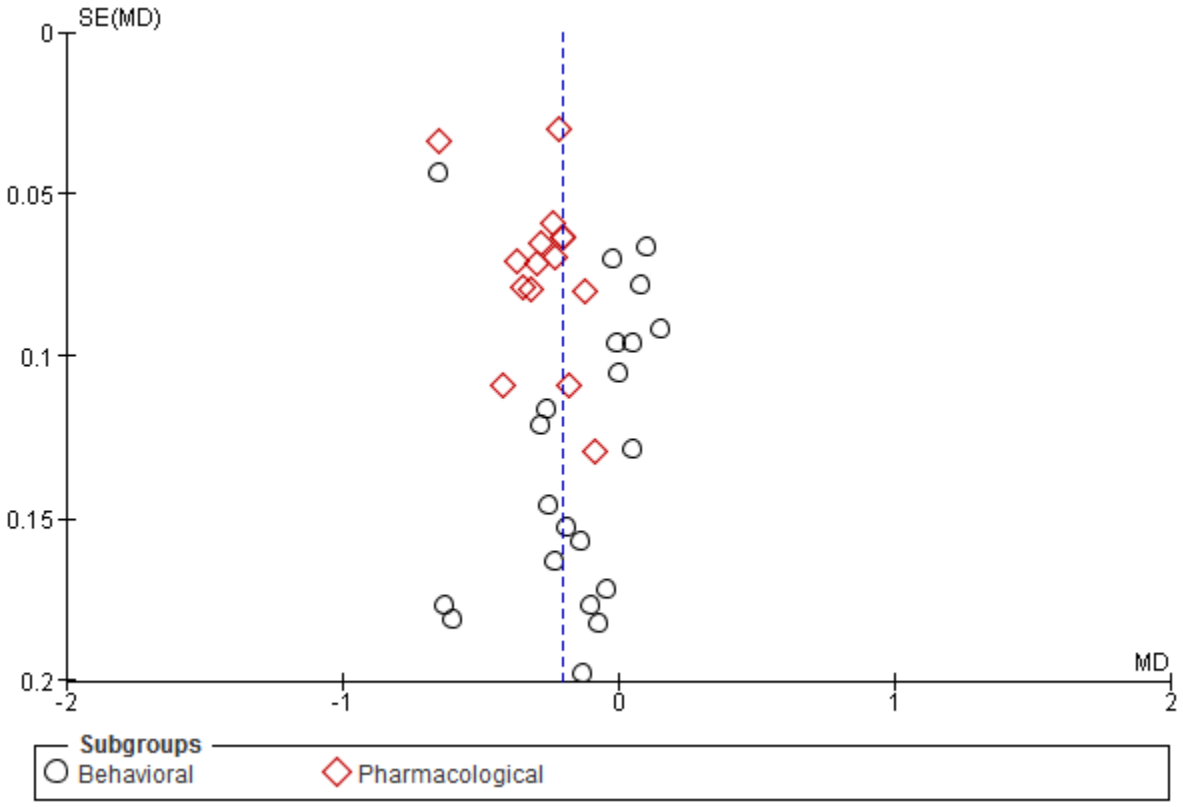
[17] The sample size is adequate (2,882 intervention arm, 2,875 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.2829 (-0.3796, -0.1862)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.219). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 7.1: Effect of Treatment Interventions on LDL-C – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 7.1: Effect of Treatment Interventions on LDL-C – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in LDL-C – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.017*
Behavioural Interventions	0.165
Pharmacological plus Behavioural Interventions	0.219

* Significant $p \leq 0.05$

Evidence Set 8: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in fasting glucose)?

- Summary of Change in Fasting Glucose Evidence
- GRADE Evidence Profile Table 8.1: Effect of Treatment Interventions on Fasting Glucose
- GRADE Summary of Findings Table 8.1: Effect of Treatment Interventions on Fasting Glucose
- Forest Plot 8.1: Effect of Treatment Interventions on Fasting Glucose – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 8.1: Effect of Treatment Interventions on Fasting Glucose – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in Fasting Glucose Evidence

Overall

- 28 studies; 12,646 participants
- Statistically significant reduction in fasting glucose level in the intervention group as compared to the control group [MD (95% CI) -0.26 mmol/L (-0.38, -0.13)]
- High heterogeneity across studies [Chi^2=789.79, df=31 (P<0.00001), I^2=96%]

Test for subgroup differences is significant [Chi^2=5.17, df=1 (P=0.02), I^2=80.7%]; primary focus of intervention does explain some of the variation across all studies

Behavioural Interventions

- 15 studies; 5,106 participants
- Statistically significant reduction in fasting glucose level in the intervention group as compared to the control group [MD (95% CI) -0.14 mmol/L (-0.23, -0.05)]
- High heterogeneity across studies [Chi^2=91.12, df=17 (P<0.00001), I^2=81%]

Pharmacological plus Behavioural Interventions

- 14 studies; 7,540 participants
- Statistically significant reduction in fasting glucose level in the intervention group as compared to the control group [MD (95% CI) -0.43 mmol/L (-0.66, -0.20)]
- High heterogeneity across studies [Chi^2=679.59, df=13 (P<0.00001), I^2=98%]

GRADE Evidence Profile Table 8.1: Effect of Treatment Interventions on Fasting Glucose

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in Fasting Glucose (mmol/L): Overall (Better indicated by lower values)											
28	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	7,381	5,265	0.2553 lower (0.3770 to 0.1335 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in Fasting Glucose (mmol/L): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
15	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	3,200	1,906	0.1402 lower (0.2328 to 0.0477 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in Fasting Glucose (mmol/L): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
14	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	4,181	3,359	0.4309 lower (0.6637 to 0.1981 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 8.1: Effect of Treatment Interventions on Fasting Glucose

Outcome: Change in Fasting Glucose (mmol/L)	Compared to the control group, the mean reduction in fasting glucose level (95% CI) in the intervention groups was	No of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**0.2553 lower** (0.3770 to 0.1335 lower)	12,646 (28 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**0.1402 lower** (0.2328 to 0.0477 lower)	5,106 (15 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**0.4309 lower** (0.6637 to 0.1981 lower)	7,540 (14 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Fasting Glucose

[1] The 28 studies are:[70-73,77,79,81,87,95-98,100,103,106,108,114-122,124,131,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Hauptman[114] presents 12 month interim outcomes for a 24 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 25 studies (89%) were rated as unclear risk and 3 studies (11%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (50%), allocation concealment (82%), and blinding of participants and/or personnel (43%); identified risks (high ratings) were primarily located in the domains of blinding of patients and/or personnel (50%), incomplete reporting (21%), and other sources of bias (57%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is high [Chi^2=789.79, df=31 (p<0.00001); I^2=96%] the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was significant [Chi^2=5.17, df=1 (p=0.02), I^2=81%). This body of evidence was not downgraded for inconsistency.

[4] Across the 28 studies, 26 included adults aged 18-64 years, and 2 included adults 65 years and older. All 28 studies included mixed gender samples. In 12 studies (43%) the participants had a high risk of CVD. In terms of intervention focus, half of the studies (n=14) were behavioural (1 diet, 2 exercise, 4 diet plus exercise, 7 lifestyle), 13 were pharmacological plus behavioural [12 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)] and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 16 studies and more than 12 months in 12 studies. One study was conducted in Canada, 1 in Canada and the US, 9 in the US, 14 in European countries, and 3 in Australia and/or New Zealand. About half of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 17 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (7,381 intervention arm, 5,265 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.2553 (-0.3770, -0.1335)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.559). This body of evidence was not downgraded for suspected publication bias.

[7] The 15 studies are:[70-73,77,79,81,87,95-98,100,103,133] Immediate post assessment for all but 2 studies; for these 2 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome 14 studies (93%) were rated as unclear risk and 1 study (7%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (40%) and, allocation concealment (80%); identified risks (high ratings) were primarily located in the domains of blinding of patients and/or personnel (93%) and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Although the statistical heterogeneity is high [Chi^2=91.12, df=17 (p<0.00001); I^2=81%] the direction of the effect is consistent across most studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[10] Across the 15 studies, 13 included adults aged 18-64 years, and 2 included adults 65 years and older. All 15 studies included mixed gender samples. In 5 studies (33%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 2 were exercise, 4 were diet plus exercise, and 8 were lifestyle. Control participants received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 7 studies and more than 12 months in 8 studies. One study was conducted in Canada, 6 in the US, 6 in European countries, and 2 in Australia. Almost all of the studies (n=14) were published in the last 5 years (2009-2013); only 1 study was published more than 5 years ago (1999). There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (3,200 intervention arm, 1,906 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.1402 (-0.2328, -0.0477)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.738). This body of evidence was not downgraded for suspected publication bias.

[13] The 14 studies are:[106,108,114-122,124,131,133] Immediate post assessment for all but 2 studies; for these 2 studies the data point at 12 months post baseline was selected (Hauptman[114] presents 12 month interim outcomes for a 24 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (86%) were rated as unclear risk and 2 studies (14%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (57%), allocation concealment (86%), and blinding of participants and/or personnel (79%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (36%), and other sources of bias (86%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

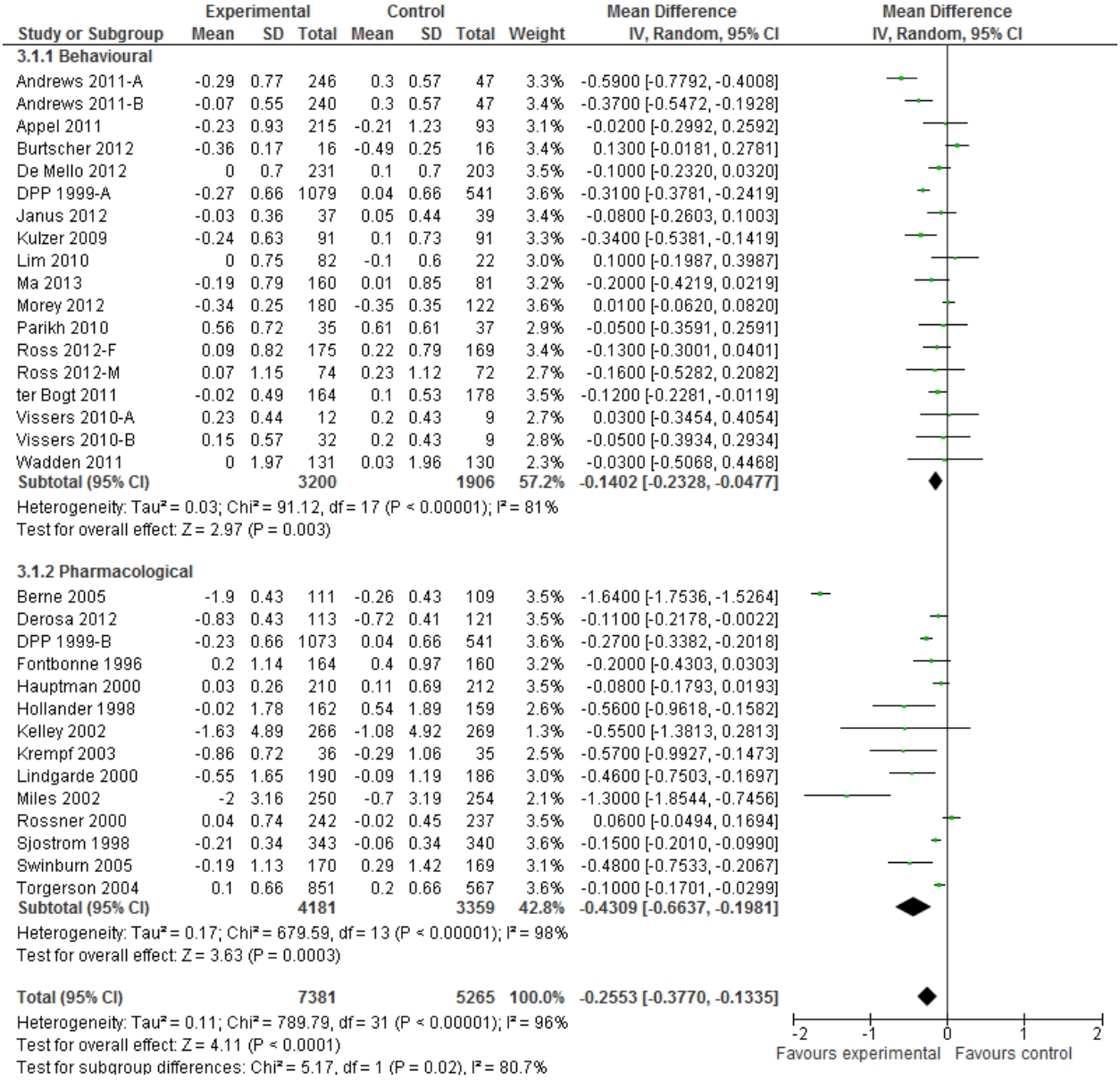
[15] Although the statistical heterogeneity is high [Chi^2=679.59, df=13 (p<0.00001); I^2=98%] the direction of the effect is consistent across most studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[16] All 14 studies included adults aged 18-64 years, and mixed gender samples. In 7 studies (50%) the participants had a high risk of CVD. Most studies (n=12) used orlistat (120 mg 3x/day) as the pharmacological plus behavioural intervention, 2 used metformin (850 mg 1x/day; 850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 9 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 4 in the US, 8 in European countries, and 1 in Australia and New Zealand. Only 1 study was published in the last 5 years (2012); the remaining 13 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

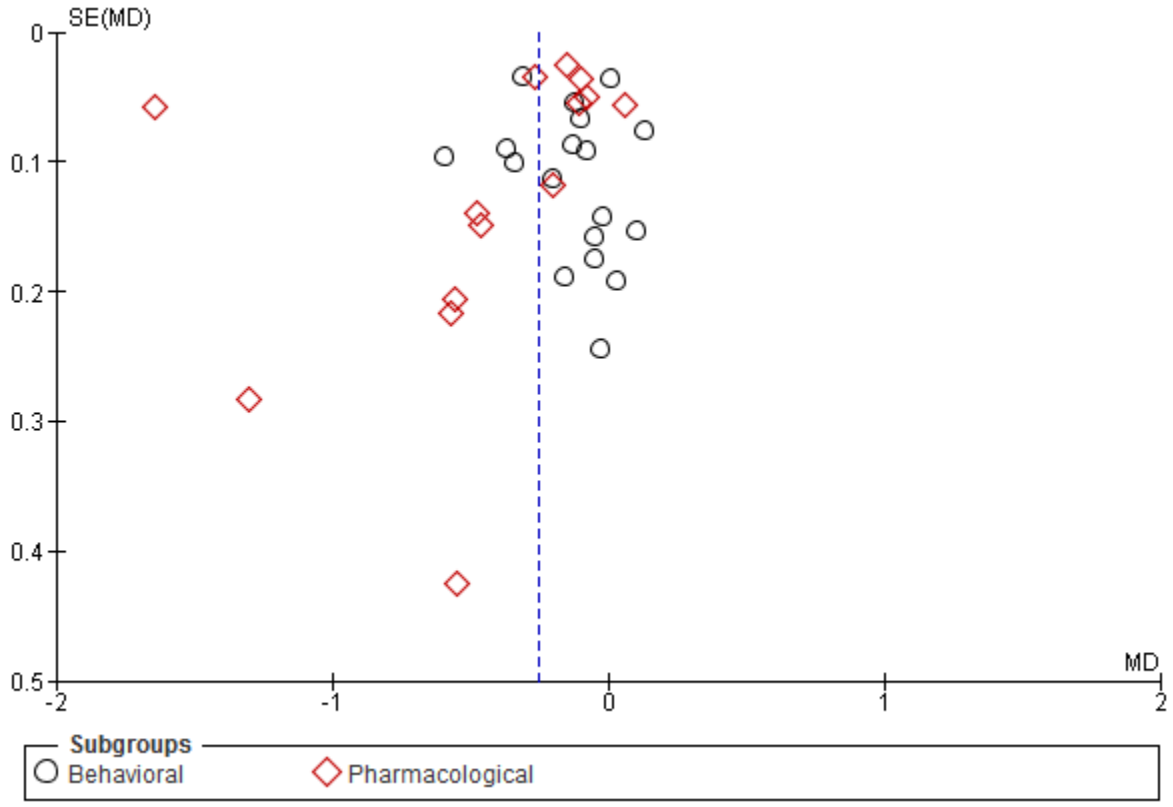
[17] The sample size is adequate (4,181 intervention arm, 3,359 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-0.4309 (-0.6637, -0.1981)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.362). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 8.1: Effect of Treatment Interventions on Fasting Glucose – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 8.1: Effect of Treatment Interventions on Fasting Glucose – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in Fasting Glucose – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.559
Behavioural Interventions	0.738
Pharmacological plus Behavioural Interventions	0.362

Evidence Set 9: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in incidence of T2D)?

- Summary of T2D Incidence Evidence
- GRADE Evidence Profile Table 9.1: Effect of Treatment Interventions on Incidence of T2D
- GRADE Summary of Findings Table 9.1: Effect of Treatment Interventions on Incidence of T2D
- Forest Plot 9.1: Effect of Treatment Interventions on Incidence of T2D – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 9.1: Effect of Treatment Interventions on Incidence of T2D – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of T2D Incidence Evidence

Overall

- 9 studies; 8,624 participants
- Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.62 (0.50, 0.77)]
- Absolute risk reduction is 5.75%
- Number needed to treat is 17 (95% CI 13, 29)
- Moderate heterogeneity across studies [Chi^2=19.51, df=9 (P=0.02), I^2=54%]

Test for subgroup differences is not significant [Chi^2=2.50, df=1 (P=0.11), I^2=60%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 7 studies; 3,198 participants
- Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.55 (0.42, 0.72)]
- Absolute risk reduction is 8.88%
- Number needed to treat is 11 (95% CI 9, 18)
- Low heterogeneity across studies [Chi^2=7.79, df=6 (P=0.25), I^2=23%]

Pharmacological plus Behavioural Interventions

- 3 studies; 5,426 participants
- Intervention participants were significantly less likely to be diagnosed with new onset T2D as compared to the control group [RR (95% CI) 0.72 (0.59, 0.87)]
- Absolute risk reduction is 3.60%
- Number needed to treat is 28 (95% CI 19, 60)
- Low heterogeneity across studies [Chi^2=2.73, df=2 (P=0.26), I^2=27%]

GRADE Evidence Profile Table 9.1: Effect of Treatment Interventions on Incidence of T2D

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARR	NNT (95% CI)		
Type 2 Diabetes Incidence: Overall														
9	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	545/4,947 (11.0168%)	557/3,677 (15.1482%)	RR 0.6207 (0.4979 to 0.7738)	57,457 fewer (from 34,265 to 76,059 fewer)	5.75%	17 (13, 29)	⊕⊕⊕O MODERATE	CRITICAL
Type 2 Diabetes Incidence: by Primary Focus of Intervention – Behavioural														
7	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	210/1,947 (10.7858%)	247/1,251 (19.7442%)	RR 0.5500 (0.4202 to 0.7198)	88,849 fewer (from 55,323 to 114,477 fewer)	8.88%	11 (9, 18)	⊕⊕⊕O MODERATE	CRITICAL
Type 2 Diabetes Incidence: by Primary Focus of Intervention – Pharmacological plus Behavioural														
3	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	335/3,000 (11.1666%)	310/2,426 (12.7782%)	RR 0.7180 (0.5925 to 0.8702)	36,035 fewer (from 16,586 to 52,071 fewer)	3.60%	28 (19, 60)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 9.1: Effect of Treatment Interventions on Incidence of T2D

Outcome: Type 2 Diabetes Incidence	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**151,482**	**94,025** (75,423 to 117,217)	**RR 0.6207** (0.4979 to 0.7738)	8,624 (9 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**197,442**	**108,593** (82,965 to 142,119)	**RR 0.5500** (0.4202 to 0.7198)	3,198 (7 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**127,782**	**91,748** (75,711 to 111,196)	**RR 0.7180** (0.5925 to 0.8702)	5,426 (3 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on Incidence of T2D

[1] The 9 studies are:[95-97,100,101,105,122,131,133] Immediate post assessment for all 9 studies (DPP[219] presents 36 month data, for other secondary outcomes 12 month interim data were extracted).

[2] Using Cochrane's Risk of Bias tool, for this outcome 8 studies (89%) were rated as unclear risk and 1 study (11%) was rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (44%) and allocation concealment (78%); identified risks (high ratings) were primarily located in the domains of blinding of patients and/or personnel (78%), selective reporting (22%), and other sources of bias (44%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Although the statistical heterogeneity is moderate [Chi^2=19.51, df=9 (p=0.02); I^2=54%] the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=2.50, df=1 (p=0.11), I^2=60%). The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 9 studies, 8 included adults aged 18-64 years, and 1 included adults 65 years and older. All 9 studies included mixed gender samples. None of the studies (0%) selected participants with a high risk of CVD. In terms of intervention focus, 6 studies were behavioural (1 diet, 1 exercise, 1 diet plus exercise, 3 lifestyle), 2 were pharmacological plus behavioural [1 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)] and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 4 studies and more than 12 months in 5 studies. Five studies were conducted in the US and 4 in European countries. Two-thirds of the studies (n=6) were published in the last 5 years (2009-2013); the remaining 3 studies were published between 1996 and 2004. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (4,947 intervention arm, 3,677 control arm), the number of events is sufficient (545 intervention arm, 557 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=0.6207 (0.4979, 0.7738)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.967). This body of evidence was not downgraded for suspected publication bias.

[7] The 7 studies are:[95-97,100,101,105,133] Immediate post assessment for all 7 studies (DPP[219] presents 36 month data, for other secondary outcomes 12 month interim data were extracted).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 7 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (43%) and allocation concealment (86%); identified risks (high ratings) were primarily located in the domains of blinding of patients and/or personnel (100%), selective reporting (29%), and other sources of bias (29%; i.e., industry funding and/or insufficient power). Given that the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is low [Chi^2=7.79, df=6 (p=0.25); I^2=23%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 7 studies, 6 included adults aged 18-64 years, and 1 included adults 65 years and older. All 7 studies included mixed gender samples. None of the studies (0%) selected participants with a high risk of CVD. In terms of intervention focus, 1 was diet, 1 was exercise, 1 was diet plus exercise and 4 were lifestyle. Control participants received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy

lifestyles). Intervention duration was 12 months or less in 3 studies and more than 12 months in 4 studies. Four studies were conducted in the US and 2 in European countries. All of the studies (n=7) were published in the last 5 years (2009-2013). There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (1,947 intervention arm, 1,251 control arm), the number of events is low (210 intervention arm, 247 control arm), and the pooled effect estimate is precise with a narrow confidence interval [RR=0.5500 (0.4202, 0.7198)]. This body of evidence was not downgraded for imprecision.

[12] There were too few studies (n<10) to assess publication bias.

[13] The 3 studies are:[122,131,133] Immediate post assessment for all 3 studies (DPP[219] presents 36 month data, for other secondary outcomes 12 month interim data were extracted).

[14] Using Cochrane's Risk of Bias tool, for this outcome 2 studies (67%) were rated as unclear risk and 1 study (33%) was rated as low risk. There was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (33%), allocation concealment (67%), blinding of participants and/or personnel (33%), incomplete reporting (33%) and selective reporting (33%); identified risks (high ratings) were primarily located in the domains of blinding of patients and/or personnel (33%) and other sources of bias (100%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

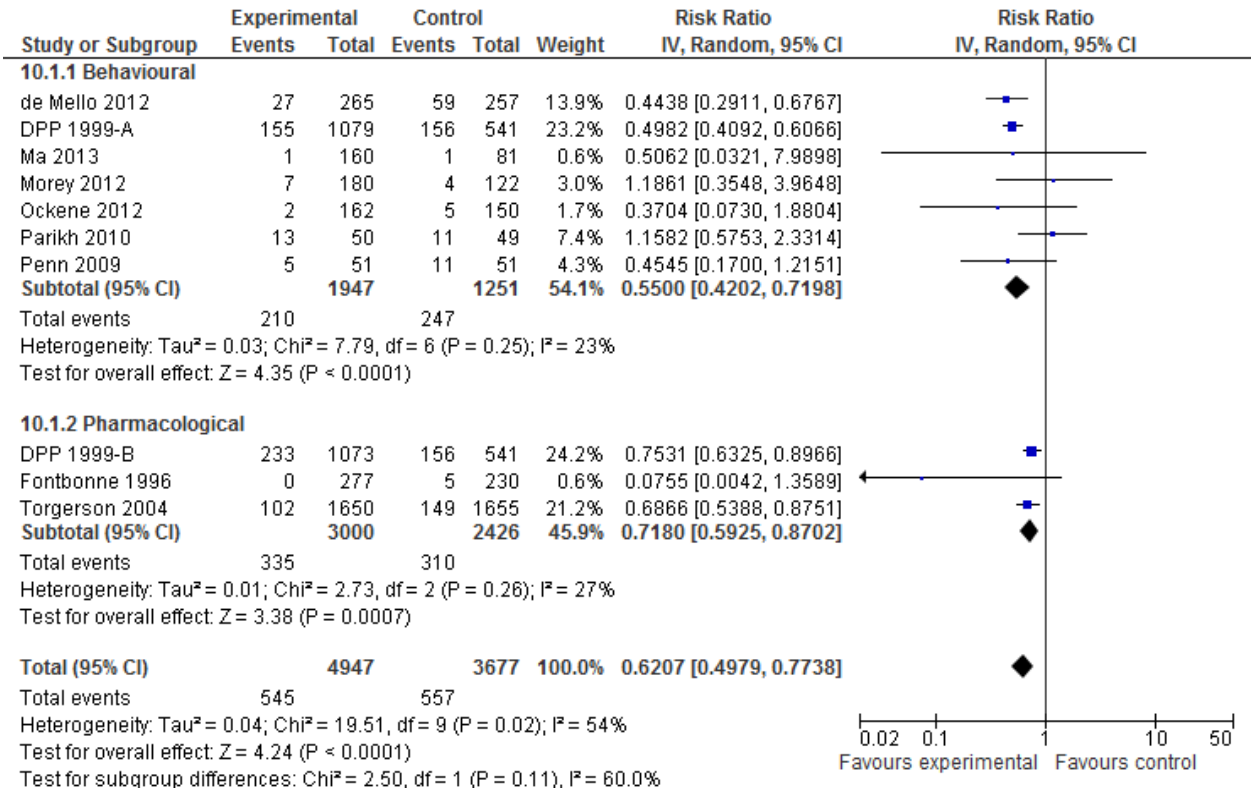
[15] Statistical heterogeneity is low [Chi^2=2.73, df=2 (p=0.26); I^2=27%], the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 3 studies included adults aged 18-64 years, and mixed gender samples. None of the studies (0%) selected participants with a high risk of CVD. One study used orlistat (120 mg 3x/day) as the pharmacological plus behavioural intervention and 2 studies used metformin (850 mg 1x/day; 850 mg 2x/day). Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 1 study and more than 12 months in 2 studies. One study was conducted in the US and 2 in European countries. All 3 studies were published more than 5 years ago (1996-2004). There were no serious concerns regarding indirectness for this body of evidence.

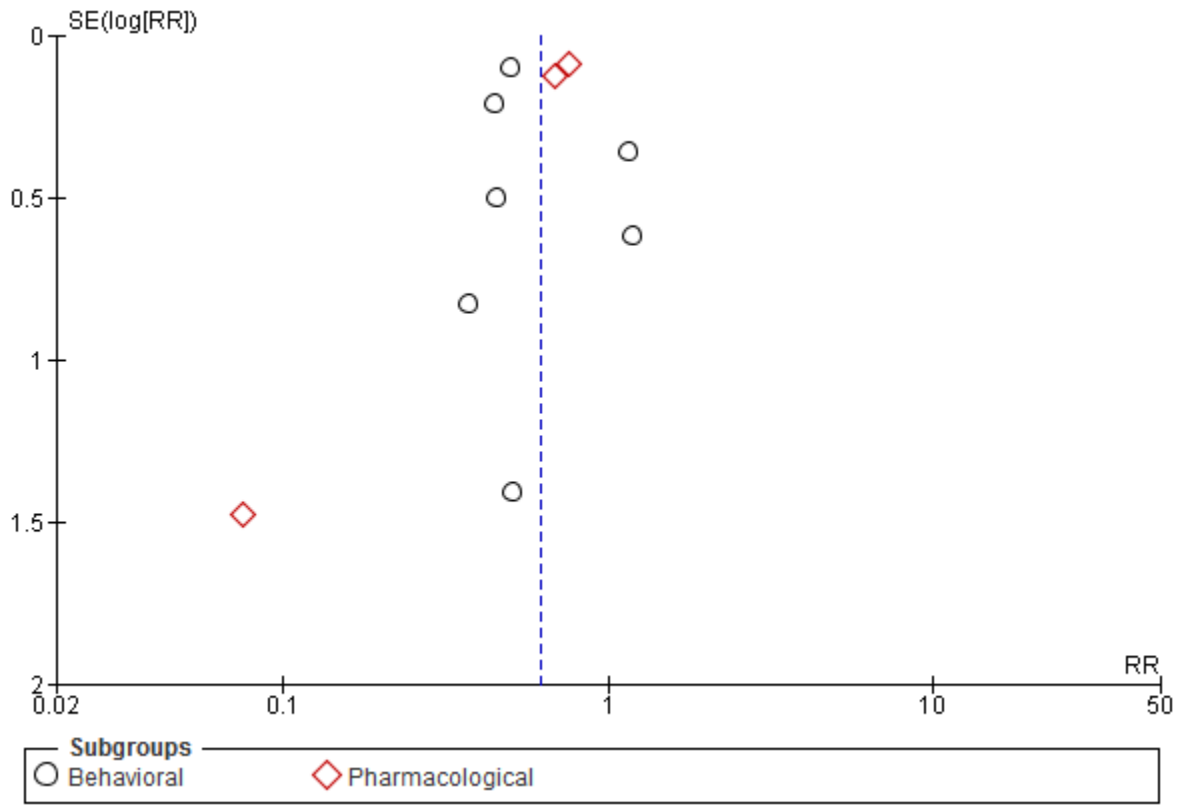
[17] The sample size is adequate (3,000 intervention arm, 2,426 control arm), the number of events is sufficient (335 intervention arm, 310 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=0.7180 (0.5925, 0.8702)]. This body of evidence was not downgraded for imprecision.

[18] There were too few studies (n<10) to assess publication bias.

Forest Plot 9.1: Effect of Treatment Interventions on Incidence of T2D – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 9.1: Effect of Treatment Interventions on Incidence of T2D – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Incidence of T2D – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.967
Behavioural Interventions	**
Pharmacological plus Behavioural Interventions	**

** Too few studies (n<10) to assess

Evidence Set 10: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in SBP)?

- Summary of Change in SBP Evidence
- GRADE Evidence Profile Table 10.1: Effect of Treatment Interventions on SBP
- GRADE Summary of Findings Table 10.1: Effect of Treatment Interventions on SBP
- Forest Plot 10.1: Effect of Treatment Interventions on SBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 10.1: Effect of Treatment Interventions on SBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in SBP Evidence

Overall

- 37 studies; 16,668 participants
- Statistically significant reduction in SBP in the intervention group as compared to the control group [MD (95% CI) -1.70 mmHg (-2.23, -1.17)]
- Moderate heterogeneity across studies [Chi^2=79.93, df=47 (P=0.002), I^2=41%]

Test for subgroup differences is not significant [Chi^2=0.01, df=1 (P=0.91), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 22 studies; 7,644 participants
- Statistically significant reduction in SBP in the intervention group as compared to the control group [MD (95% CI) -1.76 mmHg (-2.61, -0.91)]
- Moderate heterogeneity across studies [Chi^2=61.48, df=31 (P=0.0009), I^2=50%]

Pharmacological plus Behavioural Interventions

- 16 studies; 9,024 participants
- Statistically significant reduction in SBP in the intervention group as compared to the control group [MD (95% CI) -1.70 mmHg (-2.28, -1.13)]
- Low heterogeneity across studies [Chi^2=18.42, df=15 (P=0.24), I^2=19%]

GRADE Evidence Profile Table 10.1: Effect of Treatment Interventions on SBP

Quality Assessment							No. of Participants		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in SBP (mmHg): Overall (Better indicated by lower values)											
37	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	9,757	6,911	1.6962 lower (2.2265 to 1.1659 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in SBP (mmHg): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
22	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	4,618	3,026	1.7627 lower (2.6106 to 0.9149 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in SBP (mmHg): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
16	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	5,139	3,885	1.7046 lower (2.2806 to 1.1285 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 10.1: Effect of Treatment Interventions on SBP

Outcome: Change in Systolic Blood Pressure (mmHg)	Compared to the control group, the mean reduction in SBP (95% CI) in the intervention groups was	No of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**1.6962 lower** (2.2265 to 1.1659 lower)	16,668 (37 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**1.7627 lower** (2.6106 to 0.9149 lower)	7,644 (22 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**1.7046 lower** (2.2806 to 1.1285 lower)	9,024 (16 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on SBP

[1] The 37 studies are:[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,108-111,114,116-124,131,133] Immediate post assessment for all but 6 studies; for these 6 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 35 studies (95%) were rated as unclear risk and 2 studies (5%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (46%), allocation concealment (78%), blinding of participants and/or personnel (43%), and blinding of outcome assessors (73%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (51%), incomplete reporting (32%), and other sources of bias (51%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is moderate [Chi2=79.93, df=47 (p=0.002); I^2=41%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.01, df=1 (p=0.91), I^2=0%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 37 studies, 36 included adults aged 18-64 years, and 1 included adults 65 years and older. All studies included mixed gender samples. In 17 studies (46%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (1 diet, 1 exercise, 6 diet plus exercise, 13 lifestyle), 15 were pharmacological plus behavioural [14 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)], and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 6 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 22 studies and more than 12 months in 15 studies. One study was conducted in Canada, 1 in Canada and the US, 14 in the US, 17 in European countries, and 4 in Australia and/or New Zealand. Less than half of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 22 studies were published between 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (9,757 intervention arm, 6,911 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.6962 (-2.2265, -1.1659)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.615). This body of evidence was not downgraded for suspected publication bias.

[7] The 22 studies are:[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 22 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (36%), allocation concealment (73%), blinding of participants and/or personnel (14%), and blinding of outcome assessors (64%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (86%), incomplete reporting (18%), and other sources of bias (23%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is moderate [Chi^2=61.48, df=31 (p=0.0009); I^2=50%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 22 studies, 21 included adults aged 18-64 years, and 1 included adults 65 years and older. All studies included mixed gender samples. In 9 studies (41%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 1 was exercise, 6 were diet plus exercise, and 14 were lifestyle. Control participants received usual care from their physicians or no intervention; in 6 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 12 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, 8 in European countries, and 3 in Australia. Most of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 7 studies were published between 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (4,618 intervention arm, 3,026 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.7627 (-2.6106, -0.9149)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.437). This body of evidence was not downgraded for suspected publication bias.

[13] The 16 studies are:[108-111,114,116-124,131,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 14 studies (88%) were rated as unclear risk and 2 studies (12%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (56%), allocation concealment (88%), blinding of participants and/or personnel (81%), and blinding of outcome assessors (88%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (50%), and other sources of bias (88%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

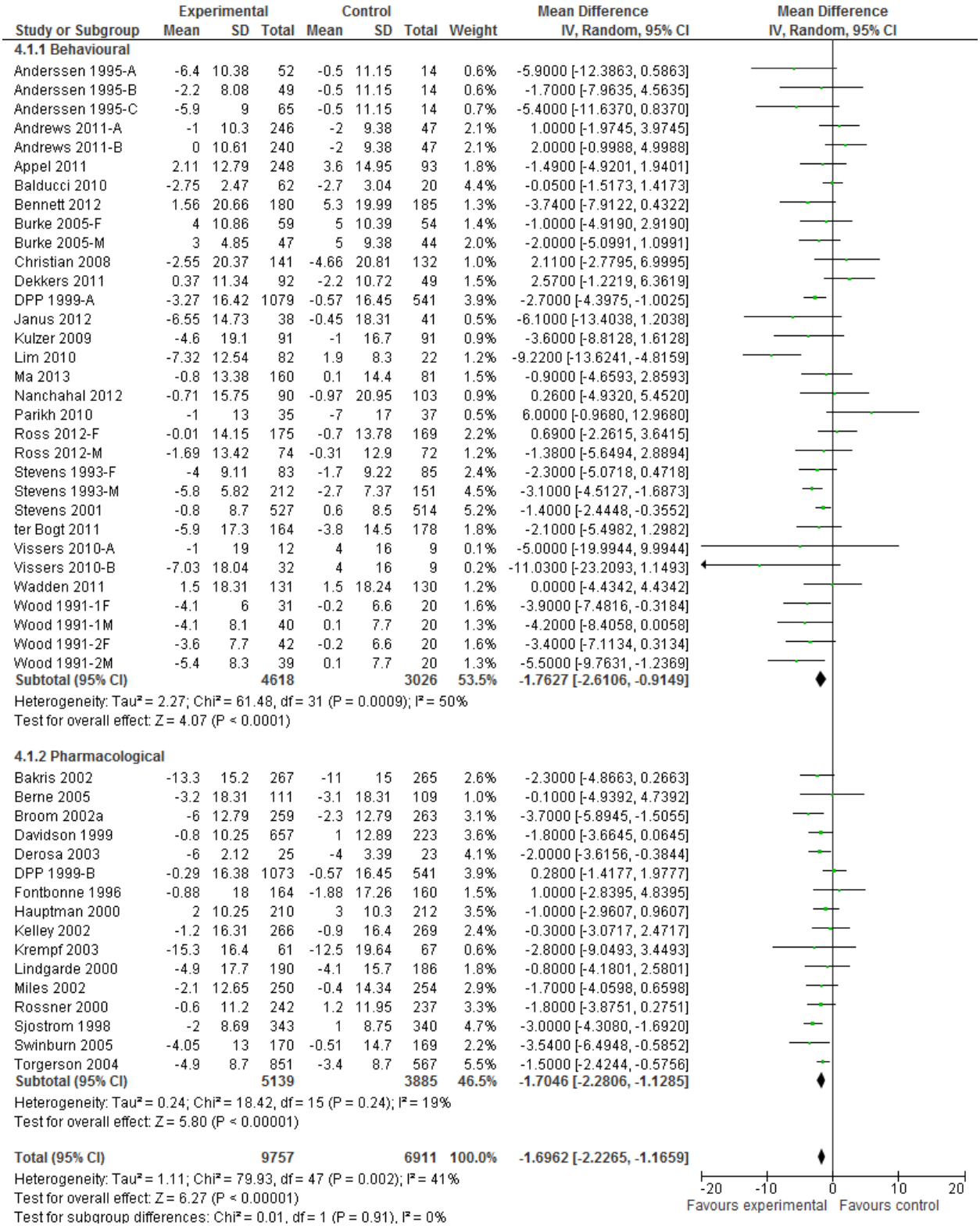
[15] Statistical heterogeneity is low [Chi^2=18.42, df=15 (p=0.24); I^2=19%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 16 studies included adults aged 18-64 years, and mixed gender samples. In 8 studies (50%) the participants had a high risk of CVD. Orlistat (120 mg 3x/day) was the pharmacological plus behavioural intervention used in 14 studies and metformin (850 mg 1x/day; 850 mg 2x/day) was used in 2 studies. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 10 studies and more than 12 months in 6 studies. One study was conducted in Canada and the US, 5 in the US, 9 in European countries, and 1 in Australia and New Zealand. None of the studies were published in the last 5 years; all 16 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

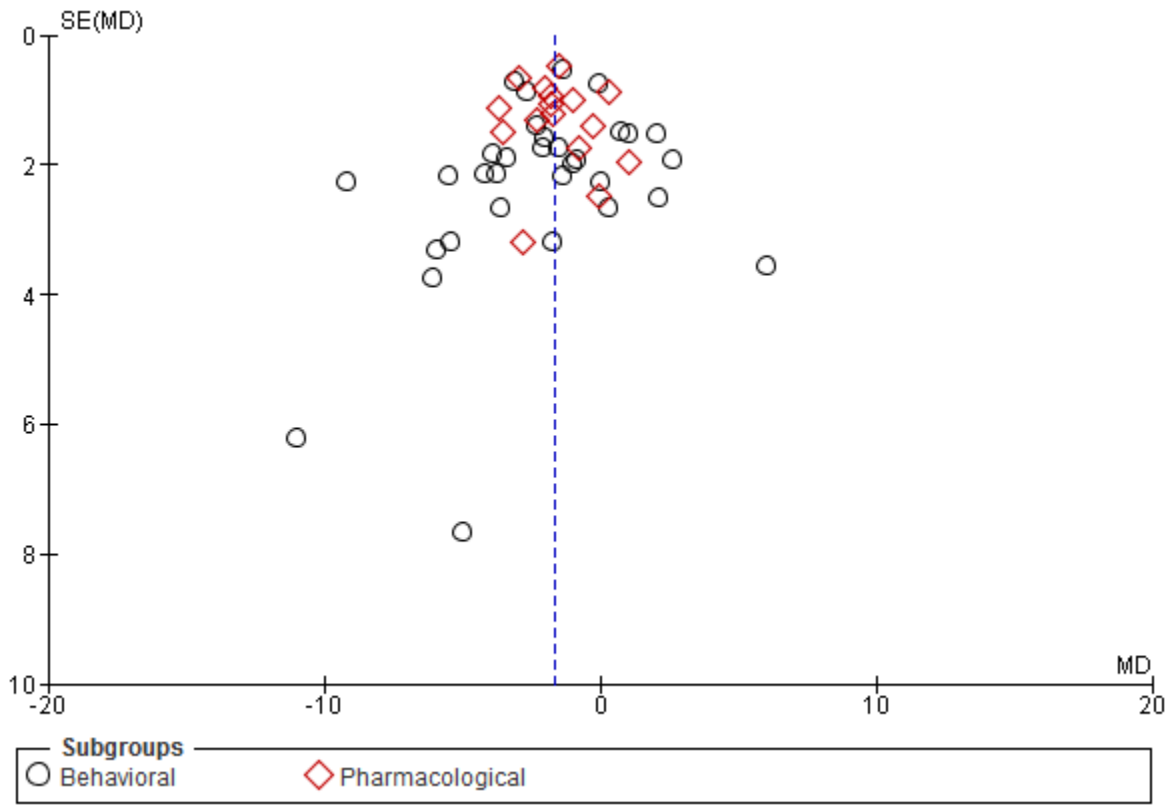
[17] The sample size is adequate (5,139 intervention arm, 3,885 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.7046 (-2.2806, -1.1285)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.680). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 10.1: Effect of Treatment Interventions on SBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 10.1: Effect of Treatment Interventions on SBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in SBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.615
Behavioural Interventions	0.437
Pharmacological plus Behavioural Interventions	0.680

Evidence Set 11: Do primary care relevant treatment interventions in overweight/obese adults lead to improved health/physiological outcomes (reduction in DBP)?

- Summary of Change in DBP Evidence
- GRADE Evidence Profile Table 11.1: Effect of Treatment Interventions on DBP
- GRADE Summary of Findings Table 11.1: Effect of Treatment Interventions on DBP
- Forest Plot 11.1: Effect of Treatment Interventions on DBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 11.1: Effect of Treatment Interventions on DBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)

Summary of Change in DBP Evidence

Overall

- 36 studies; 16,158 participants
- Statistically significant reduction in DBP in the intervention group as compared to the control group [MD (95% CI) -1.42 mmHg (-1.88, -0.96)]
- Moderate heterogeneity across studies [Chi^2=124.30, df=46 (P<0.00001), I^2=63%]

Test for subgroup differences is not significant [Chi^2=0.57, df=1 (P=0.45), I^2=0%]; primary focus of intervention does not explain variation across all studies

Behavioural Interventions

- 22 studies; 7,690 participants
- Statistically significant reduction in DBP in the intervention group as compared to the control group [MD (95% CI) -1.60 mmHg (-2.27, -0.93)]
- Moderate heterogeneity across studies [Chi^2=84.06, df=31 (P<0.00001), I^2=63%]

Pharmacological plus Behavioural Interventions

- 15 studies; 8,468 participants
- Statistically significant reduction in DBP in the intervention group as compared to the control group [MD (95% CI) -1.24 mmHg (-1.88, -0.61)]
- Moderate heterogeneity across studies [Chi^2=40.13, df=14 (P=0.0002), I^2=65%]

GRADE Evidence Profile Table 11.1: Effect of Treatment Interventions on DBP

Quality Assessment							No. of Patients		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment	Control	Mean Difference (95% CI)		
Change in DBP (mmHg): Overall (Better indicated by lower values)											
36	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	9,497	6,661	1.4209 lower (1.8831 to 0.9586 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in DBP (mmHg): by Primary Focus of Intervention - Behavioural (Better indicated by lower values)											
22	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	no serious imprecision[11]	none[12]	4,635	3,055	1.5995 lower (2.2711 to 0.9279 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in DBP (mmHg): by Primary Focus of Intervention - Pharmacological plus Behavioural (Better indicated by lower values)											
15	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	4,862	3,606	1.2423 lower (1.8786 to 0.6059 lower)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 11.1: Effect of Treatment Interventions on DBP

Outcome: Chane in Diastolic Blood Pressure (mmHg)	Compared to the control group, the mean reduction in DBP (95% CI) in the intervention groups was	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Overall	**1.4209 lower** (1.8831 to 0.9586 lower)	16,158 (36 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**1.5995 lower** (2.2711 to 0.9279 lower)	7,690 (22 studies[7])	⊕⊕⊕⊖ **moderate**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**1.2423 lower** (1.8786 to 0.6059 lower)	8,468 (15 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Effect of Treatment Interventions on DBP

[1] The 36 studies are:[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,108-111,114,116,117,119-124,131,133] Immediate post assessment for all but 6 studies; for these 6 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[2] Using Cochrane's Risk of Bias tool, for this outcome 34 studies (94%) were rated as unclear risk and 2 studies (6%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (44%), allocation concealment (78%), blinding of participants and/or personnel (42%), and blinding of outcome assessors (72%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (53%), incomplete reporting (31%), and other sources of bias (47%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is moderate [Chi^2=124.30, df=46 (p<0.00001); I^2=63%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.57, df=1 (p=0.45), I^2=0%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] Across the 36 studies, 35 included adults aged 18-64 years, and 1 included adults 65 years and older. All studies included mixed gender samples. In 16 studies (44%) the participants had a high risk of CVD. In terms of intervention focus, 21 were behavioural (1 diet, 1 exercise, 6 diet plus exercise, 13 lifestyle), 14 were pharmacological plus behavioural [13 orlistat (120 mg 3x/day), 1 metformin (850 mg 1x/day)], and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin: 850 mg 2x/day) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 6 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 21 studies and more than 12 months in 15 studies. One study was conducted in Canada, 14 in the US, 17 in European countries, and 4 in Australia and/or New Zealand. Less than half of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 21 studies were published between 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (9,497 intervention arm, 6,661 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.4209 (-1.8831, -0.9586)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.105). This body of evidence was not downgraded for suspected publication bias.

[7] The 22 studies are:[68,70-73,76-79,81-84,87,90,92,93,95,97,103,104,133] Immediate post assessment for all but 4 studies; for these 4 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Dekkers[68] provides 18 month follow-up data post completion of a 6 month intervention; Vissers[77] provides 6 month follow-up data post completion of a 6 month intervention; Burke[84] provides 12 month follow-up data post completion of a 4 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 22 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (36%), allocation concealment (73%), blinding of participants and/or personnel (14%), and blinding of outcome assessors (64%); identified risks (high ratings) were primarily located in the domains of blinding of participants and personnel (86%), incomplete reporting (18%), and other sources of bias (23%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is moderate [Chi2=84.06, df=31 (p<0.00001); I2=63%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[10] Across the 22 studies, 21 included adults aged 18-64 years, and 1 included adults 65 years and older. All studies included mixed gender samples. In 9 studies (41%) the participants had a high risk of CVD. In terms of intervention focus, 1 was diet, 1 was exercise, 6 were diet plus exercise, and 14 were lifestyle. Control participants received usual care from their physicians or no intervention; in 6 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 12 studies and more than 12 months in 10 studies. One study was conducted in Canada, 10 in the US, 8 in European countries, and 3 in Australia. Most of the studies (n=15) were published in the last 5 years (2009-2013); the remaining 7 studies were published between 1991 and 2008. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (4,635 intervention arm, 3,055 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.5995 (-2.2711, -0.9279)]. This body of evidence was not downgraded for imprecision.

[12] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.087). This body of evidence was not downgraded for suspected publication bias.

[13] The 15 studies are:[108-111,114,116,117,119-124,131,133] Immediate post assessment for all but 3 studies; for these 3 studies the data point closest to the immediate post and/or ≥ 12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions; DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[14] Using Cochrane's Risk of Bias tool, for this outcome 13 studies (87%) were rated as unclear risk and 2 studies (13%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (53%), allocation concealment (87%), blinding of participants and/or personnel (80%), and blinding of outcome assessors (87%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (47%), and other sources of bias (87%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

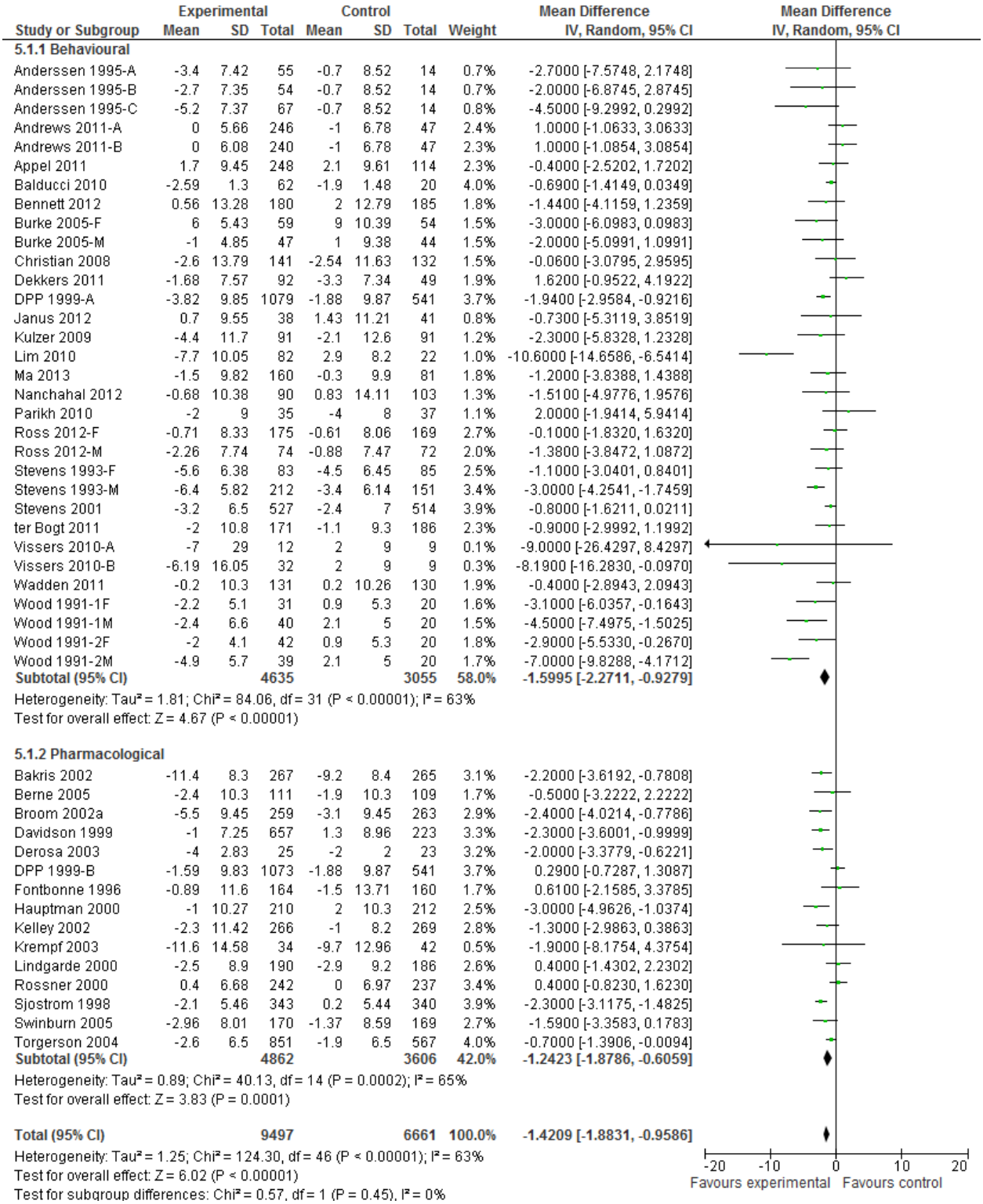
[15] Statistical heterogeneity is moderate [Chi^2=40.13, df=14 (p=0.0002); I^2=65%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 7 studies (47%) the participants had a high risk of CVD. Orlistat (120 mg 3x/day) was the pharmacological plus behavioural intervention used in 13 studies and metformin (850 mg 1x/day; 850 mg 2x/day) was used in 2 studies. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 9 studies and more than 12 months in 6 studies. Five studies were conducted in the US, 9 in European countries, and 1 in Australia and New Zealand. None of the studies were published in the last 5 years; all 15 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

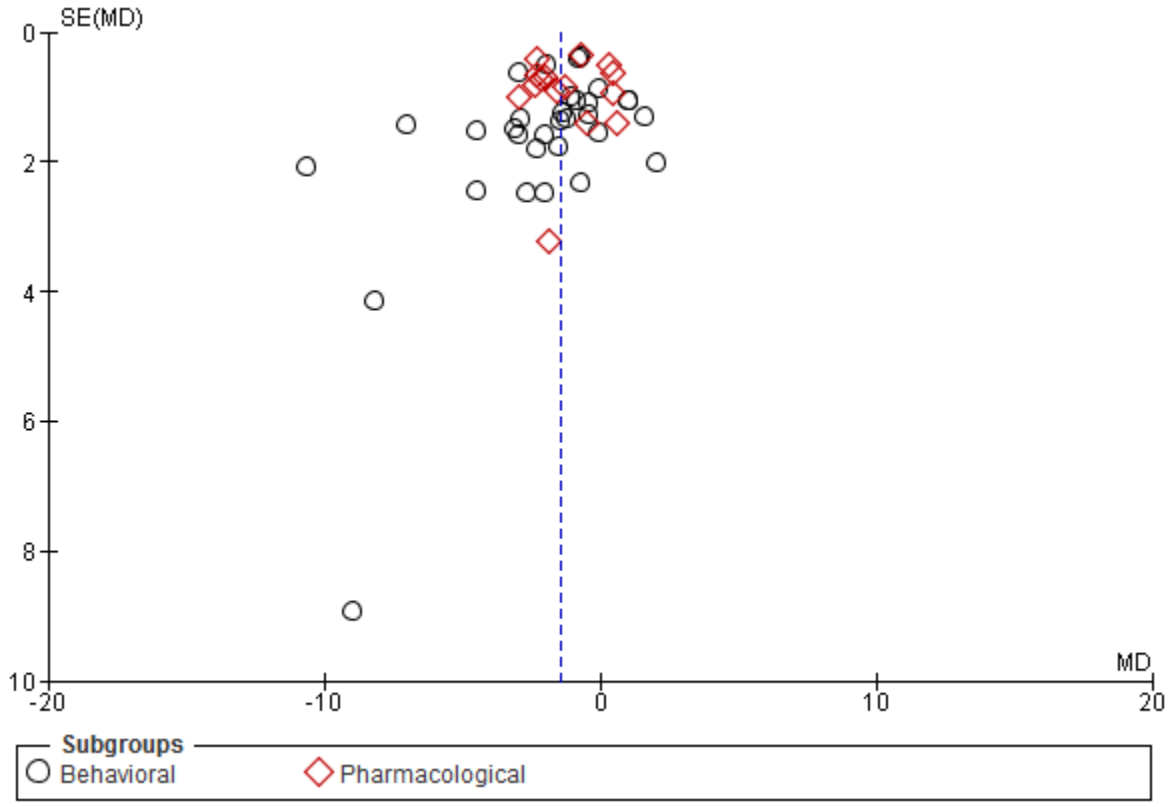
[17] The sample size is adequate (4,862 intervention arm, 3,606 control arm) and the pooled effect estimate is precise with a narrow confidence interval [MD=-1.2423 (-1.8786, -0.6059)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.841). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 11.1: Effect of Treatment Interventions on DBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 11.1: Effect of Treatment Interventions on DBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Egger's Test to Detect Publication Bias: Change in DBP – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.105
Behavioural Interventions	0.087
Pharmacological plus Behavioural Interventions	0.841

Evidence Set 12: What are the adverse effects of primary care-relevant treatment interventions on overweight/obese adults (any adverse events)?

- Summary of Any Adverse Events Evidence
- GRADE Evidence Profile Table 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events
- GRADE Summary of Findings Table 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events
- Forest Plot 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)
- Forest Plot 12.2: Adverse Effects of Treatment Interventions – Any Adverse Events – by Participants' Baseline CVD Risk Status (High Risk, Low/Unknown Risk)

Summary of Any Adverse Events Evidence

Overall

- 17 studies; 5,512 participants
- Intervention participants were significantly more likely to experience adverse events as compared to the control group [RR (95% CI) 1.16 (1.09, 1.23)]
- Absolute risk increase is 9.31%
- Number needed to harm is 11 (95% CI 7, 19)
- High heterogeneity across studies [Chi^2=59.40, df=16 (P<0.00001), I^2=73%]

Test for subgroup differences is significant [Chi^2=3.84, df=1 (P=0.05), I^2=74.0%]; primary focus of intervention does explain some of the variation across all studies

Behavioural Interventions

- 3 studies; 561 participants
- No statistically significant difference between the intervention and control group in terms of likelihood of experiencing adverse events [RR (95% CI) 0.19 (0.03, 1.16)]
- Low heterogeneity across studies [Chi^2=0.67, df=2 (P=0.41), I^2=0%]

Pharmacological plus Behavioural Interventions

- 15 studies; 4,951 participants
- Intervention participants were significantly more likely to experience adverse events as compared to the control group [RR (95% CI) 1.16 (1.09, 1.23)]
- Absolute risk increase is 10.36%
- Number needed to harm is 10 (95% CI 7, 17)
- High heterogeneity across studies [Chi^2=55.03, df=14 (P<0.00001), I^2=75%]
- Test for subgroup differences was significant for participants' baseline CVD risk status [Chi^2=4.38, df=1 (P=0.04), I^2=77.1%]

GRADE Evidence Profile Table 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARI	NNH (95% CI)		
Any Adverse Events: Overall														
17	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	1,891/2,802 (67.4875%)	1,610/2,710 (59.4096%)	RR 1.1567 (1.0888 to 1.2288)	93,095 more (from 52,756 more to 135,929 more)	9.31%	11 (7, 19)	⊕⊕⊕O MODERATE	CRITICAL
Any Adverse Events: by Primary Focus of Intervention – Behavioural														
3	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	serious imprecision[11]	none[12]	1/301 (0.3322%)	6/260 (2.3077%)	RR 0.1933 (0.0323 to 1.1576)	18,616 fewer (from 22,332 fewer to 3,637 more)	-	-	⊕⊕OO LOW	CRITICAL
Any Adverse Events: by Primary Focus of Intervention - Pharmacological plus Behavioural														
15	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	1,890/2,501 (75.5698%)	1,604/2,450 (65.4694%)	RR 1.1583 (1.0916 to 1.2290)	103,638 more (from 59,970 more to 149,925 more)	10.36%	10 (7, 17)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events

Outcome: Any Adverse Events	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**594,096**	**687,191** (646,852 to 730,025)	**RR 1.1567** (1.0888 to 1.2288)	5,512 (17 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**23,077**	**4,461** (745 to 26,714)	**RR 0.1933** (0.0323 to 1.1576)	561 (3 studies[7])	⊕⊕⊖⊖ **low**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**654,694**	**758,332** (714,664 to 804,619)	**RR 1.1583** (1.0916 to 1.2290	4,951 (15 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Adverse Effects of Treatment – Any Adverse Events

[1] The 17 studies are:[75,78,107,108,111,113,116,120,121,123,125-127,129-132] Immediate post assessment for all studies. Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. Adverse events were assessed/reported at 3, 4 or 6 months in 7 of the studies included for this outcome.[107,125-127,129,130,132]

[2] Using Cochrane's Risk of Bias tool, for this outcome 15 studies (88%) were rated as unclear risk and 2 studies (12%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (53%), allocation concealment (76%), blinding of participants and/or personnel (76%), and blinding of outcome assessors (59%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (29%), and other sources of bias (76%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is moderate [Chi^2=59.40, df=16 (p<0.00001); I^2=73%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was significant [Chi^2=3.84, df=1 (p=0.05), I^2=74%]. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] All 17 studies included adults aged 18-64 years, and most studies (n=16) included mixed gender samples; 1 included only women. In 8 studies (47%) the participants had a high risk of CVD. In terms of intervention focus, 2 were behavioural (both lifestyle), 14 were pharmacological plus behavioural (12 orlistat, 2 metformin), and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 2 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 15 studies and more than 12 months in 2 studies. One study was conducted in Europe and the US, 3 in the US, 10 in European countries, 2 in Australia and/or New Zealand, and 1 in China. About one-third of the studies (n=6) were published in the last 5 years (2009-2012); the remaining 11 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (2,802 intervention arm, 2,710 control arm), the number of events is sufficient (1,891 intervention arm, 1,610 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.1567 (1.0888, 1.2288)]. This body of evidence was not downgraded for imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.148). This body of evidence was not downgraded for suspected publication bias.

[7] The 3 studies are:[75,78,132] Immediate post assessment for all studies. Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. Adverse events were assessed/reported at 3 months in 1 of the studies included for this outcome.[132]

[8] Using Cochrane's Risk of Bias tool, for this outcome all 3 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with allocation concealment (33%), blinding of participants and/or personnel (33%), and selective reporting (67%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (67%), blinding of outcome assessment (67%) incomplete reporting (33%), and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is low [Chi^2=0.67, df=1 (p=0.41); I^2=0%], the direction of the effect is consistent across studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[10] All 3 studies included adults aged 18-64 years. Two studies included mixed gender samples; 1 included only women. In 1 study (33%) the participants had a high risk of CVD. All 3 studies used lifestyle interventions. Control participants received usual care from their physicians or no intervention; in 2 of these studies control participants received a

minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was 12 months or less in 2 studies and more than 12 months in 1 study. Two studies were conducted in the US and 1 in Australia. All 3 studies were published in the last 5 years (2010-2012). There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (301 intervention arm, 260 control arm), but the number of events is very low (1 intervention arm, 6 control arm) and the pooled effect estimate is not precise with a confidence interval that includes the no effect value [RR=0.1933 (0.0323, 1.1576)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] There were too few studies (n<10) to assess publication bias.

[13] The 15 studies are:[107,108,111,113,116,120,121,123,125-127,129-132] Immediate post assessment for all studies. Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. Adverse events were assessed/reported at 3, 4 or 6 months in 7 of the studies included for this outcome.[107,125-127,129,130,132]

[14] Using Cochrane's Risk of Bias tool, for this outcome 13 studies (87%) were rated as unclear risk and 2 studies (13%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (60%), allocation concealment (80%), blinding of participants and/or personnel (87%), and blinding of outcome assessors (67%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (33%), and other sources of bias (80%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

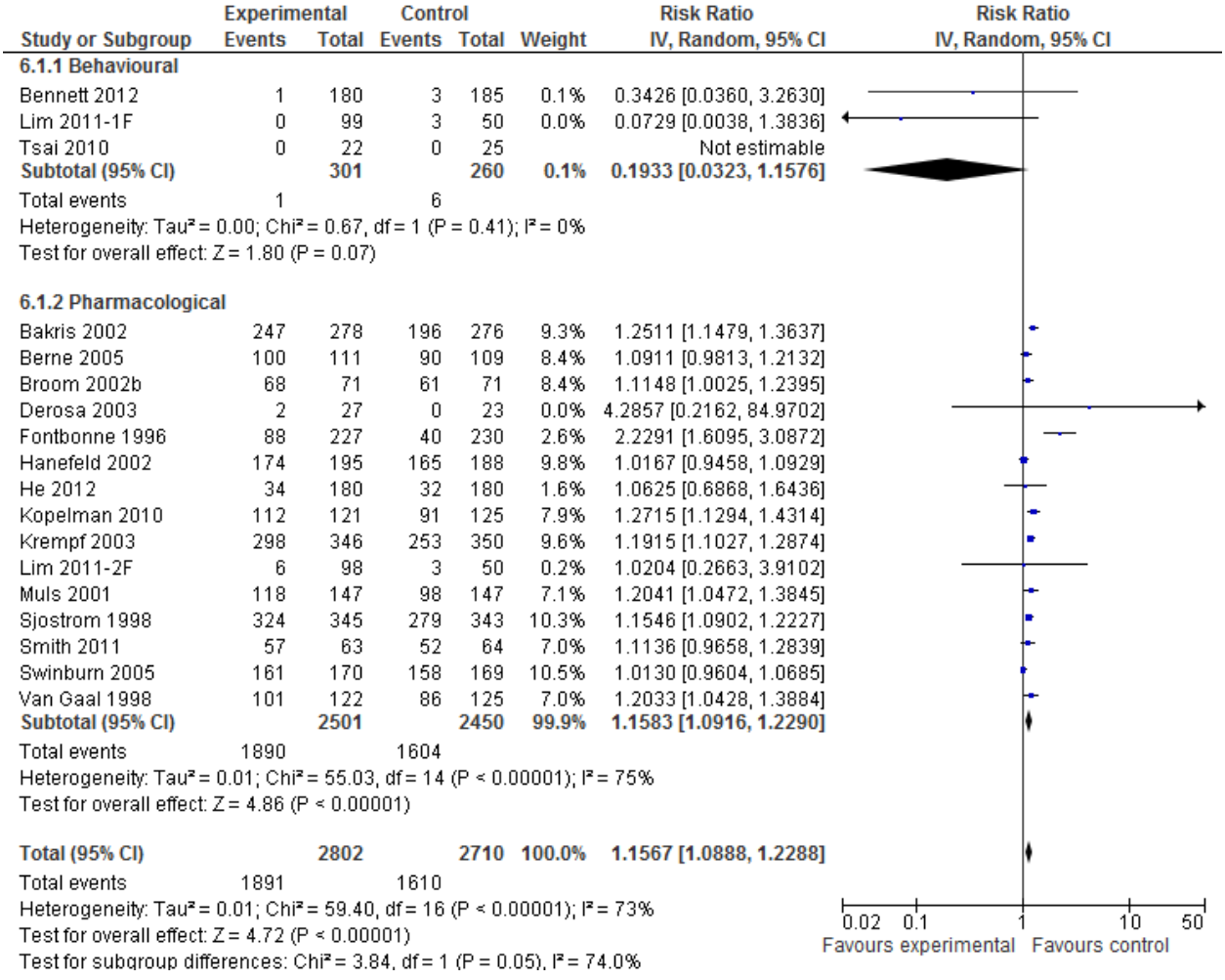
[15] Statistical heterogeneity is moderate [Chi^2=55.03, df=14 (p<0.00001); I^2=75%], the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[16] All 15 studies included adults aged 18-64 years, and mixed gender samples. In 7 studies (47%) the participants had a high risk of CVD. In terms of pharmacological plus behavioural intervention, 12 were orlistat, and 3 were metformin. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 14 studies and more than 12 months in 1 study. One study was conducted in Europe and the US, 1 in the US, 10 in European countries, 2 in Australia and/or New Zealand, and 1 in China. Four of the studies were published in the last 5 years (2009-2012); the remaining 11 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

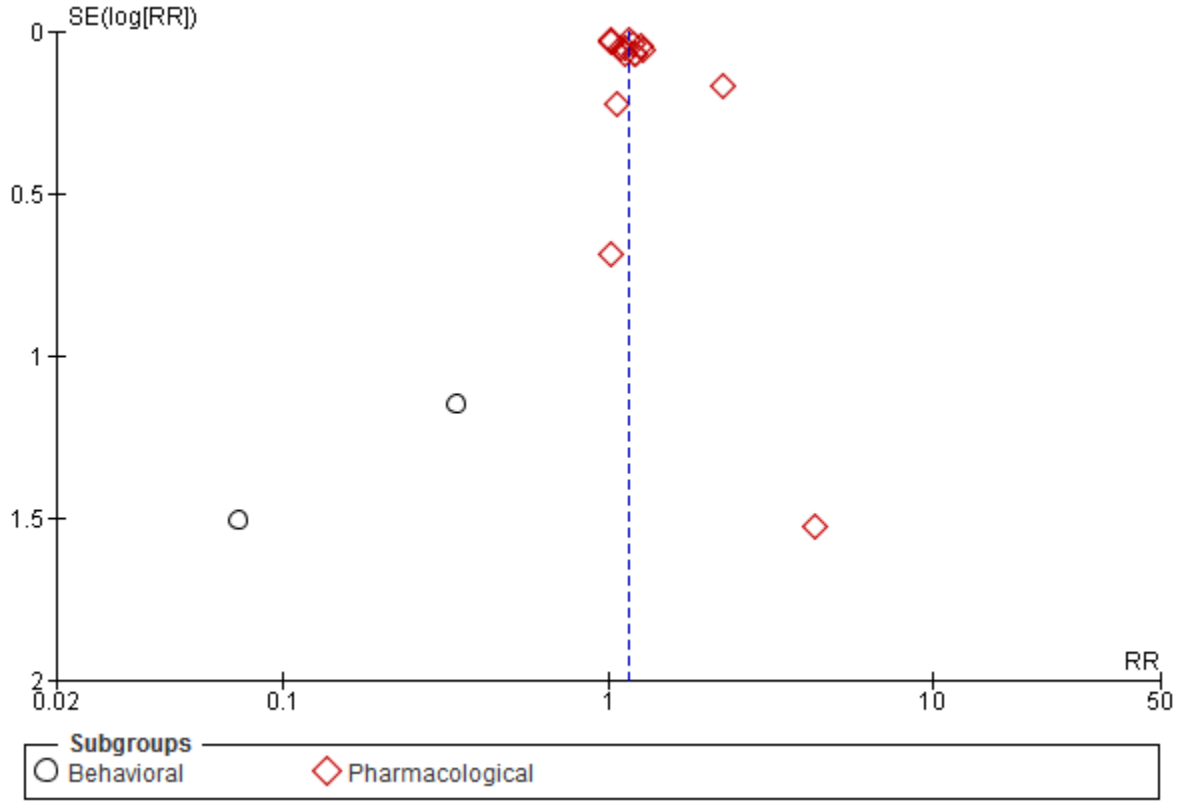
[17] The sample size is adequate (2,501 intervention arm, 2,450 control arm), the number of events is sufficient (1,890 intervention arm, 1,604 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.1583 (1.0916, 1.2290)]. This body of evidence was not downgraded for imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.053). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 12.1: Adverse Effects of Treatment Interventions – Any Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

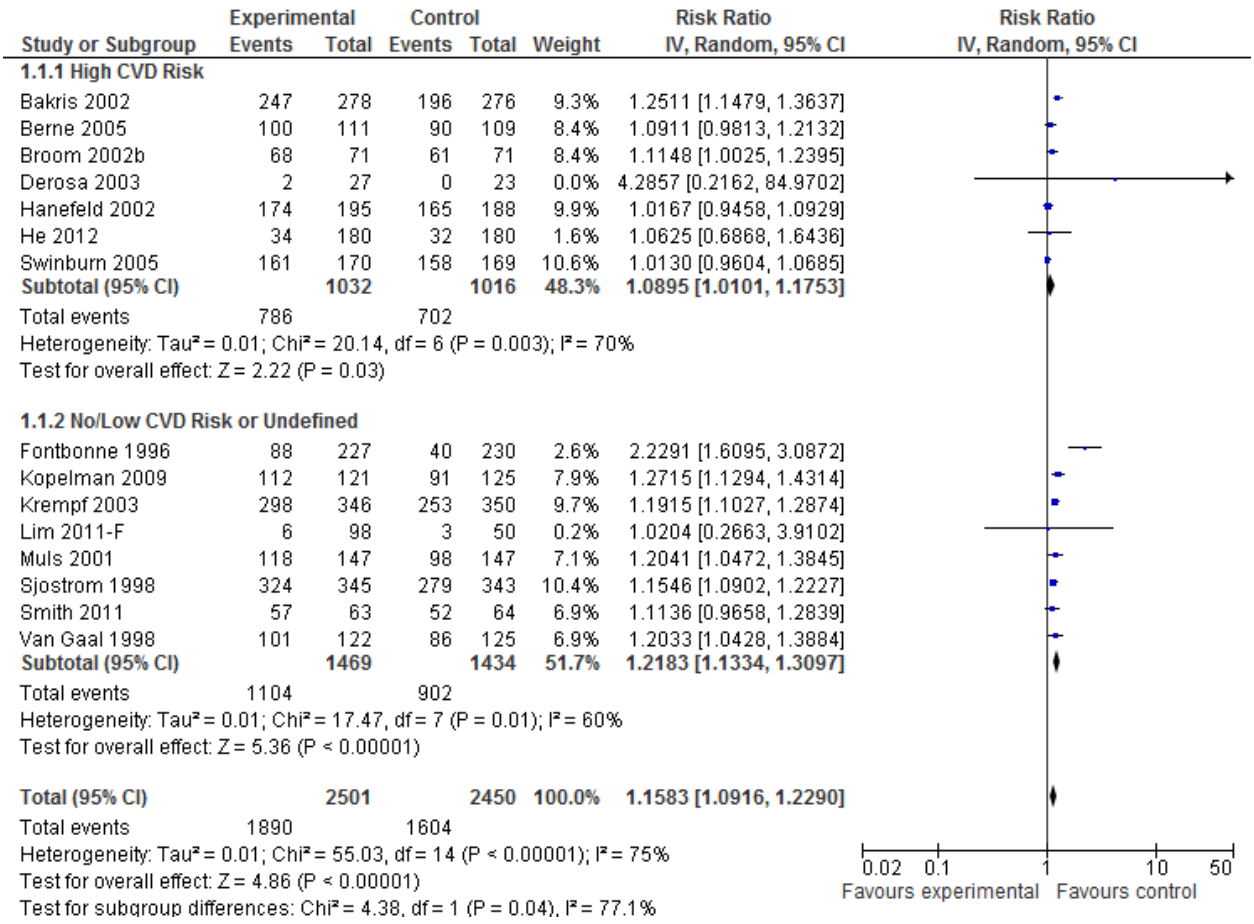


Egger's Test to Detect Publication Bias: Any Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.148
Behavioural Interventions	**
Pharmacological plus Behavioural Interventions	0.053

** Too few (n<10) to assess

Forest Plot 12.2: Adverse Effects of Treatment Interventions – Any Adverse Events – by Participants' Baseline CVD Risk Status (High, Low/Unknown)



Evidence Set 13: What are the adverse effects of primary care-relevant treatment interventions on overweight/obese adults (serious adverse events)?

- Summary of Serious Adverse Events Evidence
- GRADE Evidence Profile Table 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events
- GRADE Summary of Findings Table 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events
- Forest Plot 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)
- Forest Plot 13.2: Adverse Effects of Treatment Interventions – Serious Adverse Events –by Participants' Baseline CVD Status (High Risk, Low/Unknown Risk)

Summary of Serious Adverse Events Evidence

Overall

- 14 studies; 10,811 participants
- No statistically significant difference between the intervention and control group in terms of likelihood of experiencing serious adverse events [RR (95% CI) 1.07 (0.96, 1.20)]
- Low heterogeneity across studies [Chi^2=9.48, df=13 (P=0.74), I^2=0%]

Test for subgroup differences is not significant [Chi^2=0.60, df=1 (P=0.44), I^2=0%]; primary focus of intervention does not explain the variation across all studies

Behavioural Interventions

- 3 studies; 2,174 participants
- No statistically significant difference between intervention and control participants in terms of experiencing serious adverse events [RR (95% CI) 0.99 (0.80, 1.24)]
- Low heterogeneity across studies [Chi^2=0.79, df=2 (P=0.68), I^2=0%]

Pharmacological plus Behavioural Interventions

- 12 studies; 8,637 participants
- No statistically significant difference between the intervention and control group in terms of likelihood of experiencing serious adverse events [RR (95% CI) 1.10 (0.97, 1.25)]
- Low heterogeneity across studies [Chi^2=8.10, df=10 (P=0.62), I^2=0%]
- Test for subgroup differences was not significant for participants' baseline CVD risk status [Chi^2=0.02, df=1 (P=0.90), I^2=0%]

GRADE Evidence Profile *Table* 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARI	NNH		
Serious Adverse Events: Overall														
14	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	serious imprecision[5]	none[6]	707/5,916 (11.9506%)	493/4,895 (10.0715%)	RR 1.0733 (0.9632 to 1.1959)	7,382 more (from 3,706 fewer to 19,730 more)	-	-	⊕⊕OO LOW	CRITICAL
Serious Adverse Events: by Primary Focus of Intervention – Behavioural														
3	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	serious imprecision[11]	none[12]	189/1,318 (14.3399%)	106/856 (12.3832%)	RR 0.9948 (0.7982 to 1.2399)	644 fewer (from 24,989 fewer to 29,707 more)	-	-	⊕⊕OO LOW	CRITICAL
Serious Adverse Events: by Primary Focus of Intervention – Pharmacological plus Behavioural														
12	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	serious imprecision[17]	none[18]	518/4,598 (11.2658%)	387/4,039 (9.5816%)	RR 1.0995 (0.9710 to 1.2450)	9,534 more (from 2,779 fewer to 23,475 more)	-	-	⊕⊕OO LOW	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events

Outcome: Serious Adverse Events	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**100,715**	**108,097** (97,009 to 120,445)	**RR 1.0733** (0.9632 to 1.1959)	10,811 (14 studies[1])	⊕⊕⊖⊖ **low**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**123,832**	**123,188** (98,843 to 153,539)	**RR 0.9948** (0.7982 to 1.2399)	2,174 (3 studies[7])	⊕⊕⊖⊖ **low**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**95,816**	**105,349** (93,037 to 119,291)	**RR 1.0995** (0.9710 to 1.2450)	8,637 (12 studies[13])	⊕⊕⊖⊖ **low**[14,15,16,17,18]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Adverse Effects of Treatment – Serious Adverse Events

[1] The 14 studies are:[71,78,107,109,111,116,117,120-123,127,129,133] Immediate post assessment for all but 1 study; for this 1 exception the data point at12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention). Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. For 3 studies the adverse events were assessed/reported at 3 or 6 months.[107,127,129]

[2] Using Cochrane's Risk of Bias tool, for this outcome 12 studies (86%) were rated as unclear risk and 2 studies (14%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (43%), allocation concealment (86%), blinding of participants and/or personnel (64%), and blinding of outcome assessors (57%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (21%), blinding of outcome assessors (14%), incomplete reporting (29%), and other sources of bias (79%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is low [Chi^2=9.48, df=13 (p=0.74); I^2=0%], the direction of the effect is not consistent across studies but the confidence intervals overlap (all but one study showing no significant effect). The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.60, df=1 (p=0.44), I^2=0%). This body of evidence was not downgraded for inconsistency.

[4] All 14 studies included adults aged 18-64 years, and mixed gender samples. In 8 studies (57%) the participants had a high risk of CVD. In terms of intervention focus, 2 were behavioural (both lifestyle), 11 were pharmacological plus behavioural (all orlistat), and one included both behavioural (lifestyle) and pharmacological plus behavioural (metformin) arms. Control participants in behavioural intervention studies received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 9 studies and more than 12 months in 5 studies. One study was conducted in Europe and the US, 4 in the US, 8 in European countries, and 1 in Australia and New Zealand. Less than one-third of the studies (n=4) were published in the last 5 years (2009-2012); the remaining 10 studies were published between 1998 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (5,916 intervention arm, 4,895 control arm), the number of events is sufficient (707 intervention arm, 493 control arm) but the pooled effect estimate is not precise with a confidence interval that includes the no effect value [RR=1.0733 (0.9632, 1.1959)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.479). This body of evidence was not downgraded for suspected publication bias.

[7] The 3 studies are:[71,78,133] Immediate post assessment for all but 1 study; for this 1 exception the data point at12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention).

[8] Using Cochrane's Risk of Bias tool, for this outcome all 3 studies (100%) were rated as unclear risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with allocation concealment (100%), blinding of outcome assessors (33%), and incomplete outcome reporting (33%); identified risks (high ratings) were primarily located in the domains of blinding of participants and/or personnel (100%), blinding of outcome assessors (67%), and other sources of bias (33%; i.e., industry funding and/or insufficient power). Given that all of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Statistical heterogeneity is low [Chi^2=0.79, df=2 (p=0.68); I^2=0%], the direction of the effect is not consistent across studies but the confidence intervals overlap (all showing no significant effect). This body of evidence was not downgraded for inconsistency.

[10] All 3 studies included adults aged 18-64 years, and mixed gender samples. In 2 studies (67%) the participants had a high risk of CVD. All 3 studies used lifestyle interventions. Control participants received usual care from their physicians or no intervention; in 1 of these studies control participants received a minimal component (e.g., printed materials on weight loss and/or healthy lifestyles). Intervention duration was more than 12 months in all 3 studies. All 3 studies were conducted in the US. Two of the studies were published in the last 5 years (2011, 2012); the third study was published in 1999. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is adequate (1,318 intervention arm, 856 control arm), but the number of events is low (189 intervention arm, 106 control arm) and the pooled effect estimate is not precise with a confidence interval that includes the no effect value [RR=0.9948 (0.7982, 1.2399)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] There were too few studies (n<10) to assess publication bias.

[13] The 12 studies are:[107,109,111,116,117,120-123,127,129,133] Immediate post assessment for all but 1 study; for this 1 exception the data point at12 months post baseline was selected (DPP[133] presents 12 month interim outcomes for a 38 month intervention). Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. For 3 studies the adverse events were assessed/reported at 3 or 6 months.[107,127,129]

[14] Using Cochrane's Risk of Bias tool, for this outcome 10 studies (83%) were rated as unclear risk and 2 studies (17%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (50%), allocation concealment (83%), blinding of participants and/or personnel (75%), and blinding of outcome assessors (58%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (33%), and other sources of bias (92%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

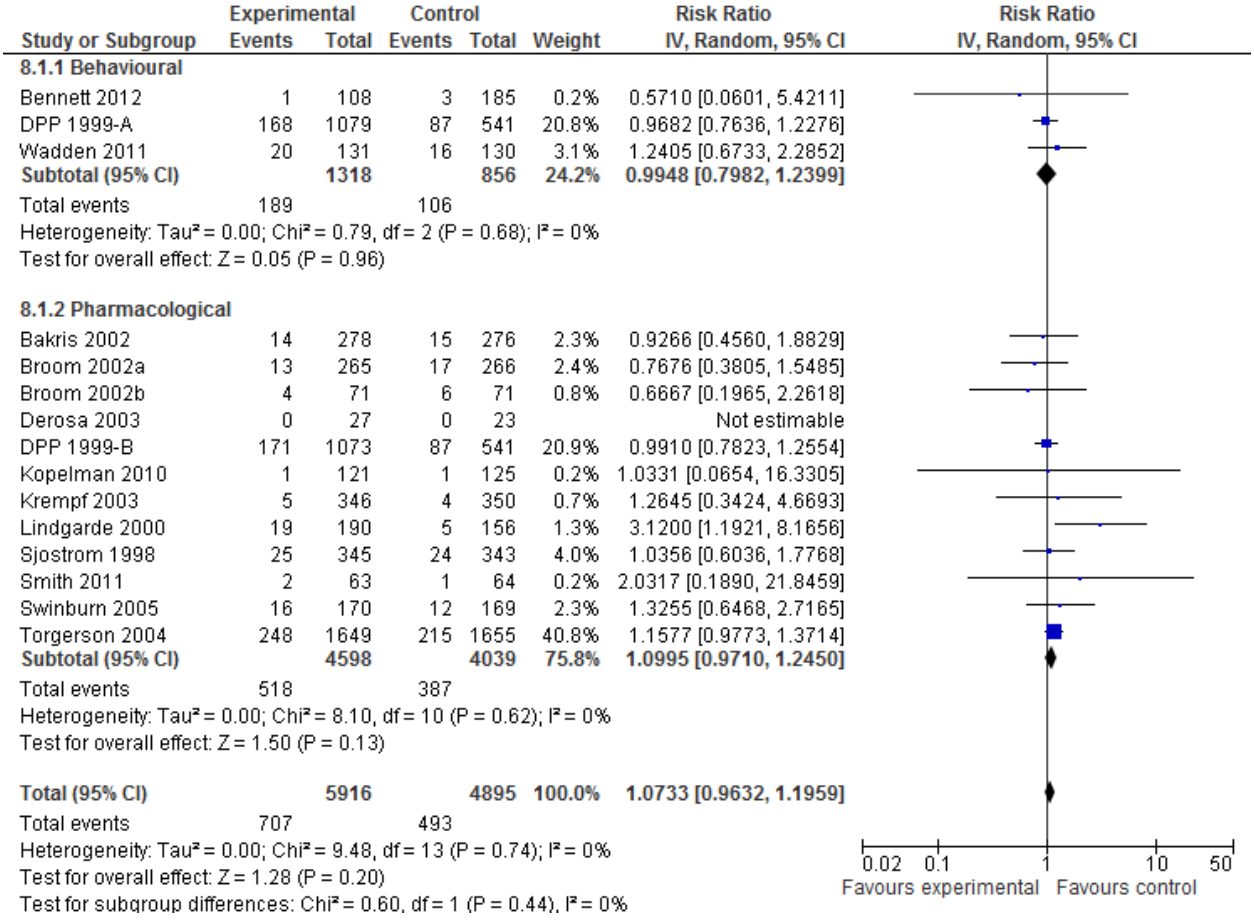
[15] Statistical heterogeneity is low [Chi^2=8.10, df=10 (p=0.62); I^2=0%], the direction of the effect is not consistent across studies but the confidence intervals overlap (all but one study showing no significant effect). This body of evidence was not downgraded for inconsistency.

[16] All 12 studies included adults aged 18-64 years, and mixed gender samples. In 6 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 11 studies used orlistat and 1 study used metformin. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 9 studies and more than 12 months in 3 studies. One study was conducted in Europe and the US, 2 in the US, 8 in European countries, and 1 in Australia and New Zealand. Two studies were published in the last 5 years (2009, 2011); the remaining 10 studies were published between 1998 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

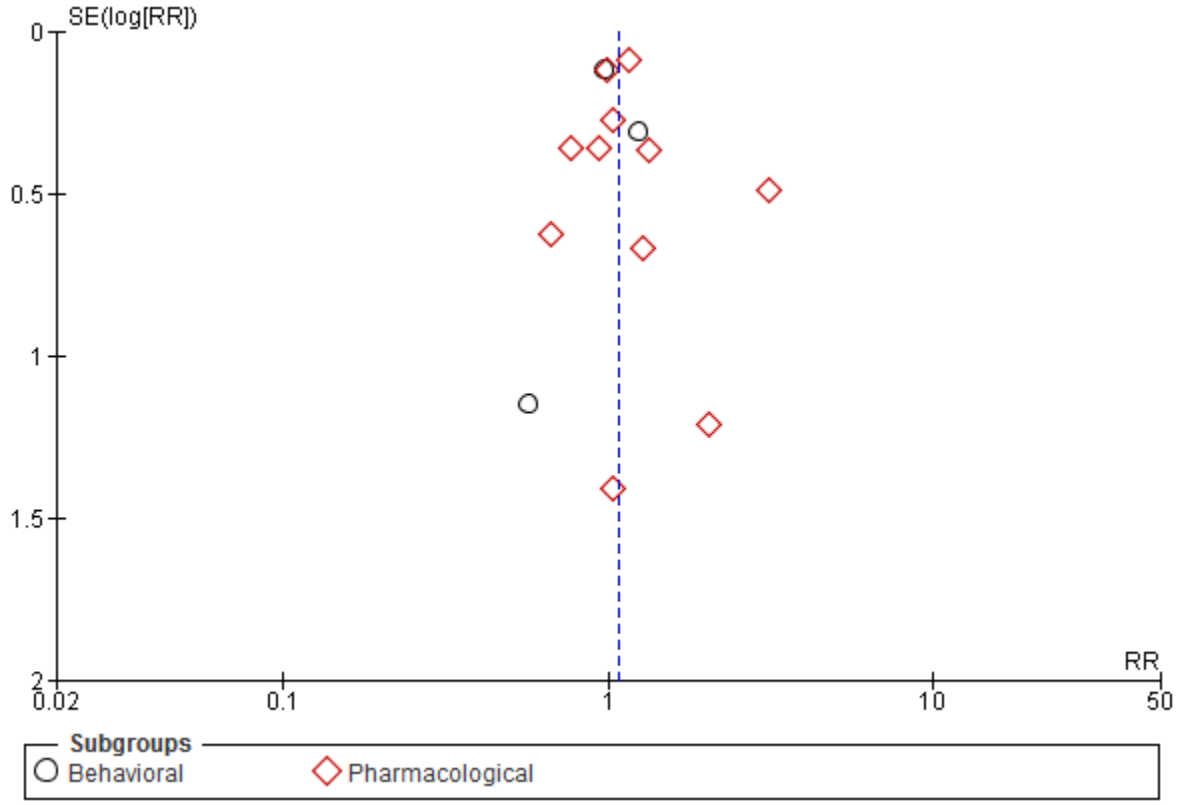
[17] The sample size is adequate (4,598 intervention arm, 4,039 control arm), the number of events is sufficient (518 intervention arm, 387 control arm) but the pooled effect estimate is not precise with a confidence interval that includes the no effect value [RR=1.0995 (0.9710, 1.2450)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.508). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 13.1: Adverse Effects of Treatment Interventions – Serious Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

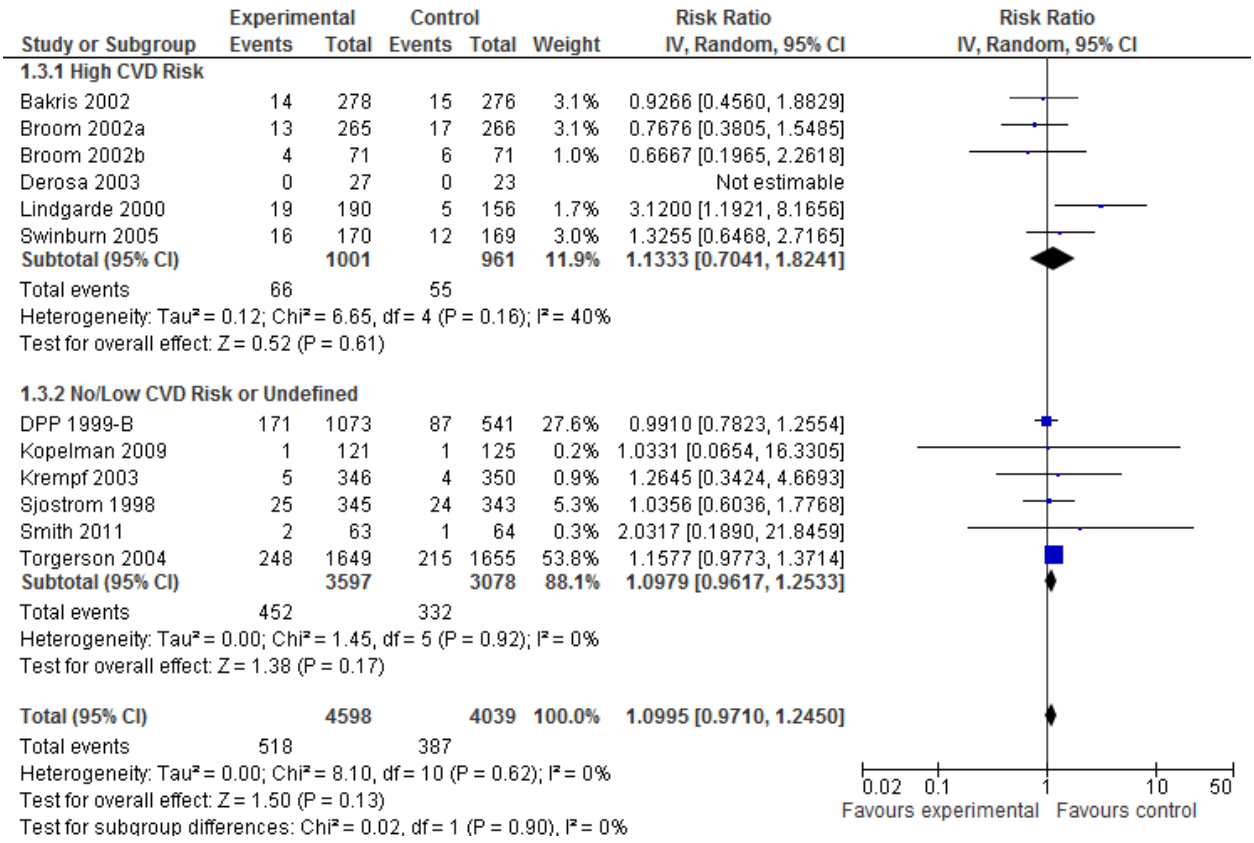


Egger's Test to Detect Publication Bias: Serious Adverse Events – Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.479
Behavioural Interventions	**
Pharmacological plus Behavioural Interventions	0.508

** Too few studies (n<10) to assess

Forest Plot 13.2: Adverse Effects of Treatment Interventions – Serious Adverse Events –by Participants' Baseline CVD Status (High Risk, Low/Unknown Risk)



Evidence Set 14: What are the adverse effects of primary care-relevant treatment interventions on overweight/obese adults (gastrointestinal events)?

- Summary of Gastrointestinal Events Evidence
- GRADE Evidence Profile Table 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events
- GRADE Summary of Findings Table 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events
- Forest Plot 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events – by Primary Focus of Intervention (Pharmacological plus Behavioural)
- Funnel Plot 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events – by Primary Focus of Intervention (Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)
- Forest Plot 14.2: Adverse Effects of Treatment Interventions – Gastrointestinal Events – by Participants' Baseline CVD Risk Status (High Risk, Low/Unknown Risk)

Summary of Gastrointestinal Events Evidence

<u>Pharmacological plus Behavioural Interventions</u>

- 23 studies; 12,954 participants
- Intervention participants were significantly more likely to experience gastrointestinal events as compared to the control group [RR (95% CI) 1.58 (1.47, 1.70)]
- Absolute risk increase is 18.72%
- Number needed to harm is 5 (95% CI 4, 7)
- High heterogeneity across studies [Chi^2=75.51, df=22 (P<0.00001), I^2=71%]
- Test for subgroup differences was not significant for participants' baseline CVD risk status [Chi^2=1.57, df=1 (P=0.21), I^2=36.3%]

GRADE Evidence Profile Table 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARI	NNH (95% CI)		
Gastrointestinal Adverse Events: by Primary Focus of Intervention - Pharmacological plus Behavioural														
23	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	reporting bias[6]	3,284/6,470 (50.7573%)	2,091/6,484 (32.2486%)	RR 1.5806 (1.4662 to 1.7039)	187,235 more (from 150,343 to 226,998 more)	18.72%	5 (4, 7)	⊕⊕OO LOW	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events

Outcome: Gastrointestinal Events	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
By Primary Focus of Intervention - Pharmacological plus Behavioural	**322,486**	**509,722** (472,829 to 549,484)	**RR 1.5806** (1.4662 to 1.7039)	12,954 (23 studies[1])	⊕⊕⊖⊖ **low**[2,3,4,5,6]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Adverse Effects of Treatment – Gastrointestinal Events

[1] The 23 studies are:[107,109,111-119,121-127,129-133] Immediate post assessment for all but 2 studies; for these 2 studies the data point at12 months post baseline was selected (Hauptman[114] presents 12 month interim outcomes for a 24 month intervention; DPP[133] presents 12 month interim outcomes for a 38 month intervention). Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. For 7 studies the adverse events were assessed/reported at 3, 4, or 6 months.[107,125-127,129,130,132]

[2] Using Cochrane's Risk of Bias tool, for this outcome 20 studies (87%) were rated as unclear risk and 3 studies (13%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (65%), allocation concealment (78%), blinding of participants and/or personnel (83%), and blinding of outcome assessors (61%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (48%), and other sources of bias (83%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

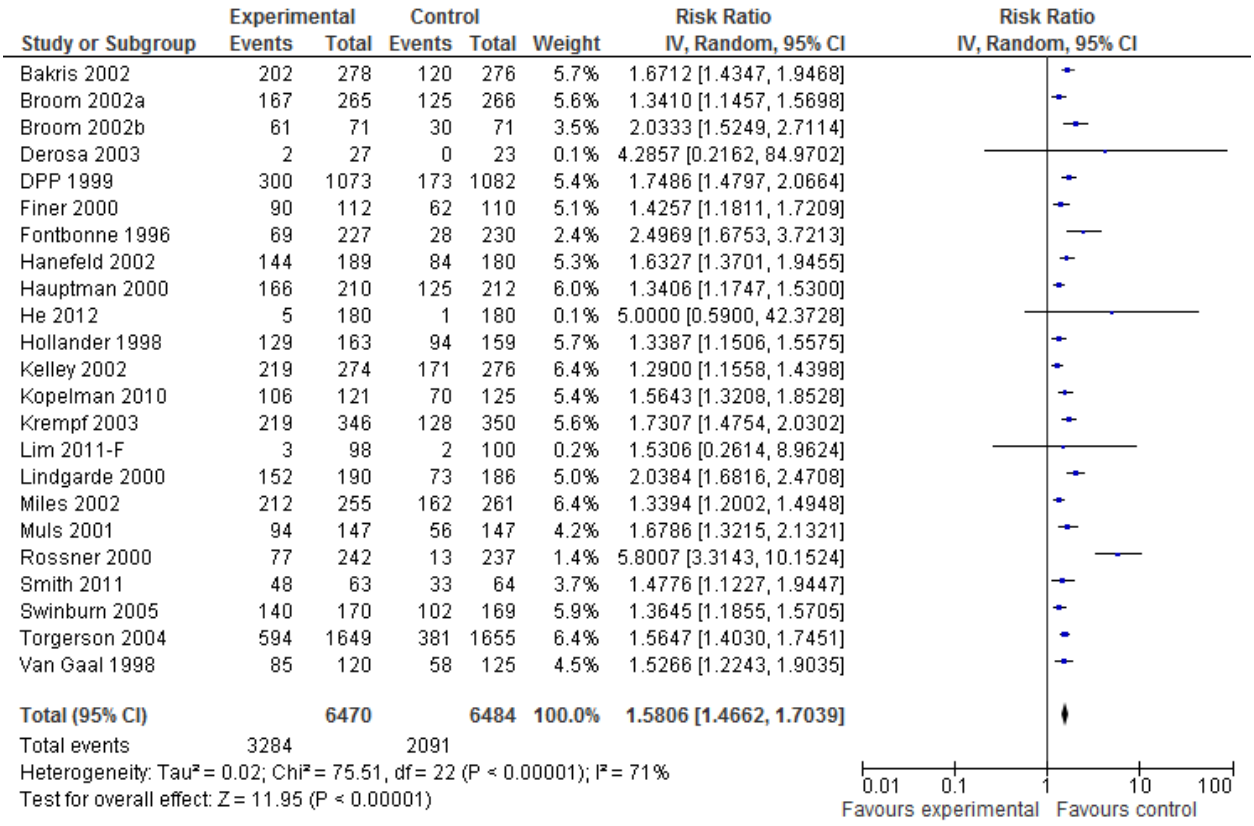
[3] Statistical heterogeneity is moderate [Chi^2=75.51, df=22 ($p<0.00001$); I^2=71%], the direction of the effect is consistent across studies and the confidence intervals overlap. The statistical heterogeneity is most likely due to small versus large treatment effects observed across studies. This body of evidence was not downgraded for inconsistency.

[4] All 23 studies included adults aged 18-64 years, and most (n=22) included mixed gender samples; 1 study included only women. In 11 studies (48%) the participants had a high risk of CVD. In terms of intervention focus, most studies (n=21) were pharmacological plus behavioural (19 orlistat, 2 metformin) and 2 included both behavioural (lifestyle) and pharmacological plus behavioural (metformin) arms. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 18 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 1 in Europe and the US, 5 in the US, 13 in European countries, 2 in Australia and/or New Zealand, and 1 in China. Only 4 studies were published in the last 5 years (2009-2012); the remaining 19 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

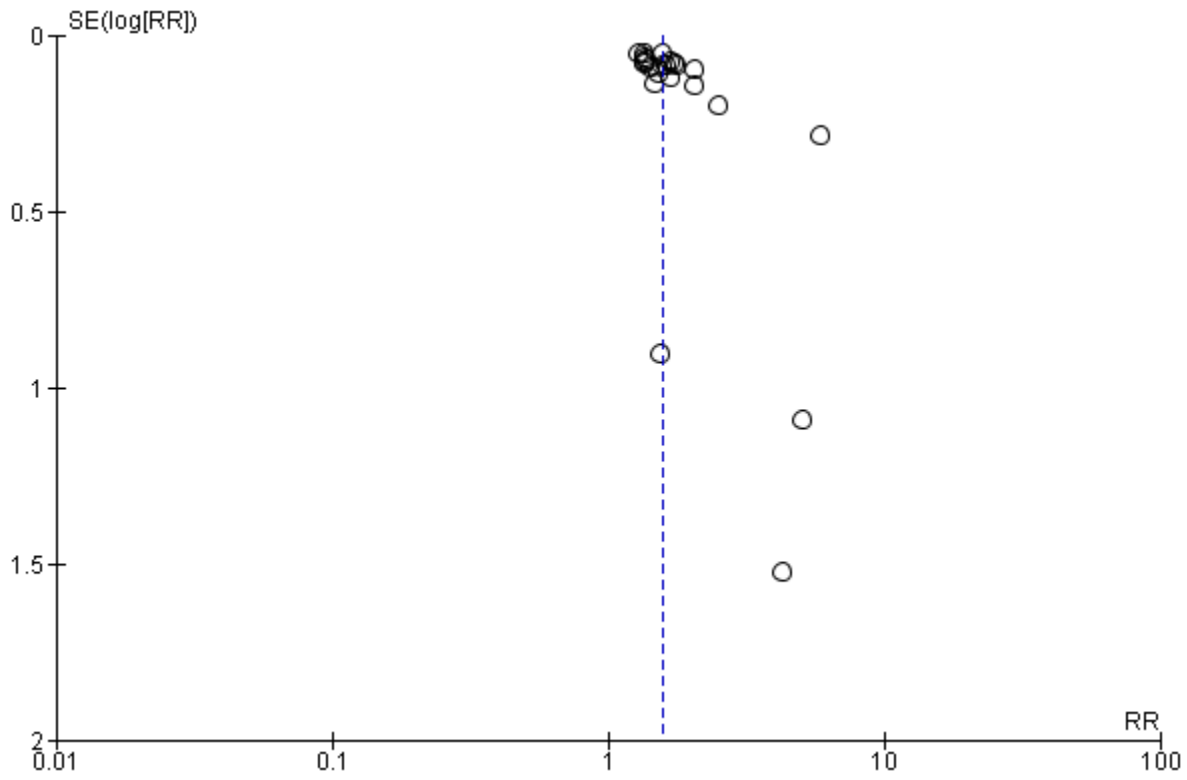
[5] The sample size is adequate (6,470 intervention arm, 6,484 control arm), the number of events is sufficient (3,284 intervention arm, 2,091 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.5806 (1.4662, 1.7039)]. This body of evidence was not downgraded for imprecision.

[6] The Egger's test was conducted to detect publication bias; results were significant (p=0.003). This body of evidence was downgraded for strongly suspected publication bias.

Forest Plot 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events – by Primary Focus of Intervention (Pharmacological plus Behavioural)



Funnel Plot 14.1: Adverse Effects of Treatment Interventions – Gastrointestinal Events -- by Primary Focus of Intervention (Pharmacological plus Behavioural)

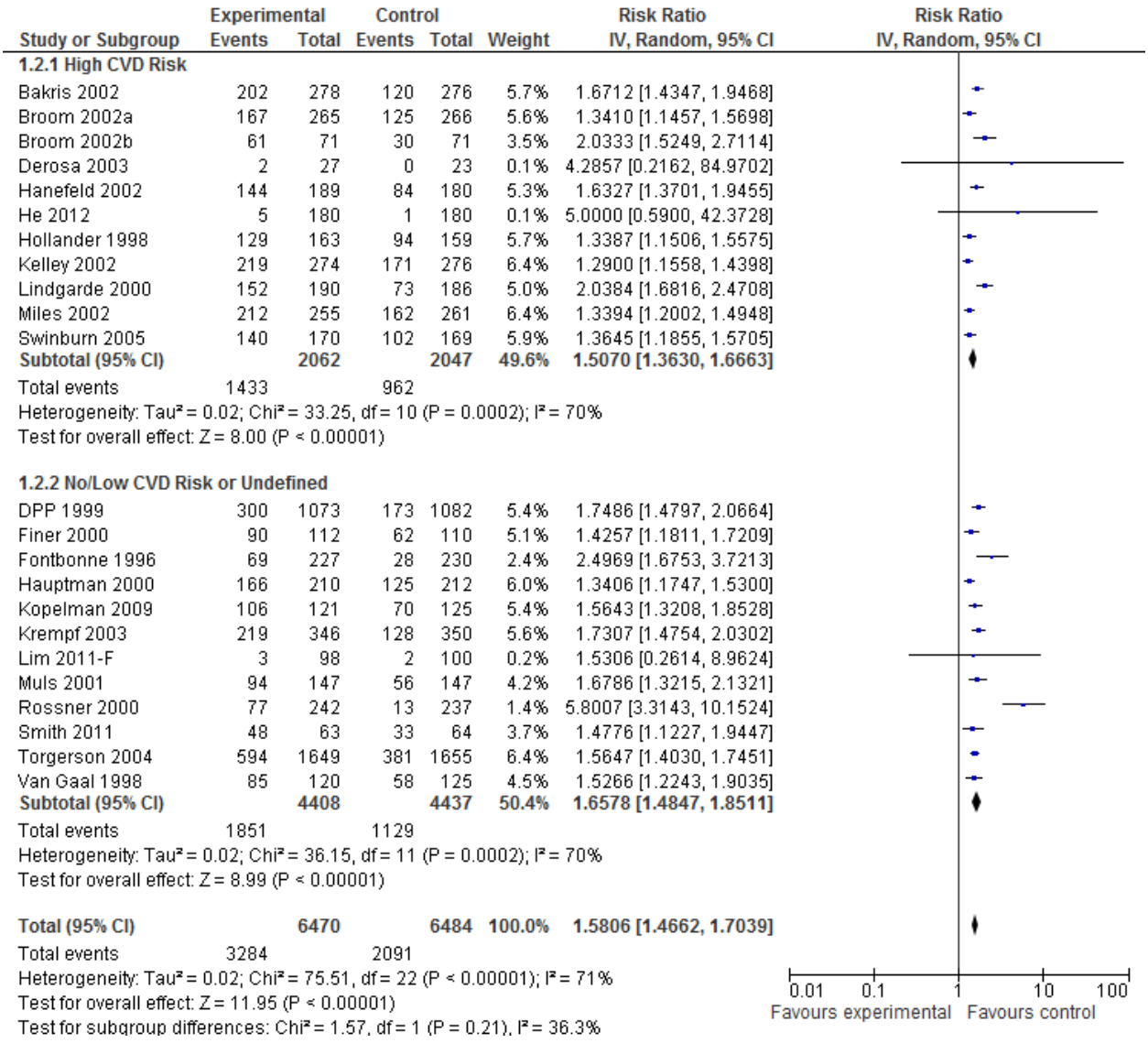


Egger's Test to Detect Publication Bias: Gastrointestinal Events -- by Primary Focus of Intervention (Pharmacological plus Behavioural)

Included Studies	P-value
Pharmacological plus Behavioural Interventions	0.003*

* Significant p≤0.05

Forest Plot 14.2: Adverse Effects of Treatment Interventions – Gastrointestinal Events – by Participants' Baseline CVD Risk Status (High Risk, Low/Unknown Risk)



Evidence Set 15: What are the adverse effects of primary care-relevant treatment interventions on overweight/obese adults (withdrawal from study due to adverse events)?

- Summary of Withdrawal due to Adverse Events Evidence
- GRADE Evidence Profile Table 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events
- GRADE Summary of Findings Table 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events
- Forest Plot 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Funnel Plot 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)
- Egger's Test Results (for Publication Bias)
- Forest Plot 15.2: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events – by Participants' Baseline CVD Risk Status (High Risk, Low/Unknown Risk)

Summary of Withdrawal due to Adverse Events Evidence

Overall

- 26 studies; 12,987 participants
- Intervention participants were significantly more likely to withdraw from studies due to adverse events as compared to the control group [RR (95% CI) 1.69 (1.43, 2.00)]
- Absolute risk increase was 3.05%
- Number needed to harm is 33 (95% CI 23, 53)
- Low heterogeneity across studies [Chi^2=29.41, df=25 (P=0.25), I^2=15%]

Test for subgroup differences is not significant [Chi^2=0.21, df=1 (P=0.65), I^2=0%]; primary focus of intervention does not explain the variation across all studies

Behavioural Interventions

- 1 study; 302 participants
- No statistically significant difference between the intervention and control group in terms of withdrawing from studies due to adverse events [RR (95% CI) 3.40 (0.16, 70.16)]
- Heterogeneity not applicable

Pharmacological plus Behavioural Interventions

- 25 studies; 12,685 participants
- Intervention participants were significantly more likely to withdraw from studies due to adverse events as compared to the control group [RR (95% CI) 1.68 (1.42, 2.00)]
- Absolute risk increase was 3.09%
- Number needed to harm is 32 (95% CI 22,47)
- Low heterogeneity across studies [Chi^2=29.21, df=24 (P=0.21), I^2=18%]
- Test for subgroup differences was significant for participants' baseline CVD risk status [Chi^2=4.63, df=1 (P=0.03), I^2=78.4%]

GRADE Evidence Profile Table 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events

Quality Assessment							No. of Participants		Effect				Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Treatment	Control	Relative (95% CI)	Absolute per Million (Range)	ARI	NNH (95% CI)		
Study Withdrawal Due to Adverse Events: Overall														
26	randomized trials[1]	serious risk[2]	no serious inconsistency[3]	no serious indirectness[4]	no serious imprecision[5]	none[6]	521/6,741 (7.7288%)	277/6,246 (4.4348%)	RR 1.6888 (1.4260 to 2.0000)	30,547 more (from 18,892 to 44,348 more)	3.05%	33 (23, 53)	⊕⊕⊕O MODERATE	CRITICAL
Study Withdrawal Due to Adverse Events: by Primary Focus of Intervention – Behavioural														
1	randomized trials[7]	serious risk[8]	no serious inconsistency[9]	no serious indirectness[10]	serious imprecision[11]	none[12]	2/180 (1.1111%)	0/122 (0%)	RR 3.3978 (0.1645 to 70.1642)	-	-	-	⊕⊕OO LOW	CRITICAL
Study Withdrawal Due to Adverse Events: by Primary Focus of Intervention – Pharmacological plus Behavioural														
25	randomized trials[13]	serious risk[14]	no serious inconsistency[15]	no serious indirectness[16]	no serious imprecision[17]	none[18]	519/6,561 (7.9104%)	277/6,124 (4.5232%)	RR 1.6838 (1.4166 to 2.0015)	30,930 more (from 21,078 to 45,300 more)	3.09%	32 (22, 47)	⊕⊕⊕O MODERATE	CRITICAL

* Footnotes appear after the Summary of Findings Table

GRADE Summary of Findings Table 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events

Outcome: Withdrawal from Study due to Adverse Events	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Number per Million Control	Corresponding Risk Number per Million Treatment			
Overall	**44,348**	**74,896** (63,241 to 88,697)	**RR 1.6888** (1.4260 to 2.0000)	12,987 (26 studies[1])	⊕⊕⊕⊖ **moderate**[2,3,4,5,6]
By Primary Focus of Intervention - Behavioural	**0**	**0**	**RR 3.3978** (0.1645 to 70.1642)	302 (1 study[7])	⊕⊕⊖⊖ **low**[8,9,10,11,12]
By Primary Focus of Intervention - Pharmacological plus Behavioural	**45,232**	**76,161** (66,310 to 90,532)	**RR 1.6838** (1.4166 to 2.0015)	12,685 (25 studies[13])	⊕⊕⊕⊖ **moderate**[14,15,16,17,18]

*The assumed risk is the mean control group risk across studies. 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).

Footnotes for GRADE Evidence Profile and Summary of Findings Tables for Adverse Effects of Treatment – Withdrawal due to Adverse Events

[1] The 26 studies are:[96,106,108-127,129-131] Immediate post assessment for all but 2 studies; for these 2 studies the data point at12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions). Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. For 6 studies the adverse events were assessed/reported at 3, 4, or 6 months.[107,125-127,129,130]

[2] Using Cochrane's Risk of Bias tool, for this outcome 22 studies (85%) were rated as unclear risk and 4 studies (15%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (65%), allocation concealment (77%), blinding of participants and/or personnel (81%), and blinding of outcome assessors (69%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (42%), and other sources of bias (81%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[3] Statistical heterogeneity is low [Chi^2=29.41, df=25 (p=0.25); I^2=15%], the direction of the effect is consistent across most studies and the confidence intervals overlap. The test for subgroup differences (behavioural, pharmacological plus behavioural) was not significant [Chi^2=0.21, df=1 (p=0.65), I^2=0%). This body of evidence was not downgraded for inconsistency.

[4] Across the 26 studies, 25 included adults aged 18-64 years, and 1 included adults 65 years and older. All studies included mixed gender samples. In 13 studies (50%) the participants had a high risk of CVD. In terms of intervention focus, 1 was behavioural (exercise) and 25 were pharmacological plus behavioural (23 orlistat, 2 metformin). Control participants in the behavioural intervention study received usual care from their physicians. Control participants in pharmacological plus behavioural studies followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 21 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 1 in the US and Sweden, 6 in the US, 16 in European countries, 1 in Australia and New Zealand, and 1 in China. Less than one-fifth of the studies (n=5) were published in the last 5 years (2009-2012); the remaining 21 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

[5] The sample size is adequate (6,741 intervention arm, 6,246 control arm), the number of events is sufficient (521 intervention arm, 277 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.6888 (1.4260, 2.0000)]. This body of evidence was not downgraded for any serious concerns regarding imprecision.

[6] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.313). This body of evidence was not downgraded for suspected publication bias.

[7] The 1 study is:[96] Immediate post assessment for this study.

[8] Using Cochrane's Risk of Bias tool, for this outcome this single study was rated as unclear risk. There was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation and blinding of outcome assessors; identified risks (a high rating) were in the domain of blinding of participants and/or personnel. Given that the information for this outcome is from a study at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

[9] Single study therefore cannot assess inconsistency.

[10] This recently published (2012), US-based, 12 month exercise intervention study included adults 65 years and older and a mixed gender sample that was not selected for high risk of CVD. Control participants received usual care from their physicians. There were no serious concerns regarding indirectness for this body of evidence.

[11] The sample size is low (180 intervention arm, 122 control arm), the number of events is very low (2 intervention arm, 0 control arm) and the pooled effect estimate is not precise with a very wide confidence interval that includes the no effect value [RR=3.3978 (0.1645, 70.1642)]. This body of evidence was downgraded for serious concerns regarding imprecision.

[12] There were too few studies (n<10) to assess publication bias.

[13] The 25 studies are:[106,108-127,129-131] Immediate post assessment for all but 2 studies; for these 2 studies the data point at12 months post baseline was selected (Davidson[110] and Hauptman[114] present 12 month interim outcomes for 24 month interventions). Unlike the primary and other secondary outcomes, no criteria were applied to length of follow-up for adverse events. For 6 studies the adverse events were assessed/reported at 3, 4, or 6 months.[107,125-127,129,130]

[14] Using Cochrane's Risk of Bias tool, for this outcome 21 studies (84%) were rated as unclear risk and 4 studies (15%) were rated as low risk. Across studies, there was a lack of certainty (unclear ratings) regarding risk of bias associated with sequence generation (68%), allocation concealment (80%), blinding of participants and/or personnel (84%), and blinding of outcome assessors (68%); identified risks (high ratings) were primarily located in the domains of incomplete reporting (44%), and other sources of bias (84%; i.e., industry funding and/or insufficient power). Given that most of the information for this outcome is from studies at moderate risk of bias, this body of evidence was downgraded for serious study limitations.

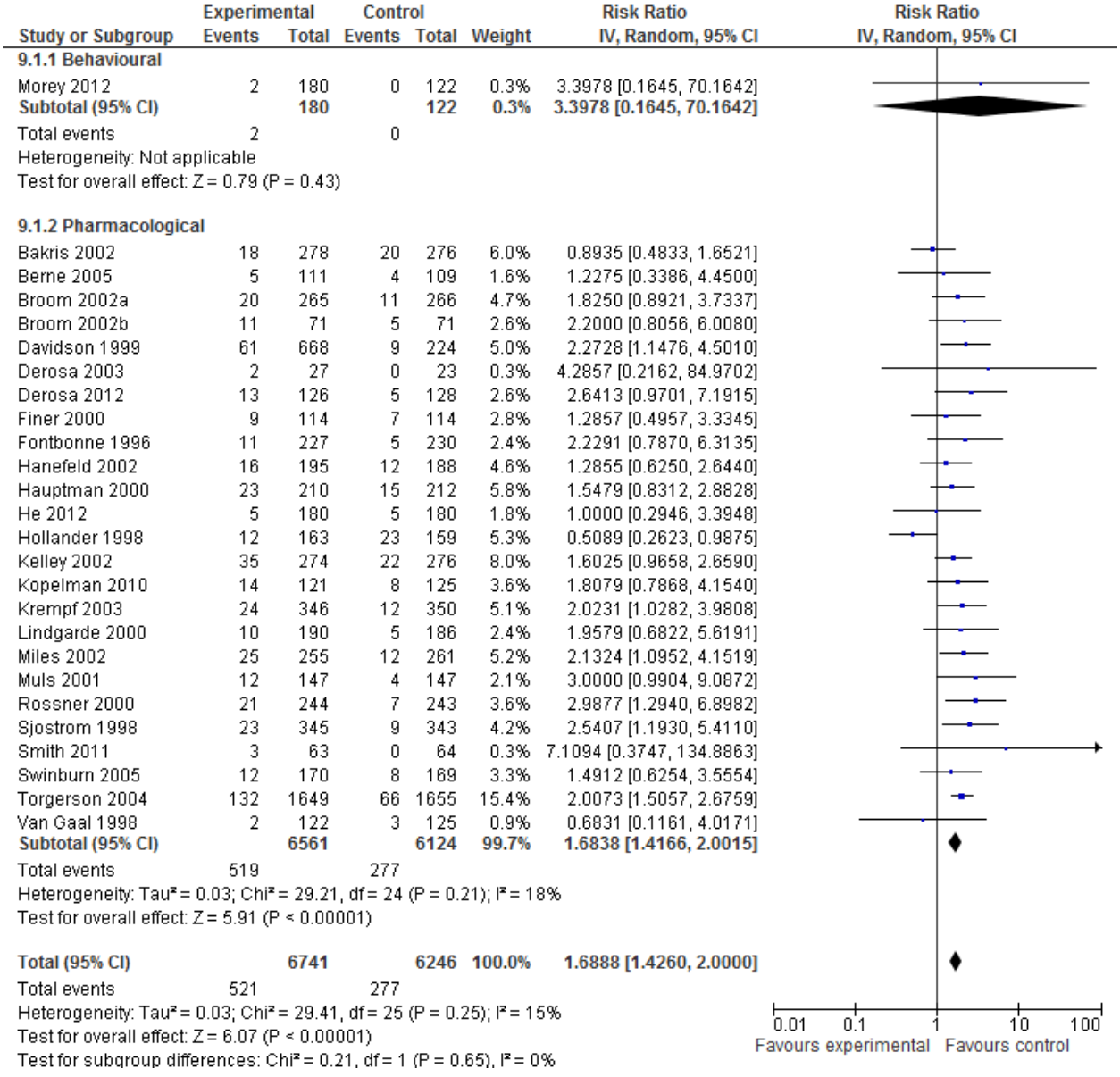
[15] Statistical heterogeneity is low [Chi^2=29.21, df=24 (p=0.21); I^2=18%], the direction of the effect is consistent across most studies and the confidence intervals overlap. This body of evidence was not downgraded for inconsistency.

[16] All 25 studies included adults aged 18-64 years, and mixed gender samples. In 13 studies (52%) the participants had a high risk of CVD. Most studies used orlistat as the pharmacological plus behavioural intervention (n=23) while 2 studies used metformin. Control participants followed the same diet and exercise instructions as the intervention participants but they received placebos instead of the active medications. Intervention duration was 12 months or less in 20 studies and more than 12 months in 5 studies. One study was conducted in Canada and the US, 1 in the US and Sweden, 5 in the US, 16 in European countries, 1 in Australia and New Zealand, and 1 in China. Only 4 studies were published in the last 5 years (2009-2012); the remaining 21 studies were published between 1996 and 2005. There were no serious concerns regarding indirectness for this body of evidence.

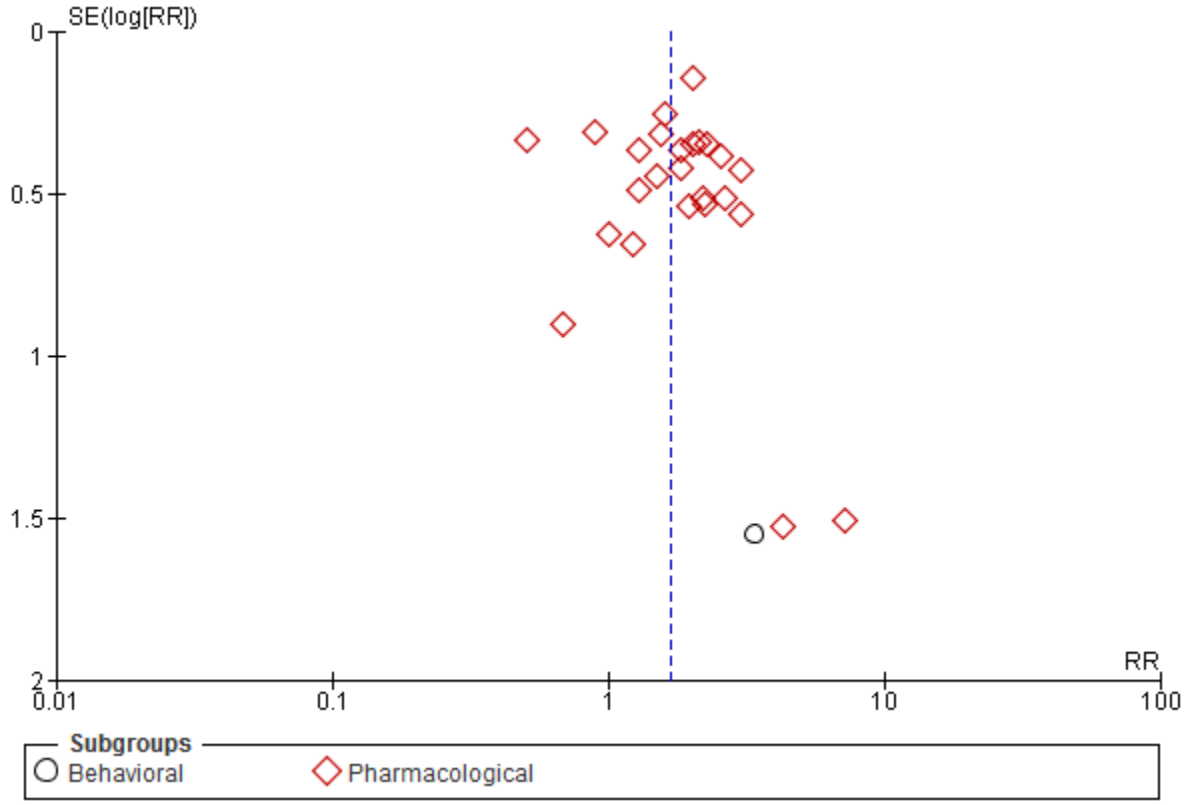
[17] The sample size is adequate (6,561 intervention arm, 6,124 control arm), the number of events is sufficient (519 intervention arm, 277 control arm) and the pooled effect estimate is precise with a narrow confidence interval [RR=1.6838 (1.4166, 2.0015)]. This body of evidence was not downgraded for any serious concerns regarding imprecision.

[18] The funnel plot for these studies and this outcome is roughly symmetrical. The Egger's test was conducted to detect publication bias; results were not significant (p=0.396). This body of evidence was not downgraded for suspected publication bias.

Forest Plot 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)



Funnel Plot 15.1: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

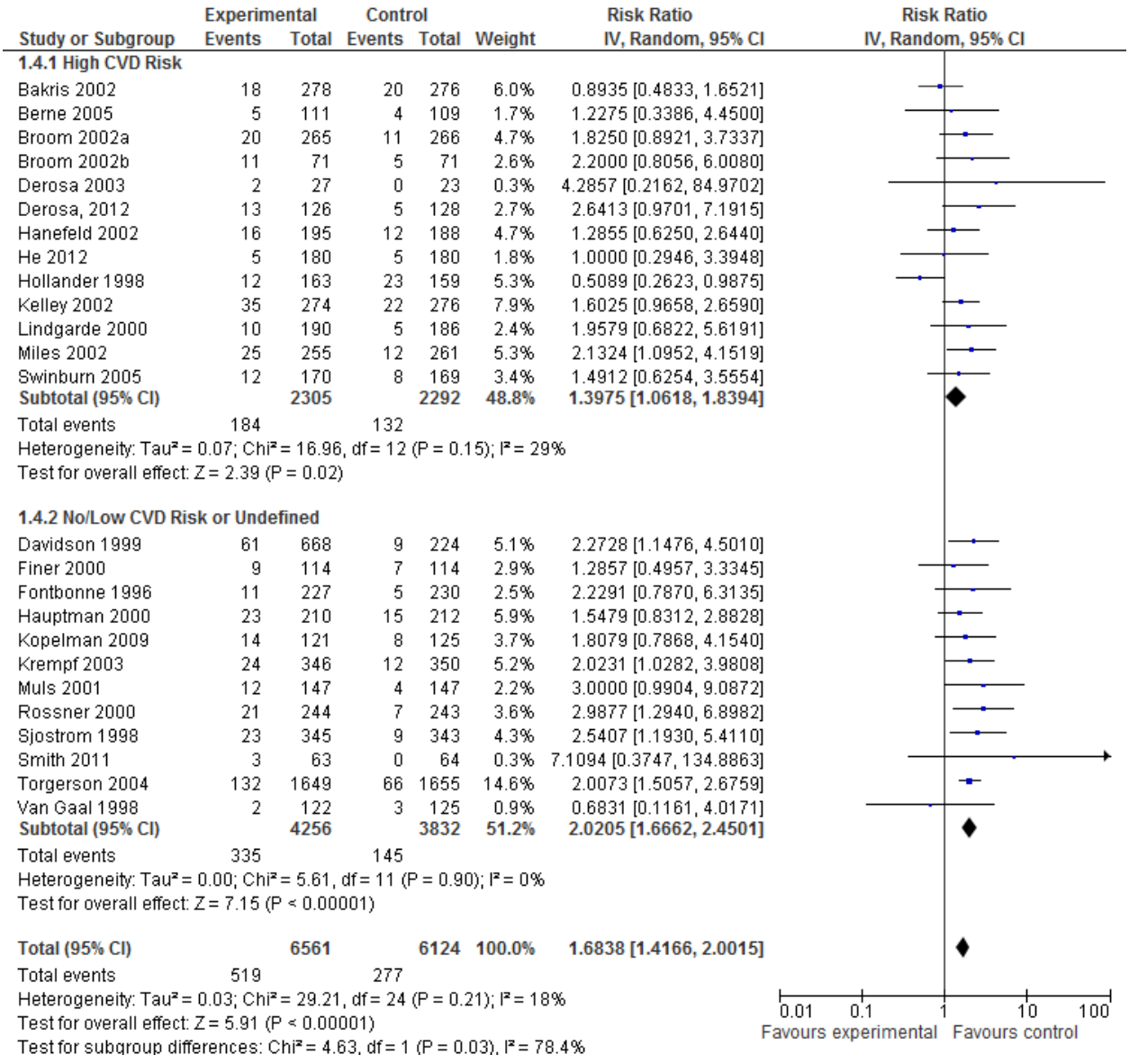


Egger's Test to Detect Publication Bias: Withdrawal due to Adverse Events - Overall and by Primary Focus of Intervention (Behavioural, Pharmacological plus Behavioural)

Included Studies	P-value
Overall	0.313
Behavioural Interventions	**
Pharmacological plus Behavioural Interventions	0.396

** Too few studies (n<10) to assess

Forest Plot 15.2: Adverse Effects of Treatment Interventions – Withdrawal due to Adverse Events – by Participants' Baseline CVD Risk Status (High Risk, Low/Unknown Risk)



Appendices

- Appendix 1: Search Strategies for Key Questions (KQ) and Contextual Questions (CQ)
- Appendix 2: Acknowledgements

Appendix 1: Search Strategies for Key Questions (KQ) and Contextual Questions (CQ)

Medline - OVID (KQ)
Last Run: April 19 2013
1. Obesity/dh, th, dt, rh
2. Obesity, Morbid/dt, dh, th, rh or Obesity, Abdominal/dt, dh, th, rh
3. Overweight/dh, dt, th, rh
4. "Behavior-Therapy"/
5. Cognitive Therapy/
6. Counseling/
7. Directive Counseling/
8. counsel?ing.ti,ab.
9. Anti-Obesity Agents/
10. orlistat.ti,ab.
11. xenical.ti,ab.
12. sibutramine.ti,ab.
13. meridia.ti,ab.
14. metformin/
15. metformin.ti,ab.
16. glucophage.ti,ab.
17. Diet, Reducing/
18. Diet, Fat-Restricted/
19. Caloric Restriction/
20. Diet Therapy/
21. (diet$ adj counsel$).ti,ab.
22. (diet$ adj education$).ti,ab.
23. (nutrition$ adj counsel$).ti,ab.
24. (nutrition$ adj education$).ti,ab.
25. (nutrition$ adj intervention$).ti,ab.
26. (diet$ adj (modif$ or therapy or intervention$ or strateg$)).ti,ab.
27. ((diet or dieting or slim$) adj (club$ or organi?ation$)).ti,ab.
28. (weightwatcher$ or weight watcher$).ti,ab.
29. Exercise/
30. Exercise Therapy/
31. Motor Activity/
32. Physical Fitness/
33. physical activity.ti,ab.
34. (exercise adj3 (program$ or intervention$)).ti,ab.
35. or/4-34
36. Obesity/
37. Obesity, Morbid/ or Obesity, Abdominal/
38. Overweight/
39. Weight Loss/
40. obes$.ti.
41. overweight.ti.

42. weight.ti.
43. or/36-42
44. 35 and 43
45. (weight loss adj (intervention$ or program$ or trial$)).ti,ab.
46. (weight reduc$ adj (intervention$ or program$ or trial$)).ti,ab.
47. (weight management adj (intervention$ or program$ or trial$)).ti,ab.
48. (weight control adj (intervention$ or program$ or trial$)).ti,ab.
49. (36 or 37 or 38) and 39
50. 1 or 2 or 3 or 44 or 45 or 46 or 47 or 48 or 49
51. limit 50 to (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial)
52. clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
53. Meta-Analysis as Topic/
54. (control$ adj3 trial$).ti,ab.
55. random$.ti,ab.
56. clinical trial$.ti,ab.
57. 52 or 53 or 54 or 55 or 56
58. 50 and 57
59. 51 or 58
60. limit 59 to "all child (0 to 18 years)"
61. limit 59 to "all adult (19 plus years)"
62. 60 not 61
63. 59 not 62
64. limit 63 to animals
65. limit 63 to humans
66. 64 not 65
67. 63 not 66
68. limit 67 to (english or french)
69. limit 68 to ed=20100801-20130419
70. (harm or harms or harmful or harmed).ti,ab.
71. (risky behavior$ or risky behaviour$).ti,ab.
72. weight cycling.ti,ab.
73. (adverse effects or mortality or toxicity).fs.
74. Mortality/
75. Morbidity/
76. death/
77. Athletic injuries/
78. Malnutrition/
79. nutritional defici$.ti,ab.
80. Arrhythmias, Cardiac/
81. Arrhythmia$.ti,ab.
82. Bone Density/
83. (bone mass adj3 loss).ti,ab.
84. Bone Resorption/
85. (death or deaths).ti,ab.
86. suicide/
87. Suicide, Attempted/

88. suicid$.ti,ab.
89. or/70-88
90. 50 and 89
91. limit 90 to ed=20100801-20130419
92. or/9-16
93. 50 and 92
94. limit 93 to ed=20100801-20130419
95. case-control studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/
96. case control$.ti,ab.
97. cohort.ti,ab.
98. longitudinal.ti,ab.
99. (follow-up or followup).ti,ab.
100. prospective$.ti,ab.
101. (comparison group$ or control group$).ti,ab.
102. observational.ti,ab.
103. retrospective studies/
104. retrospective$.ti,ab.
105. database$.ti,ab.
106. nonrandomi$.ti,ab.
107. population$.ti,ab.
108. or/95-107
109. 91 or 94
110. 108 and 109
111. limit 110 to "all child (0 to 18 years)"
112. limit 110 to "all adult (19 plus years)"
113. 111 not 112
114. 110 not 113
115. limit 114 to animals
116. limit 114 to humans
117. 115 not 116
118. 114 not 117
119. limit 118 to (english or french)
120. 69 or 119
121. exp *bariatric surgery/
122. limit 120 to ed=20100801-20130419
123. 122 not 121

EMBASE - OVID (KQ)

Last Run: April 19 2013

1. obesity/dm, dt, pc, rh, si, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Side Effect, Therapy]
2. diabetic obesity/dm, dt, pc, rh, si, th
3. abdominal obesity/dm, dt, pc, rh, si, th
4. morbid obesity/dm, dt, pc, rh, si, th
5. exp psychotherapy/
6. exp counseling/

7. counsel?ing.ti,ab.
8. antiobesity agent/
9. orlistat.ti,ab.
10. sibutramine.ti,ab.
11. meridia.ti,ab.
12. metformin/
13. metformin.ti,ab.
14. glucophage.ti,ab.
15. exp diet therapy/
16. (diet$ adj counsel$).ti,ab.
17. (diet$ adj education$).ti,ab.
18. (nutrition$ adj counsel$).ti,ab.
19. (nutrition$ adj education$).ti,ab.
20. (nutrition$ adj intervention$).ti,ab.
21. (diet$ adj (modif$ or therapy or intervention$ or strateg$)).ti,ab.
22. ((diet or dieting or slim$) adj (club$ or organi?ation$)).ti,ab.
23. (weightwatcher$ or weight watcher$).ti,ab.
24. exp exercise/
25. exp kinesiotherapy/
26. motor activity/
27. fitness/
28. (exercise adj3 (program$ or intervention$)).ti,ab.
29. physical activity.ti,ab.
30. or/5-29
31. obesity/
32. diabetic obesity/
33. abdominal obesity/
34. morbid obesity/
35. weight reduction/
36. obes$.ti.
37. overweight.ti.
38. weight.ti.
39. or/31-38
40. 30 and 39
41. (weight loss adj (intervention$ or program$ or trial$)).ti,ab.
42. (weight reduc$ adj (intervention$ or program$ or trial$)).ti,ab.
43. (weight management adj (intervention$ or program$ or trial$)).ti,ab.
44. (weight control adj (intervention$ or program$ or trial$)).ti,ab.
45. 31 or 32 or 33 or 34
46. 35 and 45
47. 1 or 2 or 3 or 4 or 40 or 41 or 42 or 43 or 44 or 46
48. limit 47 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
49. limit 47 to (meta analysis or "systematic review")
50. meta analysis/
51. controlled study/ or exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/

52. (control* adj3 trial*).ti,ab.
53. random*.ti,ab.
54. clinical trial*.ti,ab.
55. 50 or 51 or 52 or 53 or 54
56. 47 and 55
57. 48 or 49 or 56
58. limit 57 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
59. limit 57 to (adult <18 to 64 years> or aged <65+ years>)
60. 58 not 59
61. 57 not 60
62. limit 61 to animals
63. limit 61 to humans
64. 62 not 63
65. 61 not 64
66. limit 65 to (english or french)
67. limit 66 to yr="2010 -Current"
68. (harm or harms or harmful or harmed).ti,ab.
69. (risky behavior* or risky behaviour*).ti,ab.
70. weight cycling.ti,ab.
71. (ae or to or si).mp. or co.fs. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
72. exp mortality/
73. exp morbidity/
74. death/
75. sport injury/
76. exp malnutrition/
77. nutritional defici*.ti,ab.
78. exp heart arrhythmia/
79. Arrhythmia*.ti,ab.
80. bone density/
81. (bone mass adj3 loss).ti,ab.
82. bone resorption.ti,ab.
83. (death or deaths).ti,ab.
84. (disordered eating or eating disorders*).ti,ab.
85. suicide/
86. suicide attempt/
87. suicid*.ti,ab.
88. or/68-87
89. 47 and 88
90. exp case control study/ or pretest posttest control group design/
91. cohort analysis/
92. longitudinal study/
93. follow up/
94. prospective study/
95. observational study/

96. retrospective study/
97. case-control*.ti,ab.
98. cohort.ti,ab.
99. longitudinal.ti,ab.
100. (follow-up or followup).ti,ab.
101. prospective$.ti,ab.
102. (comparison group* or control group*).ti,ab.
103. observational.ti,ab.
104. retrospective*.ti,ab.
105. database*.ti,ab.
106. nonrandom*.ti,ab.
107. population*.ti,ab.
108. or/90-107
109. 89 and 108
110. limit 109 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
111. limit 109 to (adult <18 to 64 years> or aged <65+ years>)
112. 110 not 111
113. 109 not 112
114. limit 113 to animals
115. limit 113 to humans
116. 114 not 115
117. 113 not 116
118. limit 117 to (english or french)
119. limit 118 to yr="2010 -Current"
120. 67 or 119
121. exp *bariatric surgery/
122. 120 not 121
123. (pediatric* or paediatric* or child* or adolescent? or youth? or teenager? or teen?).ti,ab,jn.
124. 122 not 123

Cochrane Central Register of Controlled Trials - OVID (KQ)
Last Run: April 19 2013
1. Obesity/dh, th, dt, rh
2. Obesity, Morbid/dt, dh, th, rh or Obesity, Abdominal/dt, dh, th, rh
3. Overweight/dh, dt, th, rh
4. "Behavior-Therapy"/
5. Cognitive Therapy/
6. Counseling/
7. Directive Counseling/
8. counsel?ing.ti,ab.
9. Anti-Obesity Agents/
10. orlistat.ti,ab.
11. xenical.ti,ab.
12. sibutramine.ti,ab.
13. meridia.ti,ab.

14. metformin/
15. metformin.ti,ab.
16. glucophage.ti,ab.
17. Diet, Reducing/
18. Diet, Fat-Restricted/
19. Caloric Restriction/
20. Diet Therapy/
21. (diet$ adj counsel$).ti,ab.
22. (diet$ adj education$).ti,ab.
23. (nutrition$ adj counsel$).ti,ab.
24. (nutrition$ adj education$).ti,ab.
25. (nutrition$ adj intervention$).ti,ab.
26. (diet$ adj (modif$ or therapy or intervention$ or strateg$)).ti,ab.
27. ((diet or dieting or slim$) adj (club$ or organi?ation$)).ti,ab.
28. (weightwatcher$ or weight watcher$).ti,ab.
29. Exercise/
30. Exercise Therapy/
31. Motor Activity/
32. Physical Fitness/
33. physical activity.ti,ab.
34. (exercise adj3 (program$ or intervention$)).ti,ab.
35. or/4-34
36. Obesity/
37. Obesity, Morbid/ or Obesity, Abdominal/
38. Overweight/
39. Weight Loss/
40. obes$.ti.
41. overweight.ti.
42. weight.ti.
43. or/36-42
44. 35 and 43
45. (weight loss adj (intervention$ or program$ or trial$)).ti,ab.
46. (weight reduc$ adj (intervention$ or program$ or trial$)).ti,ab.
47. (weight management adj (intervention$ or program$ or trial$)).ti,ab.
48. (weight control adj (intervention$ or program$ or trial$)).ti,ab.
49. (36 or 37 or 38) and 39
50. 1 or 2 or 3 or 44 or 45 or 46 or 47 or 48 or 49
51. limit 50 to yr="2010 -Current"

PsycINFO – OVID (KQ)
Last Run: April 19 2013
1. exp overweight/
2. exp Obesity/
3. obes*.ti.
4. weight control/ or weight loss/
5. overweight.ti.

6. weight.ti.
7. or/1-6
8. behavior modification/ or exp behavior therapy/
9. exp *psychotherapy/ or exp cognitive behavior therapy/
10. counseling/ or group counseling/ or peer counseling/
11. counsel?ing.ti,ab.
12. exp appetite depressing drugs/
13. orlistat.ti,ab.
14. xenical.ti,ab.
15. sibutramine.ti,ab.
16. meridia.ti,ab.
17. metformin.ti,ab.
18. glucophage.ti,ab.
19. diets/ or dietary restraint/
20. diet therapy.mp.
21. (diet* adj counsel*).ti,ab.
22. (diet* adj education*).ti,ab.
23. (nutrition* adj counsel*).ti,ab.
24. (nutrition* adj education*).ti,ab.
25. (nutrition* adj intervention*).ti,ab.
26. (diet* adj (modif* or therapy or intervention* or strateg*)).ti,ab.
27. ((diet* or dieting or slim* or weight loss) adj (club* or organi?ation*)).ti,ab.
28. physical activity/ or exp exercise/ or active living/ or activity level/ or exp health behavior/ or exp locomotion/ or physical fitness/
29. physical activity.ti,ab.
30. (exercise adj3 (program* or intervention*)).ti,ab.
31. exercise.ti.
32. or/8-31
33. (weight loss adj (intervention* or program* or trial*)).ti,ab.
34. (weight reduc* adj (intervention* or program* or trial*)).ti,ab.
35. (weight management adj (intervention* or program* or trial*)).ti,ab.
36. (weight control adj (intervention* or program* or trial*)).ti,ab.
37. 7 and 32
38. 1 or 2 or 3 or 5 or 6
39. 4 and 38
40. 33 or 34 or 35 or 36 or 37 or 39
41. meta analysis/
42. clinical trials/
43. (control* adj3 trial*).ti,ab.
44. random*.ti,ab.
45. clinical trial*.ti,ab.
46. 41 or 42 or 43 or 44 or 45
47. 40 and 46
48. limit 47 to (100 childhood or 120 neonatal or 140 infancy or 160 preschool age or 180 school age or 200 adolescence)

49. limit 47 to ("300 adulthood " or 320 young adulthood or 340 thirties or 360 middle age or "380 aged " or "390 very old ")
50. 48 not 49
51. 47 not 50
52. limit 51 to animal
53. limit 51 to human
54. 52 not 53
55. 51 not 54
56. limit 55 to (english or french)
57. limit 56 to up=20100801-20130419
58. exp "side effects (treatment)"/
59. (harm or harms or harmful or harmed).ti,ab.
60. (risky behavior* or risky behaviour*).ti,ab.
61. (adverse effects or adverse events or mortality or toxicity).ti,ab.
62. morbidity/
63. weight cycling.ti,ab.
64. disordered eating.ti,ab.
65. injuries/
66. athletic injur*.ti,ab.
67. exp nutritional deficiencies/
68. nutritional defici*.ti,ab.
69. "arrhythmias (heart)"/
70. Arrhythmia*.ti,ab.
71. osteoporosis/
72. (bone mass adj3 loss).ti,ab.
73. bone resorption.mp.
74. (death or deaths).ti,ab.
75. suicide/ or attempted suicide/
76. suicid*.ti,ab.
77. or/58-76
78. 40 and 77
79. case-control studies.mp.
80. case-control.ti,ab.
81. (cohort or longitudinal or follow-up or followup or prospective*).ti,ab.
82. (comparison group* or control group*).ti,ab.
83. observational.ti,ab.
84. retrospective*.ti,ab.
85. database*.ti,ab.
86. nonrandom*.ti,ab.
87. population*.ti,ab.
88. or/79-87
89. 78 and 88
90. limit 89 to (100 childhood or 120 neonatal or 140 infancy or 160 preschool age or 180 school age or 200 adolescence)
91. limit 89 to ("300 adulthood " or 320 young adulthood or 340 thirties or 360 middle age or "380 aged " or "390 very old ")

92. 90 not 91
93. 89 not 92
94. animals/ not humans/
95. 93 not 94
96. limit 95 to (english or french)
97. limit 96 to up=20100801-20130419
98. 57 or 97

Medline - OVID (CQ)

August 16, 2013
1. exp continental population groups/
2. exp Ethnic Groups/
3. indians, north american/ or inuits/
4. first nations.tw.
5. (aboriginal? and canada).tw.
6. native canadians.tw.
7. (immigran* or new canadians).tw.
8. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian?).mp.
9. Rural Population/
10. (rural adj (population? or area? or region?)).tw.
11. Rural Health/ or Rural Health Services/
12. Healthcare Disparities/
13. Social Class/
14. poverty/
15. socioeconomic.tw.
16. Socioeconomic Factors/
17. (poor or disadvantaged or poverty or social status).tw.
18. exp homeless persons/ or vulnerable populations/
19. exp "Costs and Cost Analysis"/
20. (cost or costs).tw.
21. *"patient acceptance of health care"/ or *patient compliance/ or *patient participation/ or patient satisfaction/ or patient preference/ or *treatment refusal/
22. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
23. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
24. (patient? adj3 (acceptance or perference? or satisfaction or experience?)).tw.
25. willingness to pay.tw.
26. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
27. exp Canada/
28. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).tw.
29. (meta anal* or metaanal*).ti,ab.
30. meta-analysis.pt,ti,ab,sh.
31. (meta anal$ or metaanal$).ti,ab,sh.
32. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
33. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.

34. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
35. (medline or embase or cochrane or pubmed or pub med).ti,ab.
36. or/33-35
37. review.pt,sh.
38. 36 and 37
39. or/30-32
40. 38 or 39
41. "Process Assessment (Health Care)"/ or Quality Indicators, Health Care/ or Quality Assurance, Health Care/
42. Benchmarking/
43. (performance adj2 (indicators or measures)).tw.
44. or/41-43
45. or/1-28
46. 44 or 45
47. 40 and 46
48. Weight Reduction Programs/
49. exp obesity/pc
50. Overweight/pc
51. weight maintenance.tw.
52. weight management.tw.
53. exp *obesity/
54. *overweight/
55. *Weight Gain/
56. exp obesity/
57. overweight/
58. weight gain/
59. Weight Loss/
60. (weight or bmi or body mass index or waist circumference or obese or obesity).ti.
61. or/48-60
62. 47 and 61
63. limit 62 to yr="2007 -Current"
64. limit 63 to (english or french)
65. 29 or 30 or 31 or 32 or 33 or 34
66. 46 and 61 and 65
67. limit 66 to yr="2007 -Current"
68. limit 67 to (english or french)
69. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).ti.
70. 53 or 54 or 55 or 60
71. 69 and 70
72. limit 71 to yr="2007 -Current"
73. limit 72 to (english or french)
74. weight gain/de
75. molecular weight.ti.
76. 74 or 75

77. (Meta-analysis or review).pt. or systematic review.ti.
78. 64 and 77
79. 73 or 78
80. 79 not 76
81. limit 80 to ed=20121017-20130816

EMBASE – OVID (CQ)
August 16, 2013
1. meta analysis/
2. systematic review/
3. (systematic* adj3 (review* or overview*)).tw.
4. exp "ethnic and racial groups"/
5. first nations.tw.
6. (aboriginal? and canada).tw.
7. native canadians.tw.
8. (immigran* or new canadians).tw.
9. ((African or Asian or Indo or Columbian or Spanish or Chinese) adj2 Canadian).mp.
10. rural health care/
11. rural population/
12. (rural adj (population? or area? or region?)).tw.
13. exp economic evaluation/
14. cost.tw.
15. or/13-14
16. exp patient attitude/
17. (women? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
18. (consumer? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
19. (patient? adj3 (acceptance or preference? or satisfaction or experience?)).tw.
20. willingness to pay.tw.
21. ((conjoint or contingent) adj3 (valuation or analysis)).tw.
22. or/16-21
23. ((process or performance or outcome) adj2 (measure? or indicator?)).tw.
24. performance measurement system/
25. or/23-24
26. exp socioeconomics/
27. exp social status/
28. (poor or disadvantaged or poverty or social status).tw.
29. health care disparity/
30. miscellaneous named groups/ or lowest income group/ or medically underserved/ or vulnerable population/
31. or/4-12
32. or/26-30
33. 15 or 22 or 25 or 31 or 32
34. exp Canada/
35. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).tw.

36. or/34-35
37. *obesity/
38. *diabetic obesity/
39. *abdominal obesity/
40. *morbid obesity/
41. *weight reduction/
42. obes$.ti.
43. overweight.ti.
44. weight.ti.
45. or/37-44
46. (weight loss adj (intervention$ or program$ or trial$)).ti,ab.
47. (weight reduc$ adj (intervention$ or program$ or trial$)).ti,ab.
48. (weight management adj (intervention$ or program$ or trial$)).ti,ab.
49. (weight control adj (intervention$ or program$ or trial$)).ti,ab.
50. 37 or 38 or 39 or 40
51. 41 and 50
52. 33 and 45
53. 1 or 2 or 3
54. 15 or 22 or 25 or 31 or 32 or 36
55. 53 and 54
56. 45 or 51
57. 55 and 56
58. limit 57 to yr="2007 -Current"
59. limit 58 to (english or french)
60. (Canada or Canadian or Ontario or British Columbia or Alberta or Saskatchewan or Manitoba or Quebec or Nova Scotia or Prince Edward Island or Newfoundland or New Brunswick or Yukon or Northwest Territories or Nunavut).ti.
61. 56 and 60
62. limit 61 to yr="2007 -Current"
63. limit 62 to (english or french)
64. 59 or 63
65. limit 64 to em="201237-201332"

Appendix 2: Acknowledgements

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