The efficacy and safety of liraglutide for the management of obesity in individuals without diabetes: Systematic review and meta-analysis

A thesis submitted in fulfillment of the requirements for the degree of Master of Science in Medical Research Methodology

By

Theodoros Michailidis

Thessaloniki, December 2018
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At The Faculty of Health Sciences School of Medicine Aristotle University of Thessaloniki

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Supervisor: Apostolos Tsapas MD, PhD, MSc (Oxon)
Member of advisory Committee: Eleni Bekiari MD, MSc, PhD
Member of advisory Committee: Anna-Bettina Haidich MSc, PhD

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**Abbreviations**

ADA: American Diabetes Association  
BMI: Body Mass Index  
CENTRAL: Cochrane Central Register of Controlled Trials  
EMA: European Medicines Agency  
ES: Endocrine Society  
FDA: United States Food and Drug Administration  
FPG: Fasting Plasma Glucose  
GLP-1: Glucagon like Peptide-1  
GLP-1 RA: Glucagon like Peptide-1 Receptor Agonist  
HbA1c: Glycated haemoglobin  
ITT: Intention to Treat Analysis  
Kg: Kilograms  
MESH: Medical Subject Headings  
Mg: Milligrams  
NAFLD: Non-Alcoholic Fatty Liver Disease  
OR: Odds Ratio  
OSA: Obstructive Sleep Apnea  
RCT: Randomized Controlled Trial  
SD: Standard Deviation  
SE: Standard Error  
SR: Systematic review  
T2DM: Type 2 Diabetes Mellitus  
WC: Waist Circumference  
WMD: Weighted Mean Difference
The efficacy and safety of liraglutide for the management of obesity in individuals without diabetes: Systematic review and meta-analysis

Abstract

Background
Obesity is a disease with global burden and serious impact on health. It is related with other conditions such as hypertension, diabetes mellitus that independently or combined, increase the cardiovascular risk of an individual and can lead to death. Its prevalence is constantly rising due to poor dietary habits, sedentary lifestyle and other environmental and behavioral factors. The primary treatment of obesity is based on lifestyle modifications. If the latter fail, anti-obesity agents are administered.

Liraglutide is a GLP-1 receptor agonist (GLP-1 RA) that has been approved by FDA and EMA for the treatment of Type 2 Diabetes Mellitus (T2DM) at 1.2 and 1.8mg dose. Its efficacy on weight loss was documented in previous studies with diabetic population. In 2015 it was approved by EMA and FDA for treatment of obesity at the dose of 3.0mg. The aim of this systematic review and meta-analysis is to assess the efficacy and safety of liraglutide for management of obesity in non-diabetic individuals.

Materials and Methods
We searched Medline (via PubMed), Cochrane library (CENTRAL) and sources of grey literature for randomized controlled trials (RCT) conducted between June and October of 2018 that evaluated the efficacy and safety of liraglutide 3.0mg against placebo or any active comparator.

Results
We included five RCTs with 4,942 patients that compared liraglutide against placebo. Liraglutide reduced body weight by 5.56kg [weighted mean difference (WMD); 95% CI (-5.96, -5.16); p-value<0.00001, I²=0%]. More participants in the intervention group lost at least 5% [odds ratio OR: 4.86, 95% CI (3.76, 6.28), p-value<0.00001] or 10% of their initial body weight [OR: 5.09, 95% CI (3.65, 7.08), p-value<0.00001]. Liraglutide achieved greater effect on all weight related markers such as BMI index [WMD -2.00, 95% CI (-2.15, -1.85), p-value<0.00001, I²=0%] and waist circumference
-4.20cm [WMD, 95% CI (-4.6, -3.79), p-value<0.00001, I²=0%]. Liraglutide’s administration was associated with increased incidence of gastrointestinal disorders such as nausea and vomiting. Hypoglycemia incidence was rare and none of the recorded events was considered severe according to the trial’s investigators. However, each study had used different classification scale for the severity of hypoglycemia and consequently the reported incidence could not be presented systematically. Five events of acute pancreatitis were recorded, four to the liraglutide treated group and one in the placebo group. Cases of c-cell myeloid carcinoma were not reported across all studies.

**Conclusion**

Based on the results of this systematic review and meta-analysis, liraglutides’ effect on weight reduction accompanied with its well established safety profile, create an efficient treatment option against obesity. Further trials are needed in order to extract reliable conclusions about the comparison of liraglutide with other anti-obesity agents.
A. Introduction

Obesity incidence is surging in most western societies. The disease and other relevant comorbidities, increase morbidity and mortality. At the same time, the burden on the national health systems of each respective country seems to be unbearable. Poor dietary habits, sedentary lifestyle, anxiety, depression, reduced physical activity are some factors that lead to the rapid increase of its prevalence. While lifestyle modifications are the recommendations and guidance given to obese patients, many patients fail to reach the agreed goals. Inevitably, the medical community is in constant search for new therapeutic options to address this problem.

Liraglutide is a Glucagon Like Peptide-1(GLP-1) analogue that is being used for the treatment of diabetes. In 2015 the European Medicine Agency (EMA) and US Food and Drug Administration (FDA) approved the use of liraglutide for the treatment of obesity in obese adults with initial BMI≥30 Kg/m² or overweight individuals with BMI≥27 kg/m² at the presence of at least one weight-related comorbidity. (1)

A.1 Obesity

A.1.i History and pathogenesis

Obesity is a disease implicated with multiple pathological conditions that have serious consequences on health. (2) It is characterized by excessive fat concentration and it is classified according to the body mass index rating. An individual is considered obese or overweight if his or her BMI is >30kg/m² or ≥25kg/m² respectively. (3) The growing prevalence has turned obesity into a global menace both for adults and for children. Moreover, it has been associated with increased incidence of cardiovascular disease. Hypertension, non-alcoholic fatty liver disease, dyslipidemia, diabetes mellitus, obstructive sleep apnea are the most common comorbidities associated with obesity that contribute significantly to the increased cardiovascular risk of those people. Results from recent studies have shown the direct association between body mass index, all-cause mortality and morbidity while participants with BMI between 20 and 24.9 seems to have the lowest proportion of all-cause mortality. (4)(5) External appearance, easy fatigue with low intensity exercise, pains of musculoskeletal system are some weight related practical issues that affect daily routine and have crucial impact on each person’s self-esteem explaining at some level the co-existence of anxiety and depression among obese
individuals. Obesity is a result of both genetic and metabolic factors, but the largest share of responsibility lies upon environmental and behavioral factors such as poor dietary habits and depression. Its increasing prevalence is strongly associated with the so-called “Western lifestyle” defined by a diet high in calories and unsaturated fats along with wrong meal times and lack of physical activity.(6) The pattern is relatively simple, calories intake is higher than that of a person's energy expenditure throughout the day. Thus, body weight increases and if this condition remains chronic, it inevitably causes structural changes in the metabolic profile of the human body. More specifically, there are hormones with orexigenic activity such as ghrelin, satiety hormones such as leptin and GLP-1 and many others that through the central nervous system actually regulate the level of energy expenditure and food intake. Obesity is characterized by a devastating effect on the balance of these hormones resulting in a disorder of appetite, but mainly of satiety. For example, leptin is the responsible hormone for energy consumption and inhibition of appetite. As it is produced by adipose tissue, its serum levels in obese individuals are almost always elevated.(7) However, after a chronic state of increased body weight, patients appear to develop some degree of resistance to its action. (8) This was highlighted in experimental models with mice which showed that administration of leptin did not exert its effect on body weight regulation. Hence efforts to discover drugs targeting this pathophysiologic pathway were abandoned. (9) There are more well-recognized peptides, hormones and metabolic pathways, both central and peripheral, related to body weight regulation and the discovery of new anti-obesity medications development is based on these. (10)

A.1.ii Management of patients with obesity

All overweight or obese individuals should be advised to follow a low calorie diet (LCD) and increase their physical activity. Every patient should be informed about the scientific proofs that implicate increased body mass index (BMI) with increased cardiovascular risk (CVR) or type 2 diabetes mellitus (T2DM) incidence. In order to achieve greater weight loss and more importantly to sustain this result, the patient has to adopt the proposed lifestyle modifications by basically changing his whole way of thinking. Visits to a physician and proper management may facilitate patient’s adaptation to the essential modifications. The physician should be able to discuss with the patient about the weight loss benefits, focusing on specific benefits
regarding long-term clinically important outcomes, including incidence of cardiovascular events, diabetes, sexual function and overall quality of life. It is important to mention that obesity should not be treated as a separate entity, but the physician should also pay attention to the management of related comorbidities. For example, obesity is responsible for many cases of resistant hypertension. Results from a meta-analysis have shown that body weight reduction is also associated with a reduction in blood pressure. At the same time, it leads to enhanced response to anti-hypertensive treatment resulting to better regulation of uncontrolled hypertension.(11) Another example is a class of obese patients who also suffer from obstructive apnea syndrome. Results from several studies have shown the bi-directional relationship of these two clinical entities. In particular, the more obstructive sleep apnea is regulated, the easier is for the patient to lose weight and adapt to the proposed lifestyle modifications. On the other hand, weight loss seem to have a positive effect which leads to better regulation of the sleep apnea syndrome.(12) In conclusion, the physician should devise and offer a realistic treatment plan, acknowledging the obstacles an individual has to overcome to sustain set goals. If the patient realizes the importance of the therapeutic interventions, there are greater chances that he will adhere to the recommended lifestyle. (13)

A.1.iii Current management of obesity

A realistic goal for obese patients is loss of 5% to 10% of the initial body weight within 6 months, by adoption of a low calorie diet (LCD) and increased physical activity. Treatment of obese patients should be multifaceted and aim towards both weight loss and essential psychological support. Assessment of obesity level is achieved by means of BMI. A cut-off level of ≥25 Kg/m² is used to define overweight condition while a BMI≥30 Kg/m² is considered obesity. However, before devising a treatment strategy one should consider each person’s medical history, mental status, comorbidities, level of physical activity and baseline laboratory tests. Diet and increased physical activity are the first line treatment options. Patients should follow a low-calorie diet with a 500 – 750 kcal deficit accompanied with daily work-out. Based on existing guidance, in individuals with BMI≥ 30 kg/m² or BMI≥ 27 kg/m² with at least one weight-related comorbidity (such as hypertension, dyslipidaemia, type 2 diabetes mellitus or obstructive sleep apnoea) one should consider adjunct therapies
to strict lifestyle interventions. (13)(3) The goal of weight loss agents is to facilitate the patient’s adjustment to the low-calorie diet while at the same time achieving rapid weight loss. In patients with multiple comorbidities the whole treatment strategy should be re-assessed. Clinicians must also be vigilant for drugs that have been associated with weight gain and discontinue their administration, choosing other drugs with a more favourable weight profile. For example, several medications used for psychiatric or neurological disorders have been associated with weight gain. Modifying existing treatment plans is often a significant challenge. Hence, decisions should be made in a shared-decision manner, by the clinician, the patient and the close family.(14) In addition, one should also design a strategic body weight maintenance plan, as after an average of six months drug therapy efficacy usually weakens, with a significant proportion of patients regaining lost weight during the following year. This could be associated with increased levels of ghrelin, which has orexigenic effect, and the decreased levels of leptin respectively which are observed during the early treatment stages.(3)

A.1.iv Summary of treatment options for obesity
Currently there are only a few agents that have been approved for treatment of obesity. Orlistat, lorcaserin, the combination of bupropion/naltrexone are the anti-obesity agents that have been approved by the FDA and EMA. Orlistat is a selective pancreatic lipase inhibitor that reduces fat absorption. Compared to placebo, it is associated with a mean weight loss of approximately 3kg according to the results from a meta-analysis.(15) The most common side effect is macronutrients deficiency, especially regarding fat-soluble vitamins. This is attributed to its mechanism of action that induces the excretion of dietary fat and consequently affects the absorption of fat-soluble vitamins. (16) Patients on orlistat are advised to follow a low-calorie diet with decreased fat concentration in order to avoid gastrointestinal disorders and especially steatorrhea. Lorcaserin is another agent that acts in the nervous system as 2c-serotonin receptor agonist. It mediates its weight lowering effect by decreasing appetite centrally through the hypothalamus.(17) Phentermine/topiramate, is a combination of an amphetamine analog with an antispasmodic agent, also acting on the central nervous system. Trials have documented its efficacy in reduction of body weight compared to placebo.(18) However it should be used with caution in patients with uncontrolled hypertension.
due to its sympathomimetic way of action. This agent is not approved in Europe due to lack of sufficient safety evidence, while in the US long term use remains off-label.(19) Bupropion/naltrexone reduces appetite and increases satiety by activating the pro-opiomelanocortin metabolic pathway that acts on the hypothalamus and regulates food intake and body weight. Results from large trials have documented the significant efficacy of this combination in reducing body weight compared to placebo. Nevertheless, due to bupropion’s sympathomimetic effect, it increases hypertension similarly with phentermine and it should be avoided in hypertensive patients.(20) It is important to note that pharmacotherapy is efficacious only when is accompanied by a simultaneous adaptation to LCD and increased physical activity.

Bariatric surgery seems to be the only reliable solution for weight loss and maintenance through years. It is the most effective weight loss treatment that maintains results throughout time, and it is considered the optimal option for adults with BMI≥40 kg/m² or BMI≥35 kg/m² with the presence of at least one comorbidity associated with weight. There are suggestions to consider bariatric surgery in individuals with BMI<35kg/m² with coexistent diabetes mellitus which is not sufficiently regulated. Its induced rapid weight loss may also facilitate the greater glycemic control of diabetes. However, there is not enough evidence supporting this perspective.(21) Bariatric surgery’s long-term complications can be serious. Among the most common adverse effects are: malabsorption of essential macronutrients because of incomplete food digestion, gastroesophageal reflux symptoms as well as increasing incidence of hypoglycemia due to dumping syndrome. The necessity for new non-invasive and effective weight loss treatment options is of outmost importance.(22) Current guidance is that patients should not undergo surgery without having previously attended a dietary program and used an anti-obesity agent. Bariatric surgery should be considered only in case of treatment failure with anti-obesity agents, or in morbidly obese individuals due to increased risk of future complications.

A.2 Liraglutide

A.2.i Mechanism of action on weight loss
Liraglutide is a GLP-1 receptor agonist with prolonged duration of action. It is a modified human glucagon-like peptide-1. Results from trials for treatment of diabetes
have documented its favorable effect on body weight. It enhances fulfillment and satiety by delaying the gastric emptying, hence leading to reduction of body weight and adipose tissue concentration. (23) Its effects are mediated through the central nervous system and the GLP-1 receptors that are located both in the gastrointestinal system as well as in the brain and especially the hypothalamus. (24) It interacts with a series of peptides that regulate appetite by acting as a suppressant, reducing the feeling of appetite and the prospective food consumption. Its activity is glucose-dependent. Insulin and glucagon secretion are regulated in relation to blood glucose levels. In addition, the delay in stomach emptying leads to the corresponding delay in the entry of glucose into the bloodstream and insulin excretion, creating a fairly safe profile for its administration in non-diabetic obese individuals. (25) Side effects are mostly mild and well tolerated, and mainly concern the gastrointestinal system such as the increased incidence of nausea and vomiting especially at the treatment initiation. One additional feature that makes liraglutide attractive as therapeutic option is that it retains its effect on weight loss over time. This attribute derives from liraglutides’ direct impact on the hormones of satiety and it is very important, given the high percentage of obese individuals that regain weight. (26)

A.2.ii Efficacy assessment of liraglutide on weight reduction

Primary endpoints

In order to evaluate the efficacy of liraglutide as anti-obesity agent we assessed the absolute and relative weight reduction from baseline, which is also the main outcome in most clinical trials of anti-obesity agents, based on relevant EMA and FDA guidance. (27)(28)

Secondary endpoints

We explored the effect of liraglutide on additional weight-related endpoints and on the patient’s metabolic profile. Hence, we assessed the difference in body circumference, which is a reliable and simple indicator of central adiposity, and in body mass index. Other outcomes included the effect on the individual’s metabolic profile (hypertension, prediabetes status and dyslipidemia).

Adverse events
In order to explore the short- and long-term safety of liraglutide, we assessed its effect on the incidence of gastrointestinal disorders, hypoglycemia, acute pancreatitis and myeloid thyroid cancer.

B. Objectives
The aim of this thesis was to assess the safety and efficacy of liraglutide 3.0 mg for weight management in obese or overweight individuals without diabetes mellitus. We conducted a systematic review (SR) and meta-analysis of randomized controlled trials (RCTs) to compare the effect of liraglutide against placebo or any active comparator in overweight or obese individuals without diabetes mellitus. This systematic review and meta-analysis was conducted by one person as a thesis submission in fulfillment of the requirements for the degree of Master of Science in Medical Research Methodology.

C. Methods
C.1 Eligibility Criteria
(P)opulation
We included randomized controlled trials with overweight adults (BMI≥27 and ≤30 kg/m²) with at least one comorbidity associated with weight such as obstructive sleep apnea, hypertension, dyslipidemia (23), or obese adults (BMI≥30 kg/m²) without diabetes mellitus, irrespective of number of trial participants.

(I)ntervention - (C)omparator
We included trials that compared liraglutide 3.0 mg once daily with placebo or any other comparator, based on relative EMA and FDA guidance for use of liraglutide as adjunct therapy to lifestyle modifications for treatment of obesity.

(O)utcome
The primary aim was to evaluate the safety and efficacy of liraglutide 3.0 mg in individuals with obesity for weight management without diabetes mellitus. The primary outcomes of this SR and meta-analysis were the following:

- Change in absolute body weight measured in kg,
- The proportion of individuals who lost at least 5% of their baseline body weight, and
• The proportion of patients who lost more than 10% of their baseline body weight

According to EMA and FDA summary of product characteristics, treatment with liraglutide should be discontinued in individuals who fail to lose at least 5% of their initial bodyweight after 12 weeks of treatment. Based on this suggestion, trials with at least 12-week treatment duration were considered eligible to enter the systematic review. (1)

Secondary outcomes included:

• Change in BMI
• Change in waist circumference (WC, cm)
• Change in glycated hemoglobin (HbA1c, %)
• Effect on fasting plasma glucose (FPG, mg/dl)

Type of study
We included parallel or cross-over RCTs comparing liraglutide 3.0mg with placebo or any other active comparator with at least 12-week treatment with liraglutide.

C.2 Adverse events
Liraglutide is strongly associated with gastrointestinal disorders especially immediately after initiation of treatment. Hence, we extracted data regarding incidence of nausea, vomiting, diarrhea and constipation. Moreover, based on EMA and FDA guidance regarding cautious use of liraglutide in patients with a history of pancreatitis, we extracted evidence regarding episodes of acute pancreatitis. Hypoglycemia is a serious adverse event that in some cases may lead to death. Liraglutides’ effect is glucose-dependent, thus incidence of hypoglycemia is rare. We extracted cases of reported hypoglycemia. It should be noted that we extracted data for the number of patients with at least one episode of each adverse event rather than number of events that were reported.

C.3 Exclusion Criteria
• Studies that were not RCTs
• Studies that liraglutide was not used as adjunctive treatment to lifestyle modifications
• Studies that included participants with type 1 or 2 diabetes mellitus
• Studies that included participants that had undergone bariatric surgery
• Studies that included participants with drug-induced obesity or participants that received any other weight-lowering pharmacotherapy.
• Studies that compared liraglutide in any other dosing regimen except for 3.0 mg
• Studies with treatment duration less than 12 weeks

C.4 Information sources and search strategy
We designed our search strategy based on relevant Cochrane handbook guidance (29). We used search terms describing the intervention (liraglutide) and the studied condition (obesity). We searched two medical databases based on availability of access via Aristotle University resources. We also searched grey literature and abstracts of conferences of major medical associations for the study of obesity. We included only trials that were published in English and were held in humans.

We namely searched

• Medline (via Pubmed),
• Cochrane Library (via Cochrane Central Register of Controlled Trials)

and the following grey literature resources:

• Clinicaltrials.gov
• PROSPERO
• WHO International Clinical Trials Registry
• European Association for the Study of Obesity
• American Association of Obesity

We used both MESH and free text terms in order to search MEDLINE. We also included sensitivity-maximize filter for randomized controlled trials provided by the Cochrane collaboration in order to identify as many records as possible. We also hand searched references list of all collected trials in order to identify potential eligible studies. The search strategy was assessed according to the Peer Review of Electronic Search Strategies (PRESS) checklist. (30)
C.5 Study selection and Data collection Methods

C.5.i Study selection
We imported studies acquired into Mendeley Reference Management Software, and then removed duplicate records. Records retrieved were then screened at title and abstract level to identify those that fulfilled the inclusion criteria of the review. We then assessed eligibility of included records at full-text level to select those that would be finally included in the review.

C.5.ii Data Extraction
We compiled an extraction form in Excel based on relevant Cochrane handbook templates, paying special attention to the basic characteristics of each study. A summary of the extracted information are presented in the following table.

<table>
<thead>
<tr>
<th>Summary of the extracted information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Characteristics</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
</tr>
<tr>
<td>Intervention - Comparator</td>
</tr>
<tr>
<td>Primary Outcomes</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
</tbody>
</table>

C.6 Risk of Bias assessment
We used the Cochrane Collaboration risk of bias tool to assess the overall quality of the RCTs included, and deemed them at high, low or unclear risk of bias based on assessment for the following key domains:
We assessed the quality of each study for the primary outcomes of our review and we characterize them as “high”, “low” or “unclear risk of bias”. Trials without details for the aforementioned domains were marked as “unclear risk of bias”.

C.7 Effect measures and heterogeneity analysis
In case of continuous outcomes, such as change in body weight or BMI, we calculated weighted mean difference (WMD) between the studied groups. Extracted results were converted to the same metric scale. Continuous outcomes were presented by weighted mean difference (WMD) and standard deviation (SD) with 95% confidence intervals (CIs). Dichotomous outcomes were synthetized to calculate odds ratio (OR) with 95% CIs. Heterogeneity level was evaluated using Chi-squared test and $I^2$, with a p-value<0.1 or $I^2$>70% representing high heterogeneity. Missing data were imputed based on relevant guidance in the Cochrane handbook for Systematic Reviews. To ensure the most representative weighting of the included trials, we used an inverse variance random effects weighted model to synthesize all data. If the results showed low heterogeneity ($I^2$<30%) we utilized an inverse-variance fixed effects weighted model. In case of moderate heterogeneity (30-70%), we also utilized random effects models. We have scheduled to perform subgroup analysis according to the participant’s prediabetes status. We considered interesting to observe if there was any difference in liraglutide’s efficacy on bodyweight between individuals with and without prediabetes. In addition, we would like to record how many of the patients with prediabetes would have prediabetes, diabetes mellitus type 2 or normoglycemia after completing treatment with liraglutide. However, this was not possible due to limited data from the studies included in the review.
D. Data synthesis

In this section our data analysis is presented. We proceeded to a meta-analysis for the comparison of liraglutide versus placebo since the baseline characteristics of the included trials were quite homogenous. In cases the data were insufficient for meta-analysis the results were qualitatively presented. We have used the software program Review Manager version 5.3 for the quantitative synthesis of the extracted data.

D.1 Search results

Searching for eligible trials was conducted for trials that were published before the 22nd of October 2018. 1850 records were initially evaluated and after the removal of duplicates 958 were assessed at title and abstract level. Finally 39 records were evaluated at full-text level, and 9 records describing 5 trials were included in the systematic review and meta-analysis. The whole process is presented in the flow diagram below according to PRISMA statement. (31)
We retrieved 17 additional records through hand searching of grey literature sources: Clinicaltrials.gov (15) and Conference Abstracts (2).

1,833 records retrieved: Medline (1,369) and Cochrane Library (464)

892 record were removed as duplicates

958 records were screened by title and abstract

919 records excluded by screening at title and abstract level

39 records evaluated in full text for eligibility

30 records excluded:
- 4 did not fulfill eligibility criteria
- 4 used different dose ranges
- 3 same populations
- 6 were ongoing trials
- 5 had a wrong study design
- 6 used different interventions
- 2 recruited wrong patient population

9 records describing 5 trials included in the systematic review and meta-analysis

**Figure 1.** Flow diagram of study selection process
One study was excluded due to short treatment duration (two treatment rounds, 5 weeks each in order to assess the effect of liraglutide on body weight). Nevertheless, it is worth mentioning that participants exposed to liraglutide 3.0 mg had a statistically significant weight reduction in those 5 weeks of treatment compared to placebo group. (32) A study that evaluated liraglutide 3.0mg against placebo was excluded because it did not explicitly list type 2 diabetes as an exclusion criterion.(33) Another trial was excluded because liraglutide has not been used as an adjunct therapy to lifestyle modifications and therefore does not comply with the guidelines for its use as an obesity treatment. In this study, liraglutide was administered to a group of patients without lifestyle modifications and was compared to another group of patients who were on a low calorie diet and increased physical activity. The result is quite impressive, as it seemed that absolute weight reduction was similar between the studied groups. This highlights once again the significance of lifestyle modifications in order to achieve weight loss and that liraglutide should be administered as adjunct therapy. (34)

D.2 Study characteristics
Finally, we included five randomized controlled trials involving a total of 5,765 patients. All studies compared 3.0 mg liraglutide with placebo except the trial by Astrup et al which included also an open-label arm with orlistat, and the study by O’ Neil et al which had multiple arms of semaglutide in different dosage regimens. Data extracted from the 5 trials were synthesized for all pre-specified outcomes. Nevertheless, for the comparison against orlistat and semaglutide there were data only from a single trial, hence results are presented only qualitatively. Duration of treatment ranged from 32 to 56 weeks. One trial contributed more than 50% of the sum of participants included in this review; hence we explored robustness of the main analysis by means of a sensitivity analysis excluding data from the specific trial. (35) The basic characteristic of the included studies are presented in table 1.

D.3 Participants characteristics
All study participants were overweight or obese adults without diabetes and with at least one weight related condition. Table 1 depicts the baseline characteristics of the participants enrolled in the meta-analysis and were treated with liraglutide, placebo
or any other active comparator. Astup et al trial had an also an open-arm of treated with orlistat and O’Neil et al trial had several arms with different semaglutide doses. In both trials the baseline characteristics of the individuals recruited were quite homogenous. Participants were overweight or obese adults, mostly females except from patients included in the trial by Blackman et al, probably due to its inclusion criteria that included moderate to severe OSA, which is known to be more frequent among males.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>NCT</th>
<th>Patients</th>
<th>Duration</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Mean age (SD)</th>
<th>Weight (Kg, SD)</th>
<th>BMI (kg/m^2,SD)</th>
<th>WC (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrup 2012</strong></td>
<td>NCT00480909</td>
<td>296</td>
<td>52</td>
<td>Liraglutide 3.0mg</td>
<td>Placebo</td>
<td>25%</td>
<td>75%</td>
<td>45.9 ± 10.7</td>
<td>97.6 ± 13.7</td>
<td>34.8 ± 2.8</td>
<td>109 ± 8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Orlistat</td>
<td>25%</td>
<td>75%</td>
<td>45.9 ± 10.3</td>
<td>97.3 ± 12.3</td>
<td>34.9 ± 2.8</td>
<td>108 ± 9.9</td>
</tr>
<tr>
<td><strong>Wadden 2013</strong></td>
<td>NCT00781937</td>
<td>422</td>
<td>56</td>
<td>Liraglutide 3.0mg</td>
<td>Placebo</td>
<td>16%</td>
<td>84%</td>
<td>45.9 ± 11.9</td>
<td>100.4 ± 20.8</td>
<td>36.0 ± 5.9</td>
<td>109.4 ± 15.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>21%</td>
<td>79%</td>
<td>46.5 ± 11</td>
<td>98.7 ± 21.2</td>
<td>35.2 ± 5.9</td>
<td>107.8 ± 15.2</td>
</tr>
<tr>
<td><strong>Pi Sunyer 2015</strong></td>
<td>NCT01272219</td>
<td>3.731</td>
<td>56</td>
<td>Liraglutide 3.0mg</td>
<td>Placebo</td>
<td>21.3%</td>
<td>78.7%</td>
<td>45.2 ± 12.1</td>
<td>106 ± 21.2</td>
<td>38.3 ± 6.4</td>
<td>115.0 ± 14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>21.9%</td>
<td>78.1%</td>
<td>45.0 ± 12.0</td>
<td>106.2 ± 21.7</td>
<td>38.3 ± 6.3</td>
<td>114.5 ± 14.3</td>
</tr>
<tr>
<td><strong>Blackman 2016</strong></td>
<td>NCT01557166</td>
<td>359</td>
<td>32</td>
<td>Liraglutide 3.0mg</td>
<td>Placebo</td>
<td>71.7%</td>
<td>28.3%</td>
<td>48.6 ± 9.9</td>
<td>116.5 ± 23.0</td>
<td>38.9 ± 6.4</td>
<td>122.3 ± 14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>72.1%</td>
<td>27.9%</td>
<td>48.4 ± 9.5</td>
<td>118.7 ± 25.4</td>
<td>39.4 ± 7.4</td>
<td>122.7 ± 14.9</td>
</tr>
<tr>
<td><strong>O’ Neil 2018</strong></td>
<td>NCT02453711</td>
<td>957</td>
<td>52</td>
<td>Liraglutide 3.0mg</td>
<td>Placebo</td>
<td>35%</td>
<td>65%</td>
<td>49 ± 11</td>
<td>108.7 ± 21.9</td>
<td>38.6 ± 6.6</td>
<td>116.2 ± 13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Semaglutide 0.05mg</td>
<td>35%</td>
<td>65%</td>
<td>46 ± 13</td>
<td>114.2 ± 25.4</td>
<td>40.1 ± 7.2</td>
<td>119.5 ± 15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Semaglutide 0.1mg</td>
<td>35%</td>
<td>65%</td>
<td>47 ± 13</td>
<td>111.3 ± 23.2</td>
<td>39.1 ± 6.5</td>
<td>117.0 ± 14.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Semaglutide 0.2mg</td>
<td>36%</td>
<td>64%</td>
<td>44 ± 11</td>
<td>114.5 ± 24.5</td>
<td>40.1 ± 6.9</td>
<td>119.1 ± 15.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Semaglutide 0.3mg</td>
<td>36%</td>
<td>64%</td>
<td>47 ± 12</td>
<td>111.4 ± 23.0</td>
<td>39.6 ± 7.1</td>
<td>118.1 ± 15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Semaglutide 0.4mg</td>
<td>35%</td>
<td>65%</td>
<td>48 ± 13</td>
<td>113.2 ± 26.4</td>
<td>39.9 ± 8.8</td>
<td>119.0 ± 16.3</td>
</tr>
</tbody>
</table>

Table 1. Study characteristics
D.4 Quality assessment of included trials

Quality assessment of include trials for the primary outcomes is presented in figures 2 and 3. The evaluation was conducted in 7 domains according to the Cochrane risk of bias tool.

![Risk of bias graph](image)

**Figure 2.** Risk of bias graph: Each risk of bias item presented as percentages across all included studies.

Trials by Astrup and O’Neil were characterized as high risk of bias in the “blinding of participants and personnel” domain. In particular, in trial by Astrup et al, the sponsor and the staticians were unblinded after the 20th week of intervention and the orlistat arm was open–label from the beginning introducing potential bias. Investigators in the trial by O’Neil et al used on-demand allocation concealment. The trial was held in multiple recruitment centers and different dosage regimens of semaglutide have been evaluated. Additionally, no-one was masked to the different regimens and consequently the generated sequence could be predicted introducing bias. We deemed the trial by Blackman et al as high risk of attrition bias due to the many withdrawals without post-baseline data. Moreover, there was a high percentage of individual that did not complete the trial.
Figure 3. Risk of bias summary: Each risk of bias item for each included study

D.5 Outcomes

D.5.i Liraglutide versus placebo

Primary Efficacy Outcomes

Effect on body weight (kg)

Results are based on data from 4,857 patients. Liraglutide led to a significant reduction in body weight compared to placebo (WMD -5.56kg; 95% CI -5.96 to -5.16; p-value<0.00001; Chi²=1.84, I²=0%). Results were mainly driven by the study by Pi_Sunyer et al, which was larger than all other studies combined; hence we conducted a sensitivity analysis excluding the specific trial.
Results of the sensitivity analysis were similar with those of the main analysis, and heterogeneity remained low (WMD: -5.45; 95%CI: -6.25 to -4.64; p-value<0.00001; Chi²=1.74, I²=0%)

Percentage of participants who lost ≥5\% of their initial body weight

More participants in the liraglutide treated group (1.867/3014) achieved to lose≥5\% from their baseline bodyweight than those from placebo group (469/1843) (OD: 4.86; 95%CI: 3.76 to 6.28, p-value<0.00001). Heterogeneity level was moderate and was presented with random effects model (Chi²=7.79, I²=49%).
The results remained in favor of the liraglutide treated group even without the largest trial (OD: 5.17; 95%CI: 3.39 to 7.89) and heterogeneity level remained almost unchanged. (Chi²=7.71, I²=61%).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Liraglutide Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Odds Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrup2012</td>
<td>73</td>
<td>92</td>
<td>20</td>
<td>90</td>
<td>9.01 [4.92, 18.74]</td>
</tr>
<tr>
<td>Blackburn2018</td>
<td>81</td>
<td>175</td>
<td>33</td>
<td>178</td>
<td>27.0%</td>
</tr>
<tr>
<td>O'Neill2018</td>
<td>66</td>
<td>103</td>
<td>31</td>
<td>136</td>
<td>23.6%</td>
</tr>
<tr>
<td>Pi_Sunyer2015</td>
<td>1540</td>
<td>2437</td>
<td>332</td>
<td>1225</td>
<td>0.0%</td>
</tr>
<tr>
<td>Wadden2013</td>
<td>105</td>
<td>207</td>
<td>45</td>
<td>206</td>
<td>29.1%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>577</td>
<td>610</td>
<td>100.0%</td>
<td>5.17</td>
<td>[3.30, 7.89]</td>
</tr>
</tbody>
</table>

**Figure 7.** Odds ratio of percentage of patients who lost ≥5% of their initial body weight. Liraglutide versus placebo. Sensitivity analysis excluding the trial by Pi-Sunyer et al.

**Percentage of participants who lost >10% of their initial body weight**

The same applies to the number of patients who lost more than 10% of their initial body weight, with the results being overwhelmingly in favor of the intervention. In particular, 974 of 3014 patients taking liraglutide managed to lose more than 10% of their weight in contrast to those who received placebo who were significantly less (Placebo group 170/1843). Odds ratio for 10% loss of weight was (OD: 5.09, 95%CI: 3.65 to 7.08, p-value<0.00001) and favoring liraglutide over comparator. Heterogeneity was moderate (Chi²=6.40, I²=37%) and remained approximately the same after the removal of Pi Sunyer et al trial and the liraglutide treated group sustained its superiority over placebo.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Liraglutide Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Odds Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrup2012</td>
<td>37</td>
<td>92</td>
<td>10</td>
<td>98</td>
<td>13.7%</td>
</tr>
<tr>
<td>Blackburn2018</td>
<td>41</td>
<td>175</td>
<td>3</td>
<td>178</td>
<td>6.7%</td>
</tr>
<tr>
<td>O'Neill2018</td>
<td>35</td>
<td>103</td>
<td>14</td>
<td>136</td>
<td>16.3%</td>
</tr>
<tr>
<td>Pi_Sunyer2015</td>
<td>807</td>
<td>2437</td>
<td>100</td>
<td>1225</td>
<td>45.4%</td>
</tr>
<tr>
<td>Wadden2013</td>
<td>54</td>
<td>207</td>
<td>13</td>
<td>206</td>
<td>17.9%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3014</td>
<td>1843</td>
<td>100.0%</td>
<td>5.09</td>
<td>[3.60, 7.08]</td>
</tr>
</tbody>
</table>

**Figure 8.** Odds ratio of percentage of patients who lost >10% of their initial body weight. Liraglutide versus placebo.
In the sensitivity analysis without Pi-Sunyer trial, the results remained in favor of liraglutide and heterogeneity was low so we have used fixed effect model. [OD: 6.28, 95%CI: 4.31 to 9.14; \( \text{Chi}^2=4.19, I^2=28\% \), P-value<0.00001].

### Secondary Efficacy Outcomes

**Body Mass Index**

Liraglutide achieve greater reduction in body mass index compared to placebo (WMD:-2.00; 95%CI: -2.15 to -1.85; \( \text{Chi}^2=1.23, I^2=0\% \), p-value<0.00001). Results were verified in the sensitivity analysis following removal of the trial by Pi Sunyer. Heterogeneity was negligible in any case.
Waist Circumference (cm)

Our analysis verified the favorable effect of liraglutide on waist circumference, which is a hallmark of central obesity and adipose tissue concentration. Results were in favor of liraglutide consistently in all trials and heterogeneity was low (WMD: -4.20 cm, 95%CI: -4.60 to -3.79; Chi²=3.77, I²=0%; p <0.00001). The effect remained statistically significant in sensitivity analysis without the largest trial.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Liraglutide Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackman2016</td>
<td>-2.2</td>
<td>1.33</td>
<td>178</td>
<td>-0.6</td>
<td>1.33</td>
<td>179</td>
<td>20.8% -1.60 [-2.41, -0.79]</td>
<td></td>
</tr>
<tr>
<td>O’Neill 2018</td>
<td>-3.03</td>
<td>3.3</td>
<td>103</td>
<td>-0.69</td>
<td>3.33</td>
<td>113</td>
<td>18.0% -1.65 [-3.00, -1.33]</td>
<td></td>
</tr>
<tr>
<td>Pi_Sunyer2015</td>
<td>-3.26</td>
<td>2.43</td>
<td>745</td>
<td>-1.32</td>
<td>2.43</td>
<td>755</td>
<td>10.0% -0.40 [-2.17, -1.83]</td>
<td></td>
</tr>
<tr>
<td>Wadden2013</td>
<td>-2.1</td>
<td>2.6</td>
<td>207</td>
<td>0</td>
<td>2.6</td>
<td>206</td>
<td>60.5% -2.10 [-2.57, -1.63]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>488</td>
<td></td>
<td>521</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>-2.01 [-3.37, -1.64]</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity analysis excluding the trial by Pi-Sunyer et al.

Figure 12. Weighted mean difference for the change in waist circumference (cm). Liraglutide vs placebo.

Figure 13. Weighted mean difference for the change in waist circumference (cm). Liraglutide versus placebo. Sensitivity analysis excluding the trial by Pi-Sunyer et al.

Test for overall effect: Z = 10.53 (P < 0.00001).
Fasting plasma glucose (mg/dl) and Hba1c (%)

Liraglutide had a favorable effect on fasting plasma glucose compared to placebo (WMD: -6.85 mg/dl; 95%CI: -7.50 to -6.19; \(\chi^2=1.85\), \(I^2=0\%), p-value<0.00001).

Sensitivity analysis showed that the intervention effect was retained.

In addition, liraglutide achieved also a greater reduction in the levels of Hba1c [WMD: -0.24; 95%CI: -0.30 to -0.19; \(\chi^2=14.13\), \(I^2=72\%), p-value<0.00001].

Heterogeneity was high, even in the sensitivity analysis although the effect remained significant.
Safety Outcomes

Nausea and Vomiting

The majority of adverse events that occurred from liraglutide administration, concern the gastrointestinal system. Specifically, the incidence of nausea was significantly higher in the liraglutide group (1235/3065) compared to placebo (262/1865). [OD: 4.51; 95%CI: 3.42 to 5.94; $\chi^2$=6.83%, $I^2$=41%; $p$-value<0.00001].

Same applies to the participants that experienced at least one episode of vomiting. In that case 475 of 3065 for the intervention group had one episode of vomiting compared to controls 90/1865. The difference was again statistically significant. [OD: 2.96; 95%CI: 1.56 to 5.61; $\chi^2$=15.20, $I^2$=74%; $p$-value<0.0009] in favor of the placebo group.
Constipation and Diarrhea

Regarding constipation and diarrhea, both symptoms were more frequently reported in the intervention arms. Forest plots below illustrate this difference which appears to be significantly in favor of the placebo group. In particular 614 individuals experienced constipation in the liraglutide treated group compared to 158 in the placebo arm \([\text{OD: } 2.78, 95\% \text{CI: } 2.05 \text{ to } 3.76, \text{ Chi}^2=5.80, \text{ I}^2=31\%, \text{ p-value}<0.00001]\).

Additionally 628 participants in the intervention arm had at least one episode of diarrhea compared to 181 of the placebo group \([\text{OD: } 2.35, 95\% \text{CI: } 1.91 \text{ to } 2.89; \text{ Chi}^2=4.32, \text{ I}^2=7\%; \text{ p-value}<0.00001]\).
Incidence of hypoglycemia

Regarding hypoglycemia, we did not distinguish from the beginning which type of hypoglycemia we would extract. The American Diabetes Association (ADA) and the Endocrine Society (ES) have published in 2012 a recommended classification of hypoglycemia. (40) The five proposed categories are:

- Severe hypoglycemia
- Documented symptomatic hypoglycemia
- Asymptomatic hypoglycemia
- Probable symptomatic hypoglycemia and,
- Pseudo-hypoglycemia

The studies of our review had either different categorization of hypoglycemia severity or did not provide sufficient details about how they classified hypoglycemia (table 2). More specifically, two trials did not provide any data about the utilized hypoglycemia classification. The rest three trials have used the ADA/ES workgroup classification, although the trial by Blackman et al did not provide any data about the incidence of hypoglycemia among its population. Consequently it was not possible to synthetize the data systematically and we decided to present them qualitatively. Few hypoglycemic episodes were recorded in all included trials according to the trials’ investigators. Collected data are presented below:

i. Trials by Astrup and Blackman did not specifically clarify which types of hypoglycemia events were recorded.
ii. Trials by Astrup and Wadden they do not report which hypoglycemia scale have used in order to report their data.

iii. From the study by Blackman et al, no data were reported about the incidence of hypoglycemia.

iv. According to the investigators of four trials, most of the hypoglycemia episodes were self-reported and were not confirmed with blood measurements.

v. Data from the trial by Pi-Sunyer et al have shown that some of the recorded events were during fasting times at visits and were not accompanied with hypoglycemia symptoms.

vi. There was no recorded hypoglycemia episode that needed medical assistance and therefore none of them was characterized as severe according to the authors.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Events recorded</th>
<th>Classification</th>
<th>Events Reported</th>
<th>Severe events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrup 2012</td>
<td>No details</td>
<td>No Details</td>
<td>All</td>
<td>None</td>
</tr>
<tr>
<td>Wadden 2013</td>
<td>All</td>
<td>No details</td>
<td>All</td>
<td>None</td>
</tr>
<tr>
<td>Pi-Sunyer 2015</td>
<td>All</td>
<td>ADA/ES workgroup</td>
<td>All</td>
<td>None</td>
</tr>
<tr>
<td>Blackman 2016</td>
<td>No details</td>
<td>ADA/ES workgroup</td>
<td>No details</td>
<td>No details</td>
</tr>
<tr>
<td>‘O Neil 2018</td>
<td>All</td>
<td>ADA/ES workgroup</td>
<td>All</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 2. Trials hypoglycemia classification systems and reported incidence

**Other Adverse events**

Liraglutides’ administration is contradicted in individuals with a history of acute pancreatitis.(1) Five events of acute pancreatitis were recorded in all included trials, four in the liraglutide treated group and one in the placebo group. All included studies had an independent advisory committee that assessed those events and decided that none of those was associated with liraglutide according to the authors. Additionally liraglutide was related to the development c-cell myeloid carcinoma incidence in mice trials and therefore its use is not recommended in humans with such medical history.(41) There were no recorded cases of c-cell myeloid carcinoma across all trials.
D.5.ii Liraglutide versus orlistat
Only the trial conducted by Astrup et al had an open-arm of orlistat treated participants in which liraglutide had greater effect in all primary efficacy outcomes. Liraglutide reduced body weight compared to orlistat (WMD: -3.8 kg; 95% CI -6.0 to -1.6; p<0.001). In addition, more participants in the liraglutide group lost more than 5% of their baseline weight (73/92) compared to the orlistat treated group (44/95). Similarly, more patients lost more than 10% of their baseline weight (37/92) compared with orlistat (14/95). There were no significant differences in terms of adverse events. As mentioned above, the major adverse effects of orlistat derive from the gastrointestinal tract. Diarrhea was the predominant side effect associated with its administration, which is explained by its mechanism of action. The number of patients who experienced diarrhea in the orlistat treated group was comparatively higher than the liraglutide group. Regarding other side effects the results were quite similar between the two groups. The results of the study are consistent with the overall safety profile of orlistat.

D.5.iii Liraglutide versus semaglutide
Semaglutide is a GLP-1 receptor agonist that has been approved recently for the treatment of T2DM as monotherapy in patients with metformin intolerance or as adjunct therapy to other anti-diabetic agents. Semaglutide is administered once weekly with a starting dose of 0.25mg which is escalated every 4 weeks until the higher dosage limit of 1.0mg. The fact that semaglutide is injected once weekly while liraglutide must be injected daily gives an advantage to its administration because it is more convenient for the patient. The oral form of semaglutide is now under investigation giving a promising solution for the patients in order to avoid the discomfort and the side effects of self-injection.(42) The trial conducted by O’ neil et al assessed the effect of semaglutide on weight loss in non-diabetic obese individuals. Semaglutide was used in multiple different dosing regimens (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg), and was administered daily in contrast with the once-weekly administration for the treatment of diabetes. The efficacy of semaglutide on all primary endpoints was dose-dependent and was statistically significant compared to placebo in all cases. Additionally, doses up to 0.1 mg had a similar effect to liraglutide and any difference was not statistically significant. In particular
individuals that were treated with semaglutide 0.05mg had a mean weight loss of -6.66kg(±9.49), those treated with semaglutide 0.1mg a mean of -9.34kg(±9.39) while liraglutide treated patients had a mean weight loss of -8.47kg(±9.43). In addition, the percentage of individuals that lost at least 5% or 10% of their initial bodyweight was 54% and 19% respectively for individuals treated with semaglutide 0.05mg, 67% and 37% for the dosage of 0.1mg, while for liraglutide was 66% and 34%. As the dose of semaglutide increased to 0.2, 0.3mg, 0.4mg the effect on weight loss and other weight related parameters was greater compared to liraglutide, and differences were statistically significant. Specifically semaglutide 0.2mg achieved a mean absolute weight reduction -12.30kg(±9.43), participants in the semaglutide 0.3mg arm lost a mean -12.45kg(±9.43), while those treated with semaglutide 0.4mg lost -15.15kg(±9.29). The difference was statistically significant compared to liraglutide for all the aforementioned dosage regimens(p-value≤0.0001). Currently semaglutide is only approved for weekly administration in diabetic population and the dose must not exceed the 1mg. However, the study results are very promising regarding the future of semaglutide (with a different dosage regimen) as a novel agent against obesity. Adverse events were similar between liraglutide and semaglutide and were mainly related to gastrointestinal disorders. According to the authors, incidence of hypoglycaemia was rare among all studied arms. It is important to mention that most of recorded events were self-reported and not confirmed by blood measurements. Based on the ADA/ES workgroup classification none of those episodes was categorized as “severe” or “documented” hypoglycaemia. Events of acute pancreatitis were also few. Specifically four events of acute pancreatitis were recorded in the semaglutide treated groups, none in the liraglutide, and one in the placebo group. Nevertheless, according to the trial’s advisory committee, events were not considered to be relevant to the intervention but to patients with predisposing factors such as gallbladder disorders. Cases of c-cell myeloid carcinoma were not recorded. Further studies are needed in order non-diabetic obese individuals in order to define the appropriate dose and frequency of semaglutide for their treatment.
E. Discussion

The primary objective of the systematic review was to collect all studies that assessed the use of liraglutide for treatment of obesity in non-diabetic subjects, and synthetize them systematically. We included only trials that utilized 3.0mg of liraglutide, which has been approved for obesity treatment in non-diabetic population. The endpoints for assessing the efficacy and safety of liraglutide were selected according to EMA guidance and in symphony with previous studies and meta-analyses. Unfortunately, the majority of studies compared liraglutide to placebo, and data for the direct comparison with other approved weight loss agents are scarce. Finally 5 trials met the eligibility criteria and were included in the systematic review. Based on the results of the meta-analysis, liraglutide was superior to placebo for all three primary endpoints. In particular, it has led to a significant reduction in body weight [WMD: -5.56, 95%CI: (-5.96, -5.16), p-value<0.00001, I²=0%]. Additionally, the proportion of individuals that lost ≥5% or >10% of their baseline bodyweight in liraglutide treated group was 61.9% and 32.3% respectively compared to the placebo treated group which was 25.4% and 9.2%, a difference that was statistically significant (p-value<0.00001). We conducted a post-hoc sensitivity analysis excluding the largest population study driving the results of the main analysis, to verify robustness of our findings, and results were consistent. Regarding the categorical variables that showed relatively modest heterogeneity, liraglutide retained its superiority while removing the trial by Pi Sunyer et al. Categorical primary outcomes were presented using a random effects weighted model to calculate odds ratios and 95% confidence intervals, according to the Cochrane handbook because heterogeneity level was moderate. We have to mention that the trial by Blackman et al may was the source responsible for the increased heterogeneity levels. Participants in this study were obese individuals with obstructive sleep apnea. In fact 7% of the trial's sample size withdrew without providing any post-randomization data and a total of 23% participants in both groups did not manage to complete the study. In trials with such population it is generally observed that attrition rates are high. Polysomnographic overnight assessments are usually a burden for the patient and therefore it is difficult to retain them in the trial until completion. Additionally, a proportion of those patients withdrawn from the study as they did not notice a substantial change to their overall health status and cannot comply with the recommended modifications.(43)(38) This may be the reason why
we see such an important difference in success rates in all weight related categories between liraglutide and placebo treated groups. Regarding other weight related markers, liraglutide’s efficacy remained significant for body mass index [WMD: -2.00 index rating, 95%CI: (-2.15, -1.85), p-value<0.00001, I²=0%] and waist circumference [WMD: -4.20cm, 95%CI (-4.60, -3.79), p-value<0.00001. I²=0%].

The population of our review was non-diabetic obese patients. However, all patients in the liraglutide group experienced improvement in glycemic control, which was reflected in the reduction of both fasting plasma glucose measurements and in glycosylated hemoglobin. Based on the definition by ADA, pre-diabetes is essentially the antechamber for the onset of type 2 diabetes. It is of outmost importance for an individual to try to delay or even intercept the onset of diabetes. A subgroup analysis according to how many participants were at prediabetes status before and after treatment with liraglutide would be an interesting issue of research. However, we had data from only one trial and consequently we could not proceed to this analysis. Results from the trial by Pi-Sunyer et al have shown that the prevalence of prediabetes was reduced in the liraglutide treated participants and therefore the incidence of type 2 diabetes has decreased. It is possible that liraglutide induced weight loss accompanied with the better glycemic control have led to this outcome. On the other hand, incidence of hypoglycemia was rare across all studies according to the authors. It is important to mention that the included trials reported hypoglycemia using different classification scales of its severity. Consequently, we were unable to synthesize those data systematically. According to the investigators of all trials most of the recorded events were self-reported or during fasting times in visits without symptoms. Moreover, none of the hypoglycemic events needed medical assistance and was not characterized “as severe hypoglycemia”. Perhaps this is explained by the glucose-dependent mechanism of action which supports its safe profile for administration to non-diabetic subjects.

Concerning side effects, results are in line with the already known liraglutide safety profile, mostly limited to gastrointestinal disorders. In particular, the intervention group had an increased incidence of nausea and vomiting. Based on the authors’ claims, those events were mainly related to the four-week titration period and any withdrawals associated with such events occurred during this time. The same applies to the incidence of constipation and diarrhea which was also higher in the
intervention group without leading to an increase in the dropout rate. The incidence of acute pancreatitis was rare and according to the authors was not related with liraglutide’s administration but with other predisposing factors such as gallbladder disorders and cholelithiasis. Additionally, it seems that liraglutide had a negative impact on individuals with pre-existing cholelithiasis but those assumptions are based on the results reported only from the trial by Pi-Sunyer et al. In particular, an increased incidence of gallbladder disorders was observed in the liraglutide treated group (2.5%) compared to the placebo group (1%).(35) This effect has been also observed with the use of other weight loss drugs and may not be related to liraglutide’s administration. It is probable that rapid weight loss may aggravate a pre-existing cholelithiasis.(44) Cases of c-cell myeloid carcinoma were not recorded across all trials.

Regarding the comparison of liraglutide with other anti-obese agents; as it was mentioned before, liraglutide significantly outperforms orlistat at all primary endpoints. More studies are needed in order to assess reliably its superiority against orlistat. Semaglutide, on the other hand, is a novel drug for the treatment of type 2 diabetes, with satisfactory results, that has not been released in Greece so far. It still has not been approved anywhere worldwide as a weight loss agent. The study by O’neil et al evaluated semaglutide in different dosage regimens than those utilized for diabetes treatment. Its results are promising and its action appears to be dose-dependent. However, more studies and a better understanding of its safety profile are needed, especially since its mode and frequency of administration is different from the usual in order to achieve greater weight loss.

Strengths of our review are the following; First of all, we studied liraglutide’s efficacy and safety in non-diabetic obese population which is not frequently used as anti-obese medication in daily routine practice. We have proved that liraglutide is an efficient weight loss agent with a well-established safety profile. All included studies were at least 32 weeks duration and therefore the conclusions extracted for liraglutide’s effect of on body weight and its safety profile are considered sufficiently reliable. Our results are in line with previous meta-analysis about liraglutide’s administration in obese or overweight individuals without diabetes mellitus. On the other hand, a limitation of this systematic review is that it was conducted from one person as an MSc thesis for the Master of Science “Medical Research Methodology”.
We considered as limitation the fact that there were limited data for the comparison of liraglutide against placebo. Hence, we included only five trials in our review. There are also few data about the comparison of liraglutide with other anti-obese agents. Consequently, further studies are needed in order to extract more précised results about the effectiveness of existing therapeutic options against obesity. Finally, all included trials were sponsored by pharmaceutical companies. We would prefer to have more studies in our review that were independently funded.

F. Conclusion
In conclusion, liraglutide is an efficacious option for the treatment of obesity. Nevertheless, our conclusions are mostly based on results from placebo-controlled trials, while data from active-controlled studies were scarce. Finally, studies in obese population demonstrated that liraglutide maintained its overall safety profile.

G. Funding
No conflicts of interest to declare.
H. References

1. Park B, Road B, Sussex W. Victoza 6 mg / ml solution for injection in pre-filled pen. 2018;1–14.


I. Supplementary Material

I.1. Study Protocol

Introduction

The Western lifestyle, which has been rooted in people's everyday habits, with poor dietary habits and less and less physical activity has led to the increase of obesity incidence in both children and adults. Consequently, obesity is one of the major problems of today's society as it is associated with many serious health conditions that can lead to death while increasing the burden on the health systems of each country. Inevitably, the medical community is in constant search for new therapeutic options either pharmacologically or surgically, and always in conjunction with lifestyle modifications of the patient.

Liraglutide is a GLP-1 analogue that is constantly gaining ground in the treatment of both diabetes and obesity, and has been approved since 2015 by the major international drug organizations for unilateral administration to obese patients with specific characteristics. In summary, its long-lasting pharmacokinetic effect and the delay in gastric emptying results in weight loss which, combined with its glucose-dependent action, appears to offer an effective and at the same time a fairly safe weapon against obesity even in non-diabetic patients.

Objectives

The aim of our thesis is to assess the safety and efficacy of liraglutide 3.0mg for weight management in obese or overweight individuals without diabetes. We will conduct a systematic review and meta-analysis of randomized controlled trials that compare the effect of liraglutide against placebo or any active comparator in obese or overweight individuals without diabetes mellitus.

Eligibility Criteria

(P)opulation

We will search for studies that include overweight or obese adults without diabetes type 1 or 2. In order to define obesity we decided to follow the liraglutide 3.0mg therapeutic indications about obesity. As a result we will search for studies that include participants with BMI≥30Kg/m² or BMI≥27Kg/m² to <30Kg/m² with at least
one comorbidity associated with weight such as obstructive sleep apnea, hypertension, dyslipidemia but without diabetes mellitus type 1 or 2.

(I)ntervention

Trials that directly compare the efficacy of liraglutide 3.0mg once daily to placebo or any other comparator will be included in the review. We selected the dose of 3.0mg because in this dosage regimen liraglutide has been approved as an anti-obesity agent by the European Medicines Agency and the U.S Food and Drug administration.

(C)omparator

Placebo or any other active agent that has been used as anti-obesity agent were selected as comparators.

(O)utcome

Our goal is to evaluate the safety and efficacy of liraglutide 3.0mg in individuals with obesity for weight management without diabetes mellitus. Liraglutide is the only GLP-1 analogue that has already been approved for the treatment of obesity in the dose of 3.0mg with many trials supporting that evidence. Therefore the primary endpoints of our review will be the following:

- Absolute weight reduction in body weight measured in Kilograms,
- The proportion of individuals who lost at least 5% of their baseline body weight and
- The proportion of patients who lost more than 10% of their baseline body weight

According to the EMA and FDA the treatment with liraglutide should be stopped in cases of individuals that they did not lost at least 5% of their initial bodyweight after 12 weeks under treatment. Based on this condition we defined an at least 12-week treatment period with liraglutide 3.0mg sufficient enough in order to assess its outcomes.

Secondary outcomes included are:

- Change in BMI level
• Waist circumference (WC) difference measured in centimeters
• Changes in glycated hemoglobin (HbA1c %)
• Effect on fasting plasma glucose (FPG) measured in mg/dl

(T)ype of study

In our review we will include only randomized controlled trials with parallel group or cross-over design that compare liraglutide 3.0mg to placebo or any other active comparator. The aforementioned 12-week treatment limit was based on the official guidelines by EMA and FDA on the use of liraglutide as anti-obesity agent.

Adverse events

Liraglutide is strongly associated with gastrointestinal disorders especially at the beginning of its administration. Consequently we will count the most common adverse events such as nausea, vomiting, diarrhea and constipation. In addition, the EMA and FDA suggest using liraglutide with caution in patients that have a history of pancreatitis although, there is weak evidence supporting this assumption. In any case, we have decided to measure the participants with at least one episode of pancreatitis in studies that provide those data. Hypoglycemia is a serious adverse event that is some cases may lead into death. Despite liraglutides’ effect is glucose-related and as a result the incidence of hypoglycemia is rare, we have decided to assess such events because our study population is obese individuals without type 1 or 2 diabetes mellitus. It is important to mention that in all cases of adverse events we will count patient with at least one episode of each event and not the number of events that have occurred.

Exclusion Criteria

• Studies that were not randomized controlled trials
• Studies that liraglutide was not used as adjunctive treatment to lifestyle modifications
• Studies that include participants with diabetes mellitus type 1 or 2
• Studies that include participants which have been through any anti-obesity surgical procedure
• Studies that include participants with drug-induced obesity or participants that receive any other weight-lowering pharmacotherapy.
• Studies that compare liraglutide in any other dosing range except the 3.0mg
g• Studies with less than 12-week treatment period

Information sources and Search strategy

Our search strategy was scheduled according to the Cochrane handbook guidance for searching process. We will use search terms that may include our intervention (liraglutide) and the condition studied (obesity) as MESH and free-text. Our search will be done in some of the most important medical databases in which we could have access via the Aristotle University of Thessaloniki. We will also search for grey literature or abstract of conferences guided once more by the Cochrane handbook. We are interested only for trials that are published in English and were held on humans.

Bearing this in mind our research will be done on the following online libraries:

• PubMed/Medline
• Cochrane Central Register of Controlled Trials (CENTRAL)

Grey Literature:

• Clinicaltrials.gov
• WHO International Clinical Trials Registry
• European Association for the Study of Obesity
• American Obesity Association

Study selection and Data collection Methods

Search results will be screened through Mendeley or Covidence in order to remove possible duplicates. Potential records will be assessed at “title and abstract” level removing those that are irrelevant. The candidate records we will then be checked according to the aforementioned eligibility criteria. Once we have decided which studies met the inclusion criteria, data extraction will begin. An Excel data-extraction form will be used for data registration paying specific attention to each studies basics characteristic. The whole process will be presented as flow diagram according to PRISMA statement.

Risk of bias assessment
The Cochrane Collaboration risk of bias tool will be our guide for the evaluation of the included randomized controlled trials quality in all cases of study design, parallel or cross-over. The quality of included trials will assessed for the primary outcome this tool for each study and then they will characterize them as of high, low or unclear risk of bias. The overall quality of included studies will be assessed in the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Incomplete outcome data
- Selective reporting
- Other bias (Cross-over design, carry over effect etc.)

**Data synthesis**

After the qualitative synthesis of the data, if the included studies are more than three and show homogeneity in the basic characteristics of the participants as well as in the way of intervention (dosage, route of administration), we will proceed to the quantitative synthesis. For continuous variables we will use mean and standard deviation with 95% confidence intervals while regarding to dichotomous variables, they will be expressed as odds or risk ratio. Heterogeneity will be assessed using Chi-squared test and I^2 with a p-value< 0.1 and I^2 > 70% to indicate high heterogeneity respectively. In order to have the most representative weighting of the included trials we will synthesize our data using an inverse variance random effects weighted model and if our data show low heterogeneity (I^2<30%) we will proceed to inverse-variance fixed effects weighted model. Subgroup analysis will be performed according to prediabetes status if it had been evaluated at the beginning of each trial. In case of moderate heterogeneity (30-70%), we also utilized random effects models. All the aforementioned statistical analysis will be performed using the software program RevMan 5.3. We would like here to mention that in case of trials with different design (parallel/crossovers) we will use a multilevel random effects model in order to synthesize our data with accuracy and credibility. If our data are too heterogeneous (>70%) we will not conduct meta-analysis but only the systematic
review. Sensitivity analysis will concern the primary outcomes. Funnel plots will be used to evaluate the possibility of publication bias.

I.2. Search Strategy

**Pubmed/MEDLINE**

#1. Liraglutide (MESH)
#2. "Liraglutide"
#3. GLP-1
#4. Glucagon like peptide-1
#5. “Glucagon like peptide-1 receptor agonist
#6. “Glucagon like peptide-1 analogue
#7. “NN2211”
#8. “Victoza”
#9. “Saxenda”
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#11. Obesity (MESH)
#12. “Obesity”
#13. “Overweight”
#14. “Obese”
#15. “Weight”
#16. “Weight loss” (MESH)
#17. “Weight loss”
#18. “Weight management”
#19. “Weight reduction”
#20. “bodyweight”
#21. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22. #10 AND #21
#24. #22 AND #23

**COCHRANE**

MeSH descriptor: [Liraglutide] explode all trees

MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees

MeSH descriptor: [Obesity] explode all trees

MeSH descriptor: [Body Weight Changes] explode all trees
### 1.3. PRISMA checklist

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<thead>
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<td>TITLE</td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td>ABSTRACT</td>
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<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>6</td>
</tr>
<tr>
<td>INTRODUCTION</td>
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<td>Rationale</td>
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<td>Describe the rationale for the review in the context of what is already known.</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td>METHODS</td>
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<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>14-19</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>16</td>
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<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<tr>
<td>Summary measures</td>
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<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
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<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>NA</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
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<tr>
<td>RESULTS</td>
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<tr>
<td>Study selection</td>
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<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
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<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>21</td>
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<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
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<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>25-37</td>
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<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
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<td>Risk of bias across studies</td>
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<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>NA</td>
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<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>NA</td>
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<tr>
<td>DISCUSSION</td>
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<td>Summary of evidence</td>
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<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
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<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>37-40</td>
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<tr>
<td>Conclusions</td>
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<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>40</td>
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</table>