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Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials

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ABSTRACT

Orlistat, an inhibitor of intestinal lipase, promotes body weight reduction. The lipid-lowering efficacy of orlistat is controversial and the effect of orlistat-induced body weight reduction on lipid changes has not been explored in meta-regression analyses. A systematic literature search was conducted to identify randomized controlled trials investigating the efficacy of orlistat on plasma total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides and lipoprotein(a) levels. Thirty-three studies were included in the meta-analysis (5522 and 4210 participants in the orlistat therapy and control groups, respectively). Orlistat reduced body weight (weighted mean difference: −2.12, $p < 0.001$), total-cholesterol (weighted mean difference: −0.30 mmol/L, $p < 0.001$), low-density lipoprotein cholesterol (weighted mean difference: −0.27 mmol/L, $p < 0.001$), high-density lipoprotein cholesterol (weighted mean difference: −0.034 mmol/L, $p < 0.001$) and triglyceride (weighted mean difference: −0.09 mmol/L, $p < 0.001$) concentrations, while no effect on lipoprotein(a) was observed. Total- and low-density lipoprotein cholesterol-lowering were associated negatively with duration of orlistat treatment and positively with body weight changes. In conclusion, Orlistat treatment slightly reduces cholesterol and triglyceride levels, but not lipoprotein(a) levels. Total- and low-density lipoprotein cholesterol levels reductions are more consistent in patients with greater body weight reduction and shorter duration of orlistat treatment.

1. Introduction

Orlistat is a reversible pancreatic and gastric lipase inhibitor that blocks absorption of 30% of ingested fat when eating a hypocaloric diet that roughly contains 30% of energy as fat [1]. It is an effective adjunctive therapeutic option to lifestyle modifications in the treatment of obesity. Accordingly, there is evidence that orlistat plus lifestyle changes achieve greater body weight (BW) loss than lifestyle changes alone [2]. A 4-year-long study supported additional beneficial effects of treatment with orlistat, in that this drug reduced the development of diabetes mellitus in people with prediabetes [3]. In addition, orlistat has a good long-term safety profile and serious adverse events are rare; hence, it is approved for use also in adolescents [4]. Despite this evidence, a high rate of gastrointestinal side effects limits adherence to treatment and its popularity among the patients [5].

Dyslipidemia is an established risk factor for ischemic cardiovascular disease (CVD) [6,7]. The relationship between most of the dyslipidemias, such as hypercholesterolemia, i.e. elevated total and/or low-density lipoprotein (LDL)-cholesterol (LDL-C), hypertriglyceridemia and low high density lipoprotein (HDL)-cholesterol (HDL-C) levels, and the risk of CVD is consistent [8–12]. Also, the combination of multiple lipids and lipoprotein abnor-

Abbreviations: BMI, body mass index; BW, body weight; CI, confidence interval; CMA, Comprehensive Meta-Analysis; CVD, cardiovascular disease; HDL, high density lipoprotein; HDL-C, high density lipoprotein-cholesterol; LDL, low density lipoprotein; LDL-C, low density lipoprotein-cholesterol; Lp(a), lipoprotein(a); PRISMA, preferred reporting items for systematic reviews and meta-analysis; RCT, randomized controlled trial; SD, standard deviations; SEM, standard error of the means; TC, total cholesterol; TG, triglyceride; WMD, weighted mean difference.

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malities is common [13] and shows a detrimental cumulative impact on CVD risk [6]. Interestingly, the association of multiple lipid and lipoprotein abnormalities is frequent in obese patients, considering that approximately 60–70% of obese patients are dyslipidemic [14]. Obese patients often have elevated triglycerides, decreased HDL-C, and usually only moderately elevated LDL-C but an increased number of small, dense LDL-particles which are considered highly atherogenic [15,16]. Hence, therapeutic strategies which are effective in positively influencing all these lipid parameters are warranted; this need is felt especially in obese patients, in whom it would be desirable to have drugs that act simultaneously on BW and on plasma lipids as well. As BW loss has itself an effect on plasma lipids, it is, however, challenging to distinguish between the BW-dependent and the drug-dependent effects on plasma lipid levels.

There are data indicating that after 1 year of treatment, orlistat might be associated with a significant improvement in cardiovascular risk factors, including reductions in systolic and diastolic blood pressures, fasting glucose and blood lipids [17]. As regards specifically lipid levels, a number of randomized controlled trials (RCTs) has explored the impact of orlistat on plasma total-cholesterol (TC), LDL-C, HDL-C or triglyceride (TG) levels [18–50]. Only few studies examined whether plasma lipoprotein(a) [Lp(a)] levels are affected by orlistat treatment [40,46]. Some of these studies reported that orlistat may improve lipid profile, while in other studies orlistat failed to have any significant effect on most lipids and lipoproteins. Thus, data regarding the effects of orlistat on the plasma lipid profile are still controversial.

Because high dropout rates have been reported in long-term BW loss trials with orlistat [3], the potential confounding effect of duration of treatment on orlistat-induced lipid changes is a matter of particular interest. In addition, because the main goal of treatment with orlistat is to ensure a permanent BW reduction [1,2,4,5] and diet-associated BW loss is commonly associated with beneficial changes in lipids levels [51,52], one may expect that BW changes during orlistat treatment should have a significant impact on plasma lipid and lipoprotein levels.

In order to answer these questions, we performed a systematic review of the literature and a meta-analysis of RCTs to elucidate the impact of orlistat therapy on plasma TC, LDL-C, HDL-C, TG and Lp(a) concentrations; moreover, we tested the impact of dose and duration of orlistat treatment and orlistat-induced BW changes on the possible changes in plasma lipid and lipoprotein concentrations.

2. Methods

2.1. Search strategy

The guidelines of the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [53] were exploited for the study design. A literature search through electronic databases PubMed-Medline, SCOPUS, Web of Science, and Google Scholar was carried out from inception to december 25, 2014. The following search terms in titles and abstracts (also in combination with MESH terms) were used: (orlistat) AND (hyperlipidemia OR hyperlipidaemia OR hyperlipidemic OR hyperlipidaemic OR dyslipidemia OR dyslipidaemia OR dyslipidemic OR dyslipidaemic OR hypercholesterolemia OR hypercholesterolaemia OR hypercholesterolemic OR hypercholesterolaemic OR "low-density lipoprotein" OR "high-density lipoprotein" OR cholesterol OR triglycerides OR LDL OR LDL-C OR LDL-cholesterol OR HDL-OR HDL-C OR HDL-cholesterol). The wild-card term "*" was used to increase the sensitivity of the search strategy and to avoid missing interchangeable formats of dyslipidemia, hyperlipidemia and hypercholesterolemia.

2.2. Study selection

Eligible studies were identified by the following criteria: (i) RCTs with either case-control or case-cross-over design, (ii) investigation of the effects of orlistat on plasma/serum concentrations of lipids and/or lipoproteins comprising TC, LDL-C, HDL-C, TGs and Lp(a), (iii) providing sufficient information on baseline and end-trial plasma/serum lipid concentrations in both orlistat and control groups. Exclusion criteria were (i) experimental studies, (ii) uncontrolled studies, and (iii) administration of lipid-lowering drugs (e.g. statins, fibrates, ezetimibe, bile acid sequestrants or *n*-3 polyunsaturated fatty acids and their esters) in the study groups without appropriate controlling, and (iv) lack of sufficient information on baseline or end-trial lipid concentrations. In case of the latter item, authors of the article(s) were contacted (single time *via* e-mail) and requested to provide necessary numerical data.

Articles were screened by two reviewers (AS and LES) to remove ineligible articles. Disagreements were resolved by discussion and referring to a third reviewer (MS), if required.

2.3. Data extraction

The following data were abstracted from reviewed eligible studies: 1) first author's name; 2) year of publication; 3) country where the study was performed; 4) study design; 5) number of participants in the orlistat and control groups; 6) dose of orlistat therapy; 7) treatment duration; 9) age, gender, and body mass index (BMI) of study participants; 10) baseline systolic and diastolic blood pressure values; and 11) data regarding baseline and follow-up plasma concentrations of TC, LDL-C, HDL-C, TGs and Lp(a).

Data extraction was performed by 2 reviewers (LES and MS), and disagreements were resolved by a third reviewer (AS).

2.4. Quality assessment

Risk of bias assessment in the included studies was performed according to the Cochrane instructions (2008). Each study was evaluated based on the following items: sequence generation adequacy, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. A judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias, according to the recommendations of the Cochrane Handbook. The item "unclear" was used to indicate either an unclear or unknown risk of bias.

Risk-of-bias assessment was performed by 2 reviewers (LES and MS), and disagreements were resolved by a third reviewer (AS).

2.5. Quantitative data synthesis

Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) was used in this meta-analysis [54]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up−measure at baseline. For single-arm cross-over trials, net change in plasma concentrations of lipid indices were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated to mg/dL. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the methods described by Wan et al. [55] and the Cochrane handbook for systematic reviews of interventions. Missing SD values were imputed by the pooled SD of all studies. When only the standard error of the mean (SEM) was reported, standard deviation (SD) was esti-

mated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. In order to avoid unit-of-analysis error due to double-counting of subjects in the trials with more than 1 treatment arm, the control group was evenly (where possible) divided. Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at the end of follow-up in the treatment group−measure at baseline in the treatment group) − (measure at the end of follow-up in the control group−measure at baseline in the control group). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied [56]. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI. Inter-study heterogeneity was assessed using Cochran Q test and I^2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis [57,58].

2.6. Meta-regression

A weighted random-effects meta-regression using unrestricted maximum likelihood model was performed to assess the association between the overall estimate of effect size with potential moderator variables including duration of treatment with orlistat and orlistat-induced BW changes.

2.7. Publication bias

Visual inspection of asymmetry in the Begg's funnel plots as well as Egger's weighted regression and "fail safe N" tests was used to explore the presence of potential publication bias in the analyses. Adjustment of the results for the effects of publication bias was performed by using the Duval & Tweedie "trim and fill" method [59].

3. Results

3.1. Flow of studies

Our literature search yielded 110 relevant citations. Of these, 29 studies were non-original and, therefore, excluded. After screening the remaining 81 records, 35 were excluded because they did not meet the inclusion criteria. Then, 46 full text articles were carefully assessed and reviewed. From these, 13 studies were excluded for being uncontrolled (n = 4), duplicate data reporting (n = 2), not presenting numerical values (n = 2), having a non-English language (n = 2) and presenting incomplete lipid data (n = 3). In total, 33 studies met the predefined inclusion criteria and were included in the meta-analysis. The study selection process is shown in Fig. 1.

3.2. Characteristics of included studies

A total of 9732 subjects were recruited from 33 eligible RCTs, including 5522 and 4210 participants in the orlistat therapy and control groups (individuals of the cross-over trials were considered in both orlistat and control groups), respectively. Included studies were published between 1994 and 2010. The most of the evaluated clinical trials used orlistat at a dose of 360 mg/day. However, three studies investigated orlistat 180 mg/day [33,46,49], two studies investigated orlistat 90 mg/day [33,49], and one study investigated orlistat 30 mg/day [49]. The range of intervention periods was

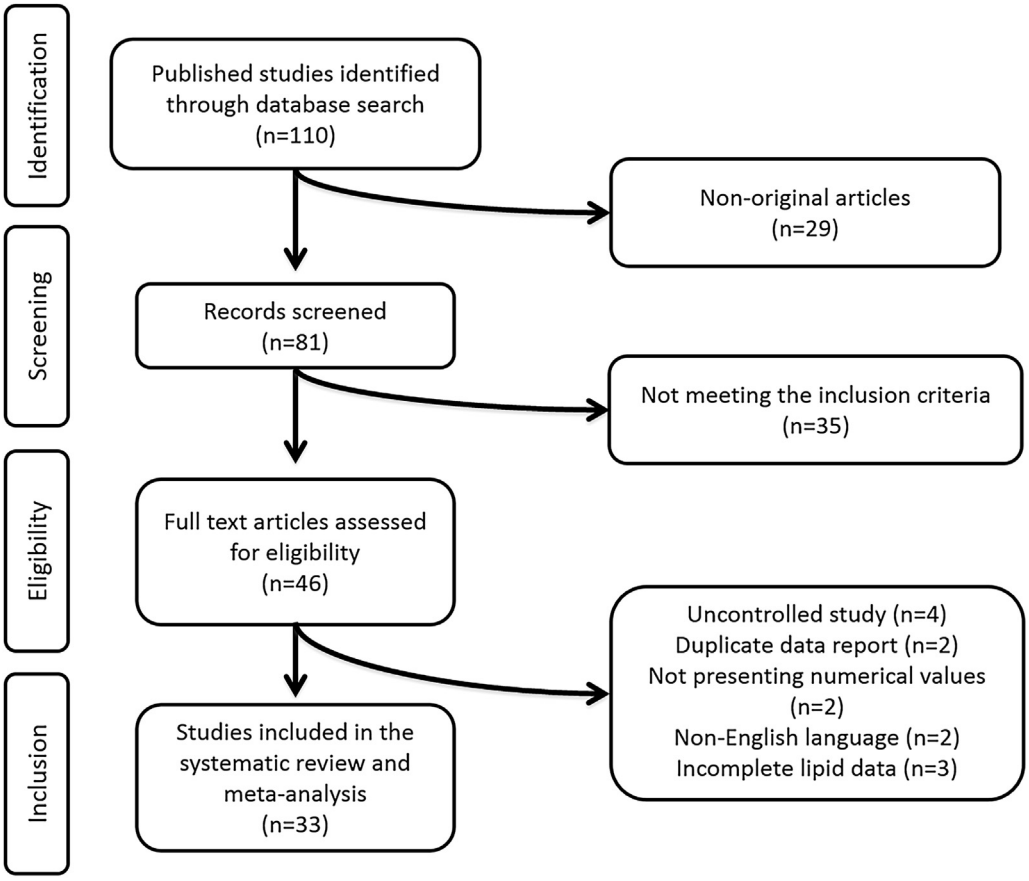

Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

Table 1
Demographic characteristics of the included studies.

References	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)	Triglycerides (mmol/l)	Lp(a) (mg/l)
Audikovszky et al. (2007)	Randomized controlled trial	Obesity	6 months	78 61	Orlistat 360 mg/day Control	49.3 ± 11.4 47.6 ± 8.5	43 (55.1) 33 (54.0)	36.1 ± 3.2 35.5 ± 4.4	145.6 ± 17.5 141.8 ± 15.8	92.6 ± 10.4 90.3 ± 9.3	6.2 ± 1.1 6.1 ± 1.1	3.7 ± 0.8 3.4 ± 1.2	1.2 ± 0.4 1.2 ± 0.3	2.2 ± 1.1 2.2 ± 1.0	
Bakris et al. (2002)	Randomized, double-blind, placebo-controlled	Obesity and hypertension	1 year	267 265	Orlistat 360 mg/day Placebo	53.2 ± 0.5 52.5 ± 0.5	169 (63.2) 156 (58.8)	35.8 ± 3.9 35.4 ± 4.0	154.2 ± 13.4 150.8 ± 12.7	98.4 ± 3.7 98.3 ± 3.5	5.8 ± 1.0 5.8 ± 1.0	3.6 ± 0.9 3.6 ± 1.0	1.2 ± 0.4 1.2 ± 0.3	2.2 ± 1.7 2.2 ± 1.7	
Bergholm et al. (2003)	Randomized, double-blind, placebo-controlled	Obese nondiabetic women	3–6 months	23 24	Orlistat 360 mg/day Placebo	39 ± 4.7 39 ± 4.8	23 (100) 24 (100)	32.3 ± 1.9 32.3 ± 1.9	126 ± 14.3 123 ± 9.7	85 ± 9.5 80 ± 9.7	ND ND	3.5 ± 0.7 3.1 ± 0.5	1.3 ± 0.2 1.2 ± 0.2	1.4 ± 0.7 1.3 ± 0.6	
Bloch et al. (2003)	Randomized controlled trial	Hypertension and overweight/ obesity	3 months	103 101	Orlistat 360 mg/day Control	55.0 ± 11.5 56.7 ± 9.9	84 (81.6) 85 (84.2)	36.6 ± 6.4 35.4 ± 6.4	163.0 ± 25.8 158.9 ± 27.1	102.7 ± 17.5 96.7 ± 15.8	6.1 ± 1.6 6.0 ± 1.2	ND ND	1.0 ± 0.2 1.0 ± 0.2	2.3 ± 3.4 2.2 ± 1.8	
Chou et al. (2007)	Randomized, cross-over	Obesity and type 2 diabetes	3 months	14 20	Orlistat 360 mg/day Sibutramine 10 mg/day	49 ± 12	29 (85.2)	ND	142.0 ± 19.2 138.7 ± 15.9	80.5 ± 8.2 79.3 ± 11.0	5.4 ± 0.9 5.2 ± 1.1	3.6 ± 0.8 3.8 ± 1.0	1.0 ± 0.4 0.8 ± 0.2	1.6 ± 1.0 1.3 ± 0.7	
Beck-da-Silva et al. (2005)	Randomized controlled trial	Obesity and heart failure	3 months	11 10	Orlistat 360 mg/day Control	49.5 ± 14 49.7 ± 13	2 (18.1)2 (20.0)	43.1 ± 10.8 41.8 ± 9.4	ND ND	ND ND	5.4* 5.2*	3.0 ± 1.4 3.2 ± 0.6	ND ND	3.0 ± 1.7 2.5 ± 2.1	
Davidson et al. (1999)	Randomized, double-blind, placebo-controlled	Obesity	2 years	657 223	Orlistat 360 mg/day Placebo	43.3 ± 0.6 44.0 ± 0.7	544 (82.8) 197 (88.3)	36.2 ± 0.1 36.5 ± 0.9	ND ND	ND ND	4.9 ± 0.07 4.9 ± 0.06	3.0 ± 0.06 3.1 ± 0.05	1.1 ± 0.02 1.2 ± 0.02	1.5 ± 0.06 1.4 ± 0.04	
de Castro et al. (2009)	Randomized, double-blind, placebo-controlled	Obesity and hypercholes-terolemia	6 months	57 49	Orlistat 360 mg/day Placebo	47.1 ± 10.5 48.0 ± 11.1	40 (70.1) 35 (71.4)	35.7 ± 5.1 36.0 ± 5.6	ND ND	ND ND	6.7 ± 0.9 6.8 ± 1.0	4.6 ± 0.8 4.6 ± 0.8	1.4 ± 0.3 1.4 ± 0.3	1.5 ± 0.7 1.7 ± 0.8	
Derosa et al. (2005)	Randomized, double-blind, controlled	Obesity and hypertension	1 year	57 58	Orlistat 360 mg/day Sibutramine 10 mg/day	50 ± 4 51 ± 5	29 (50.8) 30 (51.7)	33.1 ± 1.9 33.5 ± 1.8	145 ± 3 146 ± 3	96 ± 4 96 ± 5	5.0 ± 0.5 5.1 ± 0.6	3.2 ± 0.4 3.3 ± 0.4	1.2 ± 0.2 1.2 ± 0.1	1.7 ± 0.4 1.8 ± 0.5	
Derosa et al. (2003)	Randomized, double-blind, placebo-controlled	Obesity and hypercholes-terolemia	1 year	27 23	Orlistat 360 mg/day Placebo	51.6 ± 8.3 52.4 ± 10.2	14 (51.9) 12 (52.2)	32.0 ± 1.3 31.7 ± 1.0	131 ± 3 132 ± 5	85 ± 4 84 ± 3	6.7 ± 0.5 6.9 ± 0.6	5.0 ± 0.5 5.0 ± 0.6	1.1 ± 0.1 1.1 ± 0.1	1.5 ± 0.4 1.4 ± 0.3	
Erdmann et al. (2004)	Randomized, double-blind, placebo-controlled	Obesity and hypercholes-terolemia	6 months	192 192	Orlistat 360 mg/day Placebo	46.3 ± 11.2 45.8 ± 12.2	142 (73.9) 135 (70.3)	33.5 ± 3.6 34.2 ± 3.7	ND ND	ND ND	6.0 ± 0.7 6.0 ± 0.6	4.2 ± 0.5 4.1 ± 0.5	1.3 ± 0.3 1.3 ± 0.3	1.9* 1.9*	
Filippatos et al. (2008)	Randomized, open-label	Obesity and metabolic syndrome	6 months	28 28 27	Orlistat 360 mg/day Fenofibrate 200 mg/day Orlistat 360 mg/day + Fenofibrate 200 mg/day	52 ± 9 54 ± 11 52 ± 10	23 (82.1) 20 (71.4) 23 (85.1)	35 ± 6 34 ± 6 35 ± 6	140 ± 10 142 ± 16 141 ± 13	86 ± 9 84 ± 7 85 ± 9	7.8 ± 1.4 7.7 ± 0.9 8.0 ± 1.4	4.3 ± 1.1 4.1 ± 0.7 4.3 ± 1.2	1.4 ± 0.3 1.3 ± 0.2 1.4 ± 0.3	2.2 (0.9-5.3) 2.5 (1.0-4.5) 2.4 (0.9–4.9)	
Finer et al. (2000)	Randomized, double-blind, placebo-controlled	Obesity	1 year	110 108	Orlistat 360 mg/day Placebo	41.5 ± 10.5 41.4 ± 10.0	98 (89.1) 95 (88.0)	36.8 ± 3.6 36.8 ± 3.7	ND ND	ND ND	5.6 ± 0.9 5.6 ± 0.9	3.6 ± 0.8 3.6 ± 0.8	1.2 ± 0.2 1.2 ± 0.2	ND ND	

Guy-Grand et al. (2004)	Randomized, double-blind, placebo-controlled	Obesity with either type 2 diabetes, hypertension or hypercholes-terolemia	6 months	97 96 304 310 98 99	Type 2 diabetes Orlistat 360 mg/day Placebo Hypertension Orlistat 360 mg/day Placebo Hypercho-lesterolemia Orlistat 360 mg/day Placebo	51.2 ± 0.8 53.6 ± 0.8 49.1 ± 0.6 49.5 ± 0.5 46.9 ± 1.1 46.6 ± 1.1	51 (52.6) 55 (57.3) 211 (69.4) 201 (64.8) 73 (74.5) 73 (73.7)	33.8 ± 0.3 33.5 ± 0.4 34.3 ± 0.2 33.9 ± 0.2 33.1 ± 0.3 33.5 ± 0.3	139.6 ± 1.5 141.7 ± 1.6 150.0 ± 0.8 152.2 ± 0.9 128.3 ± 1.5 130.5 ± 1.8	86.2 ± 0.9 86.5 ± 1.0 96.9 ± 0.3 97.0 ± 0.3 82.9 ± 0.9 82.1 ± 0.9	ND ND ND ND ND ND	3.5 ± 0.0 3.5 ± 0.1 3.6 ± 0.0 3.6 ± 0.0 4.4 ± 0.1 4.2 ± 0.1	ND ND ND ND ND ND	ND ND ND ND ND ND		
Halpern et al. (2003)	Randomized, double-blind, placebo-controlled	Obesity and type 2 diabetes	6 months	164 174	Orlistat 360 mg/day Placebo	50.8 ± 1.3 50.7 ± 1.4	117 (71.3) 117 (67.2)	34.6 ± 0.8 34.5 ± 0.9	ND ND	ND ND	6.0 ± 0.1 6.3 ± 0.1	3.8 ± 0.0 4.0 ± 0.1	1.1 ± 0.0 1.1 ± 0.0	2.3 ± 0.1 2.7 ± 0.1	
Hill et al. (1999)	Randomized, double-blind, placebo-controlled	Obesity	1 year	186 171 179 184	Orlistat 90 mg/day Orlistat 180 mg/day Orlistat 360 mg/day Placebo	46.8 ± 10.9 46.1 ± 9.1 45.9 ± 9.3 46.4 ± 9.4	157 (84.4) 136 (79.5) 156 (87.1) 156 (84.7)	32.6 ± 2.7 32.9 ± 2.6 32.8 ± 2.6 32.8 ± 2.7	ND ND ND ND	ND ND ND ND	ND ND ND ND	ND ND ND ND	ND ND ND ND	ND ND ND ND	
Hsieh et al. (2005)	Randomized controlled trial	Obesity	1 year	51 55	Orlistat 360 mg/day Control	36.3 ± 5.8 35.5 ± 6.7	30 (58.8) 30 (54.5)	31.1 ± 2.1 31.1 ± 2.3	ND ND	ND ND	6.1 ± 0.9 6.0 ± 1.0	4.1 ± 1.0 4.1 ± 1.0	1.1 ± 0.2 1.1 ± 0.2	1.9 ± 0.5 1.8 ± 0.6	
Jayagopal et al. (2005)	Randomized, open-label	Polycystic ovary syndrome	3 months	10 11	Orlistat 360 mg/day Metformin 1500 mg/day	27 ± 4.1	10 (100) 11 (100)	36.7 ± 15.1	ND ND	ND ND	4.5 ± 0.6 4.9 ± 0.9	2.7 ± 0.6 3.1 ± 0.6	1.1 ± 0.6 1.1 ± 0.6	1.4 ± 0.9 1.2 ± 0.6	
Kelley et al. (2002)	Randomized, double-blind, placebo-controlled	Overweight and obese with type 2 diabetes	1 year	266 269	Orlistat 360 mg/day Placebo	57.8 ± 8.1 58.0 ± 8.2	150 (56) 151 (56)	35.8 ± 3.2 35.6 ± 4.9	135.1 ± 14.6 134.9 ± 14.9	79.4 ± 8.1 80.9 ± 9.9	5.4 ± 1.1 5.4 ± 1.1	3.3 ± 0.9 3.3 ± 0.9	1.0 ± 0.3 1.0 ± 0.3	2.3 ± 1.6 2.3 ± 1.3	
Lindgärde et al. (2000)	Randomized, double-blind, placebo-controlled	Obesity	1 year	190 186	Orlistat 360 mg/day Placebo	53.7 ± 9.4 53.2 ± 9.9	124 (65.2) 115 (61.8)	33.2 ± 3.0 33.2 ± 3.1	146 ± 19 145 ± 17	87 ± 10 88 ± 10	6.1 ± 1.2 6.0 ± 1.1	3.7 ± 1.3 3.6 ± 1.4	ND ND	ND ND	
Lucas et al. (2003)	Randomized, double-blind, placebo-controlled	Type IIA and IIB dyslipidemia	1 year	51 41 59 30	Type IIA Orlistat 360 mg/day Placebo Type IIB Orlistat 360 mg/day Placebo	45 ± 10 49 ± 10 48 ± 9 50 ± 10	45 (88.2) 39 (95.1) 37 (62.7) 23 (76.6)	35.9 ± 3.8 34.9 ± 3.5 35.5 ± 3.2 37.7 ± 3.6	ND ND ND ND	ND ND ND ND	6.5 ± 0.7 6.4 ± 0.8 7.3 ± 0.8 7.2 ± 0.7	4.7 ± 0.6 4.8 ± 0.7 4.8 ± 0.6 4.7 ± 0.4	1.4 ± 0.3 1.4 ± 0.3 1.1 ± 0.3 1.2 ± 0.3	1.0 ± 0.2 1.0 ± 0.1 3.2 ± 1.0 3.2 ± 0.7	
Miles et al. (2002)	Randomized, double-blind, placebo-controlled	Overweight and obese with type 2 diabetes	1 year	250 254	Orlistat 360 mg/day Placebo	52.5 ± 6.3 53.7 ± 6.3	48 (19.2) 48 (18.8)	35.6 ± 4.7 35.2 ± 3.1	132.7 ± 14.2 132.1 ± 14.3	ND ND	5.4 ± 0.9 5.4 ± 0.9	3.1 ± 0.9 3.2 ± 0.9	0.9 ± 0.3 0.9 ± 0.3	2.8 ± 1.7 2.6 ± 1.4	
Muls et al. (2001)	Randomized, double-blind, placebo-controlled	Obesity and hypercholes-terolemia	6 months	147 143	Orlistat 360 mg/day Placebo	49.6 ± 10 47.5 ± 11	120 (81.6) 114 (79.7)	32.9 ± 3.5 33.0 ± 3.7	133.6 ± 13.3 130.6 ± 12.1	83.1 ± 7.4 82.2 ± 8.3	7.3 ± 0.7 7.2 ± 0.7	5.0 ± 0.6 5.0 ± 0.6	1.4 ± 0.3 1.4 ± 0.3	1.7 ± 0.6 1.6 ± 0.6	340 ± 44 426 ± 63
Nakou et al. (2008)	Randomized, open-label	Overweight and obese with hypercholes-terolemia	6 months	29 28 29	Orlistat 360 mg/day Ezetimibe 10 mg/day Orlistat 360 mg/day + Ezetimibe 10 mg/day	54 ± 9 55 ± 11 55 ± 10	22 (75.8) 20 (71.4) 20 (68.9)	35.7 ± 6.7 35.8 ± 6.0 35.5 ± 6.1	ND ND ND	ND ND ND	6.4 ± 1.1 6.5 ± 0.8 6.6 ± 0.8	4.2 ± 1.0 4.3 ± 0.7 4.4 ± 0.8	1.3 ± 0.2 1.4 ± 0.2 1.4 ± 0.2	1.7 (0.7-3.9)** 1.7 (0.9-2.2)** 1.7 (1.0–2.9)**	

Table 1 (*Continued*)

References	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)	Triglycerides (mmol/l)	Lp(a) (mg/l)
Pathan et al. (2004)	Randomized, open-label	Overweight and obese with type 2 diabetes	6 months	21 15	Orlistat 360 mg/day Control	44.7 ± 6.2 44.4 ± 7.0	ND ND	31.6 ± 3.5 29.8 ± 3.2	ND ND	85.0 ± 10.7 82.6 ± 8.8	6.1 ± 0.9 5.4 ± 0.9	3.7 ± 0.9 3.4 ± 0.6	1.2 ± 0.3 1.4 ± 0.7	2.4 ± 0.8 1.8 ± 0.6	
Poston et al. (2003)	Randomized, controlled, open-label	Obesity	1 year	56 52	Orlistat 360 mg/day Control	42.4 ± 9.2 43.7 ± 9.2	56 (100) 52 (100)	36.0 ± 5.2 37.8 ± 6.2	122.3 ± 14.2 120.0 ± 14.2	77.2 ± 10.3 79.1 ± 9.1	4.8 ± 0.8 4.8 ± 0.8	3.0 ± 0.6 2.9 ± 0.6	1.2 ± 0.3 1.3 ± 0.4	1.5 ± 0.6 1.5 ± 0.7	
Reaven et al. (2001)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	1 year	85 43 71 48	Metabolic syndrome Orlistat 360 mg/day Placebo Non-Metabolic syndrome Orlistat 360 mg/day Placebo	46 ± 8 42 ± 10 44 ± 1 46 ± 11	38 (44.7) 21 (48.8) 71 (100) 44 (91.6)	35.7 ± 3.5 36.0 ± 3.3 35.5 ± 3.1 35.0 ± 3.8	130 ± 16 130 ± 12 124 ± 14 126 ± 13	83 ± 9 86 ± 9 80 ± 8 80 ± 9	ND ND ND ND	3.5 ± 0.9 3.5 ± 0.8 3.1 ± 0.8 3.2 ± 0.8	0.8 ± 0.1 0.8 ± 0.1 1.7 ± 0.2 1.7 ± 0.1	3.5 ± 1.5 3.4 ± 1.2 0.7 ± 0.1 0.7 ± 0.1	
Richelsen et al. (2007)	Randomized, double-blind, placebo-controlled	Obesity	3 years	153 156	Orlistat 360 mg/day Placebo	47.2 (20–64)† 46.7 (19–63)†	77 (50.3) 80 (51.3)	37.4 (30.1–45.2)† 37.6 (30.0–45.0)†	144 ± 19.3 144 ± 17.3	90.8 ± 11.6 90.7 ± 10.4	5.9 ± 1.2 6.0 ± 1.0	3.7 ± 1.0 3.7 ± 0.9	1.1 ± 0.2 1.1 ± 0.2	2.3 ± 1.2 2.5 ± 1.4	
Rössner et al. (2000)	Randomized, double-blind, placebo-controlled	Obesity	2 years	239 242 237	Orlistat 180 mg/day Orlistat 360 mg/day Placebo	44.7 ± 10.7 43.6 ± 11.4 44.3 ± 10.8	183 (76.5) 202 (83.4) 206 (86.9)	35.2 ± 3.9 34.7 ± 3.7 35.3 ± 4.1	128.4 ± 14.5 125.5 ± 14.9 127.3 ± 16.1	81.5 ± 10.3 79.5 ± 9.4 81.2 ± 9.8	5.3 ± 1.1 5.2 ± 0.9 5.4 ± 1.1	3.4 ± 0.8 3.4 ± 0.8 3.5 ± 0.9	1.1 ± 0.3 1.1 ± 0.3 1.1 ± 0.3	1.7 ± 1.4 1.5 ± 0.9 1.5 ± 0.8	280.2 ± 346.0 328.5 ± 409.0 284.1 ± 357.9
Sjöström et al.(1998)	Randomized, double-blind, placebo-controlled	Obesity	1 year	343 340	Orlistat 360 mg/day Placebo	45.2 (20–76)† 44.3 (18–77) †	284 (82.8) 283 (83.2)	36.0 (28.3–47.2) † 36.1 (29.2–43.5) †	129 ± 11.1 128 ± 11.0	82.4 ± 7.4 81.9 ± 7.3	5.3 ± 0.5 5.3 ± 0.5	3.5 ± 0.5 3.5 ± 0.5	1.1 ± 0.1 1.1 ± 0.1	1.6 ± 0.9 1.5 ± 0.9	
Swinburn et al. (2005)	Randomized, double-blind, placebo-controlled	Obesity	1 year	170 169	Orlistat 360 mg/day Placebo	52.0 ± 7.5 52.5 ± 7.4	104 (61.1) 89 (52.6)	37.6 ± 5.1 38.0 ± 4.9	137.3 ± 15.7 136.0 ± 15.2	84.0 ± 9.9 84.5 ± 9.0	5.6 ± 1.1 5.5 ± 0.9	3.5 ± 0.9 3.4 ± 0.8	1.1 ± 0.2 1.1 ± 0.3	1.7 ± 0.7 1.8 ± 0.9	
Tonstad et al. (1994)	Randomized, double-blind, placebo-controlled	Hypercholes-terolemia	2 months	33 33 35 35 36	Orlistat 30 mg/day Orlistat 90 mg/day Orlistat 180 mg/day Orlistat 360 mg/day Placebo	51 ± 10 55 ± 9 53 ± 10 52 ± 9 53 ± 10	12 (36.3) 16 (48.4) 14 (40.0) 14 (40.0) 14 (38.8)	25.2 ± 3.0 25.7 ± 2.3 24.4 ± 2.5 25.1 ± 2.9 25.0 ± 2.2	ND ND ND ND ND	ND ND ND ND ND	ND ND ND ND ND	ND ND ND ND ND	1.2 ± 0.2 1.2 ± 0.3 1.2 ± 0.3 1.1 ± 0.3 1.2 ± 0.2	1.6 ± 0.7 1.8 ± 0.9 1.6 ± 0.5 1.9 ± 1.1 1.7 ± 0.7	
Yancy et al. (2010)	Randomized, controlled trial	Overweight or obesity	1 year	74 72	Orlistat 360 mg/day Control	52.0 ± 9.2 52.9 ± 10.2	21 (28) 20 (28)	38.8 ± 7.0 39.9 ± 6.9	128.2 ± 15.5 135.0 ± 17.0	85.0 ± 10.4 89.6 ± 9.7	4.8 ± 0.9 4.7 ± 0.8	3.1 ± 0.8 3.0 ± 0.8	1.0 ± 0.3 1.0 ± 0.2	1.6 ± 0.8 1.6 ± 0.8	

Values are expressed as mean ± SD.
Abbreviations: ND, no data; BMI, body mass index; IQR, interquartile range.
*Mean only.
*Median (IQR).
†Mean (range).

Table 2
Assessment of publication bias in the meta-analysis of orlistat's effects on plasma lipid concentrations.

	Corrected effect size[a]		Begg's rank correlation test,			Egger's linear regression test			Imputed studies	Fail safe N test
	WMD	95% CI	Kendall's Tau[a]	*z*-value	*p*-value	Intercept	95% CI	*p*-value	*n*	*n*[b]
Total cholesterol	−0.28	−0.33, −0.23	−0.35	3.06	0.002	0.51	−0.23, 1.25	0.168	6	8847
LDL-C	−0.22	−0.29, −0.14	−0.53	4.92	<0.001	1.93	−0.18, 4.03	0.072	12	305
HDL-C	−0.04	−0.05, −0.03	−0.11	0.91	0.361	−0.11	−0.82, 0.61	0.765	3	1827
Triglycerides	−0.09	−0.12, −0.05	−0.06	0.51	0.610	0.08	−0.47, 0.62	0.778	2	500

[a] With continuity correction.
[b] Number of theoretically missing studies to bring the *p*-value to > 0.05.

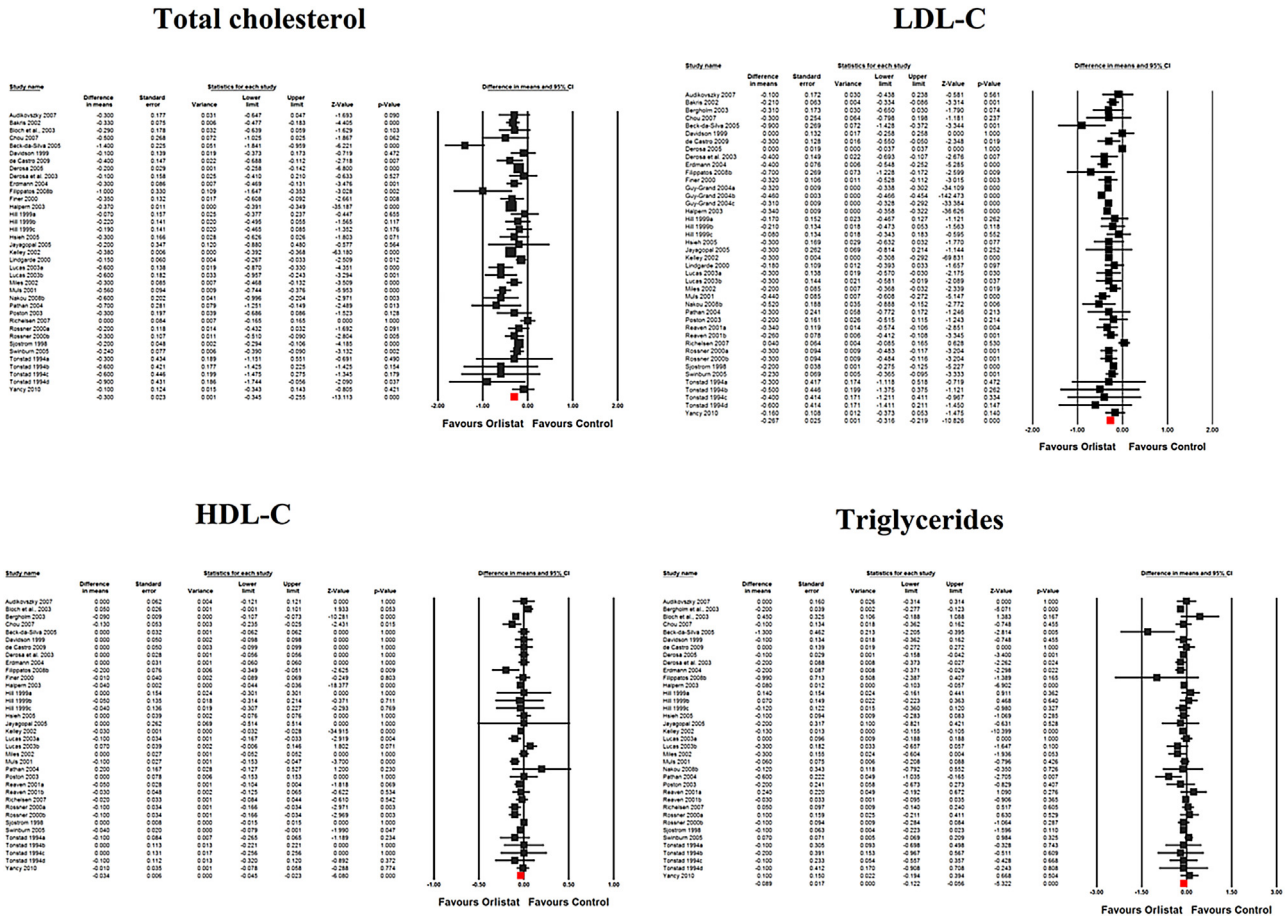

Fig. 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of orlistat on plasma lipid concentrations.

from 2 months [49] up to 3 years [45]. Regarding study design, all included studies were parallel-group, but only one study exhibited cross-over design [22]. Selected trials enrolled subjects with either type 2 diabetes [22,31,32,36,39,42] or nondiabetics [20], hypertension [19,21,26,31], overweight [21,36,39,41,42,50], obesity [18–34,36,37,39–43,45–48,50], heart failure [23], hypercholesterolemia [25,27,28,31,40,41,49], metabolic syndrome [29,44], polycystic ovary syndrome [35], and type IIA and IIB dyslipidemia [38]. Finally, only two studies measured concentrations of Lp(a) [40,46]. Anthropometric and biochemical characteristics of the evaluated studies are presented in Table 1.

3.3. Risk of bias assessment

Regarding sequence generation, several studies were characterized by insufficient information. In addition, most of included studies showed lack of information about allocation concealment. Most of the assessed trials exhibited high or unclear risk of bias with respect to blinding of participants, personnel and outcome assessors, whereas only two studies presented low risk of bias [26,30]. However, all included trials had low risk of bias in terms of selective outcome reporting and incomplete outcome data. Details of the quality of bias assessment are shown in Table 2.

3.4. Effect of orlistat on body weight and plasma lipid concentrations

As expected, treatment with orlistat was associated with a significant reduction in BW (WMD: −2.12, 95% CI: −2.51, −1.74, $p < 0.001$). Overall, the impact of orlistat on plasma concentrations of TC, LDL-C, HDL-C, TGs and Lp(a) was assessed in 37, 42, 36, 37 and 3 treatment arms, respectively. Orlistat treatment was found to significantly reduce plasma concentrations of TC (WMD: −0.30 mmol/L, 95% CI: −0.34, −0.25, $p < 0.001$; Fig. 2), LDL-C (WMD:

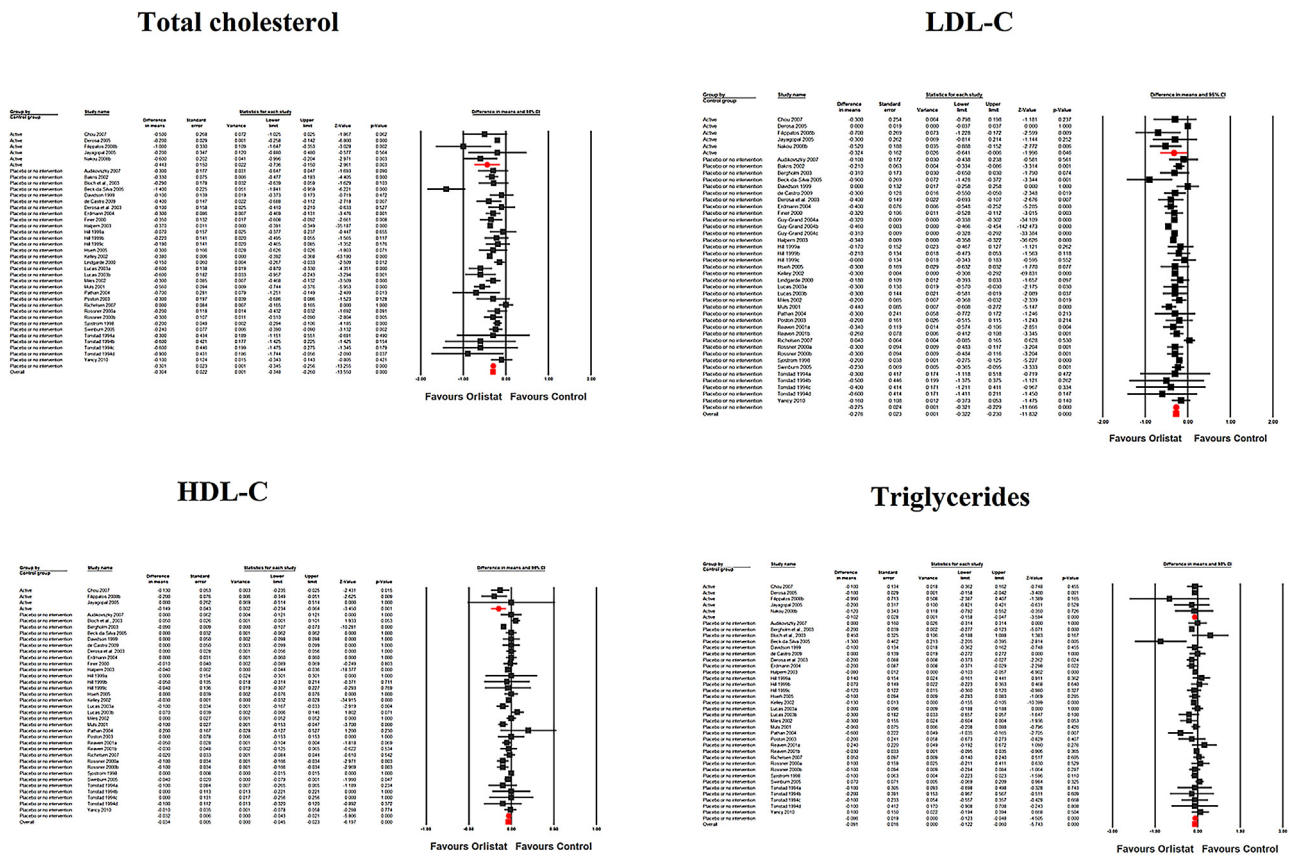

Fig. 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of orlistat on plasma lipid concentrations in the subgroups of trials with active and inactive control groups.

−0.27 mmol/L, 95% CI: −0.32, −0.22, $p < 0.001$; Fig. 2), TGs (WMD: −0.09 mmol/L, 95% CI: −0.12, −0.06, $p < 0.001$; Fig. 2), and HDL-C concentrations (WMD: −0.034 mmol/L, 95% CI: −0.04, −0.02, $p < 0.001$; Fig. 2); while no significant effect on Lp(a) was observed (WMD: −0.17 mmol/L, 95% CI: −0.38, 0.04, $p = 0.116$). All these effects were robust in the sensitivity analysis (Fig. S**1**), and the overall estimate of effect size was not significantly driven by a single study. The only exception was the small size Lp(a) meta-analysis which was sensitive to the study by Muls et al. [40], resulting in a significant reduction in plasma Lp(a) concentrations (WMD: −0.29 mmol/L, 95% CI: −0.48, −0.10, $p = 0.003$).

When the meta-analysis was stratified according to the type of control group in the included randomized trials, significant reductions in plasma TC, LDL-C, TGs and HDL-C concentrations were observed in both subsets of trials with placebo/no intervention (WMD: −0.30 mmol/L, 95% CI: −0.34, −0.26, $p < 0.001$ [TC]; WMD: −0.27 mmol/L, 95% CI: −0.32, −0.23, $p < 0.001$ [LDL-C]; WMD: −0.09 mmol/L, 95% CI: −0.12, −0.05, $p < 0.001$ [TGs]; WMD: −0.03 mmol/L, 95% CI: −0.04, −0.02, $p < 0.001$ [HDL-C]) and active control groups (WMD: −0.44 mmol/L, 95% CI: −0.74, −0.15, $p = 0.003$ [TC]; WMD: −0.32 mmol/L, 95% CI: −0.64, −0.01, $p = 0.046$ [LDL-C]; WMD: −0.10 mmol/L, 95% CI: −0.16, −0.05, $p < 0.001$ [TG]; WMD: −0.15 mmol/L, 95% CI: −0.23, −0.06, $p = 0.001$ [HDL-C]) (Fig. 3).

Another subgroup analysis was performed to evaluate the association between administered dose and the lipid-lowering activity of orlistat. The results revealed significant effect of orlistat on plasma levels of TC, LDL-C and HDL-C at both standard prescription dose of 360 mg/day (WMD: −0.31 mmol/L, 95% CI: −0.35, −0.26, $p < 0.001$ [TC]; WMD: −0.27 mmol/L, 95% CI: −0.32, −0.22, $p < 0.001$ [LDL-C]; WMD: −0.03 mmol/L, 95% CI: −0.04, −0.02, $p < 0.001$ [HDL-C]) and lower doses (WMD: −0.20 mmol/L, 95% CI: −0.35, −0.06, $p = 0.007$ [TC]; WMD: −0.26 mmol/L, 95% CI: −0.39, −0.13, $p < 0.001$ [LDL-C]; WMD: −0.08 mmol/L, 95% CI: −0.14, −0.03, $p = 0.003$ [HDL-C]). The only exception was plasma TGs, for which a significant reduction was only observed at 360 mg/day (WMD: −0.10 mmol/L, 95% CI: −0.13, −0.06, $p < 0.001$) but not at lower doses (WMD: 0.05 mmol/L, 95% CI: −0.10, 0.21, $p = 0.490$) (Fig. 4).

3.5. Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in plasma lipid concentrations with either duration of treatment with orlistat or orlistat-induced BW changes. The results revealed an inverse association between the TC—(slope: 0.01; 95% CI: 0.01, 0.02; $p = 0.00003$) and LDL-C-lowering (slope: 0.01; 95% CI: 0.01, 0.02; $p = 0.00005$) activities of orlistat with the treatment duration. In contrast, no significant association was found between changes in plasma HDL-C (slope: −0.001; 95% CI: −0.003, 0.001; $p = 0.465$) and TGs (slope: 0.004; 95% CI: −0.002, 0.009; $p = 0.194$) concentrations with duration of treatment (Fig. 5). Duration of orlistat treatment was not associated with orlistat-induced BW loss (slope: −0.06; 95% CI: −0.12, 0.001; $p = 0.056$). With respect to BW changes, significant associations were found with LDL-C (slope: 0.03; 95% CI: 0.005, 0.06; $p = 0.018$) and TC (slope: 0.06; 95% CI: 0.03, 0.09; $p = 0.0001$) but not HDL-C (slope: −0.004; 95% CI: −0.01, 0.004; $p = 0.302$) and TGs (slope: −0.002; 95% CI: −0.02, 0.02; $p = 0.881$) (Fig. 6).

3.6. Publication bias

Visual inspection revealed asymmetric funnel plots for the meta-analyses of orlistat's effects on plasma lipid concentrations. Using "trim and fill" method, 6, 12, 3 and 2 potentially missing

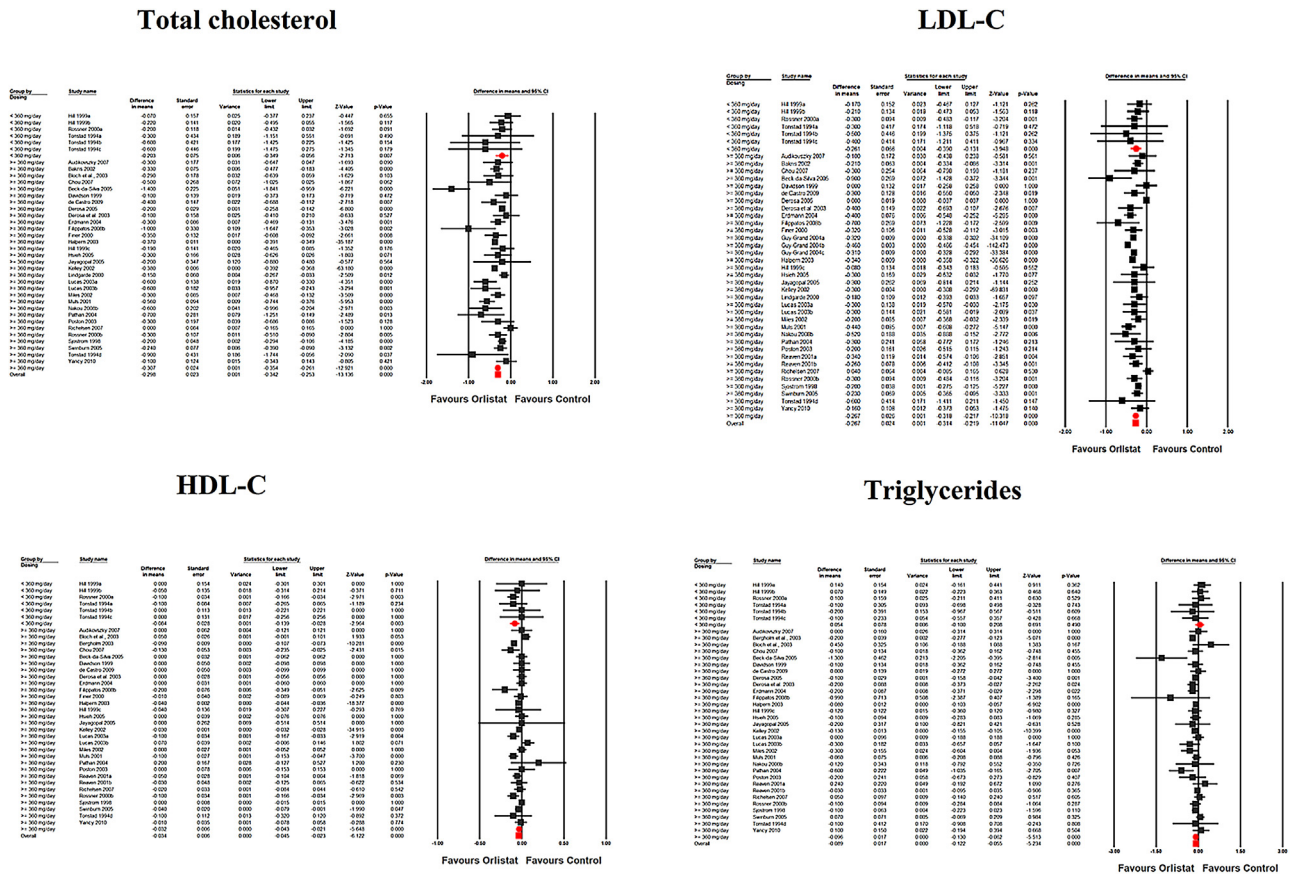

Fig. 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of orlistat on plasma lipid concentrations in the subgroups of trials with doses of ≥360 mg/day and lower.

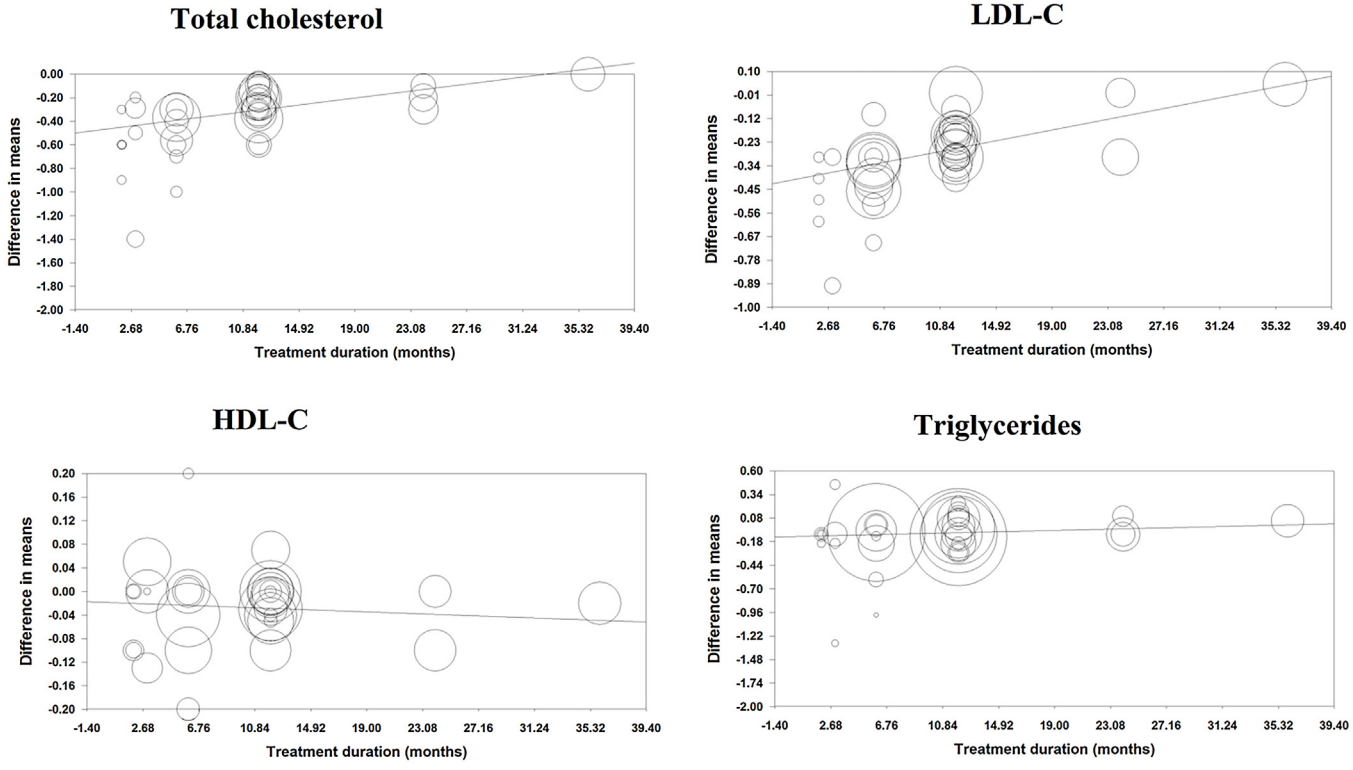

Fig. 5. Random-effects meta-regression plots of the association between mean changes in plasma concentrations of lipids and duration of treatment with orlistat.

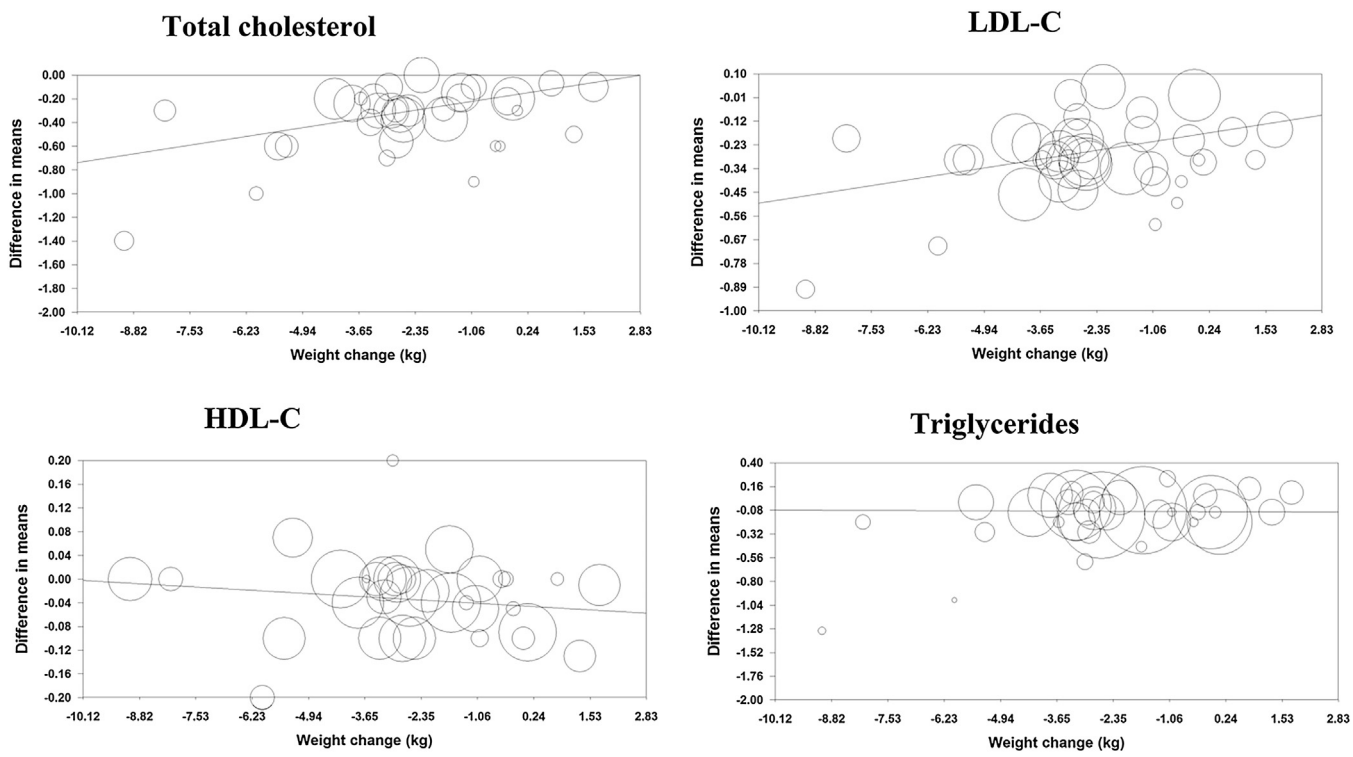

Fig. 6. Random-effects meta-regression plots of the association between mean changes in plasma concentrations of lipids and changes in body weight following treatment with orlistat.

studies were imputed for the meta-analyses of TC, LDL-C, HDL-C and TGs, respectively (Fig. S**2**). Corrected effect sizes remained statistically significant following imputation of potentially missing studies (Table 2). The results of "trim and fill" correction, Egger's linear regression, Begg's rank correlation, and "fail safe N" tests are summarized in Table 2.

4. Discussion

This meta-analysis of RCTs indicated that treatment with orlistat is associated with a slight but significant decrease in plasma TC, LDL-C, HDL-C and TG concentrations, whereas plasma Lp(a) levels were not affected by orlistat treatment. Also, a significant BW reduction was observed after orlistat treatment.

TC and LDL-cholesterol reduction due to orlistat treatment was a fairly consistent finding, since decreases in TC concentrations were reported in 36 of 37 treatment arms, and decreases in LDL-C were reported in 39 of 42 treatment arms. It is intriguing that in 3 studies which did not report such reductions [24,26,45], the average duration of treatment with orlistat was longer (26 months, range 12–36 months) than the one observed in the remaining studies (9 months, range 2–24 months). Specifically, in the study by Davidson et al. [24], while LDL-C decreased after 1 year of orlistat treatment, this effect was lost at the end of the second year of treatment, thus suggesting a possible U-shaped curve describing an early orlistat-induced LDL-C reduction followed by long-term time-related loss of effect of orlistat therapy. However, the same trend was not observed in the other 2 studies [26,45]. Thus, in the study by Richelsen et al. [45] the LDL-C-lowering associated with the initial very-low-energy diet was lost after 18 months of orlistat treatment and remained weak at 36 months. In the study by Derosa et al. [26], a progressive decrease in plasma LDL-C levels at 6 and 12 months of orlistat treatment was observed, but these reductions were not significant as compared with the sibutramine control group. Based on these premises, we explored the association between the duration of orlistat treatment and TC and LDL-C reduction. Meta-regression analysis revealed a significant inverse association between treatment duration and TC- and LDL-C-lowering effects of orlistat. Poor long-term adherence to orlistat treatment might explain this result. Accordingly, high dropout rates have been reported in weight loss trials with orlistat, reaching a dramatic 57% in the 4-year "XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study [3]. In a large population-based administrative database from British Columbia (Canada), Padwal et al. [60] explored the 2-year persistence with orlistat therapy. The authors found that only 2% of patients persisted with orlistat therapy after 2 years and that discontinuation rates were much higher than those observed in RCTs. Similarly, in a post-marketing study from HMO pharmacy data of one million individuals, it is remarkable that the mean duration of purchasing orlistat for weight loss was only 2.1 months while less than 2% of subjects completed 12 months of weight loss medication therapy [61]. Therefore, based on current evidence of poor long-term adherence to orlistat treatment due to adverse events [62], it is likely that the early discontinuation of orlistat treatment explains the apparent loss of cholesterol-lowering efficacy observed in the studies cited. It is unlikely that the effect of orlistat on lipid levels would diminish with time, because the potency of orlistat on fat absorption remained the same after 44 weeks of treatment [33]. Thus, whether longer duration of those studies reporting a significant cholesterol-lowering following orlistat therapy might attenuate or even abolish this effect might be hypothesized.

This meta-analysisand the meta-regression allowed us to explore the impact of orlistat treatment on BW changes and the putative confounding effect of duration of orlistat treatment on BW changes. In this regards, we confirmed that orlistat treatment is paralleled by a significant BW loss, and that orlistat-induced BW reduction was not influenced by the duration of orlistat treatment as it was the case with plasma TG and HDL-C changes.

We also explored the putative confounding effect of orlistat-induced BW loss on changes in plasma lipid concentrations. TC

and LDL-C reductions appeared to be partly driven by the concomitant orlistat-induced BW reduction. Accordingly, meta-regression revealed a mild positive association between BW change and TC and LDL-C reductions. Therefore, greater BW loss should be achieved in patients receiving orlistat therapy in order to obtain more significant plasma TC and LDL-C reductions. These results were quite predictable in the light of the results of a previous meta-analysis showing that BW reduction by diet reduced significantly TC and LDL-C [52]. However, we cannot rule out additional orlistat-induced TC- and LDL-C-lowering unrelated to BW loss. In this regard, it has been suggested that treatment with orlistat could be associated with a greater decrease in plasma LDL-C concentrations than that which would be expected from BW loss alone [24]. This assumption might be confirmed by the observation that orlistat rapidly decreased the absorption of ingested cholesterol by 25% in subjects with abdominal obesity, before BW loss was reached [63]. Additional mechanisms might also explain this assumption. Indeed, because fat meals increase the risk of unpleasant gastrointestinal side effect from orlistat, avoidance of high fat food is recommended in patients taking orlistat. Therefore, limited dietary fat consumption might also have a role in further reducing plasma TC and LDL-C concentrations.

An additional finding emerging from this study is that orlistat-induced TC- and LDL-C-lowering was significant not only at standard prescription dose of 360 mg/daily but also at lower doses. This result might suggest that the cholesterol-lowering pathway which is positively influenced by orlistat is already saturated by lower doses of this drug. Accordingly, the relationship between orlistat dose and fat absorption is curvilinear, so that increasing the dose of orlistat above 120 mg does not cause additional decreases in fat absorption [64,65]. Irrespective of these assumptions, this meta-analysis cannot provide a mechanistic explanation of this result; moreover, the possible effect of poor treatment adherence cannot be ruled out.

Large observational, epidemiological, genetic and Mendelian randomisation studies support the allegation that elevated TGs, either fasting or non-fasting, are associated with increased risk for CVD [2,66,67].

Orlistat treatment was associated with a reduction of plasma TGs in 26 of 37 treatment arms, whereas 3 treatment arms revealed a neutral effect on TGs and 8 treatment arms showed a slight TG-increasing effect.

Despite an overall statistically significant TG-lowering effect of orlistat, the magnitude of this reduction (−0.089 mmol/L) is really modest. Moreover, neither duration of orlistat treatment nor the degree of BW loss had an influence on changes of plasma TG levels. Since the changes of plasma TG concentrations were minimal, the clinical relevance of orlistat-induced TG reduction is most probably insignificant. The dose of orlistat was the only variable that was able to influence its TG-lowering effect; accordingly, orlistat-induced TG-lowering was significant when a dose ≥360 mg/day was administered, but not when lower doses were used. Nevertheless, also in those studies in which higher doses of orlistat were used, a very modest reduction of plasma TGs was observed (−0.096 mmol/L).

Orlistat treatment was associated with a slight reduction of plasma HDL-C concentration in 19 of 36 treatment arms, whereas 14 treatment arms revealed a neutral effect on HDL-C and 3 treatment arms a slight HDL-C-increasing effect. HDL-C-lowering, however, is not a favourable effect [15].

As for TGs, neither duration of orlistat treatment nor the degree of BW loss had an influence on HDL-C changes. Also, slight but significant plasma HDL-C reductions were recorded in trials using either higher or lower doses of orlistat. Intriguingly, despite the well-recognized inverse association between plasma TG and HDL-C levels, this meta-analysis shows a concordant decrease of both TG and HDL-C levels following orlistat therapy. However, this results is not unexpected in the light of the inhibitory effect of orlistat on intestinal fat absorption [63–65] and the previous observations of a direct association between intestinal cholesterol absorption and plasma HDL-C levels [68,69]. Irrespective of the mechanisms explaining the orlistat-induced HDL-C-lowering, it should be underlined that even modest decreases of 1 mg/dL (0.0258 mmol/L) of HDL-C levels are associated with a significant 2–3% increase in the risk of future CV events [70]. Thus, whether this slight HDL-C reduction might have a prognostic impact that counteracts the possible beneficial effect of orlistat-induced BW loss and TC, LDL-C and TG reductions should be still clarified.

It is well known that there is a strong and specific association between elevated Lp(a) levels and increased CVD risk [71]. The impact of orlistat on plasma concentrations of Lp(a) was assessed in 2 studies, for a total of 3 treatment arms. Overall, no significant effect on Lp(a) was observed, thus suggesting that neither orlistat-induced reduction in intestinal fat absorption nor additional mechanisms related to orlistat treatment have any impact on Lp(a) metabolism. However, it should be kept in mind that only two studies with a limited number of patients were included in this meta-analysis. Therefore, definitive conclusions on the possible effects of orlistat on Lp(a) should be made based upon studies with larger sample sizes.

Strengths of our study include the consistent number of RCTs that have been included in this meta-analysis and the effort to examine the impact of multiple confounders of the lipid-lowering effects of orlistat. The present study is subject to some limitations as well. First, we stated that poor long-term adherence might impair the beneficial effects of orlistat on TC and LDL-C; however, this conclusion is merely speculative and additional unexplored mechanisms might help to explain our findings. Second, the assumption of a possible impact of orlistat on lipid levels which is independent of BW loss is merely hypothetical; although there is some evidence in the literature supporting this hypothesis, our meta-analysis could not verify it. Third, available studies did not assess the association between orlistat-induced alterations in plasma lipids and CVD outcomes. Thus, whether the observed changes in BW and plasma lipids may have an impact on CVD risk cannot be concluded from this meta-analysis. Finally, the possible neutral effect of orlistat on plasma Lp(a) levels needs to be verified in larger studies and meta-analyses.

5. Conclusions

This meta-analysis of 9732 subjects shows favorable effects of orlistat on BW, TC, LDL-C, and TG, while the effects on HDL-C were unfavorable. In only 2 studies also Lp(a) concentration was measured, and no effect of orlistat was observed. Greater BW reduction and lower duration of orlistat treatment promote more consistent TC and LDL-C level reductions. The importance of using orlistat at an effective dose is evident to reach significant TG reductions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2017.05.022.

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