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SYSTEMATIC REVIEW

Improvement of plasma adiponectin, leptin and C-reactive protein concentrations by orlistat: a systematic review and meta-analysis

Correspondence Dr Amirhossein Sahebkar, Pharm.D, Ph.D, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box: 91779–48564, Iran. Tel .: +98 513 800 2288; Fax: +98 513 800 2287; E-mail: sahebkara@mums.ac.ir

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Giuseppe Derosa[1,2,3], Pamela Maffioli[1,4] and Amirhossein Sahebkar[5,6]

[1]Department of Internal Medicine and Therapeutics, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy, [2]Center for the Study of Endocrine-Metabolic Pathophysiology and Clinical Research, University of Pavia, Pavia, Italy, [3]Molecular Medicine Laboratory, University of Pavia, Pavia, Italy, [4]PhD School in Experimental Medicine, University of Pavia, Pavia, Italy, [5]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, and [6]Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

AIMS

To conduct a systematic review and meta-analysis of relevant randomized clinical trials (RCTs) to ascertain the effect size of orlistat in modulating plasma levels of adipokines, ghrelin and C-reactive protein (CRP).

METHODS

Medline, SCOPUS, Web of Science and Google Scholar databases were searched. A random-effects model and the generic inverse variance method were used for quantitative data synthesis. Heterogeneity was quantitatively assessed using I^2 index. Sensitivity analyses were conducted using the one-study remove approach. Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of duration of treatment, percentage change in body mass index (BMI) and baseline BMI values as potential confounders of the estimated effect size.

RESULTS

Meta-analysis suggested a significant increase in plasma levels of adiponectin [weighted mean difference (WMD): 19.18%, 95% confidence interval (CI): 5.80, 32.57, $p = 0.005$] and significant reductions in plasma levels of leptin (WMD: −13.24%, 95% CI: −20.69, −5.78, $p = 0.001$) and CRP (WMD: −11.52%, 95% CI: −16.55, −6.49, $p < 0.001$) following treatment with orlistat. In meta-regression, changes in plasma concentrations of adiponectin, leptin and CRP were associated with duration of treatment, but not with either change in BMI or baseline BMI values.

CONCLUSION

Orlistat is effective in increasing plasma concentrations of adiponectin and decreasing those of leptin and CRP.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Orlistat acts by blocking gastrointestinal lipase
- Orlistat has been proven to be effective in reducing body weight

WHAT THIS STUDY ADDS

- Effects of orlistat on insulin-resistance are not well established
- Our meta-analysis proved that orlistat is effective in increasing plasma concentrations of adiponectin
- Orlistat also decreased leptin and C reactive protein levels

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Introduction

Overweight and obesity are conditions that substantially raise the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnoea and respiratory problems, and endometrial, breast, prostate, and colon cancers [1]. Insulin resistance is the major contributor to cardio-metabolic complications of obesity [2]. Insulin resistance is a pathological state in which insulin action is impaired in target tissues including liver, skeletal muscle, and adipose tissue [3]. Adipose tissue plays an important role in insulin-resistance: it releases a large number of bioactive mediators which modulate haemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis [4]. In particular, leptin and adiponectin are adipokines that appear to be produced exclusively by adipocytes [5]. Adiponectin is an adipose-specific collagen-like plasma protein that is exclusively expressed in human adipose tissue [6, 7], but its expression decreases with increase in adiposity [8]. Adiponectin actions include decreased gluconeogenesis, increased glucose uptake, triglyceride clearance, and protection from endothelial dysfunction. Leptin is strongly related in its structure to pro-inflammatory cytokines and plays a major role in body weight regulation; in particular, leptin controls food intake, producing a feeling of satiety, and energy expenditure [9]. Obesity is also linked to inflammatory state, because inflammation may be one of the links among obesity and insulin resistance, hypertension and cardiovascular disease [10]. In this regard, C-reactive protein (CRP) is a marker of inflammation, and elevated basal levels of CRP have been linked to increased risk of diabetes, hypertension and cardiovascular disease [10].

After the withdrawal of sibutramine's license due to the publication of data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) [11], orlistat had been the only molecule licensed in Europe as an anti-obesity drug until January 2015, when liraglutide, an anti-diabetic drug, was licensed for the treatment of obesity [12]. Orlistat has a unique molecular structure, which allows it to bind to the active site of gastrointestinal lipase and block that enzyme activity. The enzyme is thus unable to break triglycerides (TG) down into their component parts [13]. Orlistat proved to be effective in reducing body weight [14–17]; however, the effects of orlistat on insulin resistance are not well established, and findings of randomized controlled trials (RCTs) have not been conclusive [13]. Hence, the aim of the present study was to conduct a systematic review and meta-analysis of relevant RCTs in order to ascertain the effect size of orlistat in modulating insulin resistance.

Methods

Search strategy

To perform the present study, the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed [18]. A search in Medline, SCOPUS, Web of Science and Google Scholar databases was performed using the following terms in titles and abstracts: (adiponectin OR leptin OR adipokine OR adipokines OR adipocytokine OR adipocytokines OR "C-reactive protein" OR CRP OR hsCRP OR hs-CRP) AND (orlistat OR xenical). In order to increase the accuracy of search and avoid missing studies, the wild-card term '*' was used. The last search was performed on 18 May 2015.

Study selection

The eligibility criteria for inclusion of studies in the meta-analysis were: (i) being a randomized parallel-group or cross-over controlled trial; (ii) comparison of the effect of orlistat in monotherapy versus control represented by diet alone or placebo; (iii) treatment effects on fasting concentrations of adipokines or CRP in serum or plasma, considering that there is evidence of a variation of adipokines in post-prandial phase [19]; (iv) providing baseline and end-treatment plasma concentrations of adipokines or CRP in both orlistat and control groups, or presenting the net change values; and (v) English language. Exclusion criteria were: (i) non-interventional studies; (ii) single-arm and uncontrolled trials; (iii) case-control, cross-sectional or cohort studies; (iv) measurement of post-prandial (instead of fasting) concentrations of adipokines or CRP; and (v) insufficient information on baseline or end-treatment plasma concentrations of adipokines or CRP.

Data extraction

After reading the studies that met the inclusion criteria, the following information were extracted: (i) first author's name; (ii) publication year; (iii) study location; (iv) study design; (v) dose and duration of treatment with orlistat; (vi) inclusion criteria and baseline disease; (vii) number of subjects in the orlistat and control groups; (viii) age, gender and body mass index (BMI) of the studied populations; and (ix) plasma adipokines/CRP concentrations at baseline and study end, or changes in the mentioned parameters during the course of the trial.

Quality assessment

Risk of bias in the included studies was evaluated according to the Cochrane criteria [20]. Risk of bias assessment according to the Cochrane criteria includes the following items: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the *Cochrane Handbook*, a judgment of 'yes' indicated low risk of bias, while 'no' indicated high risk of bias. Labelling an item as 'unclear' indicated an unclear or unknown risk of bias.

Quantitative data synthesis

The meta-analysis procedure was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [21]. Change scores (defined as net changes in measurements) were calculated as follows: value at the end of treatment period − value at baseline. For cross-over trials, change scores for plasma concentrations of adiponectin, leptin and CRP were calculated by subtracting the value after control

intervention from that reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \sqrt{[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]}$, assuming a correlation coefficient (R) = 0.5 conversion of median and interquartile range into mean and SD was performed according to the method described by Hozo *et al.* [22]. Standard error of the mean (SEM) was converted to SD using the following formula: $SD = SEM \times \sqrt{(n)}$, where n is the number of subjects. When the results were presented in multiple time points, only values reported for the longest duration of treatment were considered.

A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method was used for the meta-analysis. The reason for choosing a random-effects over a fixed-effects model was to address the inter-study heterogeneity in terms of demographic characteristics of studied populations and also differences in study designs. Heterogeneity was quantitatively assessed using the I^2 index. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using a leave-one-out approach that includes iteratively removing studies and repeating the analysis [23, 24].

Meta-regression

Random-effects meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between calculated effect size and potential confounder variables including duration of treatment, percentage change in BMI and baseline BMI values.

Publication bias

Assessment of publication bias in the meta-analysis was performed through visual inspection of Begg's funnel plot asymmetry, 'fail-safe N' method, Begg's rank correlation test, and Egger's weighted regression test. Duval & Tweedie's 'trim and fill' method was used to correct the effects of publication bias in the meta-analysis [25].

Results

Flow of included studies

The initial literature search yielded 534 articles. Of these 534 publications, 17 were selected for full-text assessment. After careful assessment, 12 articles met the inclusion criteria and were selected for meta-analysis [17, 26–36]. Reasons for rejecting the other five articles were as follows: three were uncontrolled studies, one study was not written in English, and one study [37] reported data for the overall population without providing separate numerical values for leptin levels in the orlistat and placebo groups.

A summary of the study selection process is shown in Figure 1.

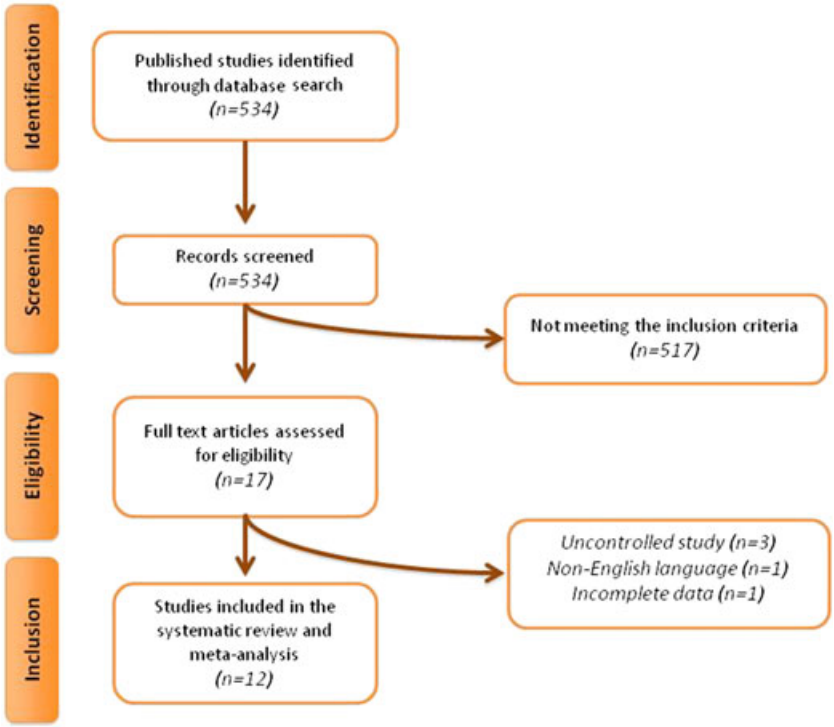

Figure 1
Flow chart of the number of studies identified and included into the meta-analysis

Table 1

Demographic characteristics of the studies included (first part)

Study	Bougoulia *et al.* 2006 [26]	Borges *et al.* 2006 [27]	Derosa *et al.* 2010 [17]	Dixon *et al.* 2008 [28]	Garcia *et al.* 2006 [29]	Hsieh *et al.* 2005 [30]
Location	Greece	Brazil	Italy	UK and Greece	USA	Taiwan
Design	Randomized, controlled parallel group	Randomized, controlled parallel group	Randomized, double-blind placebo-controlled parallel group	Randomized, non-blinded, controlled parallel group	Randomized, controlled parallel group	Randomized, double-blind placebo-controlled parallel group
Treatment duration	6 months	4 months	12 months	12 months	12 months	12 months
Inclusion criteria	Obese women with normal glucose tolerance	Overweight, hypertensive, with central obesity women	Obesity and uncontrolled type 2 diabetes mellitus	Overweight and impaired glucose tolerance	Obese women of Mexican origin (both parents), aged 21–65 years	Overweight without any major systemic disease
Orlistat dose	NS	120 mg three times a day	120 mg three times a day	120 mg three times a day	120 mg three times a day	120 mg three times a day
Control group	Hypocaloric diet	Hypocaloric diet	Placebo	Hypocaloric diet	Hypocaloric diet	Placebo
Participants	71	24	254	31	48	106
Orlistat	35	14	126	16	25	51
Control	36	10	128	15	23	55
Age (years)						
Orlistat	38.0 ± 7.1	47.9 ± 9.3	53 ± 6	NS	43.6 ± 7.9	36.3 ± 5.9
Control	35.4 ± 9·2	46.8 ± 5.8	52 ± 5	NS	44.0 ± 9.6	35.6 ± 6.7
Male/Females						
Orlistat	0/35	0/24	62/64	7/9	0/25	21/30
Control	0/36	0/14	66/62	8/7	0/23	25/30
Smokers						
Orlistat	NS	NS	46	NS	NS	NS
Control	NS	NS	41	NS	NS	NS
BMI (kg/m^2)						
Orlistat	37.2 ± 5.3	35.4 ± 5.9	33.1 ± 2.9	29.4 ± 3.0	37.7 ± 7.9	31.10 ± 2.11
Control	38.5 ± 7.0	36.0 ± 7.6	32.5 ± 2.3	27.3 ± 3.1	35.8 ± 5.28	31.12 ± 2.31
HbA_{1c} (%)						
Orlistat	NS	NS	8.4 ± 1.4	NS	6.08	NS
Control	NS	NS	8.2 ± 1.3	NS	6.00	NS
Adiponectin (μg/ml)						
Orlistat	0.0172 ± 0.0049	0.0065 ± 0.0018	5.0 ± 1.3	11.79 ± 5.35	NA	4.56 ± 1.06
Control	0.0205 ± 0.0062	0.0074 ± 0.0034	4.8 ± 1.1	12.97 ± 6.31	NA	4.88 ± 1.20
Leptin (ng/ml)						
Orlistat	90.1 ± 30.0	39.4 ± 27.1	31.6 ± 15.9	NA	21.8 ± 13.0	13.89 ± 2.51
Control	88.7 ± 29.3	62.4 ± 31.9	30.9 ± 15.4	NA	18.7 ± 12.0	14.47 ± 2.56

(continues)

Table 1
(Continued)

Study	Bougoulia *et al.* 2006 [26]	Borges *et al.* 2006 [27]	Derosa *et al.* 2010 [17]	Dixon *et al.* 2008 [28]	Garcia *et al.* 2006 [29]	Hsieh *et al.* 2005 [30]
CRP (mg/l)						
Orlistat	9.37 ± 5.5	0.00095 ± 0.00081	2.5 ± 1.6	6.08 ± 4.68	NA	3.04 ± 0.34
Control	8.58 ± 3.9	0.00048 ± 0.00045	2.3 ± 1.4	5.00 ± 6.26		3.09 ± 0.18
Ghrelin (pg/ml)						
Orlistat	NA	NA	NA	NA	589 ± 225	NA
Control	NA	NA	NA	NA	596 ± 242	NA
Resistin (ng/ml)						
Orlistat	22.3 ± 8.1	NA	NA	NA	NA	NA
Control	23.7 ± 9.1	NA	NA	NA	NA	NA

Values are expressed as mean ± SD or median (interquartile range). Abbreviations: HbA_{1c}: glycated haemoglobin; TC: total cholesterol; Tg: triglicerides; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein (high sensitivity assay); NS: not stated; NA: not applicable.

Table 2
Demographic characteristics of the studies included (second part)

Study	Harrison *et al.* 2008 [31]	Madsen *et al.* 2009 [32]	Madsen *et al.* 2008 [33]	Ozcelik *et al.* 2004 [34]	Ozcelik *et al.* 2005 [35]	Ozkan *et al.* 2009 [36]
Location	USA	Denmark	Denmark	Turkey	Turkey	Turkey
Design	Randomized, controlled parallel group	Randomized double-blind, placebo-controlled parallel group	Randomized, double-blind placebo-controlled parallel group	Randomized, double-blind placebo-controlled parallel group	Randomized, double-blind placebo-controlled three parallel group	Randomized, controlled parallel group
Treatment duration	9 months	36 months	36 months	3 months	3 months	3 months
Inclusion criteria	Overweight with non-alcoholic steatohepatitis	Abdominally obese subjects with impaired fasting glucose and/or dyslipidemia	Abdominally obese subjects with impaired fasting glucose and/or dyslipidemia	Obese women aged 18–50 years	Obese women aged 18–50 years	Obese subjects
Orlistat dose	120 mg three times a day	120 mg three times a day	120 mg three times a day	120 mg three times a day	120 mg three times a day	120 mg three times a day
Control group	Hypocaloric diet	Placebo	Placebo	Placebo	Hypocaloric diet	Hypocaloric diet
Participants	41	68	93	24	24	21
Orlistat	23	35	49	14	8	11
Control	18	33	44	10	8	10
Orlistat + diet					8	
Age (years)						37.4 ± 12.4
Orlistat	47.9 ± 7.5	NS	NS	38.7 ± 2.9	38.0 ± 3.1	
Control	45.8 ± 10.7	NS	NS	40.6 ± 1.8	43.0 ± 2.1	
Male/Females						6/15
Orlistat	7/16	NS	NS	0/14	8	

(continues)

Table 2
(Continued)

Study	Harrison *et al.* 2008 [31]	Madsen *et al.* 2009 [32]	Madsen *et al.* 2008 [33]	Ozcelik *et al.* 2004 [34]	Ozcelik *et al.* 2005 [35]	Ozkan *et al.* 2009 [36]
Control	6/12	NS	NS	0/10	8	
Smokers						
Orlistat	NS	NS	NS	NS	NS	NS
Control	NS	NS	NS	NS	NS	NS
BMI (kg/m^2)						
Orlistat	37.3 ± 6.0	33.0 ± 3.3	32.7 (31.5–33.9)	37.7 ± 1.1	NA	37.7 ± 3.1
Control	35.2 ± 6.5	33.0 ± 3.9	32.8 (31.6–34.1)	39.4 ± 1.3	NA	36.2 ± 2.8
HbA_{1c} (%)						
Orlistat	5.7 ± 0.6	NA	NA	NA	NA	NA
Control	5.8 ± 1.2	NA	NA	NA	NA	NA
Adiponectin (μg/ml)						
Orlistat	$9.9 \times 10^{-6} \pm 6.3 \times 10^{-6}$	NA	0.49 (0.41–0.58)	NA	NA	NA
Control	$8.7 \times 10^{-6} \pm 3.8 \times 10^{-6}$	NA	0.5 (0.42–0.6)	NA	NA	NA
Leptin (ng/ml)						
Orlistat	NA	470.2 (336.8–656.5)		16.2 ± 1.2	16.1 ± 1.4	37.0 ± 21.0
Control	NA	352.9 (243.3–512)		19.3 ± 2.1	20.6 ± 1.7	36.4 ± 17.5
CRP (mg/l)						
Orlistat	NA	NA	2.6 (2.3–2.8)	NA	NA	NA
Control	NA	NA	2.2 (2.0–2.4)	NA	NA	NA
Ghrelin (fmol/ml)						
Orlistat	NA	NA	NA	NA	NA	59.4 ± 27.5
Control	NA	NA	NA	NA	NA	59.1 ± 34.7
Resistin (pg/ml)						
Orlistat	12.6 ± 11.2	NA	NA	NA	NA	NA
Control	11.8 ± 5.7	NA	NA	NA	NA	NA

Values are expressed as mean ± SD or median (interquartile range). Abbreviations: HbA_{1c}: glycated haemoglobin; TC: total cholesterol; Tg: triglicerides; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein (high sensitivity assay); NS: not stated; NA: not applicable.

Table 3
Risk of bias assessment in the studies considered for meta-analysis

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Bogulia *et al.* 2006 [26]	L	U	H	L	L	L
Borges *et al.* 2006 [27]	L	U	H	L	L	L
Derosa *et al.* 2010 [17]	L	L	L	L	L	L
Dixon *et al.* 2008 [28]	L	U	H	L	L	L
Garcia *et al.* 2006 [29]	L	U	U	L	L	L

(continues)

Table 3
(Continued)

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Hsieh *et al.* 2005 [30]	L	U	L	L	L	L
Harrison *et al.* 2008 [31]	L	U	H	L	L	L
Madsen *et al.* 2009 [32]	L	U	L	L	L	L
Madsen *et al.* 2008 [33]	L	U	L	L	L	L
Ozcelik *et al.* 2004 [34]	L	U	L	L	L	L
Ozcelik *et al.* 2005 [35]	L	U	H	L	L	L
Ozkan *et al.* 2009 [36]	L	U	H	L	L	L

Criteria defined for quality assessment are based on the Cochrane guidelines. Abbreviations: H: high risk of bias; L: low risk of bias; U: unclear or unrevealed risk of bias.

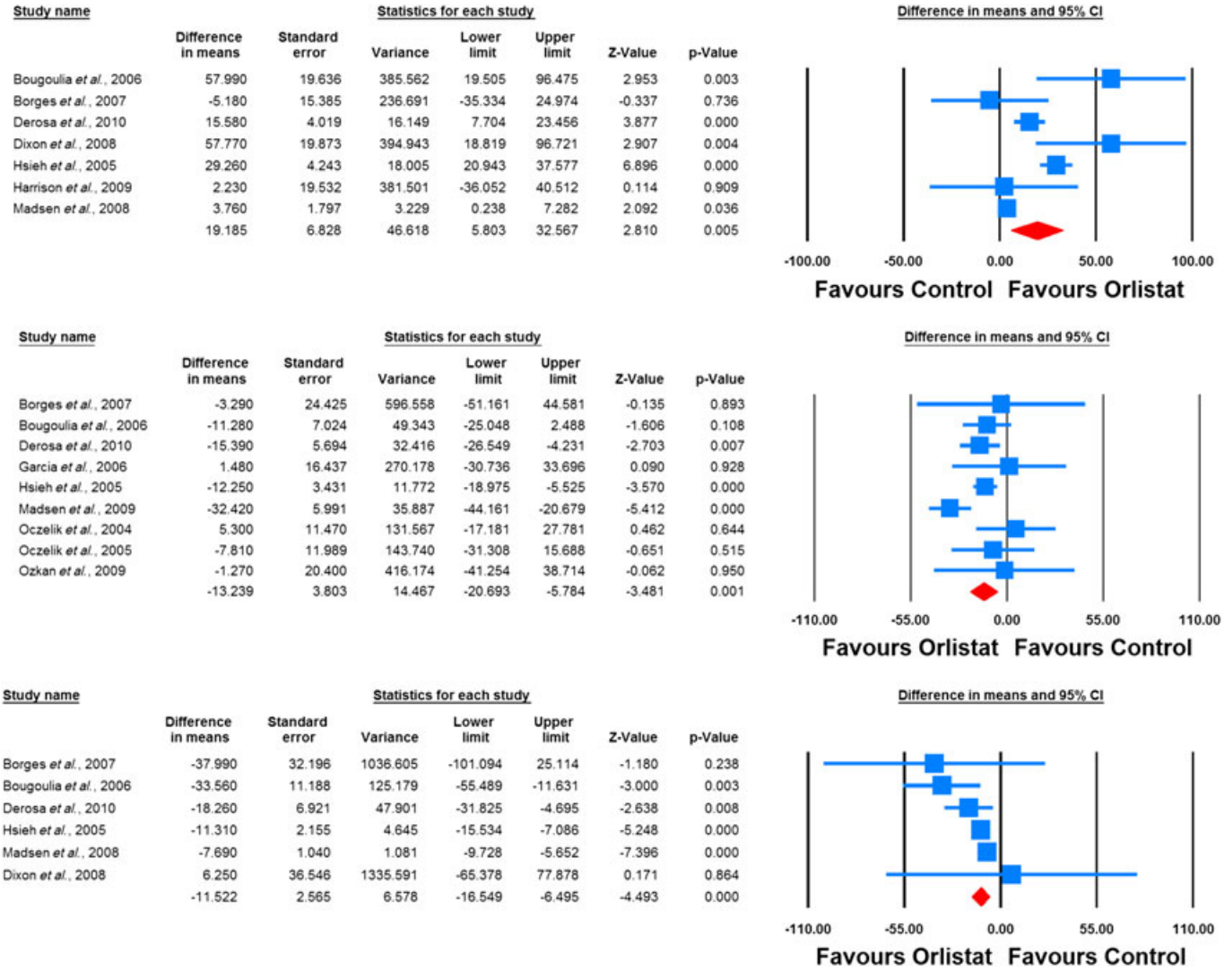

Figure 2
Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of orlistat on plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot)

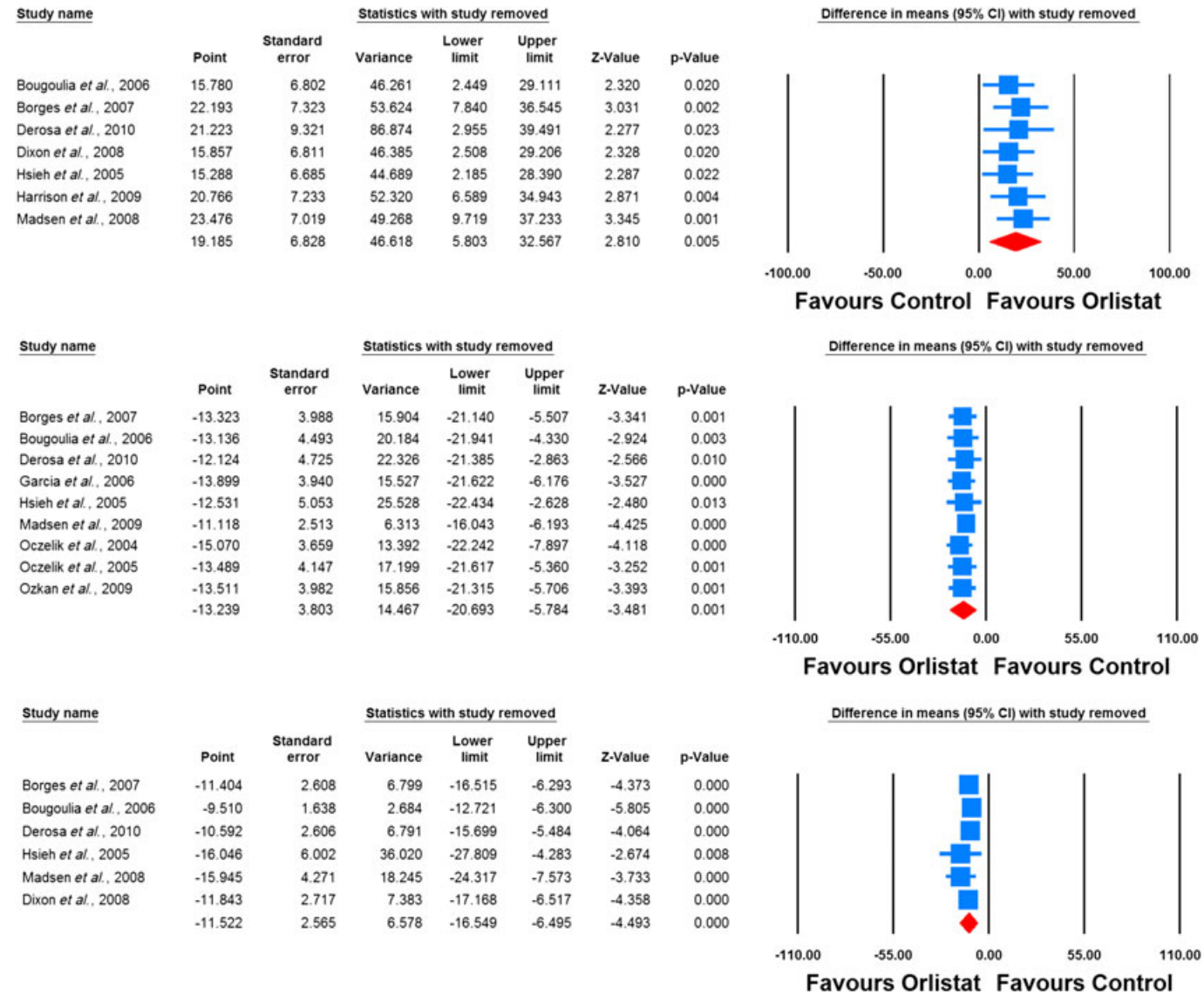

Figure 3

Leave-one-out sensitivity analysis for the impact of orlistat on plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot)

Characteristics of included studies

A total of 823 subjects were included in the 12 eligible studies, comprising 417 subjects in the orlistat group and 406 in the control group. The largest study had a population size of 254 subjects [17], while the smallest study recruited 21 subjects [36]. The included studies were published between 2004 and 2010, and were conducted in Italy [17], Greece [26], Brazil [27, 28], the UK [28], USA [29, 31], Taiwan [30], Denmark [32, 33] and Turkey [34–36].

The maximum licensed dose of orlistat (360 mg/day) was used in the included trials, with the exception of one study where the dose administered was not revealed [26]. Duration of studies ranged from 3 months [34–36], 4 months [27], 6 months [26], 9 months [31], 12 months [17, 28–30] to 36 months [32, 33]. All trials were designed as parallel-group studies [17, 26–36], all were double arm parallel-group studies [17, 26–34, 36], and one was a triple arm parallel-group study [35]. Selected studies were performed in overweight hypertensive subjects [27], in obese euglycemic subjects [26, 29, 30, 32–36], in obese type 2 diabetic patients [17], in obese patients with impaired glucose tolerance [28], and in overweight subjects with non-alcoholic steatohepatitis [31]. Baseline body weight and insulin resistance parameters were generally matched between orlistat and control groups in the included studies. All studies that measured CRP applied a high sensitivity assay. Demographic and baseline biochemical parameters of the included studies are shown in Tables 1, 2.

Quality assessment

Only one of the selected studies provided sufficient data about random sequence generation and allocation concealment [16].

Nevertheless, other potential sources of bias were sufficiently addressed by most of the included trials. Details on the risk of bias among included trials are summarized in Table 3.

Effect of orlistat on plasma adipokines and CRP

The impact of orlistat on plasma levels of leptin, adiponectin, resistin, ghrelin and CRP were reported in nine, seven, two, two and six RCTs, respectively. Meta-analysis suggested a significant increase in plasma levels of adiponectin (WMD: 19.18%, 95% CI: 5.80, 32.57, $p = 0.005$) and significant reductions in plasma levels of leptin (WMD: −13.24%, 95% CI: −20.69, −5.78, $p = 0.001$) and CRP (WMD: −11.52%, 95% CI: −16.55, −6.49, $p < 0.001$) following treatment with orlistat (Figure 2). All these effect sizes turned out to be robust in the leave-one-out sensitivity analysis. No significant change in plasma levels of resistin (WMD: 18.05, 95% CI: −27.40, 63.51, $p = 0.436$) and ghrelin (WMD: 12.47, 95% CI: 7.97, 16. 97, $p < 0.001$) were found (Figure 3).

When the studies were categorized according to the duration of treatment, adiponectin-elevating and leptin-lowering effects of orlistat were significant only in the subgroup of RCTs lasting ≥ 48 weeks (WMD: 20.28%, 95% CI: 4.89, 35.67, $p = 0.010$ [adiponectin]; WMD: −17.46%, 95% CI: −28.49, −6.43, $p = 0.002$ [leptin]). With respect to CRP, significant reductions were observed in both subgroups lasting ≥ 48 weeks (WMD: −9.50%, 95% CI: −12.84, −6.16, $p < 0.001$) and < 48 weeks (WMD: −34.04%, 95% CI: −54.75, −13.32, $p = 0.001$) (Figure 4).

Meta-regression

Random-effects meta-regression was performed to assess the impact of potential moderator variables on the adipokine and CRP responses to orlistat in the included RCTs. Changes

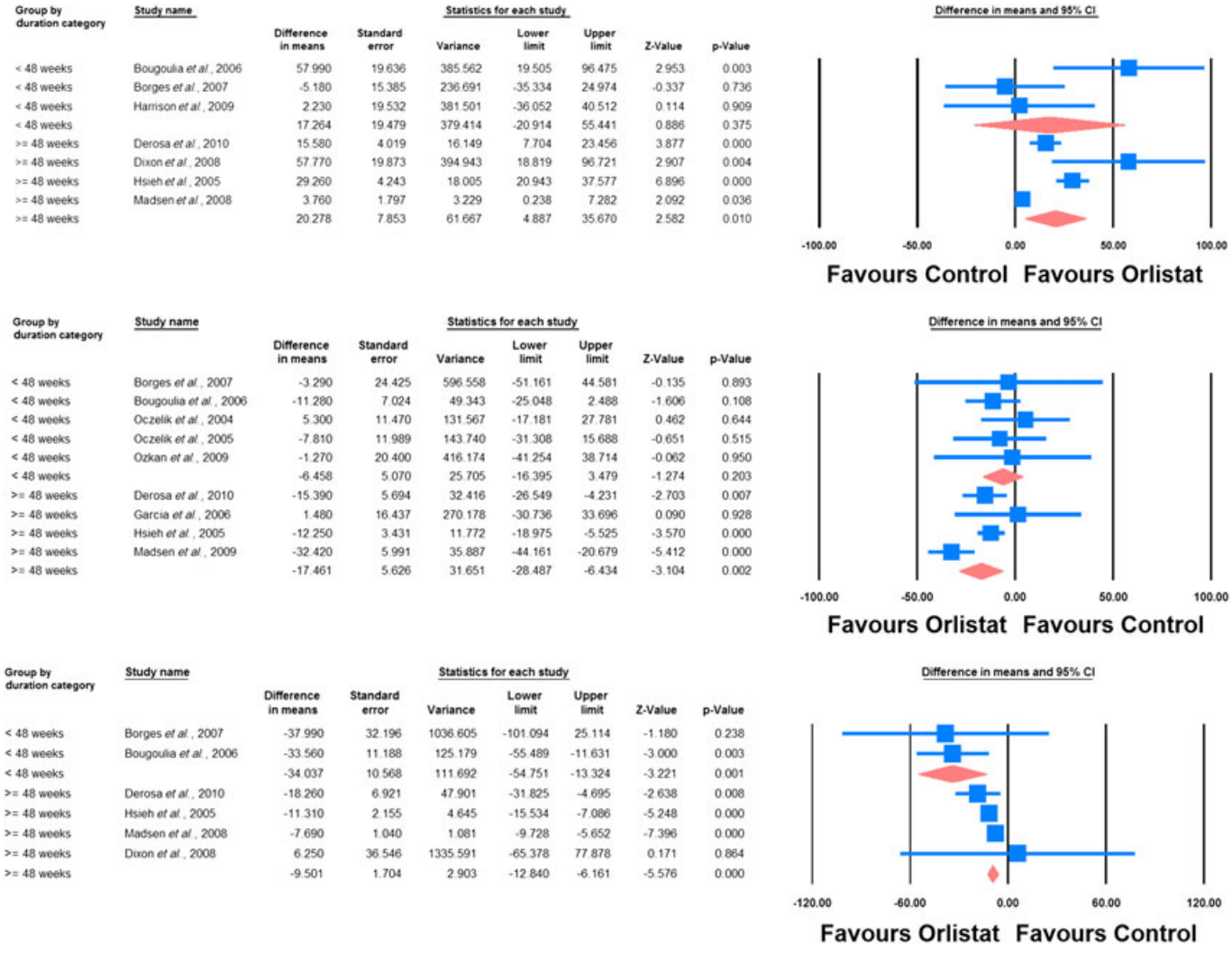

Figure 4

Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of orlistat on plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot) in subgroups of trials with treatment durations of < 48 weeks and ≥ 48 weeks

in plasma concentrations of adiponectin (slope: −0.18; 95% CI: −0.28, −0.08; $p < 0.001$), leptin (slope: −0.21; 95% CI: −0.33, −0.09; $p < 0.001$) and CRP (slope: 0.05; 95% CI: 0.01, 0.10; $p = 0.021$) were found to be significantly associated with duration of treatment with orlistat (Figure 5). Nevertheless, meta-regression did not suggest any significant association of the assessed parameters (leptin, adiponectin and CRP) with either changes in BMI or baseline BMI values (Figures 6, 7).

Publication bias

The funnel plot of precision (inverse standard error) versus effect size (mean difference) did not suggest any potential publication bias in the meta-analysis of orlistat's effect on plasma adiponectin concentrations. However, the funnel plots for the analysis of orlistat's effects on plasma leptin and CRP concentrations were asymmetric, suggesting potential publication bias. Using the 'trim and fill' method, one potentially missing study was imputed for themeta-analysis of leptin changes, yielding an imputed effect size of −11.23% (95% CI: −16.08, −6.39). With respect to the leptin meta-analysis, four potentially missing studies were imputed, yielding an effect size of −16.60% (95% CI: −23.82, −9.37) (Figure 8). For all analyses, there was no sign of publication bias according to the Begg's rank correlation, Egger's linear regression, and 'fail-safe N' tests (Table 4).

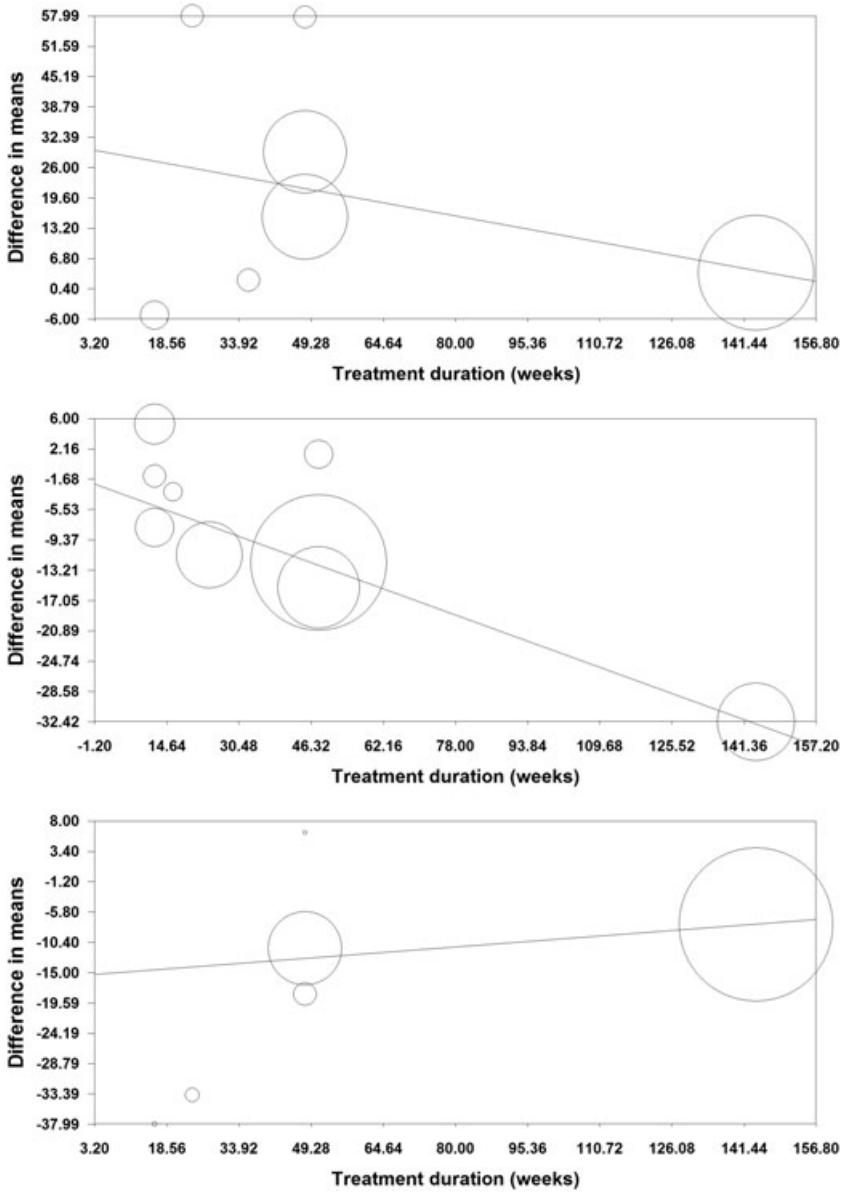

Figure 5

Meta-regression bubble plots of the association of mean changes in plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot) with treatment duration. The size of each circle is inversely proportional to the variance of change

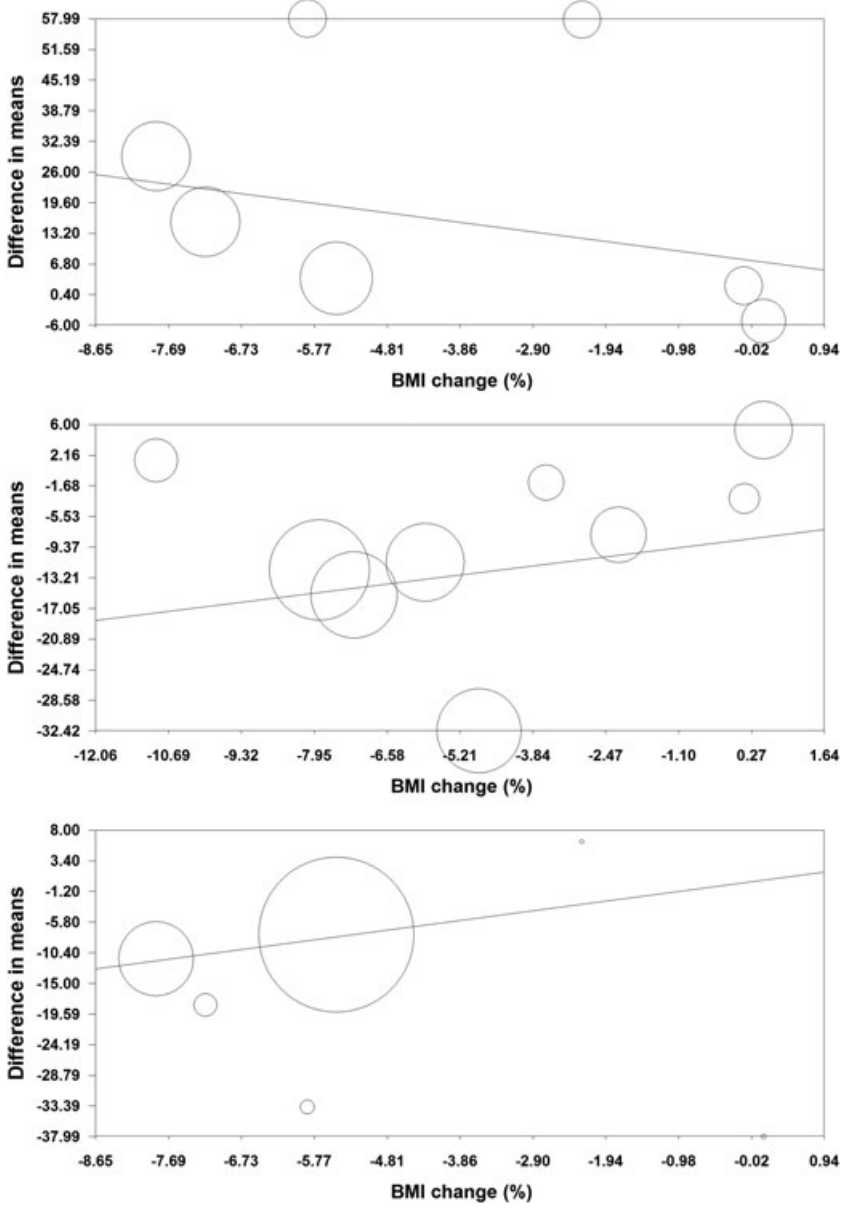

Figure 6

Meta-regression bubble plots of the association of mean changes in plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot) with percentage changes in BMI. The size of each circle is inversely proportional to the variance of change

Discussion

The main finding of the present meta-analysis is the positive effect of orlistat in increasing adiponectin and decreasing leptin and CRP levels. Adiponectin is secreted by adipocytes and has been linked to glucose and lipid regulation. Adiponectin is decreased in obesity and is inversely related to glucose and insulin levels; adiponectin stimulates oxidation of fatty acids, suppresses gluconeogenesis and inhibits monocyte adhesion, macrophage transformation, and proliferation and migration of smooth muscle cells in blood vessels [38]. Leptin, instead, contributes to body weight regulation by controlling food intake and energy expenditure at the hypothalamic level. Leptin abnormalities have been proposed to increase the propensity to obesity [39]. Regarding CRP, increased serum levels of inflammatory biomarkers have been reported in obese subjects and have been related to the degree of insulin resistance and endothelial dysfunction [40]. The positive effects of orlistat on these markers, cannot be explained only by change in body weight, as our meta-regression did not suggest any significant association between changes in plasma concentrations of leptin, adiponectin and CRP with changes in BMI. Regarding the mechanism through which orlistat increases adiponectin, a possible explanation could be the action of orlistat on intestinal microbiota: circulating endotoxin lipopolysaccharide

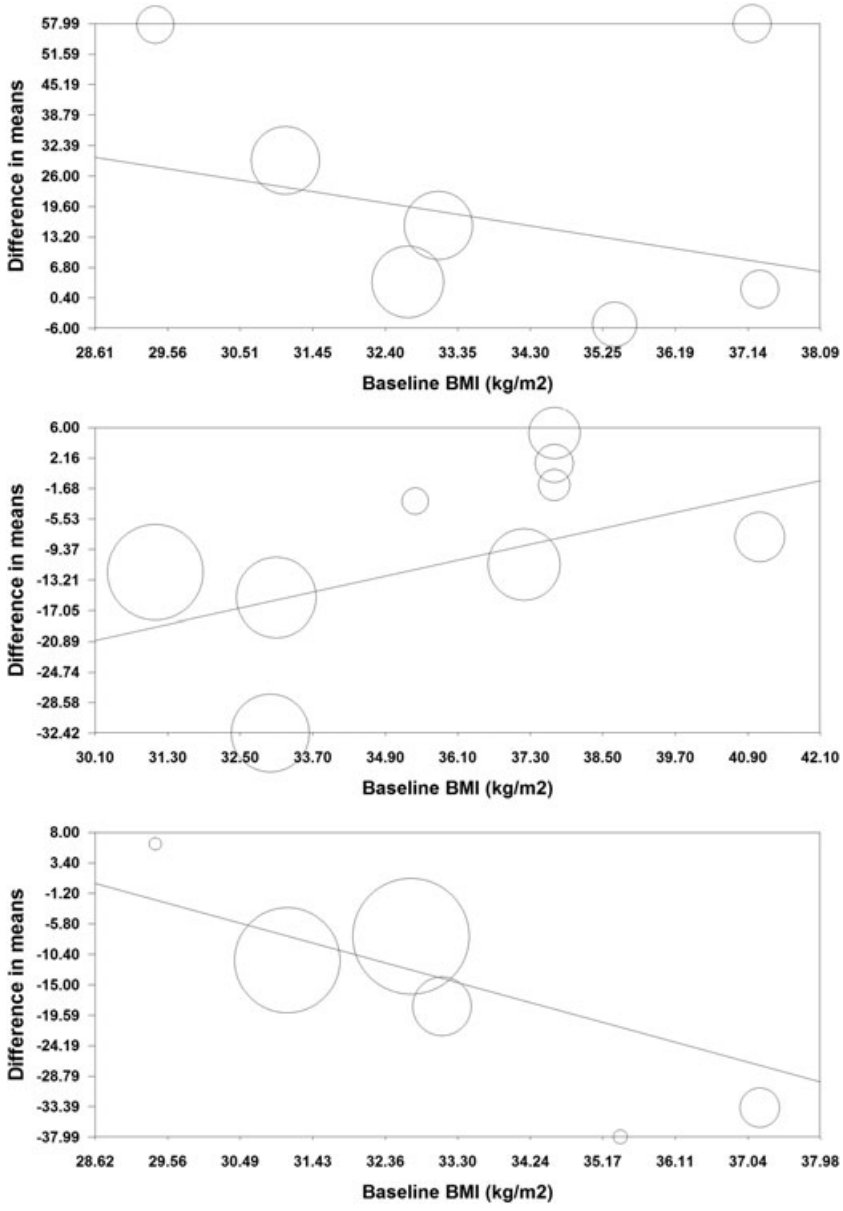

Figure 7

Meta-regression bubble plots of the association of mean changes in plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot) with baseline BMI. The size of each circle is inversely proportional to the variance of change

(LPS) is produced by commensal bacteria within the gut, and orlistat's effect on gut flora leads to a change in circulating LPS levels. This is an important effect, considering that a correlation between the reduction in LPS and the increase in adiponectin levels has been previously reported [28]. Regarding the decrease of leptin levels with orlistat, while reductions in adipose tissue and insulin resistance are influential, a direct action of orlistat has also been suggested [41], though the mechanism is still unknown. Considering orlistat effects on CRP, several mechanisms have been suggested to elucidate the obesity-related low-grade inflammation. Firstly, fat tissue is an important source of proinflammatory and anti-inflammatory substances; moreover, inflammation of the adipose tissue worsens insulin resistance. Secondly, insulin resistance can increase inflammation by interfering with the anti-inflammatory effect of insulin. Therefore reducing body weight may explain, at least in part, the CRP-lowering effect of orlistat which is in line with what has been reported previously [15–18].

Regarding ghrelin and resistin, serum ghrelin levels are reduced in obese individuals compared with age-matched non-obese controls [42], and increased during weight loss following dietary treatment. Ghrelin is secreted into the circulation from intestinal structures, and it increases appetite while decreasing adipose tissue utilization [42]. Conversely, resistin has been reported to be elevated in adipose tissue and serum of obese and insulin-resistant

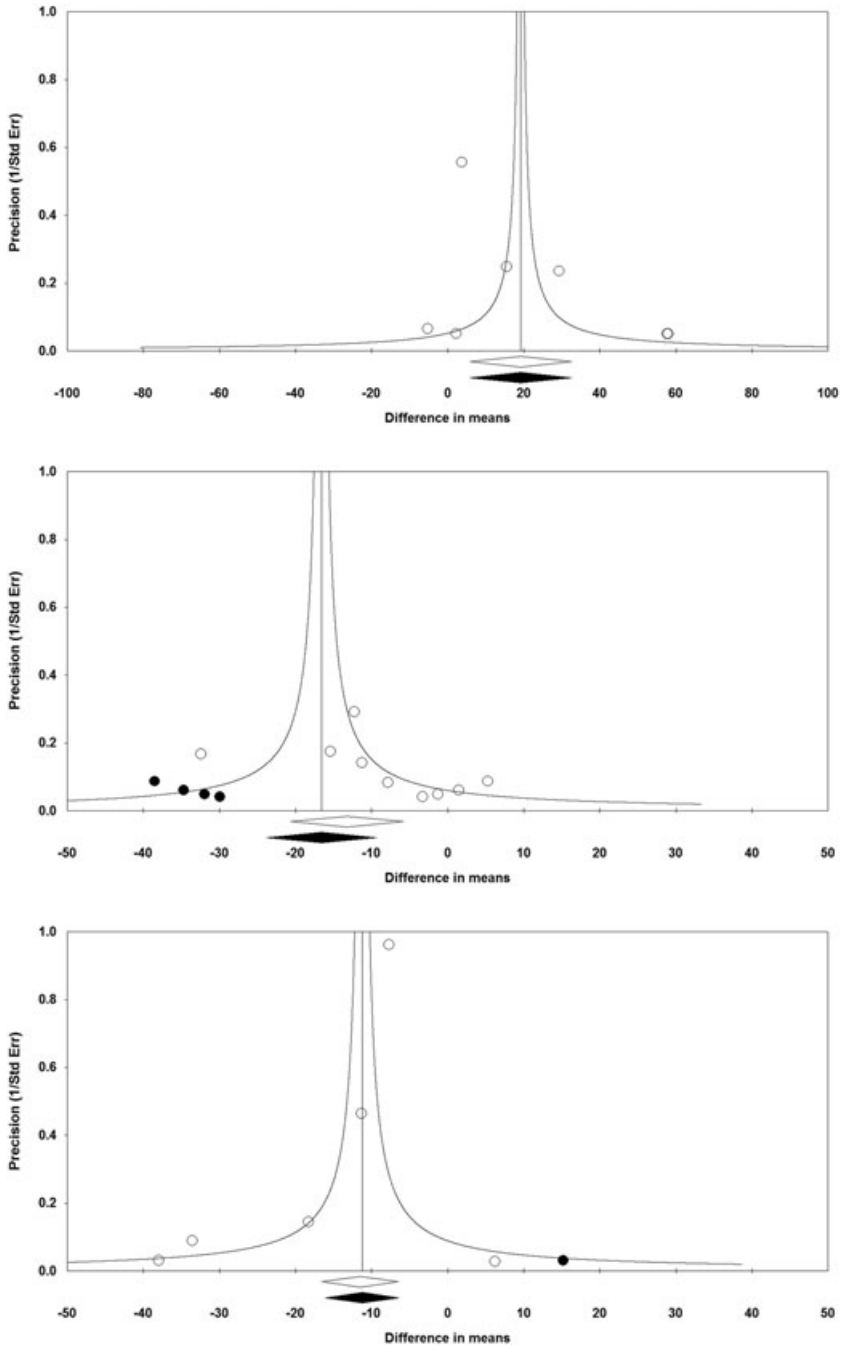

Figure 8

Funnel plot detailing publication bias in the studies reporting the impact of orlistat on plasma concentrations of adiponectin (upper plot), leptin (middle plot) and C-reactive protein (lower plot)

individuals, although studies have produced controversial results [38]. Resistin appears to confer an increased risk of inflammation and atherosclerosis. Our meta-analysis showed a neutral effect of orlistat on ghrelin and resistin levels, in contrast with what has been reported previously [14, 36]; this can be explained by the fact that previous evidence might have come from single-arm, quasi-randomized and uncontrolled studies, or even animal studies. Our pooled result comes from RCT as the highest level of evidence. Moreover, studies included in our meta-analysis enrolled obese subjects, but some studies included obese diabetic patients, and there is evidence that orlistat effects are less pronounced in diabetics. In fact, people with diabetes often take medications that are associated with weight gain; these include antihyperglycaemic, antihypertensive, pain relief and antidepressant agents [43]. In this paper we did not evaluate

Table 4

Assessment of publication bias in the meta-analysis of studies reporting the effects of orlistat on plasma concentrations of adiponectin, leptin and CRP

	Begg's rank correlation test			Egger's linear regression test					
	Kendall's Tau[a]	*z*-value	*p*-value[b]	Intercept	95% CI	*t*	df	*p*-value[b]	*n*[c]
Adiponectin	0.29	0.90	0.37	2.04	−1.54, 5.63	1.47	5	0.202	83
Leptin	0.08	0.31	0.754	0.84	−1.17, 2.84	0.99	7	0.356	40
CRP	0	0	1.000	−1.23	−2.89, 0.43	2.06	4	0.109	91

[a]With continuity correction; [b]Two-tailed; [c]The number of studies (calculated using the 'fail-safe N' method) required to make the *p*-value non-significant.

orlistat's effects on lipid changes, or glycaemic control, because they were not within the goal of this review and meta-analysis and the literature search was not specified for such effects of orlistat. However, interestingly, a recently published meta-analysis discussed this, reporting the positive effects of orlistat on glycaemic control [44]. Taking into account our results and the results reported by Aldekhail et al. [44], we can suggest a positive effect of orlistat on insulin resistance.

The present meta-analysis has some limitations. Included studies were heterogeneous regarding population characteristics, study design and duration of supplementation. Nevertheless, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random-effects mode of analysis. As is inherent with almost every meta-analysis, there is the possibility that some relevant RCTs have been missed. We tried to address this potential limitation by performing several assessments of publication bias. Finally, there was no substantial variation in the orlistat dose across the included trials, and therefore the dose dependence of the observed effect could not be evaluated.

Conclusion

The present systematic review is the first to assess the effects of orlistat on adipokines and CRP, and provides a thorough synthesis of results from RCTs. The main finding of this meta-analysis is that orlistat is effective in increasing adiponectin and decreasing leptin and CRP, but has a neutral effect on ghrelin and resistin. Future studies are warranted to assess the impact of these positive effects of orlistat on insulin sensitivity using the gold standard hyperinsulinemic euglycaemic clamp method. Further, evaluation of the effects of orlistat, either alone or combined with hypolipidemic drugs [45–47], on hard outcomes of obesity and obesity-related disorders is open to question. Also the effects of orlistat on tumour necrosis factor-α, as an adipose-derived inflammatory parameter, could be of interest for a future meta-analysis.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

All the authors were responsible for the design, conduct and data collection of this study. Amirhossein Sahebkar was responsible for the data analysis, but all authors took part in the writing of the manuscript.

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