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Short: berberine and obesity indices.

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Abstract

Background and purpose: Clinical studies investigating the effects of berberine supplementation on anthropometric indices in humans have generated inconsistent results. Thus, the objective of this systematic review and meta-analysis was to clarify the effects of berberine supplementation on obesity indices in human subjects.

Methods: Several online medical databases were systematically searched up to February 2019. All clinical trials exploring the effects of berberine supplementation on indices of obesity were included. The combined weighted mean difference (WMD) of eligible studies was assessed using a random-effects model. We evaluated publication bias by using the Egger's test.

Results: Overall, 10 studies were included. The combined outcomes suggested a significant influence of berberine administration on body mass index (BMI) (WMD: -0.29 kg/m^2, 95% CI: -0.51 to -0.08, p = 0.006) and waist circumference (WC) (WMD: -2.75 cm, 95% CI: -4.88 to -0.62, p = 0.01). However, berberine supplementation yielded no significant decline in body weight (BW) (WMD: -0.11 kg, 95% CI: -0.99 to 0.76, p = 0.79). Following the dose-response evaluation, berberine intake was found to significantly reduce BMI (r = -0.02) and WC (r = -0.72) based on treatment duration.

Conclusion: The results of the current study support the use of berberine supplementation for the improvement of obesity indices.

Keywords: Berberine; Body mass index; Body weight; Dose–response; Meta-analysis; Obesity

1. Introduction

Obesity can be attributed to an imbalance between energy expenditure and energy intake and has become a major public health problem, mainly due to its association with type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertension, insulin resistance, cardiovascular disorders and a myriad of other cardiometabolic diseases [1-2]. Although exogenous factors, such as an excessive caloric intake and a sedentary lifestyle, play the most important role in the current obesity epidemic, endogenous factors, e.g. specific gene variants may predispose certain individuals to become obese [3]. Worldwide, more than one-third of adults are affected by obesity [4]. Although traditional pharmacotherapy remains a key element in the treatment of obesity and obesity-related comorbidities, many researchers have also investigated the effects of natural products in the management of obesity. Due to their anti-obesity properties, these substances have been employed either as adjuncts to conventional drugs or in monotherapy [5-6].

One such example is the plant alkaloid berberine, which is considered an inexpensive and safe oral supplement commonly used as an over-the-counter (OTC) drug due to its myriad of effects on human health. Berberine is known to increase insulin sensitivity, lower blood glucose, reduce the risk of metabolic syndrome, improve lipid metabolism and stimulate weight loss [7]. Previous reports have highlighted that berberine increases the mRNA expression of adiponectin, inhibits the differentiation of adipocytes, regulates glucose and lipid metabolism, and decreases the secretion of leptin and resistin [8].

Recently, a randomized controlled trial reported no change in body mass index (BMI), waist circumference (WC) or body weight (BW) following berberine supplementation. However, the authors reported other beneficial metabolic effects of berberine, such as a reduction in hemoglobin A1C (HbA1c) and triglyceride levels [9]. Contrastingly, the administration of 500 mg of berberine

either twice [10] or three times daily [11] for a period of three months resulted in a decrease in BW, BMI and WC [10, 11]. The duration of the intervention seems to play a role in the effects of this natural product, since a shorter administration of berberine supplements in some clinical trials as opposed to others might explain why the authors did not record a significant decrease in BMI even if the dose of berberine was the same in all of these studies [10, 12-13].

Thus, due to the conflicting results of these previous interventions, the aim of our systematic review and meta-analysis was to evaluate the impact of berberine supplementation on obesity indices in humans.

2. Methods

The current study has been conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) protocol [14].

2.1. Search Strategy

In order to identify eligible studies, we searched several online databases (the Cochrane Library, Scopus, PubMed-MEDLINE and Google Scholar) from their establishment up to February 2019. The following medical subject headings (MeSH) and non-MeSH keywords were employed: "Berberine" AND "Cross-Over Studies" OR "Clinical Trials" OR "Double-Blind Method" OR "Random Allocation" OR "RCT" OR "Single-Blind Method" OR "Intervention Studies" OR "controlled trial" OR "randomised" OR "randomized" OR "random" OR "intervention" OR "randomly" OR "assignment" OR "placebo". Ultimately, we manually searched the references of the eligible studies to identify any missing studies relevant to our objective.

2.2. Eligibility criteria

The eligibility criteria for the search process and meta-analysis were defined *via* the PICO method: definition of the Population (P), Intervention (I), Comparison (C) and Outcomes (O). Firstly, the population consisted of adult subjects suffering from various health conditions. Secondly, we

included only randomized controlled trials in our evaluation. Thirdly, the intervention consisted in berberine supplementation to the recruited subjects. Fourthly, the included studies investigated the impact of berberine supplementation in an intervention group versus a control group. Fifthly, sufficient information on BMI, WC and BW was reported for both the intervention group and the control group. Finally, the studies were published in English. We excluded clinical trials without a suitable control group. In addition, we excluded the publications that did not provide outcome measures at the beginning of the study and at the end of the intervention.

2.3. Data extraction

Two independent investigators (J.R. and H.K.-V.) scanned and extracted the relevant information. Where necessary, a senior investigator (S.J.M.R.) helped to achieve consensus. If the information found in the articles was incomplete, we communicated with the lead authors of the papers for clarifications. The following information was extracted from each included trial: the first author of the study, the design of the study, the health status of the participants involved, the year of publication, the study location (country), the sample size of the study groups and of the control groups, the mean age of the participants, the gender of the participants, the dose of berberine administered, the duration of the intervention and the findings (means and standard deviation of the BMI, WC and BW at the beginning and the end of the study and/or changes between the beginning and the end of the supplementation with berberine). If a trial reported duplicate data, we considered the reports with complete follow-up and results.

2.4. Quality assessment of publications

The quality of the eligible trials was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias which takes into consideration the following items: allocation concealment, random sequence generation, blinding of outcome assessment, blinding of participants and personnel, selective reporting, incomplete outcome data and other probable sources of biases. In order to evaluate the quality of the selected trials, each study was allotted a

label (yes, no or unclear) and graded as low-risk, high-risk or unknown risk of bias, respectively [15].

2.5. Quantitative data synthesis

We performed all statistical analyses using the Stata program (Stata Corp. College Station, Texas, USA). The combined effect size was computed based on the mean difference and the standard deviation (SD) of the outcome measures. The random-effects model (using the DerSimonian-Laird method) was applied in order to evaluate effect sizes and the results were reported based on the weighted mean difference (WMD) and 95% confidence intervals (CI). If the SD of the mean change was not described in the publications, we calculated it using the next formula: $SD_{alteration}$= square root [($SD_{baseline}^2$ + SD_{end}^2) - (2 × R × $SD_{baseline}$ × SD_{end})] [16]. Heterogeneity was evaluated using Cochran's Q-test (significance set at less than 0.05) and the I^2 statistic were applied for calculating the percentage of heterogeneity among studies. We carried out predefined stratified analyses based on sex (women and men), berberine dosage (≤1 g and >1 g) and intervention duration (≤12 weeks and >12 weeks). Subgroup analyses for berberine dosage and intervention duration were based on the median cut-off of the qualified studies and were performed using a fixed-effects model. Publication bias was evaluated *via* the Egger's test and visual appraisal of the funnel plots [17]. The "trim and fill" approach was applied to revise any detected publication bias [18]. Sensitivity analyses were performed using the metaninf test to evaluate the consistency of the outcomes. We evaluated the non-linear possible impact of berberine dosage (g/day) and supplementation duration (weeks) by fractional polynomial modelling [19].

3. Results

3.1. Study selection and systematic review

We retrieved 1410 publications from PubMed-MEDLINE, Scopus, the Cochrane Library and Google Scholar out of which 324 were duplicate publications and therefore excluded. After

reviewing the title and abstract of the remaining papers, 979 manuscripts were subsequently excluded. In the next step, we screened the remaining 107 papers by evaluating the full-text and we excluded 98 papers due to the following reasons: inclusion of a co-intervention, review articles, duplicate data and no data of interest (**Supplementary Figure 1**). Finally, 9 articles were included in our study. Nine studies reported BMI [7, 10-13, 20-23], five reported BW [10, 13, 20-22] and seven reported WC [7, 11, 20, 22, 23]. Pérez-Rubio et al. reported WC separately for men and women [11]. The duration of the interventions varied between 4 to 52 weeks. The age of the individuals ranged from 26 to 65 years. The eligible trials were published between 2010 and 2018 [7, 10-13, 20-23]. One study was conducted on males [11] and five studies were conducted on females [7, 11, 13, 20, 22]. All studies were controlled trials and one had a cross-over design [10]. The dose of berberine supplementation ranged from 1000 to 3000 milligrams/day. The studies were conducted in various countries: five in China [7, 13, 20, 22, 23], two in Iran [12, 21], one in Italy [10] and one article included two studies conducted in Mexico [11] (Table 1).

3.2. Quality assessment

The methodological quality and risk of bias of the eligible trials are reported in **Supplementary Table 1.** Most trials had good quality based on the Cochrane collaboration's tool criteria. For some studies, the risk of bias originated from the “incomplete outcome data” item [7, 10, 12, 22, 23] and from the “blinding of participants” item [20].

3.3. Meta-analysis results

Five arms, with a total of 378 individuals (control=187 and case=191), described BW as a result measure. The pooled outcomes from the random-effects model specified that berberine intervention did not alter BW significantly (WMD: -0.11 kg, 95% CI: -0.99 to 0.76, p = 0.79), with no significant heterogeneity across the studies (I^2 = 0.0%, p = 0.49) (**Figure 1**).

Nine studies, with a total of 983 individuals (control=499 and case=484), described BMI as a result measure. The combined outcomes from the random-effects model demonstrated that berberine supplementation resulted in a significant decrease in BMI (WMD: -0.29 kg/m^2, 95% CI: -0.51 to -0.08, p = 0.006), with no significant heterogeneity across the studies (I^2 = 0.0%, p = 0.85) (**Figure 2**).

Moreover, seven studies, including a total of 841 (case=423 and control=418) individuals, presented data for WC as an outcome evaluation. The combined results from the random-effects model reported that berberine supplementation resulted in a significant reduction in WC (WMD: -1.78 cm, 95% CI: -3.17 to -0.39, p=0.01), with a significant heterogeneity across the studies (I^2= 73.5%, p= 0.001) (**Figure 3**). We stratified the studies based on the duration of the trial (weeks), the dose of berberine administered (mg/day) and the sex of the participants (female, male or both sexes included in the study) to investigate the possible sources of heterogeneity. We found heterogeneous values for the dosage of berberine (g/day) (>1 g*:* I^2=3.4%, p=0.39) and the sex of the participants (females*:* I^2=34.8%, p=0.20). Moreover, the subgroup analyses showed that berberine supplementation yielded greater reductions in WC in females (WMD: -2.45 cm, 95% CI: -3.48 to -1.43, p < 0.001) and at a dosage >1 g (WMD: -2.37 cm, 95% CI: -3.29 to -1.44, p < 0.001) (**Supplementary Table 2**). The sensitivity analysis revealed that no individual study had a significant influence on the results of this meta-analysis **(Supplementary Figure 2)**.

3.4. Non-linear dose-responses between the duration and the dose of berberine intervention and the results

Following the dose-response assessment, berberine intervention significantly reduced BMI (r= -0.02, P-nonlinearity= 0.004) depending on the duration of the intervention, but in a non-linear fashion (**Figure 4**).

3.5. Publication bias

The evaluation of the publication bias by visual examination of the funnel plots revealed possible publication bias in the meta-analysis of the effect of berberine supplementation on WC. In addition, we did not detect any publication bias for the effect of berberine supplementation on BW or BMI (**Figure 5**).

4. Discussion

The management of obesity primarily consists of lifestyle changes and pharmacological interventions, often requiring multiple drugs to achieve success [24]. Due to its anti-obesity and blood glucose-lowering properties, berberine, a plant alkaloid frequently employed in traditional Chinese medicine, has been used in humans to prevent the development of metabolic diseases [25]. Even if several studies conducted both in animals and humans have highlighted positive outcomes following supplementation with berberine, its overall efficacy remains unclear. Therefore, in the present study, we sought to evaluate the effect of berberine supplementation on indices of obesity. Thus, to accomplish this aim, the current systematic review and meta-analysis included available RCTs which examined the effects of berberine supplementation on BMI, WC and BW in adults. Our results indicate that berberine supplementation is associated with a significant reduction in BMI and WC, but not in BW. Following the subgroup analysis, we report that berberine supplementation reduced WC, particularly in females, in subjects with a baseline BMI >30 kg/m^2, when the duration of the intervention exceeded 12 weeks and when the dose exceeded 1 g/day.

Moreover, several trials have reported that berberine can also increase the energy expenditure and the consumption of lipid metabolites as primary energy sources in obese animals, in addition to lowering BW and the white adipose tissue to body weight ratio [26, 27]. Our study also reported that the administration of berberine resulted in a significant reduction of the BMI (-0.29 kg/m^2, 95% CI: -0.51 to -0.08, $p = 0.006$), with no significant heterogeneity among the evaluated studies. On the same hand, subjects who were prescribed berberine also benefited from a significant

reduction in WC (-2.75 cm, 95% CI: -4.88 to -0.62, p = 0.01), with significant heterogeneity among the evaluated studies (I^2 = 90.6 %, p = 0.001).

Our results indicated significant changes in BMI and WC following berberine supplementation. However, the independent evaluation of the effect of berberine on BW, based on the combined results from the random-effects model, revealed no significant changes in BW after supplementation with berberine. This finding is paradoxical, since BW is used in the calculation of the BMI, and might arise from a low statistical power of the studies included in the analysis, some of which having samples as low as 12 individuals/group. On the same hand, reports which included small samples might overestimate the effects of berberine supplementation as compared to studies including a higher number of recruited participants [28]. In addition, our meta-analysis included only five studies that evaluated changes in BW following berberine supplementation, whereas seven of the included studies reported information regarding the effect of berberine on BMI and WC. Clearly, this contradiction may impede the reliability and clinical applicability of our results. Although we did not report a significant decrease in BW, overall the anthropometric indices improved following berberine supplementation (e.g. WC, which is a morphological characteristic of weight loss, decreased).

Interestingly, studies conducted on preclinical models revealed that animals which were given berberine did not lose weight, but were protected against gaining weight following the intervention. Nevertheless, positive metabolic effects of berberine are frequently reported in the literature [29]. The crosstalk between obesity and insulin resistance, which contributes to the development of the metabolic syndrome, might be explained by the unfavorable changes in the secretion of adipokines in obese subjects, regarded as an early sign of an impaired function of the adipose tissue [8]. Preliminary evidence on the mechanistic effects of berberine on serum adipokines suggests that berberine supplementation improves insulin sensitivity. Yang et al. have reported that the administration of berberine inhibits the differentiation of preadipocytes in human

subjects and that patients diagnosed with metabolic syndrome who were prescribed berberine benefited from a reduction in BMI, leptin/adiponectin ratio and leptin levels [8]. Unfortunately, these inflammatory markers are not routinely measured, thus offering a pragmatic avenue for future research.

We highlighted that berberine supplementation yielded a significant reduction in BMI and WC, but not BW and that berberine was more effective in participants with a baseline BMI greater than 30 kg/m^2, in females, in subjects who were given a dose >1 g/day and in participants who received supplements for >12 weeks. However, the exact mechanisms explaining the effects of berberine on the metabolism of glucose are still unclear. Studies have reported that berberine supplementation increases glucose consumption and/or glucose uptake in adipocytes and hepatocytes even in the absence of insulin [30]. Insulin and berberine act employ different mechanisms to stimulate glucose uptake, the latter stimulating the activity of the adenosine monophosphate-activated protein kinase (AMPK) [31, 32]. Moreover, berberine upregulates the insulin receptor at a transcriptional level by stimulating the insulin receptor promoter [22, 33] and is responsible for an increase in glucose transporter-4 (GLUT-4) and glucagon-like peptide-1 (GLP-1) levels. All of the above mechanisms are associated with the anti-obesity effects of berberine [34] and may partially explain the reduction in BW and BMI recorded in our study. Moreover, the aforementioned mechanisms might explain why berberine supplementation was more efficient in participants with a baseline BMI greater than 30 kg/m^2. In terms of the metabolism of lipids, the lipid-lowering effects of berberine are apparently attributed to the stabilization of the hepatic low-density lipoprotein receptor (LDL-R) by the extracellular signal-regulated kinase-dependent pathways and also to the increase of the transcriptional activity of the LDL-R promoter [34]. Clearly, the mechanisms employed by berberine require further investigation to explain the effects of this natural compound on human health.

4.1. Strength and limitations

The primary strength of this study was that this is the first meta-analysis of RCTs to assess the impact of berberine supplementation on indices of obesity. The evidence base prior to this meta-analysis was not uniform and required a quantitative assessment which we have provided. We have demonstrated that there is sufficient evidence to conclude that berberine supplementation has a positive effect on the BMI and WC of humans. Another strength of the current meta-analysis is the assimilation of a heterogeneous sample of participants. We were also able to stratify analyses based on the duration of berberine supplementation, the dosage employed and the starting weight of the participants.

Notwithstanding, the current study has some limitations. We did not restrict the analyses in terms of patients included in the assessed studies. Consequently, this allowed for a larger number of studies and participants to be included in our analysis. Furthermore, since this is the first meta-analysis to assess the impact of berberine supplementation on obesity indices, it can serve as guidance for further investigations in the field. Since the sample sizes of some RCTs included in our analysis were small, the results of these studies might be overestimated, as previously reported
[28]. However, this was out of the operational control of our meta-analysis. Another limitation of our paper is that the number of eligible studies that could be included in our analysis was low. Thus, there is a need for more high-quality RCTs to be conducted to elucidate the effects of berberine supplementation on obesity indices. Moreover, we only considered papers that were published in English, which conceivably resulted in some potentially relevant studies being omitted, particularly given that the published studies included in our analysis originated from China [7, 13, 20, 22, 23], Iran [12, 21], Italy [10] and Mexico [11], all of which being countries where English is not the native language. An additional consideration is that we only searched the following databases: PubMed-MEDLINE, Scopus, Google Scholar and the Cochrane Library.

However, we tried to ameliorate this issue by performing supplementary searches of the reference lists of all the included studies.

4.2. Conclusion

The results of the current study support the use of berberine supplementation for the improvement of obesity indices in humans, with sub-group analyses highlighting greater improvements in dosages of >1 g/day and when the supplementation exceeded >12 weeks. However, the literature base remains equivocal as to whether significant benefits are incurred for weight loss. Thus, even though berberine effectively improved some anthropometric indices in the subjects who received the supplements, more RCTs are required to understand the clinical relevance of these findings and how these results can be translated into the current management of obesity.

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	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.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available,	3

		provide registration information including registration number.	
Eligibility criteria	6	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.	3
Information sources	7	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.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Risk of bias in individual studies	12	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.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of	4-5

		consistency (e.g., I^2) for each meta-analysis.	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	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.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-7
Results of individual studies	20	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.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-7

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	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).	7-9
Limitations	25	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).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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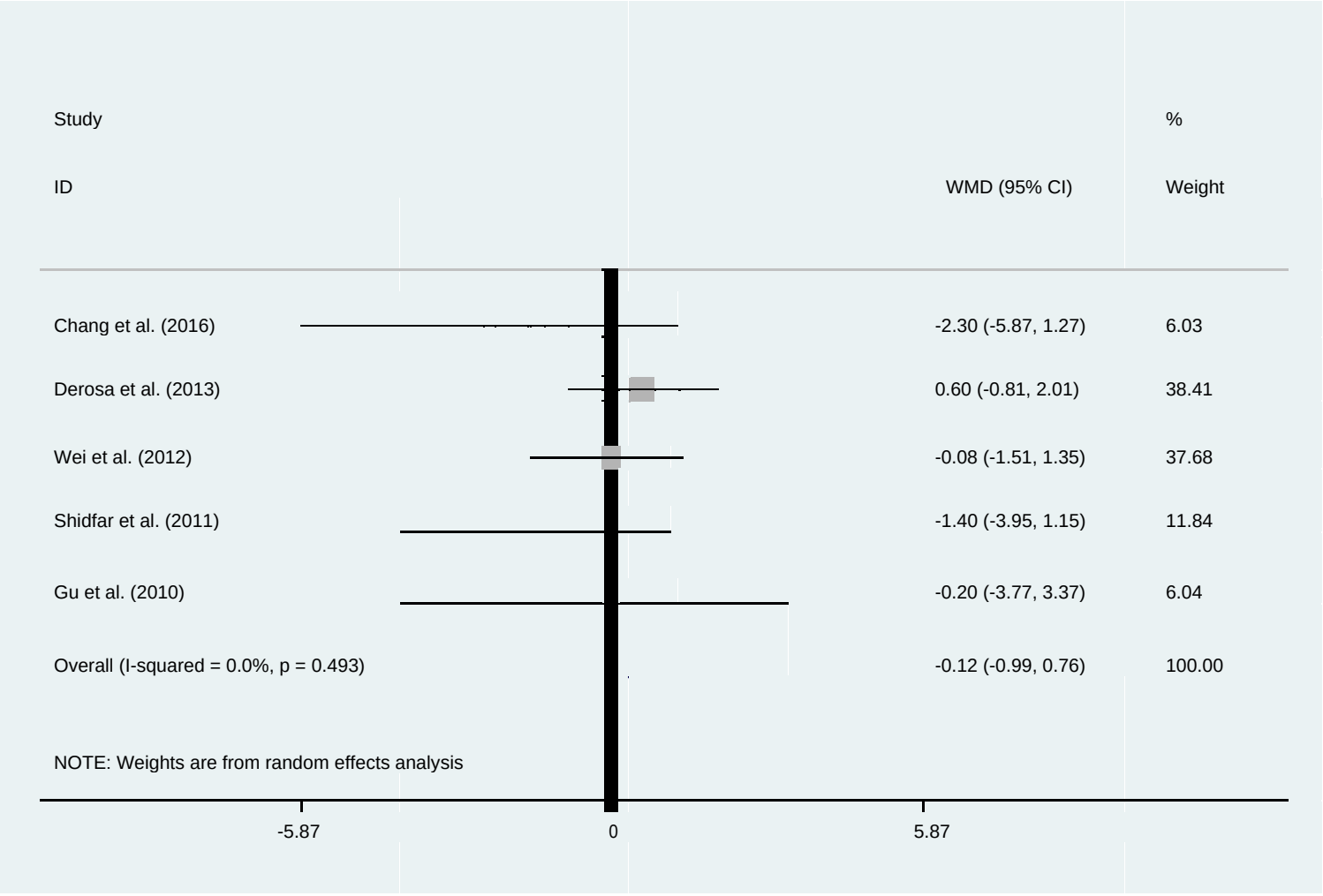


Figure 1. Forest plot of randomized controlled trials investigating the effect of berberine administration on body weight. WMD= Weighted mean difference; CI= confidence interval

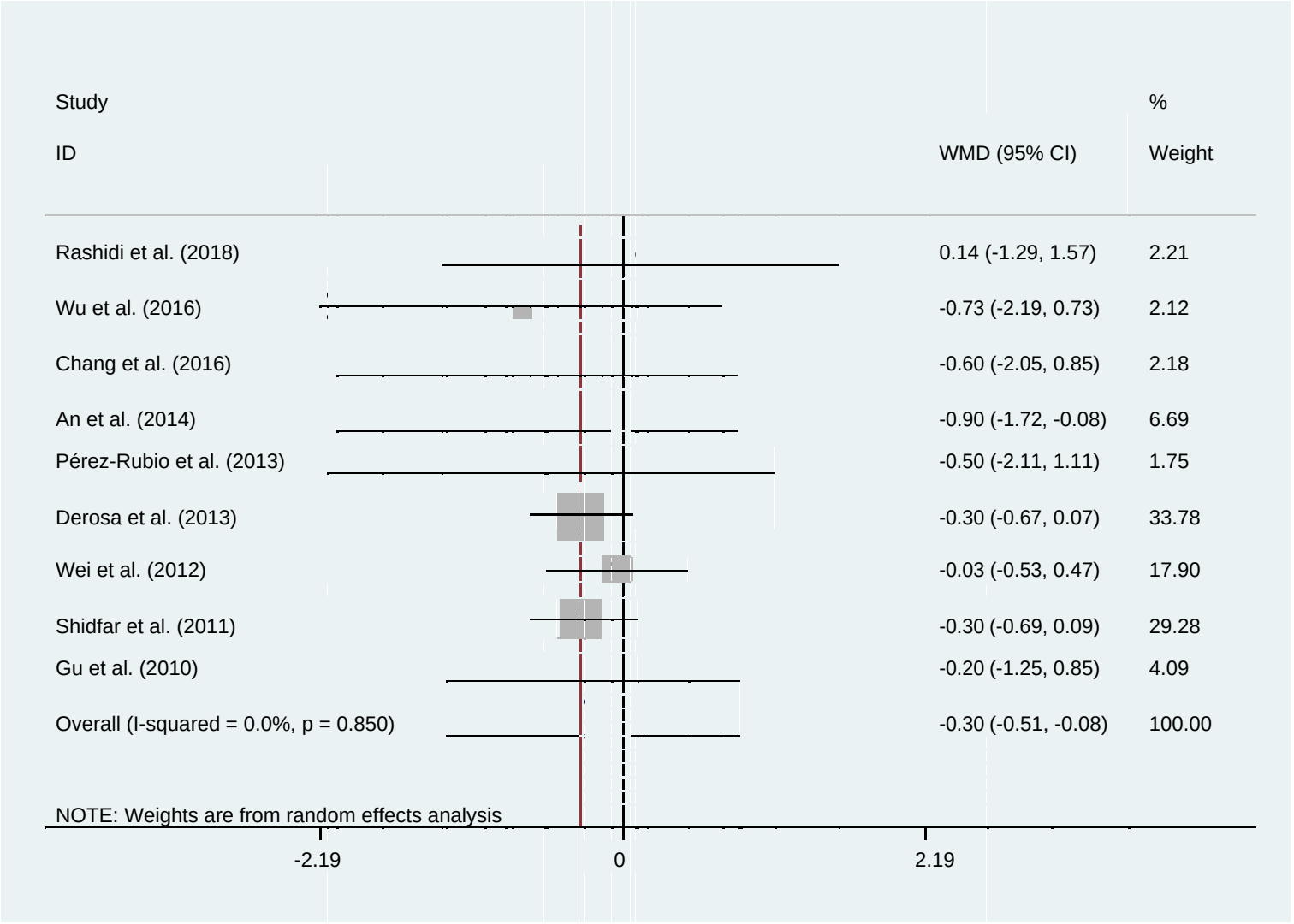


Figure 2. Forest plot of randomized controlled trials investigating the effect of berberine administration on body mass index (BMI). WMD= Weighted mean difference; CI= confidence interval

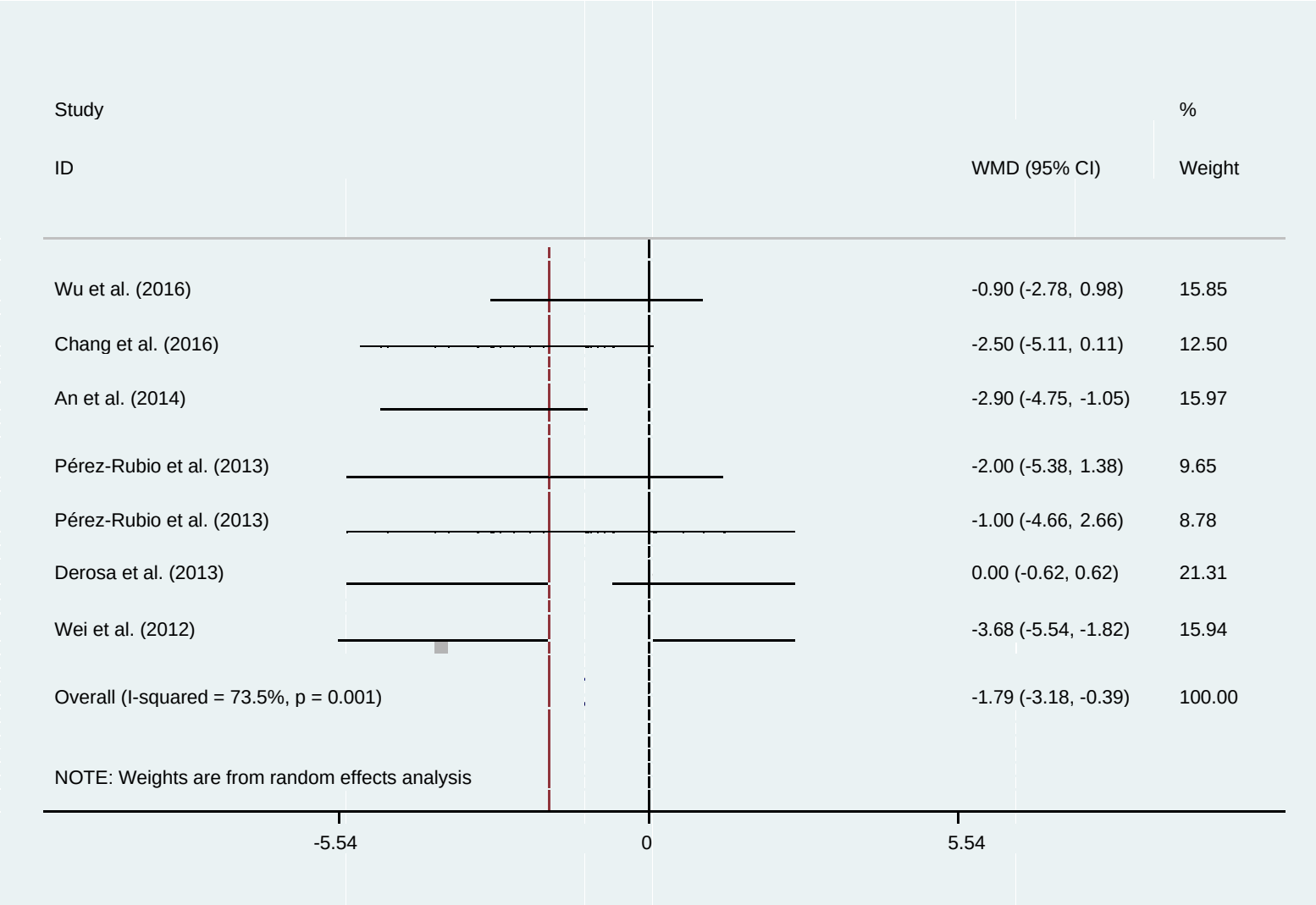


Figure 3. Forest plot of randomized controlled trials investigating the effects of berberine supplementation on waist circumference (WC). WMD= Weighted mean difference; CI= confidence interval

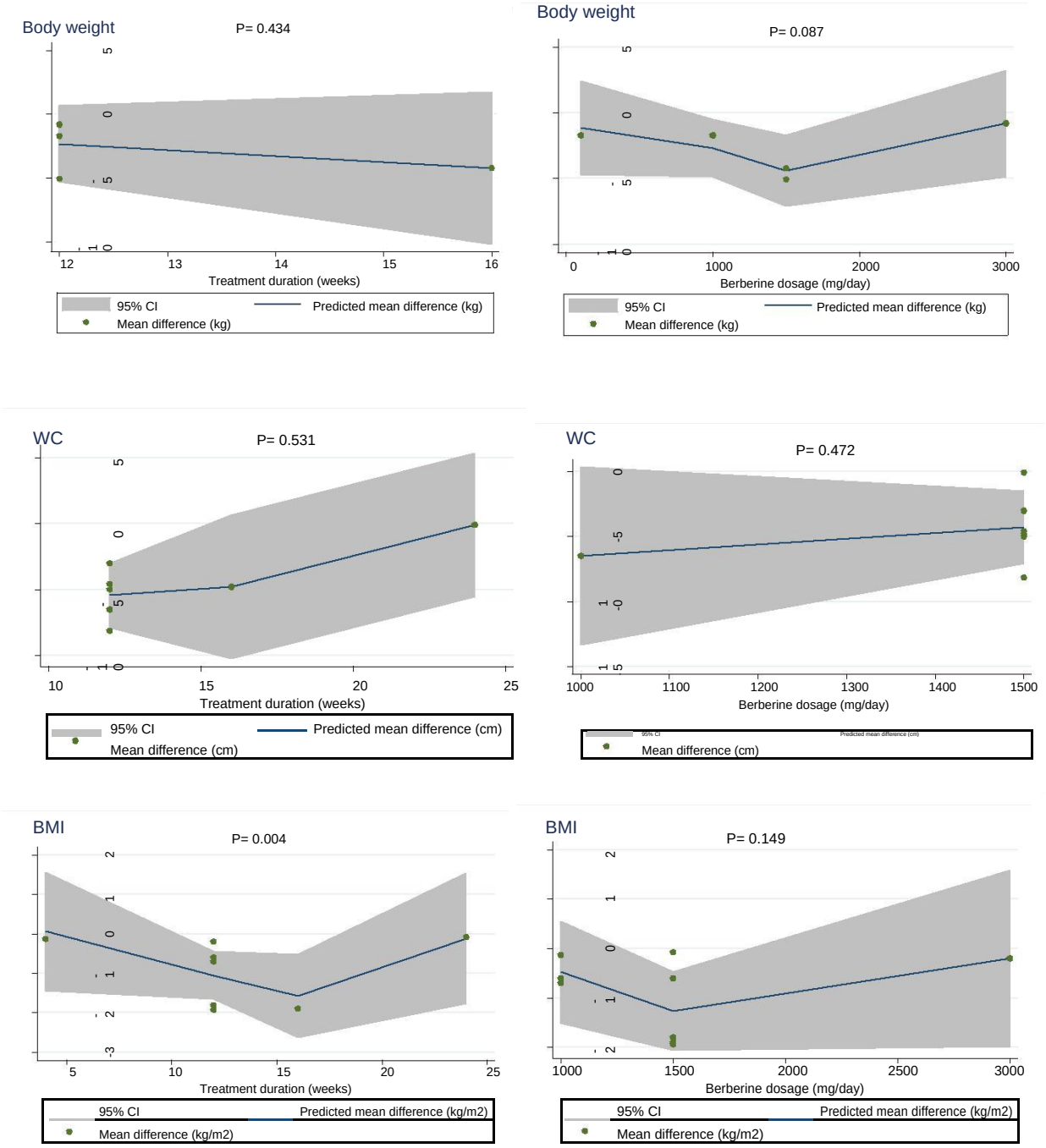
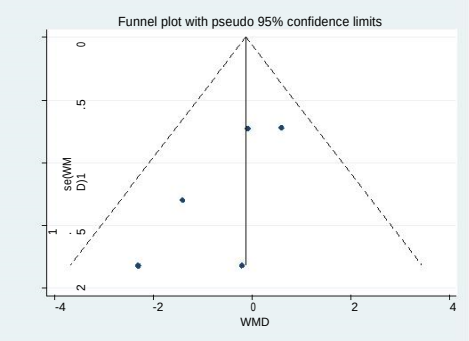
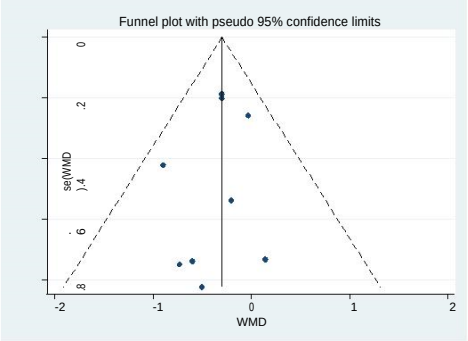


Figure 4. Non-linear dose-responses between berberine supplementation and unstandardized mean differences in body weight (kg), body mass index (BMI) (kg/m^2), and waist circumference (WC) (cm). The 95% confidence interval (CI) is depicted in the shaded regions.

A) Body weight (p= 0.13)



B) Body mass index (BMI) (p= 0.45)



C) Waist circumference (WC) (p = 0.05)

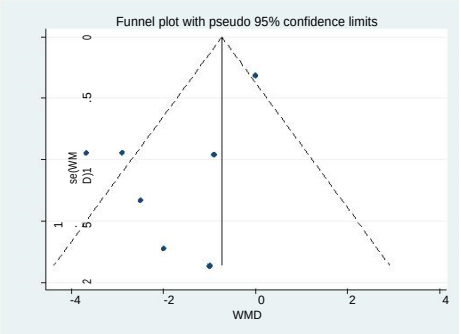


Figure 5. Funnel plot of the weighted mean difference (WMD) versus the standard error (s.e) of the WMD.

Table 1. Characteristics of included studies

Author	Country (year)	Study design (duration)	Sex	Age (year)	Patient features	Sample size: case/ placebo	Baseline body weight (kg)	Dose (mg)	Outcomes
Rashidi et al.	Iran (2018)	Parallel (4W)	Both	30 - 65	Type 2 diabetic patients	22/42	NR	1000	BMI
Wu et al.	China (2016)	Parallel (24W)	Both	27.8	Polycystic ovary syndrome	215/215	NR	1500	BMI, WC
Chang et al.	China (2016)	Parallel (16W)	Female	51.2	Patients with nonalcoholic fatty liver disease	41/39	77	1500	BMI, WC, body weight
An et al.	China (2014)	Parallel (12W)	Female	28.2	Polycystic ovary syndrome	44/43	NR	1500	BMI, WC
Perez-Rubio et al.	Mexico (2013)	Parallel (12W)	Male	30-40	Metabolic syndrome	12/12	NR	1500	BMI, WC
Perez-Rubio et al.	Mexico (2013)	Parallel	Female	30-40	Metabolic syndrome	12/12	NR	1500	WC

Derosa et al.	Italy (2013)	Crossover (12W)	Both	53	Low cardiovascular risk	68/69	72.3	1000	BMI, WC, body weight
Wei et al.	China (2012)	Parallel (12W)	Female	26	Polycystic ovary syndrome	31/28	65.11	1500	BMI, WC, body weight
Shidfar et al.	Iran (2011)	Parallel (12W)	Both	53.1	Type 2 diabetic patients	21/21	75.2	3000	BMI, body weight
Gu et al.	China (2010)	Parallel (12W)	Female	51	Type 2 diabetic patients	30/30	68.9	1000	BMI, body weight

W: week, BW: body weight, BMI: body mass index, WC: waist circumference, NR: not reported

Supplementary Table 1. Cochrane Risk of Bias Assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Rashidi et al.	L	U	L	H	L	U
Guarino et al.	L	L	L	L	L	U
Wu et al.	L	L	L	H	L	U
Chang et al.	L	U	H	L	L	U
An et al.	L	L	L	H	L	U
Perez-Rubio et al.	L	L	L	L	L	U
Perez-Rubio et al.	L	L	L	L	L	U
Derosa et al.	L	L	L	H	L	U
Wei et al.	L	L	U	H	L	L
Shidfar et al.	L	L	L	L	L	U
Gu et al.	L	L	L	L	L	U

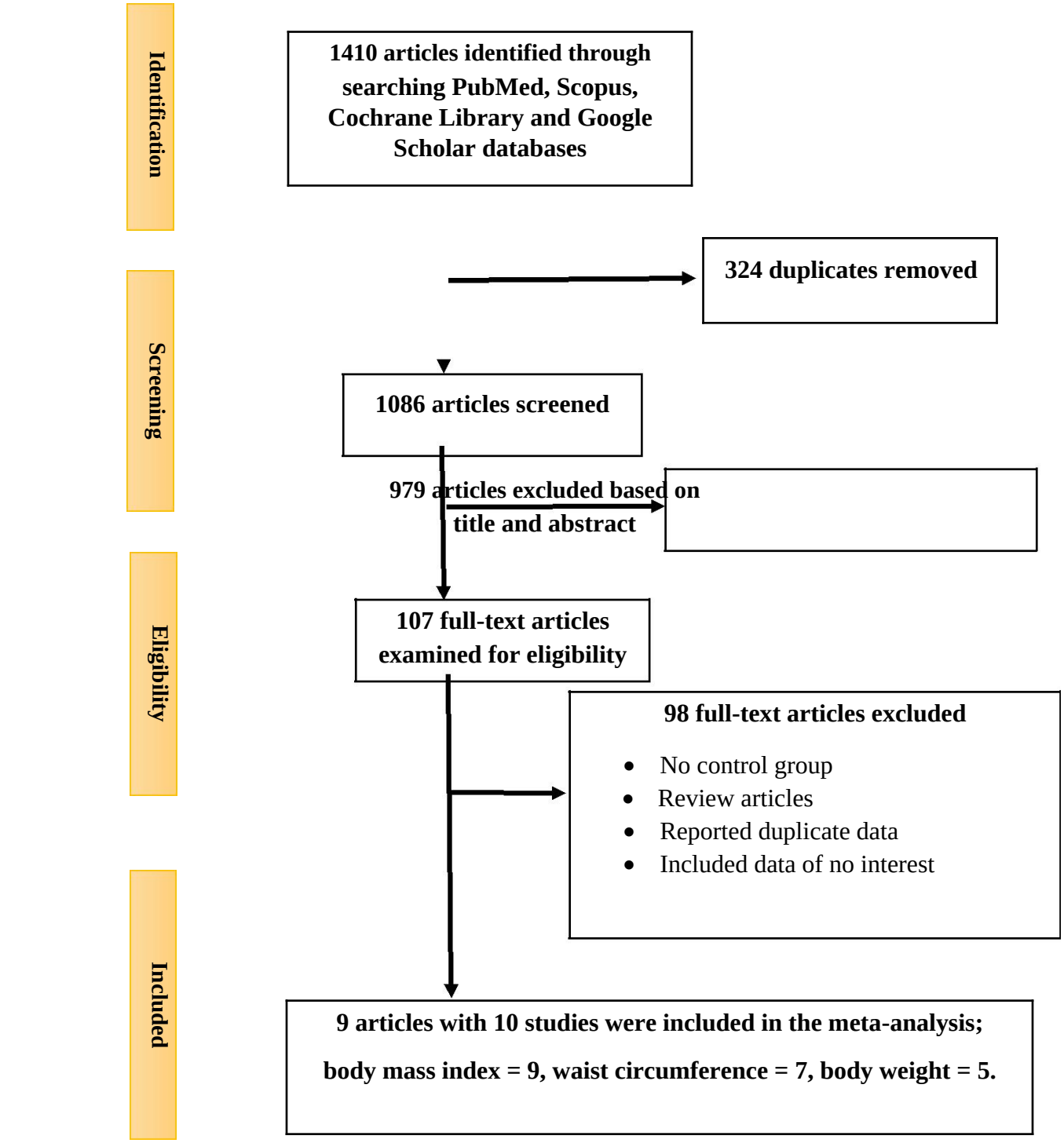
L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Supplementary Data

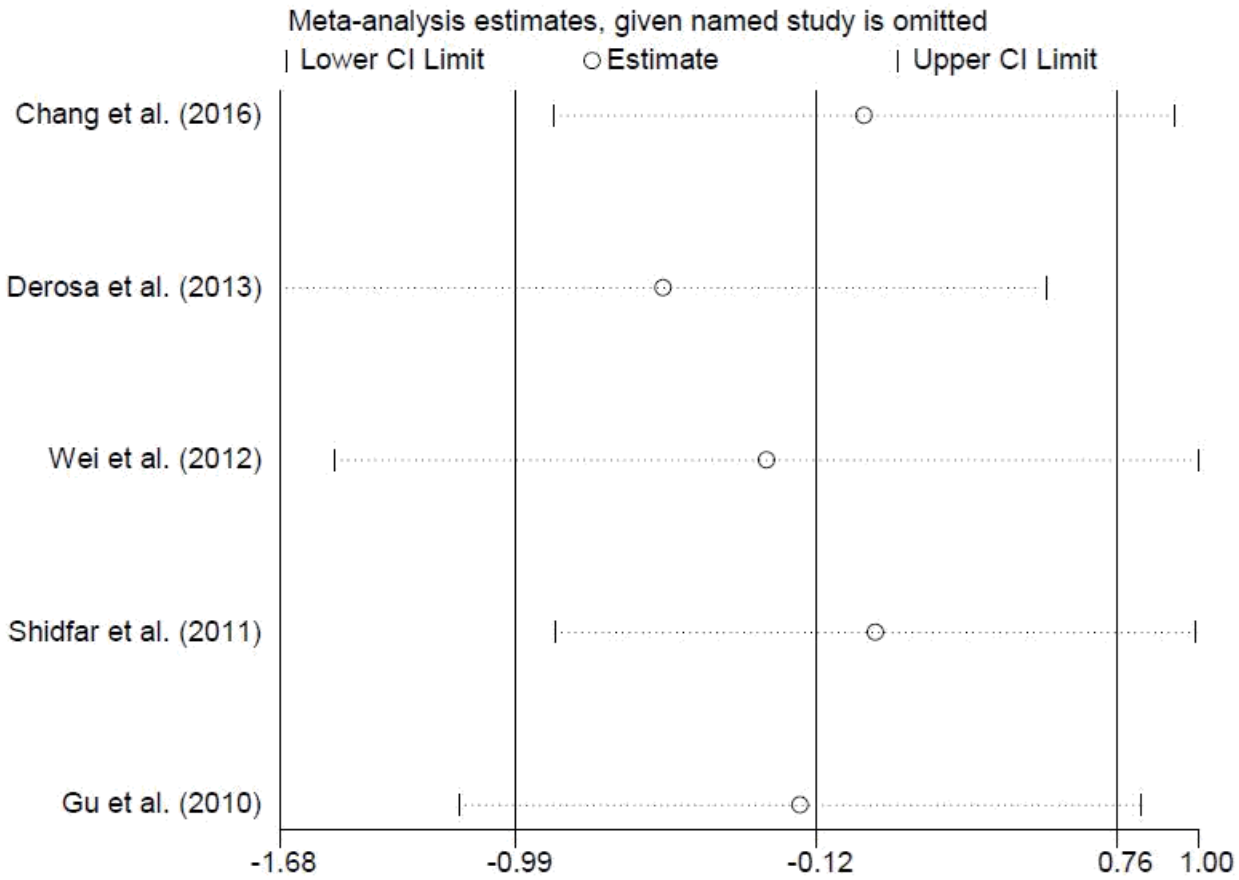
Supplemental Table 2. Subgroup analysis to assess the effect of berberine supplementation on waist circumference (WC).

Sub-group	Number of trials	WMD (95% confidences interval)	P Value	P for heterogeneity	I^2 (%)	P for between subgroup heterogeneity
Sex						0.018
Female	4	-2.458(-3.483 to -1.434)	<0.001	0.204	34.8	
Male	1	-1.000 (-4.658 to 2.658)	0.592	-	-	
Both	2	-0.133 (-0.735 to 0.469)	0.665	0.068	70.1	
Berberine dosage						0.000
≤1 g	1	0.000(-0.618 to 0.618)	1.000	-	-	
>1 g	6	-2.371(-3.293 to -1.448)	<0.001	0.395	3.4	
Intervention duration						0.000
≤12 weeks	5	-0.643(-1.189 to -0.098)	0.021	<0.001	80.7	
>12 weeks	2	-1.446 (-2.969 to 0.078)	0.063	0.329	0.0	

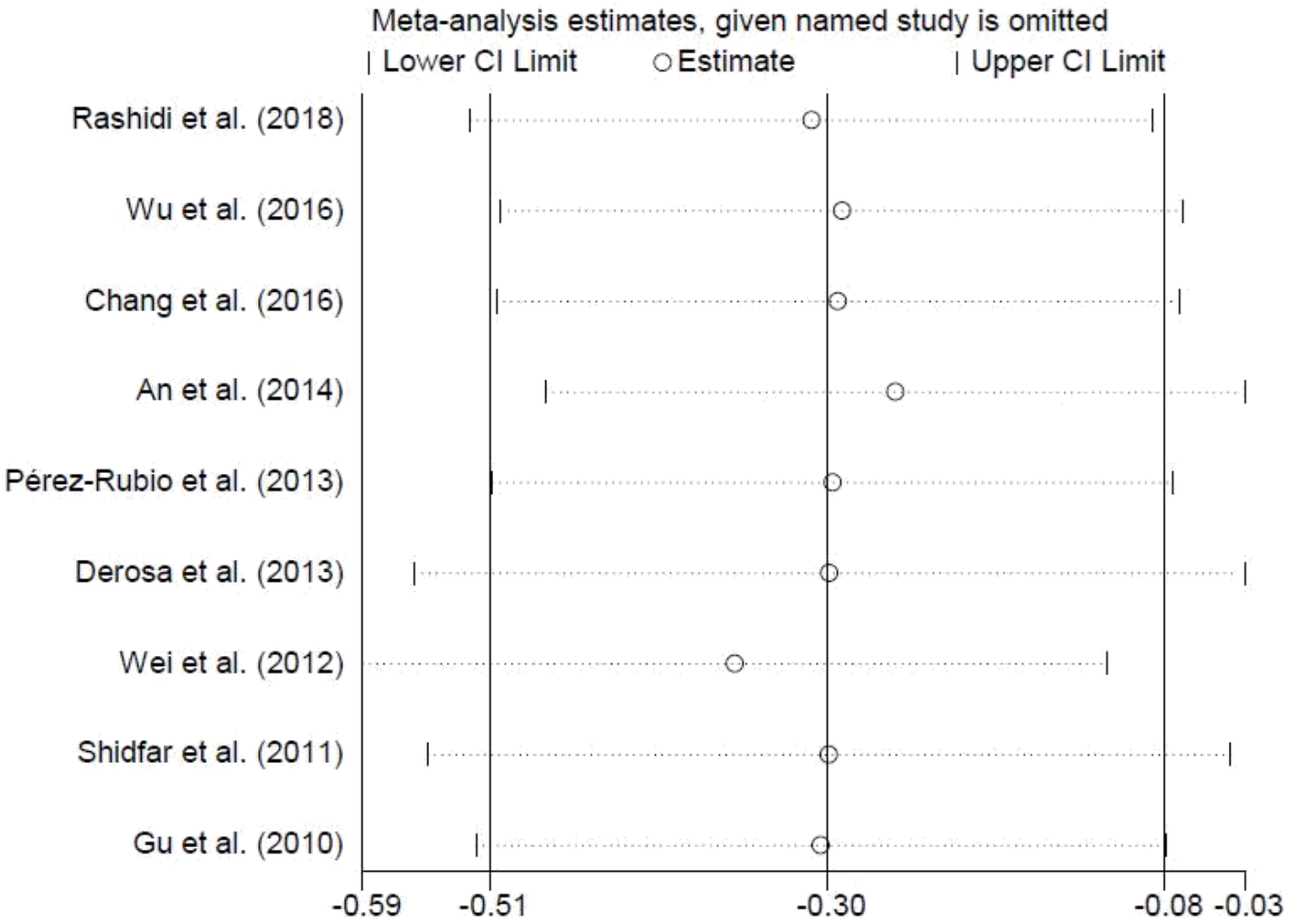
BMI = Body mass index; WC = Waist circumference; WMD= Weighted mean difference; I^2= Percentage of heterogeneity among studies



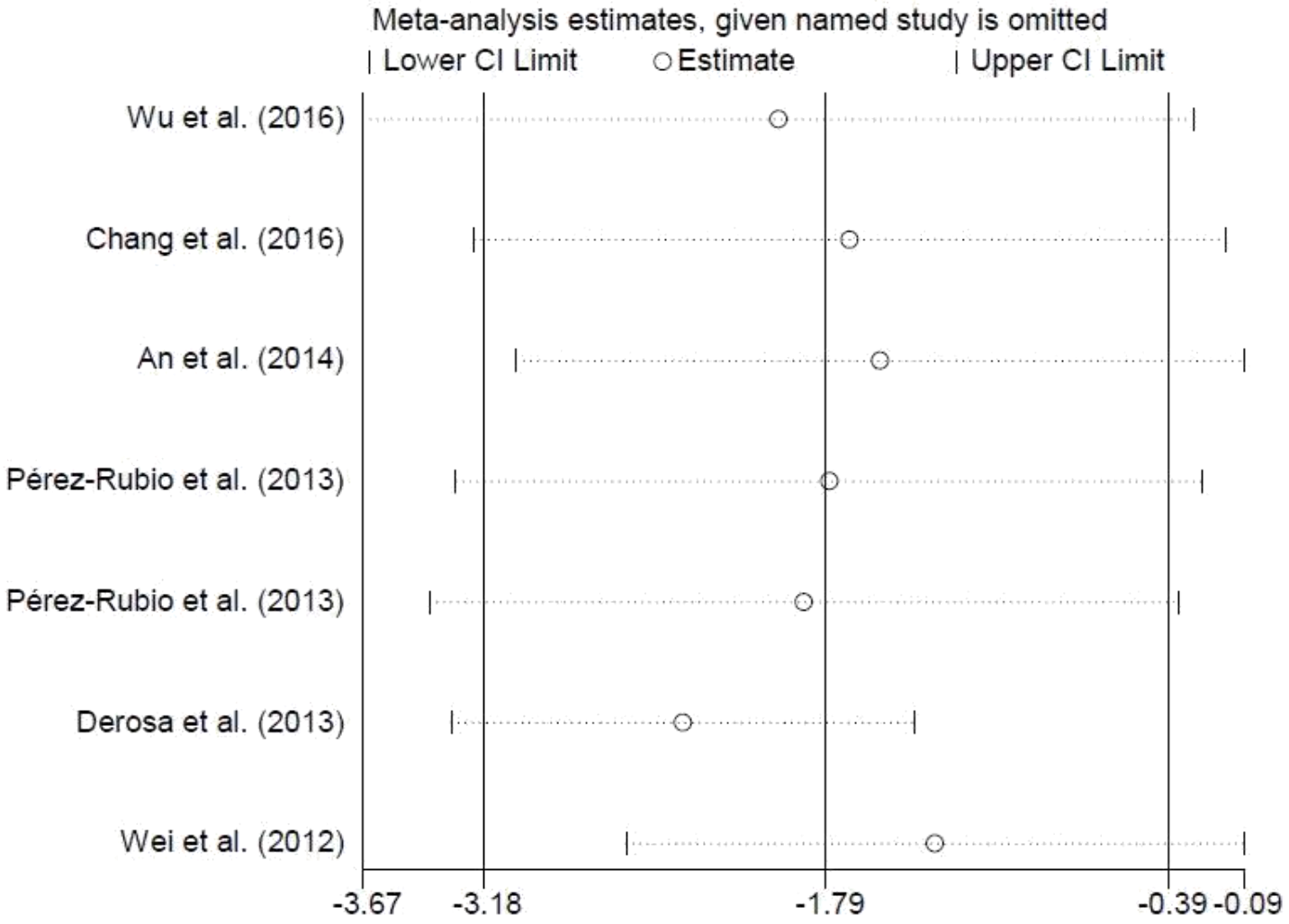
Supplementary Figure 1. Flow chart for study identification, screening, eligibility, and inclusion in the meta-analysis.



Supplementary Figure 2. A: Sensitivity analyses plot (metaninf test) plot for body weight



Supplementary Figure 2. B: Sensitivity analyses plot (metaninf test) plot for body mass index (BMI)



Supplementary Figure 2. C: Sensitivity analyses plot (metaninf test) for waist circumference (WC)