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SYSTEMATIC REVIEWS AND META-ANALYSES

The effects of green coffee bean extract supplementation on lipid profile in humans: A systematic review and meta-analysis of randomized controlled trials

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KEYWORDS
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Triglyceride

Abstract *Background and aim:* This systematic review and meta-analysis aimed to assess the effects of green coffee bean extract (GCBE) supplementation on lipid profile in adults.
Methods and results: The PubMed/Medline, Scopus, Web of sciences, and Google Scholar were systematically searched for randomized controlled trials available in English and published before February 2019. The meta-analysis was conducted using fixed effects models, and between-study heterogeneity was assessed by Cochran's Q test and I^2. A total of 17 effect sizes were included in the meta-analysis. Combined effect sizes on serum total cholesterol concentrations revealed significant effects of GCBE supplementation on serum total cholesterol [weighted mean difference (WMD): −4.51 mg/dL, 95% confidence interval (CI): −6.89, −2.12, $p < 0.001$], low density lipoprotein-cholesterol (LDL-C) (WMD: −4.38 mg/dL, 95% CI: −6.44, −2.31, $p < 0.001$), and high density lipoprotein-cholesterol (HDL-C) (WMD: 2.63 mg/dL, 95% CI: 2.20, 3.07, $p < 0.001$) compared to controls. Nevertheless, no significant changes were observed in serum triglycerides levels (WMD: −4.34 mg/dL, 95% CI: −9.00, 0.32, $p = 0.068$).
Conclusion: The evidence from available studies suggests that the GCBE supplementation leads to significant reductions in total cholesterol, HDL-C, and LDL-C levels, and has modest, but, non-significant effects on triglycerides levels.

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Introduction

Dyslipidemia is characterized by elevated levels of total or low-density lipoprotein cholesterol (LDL-C), triglycerides, and/or low levels of high-density lipoprotein cholesterol (HDL-C). Lipid profile is influenced by several factors including genetics, lifestyle and dietary factors [1] and although modifiable, dyslipidemia remains a leading risk factor for metabolic syndrome and cardiovascular disease such as coronary heart disease (CHD) [2,3]. According to World Health Organization (WHO), 4 million deaths are attributed to CHD worldwide per year [4], and 70% of patients with premature CHD symptoms demonstrate abnormal lipid metabolism. Earlier work has demonstrated that for every 10% reduction in serum total cholesterol (TC) levels, there is a 15% decline in CHD-linked mortality risk [5], highlighting the importance of dyslipidemia in CHD progression and the need to improve serum lipids in patients with dyslipidaemia.

Currently, the prevention and first-line treatment of dyslipidemia include dietary and lifestyle changes, alongside pharmacotherapy [6]. For example, physical activity and smoking cessation have well-established, beneficial effects on the lipid profile of patients with dyslipidemia [7,8] and were, therefore, cornerstones in the development of international guidelines and recommendations for patients with abnormal lipid profile [9]. Moreover, in addition to dietary recommendations relevant to diet composition, the use of several nutraceuticals is explored as potential lipid-lowering strategies. Some nutraceutical supplements have also been shown to exert positive effects on vascular function and cardiovascular disease risk [10–14].

Green coffee bean extract (GCBE) is a supplement extracted from raw coffee beans prior to fermentation and roasting and has been suggested to have several health benefits [15–17]. GSBE includes chlorogenic acid and caffeine, which may explain at least some of its therapeutic effects [18]. The efficacy of the effect of GCBE supplementation on lipid profile is still inconclusive. Recent clinical trial demonstrated that GCBE supplementation decreased serum total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) levels and plasma free fatty acids in obese women [19]. In contrast, other investigations have failed to show an improvement in lipid parameter measured in blood after supplementation of GCBE [20,21].

As such, this systematic review and meta-analysis aimed to review available randomized controlled trials (RCTs) to assess the efficacy and dose–response relationship of GCBE supplementation on parameters of lipid profile.

Methods

This systematic review protocol has been established according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guidelines [22].

Search strategy

Four independent databases (PubMed/Medline, Scopus, Web of Sciences and Google Scholar) were used to perform literature search for identifying randomized clinical trials which investigated the effects of GCBE supplements on lipid profile and were published before February 2019. Medical subject heading (MeSH) and non-MeSH terms were used with the following keywords: “chlorogenic acid” OR “green coffee” OR “green coffee extract” AND “clinical trials” OR “cross-over Studies” OR “double-blind method” OR “single-blind method” OR “random allocation” OR “RCT” OR “intervention studies” OR “intervention” OR “controlled trial” OR “randomized” OR “randomized” OR “random” OR “randomly” OR “placebo” OR “assignment”. Furthermore, a manual search was conducted on the reference lists to identify eligible articles that may have been missed.

Eligibility criteria

Inclusion criteria were: (1) RCTs with crossover or parallel study designs, (2) studies that were carried out in individuals aged ≥18 years old, (3) studies that reported sufficient TC, and/or LDL-C, and/or TG, and/or HDL-C data at baseline and follow-up in both GCBE supplementation and control groups, and (4) studies that conducted an intervention with any green coffee species.

Exclusion criteria were: (1) studies that were carried out in children, pregnant women or animals, (2) studies that were not RCTs, (3) studies that did not provide sufficient information for the outcomes in GCBE or control groups, (4) studies that evaluated the effects of GCBE alongside other components, and (5) grey literature such as conference papers, dissertations, and patents.

Data extraction

Two authors (A.N and H.K) selected studies independently without being blinded to authors, institutions, journal name, as well as trial results. Disagreements between authors concerning study selection were solved through a third independent author (Y.Z). If there was an absence in data reporting, the corresponding author was contacted via email to obtain the required data. The following data was extracted from each study: first author’s name, year of publication, age and gender of subjects, trial duration, study location, type and dosage of GCBE supplementation, study design, health status of participants, number of participants in each group, mean and standard deviation (SD) of outcome measures at baseline, post-trial follow-up and/or changes in outcome measures from baseline to the end of the study. If a study reported multiple follow-ups throughout the study duration, only the most recent data was included.

Quality assessment

The Cochrane scoring system [22] was used to determine the methodological quality and risk of bias in each of the

Table 1 Characteristics of eligible studies.

Author, Country, year	Clinical trial design	Population	Sex (percentage of men)	Treatment duration	Outcome	n	Study groups
Shekoufeh Salamat et al. Iran, 2019	randomised double-blind clinical trial/ parallel	patient with dyslipidemia	Men	8 weeks	TC,HDL-C, LDL-C, TG	34 36	Placebo 800 mg of decaffeinated GCBE with 50% chlorogenic acid
Atsushi Suzuki et al., Japan, 2019	double-blinded, placebo-controlled pilot study	healthy Japanese men	Men	2 weeks	TC,HDL-C, LDL-C, TG	8 8	Placebo 100-mL of beverage contain (300 mg/ d CGA)
Hanieh Roshan et al., Iran, 2018	randomised double-blind clinical trial/ parallel	patients with the metabolic syndrome	Both (men:81%)	8 weeks	TC,HDL-C, LDL-C, TG	22 21	Placebo 800 mg/d GCBE
Sara Martínez_López et al., Spain, 2018	randomized single-blind clinical trial/ cross-over r	Hypercholesterolemic subjects	Both (men:37%)	8 weeks	TC,HDL-C, LDL-C, TG	27 27	Placebo 6 g/d coffee contain (445 mg CGA & 121 mg caffeine)
		normocholesterolemic subjects	Both (men:40%)	8 weeks	TC,HDL-C, LDL-C, TG	25 25	Placebo 6 g/d coffee contain (445 mg CGA & 121 mg caffeine)
Satoko Fukagawa et al., Japan, 2017	randomized single-blind clinical trial/ cross-over	healthy women with xerotic skin	Women	8 week	TC,HDL-C, LDL-C, TG	26 23	Placebo 270 mg/d GCBE
Fatemeh Haidari et al., Iran, 2017	randomised double-blind clinical trial/ parallel	obese women	Women	8 weeks	TC,HDL-C, LDL-C, TG	34 30	Placebo 400 mg/d GCBE
Hedayat Allah Shahmohammadi et al., Iran, 2017	randomised double-blind clinical trial/ parallel	Non-Alcoholic Fatty Liver Disease	Both (NR)	8 weeks	TC,HDL-C, LDL-C, TG	22 22	Placebo 1000 mg/d GCBE
Gloria M Agudelo-Ochoa et al. Colombia, 2016	controlled clinical trial was single-blinded	Healthy Adults	Both (men:50%)	8 weeks	TC,HDL-C, LDL-C, TG	25 25 25	Placebo 400 mL coffee/d contain (420 mg CGA) 400 mL coffee/d contain (780 mg mg CGA)
Tae-Su Kim et al. Korea, 2012	randomised double-blind clinical trial/ parallel	Mildly Obese Women	Women	8 weeks	TC	10 10	Placebo 210 mg/d dextrin +100 mg/ d GCBE(Chlorogenic acids = 29.4%, Caffeine = 13.6%)
Park Ju Yeon et al., south Korea, 2008	randomised double-blind clinical trial/ parallel	Overweight women	women	8 weeks	TC,HDL-C, LDL-C, TG	20 23	Placebo 200 mg/d GCBE
Ryuji OCHIAI et al., Japan, 2008	randomized, placebo-controlled, cross-over study	patients with essential hypertension	Both (men:87%)	4 weeks	TC,HDL-C, LDL-C, TG	15 16	Placebo 368 ml GCBE drink contain 598 mg/ d CGAs
Takuya Watanabe et al., Japan, 2006	randomised double-blind clinical trial/ parallel	adults with mild hypertension	Both (men:39%)	12 weeks	TC,HDL-C, LDL-C, TG	14 14	Placebo 125 mL/day fruit and vegetable juice mixed with GCBE contain 140 mg/d CGA
Kazuya KOZUMA et al., Japan,2005	randomised double-blind clinical trial/ parallel	Mildly hypertensive patient	Men	4 weeks	TC,HDL-C, LDL-C, TG	29 31 28 29	Placebo 185 mg/d GCBE 93 mg/d GCBE 46 mg/d GCBE

GCBE: green coffee bean extract, CGA: Chlorogenic acids, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: total glycerides, NR: not reported.

included studies. Possible sources of bias in randomized trials were assessed, including the random sequence generation, the allocation concealment, the blinding of study participants and personnel, the blinding of outcome assessment, the incomplete outcome data, the selective reporting, and other biases. Three scores of yes, no, and unclear could be given to each before mentioned item, which are referred as high risk, low risk, and unknown risk respectively (Supplemental Table 1).

Data synthesis and statistical analysis

Mean change and standard deviation (SD) of the outcome measures were used to estimate the mean difference between the intervention group and the control group at follow-up. If data was reported in a different format, standard calculations were performed to derive the mean and SD [23,24]. For example, if the SD of the mean difference was not reported in the studies, it was calculated using the following formula: SD_{change} = square root $[(SD_{baseline}{}^2 + SD_{final}{}^2) - (2 \times R \times SD_{baseline} \times SD_{final})]$. In order to estimate effect sizes, the fixed effects model was used and results were provided across weighted mean difference (WMD) and 95% confidence intervals (CI). Subgroup analyses were conducted to discover potential sources of heterogeneity among the studies. Sensitivity analysis was performed to discover the impact of each study on the overall effect size by using the one-study exclusion (leave-one-out) method. Publication bias were assessed by means of visual calculation of funnel plots and Egger's tests [25]. If any publication bias was detected, it was tested via the 'trim and fill' approach [26]. All statistical analyses were implemented using Stata software (Stata Corp. College Station, Texas, USA).

Results

Study selection

The electronic search strategy retrieved a total of 1224 records, 806 of which were unique. After screening of the title and abstract, 25 publications met our selection criteria and underwent full-text review. After full-text assessment, 13 publications [17,19,20,27–35,38] with 17 studies were included in this meta-analysis (Supplemental Fig. 1).

Characteristics of the included studies

The characteristics of the included studies are detailed in Table 1. These studies were published between 2005 and

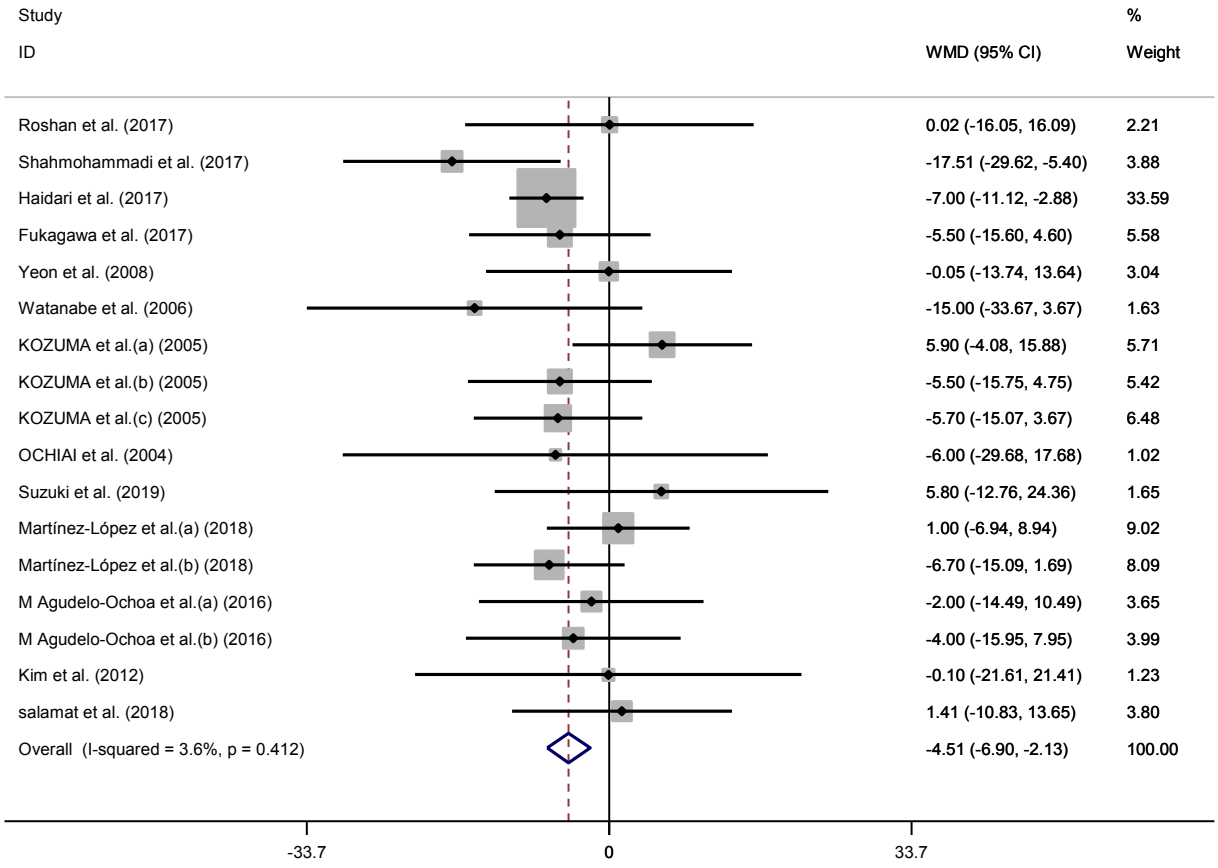

Figure 1 Forest plot of randomized controlled trials investigating the effects of green coffee administration on Total Cholesterol (TC).

2019 (February) and were conducted in Iran [17,20,29,19], South Korea [32,33], Spain [28], Colombia [31], and Japan [27,30,34,35,36]. The follow-up period ranged from 2 to 12 weeks. The daily supplementation dose of green coffee varied between 46 and 6000 mg. Apart from studies which included both sexes, four trials were conducted in women only [19,30,32,33] and six studies were performed in men only [17,27,36]. The sample size of the RCTs ranged from 16 [27] to 70 [17,27]. Participants in the included studies were healthy [27,28,31], obese/overweight individuals [19,32,33] or patients with various comorbidities including metabolic syndrome [20], non-alcoholic fatty liver disease [29] and women with xerotic eczema [30], dyslipidemia [17,28], and hypertension [35,36].

Meta-analysis results

Effect of GCBE supplementation on TC levels

In total, 776 participants were assessed across 17 studies (cases = 387, controls = 389), which reported serum TC levels as an outcome measure. Overall results from the fixed effects model indicated that GCBE supplementation administration resulted in significant change in TC levels after GCBE supplementation (weight mean difference (WMD): −4.51 mg/dL, 95% CI: −6.89, −2.12, $p < 0.001$), without significant heterogeneity among the studies ($I^2 = 3.6\%$, $p = 0.412$) (Fig. 1). In the subgroup analyses, studies that explored GCBE supplementation dosages ≥400 mg (WMD: −5.27 mg/dL, 95% CI: −8.13, −2.41, $p < 0.001$), and had an intervention duration between 8 and 11 (WMD: −5.086 mg/dL, 95% CI: −7.787, −2.386, $p < 0.001$) resulted in a greater reduction in TC levels (Supplementary Table 2).

Effect of GCBE supplementation on HDL-C levels

Serum HDL-C levels was assessed in 16 studies with a total of 755 participants (case = 376 and control = 379). Combined results from the fixed effects model indicated that HDL-C levels did change significantly following GCBE administration (WMD: 2.63 mg/dL, 95% CI: 2.20, 3.07, $p < 0.001$). The heterogeneity among the studies ($I^2 = 46.2\%$, $p = 0.022$) was moderate (Fig. 2) and could be explained by intervention duration, GCBE dosage and participants' characteristics (i.e., sex). Interestingly, increases in HLD-C levels after green coffee consumption was significant when GCBE supplementation dose was ≥400 mg (WMD: 2.76 mg/dL, 95% CI: 2.32, 3.21, $p < 0.001$) compared to lower supplementation doses (<400 mg) (WMD: 0.663 mg/dL, 95% CI: −1.07, 2.39, $p = 0.454$). Furthermore, interventions with longer supplementations durations (8−11 weeks) (WMD: 2.75 mg/dL, 95% CI: 2.31, 3.19; $p < 0.001$) and studies conducted in women green

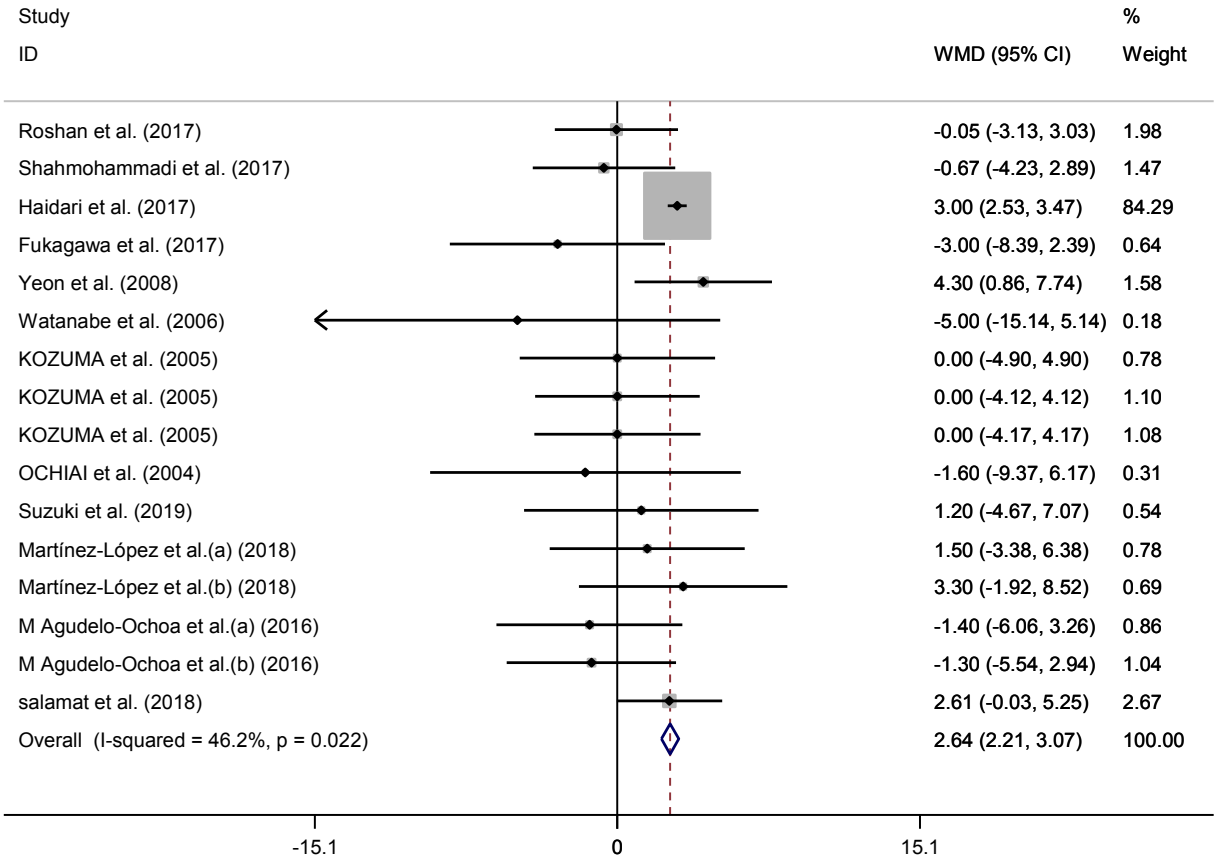

Figure 2 Forest plot of randomized controlled trials investigating the effects of green coffee administration on HDL.

coffee administration resulted in a greater increasing in HDL (WMD: 2.97 mg/dL, 95% CI: 2.51, 3.44, $p < 0.001$).

Effect of GCBE supplementation on LDL-C levels

LDL-C levels were assessed in 16 studies with a total of 727 participants (cases = 363 and control = 364). Pooled results from the fixed effects model indicated that LDL-C levels did change significantly after green coffee consumption (WMD: −4.38 mg/dL, 95% CI: −6.44, −2.31, $p < 0.001$). There was moderate heterogeneity among studies ($I^2 = 38.3\%$, $p = 0.060$) (Fig. 3). In the subgroup analyses, we found that intervention duration, GCBE supplementation dosage and participants' sex largely explained the observed heterogeneity. Similar to the TC results, studies which i) used GCBE supplementation doses ≥400 mg (WMD: −4.89 mg/dL, 95% CI: −7.24, −2.53, $p < 0.001$), ii) had an intervention duration ≥ 12 weeks (WMD: −11.931 mg/dL, 95% CI: −22.54, −1.32, $p = 0.028$), and iii) were conducted in women (WMD: −8.026 mg/dL, 95% CI: −11.187, −4.866, $p < 0.001$) resulted in greater reduction in LDL-C levels.

Effect of GCBE supplementation on TG

A total of 16 studies, including 756 participants (case = 377 and control = 379), investigated the effects of GCBE on TG levels. Pooled results from the fixed effects model indicated that TG levels did not change significantly after GCBE consumption (WMD: −4.34 mg/dL, 95% CI: −9.00, 0.32, $p = 0.068$) and there was no significant heterogeneity among studies ($I^2 = 1.3\%$ %, $p = 0.437$) (Fig. 4).

Non-linear dose–response relationships between dose and duration of GCBE supplementation and outcomes

Evaluation of the dose–response relationships between dose and duration of GCBE supplementation and markers of lipid metabolism, did not indicate significant associations based on treatment duration and GCBE dosage (Fig. 5).

Sensitivity analysis

To assess the impact of each single study on the combined effect size, we removed each trial from the analysis, step by step and accounted for their individuality. We observed no significant effects of any individual study on the combined effect sizes of TC, LDL-C, TG or HDL-C levels.

Publication bias

Visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of GCBE supplementation on TC, LDL-C and TG levels (Supplemental Fig. 2). Egger's linear regression test confirmed this finding (TC: $p = 0.331$, LDL: $p = 0.140$ and TG: $p = 0.424$).

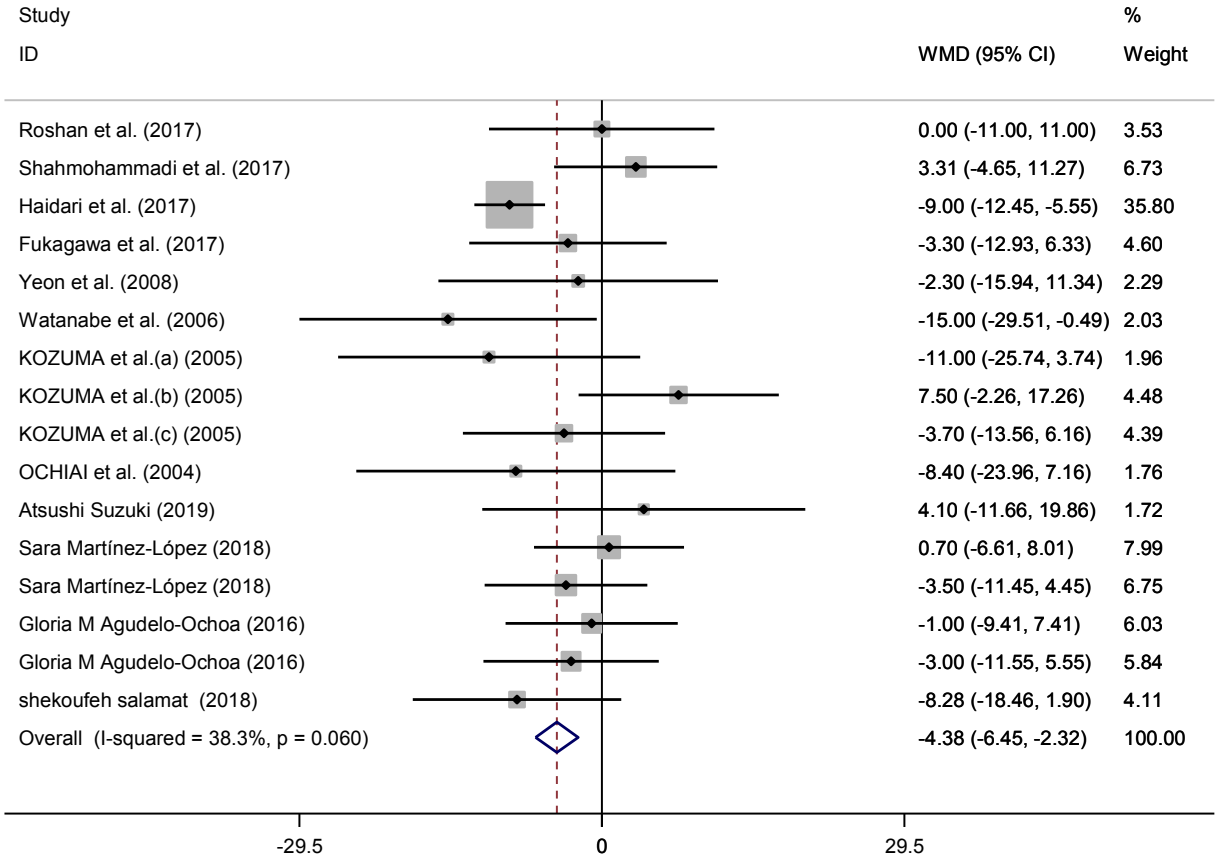

Figure 3 Forest plot of randomized controlled trials investigating the effects of green coffee extract supplementation on LDL-C.

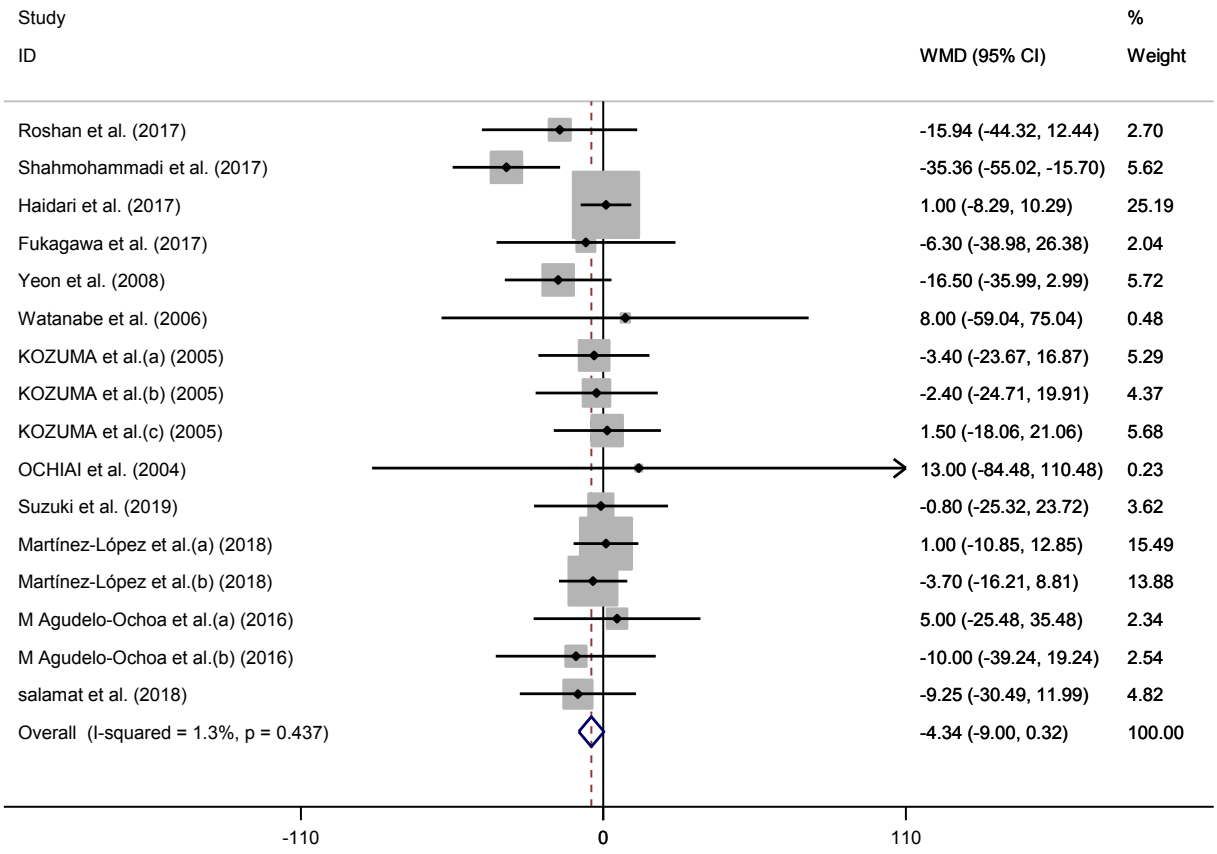

Figure 4 Forest plot of randomized controlled trials investigating the effects of green coffee extract supplementation on TG.

However, there was a significant publication bias in the meta-analysis of GCBE supplementation on HDL-C levels (Egger's test: $p = 0.000$). The 'trim and fill' sensitivity method did not show any negative unpublished studies that assessed HDL-C levels.

Discussion

In this meta-analysis of 17 randomized controlled trials, subjects who received GCBE supplementation had significantly lower total cholesterol (−4.51 mg/dL), HDL-C (2.63 mg/dL), and LDL-C (−4.38 mg/dL) levels compared to controls. We also observed modest improvements in TG levels following GCBE administration, which, however, did not reach statistical significance. Between-group comparisons by sex revealed that the lowering effects of GCBE supplementation on LDL-C and TG levels and its positive impact on HDL-C levels were significantly greater in women. Greater lipid-lowering effects were also seen in GCBE interventions which had a duration 8−11 weeks and tested higher supplementation doses (≥400 mg/day). Taken together, these findings suggest that GCBE supplementation exerts some beneficial effects on lipid profile, however, these effects appear to be dependent on participants' characteristics and featured of the supplementation.

The effect of green coffee on lipid profile may be mediated by several possible mechanisms. GCBE contains a significant amount of chlorogenic acid, which has been shown to decrease total cholesterol levels in the serum/liver by inhibiting the intestinal absorption, transfer, and hepatic biosynthesis of lipids and cholesterol [37,38]. In addition to these actions of chlorogenic acid on lipid metabolism, experimental studies have shown that chlorogenic acid may upregulate the expression of PPAR-α, which, in turn, regulates the expression of major genes for lipid and lipoprotein metabolism [38,39,40].

Indeed, the effects of chlorogenic acid on serum lipids shown in previous clinical and preclinical studies appear to be similar to those observed in the current meta-analysis. For example, consumption of food enriched with chlorogenic acid resulted in significant improvements in lipids assessed in blood [20]. Another investigation demonstrated that supplementation with chlorogenic acid caused a significant reduction in serum free fatty acid, total cholesterol, triglyceride, and a significant increase in HDL-C levels in a rat model of dyslipidemia [29].

The moderate statistical heterogeneity estimated in the analyses for HDL cholesterol may have been due to variations in participants' characteristics in the various RCTs. The intervention duration, GCBE dosage and gender of study participants could explain the heterogeneity. In

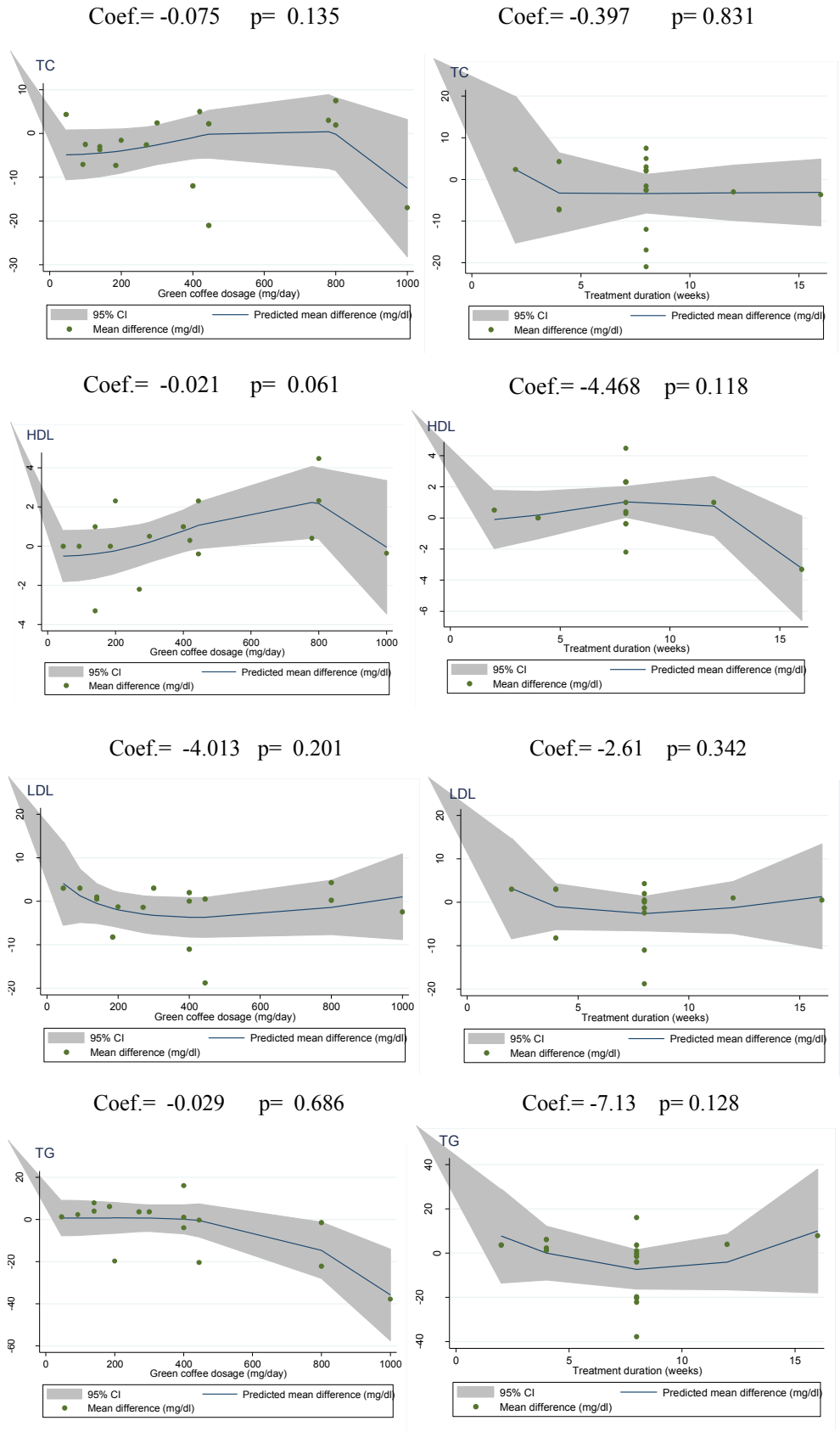

Figure 5 Non-linear dose-responses between green coffee extract supplementation and unstandardized mean difference in TC, HDL, LDL and TG. The 95% CI is depicted in the shaded regions.

addition, a small sample size in some of studies may have contributed to this heterogeneity. Other studies have already shown decreases in blood pressure in essential hypertension [30,36,37], improvements in glycaemic control [20], and now significant decreases in total cholesterol.

It is worth mentioning that despite the overall beneficial effects of GCBE on markers of lipid metabolism, an elevation in LDL-C and reduction in HDL-C levels were observed in three RCTs [30,36,37].The investigators in the mentioned RCTs suggested that the adverse effects of GSBE on serum lipids were probably related to the differences in the coffee roasting methods and requires further research [41,42]. Another explanation may be that chlorogenic acid is subject to structural changes, such as oxidation, and, degradation of this compound may differentially affect serum markers of lipid metabolism [43]. Conversely, there are some concerns about potential hepatotoxic effects of green coffee extracts. In an earlier investigation, 2 g of chlorogenic acid/day increased homocysteine concentrations (risk factor for cardiovascular disease) in coffee drinkers [34]. In that study, adverse events appeared, when concentrated green coffee was consumed over a week. Therefore, the potential risk for cardiovascular disease in humans may be due to the acute ingestion of higher levels of chlorogenic acid for a short-term period.

A major strength of this meta-analysis is that multiple subgroup analyses were performed to examine the potential impact of supplementation (*i.e*, dose and intervention duration) and participants' characteristics (*i.e*, sex, baseline lipid profile) in the relationship between GCBE supplementation and lipid profile. The presence of moderate heterogeneity and the low numbers of RCTs in some subgroup analyses are the main limitations of the present study. Furthermore, the median study duration of 8 weeks prevents authors from making conclusions about the effectiveness of green coffee extracts in the longer-term.

Conclusion

The available evidence from studies suggests that supplementation with green coffee extracts results in significant reductions in total cholesterol, HDL-C, and LDL-C levels and in modest, but non-significant, improvements in TG levels.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.10.002.

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