The effects of guar gum supplementation on lipid profile in adults: A GRADE-assessed systematic review, meta-regression, and dose-response meta-analysis of randomized placebo-controlled trials

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Abstract

Recent meta-analytic work indicated that guar gum supplementation might improve lipid profile markers in different populations. However, critical methodological limitations such as the use of some unreliable data and the lack of inclusion of several relevant studies, and the scarcity in assessments of regression and dose-specific effects make it difficult to draw meaningful conclusions from the meta-analysis. Therefore, current evidence regarding the effects of guar gum supplementation on lipid profile remains unclear. The present systematic review, meta-regression, and dose-response meta-analysis aimed to examine the effects of guar gum supplementation on lipid profile (total cholesterol [TC], low-density lipoprotein [LDL], triglyceride [TG], and high-density lipoprotein [HDL]) in adults. Relevant studies were obtained by searching the PubMed, SCOPUS, Embase, and Web of Science databases (from inception to September 2021). Weighted mean differences (WMD) and 95% confidence intervals (95% CI) were estimated via a random-effects model. Heterogeneity, sensitivity analysis, and publication bias were reported using standard methods. Pooled analysis of 19 randomized controlled trials (RCTs) revealed that guar gum supplementation led to significant reductions in TC (WMD: -19.34 mg/dL, 95% CI: -26.18, -12.49, p<0.001) and LDL (WMD: -16.19 mg/dL, 95% CI: -25.54, -6.83, p=0.001). However, there was no effect on TG and HDL among adults in comparison with control group. Our outcomes suggest that guar gum supplementation lowers TC and LDL in adults. Future large RCTs on various populations are needed to show further beneficial effects of guar gum supplementation on lipid profile and establish guidelines for clinical practice.

Keywords: Guar gum supplementation, Lipid profile, Meta-analysis.

Introduction

Dyslipidemia is generally due to abnormal lipid metabolism, which results in increased concentrations of total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), and/or reduced high-density lipoprotein (HDL) [1]. Clinical studies also suggest that this condition elevates the risk of cardiovascular disease mortality by facilitating the onset and progression of atherosclerosis [2]. In fact, prolonged exposure to even moderately elevated cholesterol concentrations is known to increase the risk of cardiovascular disease later in life [3; 4; 5]. Therefore, identifying effective interventions for the improvement of lipid profile is an important public health concern.

There are several approaches for controlling dyslipidemia, including safe and secure methods such as dietary interventions, and unlike pharmacological therapies, they do not cause any long-term side effects [6; 7; 8; 9]. Interventions that improve dietary soluble fiber intake, in particular, have received considerable interest due to their hypolipidemic effects and effectiveness in reducing the prescribed dose of statins [10; 11; 12; 13].

Guar gum is a rich source of soluble fiber [14] and is derived from the seeds of the *Cyamopsis tetragonoloba* plant [15]. Numerous clinical trials have examined the effects of guar gum supplementation on various diseases, such as diabetes, irritable bowel syndrome, dyslipidemia, etc. [16; 17; 18; 19]. Animal studies suggest that guar gum supplementation has hypolipidemic effects [20; 21; 22]. While numerous human studies have been performed to investigate the effects of guar gum supplementation on lipid profile, results have been contradictory. Indeed, some studies have shown that guar gum supplementation effectively improves lipid profile [16; 19; 23], while others do not show such an effect [24; 25]. Recently, a meta-analysis has been published on the topic by Wang et al. [26], which revealed that guar gum supplementation significantly decreased serum concentrations of LDL and TC, but did not affect TG and HDL. However, two critical limitations make it difficult to draw meaningful conclusions from their investigation. The first is the failure to incorporate six relevant studies on the topic [18; 19; 27; 28; 29; 30] that meet the inclusion criteria set forth by Wang et al. [26]. The second limitation is that four studies without a placebo/control group were incorporated in the analysis [31; 32; 33; 34], and therefore

their outcomes may not account for some unspecific effects of observation and expectation (i.e., the Hawthorne and Placebo effects). Consequently, the overall effects of guar gum supplementation on lipid profile remain unclear. Thus, we sought to conduct a systematic review, meta-regression, and dose-response meta-analysis of randomized placebo-controlled trials (RCTs) to quantitatively assess the effects of guar gum supplementation on lipid profile markers in adults based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35].

Experimental methods

Search strategy

We searched PubMed, Embase, Scopus, and Web of Science databases from inception through September 2021, by using the following terms: Guar OR Guaran, which was paired with the following words: Intervention OR "Intervention Study" OR "Intervention Studies" OR "controlled trial" OR randomized OR random OR randomly OR placebo OR "clinical trial" OR Trial OR "randomized controlled trial" OR "randomized clinical trial" OR RCT OR blinded OR "double blind" OR "double blinded" OR trial OR "clinical trial" OR trials OR "Pragmatic Clinical Trial" OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR parallel OR "parallel study" OR "parallel trial". There were no date and language restrictions included in each of the database searches. Additional studies not captured by our database search were retrieved via a manual search of references from the originally identified reviews and research reports.

Study selection and eligibility criteria

Two authors (MZ and OA) reviewed the titles, abstracts, references, and full-texts of relevant articles to select eligible studies. The inclusion criteria were as follows: 1) adult participants who had supplemented with guar gum for ≥2 weeks; 2) the studies had a control group where the only difference between the treatment and control groups was the supplementation of guar gum; 3) the trial reported effects on TC, TG, LDL or HDL; 4) the use of an RCT design; 5) guar gum not being administered as part of a multicomponent supplement in either the experimental

or control group. The exclusion criteria were as follows: 1) trials that enrolled children or pregnant women; 2) not focusing on our outcomes; 3) animal, review, conference, and case-report studies.

Risk of bias

The quality of eligible studies was assessed using the Cochrane risk of bias tool for RCTs [36]. Two independent investigators (TM and MDM) completed this checklist for each included paper. Methodological features applied for assessment were: 1) adequate sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting (reporting bias), and 7) other potential sources of bias. Based on the mentioned items, studies were classified in terms of bias into three groups: low risk, moderate risk, and high risk of bias [36].

Data extraction

The following data were extracted from included studies by two authors (MZ and OA) independently: study characteristics (the first author, country, year of publication, study design, sample size in each group, study duration, intervention type, and dose), participant characteristics (mean age, sex, body mass index [BMI]), as well as the mean and standard deviation (SD) of TC, LDL, HDL, and TG concentrations in pre-intervention and post-intervention. In this study, all values were converted to a milligram per deciliters (mg/dL).

Statistical analysis

We performed this meta-analysis using STATA statistical software (version 14; STATA Corp LP). Treatment effects were defined as the weighted mean differences (WMD) and 95% confidence intervals (CIs) and were determined using the random-effects model, following the DerSimonian and Laird method [37]. We calculated changes in TC, LDL, HDL, and TG concentrations between the intervention and control groups from baseline to the end of the intervention period, and the following formula was used to calculate SD change from SD baseline and final: SD^2 baseline + SD^2 final – (2 × R × SD baseline × SD final) [38]. Pre-specified subgroup analyses were performed according to baseline serum lipid profile (TG, TC, LDL, and

HDL), guar dosage (≤15 g/day vs. >15 g/day); duration of the intervention (≥12 weeks vs. < 12 weeks); diabetes status of participants (diabetic vs. non-diabetic participants). Sensitivity analyses were performed to assess the stability of the results by removing one study at a time to identify the impact of individual studies on the pooled effect size. Funnel plots and Egger's regression test were used to assess the publication bias. A *p*-value of < 0.05 was considered statistically significant in this trial unless otherwise specified [39].). The potential non-linear effects of guar dose (g/day) and intervention duration (weeks) were investigated using fractional polynomial modeling. Also, we enforced the meta-regression to differentiate the confounders and linear relations among the effect size and sample size, duration and intervention dosage [40].

Certainty assessment

The overall certainty of evidence across the studies was graded according to the GRADE guidelines (Grading of Recommendations Assessment, Development, and Evaluation) Working Group. According to the corresponding evaluation criteria, the quality of evidence was classified into four categories: high, moderate, low, and very low [41].

Results

Study selection

In the primary search, we detected a total of 1940 records, where 823 duplicates were identified and removed. After screening based on title and abstract, 26 articles were retained for further evaluation. Three articles were excluded because they did not report lipid profiles. Also, four other studies were excluded from the study because they did not have a control group. Subsequently, nineteen eligible studies were included in qualitative and quantitative synthesis (meta-analysis) [18; 19; 25; 28; 30; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54] (Figure 1).

Characteristics of the included studies

The general characteristics of the included studies are outlined in Supplementary Table 1. The studies were published between 1980 and 2013 and were carried out in Finland [25; 30; 42; 44; 45; 49;

[51; 53; 55], USA [43; 46; 50], UK [28; 47; 52; 54], Ireland [48], Brazil [18] and Saudi Arabia [56]. The follow-up period ranged from 3 to 26 weeks, while the daily recommended dosage of guar gum varied between 8.3 and 39 g. All studies were conducted using both genders, except for two trials performed exclusively on women [25; 42] and two on men [45; 50]. The sample size in the included trials ranged from 14 to 58. Overall, 525 participants were amalgamated in these studies, of which 268 individuals were allocated to guar gum supplementation and 257 participants to the placebo group. The mean age of the participants ranged from 25 to 61.3 years old and included patients with hypercholesterolemia [42; 45; 51; 53; 54], type 2 diabetes [18; 19; 28; 44; 46; 47; 48; 49; 52], type 1 diabetes [30], menopausal women [25], and healthy participants [43; 50] (Table 1).

Effect of guar gum supplementation on TG concentrations

Sixteen studies, including a total of 477 participants (case=283, and control=272), reported TG as an outcome measure. Overall results from the random-effects model suggested that guar gum supplementation resulted in a non-significant decrease in TG concentrations (WMD: -2.80 mg/dL, 95% CI: -10.05, 2.45, $p = 0.233$) (**Figure 2A)**. Heterogeneity was not observed between studies. Also, subgroup analysis demonstrated the same results (Supplementary Table 3).

Effect of guar gum supplementation on TC concentrations

Pooling effect sizes from 17 publications, including 499 participants (case=289, and control=288), we found that guar gum supplementation had a significant effect on TC concentrations compared with placebo (WMD: -19.34 mg/dL, 95% CI: -26.18, -12.49, $p < 0.001$), with considerable between-study heterogeneity ($I^2 = 69.4\%$, $p < 0.001$) (**Figure 2B)**. Subgroup analysis based on guar gum dosage, baseline TC concentrations, trial duration, and diabetes status revealed that these factors explained the heterogeneity. In addition, diabetes status is known as a source of heterogeneity (Supplementary Table 3).

Effect of guar gum supplementation on LDL concentrations

The influence of guar gum supplementation on LDL concentrations was evaluated in 12 trials, including 369 participants (case=190, and control=179). The pooled estimates highlighted that

in participants who supplemented with guar gum, LDL concentrations were significantly decreased compared to placebo (WMD: -16.19 mg/dL, 95% CI: -25.54, -6.83, $p = 0.001$). There was a significant between-study heterogeneity (I^2=76.2%, $p < 0.001$) (**Figure 2C)**. Subgroup analysis revealed that baseline LDL concentrations and diabetes status were sources of heterogeneity. In addition, the results remained significant when baseline LDL ≥ 130 mg/dL, trial duration <12 or ≥12 weeks, intervention dose <15 g/d, and in non-diabetic participants (Table 3).

Effect of guar gum supplementation on HDL concentrations

Overall, 15 eligible studies, including a total of 441 participants (case=226, and control=215), examined the effect of guar gum supplementation on HDL concentrations. Combining their findings based on a random-effects model, we found that HDL concentrations did not significantly change after intervention (WMD: -0.59 mg/dL, 95% CI: -1.92, 0.73, $p = 0.382$) compared to the control group, with no significant between-study heterogeneity (**Figure 2D)**. Subgroup analysis showed that guar gum supplementation significantly increased HDL concentrations only when baseline HDL concentrations were ≥50 mg/dL (Table 3).

Publication bias

Evaluation of publication bias by visual inspection of funnel plot revealed no evidence of publication bias in the meta-analysis of guar gum supplementation on TG, TC, LDL, and HDL concentrations, respectively (**Figure 3A-D)**.

Quality assessment

All studies were low risk for random sequence generation, except for 1 study that was unclear [19]. None of the studies reported allocation concealment, and 3 of the studies had high risk [18; 19; 57]. All studies had a high risk of bias for other sources of bias. All studies had a low risk of bias regarding selective reporting except for seven studies [19; 25; 30; 42; 44; 48; 49]. Moreover, all studies had a low risk of bias regarding blinding participants and personnel, except for 3 studies [19; 28; 50]. Four studies had a low risk of bias regarding blinding outcome assessors [18; 19; 50; 54] (Supplementary Table 2).

Grading of evidence

The GRADE profile for the certainty of the evidence is included in Table 4. Both TG and HDL were regarded as moderate quality due to serious limitations in indirectness and imprecision. The evidence relating to TC was moderate-quality because of serious limitations in indirectness and inconsistency. Evidence regarding LDL was identified as low quality, owing to very serious limitations in inconsistency and serious limitations in indirectness.

Linear meta-regression and non-linear relationship between dose and duration of intervention and changes in lipid profile

There was no linear (figure 4 and 5) and non-linear (figure 6 and 7) relationship between changes in dose and duration of intervention and changes in lipid profile. However, there was a significant non-linear relationship between changes in dose of guar supplementation and alteration in HDL (coefficiency=1.496724, p=0.044) (Table 5).

Discussion

The present systematic review and meta-analysis of RCTs examined the effects of guar gum supplementation on lipid profile in adult populations. Our results showed that guar gum supplementation significantly reduces TC and LDL; however, there was no significant effect on TG and HDL concentrations. Moreover, there was a significant non-linear relationship between changes in dose of guar supplementation and alteration in HDL concentrations.

In addition to pharmacological therapy for the treatment of dyslipidemia, a primary focus of many researchers has been to establish efficacious and alternative treatments with lesser side effects. Indeed, many experimental and human studies have shown that guar gum supplementation exhibits hypocholesterolemic properties [58]. Accordingly, the present study indicated that guar gum supplementation significantly decreased TC and LDL concentrations. Concordant with our findings, a non-randomized clinical study demonstrated that daily guar gum supplementation for three months significantly decreased TC, with no effect on TG concentrations [59]. In addition, in a double-blind cross-over trial conducted by Niemi et al., 12 weeks of guar gum supplementation resulted in 10% lower cholesterol, without any significant

change in HDL or TG concentrations [32]. Further, Wirth et al. showed that, in patients with familial hypercholesterolemia, guar gum supplementation significantly reduced plasma TC and LDL concentrations after three months when administered concurrently with bezafibrate [60]. Similarly, Tuomilehto et al. reported that a combination of gemfibrozil and guar gum supplementation significantly lowered TC and LDL concentrations and improved HDL/LDL ratio [61]. Clinically, declines of 39 mg/dL in TC and LDL concentrations can lessen all-cause mortality by 25% and 16% and coronary heart disease mortality by 25% and 28%, respectively [62]. Therefore, the results from our pooled analysis showing significant reductions in TC (-19.34 mg/dL) and LDL (-16.19 mg/dL) concentrations support the clinical significance of guar gum supplementation as a nonpharmacological strategy for lipid control.

Our study did not show any significant influence of guar gum supplementation on TG and HDL concentrations. Indeed, findings from previous studies in this area align with our outcomes [16; 63; 64]. Bosello et al. showed that a 60-day intervention with guar gum supplementation decreased TC and led to plasma TG concentrations reduction in patients suffering from familial combined hyperlipoproteinemia [65]. A murine experimental study indicated that when rats were fed with a guar gum diet, a significant decrease in cholesterol and TG concentrations along with higher HDL and HDL/LDL ratio was noted [22]. In another study conducted by Gatti et al., guar gum supplementation yielded a reduction of TG and TC concentrations when administered as guar-enriched pasta in diabetic and hyperlipidemic patients [66]. Dietary treatment in this study was so strict that the intake of ethanol and sucrose, with their known hypertriglyceridemic effects, was excluded [66; 67]. Yamamoto et al. observed that a mixture of xanthan and guar gum supplementation had a hypotriglyceridemic effect in diabetic rats, which might be due to high viscosity of intestinal content that resulted in delayed absorption of triacylglycerol [68]. Moreover, Pasquier et al. hypothesized that high- and medium-viscous fibers could change the emulsification of dietary lipids and a subsequent reduction of triglyceride lipolysis in the duodenum [69] as our subgroup analyses showed that guar gum supplementation, specifically in diabetic patients, decreased TG concentrations. One possible explanation for this result is the use of anti-diabetic drugs such as metformin, which has been reported to be

accompanied by decreases in TG [70]. Another explanation for a tendency toward reducing TG concentrations might be due to small but significant weight loss, as reported by Jenkins et al. [71]. Thus, further investigations are necessary to clarify the effect of guar gum supplementation on TG concentrations.

The mechanisms through which soluble fibers, such as guar, might affect lipid profile are unclear. Studies suggest that when micelles are forming in the lumen, soluble fibers bind to bile acids or cholesterol, leading to decreased enterohepatic circulation [72; 73]. Viscosity, a physicochemical property associated with dietary fibers (particularly soluble dietary fibers), also contributes to the physiologic effects of dietary fiber via decreases in the diffusion of nutrients [74]. This is accomplished by reduced contact between food and digestive enzymes, altered contractile movements, slowed gastric emptying, and a thickening of the unstirred water layer through which glucose and cholesterol diffuse in the lumen [74]. Soluble fibers inhibit the reabsorption of bile acids from the intestine, and they might also interfere with cholesterol absorption [75]. As the fecal loss of bile acids increases and the bile acid pool decreases, the liver produces more bile acids from cholesterol, lessening hepatic free cholesterol concentrations [76]. When cholesterol reduces, an up-regulation of LDL receptors occurs, leading to higher clearance of LDL [73]. Another suggested mechanism is the mediating effect of short-chain fatty acids (SCFAs) produced due to bacterial fermentation that contributes to the prevention of hepatic fatty acid synthesis [77].

Some limitations need to be considered when interpreting our results. Although guar gum was used in different dosages and forms, the impact of the various forms of guar gum was not examined. Further investigations are required to address questions specific to efficacy, compliance, and side effects. In addition, the intervention period varied among the studies. Finally, except for one study, all the included studies were conducted among western countries; therefore, examining the influences of guar gum supplementation in non-western countries and other races are necessitated.

Conclusion

In conclusion, guar gum supplementation seems to favorably affect TC and LDL but without significant alterations in TG and HDL concentrations. Given the limitations of the included studies, further investigations with various guar forms in different countries are needed to shed light on this issue.

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Conflicts of Interest: The authors declare no conflict of interest.

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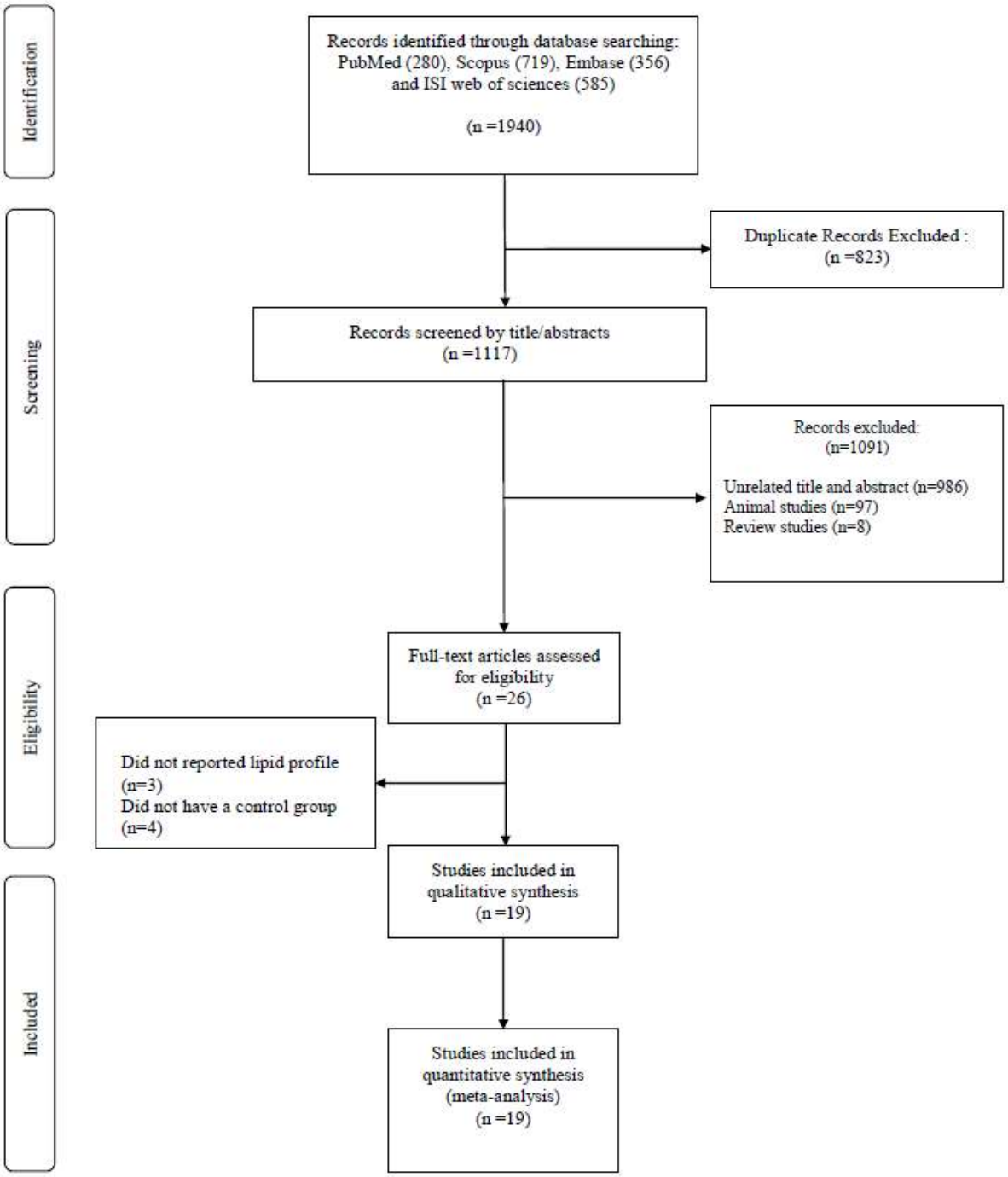
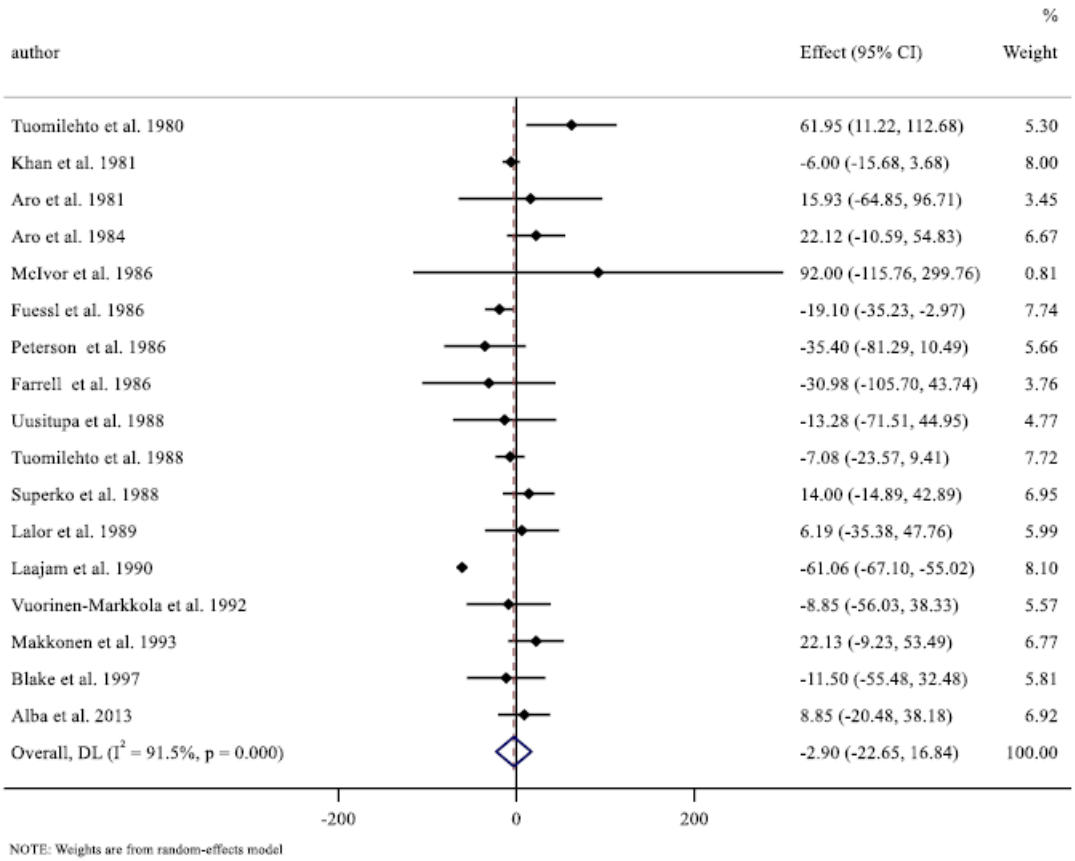
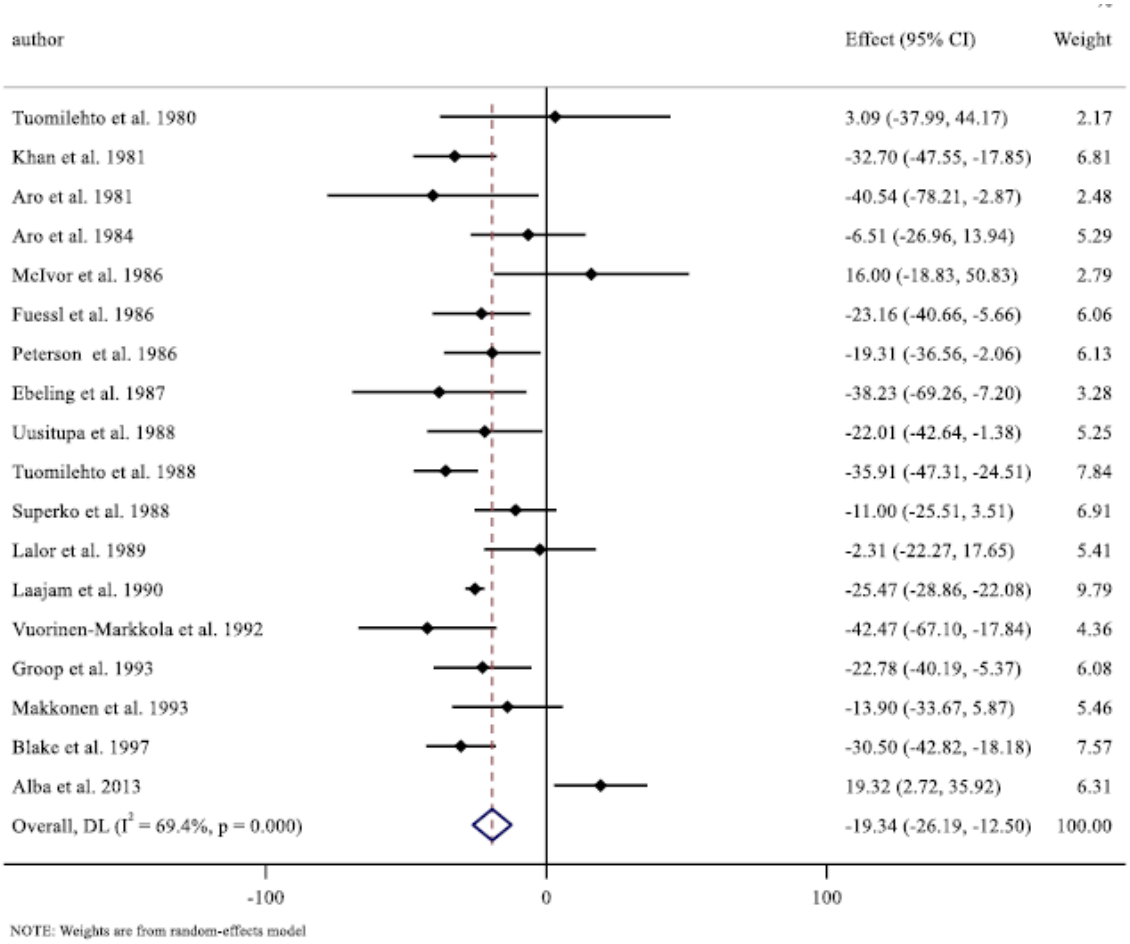


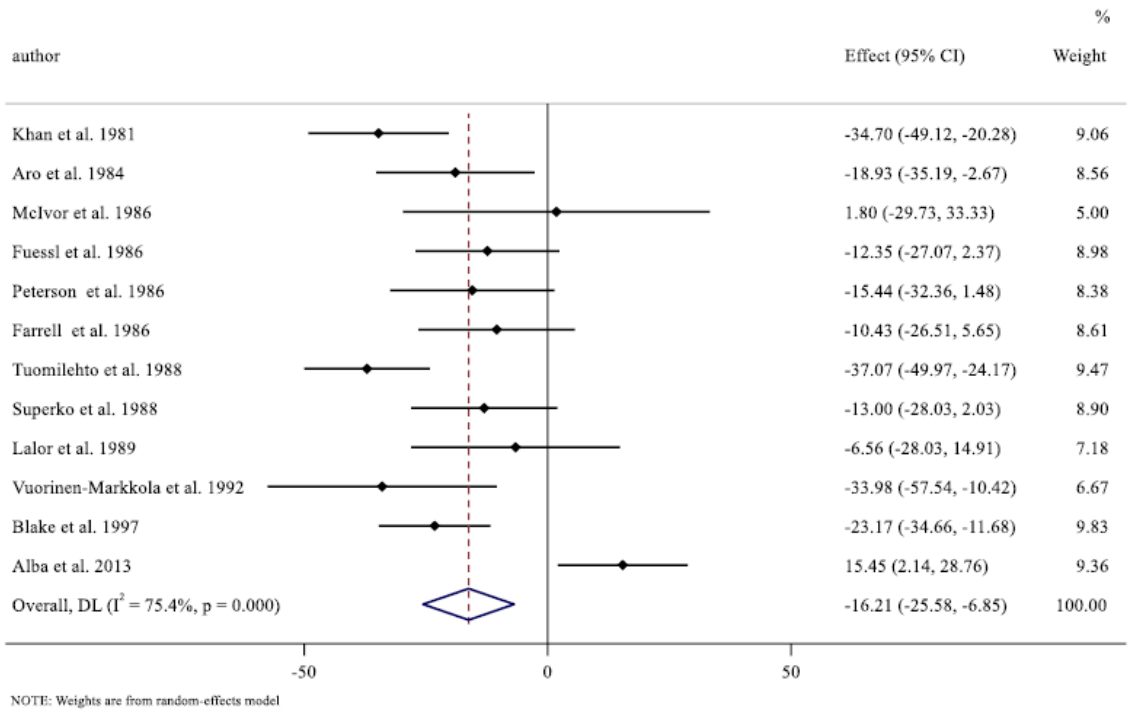
Figure 1. Flowchart of study selection for inclusion trials in the systematic review.



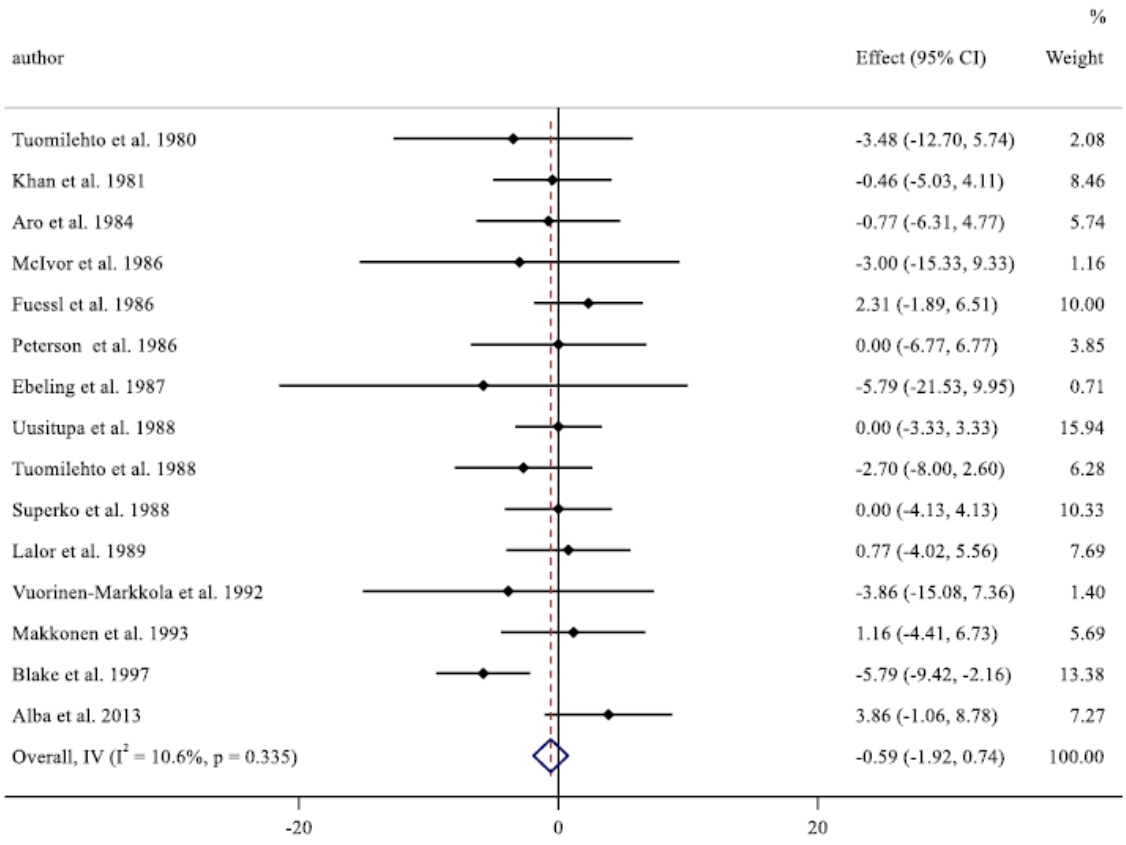
A) TG



B) TC

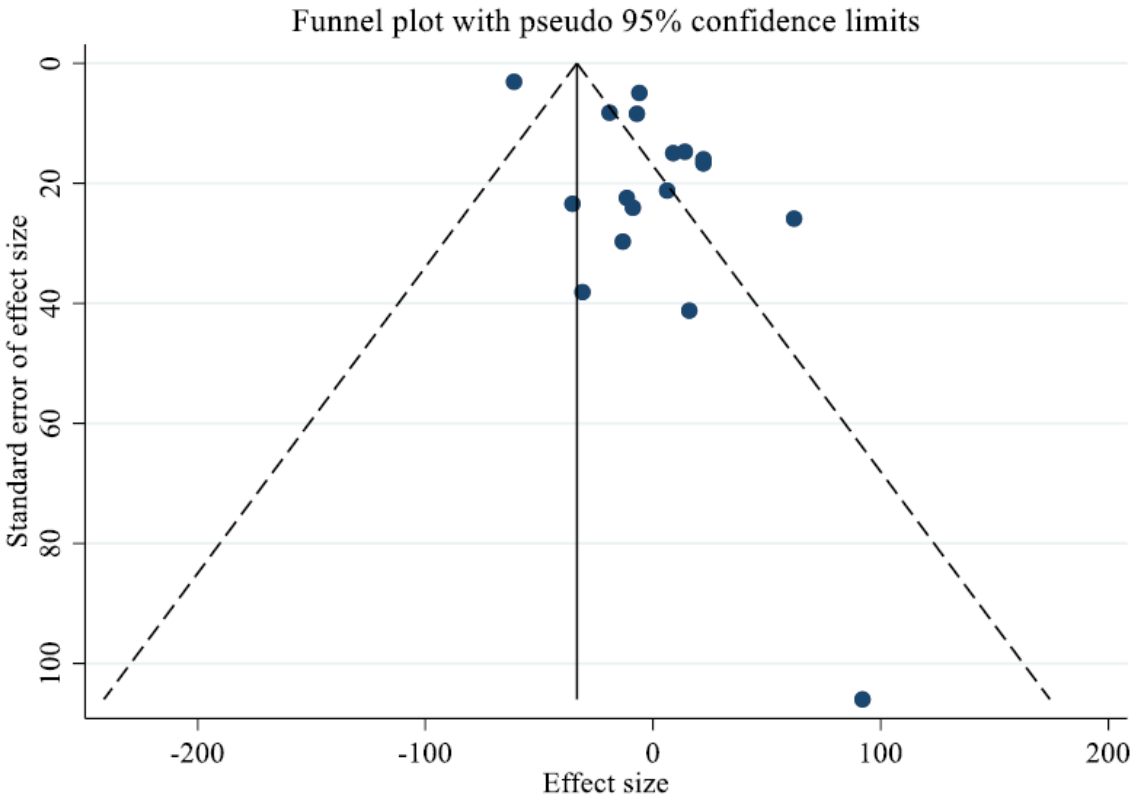


C) LDL

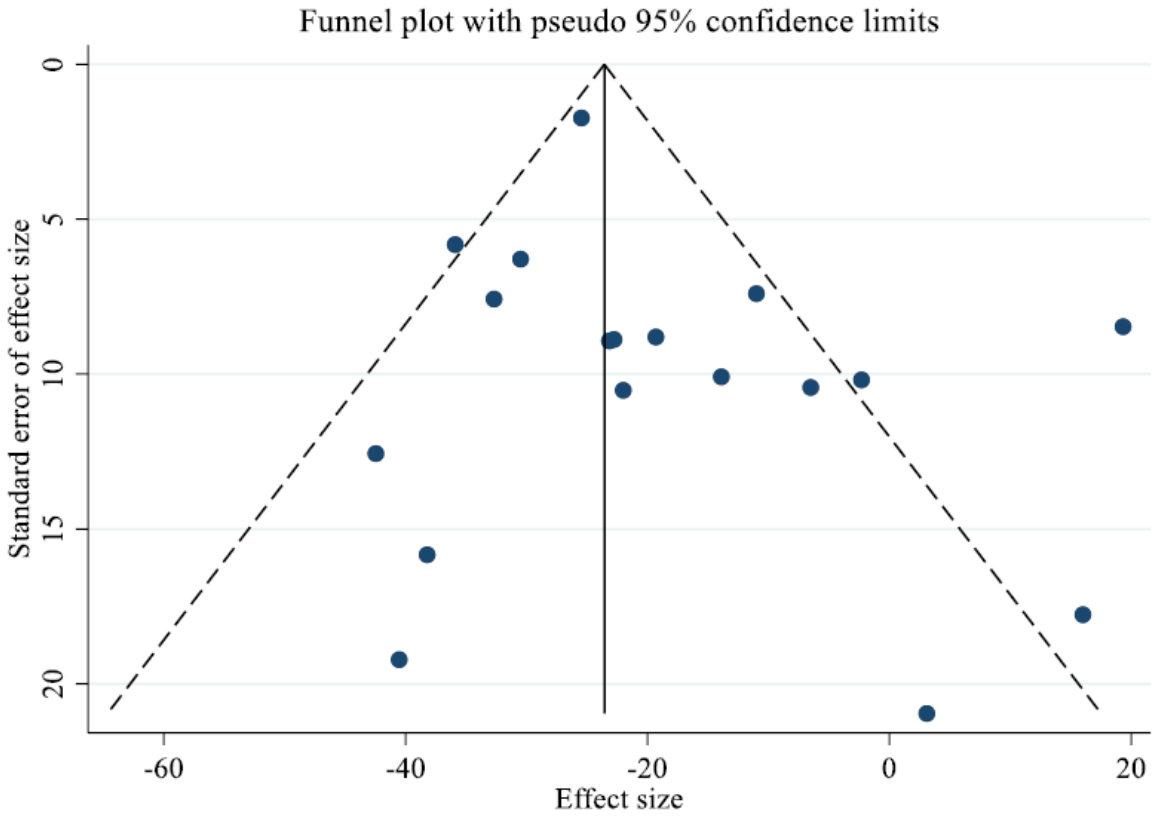


D) HDL

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of guar gum supplementation on; A) TG; B) TC; C) LDL cholesterol; and D) HDL cholesterol.



A) TG



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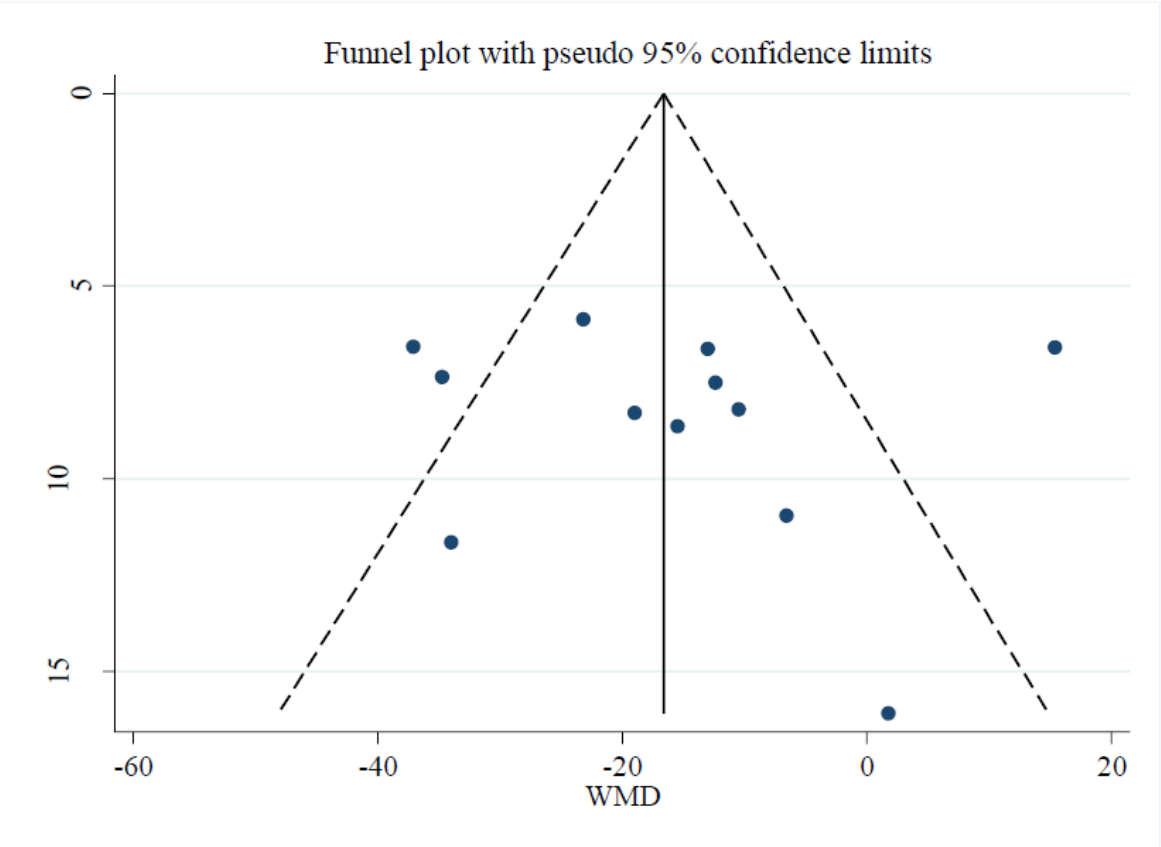

C) LDL

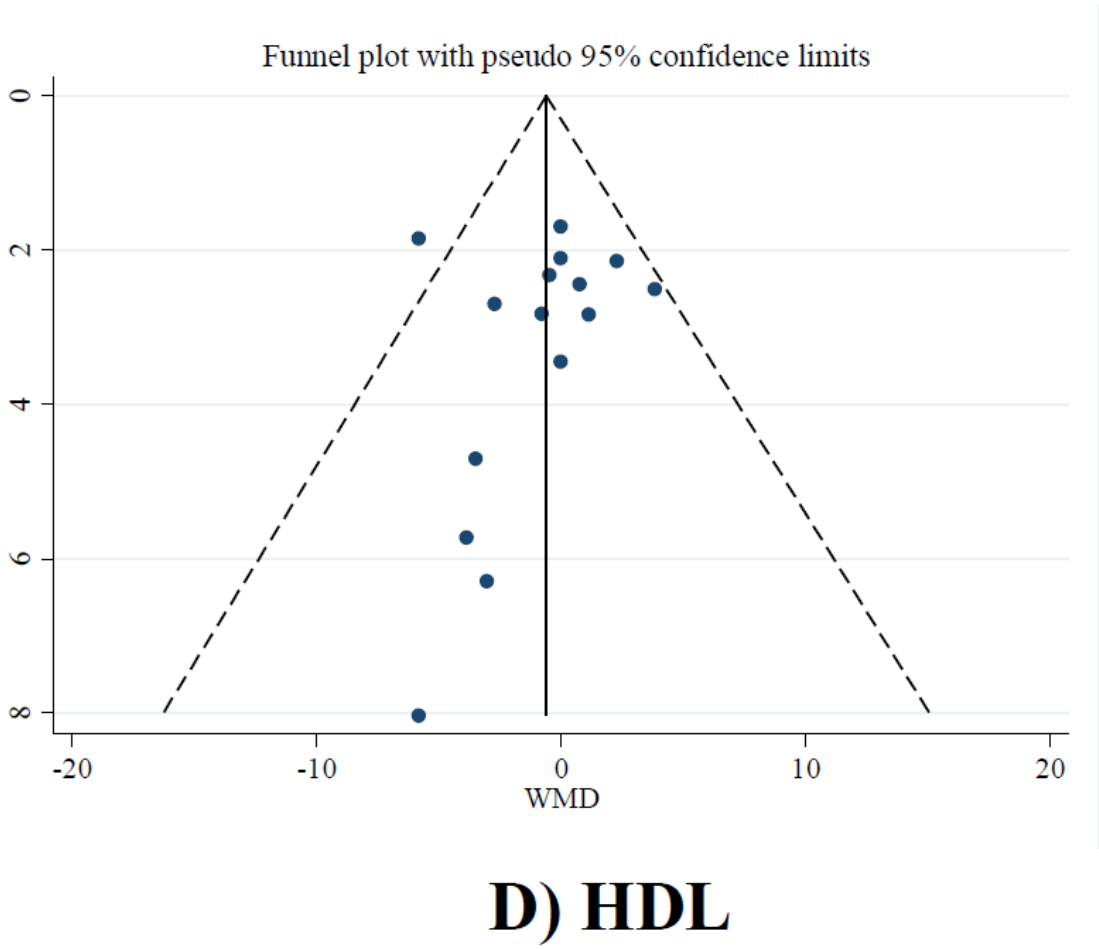

Figure 3. Funnel plot for the effect of guar gum supplementation on; A) TG; B) TC; C) LDL cholesterol; and D) HDL cholesterol.