The Effect of Honey on Lipid Profiles: A Systematic Review and Meta-analysis of Controlled Clinical Trials

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Abstract

Honey is known not only as a natural food but also as complementary medicine. According to the controversial evidence about the effects of honey on blood lipids, this meta-analysis was performed to investigate the potential effects of honey on lipid profiles. Relevant studies were identified by searching PubMed, Web of Science (WOS), Scopus, EMBASE, and Cochrane databases. All human controlled clinical trials (either with a parallel or a crossover design) published in English that reported changes in serum lipid markers (Total Cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), and LDL-C/HDL-C ratio) following honey consumption were considered. Standardized Mean Differences (SMDs) and their respective 95% Confidence Intervals (CIs) were calculated to assess the changes in lipid profiles following honey consumption by random effects model. Statistical heterogeneity, sensitivity analysis, publication bias, and quality of the included studies were assessed, as well. The meta-analysis of 23 trials showed that honey had no significant effects on TC, TG, LDL-C, HDL-C, and LDL-C/HDL-C ratio. Significant heterogeneity was seen among the studies for all the studied factors (I2 index > 50%). Subgroup analysis based on the lipid profile status, types of honey, and intervention duration revealed no significant effect on TC, TG, LDL-C, and HDL-C. Quality of the evidences varied form very low to moderate according to various parameters. In conclusion, honey consumption did not affect serum lipid profiles (TC, TG, LDL-C, HDL-C, and LDL-C/HDL-C ratio).

Keywords: Honey, Cholesterol, Triglyceride, High-density lipoprotein, Low-density lipoprotein, Dyslipidemia, Metabolic risk factors

1. Introduction

Cardiovascular Diseases (CVDs) are the main cause of morbidity and mortality, accounting for 31% of all global deaths. Lipid abnormalities are the most important contributors to CVDs that include increased concentrations of Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), and Triglycerides (TG) as well as decreased concentrations of High Density Lipoprotein Cholesterol (HDL-C) and its combinations [(1)].

Diet modification remains the main strategy for CVD management and lipid profile control. The important role of a healthy diet and natural food in promoting health, improving general well-being, and reducing the risk of some chronic diseases has been widely accepted [(2)]. Functional foods, known as nutraceuticals, therapeutic foods, or super foods, have a targeted effect on the function of organisms and can promote physiological and/or psychological health [(3)]. Bee products, such as honey, propolis, and royal jelly, have been classified as foods with functional properties [(4)].

Honey is a natural food containing numerous beneficial compounds, such as proteins, amino acids, vitamins, minerals, and phytochemicals. Caffeic and p-Coumaric acids, Catechin, Quercetin, Chrysin, and Kaempferol are the common phenolic compounds and flavonoids in honey [(5)]. Honey has been considered a complementary medicine since the earliest times [(6)]. Recent studies have highlighted that honey has numerous medical outcomes with its anti-obesity, anti-hypertensive, and anti-diabetic properties, positive-cardiovascular effects, and hypolipidemic activities [(7; 8; 9; 10; 11)]. These properties of honey are mainly related to its phenolic compounds, which define its unique biological activities, flavor, and aroma [(12)].

Despite these potential health benefits, 95% of honey dry matter contains carbohydrates, especially fructose and glucose [(5)]. Fructose as a dietary sugar has been suggested to be a main factor that increases lipid synthesis. Therefore, chronic high fructose consumption might reinforce the capacity of lipid synthesis and increase plasma lipid concentration that promote CVDs [(13)]. Hence, there is controversy about the effects of honey on lipid profiles.

The latest meta-analysis on 10 trials revealed the beneficial effects of honey on lipid profiles, including LDL-C, TG, and HDL-C [(14)]. However, some recent studies have not confirmed the lipid-lowering properties of honey [(15; 16)]. Despite the numerous potential biological activities mentioned above, the real effects of honey consumption on cardiovascular systems and lipid

profiles are still a matter of debate. The current study updated the previous meta-analysis on the effect of honey on lipid profiles [14], and included several more recent trials (23 studies) to draw a better conclusion in this regard.

2. Methods

2.1 Search Strategy

Two investigators independently conducted literature searches in five databases (PubMed, Web of Science (WOS), Cochrane, Scopus, and EMBASE) until February 2021 to find controlled clinical trials. The following keywords were used: ((honey*)) AND ((cholesterol*) OR (LDL*) OR (TC) OR (HDL*) OR (triglyceride*) OR (TG) OR (lipoprotein*) OR ("lipid profile") OR (Lipid*) OR ("cardiovascular disease") OR ("heart disease") OR (hypercholesterolemia*)) NOT ((rat) OR (mouse) OR (vitro*) OR (animal*)). Titles and abstracts were screened by two independent investigators (Z.GH and Z.S) and full-texts were assessed for eligibility.

2.2 Eligibility criteria

The inclusion criteria for the studies were (1) being published in English and (2) being a controlled clinical trial (either parallel or crossover design). However, (1) non-human studies (animal, in-vitro, and in-vivo studies), (2) cross-sectional studies, (3) reviews, (4) grey literature (book chapters, abstracts in conferences, editorials, letters, and seminars), (5) studies without any control groups, and (6) studies lacking information for extracting mean and SD (or SE) were excluded. No restriction was considered on the type of controlled clinical trial (crossover or parallel; randomized or non-randomized), type of honey, dose of honey, intervention duration, and participants (age, sex, Body Mass Index (BMI), and health condition).

In this meta-analysis, all lipid profiles; i.e., TC, TG, LDL-C, HDL-C, and LDL-C/HDL-C ratio, were considered primary outcomes.

2.3 Methodological quality appraisal

For assessing the quality of Randomized Clinical Trials (RCTs) based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions, the Cochrane Collaboration Risk of Bias Tool (CCRT) was used [17]. The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and researchers, blinding

of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Finally, the potential sources of bias were classified into “low”, “high”, and “unclear” categories.

Quality assessment of non-randomized studies was performed by using the ROBINS-I tool [18]. The following domains were assessed: bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to deviations from the intended interventions, bias due to missing data, bias in measurement of the outcome, and bias in selection of the reported results. Finally, the potential sources of bias were classified into “low”, “moderate”, “serious”, and “critical” categories.

2.4 GRADE profile

Overall assessment of evidences was done using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [19]. In this context, six criteria were considered to evaluate the quality of the evidences, including risk of bias, inconsistency, indirectness, imprecision, publication bias, and effect size.

2.5 Statistical analysis

The mean difference and SD of the changes between baseline and post-intervention were used for control and intervention groups (for crossover studies: different conditions of control and intervention) to assess the pooled final effects. To calculate SD in cases where it was expressed as SE or upper and lower limits, the following formula was employed: SD = $\sqrt{n} \times$ SE or $\sqrt{n} \times$ (upper limit – lower limit) / 3.92. The differences in the mean values at baseline and at the end of the study were used for the time that the effect size was not reported. The mean and SD were elicited from the reviewed studies and the data were report differently. Hozo et al. used this method as follows: SD=square root [(SD pre-treatment) 2 + (SD post-treatment) 2 – (2R × SD pre-treatment × SD post-treatment)] [20]. One mmol/l was considered equivalent to 38.66976 mg/dL for TC, LDL-C, and HDL-C and to 88.57396 mg/dL for TG. The random effects model (DerSimonian and Laird method) was used in order to estimate the effect size and the results were reported across Weighted Mean Difference (WMD) and 95% Confidence Intervals (CI). Statistical heterogeneity was examined with the I^2 test by using random inverse-variance heterogeneity. Moderate heterogeneity was defined as I^2 values >50%. Subgroup analysis was

done to determine the sources of heterogeneity based on the lipid profile status of the participants at baseline [dyslipidemia status (at least one of these: mean TC>200 mg/dL, TG>200 mg/dL, LDL-C>130 mg/dL, or HDL-C<40mg/dL) and normal lipid profile status], and intervention duration [≤8 weeks, >8 weeks, and acute studies]. The publication bias was evaluated by assessing funnel plots and Egger's test. Sensitivity analysis was also performed for all lipidemic indices. STATA, V13.0 was used for meta-analysis, and $p<0.05$ was considered significant.

3. Results

3.1 Search results

The process of selection of 23 trials for the meta-analysis has been presented in Figure 1. Accordingly, five databases were searched and 1188 references were identified, 1156 ones of which were excluded due to their titles and abstracts (443 duplicates and 713 irrelevant studies). For the 32 studies included up to this step, full-texts were assessed for eligibility and nine studies were excluded due to the following reasons: 1) not including a control group and 2) insufficient information. Finally, 23 trials and 1109 subjects were entered into the meta-analysis (Figure 1).

3.2 Characteristics of the included studies

The characteristics of the included studies have been shown in Table 1. The publication date for these studies ranged from 1988 to 2020. The studies were done in Iran (n=6) [15; 21; 22; 23; 24; 25], USA (n=2) [16; 26], Malaysia (n=3) [27; 28; 29], Indonesia (n=2) [30; 31], Pakistan (n=2) [32; 33], Turkey (n=1) [34], New Zealand (n=1) [35], Egypt (n=1) [36], Germany (n=1) [37], Nigeria (n=1) [38], Dubai (n=1) [39], Saudi Arabia (n=1) [40], and Greece (n=1) [41]. The studies were performed on healthy, overweight, obese, glucose-intolerant, and hyperlipidemic participants, diabetics (type 2, type 1, and nephropathy diabetics), postmenopausal women, individuals undergoing elective surgery, and asymptomatic treatment-naïve HIV-infected patients. The mean ages of the participants ranged from 11 to 62 years. Among the included trials, five used a crossover design, while 18 followed a controlled parallel design. One study was only conducted on females [30], three were only performed on males [22; 32; 33], and the remaining 19 included both sexes. BMI ranged from 21-36 kg/m^2, while this measure was not mentioned in seven studies [24; 30; 32; 33; 34; 39; 40]. Moreover, various types of honey, such as natural, native, and formulated, as well as honey vinegar were tested. Furthermore, the intervention duration ranged from 180 minutes to six

months. TC, TG, LDL-C, HDL-C, LDL/HDL-C ratio, and Very Low Density Lipoprotein Cholesterol (VLDL-C) were measured in 20, 21, 19, 18, 2, and 1 out of the 23 trials, respectively. Details of the methodological quality assessment have been presented in Tables 3.a and 3.b.

3.3 Risk of bias assessment

As shown in Table 3.a, except for four studies [27; 30; 31; 38] that did not perform randomization and their quality assessment was done separately according to the ROBINS-I tool (Table 3.b), randomization was done in the rest of studies and, consequently, they were regarded as having a low risk of bias. Concealment was mentioned in one study [21], which was regarded as having a low risk of bias in allocation concealment. However, six studies [22; 26; 33; 34; 37; 40] had an unclear risk of bias and the other 13 studies had a high risk of bias. Furthermore, five studies [21; 22; 26; 37; 40] were double-blind RCTs and were considered as having a low risk of bias for the blinding of the participants and personnel. Four trials [21; 22; 35; 40] provided a clear explanation for the blinding of outcome assessment, and other issues were considered as low risk. In this regard, one study had an unclear risk [37] and the rest had a high risk of bias. Four studies [16; 27; 32; 34] were not clear in providing complete outcome data, and one [26] was found to have a high risk. Moreover, five studies [15; 16; 21; 28; 36] had a low risk of bias in selective reporting, while the remaining 14 had an unclear risk of bias. Two studies [28; 34] had other sources of bias. Except for four studies [21; 22; 37; 40] that had an unclear risk of bias, the other 15 trials were found to have a high risk of bias for at least one of the six main domains. Therefore, these studies had a “high” quality.

As shown in Table 3.b, in case of bias due to confounding and bias in selection of the reported results, two of the studies had a moderate risk of bias [30; 38] and two others had a low risk of bias [27; 31]. Considering bias in selection of participants, bias in classification of interventions, and bias due to deviations from the intended interventions, the information given for all four studies was insufficient. In contrast, bias in measurement of the outcome was serious for all four studies. In case of bias due to missing data, except for one study [38] with a low risk of bias, the information for the rest of studies was not sufficient. All four studies seemed to be at a serious risk of bias in at least one domain. Therefore, the quality of these studies was found to be high.

3.4 Quality of evidence

GRADE results have been presented in Table 4. The quality of evidence was found to be moderate for serum TC, TG, and HDL-C concentrations. However, GRADE quality was low for serum LDL-C concentration and very low for serum LDL/HDL-C ratio due to the limited sample size, considerable statistical heterogeneity, and serious risk of bias.

3.5 Main documents

3.5.1 Effect of honey on TC

As stated above, 20 out of the 22 trials assessed the effect of honey consumption on TC level. The results revealed that honey consumption had no significant effects on TC [SMD: -0.15 mg/dL; 95% CI: -0.38, 0.08; *P*=0.194]. In other words, honey lowered TC by 0.15 mg/dL, which was not statistically significant (Figure 2). There was a significant moderate heterogeneity among the studies (I^2=69.9%; *P*=0.000). Thus, the studies were stratified to find the possible sources of heterogeneity. The results showed that baseline lipid profile status was the possible source of heterogeneity. Subgroup analysis according to the participants' lipid profile status at baseline showed no significant effects of honey on TC concentration among the participants with dyslipidemia and normal lipid profiles (Table 2).

3.5.2 Effect of honey on TG

The effect of honey consumption on TG was assessed in 21 trials. The results indicated that honey consumption had no significant effects on TG [SMD: -0.0 mg/dL; 95% CI: -0.23, 0.23; *P*=1.00], with significant moderate heterogeneity among the trials (I^2=73.7%; *P*=0.000) (Figure 3). Subgroup analysis based on lipid profile status and intervention duration revealed that honey had no significant impacts on TG concentration (Table 2).

3.5.3 Effect of honey on LDL-C

The effect of honey on LDL-C concentration was reported in 19 trials. The results showed that honey had no significant effects on LDL-C concentration [SMD: -0.12 mg/dL; 95% CI: -0.33, 0.09; *P*=0.274; I^2=64.6%, *P*=0.000] (Figure 4). The results of subgroup analysis regarding the participants' lipid profile status and intervention duration demonstrated that honey had no significant impacts on LDL-C concentration (Table 2).

3.5.4 Effect of honey on HDL-C

The effect of honey on HDL-C concentration was examined in 18 trials. The results indicated that honey had no significant effects on HDL-C concentration [SMD: 0.04 mg/dL; 95% CI: -0.19, 0.28; P=0.718; I^2=70.9%, P=0.000] (Figure 5). Intervention duration was identified as the possible source of heterogeneity. Subgroup analysis according to the participants' lipid profile status and intervention duration showed that honey consumption had no significant effects on HDL-C concentration (Table 2).

3.5.5 Effect of honey on LDL/HDL-C, Total-/HDL-C, and VLDL-C

The effect of honey on the LDL-C/HDL-C ratio was evaluated in two trials. According to the findings, honey lowered the LDL-C/HDL-C ratio by 0.26 mg/dL, which was not statistically significant [SMD: -0.17 mg/ dL; 95% CI: -1.296, 0.955; P=0.767, I^2=88.1%, P=0.004] (Figure 6). Moreover, Arani et al. [21] examined the effect of consumption of probiotic honey for 12 weeks on Total-/HDL-c and VLDL-C among nephropathy diabetics. The results revealed a significant decrease in the Total-/HDL-C ratio (P=0.04), but no significant difference in VLDL-C (P>0.05).

3.5.6 Publication bias

Based on the funnel plot and Egger's test, publication bias was found in the trials on LDL-C (P=0.020), but not in those on TC (P=0.316), TG (P=0.350), HDL-C (P=0.674), and LDL-C/HDL-C ratio (Figure 7).

3.5.7 Sensitivity analysis

Sensitivity analysis was conducted for the meta-analysis of the effect of honey on TC, TG, LDL-C, HDL-C, and LDL-C/HDL-C ratio. In the sensitivity analysis of each outcome, the results were not affected by any single study.

4. Discussion

To the best of our knowledge, this meta-analysis was an update of a previous meta-analysis to review the available literature and current control trials about the effects of honey consumption on lipid profiles in adults. In other words, this study updated the results of a previous meta-analysis regarding the effects of honey on blood lipids. In that study, 10 eligible trials on the effects of honey on blood lipids were assessed and the final results were reported with low certainty. The results revealed the positive impact of honey consumption on some blood lipids, including LDL-C, TG, and HDL-C [(14)]. It should be noted that the previous research was conducted on 10 studies. The current meta-analysis, however, was conducted on 23 studies on the effects of honey on blood lipids and different results were found. It was reported in the current study that honey consumption could not affect blood lipids significantly. Hence, the results of the previous meta-analysis by Tul-Noor et al. [(14)] should be interpreted with caution. In addition, more reviews or RCTs are needed to draw a better conclusion about the effects of honey on blood lipids.

The results of the current study showed that honey did not have any significant effects on TC, TG, HDL-C, LDL-C, and VLDL-C concentrations as well as on the LDL-C/HDL-C ratio. However, there was a high heterogeneity among the studies about the effects of honey on blood lipids, which was decreased by sub-group analysis and taking into account the characteristics of the included studies, such as duration and baseline lipid profiles. In the same line, Wahab et al. disclosed that honey had no significant effects on lipid profiles amongst postmenopausal women [(42)]. In another study performed on healthy adults, it was hypothesized that compared to sucrose, honey consumption did not negatively affect blood lipids, including HDL-C and LDL-C. They believed that honey consumption could reduce energy and carbohydrate intake without negatively affecting blood lipids compared to sucrose among healthy participants [(16)]. In another study, eight weeks of honey consumption led to a reduction in LDL-C, TC, and TG concentrations and LDL-C/HDL-C ratio in diabetic patients, which was on the contrary to the results of the current meta-analysis [(24)]. The difference might be pertinent to the study population. Al-waili et al. attributed the hypolipidemic effects of natural honey to its special ingredients [(39)]. The difference between the aforementioned study [(39)] and the current one might result from the fact that the present study findings were not differentiated based on the consumption of artificial

or natural honey since this was not mentioned in all the included studies. On the other hand, the fructose content of honey (especially artificial honey) could increase blood TG level due to its effect on postprandial lipid profiles [43]. However, the present study results revealed no significant increase in TG concentration after honey consumption, which could be justified by the antioxidant content of honey, such as vitamin C, beta-carotene, and glutathione reductase [44]. In contrast, niacin is present in honey and can inhibit lipolysis in adipose tissue, eventually reducing hepatic TG synthesis [33]. That is why no increase was detected in TG concentration after honey consumption in spite of its fructose content. Moreover, regarding the sub-group analysis, the results of lipid profiles did not change considering baseline lipid concentrations following honey consumption.

Obviously, fructose in various foods can affect serum TG level by bypassing phosphofructokinase regulatory step in glycolysis pathway, which can cause hypertriglyceridemia [45]. Nevertheless, the effect of honey fructose on increasing the TG concentration has not been reported due to the active and beneficial ingredients of honey, such as antioxidants, that can positively affect the serum TG concentration [36], but it might reduce the hypolipidemic effects of honey on blood lipids as no change was reported in blood lipids following honey consumption in the present review. Flavonoids are among these important constituents showing antioxidant and hypolipidemic effects [36; 46]. On the other hand, the effects of honey fructose on serum TG level depend on a variety of factors. For example, fructose or glucose consumption has been found to be associated with increased TG levels in hypercaloric diets, but not in weight maintenance diets [47; 48]. Furthermore, when fructose in the diet was replaced with a large amount of starch, it could induce hypertrigyceridemia even in controlled diets [49; 50]. Hence, the whole diet or other constituents of a diet, especially the calorie or starch content, should be taken into account while assessing the effects of honey on serum TG level to better elucidate the exact effects of honey on this parameter. Yet, the most important fact in the current meta-analysis was that the consumed fructose was in the form of honey, which had other ingredients that could modulate its final effects.

As a natural food, honey can lead to protection against Metabolic Syndrome (MetS). It can prevent obesity and exert hypotensive, hypolipidemic, and anti-diabetic effects. It can affect insulin sensitivity, as well. All the aforementioned effects are related to the low glycemic index

of honey that prevents fat accumulation in the body. However, the beneficial effects of honey have been poorly confirmed in diabetic patients and need to be further investigated in randomized clinical trials to better elucidate the exact effects [51]. In spite of the hypoglycemic effects of natural honey, it was reported that it could possibly increase HbA1C in some diabetic patients [52]. Considering the hypolipiodemic effects of honey, despite acceptable results, a previous review indicated that these effects were confirmed in some studies but not in some others [53]. The effect of honey on blood lipids could be affected by different factors, including gender, type of honey, population, and geographical condition. Hence, further studies have to be conducted on the issue to draw a better conclusion. It is important to state that the results of the present study were not affected by any individual study according to the sensitivity analysis.

Strengths of the study

The results of the current meta-analysis pooled the available RCTs considering the effects of honey consumption on serum lipids. The study had some strengths. Firstly, there was a high heterogeneity among the studies. However, subgroup analysis was conducted considering the differences among the studies, including study duration, baseline serum lipid values, and their effects on changes in serum lipids after honey consumption, which was the main strength of the study. The large number of the studies included can be mentioned as another strong point.

Limitations of the study

This study had several limitations. Firstly, it was not registered in PROSPERO. In addition, a significant heterogeneity was encountered due to various regimens, doses, durations, center settings, and populations, and the results should be interpreted with caution. Besides, the studies could not be differentiated based on the utilization of natural or artificial honey, as it was not mentioned in all the included studies. In some studies, artificial or formulated honey was compared to natural honey, while many included studies explored the effects of honey compared to other sugar-containing foods and did not clearly define the type of honey consumed. Hence, differentiation of the studies based on the type of honey was not possible. Another limitation of the study was that the whole diet or dietary components of the study participants could not be investigated, as it was not reported in the included studies. As another limitation, most of the included studies originated from Eastern countries and the results could not be generalized to

Western countries. Finally, some studies suffered from some sources of bias, which should be considered while interpreting the results.

Conclusions

To sum up, the findings of this meta-analysis demonstrated that honey consumption had no effects on serum lipids, including TC, TG, HDL-C, LDL-C, LDL/HDL, and VLDL-C. However, to ensure the generalizability of the results, future studies with larger sample sizes, different populations, and various types of honey are required to clarify the effects of honey consumption on serum lipid profiles. In addition, the whole diet or dietary components have to be considered while assessing the effects of honey on serum lipid profiles in various populations.

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Conflicts of interest

The authors declare no conflict of interest.

Authorship

Z.GH, Z.S, and N.N were substantially involved in the inclusion of the scientific contents and bibliographical search as well as in the careful reading and discussion of the final version. Z.GH, Z.S, and M.Z contributed to the initial design as well as to the manuscript preparation and discussion. Z.GH, M.Z, and B.P participated in data analysis and interpretation. Z.GH, Z.S, N.N, and B.P wrote and revised the manuscript. All authors read and approved the final manuscript.

Abbreviations

CVDs: Cardiovascular Diseases; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; VLDL-C: Very-Low-Density Lipoprotein Cholesterol; BMI: Body Mass Index; SMD: Standardized Mean Differences; CIs: Confidence Intervals; SD: Standard Deviation; SE: Standard Error; CCRT: Cochrane Collaboration Risk of bias Tool.

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TABLE 1. The characteristics of the clinical trials included in the meta-analysis of the effect of honey on lipid profiles

First author (year)	Country	Participants	Age[1], y	Number, sex	BMI	Study design	Duration	Intervention	Dose of honey	Control	Outcome
Tang et al. (2020) [29]	Malaysia	Asymptomatic, treatment -naïve HIV -infected patients	39.5	45, M/F	21	Parallel RCT	6 months	Tualang Honey	60 g	No H	**TC, TG, LDL-C, and HDL-C**
Sadeghi et al. (2020) [15]	Iran	Type 2 diabetics	57.5±9.8	18 M/24 F	27.8	Crossover RCT[2]	8 weeks	Natural H[4] + dietary recommendations	50 g/day	Dietary advice	**TC[5], TG[6], LDL-C[7], and HDL-C[8]**
Al-Tamimi et al. (2020) [16]	USA	Healthy adults	32.9±1.7	21 M/16 F	25.4	Crossover RT[3]	4 weeks	Clover H	1.2 g CHO/kg/ day	Sucrose	**TC, LDL-C and HDL-C**
Rashid et al. (2019) [27]	Malaysia	Impaired fasting glucose P[10]	51.6±11.5	30 M/30 F	29.7	Quasi-experimental	30 days	Kelulut H	30 g/day	No H	**TC, TG, LDL-C, and HDL-C**
Cholifah et al. (2019) [30]	Indonesia	Hyper cholesterolemia P	>20	5 M/27 F	-	Quasi-experimental	2 weeks	Nephelium longata L H	_	No H	**TC**
Jayadi et al. (2019) [31]	Indonesia	Individuals with central obesity	41.5±9.53	46, M/F	29.2	Quasi-experimental	60 days	Indonesian H + obesity education	70 g/day	Obesity education	**TC, TG, LDL-C, and HDL-C**
First author (year)	**Country**	**Participants**	**Age[1], y**	**Number, sex**	**BMI**	**Study design**	**Duration**	**Intervention**	**Dose of honey**	**Control**	**Outcome**
Arani et al. (2018) [21]	Iran	Diabetic	61.5±8.81	60, M/F	30.7	Parallel RCT	12 weeks	Probiotic H	25 g/day	Control H	**TC, TG, LDL-C, HDL-**

		nephropathy P									**C, VLDL-C[9], and Total-/HDL-C ratio**
Rasad et al. (2018) [22]	Iran	Young healthy subjects	22.88±1.77	60 M	22.9	Parallel RCT	6 weeks	Natural H	70 g/day	Sucrose	**TC, TG, LDL-C, and HDL-C**
Enginyurt et al. (2017) [34]	Turkey	Type 2 diabetics	18-80	8 M/8 F	-	Parallel RCT	4 months	Pure H	25 g/day	No H	**TC, TG, LDL-C, and HDL-C**
Bhatti et al. (2016) [32]	Pakistan	Hyperlipidemic smokers P	35-65	40 M	-	Parallel trial	30 days	H in local market	21 g/day	Atorvastatin (10 mg/d)	**TC, TG, LDL-C, and HDL-C**
Raatz et al. (2015) [26]	USA	Glucose-tolerant and –intolerant individuals	45.5±3.24	16 M/39 F	28.7	Crossover RT	2 weeks	Blend of H	50 g of CHO/day	Sucrose	**TC, TG, LDL-C, and HDL-C**
Whitfield et al. (2015) [35]	New Zealand	Type 2 diabetics	61.7±6.2	7 M/5 F	36.6	Crossover RT	40 days	Formulated H	53.5 g/day	Non-formulated H	**TC, TG, LDL-C, and HDL-C**
First author (year)	**Country**	**Participants**	**Age[1], y**	**Number, sex**	**BMI**	**Study design**	**Duration**	**Intervention**	**Dose of honey**	**Control**	**Outcome**
Derakhshandeh et al. (2014) [23]	Iran	Healthy subjects	29.97±6.06	22 M/39 F	24	Parallel RCT	4 weeks	Natural H vinegar Syrup + normal diet	21.66 g/day	Normal diet	**TC, TG, LDL-C, HDL-C, and LDL/HDL ratio**

Majid et al. (2014) [33]	Pakistan	Young healthy males	20.06±0.14	63 M	-	Parallel RCT	4 weeks	Natural H+ diet	70 g/day	Diet	**TC, TG, LDL-C, and HDL-C**
Abdulrhman et al. (2013) [36]	Egypt	Type 1 diabetics	11.35±4.48	10 M/10 F	21	Crossover RT	12 weeks	Egyptian clover H	0.5mL /kg/day	No H	**TC, TG, LDL-C, and HDL-C**
Nik Hussain et al. (2012) [28]	Malaysia	Postmenopausal women	55.4±3.15	79 F	27.6	Parallel RCT	4 months	Tualang H	20 g/day	Hormonal replacement therapy	**TC, TG, LDL-C, and HDL-C**
Bahrami et al. (2009) [24]	Iran	Type 2 diabetics	57.2 ± 8.4	13 M/35 F	-	Parallel RCT	8 weeks	Natural H	2.5 g/kg/day	No H and drug	**TC, TG, LDL-C, HDL-C and LDL/HDL ratio**
Munstedt et al. (2009) [37]	Germany	Hyper cholesterolemia P	60.7±10.12	30 M/30 F	25.5	Parallel RCT	14 days	Mixed blossom (polyfloral) H	75 g/day	Honey-comparable sugar	**TC, TG, LDL-C, and HDL-C**
First author (year)	**Country**	**Participants**	**Age[1], y**	**Number, sex**	**BMI**	**Study design**	**Duration**	**Intervention**	**Dose of honey**	**Control**	**Outcome**
Yaghoobi et al. (2008) [25]	Iran	Subjects BMI >25 kg/m2	41.2±9.2	24 M/31 F	31.3	Parallel RCT	30 days	Natural H	70 g/day	Sucrose	**TC, TG, LDL-C, and HDL-C**
Onyesom (2005) [38]	Nigeria	Healthy moderate alcohol drinkers (<30 g	23.6±7.4	25 M/25 F	25.2	Parallel CT	600 min after digestion	Ethanol + citrus H from the orange tree	1.25 ml/kg	Ethanol	**TG**

		ethanol/day)									
Al-waili (2004) [39]	Dubai	Hyperlipidemia P	35-60	7 M/4 F	-	Experimental	3 hours after digestion	Natural H	75 g	Artificial H	**TC, TG and, LDL-C**
Naguib et al. (2001) [40]	Saudi Arabia	Patients undergoing elective surgery	32.4±10.75	66 M/84 F	-	Parallel RCT	2 hours before surgery	Natural H	60 ml	Continued overnight fast	**TG**
Katsilambros et al. (1988) [41]	Greece	Type 2 diabetics	55±22.22	6 M/6 F	28.9	Parallel RCT	180 min after digestion	Natural H	33 g	White bread	**TG**

[1] Mean ± SD or range, [2] Randomized clinical trial, [3] Clinical trial, [4] Honey, [5] Total cholesterol, [6] Triglycerides, [7] Low-density lipoprotein-cholesterol, [8] High-density lipoprotein-cholesterol, [9] Very low-density lipoprotein-cholesterol, [10] Patients

- Not mentioned

Table 2. Subgroup analyses of TC, TG, LDL-C, and HDL-C based on the baseline lipid profile status and intervention duration

Subgroup		**Studies, n**	**SMD**	**95% CI**	**Heterogeneity (I^2, *P* value)**
Total Cholesterol					
Baseline lipid profile status	Dyslipidemia	15	-0.15	-0.48, 0.18	77.4%, 0.000 (0.369)
	Normal lipid profile	5	-0.12	-0.33, 0.08	0.0%, 0.928 (0.238)
Intervention duration	≤ 8 weeks	13	-0.07	-0.33, 0.19	67.6%, 0.000 (0.598)
	>8 weeks	6	-0.32	-0.85, 0.21	78.3%, 0.000 (0.237)
	Acute	1	-0.42	-1.57, 0.73	(0.474)
Triglyceride					
Baseline lipid profile status	Dyslipidemia	14	-0.15	-0.38, 0.09	54.5%, 0.008 (0.228)
	Normal lipid profile	7	0.26	-0.19, 0.71	84.9%, 0.000 (0.258)
Intervention duration	≤ 8 weeks	11	-0.09	-0.35, 0.16	61.2%, 0.004 (0.463)
	>8 weeks	6	0.10	-0.32, 0.52	66.4%, 0.011 (0.631)
	Acute	4	0.01	-0.92, 0.94	90.5%, 0.000 (0.987)
LDL- Cholesterol					
Baseline lipid	Dyslipidemia	14	-0.07	-0.36, 0.21	68.2%, 0.000

profile status					(0.608)
	Normal lipid profile	5	-0.22	-0.53, 0.08	52.9%, 0.075 (0.151)
Intervention duration	≤ 8 weeks	12	-0.14	-0.40, 0.11	65.4%, 0.001 (0.271)
	>8 weeks	6	-0.04	-0.51, 0.42	72.7%, 0.003 (0.852)
	Acute	1	-0.42	-1.57, 0.72	.(0.470)
HDL- Cholesterol					
Baseline lipid profile status	Dyslipidemia	13	0.02	-0.29, 0.33	73.6%, 0.000 (0.897)
	Normal lipid profile	5	0.08	-0.30, 0.45	68.8%, 0.012 (0.681)
Intervention duration	≤ 8 weeks	12	-0.07	-0.38, 0.24	76.7%, 0.000 (0.657)
	>8 weeks	6	0.28	-0.01, 0.57	30.7%, 0.205 (0.061)

SMD, standardized mean difference; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol.

Table 3.a. Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool

Study, Year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall assessment of risk of bias
Abdulrhman et al. (2013) [36]	Low	High	High	High	Low	Low	Low	High
Al-Tamimi et al. (2020) [16]	Low	Unclear	High	High	Unclear	Low	Low	High
Al-waili (2004) [39]	Low	High	High	High	Low	Unclear	Low	High
Arani et al. (2018) [21]	Low	Low	Low	Low	Low	Low	Low	Low
Bahrami et al. (2009) [24]	Low	High	High	High	Low	Unclear	Low	High
Bhatti et al. (2016) [32]	Low	High	High	High	Low	Unclear	Low	High
Derakhshandeh et al. (2014) [23]	Low	High	High	High	Low	Unclear	Low	High

Enginyurt et al. (2017) [34]	Low	Unclear	High	High	Unclear	Unclear	Unclear	High
Study, Year (reference)	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other sources of bias**	**Overall assessment of risk of bias**
Katsilambros et al. (1988) [41]	Low	High	High	High	Low	Unclear	Low	High
Majid et al. (2014) [33]	Low	High	High	High	Low	Unclear	Low	High
Munstedt et al. (2009) [37]	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear
Naguib et al. (2001) [40]	Low	Unclear	Low	Low	Low	Unclear	Low	Unclear
Nik Hussain et al. (2012) [28]	Low	High	High	High	Low	Low	Unclear	High
Raatz et al. (2015) [26]	Low	Unclear	Low	High	High	Unclear	Low	High

Rasad et al. (2018) [22]	Low	Unclear	Low	Low	Low	Unclear	Low	Unclear
Sadeghi et al. (2020) [15]	Low	High	High	High	Low	Low	Low	High
Tang et al. (2020) [29]	Low	High	High	High	Low	Unclear	Low	High
Study, Year (reference)	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other sources of bias**	**Overall assessment of risk of bias**
Whitfield et al. (2015) [35]	Low	High	High	Low	Low	Unclear	Low	High
Yaghoobi et al. (2008) [25]	Low	High	High	High	Low	Unclear	Low	High

Table 3.b. Bias domains included in the ROBINS-I tool

Study					
Bias domain	**Category of bias**	**Cholifah et al. (2019) [30]**	**Jayadi et al. (2019) [31]**	**Onyesom (2005) [38]**	**Rashid et al. (2019) [27]**
Pre-intervention domains					
Bias due to confounding	**Confounding**	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias
Bias in selection of participants into the study	**Selection bias**	No information	No information	No information	No information
At-intervention domain					
Bias in classification of interventions	**Information bias**	No information	No information	No information	No information
Post-intervention domains					

Bias due to deviations from intended interventions	**Confounding**	No information	No information	No information	No information
Bias due to missing data	**Selection bias**	No information	No information	Low risk of bias	No information
Bias in measurement of the outcome	**Information bias**	Serious risk of bias	Serious risk of bias	Serious risk of bias	Serious risk of bias
Bias in selection of the reported result	**Reporting bias**	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias
Risk-of-bias judgment		Serious risk of bias	Serious risk of bias	Serious risk of bias	Serious risk of bias

Table 4. Summary of the findings

The effects of honey consumption on blood lipid profiles										
	Absolute effect WMD (95 % CI)	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	GRADE quality
Serum TC	-0.15 (-0.38, 0.08)	20	RCT CT	-2 €	1 £-	0	+2 $	0	0	+ + + − Moderate
Serum TG	-0.0 (-0.23, 0.23)	21	RCT CT	2 -	1 -	0	+2	0	0	+ + + − Moderate
Serum LDL-C	-0.12 (-0.33, 0.06)	19	RCT CT	2 -	1 -	0	+2	-1 ¥	0	+ + − − Low
Serum HDL-C	0.04, (-0.19, 0.28)	18	RCT CT	2 -	1 -	0	+2	0	0	+ + + − Moderate

Serum LDL/HDL-C	-0.26 (-0.94, 0.45)	2	RCT	2 -	1 -	0	-1 π	0	0	− − − − Very low

The symbols + + − − show the quality of the evidence.

Abbreviations: WMD, weighted mean difference; CI, confidence interval; GRADE, grades of recommendation, assessment, development, and evaluation; RCT, randomized controlled trial; CT, controlled trial.

€ Down-graded two levels as the serious risk of bias.

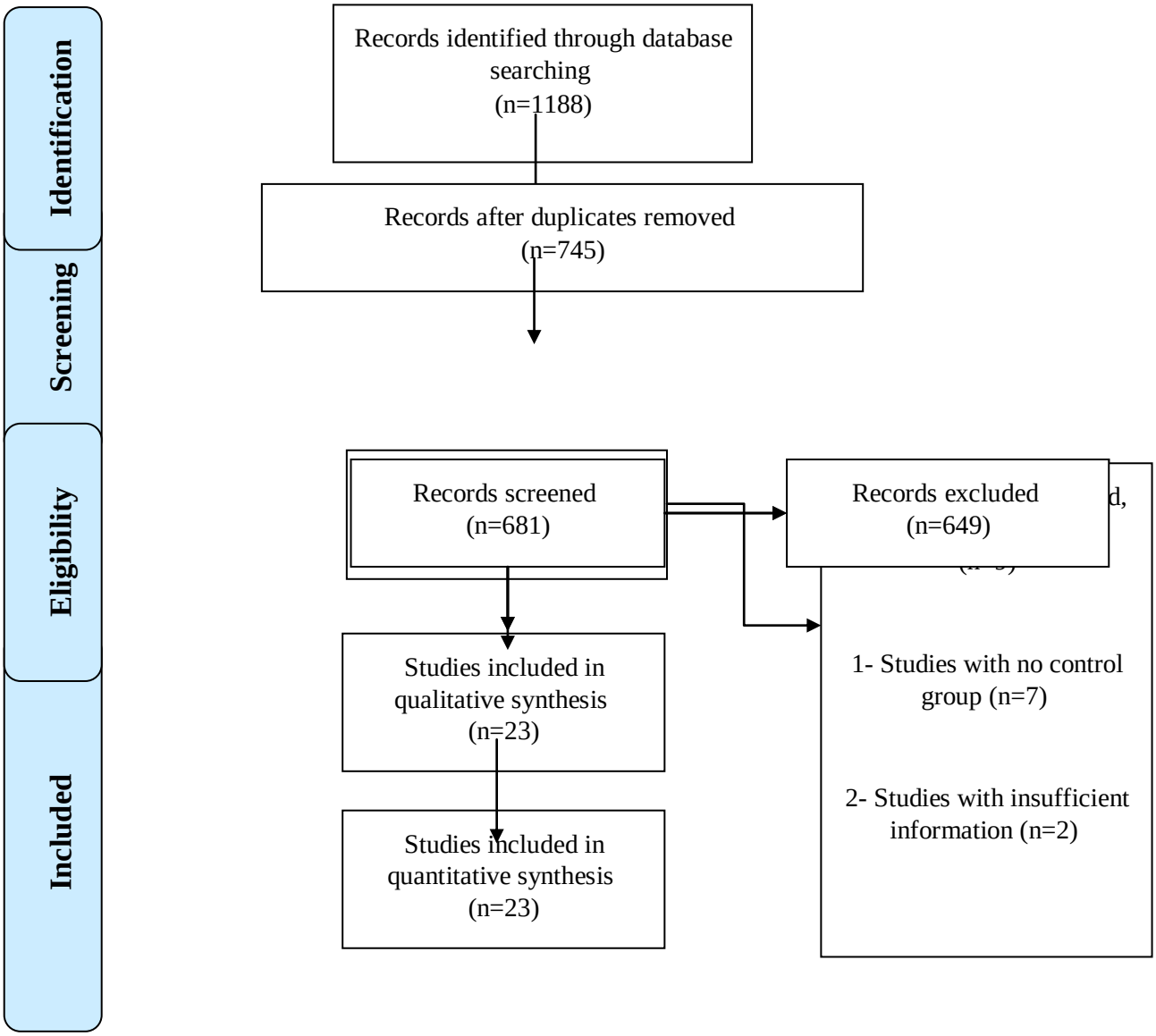
£ Down-graded one level as the statistical heterogeneity was >50%.

$ Up-graded two levels as the as the number of studies was >5 and imprecision was considerable.

π Down-graded one level as the as the number of studies was <5 and imprecision was considerable.

¥ Down-graded one level as the publication bias was considerable (P=0.020).

Figure 1. Flow chart of the study selection process



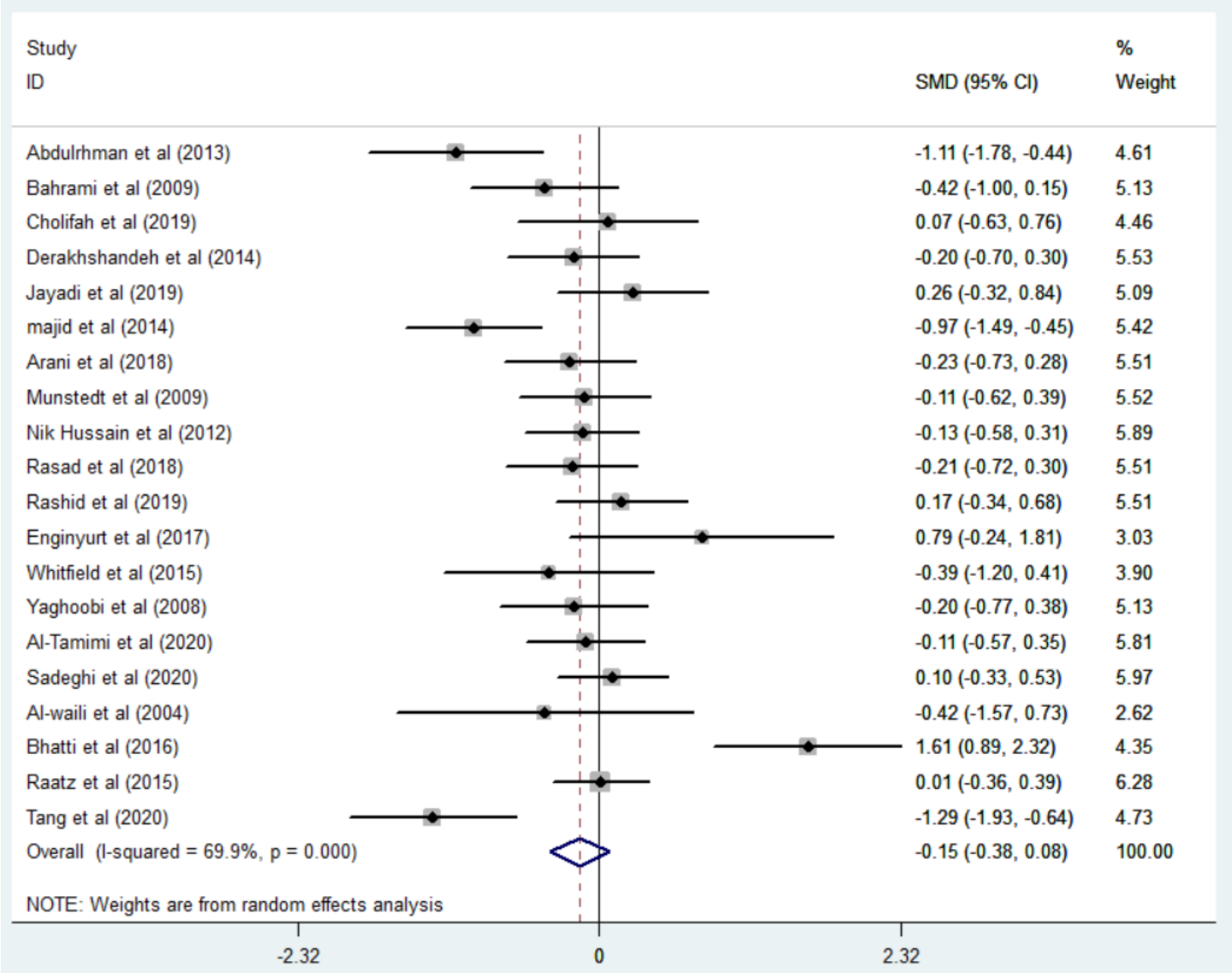


Figure 2. Forest plot of the clinical trials examining the effect of honey on TC (mg/dL). Data have been expressed as SMDs between treatment and control groups with 95% CIs. Estimates were pooled using the random-effects, inverse-variance model. SMD, standardized mean difference.

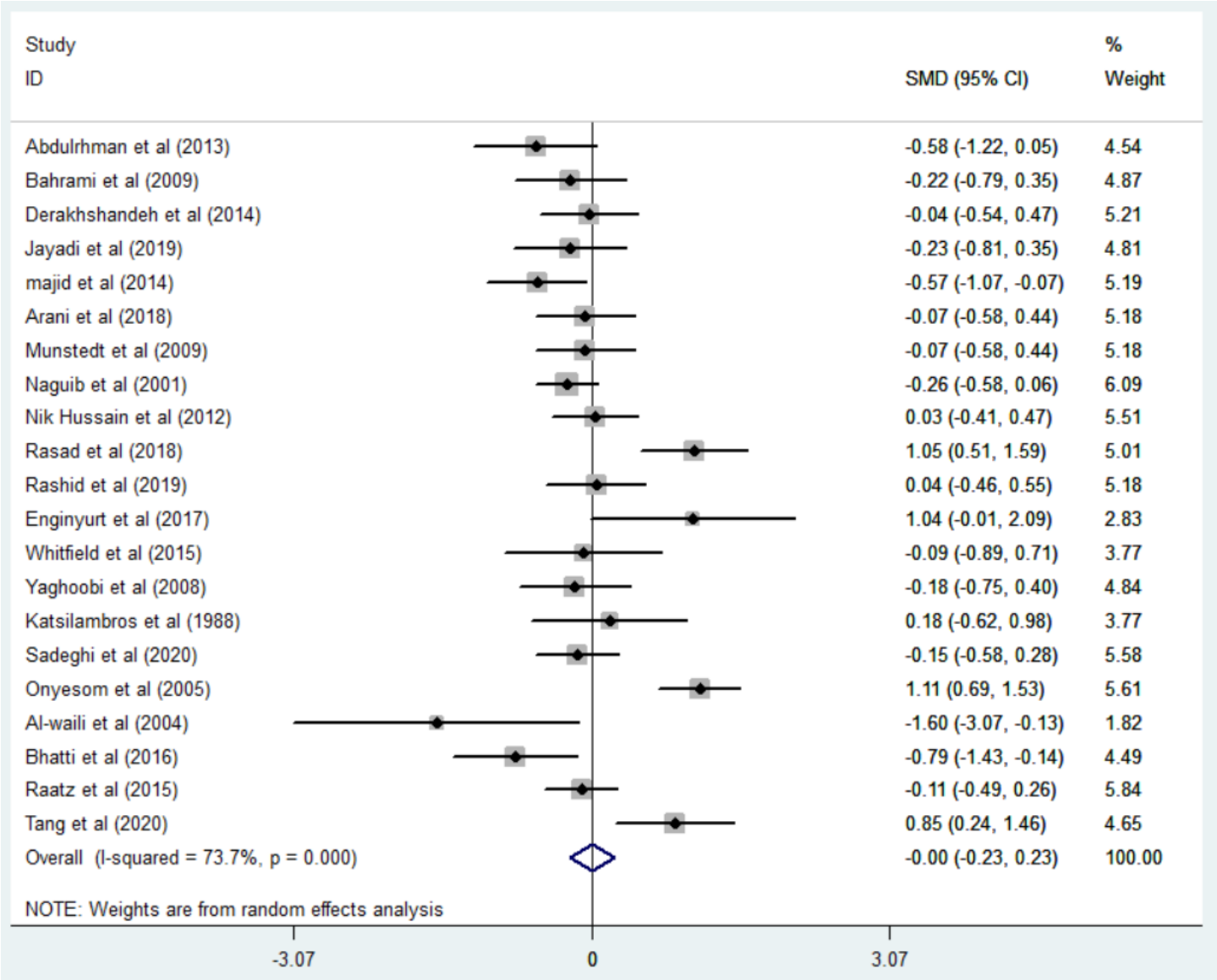


Figure 3. Forest plot of the clinical trials examining the effect of honey on TG (mg/dL). Data have been expressed as SMDs between the treatment and control groups with 95% CIs. Estimates were pooled using the random-effects, inverse-variance model. SMD, standardized mean difference.

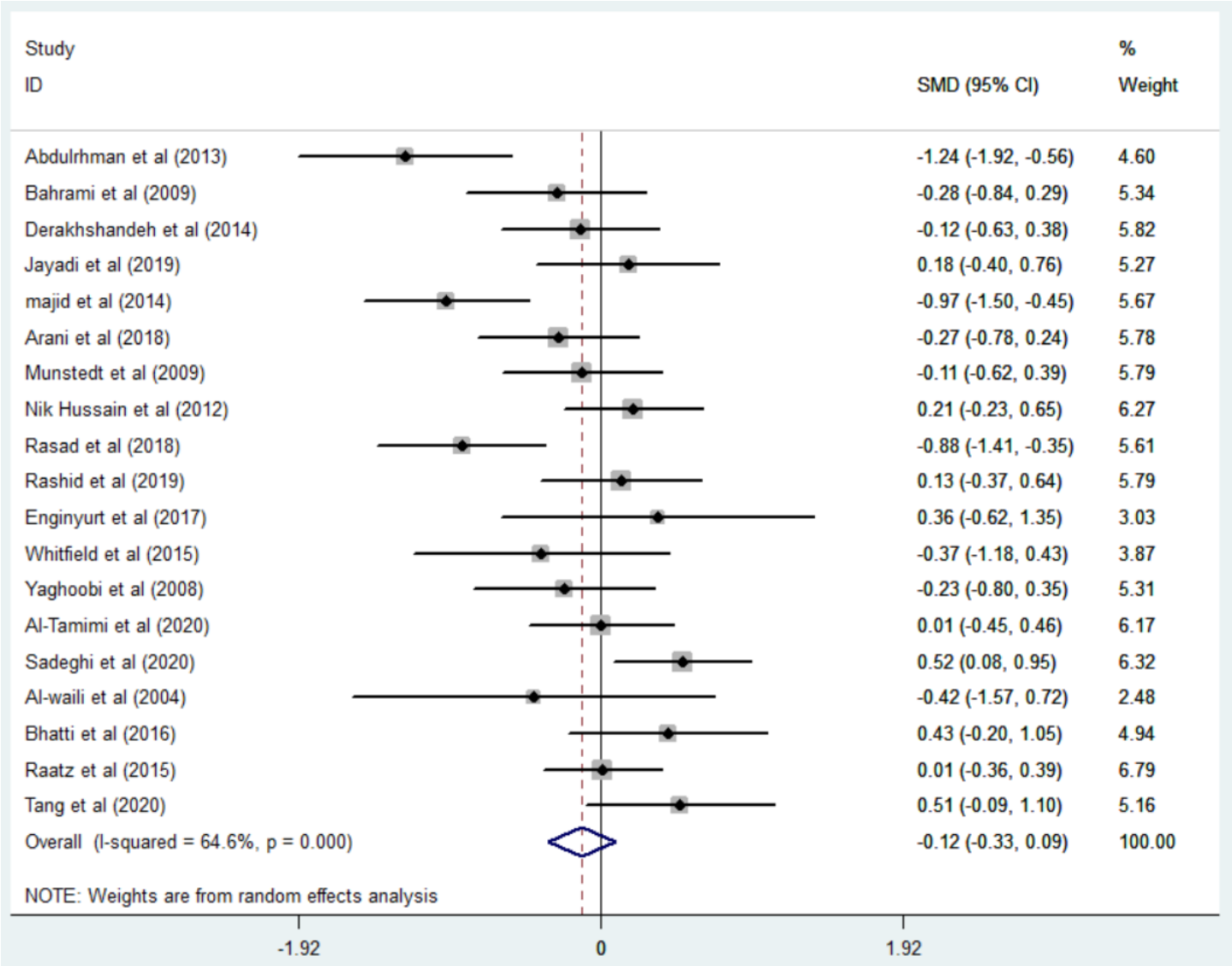


Figure 4. Forest plot of the clinical trials examining the effect of honey on LDL-C (mg/dL). Data have been expressed as SMDs between the treatment and control groups with 95% CIs. Estimates were pooled using the random-effects, inverse-variance model. SMD, standardized mean difference.

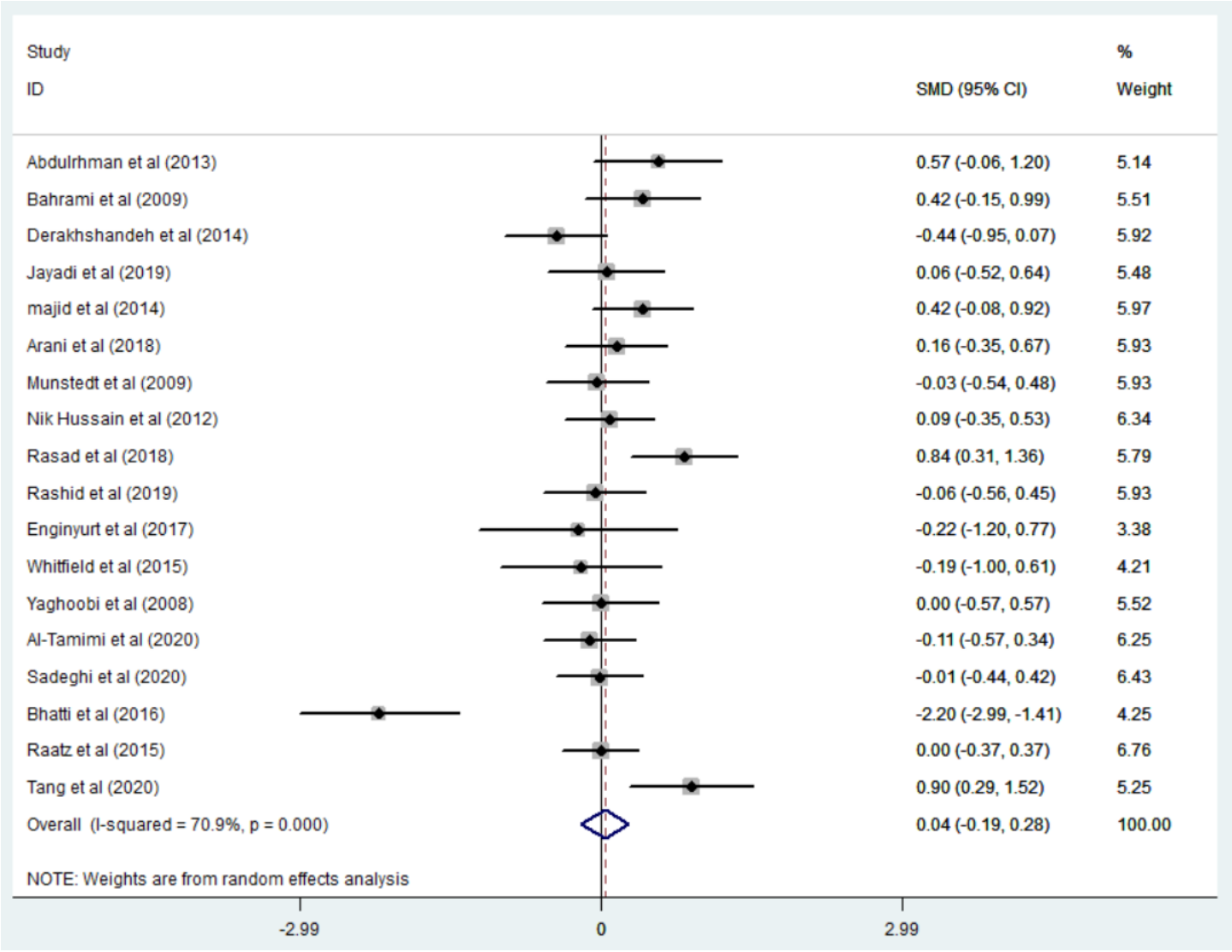


Figure 5. Forest plot of the clinical trials examining the effect of honey on HDL-C (mg/dL). Data have been expressed as SMDs between the treatment and control groups with 95% CIs. Estimates were pooled using the random-effects, inverse-variance model. SMD, standardized mean difference.

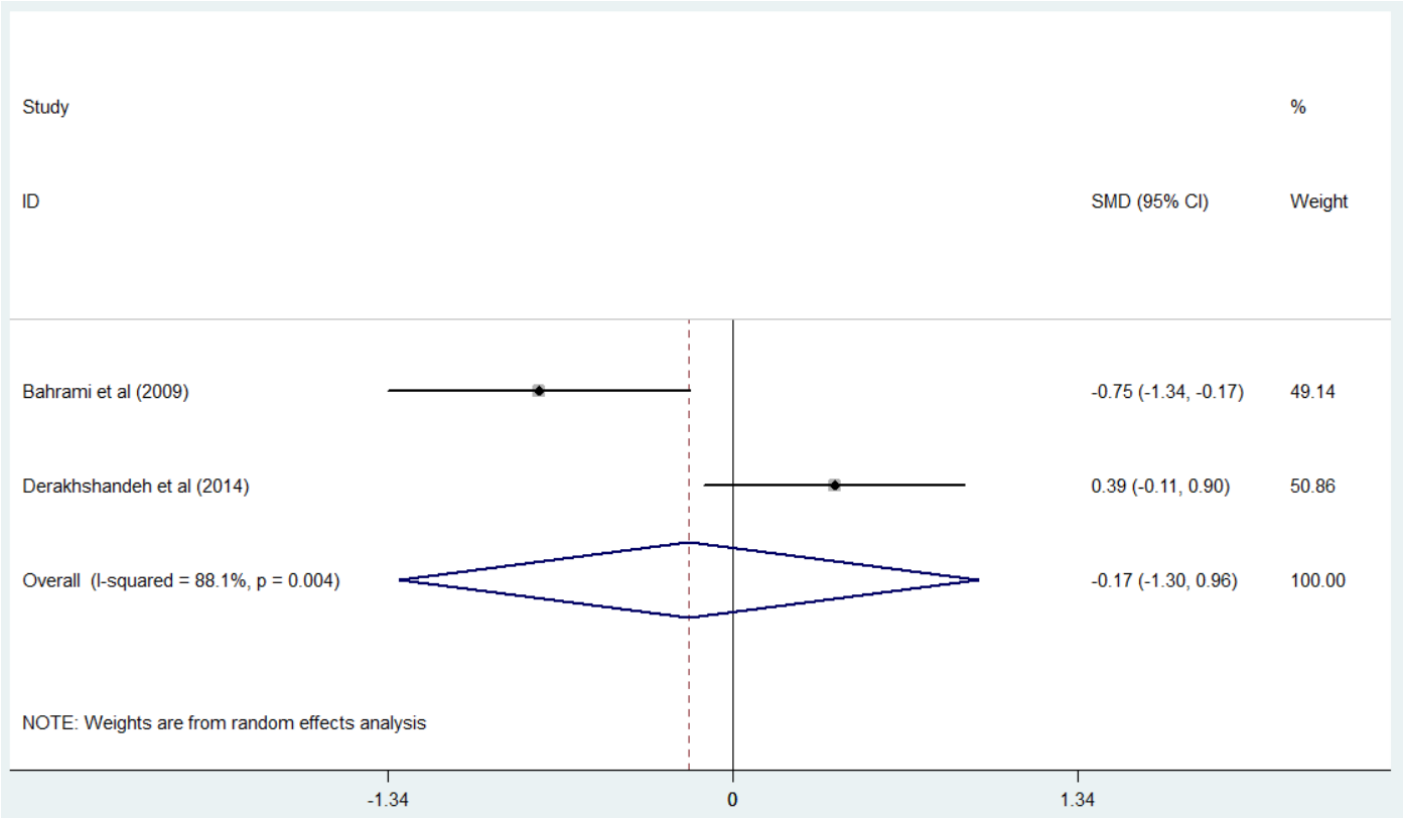


Figure 6. Forest plot of the clinical trials examining the effect of honey on LDL/HDL-C (mg/ dL). Data have been expressed as SMDs between the treatment and control groups with 95% CIs. Estimates were pooled using the random-effects, inverse-variance model. SMD, standardized mean difference.

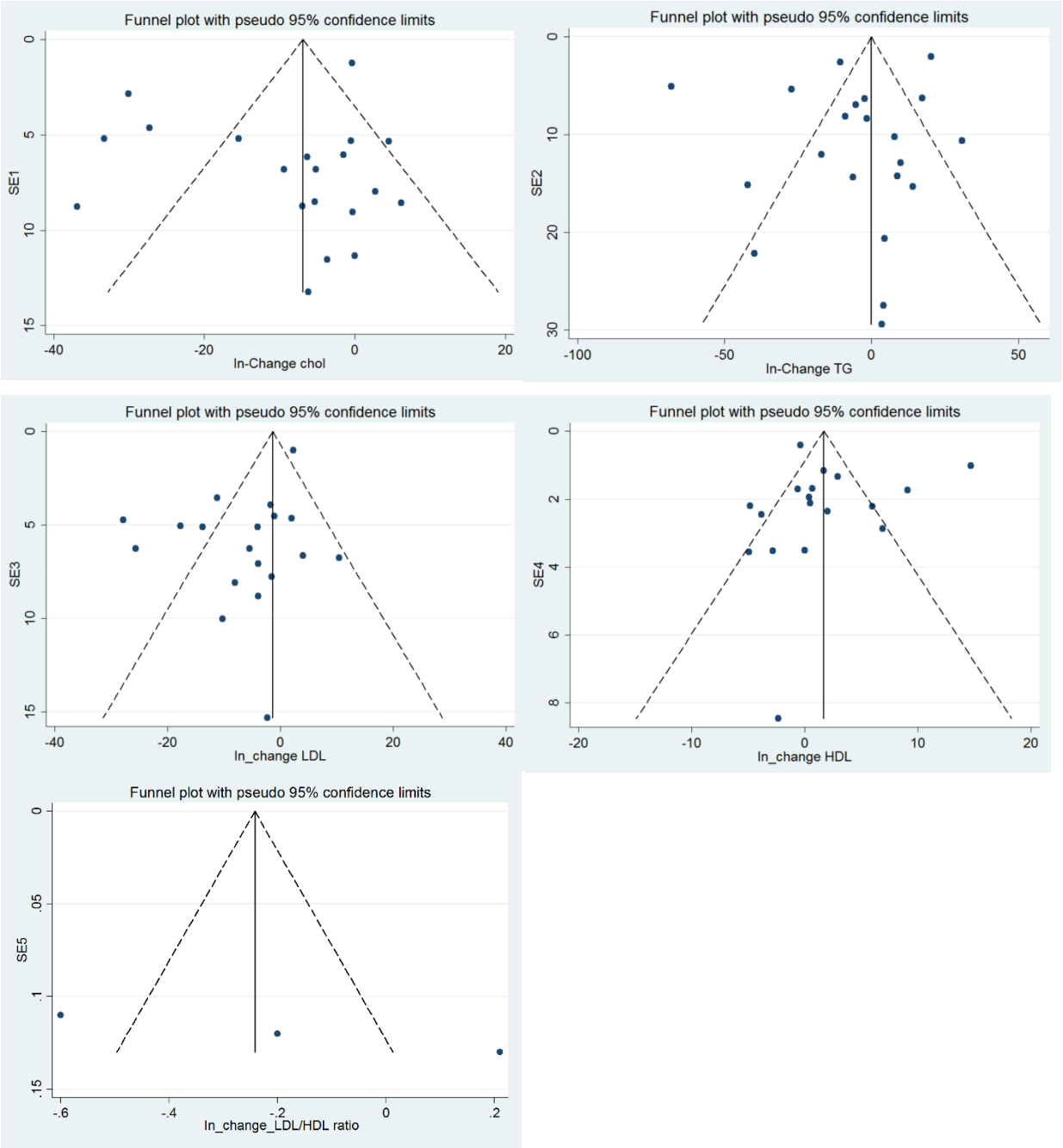


Figure 7. Funnel plot for the identification of publication bias in the trials on TC, LDL-C, HDL-C, and LDL-C/HDL-C ratio