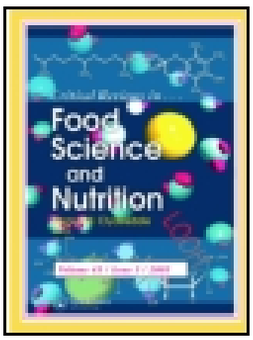

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REVIEW

The effects of quercetin supplementation on lipid profiles and inflammatory markers among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials

Reza Tabrizi[a], Omid Reza Tamtaji[b], Naghmeh Mirhosseini[c], Kamran B. Lankarani[d], Maryam Akbari[a], Seyed Taghi Heydari[d], Ehsan Dadgostar[e], and Zatollah Asemi[b]

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ABSTRACT

Aims: This systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to determine the effect of quercetin administration on lipid profiles and inflammatory markers among patients with metabolic syndrome (MetS) and related disorders.

Methods: We searched systematically online databases including Cochrane Library, EMBASE, MEDLINE, and Web of Science to identify the relevant RCTs until November 2018. *Q*-test and I^2 statistics were applied to assess heterogeneity among included studies. Data were combined using fixed- or random-effects model and presented as standardized mean difference (SMD) with 95% confidence interval (CI).

Results: Out of 591 citations, 16 RCTs were included in the meta-analysis. The pooled findings showed that quercetin consumption significantly decreased total-cholesterol (SMD = −0.98; 95% CI, −1.48, −0.49; $p < 0.001$; I^2: 94.0), LDL-cholesterol (SMD = −0.88; 95% CI, −1.35, −0.41; $p < 0.001$; I^2: 92.7) and C-reactive protein (CRP) levels (−0.64; 95% CI, −1.03, −0.25; $p = 0.001$; I^2: 90.2). While, quercetin supplementation did not significantly affect triglycerides (TG) (SMD = −0.32; 95% CI, −0.68, 0.04; $p = 0.08$; I^2: 84.8), HDL-cholesterol (SMD = 0.20; 95% CI, −0.20, 0.24; $p = 0.84$; I^2: 70.6), interleukin 6 (IL-6) (SMD = −0.69; 95% CI, −1.69, 0.31; $p = 0.17$; I^2: 94.5) and tumor necrosis factor-alpha (TNF-α) levels (SMD = −0.06; 95% CI, −0.25, 0.14; $p = 0.58$; I^2: 35.6)

Conclusions: In summary, the current meta-analysis demonstrated that quercetin supplementation significantly reduced total-cholesterol, LDL-cholesterol, and CRP levels, yet did not affect triglycerides, HDL-cholesterol, IL-6 and TNF-α among patients with MetS and related disorders.

KEYWORDS
Quercetin; metabolic syndrome; lipid profiles; inflammatory markers; meta-analysis

Introduction

Dyslipidemia, defined as elevated levels of triglycerides and cholesterol (particularly LDL-cholesterol), and reduced levels of HDL-cholesterol, has been introduced as a strong risk factor for the commencement and progression of atherosclerosis, which in turn results in cardiovascular disease (CVD) (Stokes et al. 2002; Stapleton et al. 2010). In addition, hypercholesterolemia is correlated with overproduction of free radicals, reactive oxygen species (ROS) and inflammatory markers which subsequently leads to increased oxidative damage (Yildirim, Senchenkova, and Granger 2016; Mollazadeh et al. 2018). On the other hand, increased circulating markers of inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are consistently linked to the risk of hypertension, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS) and CVD (Shai et al. 2005; Ridker 2009).

Among bioflavonoids, quercetin is known to have the highest antioxidative properties (Morel et al. 1993). Quercetin belongs to flavonols that exists amply in apples, berries, onions, red wine, cabbage and nuts (Naderi et al. 2003). An extensive variety of quercetin activities has been claimed, including anti-inflammatory, antioxidative, antiatherosclerotic and anticarcinogenic effects (Lotito and Frei 2006; Mamani-Matsuda et al. 2006). In a study conducted by Lu et al. (2015), consumption of quercetin-enriched onion juice for 8 weeks significantly attenuated total-, LDL- and HDL-cholesterol levels in healthy individuals with mild hypercholesterolemia. Furthermore, consuming quercetin-rich foods in obese post-menopausal women upregulated LDL receptor expression and decreased the levels of LDL-cholesterol (Arai et al. 2000). The results of a meta-analysis consisting of seven randomized controlled trials (RCTs) indicated a significant reduction of circulating CRP concentrations in both healthy and ill individuals following

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quercetin supplementation (Mohammadi-Sartang et al. 2017). While, quercetin administration at a dosage of 250 mg/day for 8 weeks did not influence glycemic control and lipid profiles among patients with T2DM (Mazloom et al. 2014). In another study, 500 mg/day quercetin supplementation for 10 weeks significantly reduced systolic blood pressure, but had no impact on other cardiovascular risk factors and inflammatory cytokines in diabetic patients (Zahedi et al. 2013). The differences in study design, population characteristics, the dosage of quercetin utilized, and the duration of intervention might explain the discrepancies among the results of published trials.

To our best knowledge, there is no published systematic review or meta-analysis assessing the effect of quercetin administration on lipid profiles and inflammatory markers in human. Thus, the current meta-analysis was carried out to summarize the present evidence of RCTs regarding the effects of quercetin administration on lipid profiles and inflammatory markers among patients with metabolic disorders.

Materials and methods

Search strategy and study selection

We searched systematically online databases including Cochrane Library, EMBASE, MEDLINE, and Web of Science until November 2018 to identify the relevant RCTs investigating the effects of quercetin supplementation on lipid profiles and inflammatory markers. Literature reviews were conducted using the following MeSH and text words: patients ["metabolic disease" OR "Mets" OR "diabetes" OR "T2DM" OR "overweight" OR "obese" OR "polycystic ovary syndrome (PCOS)" OR "hypertension" OR "blood pressure (BP)" OR "coronary heart disease (CHD)" OR "chronic kidney disease (CKD)" OR "non-alcoholic fatty liver disease (NAFLD)" OR "hypercholesterolemia"], intervention ["quercetin" AND "intake" OR "supplementation"], and outcomes ["triglycerides (TG)" OR "total cholesterol" OR "LDL-cholesterol" OR "HDL-cholesterol" OR "CRP" OR "IL-6" OR "TNF-α"]. To reduce the chance of missing any relevant study, we searched manually the reference lists of included articles. Also we searched for the findings of ongoing RCTs in the following databases: International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs. There were no limitations for the date and the language of the publications when searches were conducted. The search and selection of RCTs were performed by two independent reviewers (R.T. and E.D.). Any disagreements resolved through the discussion with a third reviewer (Z.A.).

Inclusion criteria

Clinical trials that met the following inclusion criteria were included in the meta-analysis: original human studies with a RCT design (either parallel or cross-over), treatment and control groups were administered quercetin supplement and placebo, respectively, and clinical trial reported means, SDs, standard error of the mean (SEMs), or related 95% confidence intervals (CIs) for intervention and placebo groups at baseline and end of the intervention for triglycerides, total-, LDL-, HDL-cholesterol, CRP, TNF-α, and IL-6 levels among patients with MetS and related disorders. Animal experiments, *in vitro* studies, case reports, case series, observational studies, trial protocols or abstracts without findings, and clinical trials did not have a control group were excluded from the meta-analysis.

Data extraction and quality assessment

The authors used the Cochrane Collaboration risk of bias tool to evaluate the quality of the included RCTs, using the following risk of bias items: 'randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, and the other sources of bias'. Data were extracted, using a standard excel form, included: first author's name, publication year, location of the study, age, study design, number of subjects (in both intervention and placebo groups), type of intervention, dosage and duration of the supplementation, type of disease, the mean (SD) changes of lipid profiles and inflammatory markers between intervention and control groups. If studies outcomes were reported by various strata of variables such as dose, type, and duration of intervention, each strata was considered as a separate trial in the current meta-analysis.

Data synthesis and statistical analysis

All statistical analyses were performed using STATA version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). Pooled effect size was defined as the standardized mean difference (SMD) with 95% CI calculated using fixed- or random-effects model. Heterogeneity among included studies was statistically assessed using Cochran's Q and I^2 tests. The source of heterogeneity was explored using subgroup analyses according to some of the potential moderator variables including type of intervention (quercetin enriched onion juice vs. quercetin plus other nutrients vs. quercetin), dosage of intervention (<100 mg/day vs. 101–250 mg/day vs. >250 mg/day), duration of intervention (≤8 vs. >8 weeks), type of disease (hypercholesterolemic vs. obese or overweight vs. other disease), and type of study (parallel vs. cross-over design). Sensitivity analyses were used to examine the influence of each trial on the validity of the pooled SMDs. Egger's regression test was applied to identify evidence of possible publication bias among included trials. p Values less than 0.05 were considered statistically significant.

Results

Out of 591 potential reports, after checking titles and abstracts and removing duplicates or irrelevant articles, 16 articles (or 24 effect sizes) were eligible to be included in the

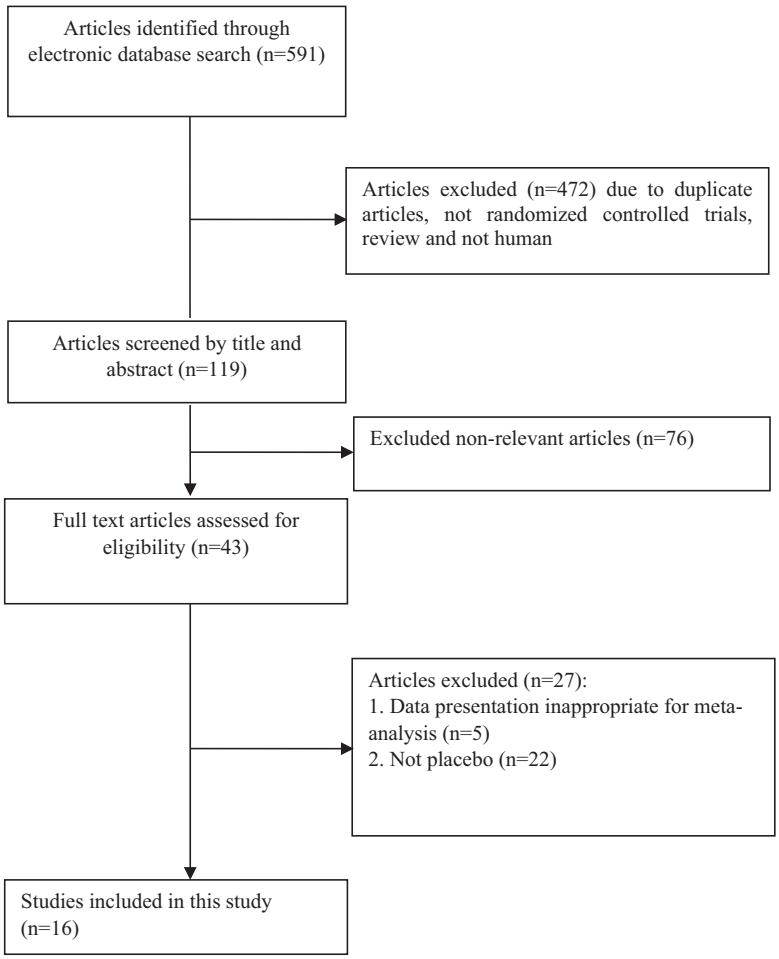


Figure 1. Literature search and review flowchart for selection of studies.

current meta-analysis. The flowchart of step by step process of RCTs identification and selection is illustrated in Figure 1.

Sixteen studies were randomized, placebo-controlled trial, of them eight studies were conducted using parallel design and other eight cross-over. Considering 24 trials included in the meta-analysis, the overall number of subjects was 1575, of which 790 subjects were in intervention group and 785 control group. Eighteen trials determined the effects of quercetin supplementation on triglyceride (Clifton 2004; Edwards et al. 2007; Egert et al. 2010; Qureshi et al. 2013; Zahedi et al. 2013; Mazloom et al. 2014; Lu et al. 2015; Chekalina et al. 2016; Cialdella-Kam et al. 2016; Cicero et al. 2016; Brüll et al. 2017a), twenty-one on total cholesterol (Clifton 2004; Edwards et al. 2007; Egert et al. 2009; Egert et al. 2010; Qureshi et al. 2013; Zahedi et al. 2013; Mazloom et al. 2014; Brüll et al. 2015; Lu et al. 2015; Chekalina et al. 2016; Cialdella-Kam et al. 2016; Cicero et al. 2016; Brüll et al. 2017a; Nieman et al. 2017), twenty on LDL- and HDL-cholesterol (Clifton 2004; Edwards et al. 2007; Egert et al. 2009; Egert et al. 2010; Qureshi et al. 2013; Zahedi et al. 2013; Mazloom et al. 2014; Brüll et al. 2015; Lu et al. 2015; Chekalina et al. 2016; Cialdella-Kam et al. 2016; Cicero et al. 2016; Brüll et al. 2017b), fifteen on CRP (Egert et al. 2009; Egert et al. 2010; Qureshi et al. 2013; Zahedi et al. 2013; Brüll et al. 2015; Cialdella-Kam et al. 2016; Cicero et al. 2016; Brüll et al. 2017b; Nedoborenko et al. 2017; Nieman et al. 2017), five on IL-6 (Zahedi et al. 2013; Cialdella-Kam et al. 2016; Nedoborenko et al. 2017; Nieman et al. 2017), and seven on TNF-α levels (Egert et al. 2009; Egert et al. 2010; Zahedi et al. 2013; Chekalina et al. 2016; Cialdella-Kam et al. 2016; Brüll et al. 2017b). The dosage of quercetin varied from 3.12 to 3000 mg/day, and the duration of intervention with quercetin supplements ranged from a few hours to 12 weeks. Eight trials were performed among patients with hypercholesterolemia, eleven obese or overweight individuals, and six participants with other diseases. Table 1 shows the characteristics of included RCTs.

Main outcomes

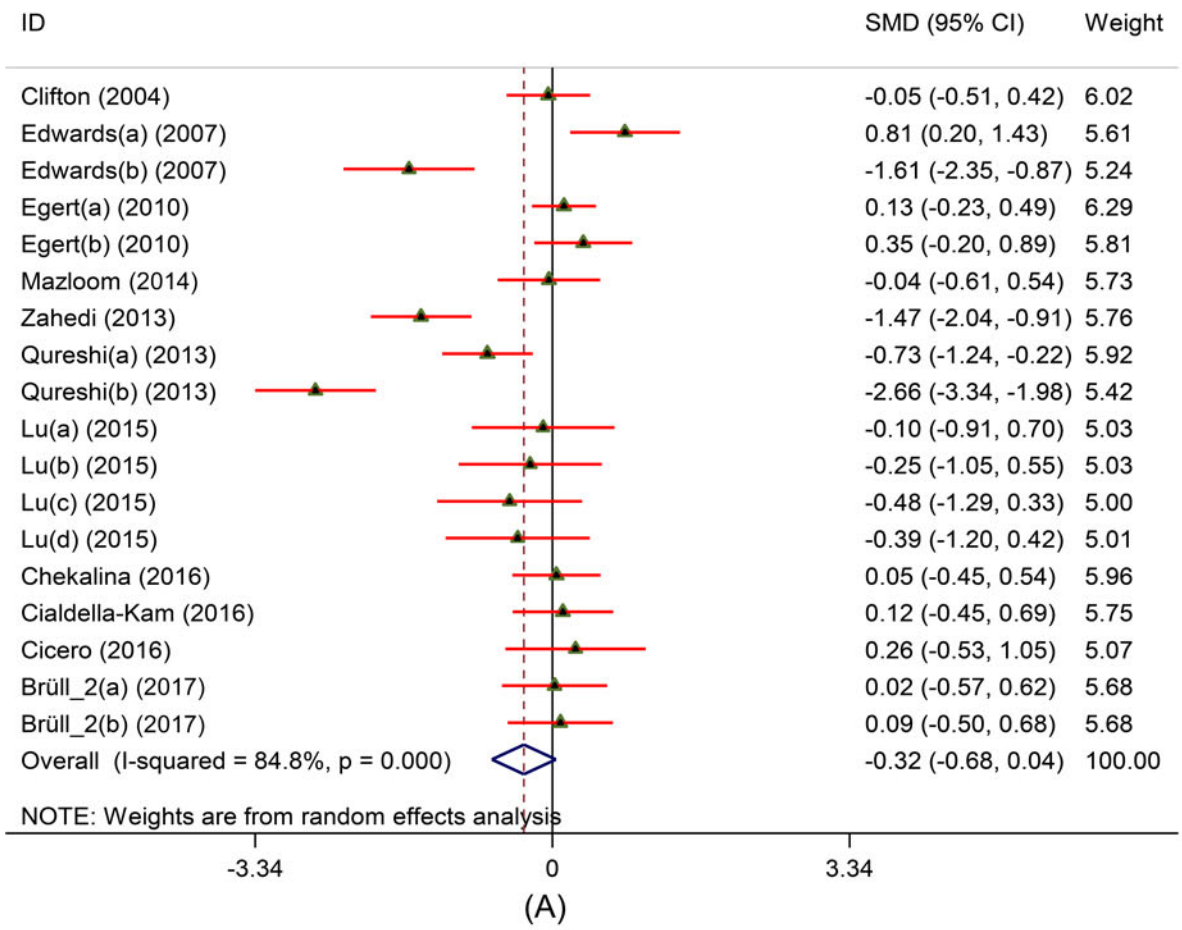
Pooled effects of quercetin on lipid profiles

The forest plots indicating the effect of quercetin supplementation on lipid profiles are illustrated in Figure 2. We found that quercetin consumption significantly decreased total (SMD = −0.98; 95% CI, −1.48, −0.49; $p < 0.001$; I^2: 94.0) and LDL-cholesterol levels (SMD = −0.88; 95% CI, −1.35, −0.41; $p < 0.001$; I^2: 92.7). However, the pooled

Table 1. Characteristics of included studies.

References	Publication year	Sample size (control/ intervention)	Country/population	Intervention/ daily dose	Duration	Presented data	Age (y) (control, intervention)
Chekalina et al. (2016)	2016	33/30	Ukraine/CVD	Quercetin/3000 mg	8 weeks	TG, TC, LDL-C, HDL-C, TNF-α	Aged (48–72)
Cialdella-Kam et al. (2016)	2016	24/24	USA/obese	Quercetin plus other nutrients/ 1000 mg	10 weeks	TG, TC, LDL-C, HDL-C, CRP, TNF-α, and IL-6	55.3 ± 7.3, 56.9 ± 9.3
Cicero et al. (2016)	2016	13/12	Italy/HCH	Quercetin plus other nutrients/50 mg	4 weeks	TG, TC, LDL-C, HDL-C, and CRP	53.65 ± 8.67, 52.78 ± 8.33
Lu et al. (2015) (a)	2015	12/12	China/HCH	Quercetin rich onion juice/3.12 mg	2 weeks	TG, TC, LDL-C, HDL-C	Aged (35–55)
Lu et al. (2015) (b)	2015	12/12	China/HCH	Quercetin rich onion juice/3.12 mg	6 weeks	TG, TC, LDL-C, HDL-C	Aged (35–55)
Lu et al. (2015) (c)	2015	12/12	China/HCH	Quercetin rich onion juice/3.12 mg	8 weeks	TG, TC, LDL-C, HDL-C	Aged (35–55)
Lu et al. (2015) (d)	2015	12/12	China/HCH	Quercetin rich onion juice/3.12 mg	10 weeks	TG, TC, LDL-C, HDL-C	Aged (35–55)
Mazloom et al. (2014)	2014	21/26	Iran/T2DM	Quercetin/250 mg	8 weeks	TG, TC, LDL-C, HDL-C	51.5 ± 8.6, 52.9 ± 7.0
Nedoborenko et al. (2017)	2017	15/15	Ukraine/obese	Quercetin plus other nutrients/4 mg	3 days ± 60th	CRP and IL-6	40.3 ± 7.59
Nieman et al. (2017) (a)	2017	52/51	USA/obese	Quercetin plus other nutrients/104 mg	12 weeks	TC, CRP, and IL-6	50.3 ± 1.6, 50.3 ± 2.0
Nieman et al. (2017) (b)	2017	52/51	USA/obese	Quercetin plus other nutrients/104 mg	4 weeks	CRP and IL-6	50.3 ± 1.6, 50.3 ± 2.0
Zahedi et al. (2013)	2013	28/34	Iran/T2DM	Quercetin/500 mg	10 weeks	TG, TC, LDL-C, HDL-C, CRP, TNF-α, and IL-6	46.4 ± 4.5
Brüll et al. (2015)	2015	68/68	Germany/obese and (pre-HTN)	Quercetin/162 mg	6 weeks	TC, LDL-C, HDL-C, and CRP	47·4 ± 10·5
Brüll et al. (2017a) (b)	2017	68/68	Germany/obese and (pre-HTN)	Quercetin/162 mg	6 weeks	CRP and TNF-α,	47.4 ± 10.5
Brüll et al. (2017b) (a)	2017	22/22	Germany/obese and (HTN)	Quercetin/54 mg	2 h postprandial	TG, TC, LDL-C, HDL-C, and CRP	48.1 ± 10.9
Brüll et al. (2017b) (b)	2017	22/22	Germany/obese and (HTN)	Quercetin/54 mg	4 h postprandial	TG, TC, LDL-C, HDL-C, and CRP	48.1 ± 10.9
Clifton (2004)	2004	35/35	Australia/HCH or HTN	Quercetin plus other nutrients/ 1000 mg	12 weeks	TG, TC, LDL-C, and HDL-C	58
Edwards et al. (2007) (a)	2007	22/22	USA/HTN	Quercetin/730 mg	12 weeks	TG, TC, LDL, and HDL-C	49.2 ± 2.9
Edwards et al. (2007) (b)	2007	19/19	USA/pre-HTN	Quercetin/730 mg	12 weeks	TG, TC, LDL, and HDL-C	47.8 ± 3.5
Egert et al. (2009) (b)	2009	93/93	Germany/ overweight	Quercetin/150 mg	6 weeks	TC, LDL-C, HDL-C, CRP, and TNF-α	45·1 ± 10·53
Egert et al. (2010) (a)	2010	60/60	Germany/over-weight with apoE3 phenotypes	Quercetin/150 mg	6 weeks	TG, TC, LDL-C, HDL-C, CRP, and TNF-α	45 ± 10.5
Egert et al. (2010) (b)	2010	26/26	Germany/over-weight with apoE4 phenotypes	Quercetin/150 mg	6 weeks	TG, TC, LDL-C, HDL-C, CRP, and TNF-α	45 ± 10.5
Qureshi et al. 2013) (a)	2013	32/32	Pakistan/(sub-group c)	Quercetin plus other nutrients/50 mg	6 weeks	TG, TC, LDL-C, HDL-C, and CRP	58.15 ± 0.77
Qureshi et al. (2013) (b)	2013	32/32	Pakistan/HCH (sub-group D)	Quercetin plus other nutrients/50 mg	6 weeks	TG, TC, LDL-C, HDL-C, and CRP	57.14 ± 1.33

CAD, coronary artery disease; HCH, hypercholesterolemic; T2DM, type 2 diabetes mellitus; pre-HTN, pre-hypertension; TG, triglycerides; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; CRP, C-reactive protein; IL-6, interlokin-6; TNF-α, tumor necrosis factor alpha.



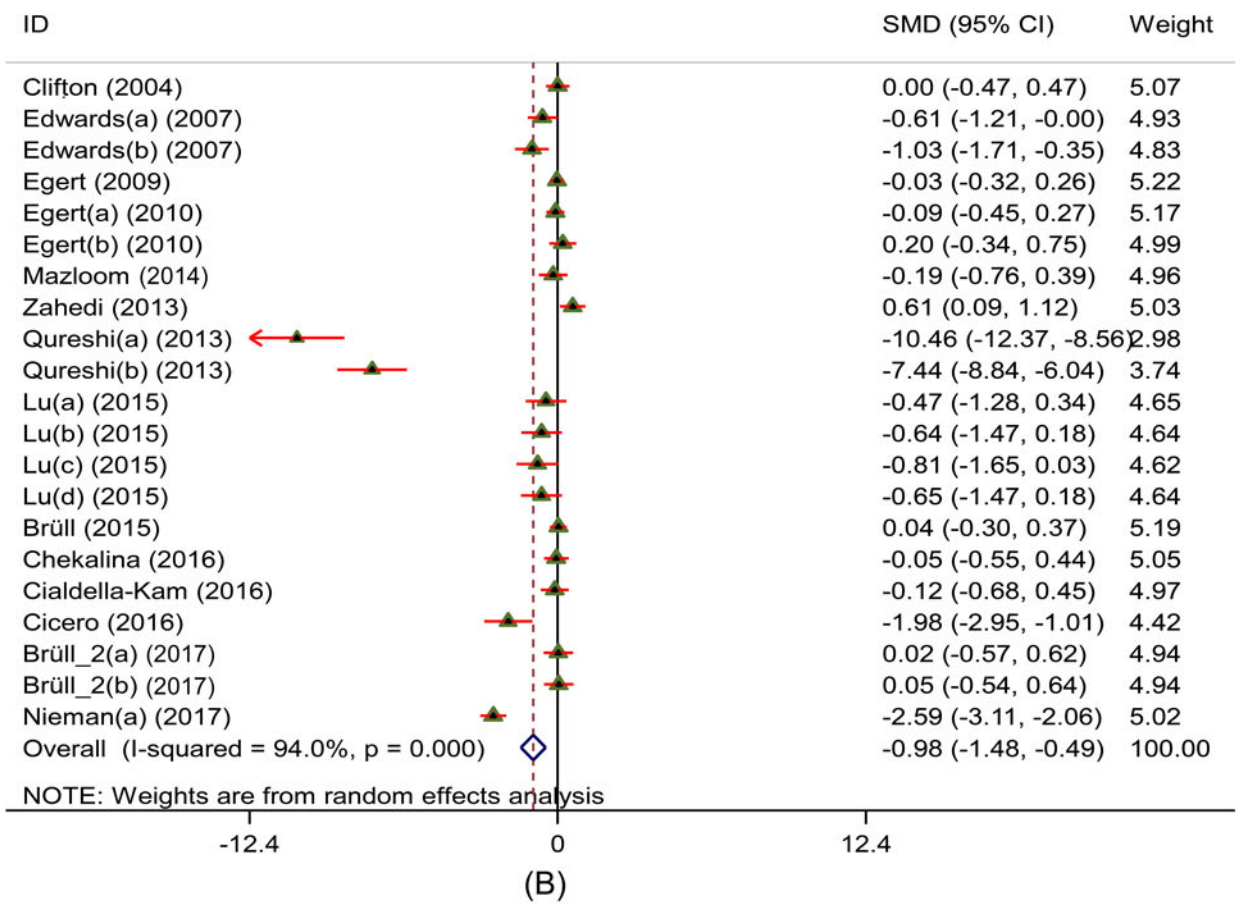
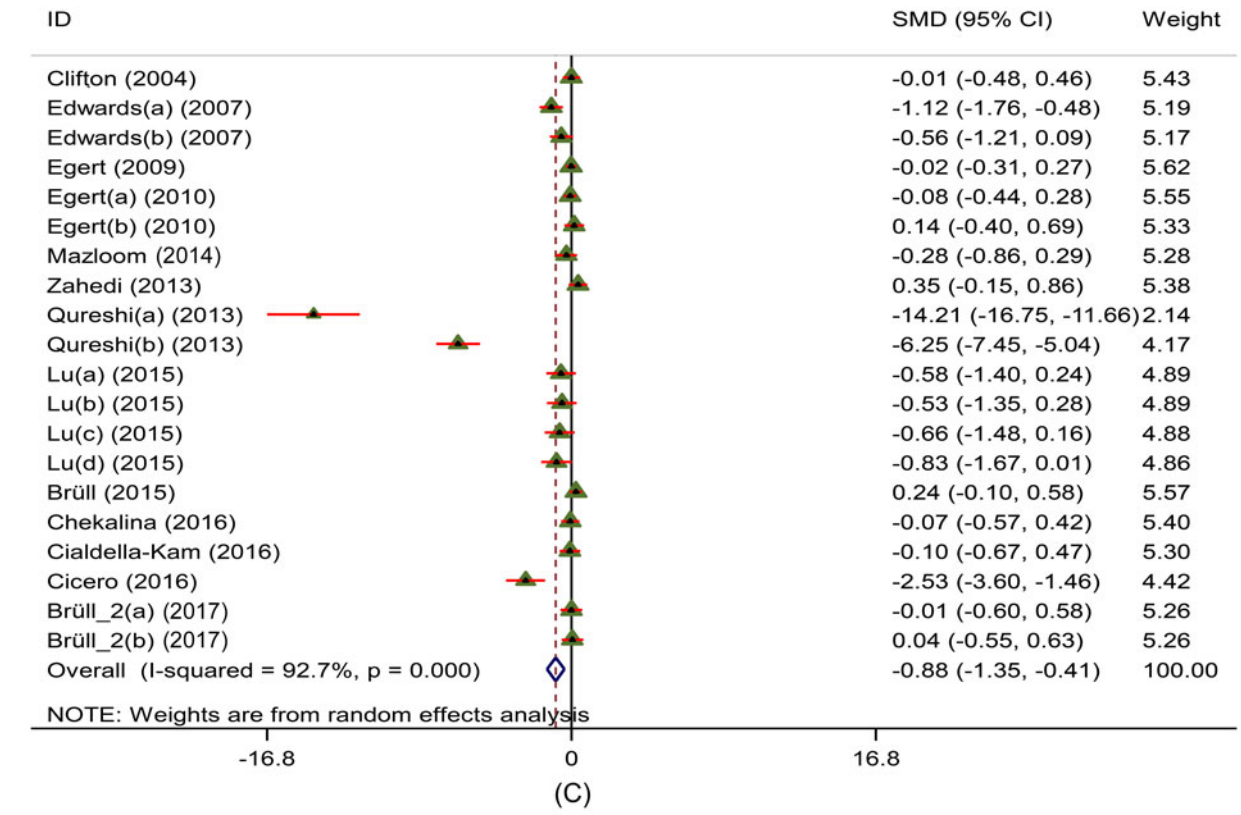


Figure 2. Meta-analysis lipid profiles and inflammatory markers standardized mean differences estimates for (A) triglycerides, (B) total-, (C) LDL-, (D) HDL-cholesterol, (E) CRP, (F) IL-6, and (G) TNF-α levels in quercetin and control groups (CI = 95%).



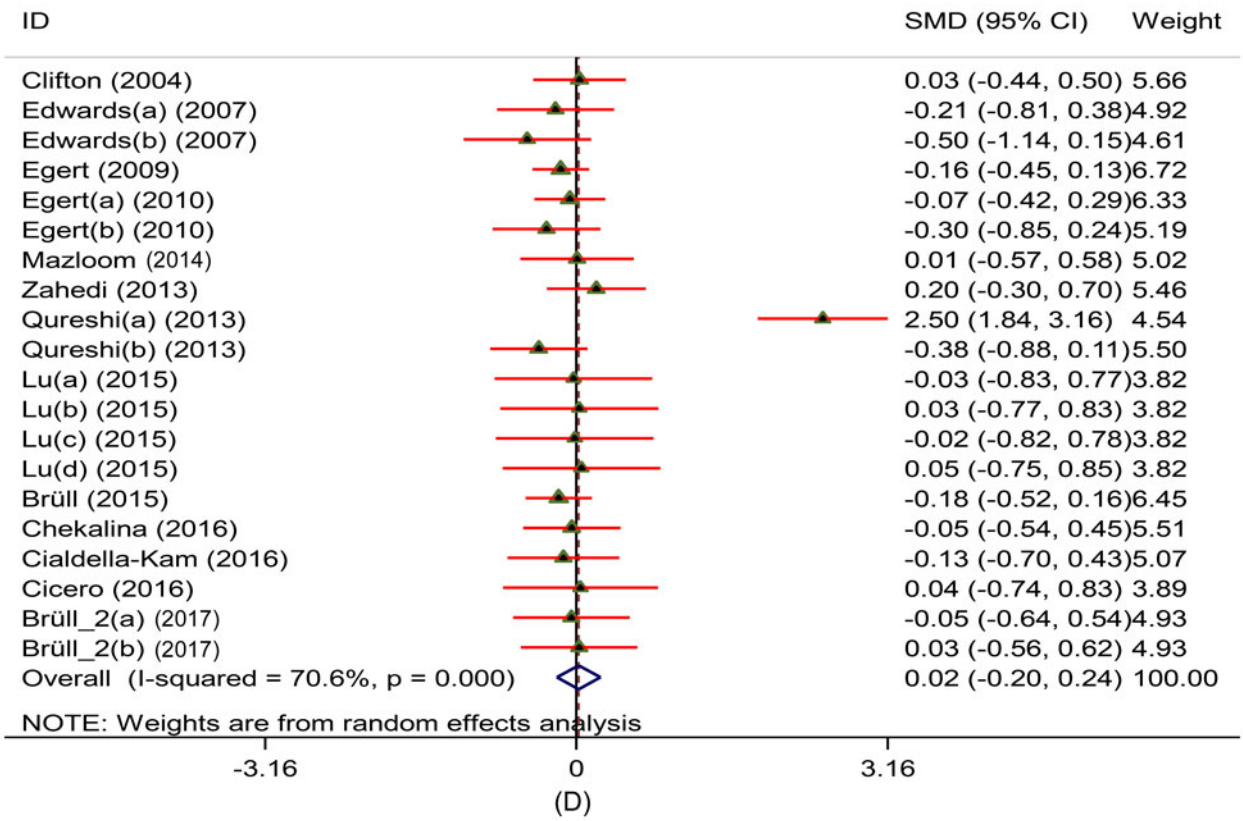
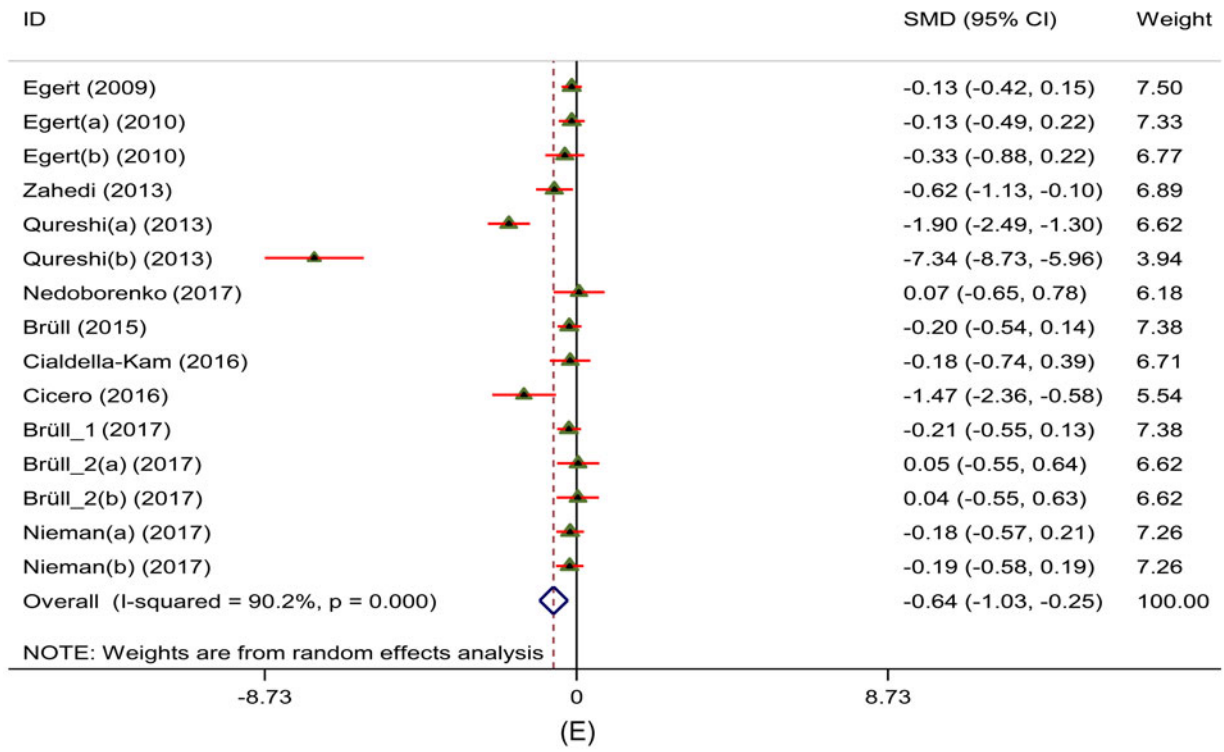
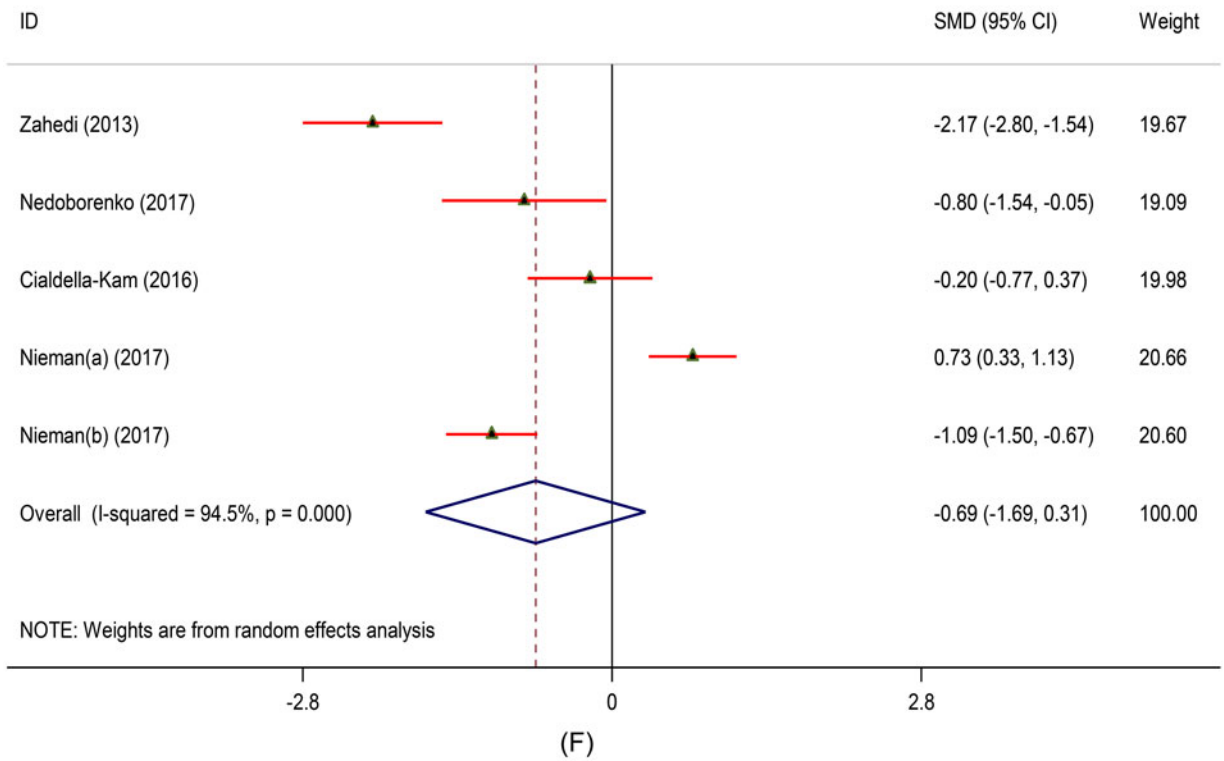


Figure 2. Continued.

findings showed no significant effect of quercetin supplementation on triglycerides (SMD = −0.32; 95% CI, −0.68, 0.04; $p = 0.08$; I^2: 84.8) and HDL-cholesterol levels (SMD = 0.20; 95% CI, −0.20, 0.24; $p = 0.84$; I^2: 70.6). Because of the evidence of significant heterogeneity across included trials for lipid profiles, random-effects model was used to pool data. Estimation of the influences of quercetin consumption on the studied markers in both intervention and placebo



(E)



(F)

Figure 2. Continued.

groups (SMD) at baseline and end of intervention are presented in Table 2.

For total-, LDL-, and HDL-cholesterol levels, findings of sensitivity analyses remained consistent after excluding each trial. For triglyceride, after excluding Edwards et al.$_{(a)}$ study (Edwards et al. 2007) the pooled effect size significantly changed to SMD = −0.38; 95% CI, −0.74, −0.02.

Pooled effects of quercetin on inflammatory markers

The pooled effect of quercetin consumption on CRP levels was estimated using fifteen trials. There was a significant reduction in CRP levels (SMD = −0.64; 95% CI, −1.03, −0.25; $p = 0.001$; I^2: 90.2) among patients supplemented with quercetin compared to placebo groups. However, we found that quercetin supplementation did not statistically

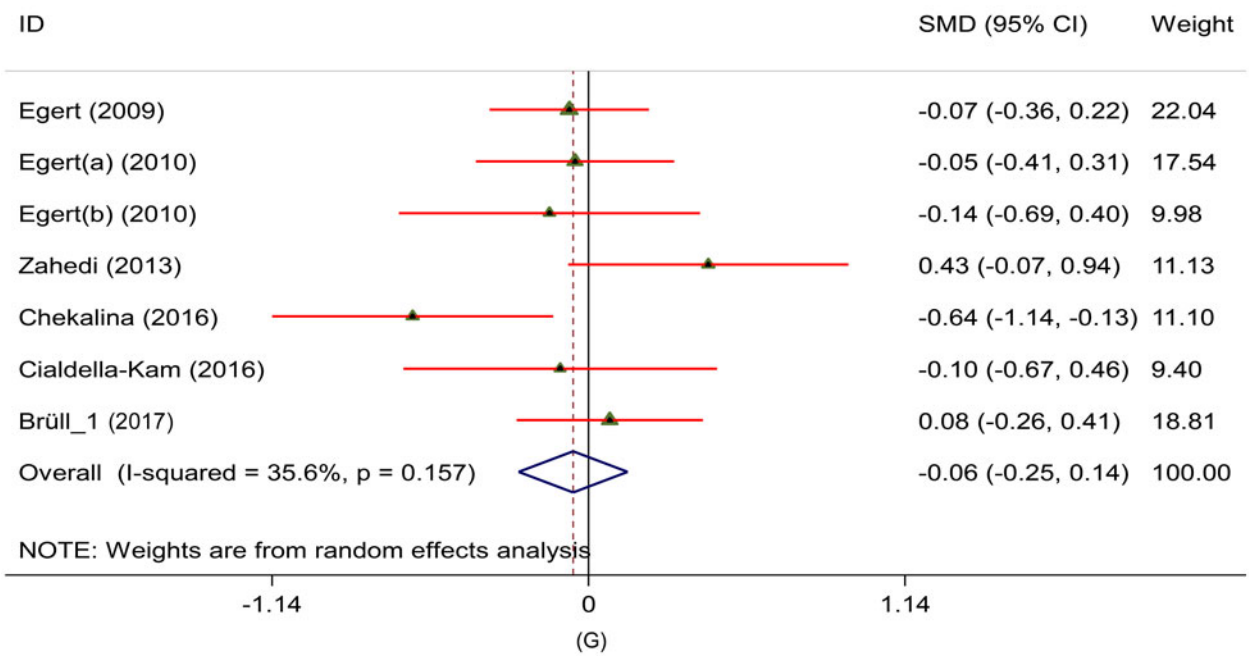


Figure 2. Continued.

Table 2. Estimation of the effects of quercetin supplementation on lipid profiles and inflammatory markers with confidence interval 95% between the intervention and control groups.

Parameter		Number of study	Standardized mean difference	95% CI	Heterogeneity I^2 (%)	Heterogeneity Q	Heterogeneity p-value
Triglyceride	Intervention group (after vs. before)	17	−0.30	−0.71, 0.71	88.4	137.75	<0.001
	Placebo group (after vs. before)	17	0.06	−0.23, 0.35	76.2	67.25	<0.001
	Intervention vs. placebo group	18	−0.32	−0.68, 0.04	84.8	111.90	<0.001
Total cholesterol	Intervention group (after vs. before)	20	−1.00	−1.50, −0.51	93.7	303.22	<0.001
	Placebo group (after vs. before)	20	−0.31	−0.69, 0.07	90.2	193.60	<0.001
	Intervention vs. placebo group	21	−0.98	−1.48, −0.49	94.0	331.05	<0.001
LDL-cholesterol	Intervention group (after vs. before)	19	−0.83	−1.31 , −0.36	92.8	248.75	<0.001
	Placebo group (after vs. before)	19	−0.24	−0.58, 0.09	86.8	136.07	<0.001
	Intervention vs. placebo group	20	−0.88	−1.35, −0.41	92.7	261.72	<0.001
HDL-cholesterol	Intervention group (after vs. before)	19	0.19	−0.19, 0.58	89.7	175.28	<0.001
	Placebo group (after vs. before)	19	0.12	−0.13, 0.36	76.1	75.46	<0.001
	Intervention vs. placebo group	20	0.20	−0.20, 0.24	70.6	64.67	<0.001
CRP	Intervention group (after vs. before)	14	−0.45	−0.91, 0.01	92.8	180.13	<0.001
	Placebo group (after vs. before)	14	0.11	−0.05, 0.27	47.2	24.60	0.02
	Intervention vs. placebo group	15	−0.64	−1.03, −0.25	90.2	142.68	<0.001
IL-6	Intervention group (after vs. before)	5	−0.67	−2.06 , 0.73	96.9	130.23	<0.001
	Placebo group (after vs. before)	5	−0.28	−1.57, 1.01	0.00	112.99	<0.001
	Intervention vs. placebo group	5	−0.69	−1.69, 0.31	94.5	72.72	<0.001
TNF-α	Intervention group (after vs. before)	7	−0.61	−1.21, −0.01	92.5	79.91	<0.001
	Placebo group (after vs. before)	7	−0.39	−0.90, 0.11	89.5	57.25	<0.001
	Intervention vs. placebo group	7	−0.06	−0.25, 0.14	35.6	9.32	0.01

affect IL-6 (SMD = −0.69; 95% CI, −1.69, 0.31; $p = 0.17$; I^2: 94.5) and TNF-α levels (SMD = −0.06; 95% CI, −0.25, 0.14; $p = 0.58$; I^2: 35.6) (Figure 2). Due to the heterogeneity existing across included trials, random-effects model was used to pool the data showing the effect of quercetin supplementation on inflammatory markers. Sensitivity analyses indicated no change in the pooled effect of inflammatory markers, expect for IL-6, which changed significantly after excluding Nieman et al.$_{(b)}$ study (Nieman et al. 2017) (SMD = −1.06; 95% CI, −1.82, −0.29). The lower and higher pooled SMD for lipid profiles and inflammatory markers in post-sensitivity analysis are summarized in Table 3.

Subgroup analyses for lipid profiles and inflammatory markers

Subgroup analyses for lipid profiles and inflammatory markers were done based on potential moderator variables including type of intervention, dosage and duration of supplementation, type of disease, and type of study design. The findings of subgroup analyses did not indicate any statistically significant subgroup-effect interaction for triglycerides, HDL-cholesterol, and TNF-α. However, type and dosage of intervention for total-, LDL-cholesterol, and CRP, duration of intervention for total-, LDL-cholesterol, and IL-6, also type of disease for total- and LDL-

Table 3. The effects of quercetin supplementation on lipid profiles and inflammatory markers based on sensitivity analysis.

	Pre-sensitivity analysis				Post-sensitivity analysis		
Variables	No. of studies included	Pooled SMD (random effect)	95% CI	Upper and lower of effect size	Pooled SMD (random effect)	95% CI	Excluded studies
Triglycerides	18	−0.32	−0.68, 0.04	Upper	−0.17	−0.46, 0.10	Qureshi et al. (2013) (b)
				Lower	−0.38	−0.74, −0.02	Edwards et al. (2007) (a)
Total cholesterol	21	−0.98	−1.48, −0.49	Upper	−0.65	−1.07, −0.24	Qureshi et al. (2013) (a)
				Lower	−1.07	−1.58, −0.55	Zahedi (2013)
LDL-cholesterol	20	−0.88	−1.35, −0.41	Upper	−0.53	−0.89, −0.17	Qureshi et al. (2013) (a)
				Lower	−0.97	−1.47, −0.46	Brüll et al. (2015)
HDL-cholesterol	20	0.20	−0.20, 0.24	Upper	0.04	−0.18, 0.27	Edwards et al. (2007) (b)
				Lower	−1.08	−0.22, 0.01	Qureshi et al. (2013) (a)
CRP	15	−0.64	−1.03, −0.25	Upper	−0.33	−0.55, −0.11	Qureshi et al. (2013) (b)
				Lower	−0.70	−1.13, −0.26	Egert et al. (2009)
IL-6	5	−0.69	−1.69, 0.31	Upper	−0.32	−1.25, 0.60	Zahedi et al. (2013)
				Lower	−1.06	−1.82, −0.29	Nieman et al. (2017) (a)
TNF-α	7	−0.06	−0.25, 0.14	Upper	0.01	−0.15, 0.16	Chekalina et al. (2016)
				Lower	−0.10	−0.27, 0.06	Zahedi et al. (2013)

cholesterol was significantly affected by subgroup-effect interactions (Table 4).

Publication bias and risk of bias assessment

There was no evidence of publication bias for assessing the effects of quercetin consumption on triglycerides ($B = -2.99$, $p = 0.27$), HDL-cholesterol ($B = 1.44$, $p = 0.30$), IL-6 ($B = -7.95$, $p = 0.40$), TNF-α levels ($B = -0.70$, $p = 2.02$) using Egger's regression test in current meta-analyses. However, the existence of publication biases was determined using Egger's linear regression for total-cholesterol ($B = -6.93$, $p = 0.001$), LDL-cholesterol ($B = -7.07$, $p < 0.001$), and CRP levels ($B = -5.79$, $p = 0.01$). The authors used non parametric method (Duval and Tweedie) to estimate the results of censored trials for parameters with publication bias. Findings showed that the overall pooled SMDs for theses parameters did not significantly change between pre- and post-included censored trials. Details of the methodological quality assessment of all included trials based on authors' judgments are presented in Figure 3.

Discussion

To our best knowledge, this is the first meta-analysis of RCTs assessing the effect of quercetin supplementation on lipid profiles and inflammatory markers in patients with MetS and related disorders. The current meta-analysis demonstrated that quercetin supplementation significantly reduced total-, LDL-cholesterol, and CRP levels, yet did not affect other lipid profiles and inflammatory markers in these patients.

Effects on lipid profiles

Existing evidence are promising regarding the effect of quercetin on total- and LDL-cholesterol levels, yet triglycerides and HDL-cholesterol levels might not be influenced by quercetin among patients with MetS and related disorders. Hypolipidemic effects of quercetin intake in human clinical studies have been controversial. Supplements with quercetin-rich onion powder in hyperlipidemic patients (Lee et al. 2008), grape juice in both hemodialysis patients and healthy subjects (Castilla et al. 2006), and grape powder in pre- and postmenopausal women (Zern et al. 2005) have demonstrated beneficial effects on lipid profiles in human studies. Besides current evidence of controlled clinical studies, epidemiological evidence has indicated that consumption of dietary quercetin is negatively correlated with circulating levels of LDL-cholesterol (Arai et al. 2000). Lu et al. (2015) demonstrated that taking quercetin-rich onion juice for 8 weeks by healthy subjects with mild hypercholesterolemia significantly attenuated total-, LDL- and HDL-cholesterol levels. In addition, consuming quercetin-rich food in obese post-menopausal women upregulated LDL receptor expression and decreased LDL-cholesterol levels (Arai et al. 2000). A 10-week supplementation of 100 mg/day quercetin in healthy smoker males could significantly improve the components of lipid profiles, except triglycerides (Lee et al. 2011). However, daily supplementation with 250 mg quercetin for 8 weeks did not influence lipid profiles among patients with T2DM (Mazloom et al. 2014). Moreover, Egert et al. (2009) reported that 150 mg/day quercetin supplementation for 6 weeks resulted in no significant alterations in lipid profiles among overweight healthy subjects with high cardiovascular risk phenotype. The difference in dosages of quercetin used, the route of supplementation and the type of quercetin used (only

Table 4. The assess of quercetin supplementation on lipid profiles and inflammatory markers based on subgroup analysis.

Parameter	Triglycerides	Total-cholesterol	LDL-cholesterol	HDL-cholesterol	CRP	IL-6	TNF-α
Type of intervention							
Quercetin rich onion juice							
K	6	6	6	6	2	—	—
SMD	−0.13	−0.32	−0.33	−0.00	0.04	—	—
(95% CI)	(−0.42, 0.16)	(−0.62, −0.01)	(−0.63, −0.03)	(−0.29, 0.29)	(−0.38, 0.46)		
p-value	0.379	0.043	0.033	0.993	0.845	—	—
I^2	0.0	8.2	4.1	0.0	0.0	—	—
Q	1.99	5.44	5.21	0.07	0.00	—	—
Quercetin plus other nutrients							
K	5	6	5	5	7	4	1
SMD	−0.61	−3.59	−4.31	0.40	−1.44	−0.33	−0.10
(95% CI)	(−1.54, 0.33)	(−5.62, −1.56)	(−7.00, −1.62)	(−0.54, 1.35)	(−2.46, −0.42)	(−1.26, 0.61)	(−0.67, 0.46)
p-value	0.203	0.001	0.002	0.405	0.006	0.493	0.722
I^2	92.2	97.9	98.1	92.6	95.3	92.7	—
Q	51.52	233.51	210.80	53.92	27.69	41.03	0.00
Quercetin							
K	7	8	9	9	6	1	6
SMD	−0.24	−0.08	−0.10	−0.13	−0.22	−2.17	−0.05
(95% CI)	(−0.83, 0.36)	(−0.32, 0.15)	(−0.34, 0.14)	(−0.27, 0.02)	(−0.37, −0.07)	(−2.80, −1.54)	(−0.28, 0.17)
p-value	0.435	0.491	0.411	0.081	0.004	<0.001	0.647
I^2	88.4	57.8	59.2	0.0	0.0	—	46.1
Q	111.90	18.98	19.61	3.96	3.03	72.72	9.28
Dosage of intervention							
<100 mg/day							
K	9	9	9	9	6	1	—
SMD	−0.48	−2.31	−2.50	0.24	−1.66	−0.80	—
(95% CI)	(−1.06, 0.11)	(−3.74, −0.88)	(−3.95, −1.05)	(−0.35, 0.83)	(−3.11, −0.21)	(−1.54, −0.05)	
p-value	0.109	0.001	0.001	0.421	0.025	0.036	—
I^2	84.5	96.1	96.2	85.2	95.9	—	—
Q	51.58	206.71	209.49	54.19	122.35	0.00	—
101–250 mg/day							
K	3	6	5	5	7	2	4
SMD	0.14	−0.43	0.02	−0.14	−0.18	−0.18	−0.03
(95% CI)	(−0.12, 0.41)	(−1.11, 0.25)	(−0.14, 0.19)	(−0.31, 0.03)	(−0.32, −0.05)	(−1.96, 1.61)	(−0.21, 0.14)
p-value	0.286	0.216	0.781	0.097	0.009	0.845	0.723
I^2	0.0	94.1	0.0	0.0	0.0	97.4	0.0
Q	0.92	84.34	0.517	0.83	0.49	38.47	0.63
>250 mg/day							
K	6	6	6	6	2	2	3
SMD	−0.34	−0.17	−0.22	−0.07	−0.41	−1.18	−0.10
(95% CI)	(−1.04, 0.36)	(−0.59, 0.25)	(−0.60, 0.16)	(−0.29, 0.15)	(−0.84, 0.02)	(−3.11, 0.75)	(−0.73, 0.53)
p-value	0.335	0.428	0.263	0.533	0.060	0.231	0.750
I^2	89.2	71.3	65.9	0.0	21.8	95.2	76.6
Q	46.28	17.45	14.68	3.27	1.28	20.64	8.53
Duration of intervention							
≤8							
K	12	14	14	14	12	2	5
SMD	−0.27	−1.20	−1.21	0.08	−0.76	−1.02	−0.11
(95% CI)	(−0.69, 0.15)	(−1.83, −0.56)	(−1.86, −0.56)	(−0.23, 0.38)	(−1.24, −0.27)	(−1.38, −0.66)	(−0.31, 0.09)
p-value	0.207	<0.001	<0.001	0.49	0.002	<0.001	0.277
I^2	83.4	94.5	94.7	78.8	92.2	0.0	27.1
Q	66.40	237.91	245.05	61.21	140.63	0.45	5.49
>8							
K	6	7	6	6	3	3	2
SMD	−0.42	−0.62	−0.33	−0.06	−0.30	−0.53	0.18
(95% CI)	(−1.16, 0.32)	(−1.45, 0.21)	(−0.77, 0.11)	(−0.30, 0.17)	(−0.57, −0.03)	(−2.17, 1.10)	(−0.34, 0.70)
p-value	0.266	0.142	0.141	0.54	0.031	0.524	0.500
I^2	88.7	93.1	69.9	0.0	1.3	96.5	47.6
Q	44.40	7	16.68	3.35	2.03	57.86	1.91
Type of disease							
Hypercholesterolemic							
K	7	7	7	7	3	—	—
SMD	−0.64	−3.07	−3.38	0.32	−3.50	—	—
(95% CI)	(−1.36, 0.09)	(−5.04, −1.11)	(−5.39, −1.36)	(−0.48, 1.12)	(−6.26, −0.74)		
p-value	0.085	0.002	0.001	0.435	0.013	—	—
I^2	85.7	96.5	96.6	88.6	96.4	—	—
Q	41.95	171.96	174.89	52.60	56.10	—	—
Obese or overweight							
K	5	8	7	7	11	4	5
SMD	0.14	−0.31	0.04	−0.13	−0.15	−0.33	−0.04
(95% CI)	(−0.08, 0.37)	(−0.85, 0.23)	(−0.12, 0.19)	(−0.29, 0.02)	(−0.28, −0.03)	(−1.26, 0.61)	(−0.21, 0.13)
p-value	0.210	0.265	0.654	0.091	0.015	0.493	0.657
I^2	0.0	91.9	0.0	0.0	0.0	92.7	0.0
Q	0.73	86.11	2.34	0.97	1.87	41.03	0.69

(*continued*)

Table 4. Continued.

Parameter	Triglycerides	Total-cholesterol	LDL-cholesterol	HDL-cholesterol	CRP	IL-6	TNF-α
Other diseases							
K	6	6	6	6	1	1	2
SMD	−0.37	−0.18	−0.25	−0.05	−0.62	−2.17	−0.10
(95% CI)	(−1.06, 0.32)	(−0.60, 0.24)	(−0.63, 0.14)	(−0.27, 0.17)	(−1.13, −0.10)	(−2.80, −1.54)	(−1.15, 0.96)
p-value	0.294	0.400	0.205	0.661	0.018	<0.001	0.849
I^2	88.9	71.4	66.1	0.0	—	—	88.3
Q	45.07	17.51	14.74	3.26	0.00	0.00	8.53
Type of study							
Parallel design							
K	9	10	9	9	6	5	3
SMD	−0.26	−0.67	−0.47	0.02	−0.34	−0.69	−0.10
(95% CI)	(−0.65, 0.12)	(−1.34, −0.01)	(−0.89, −0.05)	(−0.20, 0.23)	(−0.65, −0.04)	(−1.69, 0.31)	(−0.73, 0.53)
p-value	0.180	0.047	0.027	0.887	0.028	0.174	0.750
I^2	66.2	90.4	70.8	0.0	49.7	94.5	76.6
Q	23.64	93.68	27.39	0.89	9.93	72.72	8.53
Cross-over design							
K	9	11	11	11	9	—	4
SMD	−0.38	−1.31	−1.29	0.04	−0.87	–	−0.03
(95% CI)	(−0.98, 0.22)	(−2.05, −0.58)	(−2.04, −0.55)	(−0.32, 0.40)	(−1.48, −0.27)		(−0.21, 0.14)
p-value	0.209	<0.001	0.001	0.823	0.005	—	0.723
I^2	90.9	95.6	95.7	84.3	94.0	—	0.0
Q	88.17	229.50	233.69	63.54	132.71	–	0.63

quercetin or combined quercetin with other nutrients), study design, and characteristics of study populations are some of the possible reasons explaining discrepant results regarding the effect of quercetin on lipid profiles among these studies. Quercetin intake may activate AMP-activated protein kinase (AMPK) and prevent lipid accumulation in the liver (Zang et al. 2006). AMPK subsequently inhibits the activity of Acetyl-CoA carboxylase and carbohydrate response element-binding protein, and the gene expression of sterol regulatory element-binding transcription factor 1c (Browning and Horton 2004). In addition, quercetin intake may increase the gene expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ) (Beekmann et al. 2015). PPAR-γ plays main functions in the metabolism of lipid and insulin (Beekmann et al. 2015).

Effects on inflammatory markers

The current meta-analysis demonstrated that quercetin supplementation significantly reduced CRP levels, but did not affect IL-6 and TNF-α among patients with MetS and related disorders. Increased circulating inflammatory markers have been recognized as a strong predictor of cardiovascular disease (Venugopal, Devaraj, and Jialal 2005) which plays main functions in atherosclerotic progression (Pasceri, Willerson, and Yeh 2000). The potential role of quercetin intake in decreasing inflammation in animal (Das et al. 2013) and human (Askari et al. 2012) models, reinforces the hypothesis that quercetin supplementation may reduce CVD incidence and protect against atherosclerotic progression by decreasing the CRP levels. In a meta-analysis conducted by Mohammadi-Sartang et al. (2017), quercetin supplementation resulted in a significant reduction in the circulating CRP concentrations in both healthy and diseased individuals. The observed beneficial effect of quercetin intake on circulating CRP concentrations in the current meta-analysis was confirmed by previous experimental (Bhaskar et al. 2013) and RCTs findings (Zahedi et al. 2013). However, anti-inflammatory effects of quercetin intake are different in humans and animals (Rivera et al. 2008) which may be the result of diverse concentrations of inflammatory markers or physiological dissimilarities between animals and humans. The mechanisms by which quercetin may reduce CRP levels are not clear. Several mechanisms were claimed for the anti-inflammatory and potential CRP-lowering role of quercetin. Inhibiting nuclear factor-kB (NF-κB) signaling pathways, the reduction of leukotriene B4 formation in leukocytes (Loke et al. 2008) and suppression of nitric oxide production (Kumazawa, Kawaguchi, and Takimoto 2006) are some of the hypotheses that have been tested in experimental studies and RCTs. Quercetin and its metabolites at physiological levels can suppress the expression of key molecules involved in monocyte recruitment such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1 and monocyte chemoattractant protein-1 gene expression (Tribolo et al. 2008; Panicker et al. 2010; Chen et al. 2012). In addition, antioxidant properties of quercetin could be responsible for its anti-inflammatory effects. Quercetin was documented to suppress IκB kinase and C-Jun kinase which subsequently could result in the suppression of NF-κB activation (Peet and Li 1999; Yoshizumi et al. 2002). Quercetin has also significant effect on the attenuation of inflammatory processes initiated by the oxidized low-density lipoprotein and this effect is through regulating the Toll-like receptors-NF-κB signaling pathway (Bhaskar, Sudhakaran, and Helen 2016).

This meta-analysis had few limitations. There were few eligible RCTs and a modest number of participants to be included in the meta-analysis. Diverse range of doses of quercetin were administered for intervention in the included studies. Substantial heterogeneity was seen across studies, which was expected considering differences in participants' characteristics (e.g. gender, geographic region, genetic

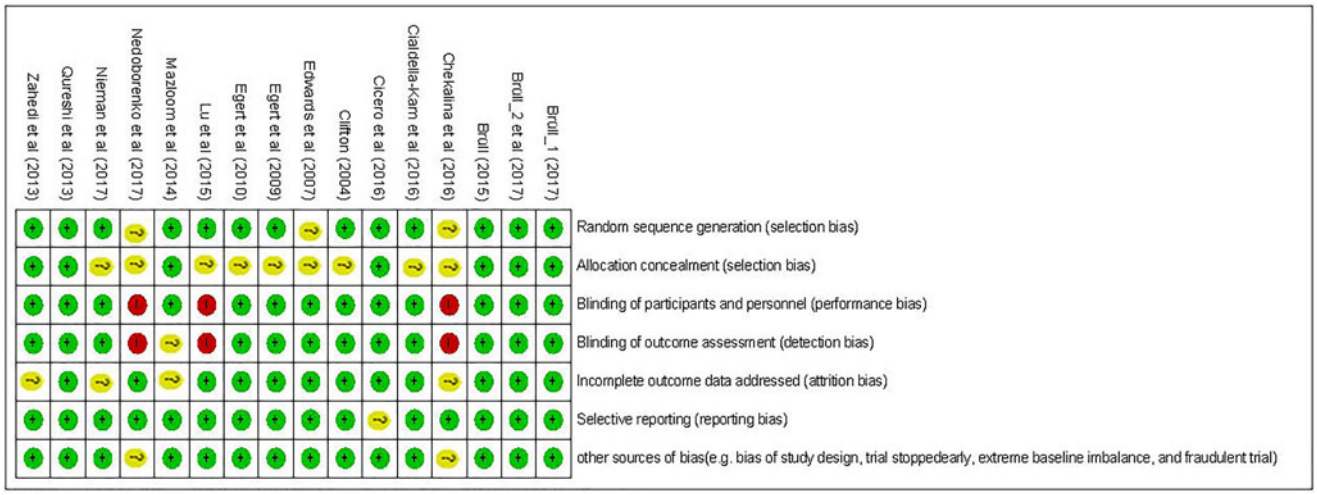


Figure 3. The methodological quality of included studies (risk of bias).

background, and gene-environment interactions), duration of study and dosage of quercetin used.

Conclusions

In summary, the current meta-analysis demonstrated that quercetin supplementation significantly improved lipid profile and inflammatory status by reducing total-, LDL-cholesterol, and CRP levels. Yet it did not affect other lipid profiles and inflammatory markers among patients with MetS and related disorders.

Abbreviations

CAD	coronary artery disease
CRP	C-reactive protein
HCH	hypercholesterolemic
HDL-C	high density lipoprotein-cholesterol
IL-6	interlokin-6
LDL-C	low density lipoprotein-cholesterol
pre-HTN	pre-hypertension
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglycerides
TNF-α	tumor necrosis factor alpha

Disclosure statement

No potential conflict of interest was reported by the authors.

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Author contributions

RT, O-RT, NM, K-BL, MA, S-TH, and ED contributed into the conception, design, statistical analysis and drafting of the manuscript. ZA supervised the study. All authors confirmed the final version for submission.

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