




REVIEW

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# Effect of evening primrose oil supplementation on lipid profile: A systematic review and meta-analysis of randomized clinical trials

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**Background:** Studies have shown that evening primrose oil (EPO) supplementation might be effective in improving lipid profile, however, the results are inconsistent. This study was performed to determine the direction and magnitude of the EPO effect on the lipid profile.

**Methods:** PubMed, Scopus, Cochrane Library, Embase and Web of Science databases and Google Scholar were searched up to September-2019. Meta-analysis was performed using the random-effects model. Lipid profile including high-density lipoprotein (HDL), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) was considered as the primary outcome.

**Results:** A total of 926 articles were identified through database searching, of which, six RCTs were included in the meta-analysis. There were six studies on HDL, TC, and TG and four studies on LDL. EPO supplementation had no significant effect on TC, TG, LDL, and HDL. However, in subgroup analysis, a significant reduction in TG at a dose of  $\leq 4$  g/day (weighted mean difference [WMD] =  $-37.28$  mg/dl; 95% CI:  $-73.53$  to  $-1.03$ ,

**Abbreviations:** AA, arachidonic acid; CVD, cardiovascular disease; EFA, essential fatty acids; EPO, evening primrose oil; GLA, gamma-linolenic acid; HDL, high-density lipoprotein; LA, linoleic acid; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome; SD, standard deviation; SEM, standard error of the means; TC, total cholesterol; TG, triglyceride; WMD, weighted mean difference.

$p = .044$ ) and a significant increase in HDL in hyperlipidemic subjects (WMD = 5.468 mg/dl; 95% CI: 1.323 to 9.614,  $p = .010$ ) was found.

**Conclusion:** Oral intake of EPO at a dose of  $\leq 4$  g/day significantly reduces serum TG levels and significantly increases HDL levels in hyperlipidemic subjects.

#### KEYWORDS

cardiovascular diseases, evening primrose oil, gamma-linolenic acid, hyperlipidemia, lipid profile, meta-analysis

## 1 | INTRODUCTION

Cardiovascular disease (CVD) is one the major cause of mortality worldwide (Shayganni, Bahmani, Asgary, & Rafeian-Kopaei, 2016). It has been estimated that 29.6% of all deaths in 2010 were due to CVD. Also, in 2013, CVD was responsible for 42 and 51% of all deaths in Europe among men and women, respectively (Nichols, Townsend, Scarborough, & Rayner, 2014). Triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC) as lipid profile, play an important role in CVD onset. Former studies have shown that high LDL and TG and low HDL levels are determinant factors for the progress of atherosclerosis and cardiovascular complications (Barter et al., 2007; Gordon, Kannel, Castelli, & Dawber, 1981). Moreover, there is a substantial association between dietary fat intake, lifestyle, and serum lipids (Toeller, Buyken et al., 1999).

The utilization of medicinal herbs and plant-sourced bioactive compounds is widely increasing around the world due to their beneficial effects on dyslipidemia, diabetes, and cardiovascular diseases (Cicero et al., 2017; Gothai et al., 2016; Sahebkar et al., 2016). Besides, the side-effects related to the medicinal plants are much less than chemical medications (Al-Snafi, 2015). Evening primrose, with the scientific name of *Oenothera biennis*, is an ancient medicinal herb which is originated from Mexico and Central America (Montserrat-de la Paz, Fernández-Arche, Ángel-Martín, & García-Giménez, 2012). Evening primrose has many beneficial health effects such as anti-oxidant, anti-diabetic, antiinflammatory, and anti-cancer activities (Munir, Semmar, Farman, & Ahmad, 2017).

Previous studies have shown that essential fatty acids have a considerable impact on the lipid profile. Gamma linolenic acid (GLA, 18:3 n-6) is a metabolite of linoleic acid (LNA, 18:2 n-6), which is produced during conversion of LNA to arachidonic acid (AA, 20:4 n-6) (Barre, 2001; Bayles & Usatine, 2009) and has antiinflammatory effect through the production of prostaglandins series 1 and leukotrienes series 3 (Fan & Chapkin, 1998). Evening primrose oil (EPO) is consist of several fatty acids such as LNA (70–74%), GLA (8–10%), oleic acid (6–7%), and palmitic acid (6–7%) (Montserrat-de la Paz, Fernandez-Arche, Angel-Martín, & Garcia-Gimenez, 2014). Therefore, EPO is known as a rich source of GLA which has a beneficial effect on diseases like systemic sclerosis (Senapati, Banerjee, & Gangopadhyay, 2008), rheumatoid arthritis (Jäntti, Seppälä, Vapaatalo, & Isomäki, 1989), and diabetes (Cameron & Cotter, 1997).

EPO is more known for its effects on systemic diseases and conditions associated with chronic inflammation, such as atopic dermatitis and rheumatoid arthritis. It also is used for several conditions such as polycystic ovary syndrome (PCOS), cancer, and ulcerative colitis (Kleijnen, 1994). EPO, due to its essential fatty acids (EFA), has a direct effect on immune cells (Vassilopoulos, Zurier, Rossetti, & Tsokos, 1997) and an indirect role in cytokines and eicosanoids production (Fan & Chapkin, 1998). Moreover, while some lipid-lowering medications like statins and fibrates have many side-effects such as myopathies and hepatic adverse reactions, EPO is completely safe to improve lipid profile (Sgro & Escousse, 1991; Taylor & Thompson, 2015). There are several studies investigating the effect of EPO supplementation on changes in lipid profiles in humans; however, the results are controversial. Therefore, this meta-analysis of randomized clinical trials was conducted to determine the direction and magnitude of the effect of EPO supplementation on lipid profile.

## 2 | METHODS

### 2.1 | Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane handbook for systematic reviews of interventions were followed during all steps of this study (Higgins & Green, 2011; Moher, Liberati et al., 2009). Two authors independently searched Google Scholar and multiple databases, including PubMed (Medline) (<http://www.ncbi.nlm.nih.gov/PubMed>), Embase, Cochrane Library, Scopus (<http://www.scopus.com>) and Web of Science from inception to September 2019. The following search terms were used in the current study: evening primrose oil (keyword search using words “evening primrose,” “evening primrose oil”) and terms related to lipid profiles (including MeSH search using “Hypercholesterolemias,” “lipoproteins, HDL,” “cholesterol, LDL,” “cholesterol, HDL,” “lipoproteins, LDL,” “Hyperlipidemias,” “Dyslipidemias,” “Triglycerides,” and keyword search using words “lipoprotein triglyceride,” “LDL,” “HDL,” “Total cholesterol,” “TG,” “triglyceride,” “Triacylglycerol,” “TAG,” “lipid profile,” “low density lipoprotein,” “high density lipoprotein,” “blood lipids,” “cholesterol”). Hand-search of the references list of RCTs and previous related reviews was performed to include other potentially eligible trials.

## 2.2 | Selection criteria

The title and abstract of studies were reviewed by two reviewers (M.K. and M.Z.) independently to identify the relevant studies, and discrepancies were resolved through discussion with the third researcher (M.E.). Human trials were included if they met the following inclusion criteria: (a) population: adults (age  $\geq 18$  years old), (b) intervention: oral supplementation with EPO compared to placebo group, (c) outcome: presenting sufficient information on intended variables (HDL, LDL, TG, TC) concentrations and their corresponding SD at the end of the study in each group, (d) study design: randomized clinical trial with either crossover or parallel designs (e) study population: hyperlipidemic or nonhyperlipidemic subjects. Exclusion criteria were the following: (a) nonclinical trials, (b) using a mixture of EPO with vitamins or other agents except vitamin D in maximum dose of 1,000 IU per day because vitamin D co-supplementation does not affect lipid profile (Wang, Xia, Yang, & Peng, 2012), (c) studies last for less than 6 weeks.

## 2.3 | Data extraction

Two reviewers (M.K. and M.E.) independently screened and extracted study characteristics from the original articles, including first author, country, study population, year, sex, sample size, EPO dose, treatment duration, and outcome data. Moreover, the mean and SD of the lipid profile components (HDL, LDL, TG, and TC) were extracted and each component were converted to the standard unit (mg/dl). For cross-over trials, only data from the first part of the study (before the wash-out period) was used for analysis.

## 2.4 | Quality assessment

The quality of the included studies was evaluated by Cochrane Collaboration's Tool in the fields of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias (Higgins et al., 2011). Two authors (H.K.V. and S.M.M.) independently assessed study quality and discrepancies were resolved by consensus.

## 2.5 | Statistical analysis

Stata 14.0 (Stata Corporation, College Station, TX) was used for performing the statistical analysis of this study. Effect size was defined as weighted mean difference (WMD) and 95% confidence interval (CI) and was calculated based on the means and corresponding SDs of lipid profile components (HDL, LDL, TG, TC) for both intervention and control groups. A random-effects model was used for all analyses using restricted maximum likelihood method. We calculated 95% CI for  $I^2$  test using the method reported by Borenstein, Hedges, Higgins, and Rothstein (2009). To identify potential sources of heterogeneity, sensitivity analysis, and predefined subgroup analysis were

conducted; subgroup analysis was performed based on EPO dosage, trial duration, intervention type (EPO or EPO co-supplementation with vitamin D), and study population (hyperlipidemic or non-hyperlipidemic) of participants. SD was calculated when data was reported as the SEM by multiplying SEM by the square root of the sample size ( $SD = SEM \times \sqrt{n}$ ). Publication bias was evaluated using Egger's statistical test (Egger, Smith, Schneider, & Minder, 1997). For all statistical analyses,  $p$ -value  $< .05$  was considered statistically significant.

## 3 | RESULTS

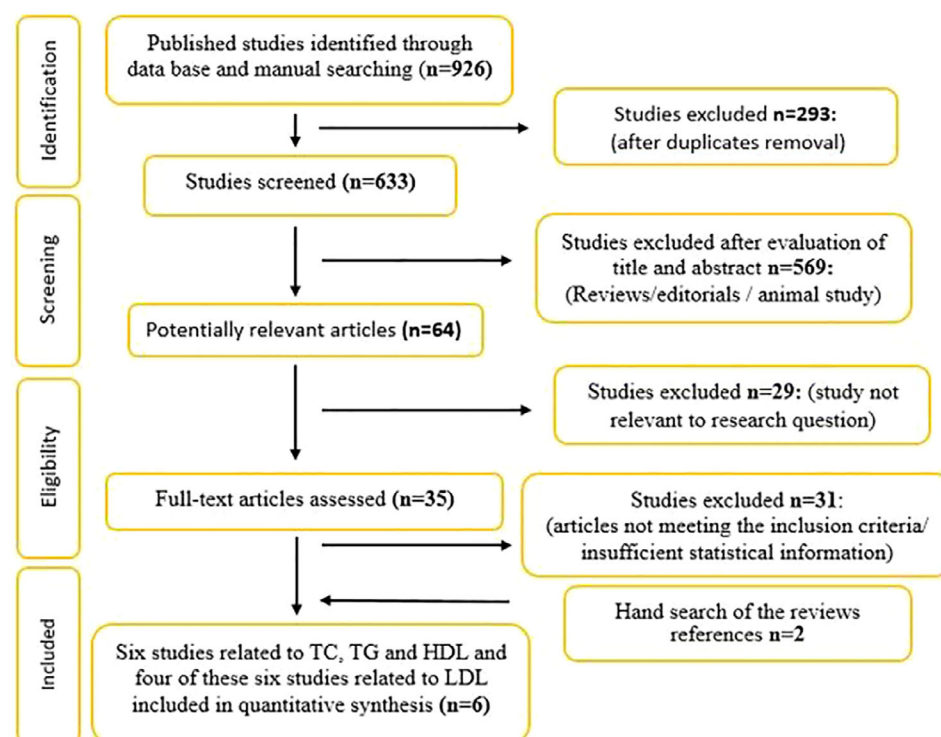
### 3.1 | Literature search and study characteristics

A total of 926 studies were identified through electronic and hand searches. We obtained 504 articles from PubMed, 206 articles from Scopus, 83 articles from Embase, 21 articles from Cochrane Library, and 112 articles from Web of Science. After removing 293 duplicates and screening based on the inclusion and exclusion criteria, six eligible studies with nine datasets for TC, TG, and HDL and four studies with six data sets for LDL were found and enrolled in the meta-analysis (Abraham, Riemersma, Elton, Macintyre, & Oliver, 1990; Guivernau, Meza, Barja, & Roman, 1994; Ishikawa et al., 1989; Jamilian et al., 2016; Jäntti, Nikkari, Solakivi, Vapaatalo, & Isomäki, 1989; Nasri et al., 2017). The details of the study selection process are shown in Figure 1.

The smallest included study had a population size of six participants, while the largest study had 60 participants. Included trials were published between 1988 and 2017, and were conducted in Japan (Ishikawa et al., 1989), Finland (Jäntti, Nikkari, et al., 1989), Iran (Jamilian et al., 2016, Nasri et al., 2017), Chile (Guivernau et al., 1994) and Scotland (Abraham et al., 1990). The mean age of participants in these trials ranged from 20 to 53 years. Ranges of EPO doses varied between 1 and 27.8 g/day and were administered orally in all included trials. The duration of intervention ranged between 6 and 17 weeks. One trial was designed as crossover (Ishikawa et al., 1989) and five trials as parallel design (Abraham et al., 1990, Guivernau et al., 1994, Jamilian et al., 2016, Jäntti, Nikkari, et al., 1989, Nasri et al., 2017). Among the included studies, two trials used EPO in combination with vitamin D (Jamilian et al., 2016, Nasri et al., 2017). The characteristics of the included studies are shown in Table 1. Oral supplementation with EPO was well tolerated in all of the trials.

### 3.2 | Quality of included trials

The methodological quality of individual studies is presented in Figure 2. Some RCTs reported that patients were assigned randomly into intervention or control groups without describing the process of randomization (Guivernau et al., 1994; Ishikawa et al., 1989; Jäntti, Nikkari, et al., 1989). Two of the trials did not explain the allocation concealment procedure of the study (Abraham et al., 1990; Ishikawa et al., 1989).



**FIGURE 1** The flow diagram describing the process of screening and excluded articles [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Characteristics of studies included in the meta-analysis

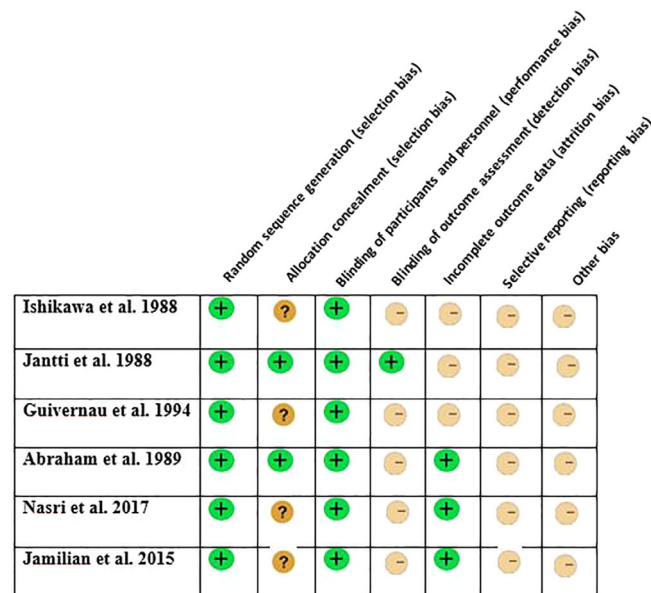
Author and year	Country	Study population	Sex	Dose (g/d)	Duration (week)	Sample size	Mean age	Study design	Outcome (mean $\pm$ SD)
Ishikawa et al. 1989	Japan	HC with and without HT	M/F	3.6	8	9	53	C	TC (265 $\pm$ 24), TG (229 $\pm$ 62), HDL (42 $\pm$ 11)
Ishikawa et al. 1989	Japan	HC with and without HT	M/F	3.6	8	19	53	C	TC (273 $\pm$ 40), TG (136 $\pm$ 42), HDL (49 $\pm$ 12)
Jantti et al. 1989	Finland	RA	M/F	18.5	12	18	20	P	TC (204 $\pm$ 50), TG (106 $\pm$ 35), HDL (61 $\pm$ 19)
Guivernau et al., 1994	Chile	HL	M	3	17	12	40	P	TC (194 $\pm$ 76), TG (150 $\pm$ 121), HDL (42 $\pm$ 10), LDL (125 $\pm$ 79)
Abraham et al. 1990	Scotland	Healthy subjects	M	9.3	17	9	45	P	TC (266 $\pm$ 61), TG (134 $\pm$ 69), HDL (55 $\pm$ 14), LDL (191 $\pm$ 52)
Abraham et al. 1990	Scotland	Healthy subjects	M	18.5	17	6	45	P	TC (283 $\pm$ 39), TG (201 $\pm$ 56), HDL (49 $\pm$ 12), LDL (188 $\pm$ 43)
Abraham et al. 1990	Scotland	Healthy subjects	M	27.8	17	8	45	P	TC (246 $\pm$ 51), TG (94 $\pm$ 45), HDL (57 $\pm$ 14), LDL (177 $\pm$ 48)
Nasri et al., 2017	Iran	PCOS	F	1	12	60	25	P	TC (161 $\pm$ 28), TG (113 $\pm$ 52), HDL (45 $\pm$ 8), LDL (93 $\pm$ 24)
Jamilian et al. 2016	Iran	GDM	F	1	6	60	29	P	TC (183 $\pm$ 45), TG (146 $\pm$ 83), HDL (65 $\pm$ 12), LDL (89 $\pm$ 31)

Note: Mean  $\pm$  SD were reported for the intervention group.

Abbreviations: GDM, gestational diabetes mellitus; HC, hypercholesterolemic; HDL, high density lipoprotein; HL, hyperlipidemic; HT, hypertriglyceridemia; LDL, low density lipoprotein; PCOS, polycystic ovary syndrome; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglyceride.

### 3.3 | Evening primrose oil and total cholesterol

Results of meta-analysis showed that supplementation with EPO did not significantly alter serum TC levels with random effects analysis (WMD = -13.23 mg/dl; 95% CI: -28.95 to 2.49,

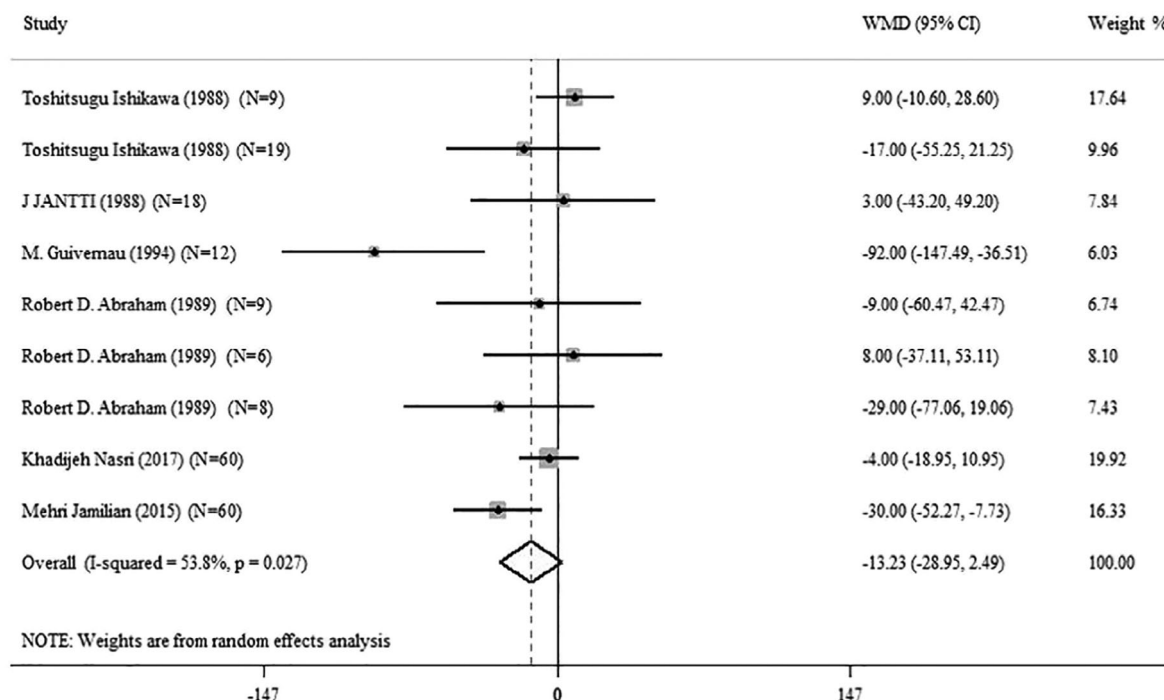


**FIGURE 2** Assessment of quality of studies by the Cochrane Collaboration's tool [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

$p = .099$ ), however, this analysis was associated with significant heterogeneity ( $I^2 = 53.8\%$ ;  $p = .027$ ) (Figure 3). Subgroup analyses based on the dose of EPO, trial duration, and supplementation type were performed to clarify the source of heterogeneity (Table 2). There was no significant effect of EPO in trials with follow-up duration  $\leq 12$  weeks (WMD = -7.43 mg/dl; 95% CI: -22.11 to 7.27,  $p = .32$ ) and  $> 12$  weeks (WMD = -28.65 mg/dl; 95% CI: -69.48 to 12.17,  $p = .16$ ). In addition, TC levels were not considerably changed after an assortment of studies according to the gender and age of the participants. Also, removing each single study using sensitivity analysis revealed no significant outcomes.

### 3.4 | Evening primrose oil and triglyceride

EPO supplementation marginally reduced triglyceride levels (WMD = -23.59 mg/dl; 95% CI: -51.09 to 3.89,  $p = .093$ ) (Figure 4). As reported in Table 2, subgroup analyses were done based on the subgroups defined in the study and found no significant effect of EPO supplementation on triglyceride levels in all subgroups except when the trials were classified according to the dose of EPO supplementation. A significant reducing effect of EPO on triglyceride was found in trials with  $\leq 4$  g/day dose (WMD = -37.28 mg/dl; 95% CI: -73.53 to -1.03,  $p = .044$ ), but not in studies with  $> 4$  g/day of EPO (WMD = -0.96 mg/dl; 95% CI: -41.37 to 39.81,  $p = .96$ ). In the sensitivity analysis, the pooled effect size did not depend on excluding single or a few studies.



**FIGURE 3** Forest plot presenting weighted mean difference and 95% confidence intervals (CIs) for the impact of evening primrose oil (EPO) supplementation on total cholesterol levels

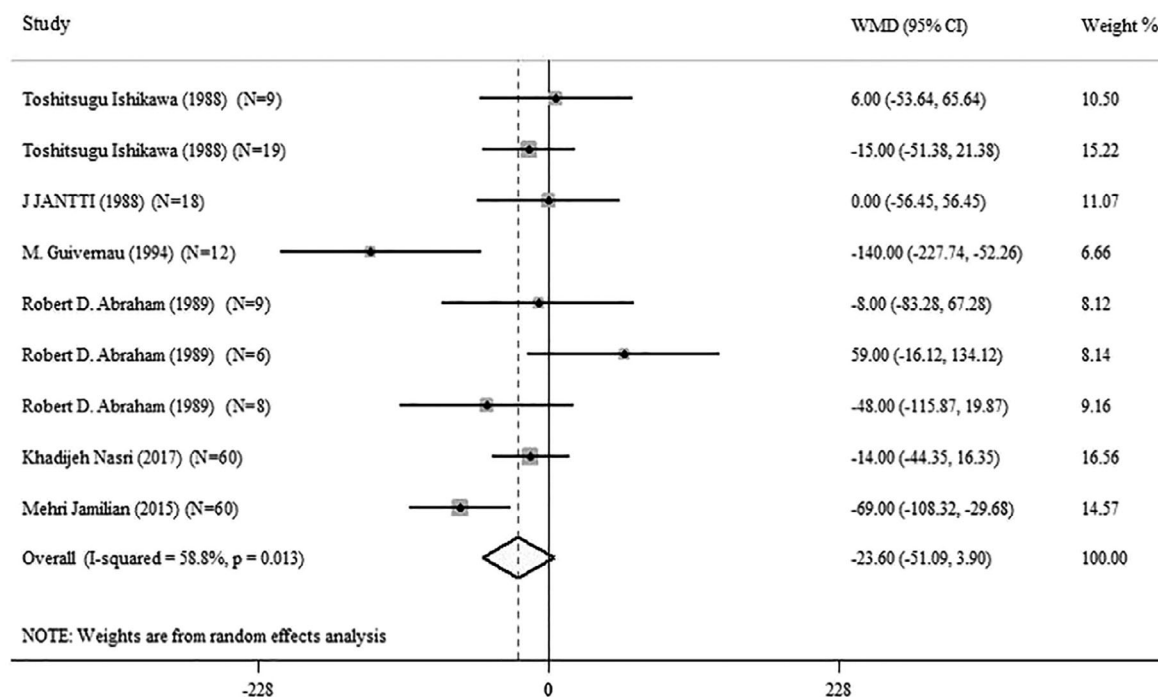
**TABLE 2** Results of subgroup analysis of included randomized controlled trials in meta-analysis of EPO supplementation and lipid profile

Variable	Supplementation dose		Co-supplementation		Trial duration		Study population	
	> 4 g/day	≤ 4 g/day	EPO	EPO + Vit D	> 12 weeks	≤ 12 weeks	HL	Non-HL
<b>TG</b>								
No. of comparison	4	5	7	2	4	5	4	5
WMD (95% CI)	-0.963 (-41.739, 39.814)	-37.288 (-73.538, -1.037)	-16.61 (-51.510, 18.290)	-40.020 (-93.840, 13.800)	-32.229 (-108.370, 43.911)	-21.654 (-47.130, 3.822)	-46.947 (-96.245, 2.351)	-7.339 (-33.120, 18.442)
p-value	.963	.044	.351	.145	.407	.096	.062	.577
$I^2$ (%) (95%CI)	20.63 (0.00-67.15)	48.54 (0.00-81.14)	51.87 (0.00-80.82)	67.25 (0.00-92.60)	28.66 (0.00-72.17)	66.90 (3.30-88.67)	47.36 (0.00-82.53)	2.45 (0.00-21.97)
p-heterogeneity	0.28	0.10	0.0006	0.08	0.23	0.02	0.12	0.39
<b>TC</b>								
No. of comparison	4	5	7	2	4	5	4	5
WMD (95% CI)	-5.996 (-29.761, 17.770)	-18.184 (-40.622, 4.253)	-13.49 (-36.32, 9.34)	-15.64 (-40.97, 9.70)	-28.657 (-69.484, 12.170)	-7.439 (-22.117, 7.240)	-26.013 (-59.327, 7.300)	-4.566 (-17.219, 8.088)
p-value	.621	.112	.247	.227	.169	.321	.126	.479
$I^2$ (%)	0.0 (0.00-83.62)	57.45 (0.00-84.20)	54.50 (0.00-78.84)	53.96 (0.00-88.67)	45.84 (0.00-81.98)	26.35 (0.00-70.72)	60.63 (0.00-86.84)	0.00 (0.00-63.90)
p-heterogeneity	0.72	0.05	0.56	0.14	0.12	0.24	0.05	0.85
<b>LDL</b>								
No. of comparison	3	3	4	2	4	2	2	4
WMD (95% CI)	-11.761 (-35.584, 12.061)	-32.165 (-69.301, 4.971)	-34.360 (-77.790, 9.060)	-9.730 (-33.250, 13.780)	-34.361 (-77.787, 9.065)	-9.733 (-33.246, 13.781)	-67.015 (-163.634, 29.604)	-1.543 (-13.632, 10.545)
p-value	.333	.090	.121	.417	.121	.417	.174	.802
$I^2$ (%)	0.00 (0.00-85.05)	81.68 (43.21-94.09)	48.60 (0.00-100.00)	77.50 (1.57-94.85)	48.60 (0.00-100.00)	77.50 (1.57-94.85)	62.70 (0.00-91.12)	0.00 (0.00-79.10)
p-heterogeneity	0.88	0.004	0.12	0.03	0.12	0.03	0.10	0.78
<b>HDL</b>								
No. of comparison	5	4	7	2	4	5	4	5
WMD (95% CI)	2.705 (-3.559, 8.976)	2.661 (-2.737, 8.059)	3.620 (-0.510, 7.750)	-0.100 (-3.510, 3.310)	5.070 (-0.096, 10.236)	1.178 (-3.726, 6.082)	5.468 (1.323, 9.614)	-1.320 (-4.720, 2.081)
p-value	0.397	0.334	0.086	0.955	0.054	0.638	0.010	0.447
$I^2$ (%)	0.00 (0.00-78.23)	57.90 (0.00-84.35)	0.00 (0.00-82.50)	84.30 (35.54-96.18)	0.00 (0.00-100)	39.88 (0.00-77.69)	0.00 (0.00-57.64)	0.00 (0.00-99.02)
p-heterogeneity	0.80	0.04	0.60	0.01	0.50	0.15	0.42	0.46

Note: EPO supplementation significantly decreased TG levels at a dosage of ≤4g/day ( $p = 0.044$ ). EPO supplementation significantly increased HDL levels in hyperlipidemic subjects ( $p = 0.010$ ).

Abbreviations: CI, confidence interval; EPO, evening primrose oil; HDL, high density lipoprotein; HL, hyperlipidemic; LDL, low density lipoprotein; TC, total cholesterol; TG, triglyceride; Vit, Vitamin; WMD, weighted mean difference.





**FIGURE 4** Forest plot presenting weighted mean difference and 95% confidence intervals (CIs) for the impact of evening primrose oil (EPO) supplementation on triglyceride levels

### 3.5 | Evening primrose oil and LDL

On the basis of the meta-analysis of four trials with six treatment arms, the use of EPO marginally reduced serum LDL levels compared with placebo group (WMD = -20.76 mg/dl; 95% CI: -42.86 to 1.52,  $p = .068$ ) (Figure 5). There was no significant change in LDL serum levels among subgroups. In the sensitivity analysis, the pooled effect size did not depend on excluding single or a few studies.

### 3.6 | Evening primrose oil and HDL

As shown in Figure 6, supplementation with EPO did not change serum HDL levels (WMD = 1.41 mg/dl, 95% CI: -1.2 to 4,  $p = .293$ ;  $I^2 = 34\%$ ,  $p = .146$ ) in comparison with the placebo. As shown in Table 2, after categorizing studies based on the study population, supplementation with EPO resulted in a significant change in HDL levels in hyperlipidemic subjects, (WMD = 5.468 mg/dl; 95% CI: 1.323 to 9.614,  $p = .010$ ). No significant changes were observed using sensitivity analysis.

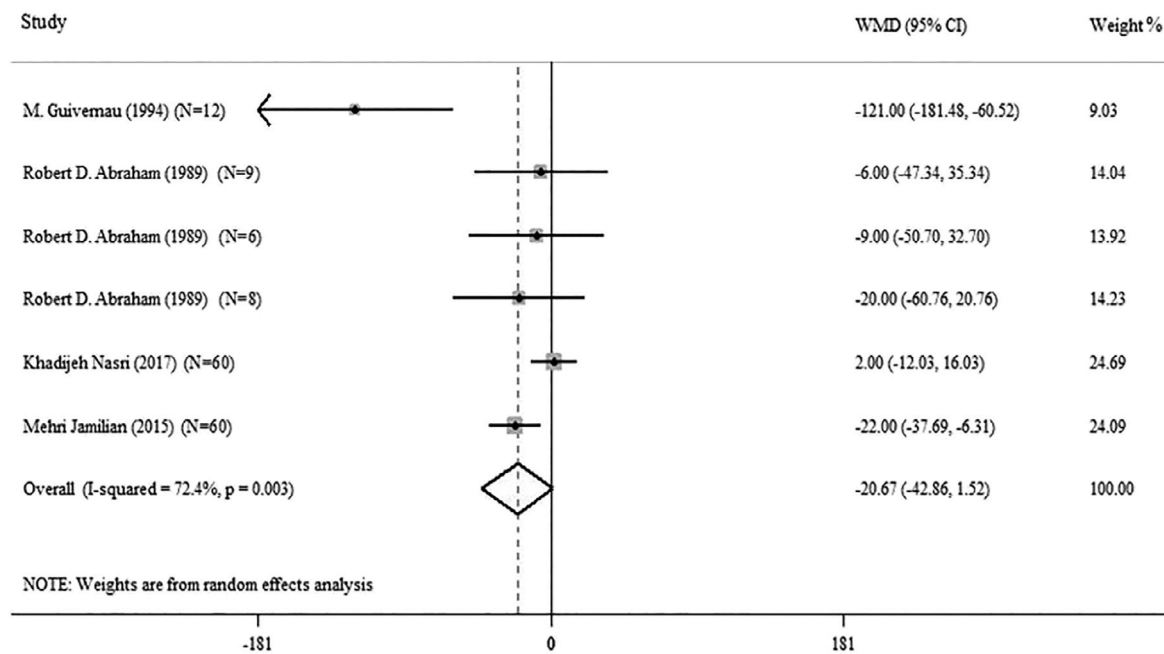
### 3.7 | Publication bias

The Egger's linear regression test did not show any evidence of publication bias for all variables ( $t = 1.25$ , 2-tailed  $p = .252$  for HDL), ( $t = -1.17$ , 2-tailed  $p = .282$ , for TC), ( $t = -0.09$ , 2-tailed  $p = .932$ , for TG), ( $t = -1.29$ , 2-tailed  $p = .266$ , for LDL).

## 4 | DISCUSSION

The results of our meta-analysis demonstrated that EPO supplementation reduced TG in a dose of  $\leq 4$  g/day and increased HDL in hyperlipidemic subjects. Moreover, there was a marginal decrease in TG, LDL, and TC levels following EPO supplementation. Moreover, stratifying the RCTs according to the duration of supplementation (lasting  $>12$  or  $\leq 12$  weeks follow-up), EPO administration dosage ( $\leq 4$  or  $>4$  g/day) and intervention type (EPO or EPO + Vitamin D) revealed no significant effect of EPO supplementation on serum lipid profile except for the effect mentioned for TG. To our knowledge, this is the first systematic review and meta-analysis that assessed the effect of EPO supplementation on lipid profiles.

Results of the study conducted by Ishikawa et al. confirmed that EPO is effective in lowering LDL-C in hypercholesterolemic patients (Ishikawa et al., 1989). Another study in vitamin D-deficient women with polycystic ovary syndrome (PCOS) showed that EPO and vitamin D co-supplementation improved TG and VLDL, but no significant effect was observed regarding other lipids (Nasri et al., 2017). Similar to these results, the study by Jamilian et al. indicated that after 6 weeks of intervention, compared with the placebo, EPO and vitamin D co-supplementation resulted in significant reductions in serum TG, TC, LDL, and TC/HDL ratio. No changes in HDL levels were observed in this study (Jamilian et al., 2016). In contrast, some studies indicated that supplementation with EPO does not influence serum lipid profiles. In a study, which was carried out by Jantti J et al, the researchers reported that serum TC and TG concentrations were not changed by EPO in rheumatoid arthritis patients (Jäntti, Nikkari, et al., 1989).



**FIGURE 5** Forest plot presenting weighted mean difference and 95% confidence intervals (CIs) for the impact of evening primrose oil (EPO) supplementation on low-density lipoprotein (LDL) levels

Similar to this result, the study by Abraham RD et al, demonstrated that EPO is not an effective hypocholesterolemic agent (Abraham et al., 1990). Dasgupta et al. found that dietary supplementation with EPO for 4 weeks could reduce serum TG levels and increase serum levels of HDL in Albino rats (Dasgupta & Bhattacharyya, 2007). In another study conducted by Guivernau et al., dietary intake of EPO (3 g/day) for 4 months significantly decreased serum levels of TG and increased HDL levels in hyperlipidemic patients (Guivernau et al., 1994). It seems that differences related to the supplementation with EPO stem from the dosage, and background disease, as this meta-analysis, found a beneficial effect of EPO on TG levels at a dose of  $\leq 4$  g/day and HDL in hyperlipidemic subjects. Moreover, these controversies might be due to the differences in EPO bioavailability and confounders such as corn oil used in formulating the placebo (Jalbert, 2013; Theander, Horrobin, Jacobsson, & Manthorpe, 2002). It should be noted that there is no study investigating the exact bioavailability of EPO, however, the supplements used in the trials might have used different fillers which can affect the overall bioavailability of EPO. Furthermore, in most studies, dietary intake of participants was not investigated. The analysis based on these criteria could provide us more accurate results regarding the lipid profile. Also, it is possible that the effect of EPO on levels of lipid profile in the selected studies has been influenced by genotype differences, through the enzymes involved in the metabolism of EPO or GLA (Siewert, Gonzalez, Lucero, & Ojeda, 2015).

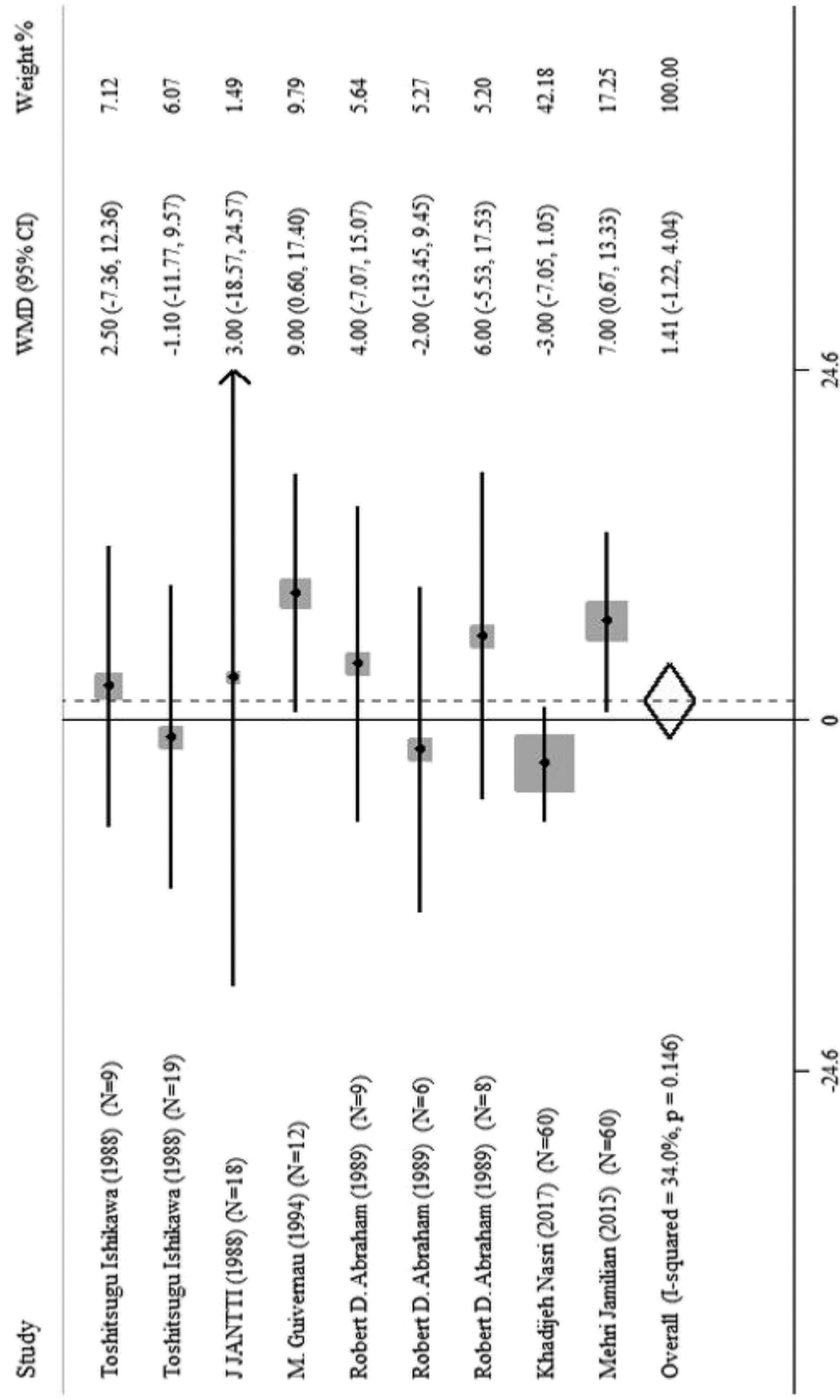
All included studies in the present meta-analysis studied the effect of EPO without any combinations, except for two studies which investigated the effect of EPO plus vitamin D on lipid profile. According to the meta-analysis of clinical trials conducted in 2012 and evaluated the effects of vitamin D on lipid profiles, vitamin D

supplementation does not improve lipid profiles in human subjects (Wang et al., 2012). Also, most of the included studies in the mentioned meta-analysis used higher doses of vitamin D ( $>1,000$  IU vitamin D per day) compared with our included studies (1,000 IU vitamin D per day). In addition, other RCTs that were conducted after 2012 confirm the fact that vitamin D has no effect on lipid profile levels in the mentioned dose (Foroozanfard et al., 2017; Moghassemi & Marjani, 2014). In addition, sub-group analysis in this study showed that co-supplementation with vitamin D does not affect the lipid profile.

It seems that EPO reduces TG levels due to its high content of GLA. Possible mechanisms of GLA in reducing TG levels might be due to its effect on inhibiting TG production in the liver and activating hormone-dependent lipase which breaks TGs to free fatty acids and glycerol following the conversion of GLA to prostaglandin  $E_1$  (Murray, Granner, Mayes, & Rodwell, 2000). Also, supplementation with EPO can improve serum HDL levels by improving insulin sensitivity (Jamilian et al., 2016). The results of our meta-analysis has an important clinical implications as improvement in TG and HDL cholesterol levels has been suggested as effective approach to delay vascular complications such as atherosclerosis, coronary heart disease, and its most dangerous clinical manifestation, myocardial infarction (Assmann & Gotto Jr, 2004). However, more clinical trials are required before implementing these findings clinically.

This study had some limitations. First, most of the trials included in this meta-analysis had few participants and the total number of included studies was few. This limitation could theoretically cause to unreliable estimates of treatment effects (Sterne, Gavaghan, & Egger, 2000); thus, the results should be interpreted cautiously because of the limited number of the included trials. Second, the





**FIGURE 6** Forest plot presenting weighted mean difference and 95% confidence intervals (CIs) for the impact of evening primrose oil (EPO) supplementation on high-density lipoprotein (HDL) levels

amount of heterogeneity was remarkable in studies on TC, TG, and HDL, which limits the generalizability of our findings. Third, some articles could be missed due to the restriction of search into the English databases. Fourth, this study has not registered in any registration database which could be considered as potential source of bias.

## 5 | CONCLUSION

The present meta-analysis showed that oral intake of EPO significantly decreased serum TG in the dose of  $\leq 4$  g/day and increased HDL in hyperlipidemic patients. No other significant changes were observed. Large-scale and high-quality clinical trials are still required to clarify the effectiveness of EPO supplementation on lipid profile levels; however, it could be beneficial in some populations. Future trials can use higher dosage of EPO and increase the intervention duration. Also, intervention on larger sample sizes is recommended.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

## AUTHOR CONTRIBUTIONS

Masoud Khorshidi and Meysam Zarezadeh designed the initial idea of this work. Masoud Khorshidi, Shahab Alizadeh, and Meysam Zarezadeh have made substantial contributions to the study design. Hamed Kord-Varkaneh, Seyed M. Mousavi, Mohammad R. Emami, Javad Heshmati, and Beheshteh Olang contributed to literature search, data acquisition and quality assessment of included trials. Masoud Khorshidi, Meysam Zarezadeh, and Naheed Aryaeian drafted the manuscript and drew the tables. Masoud Khorshidi and Naheed Aryaeian performed data analysis. Meysam Zarezadeh reviewed and edited the manuscript. The manuscript has been read and approved by all authors.

## ETHICS STATEMENT

Not applicable to this type of study.

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