

Review Article

Effect of flaxseed oil supplementation on lipid profile in adults: A systematic review and dose-response meta-analysis of randomized controlled trials

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Abstract

Objective: This study evaluated the effects of flaxseed oil (FO, derived from *Linum usitatissimum*) supplementation on lipid profile parameters in adults.

Materials and Methods: A systematic search was conducted across PubMed, Scopus, Google Scholar, and Web of Science up to February 2025, targeting randomized controlled trials (RCTs) that compared FO supplementation with a control group. A random-effects meta-analysis calculated lipid markers' weighted mean difference (WMD) and 95% confidence interval (CI).

Results: Thirty-six RCTs involving 1,959 participants were analyzed. FO supplementation significantly reduced triglyceride (TG) levels (WMD: -8.04 mg/dl; 95% CI: -15.63 to -0.45; $p=0.038$) but had no significant effect on total cholesterol (TC) (WMD: -1.15 mg/dl; 95% CI: -5.75 to 3.44; $p=0.62$), low-density lipoprotein-cholesterol (LDL-C) (WMD: 1.01 mg/dl; 95% CI: -1.35 to 3.41; $p=0.41$), or high-density lipoprotein cholesterol (HDL-C) (WMD: 0.1 mg/dl; 95% CI: -1.26 to 1.47; $p=0.88$). Subgroup analyses revealed greater TG and TC reductions in interventions <12 weeks (TG: WMD: -16.86 mg/dl, $p=0.005$; TC: WMD: -3.5 mg/dL, $p=0.03$) and significant TG decreases in obese participants (WMD: -18.29 mg/dl, $p=0.03$). HDL-C increased significantly in individuals with baseline HDL-C ≤ 40 mg/dl (WMD: 1.35 mg/dl; 95% CI: 0.3 to 2.4; $p=0.01$). Non-linear dose-response analysis showed significant associations between FO dose and LDL-C ($p=0.039$) and alpha-linolenic acid intake with LDL-C ($p=0.039$) and TC ($p=0.027$).

Conclusion: FO supplementation effectively lowers TG, especially in obese individuals and shorter interventions, and raises HDL-C in those with low baseline levels. While LDL-C and TC show minimal overall change, non-linear dose effects suggest that higher FO and α -Linolenic acid (ALA) doses may influence these markers, necessitating further research on optimal dosing.

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Introduction

Dyslipidemia is a metabolic disorder characterized by elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglycerides (TG), along with reduced concentrations of high-density lipoprotein cholesterol (HDL-C). Its prevalence varies across different populations and geographic regions, but estimates indicate that more than half of the global adult population is affected by some form of dyslipidemia (Brown et al. 2000; Joshi et al. 2014; O'Meara et al. 2004). It is well known that dyslipidemia is the leading cause of chronic disease, especially cardiovascular disease (CVD) which is attributed to the most important causes of death and disability worldwide (Eslami et al. 2025; Hedayatnia et al. 2020; Sadeghi et al. 2017; Tavakkoli-Kakhki et al. 2014). The first line of dyslipidemia drug treatment is statins, but they are associated with side effects such as muscle symptoms, including rhabdomyolysis and necrotizing autoimmune myopathy (Simic and Reiner 2015; Thompson Paul et al. 2016). Therefore, finding alternative treatments or complementary therapies is crucial.

Omega-3 fatty acids may enhance lipid profiles by reducing triglyceride levels, suppressing very-low-density lipoprotein (VLDL) production in the liver, and increasing high-density lipoprotein (HDL) cholesterol concentrations (Ferrari 2023; Liu et al. 2023; Raygan et al. 2019b).

Flaxseed, recognized as a functional food, serves as a significant plant-based source of these essential omega-3 fatty acids (Mohammadi-Sartang et al. 2018). Derived from the seeds of the time-honored plant *Linum usitatissimum*, flaxseed offers potential cardiovascular benefits due to its various properties (Mohammadi-Sartang et al. 2018). The antiatherogenic qualities of flaxseed might stem from ALA, lignans, or a combination of both (Lee and Prasad 2003). Comprising 35% oil by weight, flaxseed oil (FO) stands out as one of the most abundant plant sources of omega-3 fatty acids, with 55% of it being ALA)

(Prasad 2009). ALA acts as a precursor to longer-chain omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) (Rezaei et al. 2020b; Saleh-Ghadimi et al. 2019a).

Although fish oil contains the highest omega-3 fatty acid, it is not always palatable for everyone and often causes complaints of eructation (Covington 2004; Villani et al. 2013). Therefore, although it has beneficial health-related effects, patients' tolerance would be low. In addition to the concerns about the palatability of fish oil, people who live in inland areas have less access to seafood, so there is a need for alternative sources of omega-3 fatty acids, such as FO (Jiang et al. 2022).

FO is commonly used in the treatment of various illnesses. Multiple randomized clinical trials (RCTs) have explored how effective FO is in influencing lipid profiles (Jamilian et al. 2020a; Lemos et al. 2012b; Raygan et al. 2019b; Rezaei et al. 2020b). Certain studies indicated positive outcomes on lipid profiles (Kawakami et al. 2015b; McManus et al. 1996b; Soleimani et al. 2017a), while others found no significant advantages (Harper et al. 2006a; Vargas et al. 2011a). Variations in the groups studied, sample size, and the length of the interventions might explain these inconsistent findings. As a result, drawing a definitive conclusion about FO impact on lipid profiles based on these trials remains challenging. Due to the mixed evidence regarding the effects of FO on lipid profiles, we conducted a systematic review and meta-analysis to determine whether FO supplementation could enhance blood lipid levels.

Materials and Methods

Registration

This meta-analysis and systematic review adhered to the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) guideline (Page et al.

2021) for its execution and reporting. To ensure transparency and methodological rigor, the study protocol was pre-registered with PROSPERO (registration no. CRD42022371516) prior to data extraction, with no subsequent deviations from the protocol.

Search strategy

This meta-analysis was structured following the PRISMA statement guidelines. Initially, the PICOS criteria were established (Table 1). Relevant randomized controlled trials (RCTs) published up to February 2025 were retrieved from primary databases, including PubMed, Scopus, and Web of Science. The search utilized Medical Subject Headings (MeSH) and non-MeSH terms, such as flax*, flaxseed*, “flaxseed oil*”, “Linseed Oil*”, and “Linum usitatissimum*”, and was limited to studies involving human subjects. Google Scholar was used as a supplementary search tool to identify additional relevant studies. Search strategies are detailed in Appendix S1. Reference lists of selected studies and relevant reviews were manually screened, and a PubMed e-mail alert service was activated for new publications. However, unpublished data and clinical trial registries (e.g. ClinicalTrials.gov) were not systematically searched.

Table 1. PICOS criteria for inclusion and exclusion of studies

Parameter	Criteria
Participant	Adults
Intervention	Flaxseed oil
Comparator	Placebo
Outcomes	TG/TC/LDL/HDL
Study design	Controlled trial

Abbreviations: TG: Triglycerides; TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Study selection

Two independent researchers (A.H. and M.A.K.) evaluated the titles and abstracts of all retrieved studies to assess their eligibility for inclusion in this meta-analysis based on predefined criteria. Any

disagreements were settled through consultation with a third researcher (M.M.S.).

Studies were considered eligible for inclusion if they met the following criteria: 1) they were RCTs utilizing either a parallel or crossover design; 2) they investigated the impact of FO on lipid profiles, HDL-C, LDL-C, TG, or TG, with extractable data provided (such as sufficient lipid profile details accompanied by standard deviations [SDs], standard errors of the means [SEMs], or 95% confidence intervals [CIs] at baseline and study endpoint for both intervention and control groups); 3) they involved participants aged 18 years or older; and 4) their full-text articles were available in English.

Studies were not included if they met any of these criteria: 1) the specific effect of FO could not be isolated (e.g. if FO was combined with additional supplement and the control group received same supplement); 2) the duration of FO intake was less than 4 weeks; 3) they followed a non-RCT design, such as animal studies or observational research (e.g. cross-sectional, case-control, or cohort studies); 4) baseline and/or follow-up lipid profile data were insufficient; or 5) the study’s data duplicated findings already reported in another included publication.

Data extraction

A screening checklist based on inclusion and exclusion criteria was employed to determine eligible articles. Once the suitable articles were chosen, two authors (A.H. and M.A.K.) independently evaluated the RCT data. A standardized electronic form was used to extract details such as the first author’s name, year of publication, study location, sample size (both during registration and completion), intervention and placebo type and dosage, study design, intervention duration, participant status, and additional details like mean age and sex. The collected data included mean values and standard deviations (SDs) for the pertinent

outcomes, recorded at baseline, following the intervention, and/or representing the change from baseline to post-intervention. In studies featuring multiple arms, where interventions varied by dose or control groups, the participants were split into two groups, and two treatment arms were incorporated into the meta-analysis to prevent duplication. If data were reported over multiple periods, only the end-of-trial values were utilized. Parameter concentrations reported in varying units were converted to the most frequently used unit.

Quality and certainty assessment

The risk of bias in the included studies was systematically evaluated by two independent authors, M.A.K. and A.H., using the Cochrane quality assessment tool for RCTs. This tool evaluates seven critical domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of both participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. Each study was classified as exhibiting a low, high, or unclear risk of bias (Higgins and Green 2011).

Statistical analysis and synthesis of quantitative data

The impact of FO supplementation was assessed on several parameters: 1) HDL (mg/dl), LDL (mg/dl), TG (mg/dl), and TC (mg/dl). These measurements—HDL, LDL, TG, and TC—were standardized in milligrams per deciliter. To convert the units from millimoles per liter to milligrams per deciliter, HDL, LDL, and TC values were multiplied by 38.6, while TG values were multiplied by 88.49.

Effect sizes were presented as weighted mean differences (WMDs) accompanied by 95% CI (Mohammadi-Sartang *et al.* 2017b). The net alteration in serum or

plasma lipid levels between groups in each study was determined using the formula:

(treatment value of the group after the follow-up period minus baseline) minus (control group value at end of follow-up minus baseline)

For single-arm crossover studies, the net change in plasma lipid concentrations was calculated by subtracting the control intervention value from the treatment value. The standard deviation (SD) of the mean difference was computed with the equation:

$$SD = \text{square root} [(SD \text{ pretreatment})^2 + (SD \text{ posttreatment})^2 - (2 \times R \times SD \text{ pretreatment} \times SD \text{ posttreatment})]$$

where a correlation coefficient (R) of 0.5 was used as a conservative estimate, with R ranging from 0 to 1 (Ghersi *et al.* 2008).

When SD was unavailable but standard error of the mean (SEM) was provided, SD was derived using: $SD = SEM \times \text{square root } (n)$, where n represents the number of participants per group. If results were given as medians with ranges or 95% CIs, means and SDs were approximated following the approach outlined by Hozo *et al.* (Hozo *et al.* 2005). Data presented solely in graphical form were extracted using Plot Digitizer software.

Heterogeneity was evaluated using Cochran's Q test (with a significance threshold of $p < 0.1$) and the I^2 test to determine the extent of variation (an I^2 value of 50% or higher indicated notable heterogeneity across studies). A random-effects model was employed to calculate the pooled effect size when heterogeneity was present; otherwise, a fixed-effects model was used. Sensitivity analysis was conducted via the leave-one-out approach, where each study was excluded individually, and the analysis was repeated to evaluate its influence on the overall effect size (Mohammadi-Sartang *et al.* 2017a).

A preplanned subgroup analysis was carried out, examining baseline lipid levels, supplementation duration, health conditions, body mass index (BMI), and

study quality (assessed with the Cochrane Quality assessment), to explore their effects on the meta-analysis outcomes. Utilizing random-effects meta-regression through the application of unrestricted maximum likelihood estimation method, was applied to investigate the relationship between the overall effect size estimate and potential moderating factors, including flaxseed oil dosage, supplementation duration, and participants' BMI. Publication bias was examined through funnel plots, Begg's rank correlation, and Egger's weighted regression tests. The Duval and Tweedie "trim and fill" and "fail-safe N" methods were used to adjust for any detected publication bias (Duval and Tweedie 2000). The meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ, USA) ("Borenstein M, Hedges L, Higgins J, et al. Comprehensive Meta-Analysis Version 2.

Englewood, NJ: Biostat. 2005,").

A P-value less than 0.05 was deemed indicative of statistical significance.

Results

Selection and characteristics of included studies

The process for selecting studies is illustrated in Figure 1. Initially, 2473 reports were identified, and after

eliminating duplicates ($n = 860$), 1613 articles were left. From these, 1544 were excluded as they were either not RCTs with human participants or did not align with the PICOS criteria for this meta-analysis, as determined by a thorough review of titles and abstracts. Consequently, 69 articles deemed potentially relevant were chosen for a comprehensive full-text review. Following this detailed evaluation, 37 RCTs met the inclusion standards and were included in the meta-analysis (Akrami et al. 2018; Avelino et al. 2015; Babajafari et al. 2018; Barden et al. 2009; Blackwood et al. 2015; Dittrich et al. 2015; Ghanbari et al. 2023a; Gillingham et al. 2011; Gomes et al. 2015; Harper et al. 2006b; Jamilian et al. 2020b; Joris et al. 2020; Karakas et al. 2016; Kaul et al. 2008b; Kawakami et al. 2015c; Kelley et al. 1993; Kontogianni et al. 2013; Kuhnt et al. 2016; Layne et al. 1996; Lemos et al. 2012a; Mantzioris et al. 1994; McManus et al. 1996a; Mirfatahi et al. 2016a; Mirmasoumi et al. 2018; Pang et al. 1998; Paschos et al. 2007; Rallidis et al. 2003; Raygan et al. 2019a; Rezaei et al. 2020a; Saleh-Ghadimi et al. 2019b; Schwab et al. 2006; Soleimani et al. 2017b; Soleimani et al. 2017c; Vargas et al. 2011b; Yang et al. 2019b; Zheng et al. 2018; Zheng et al. 2016).

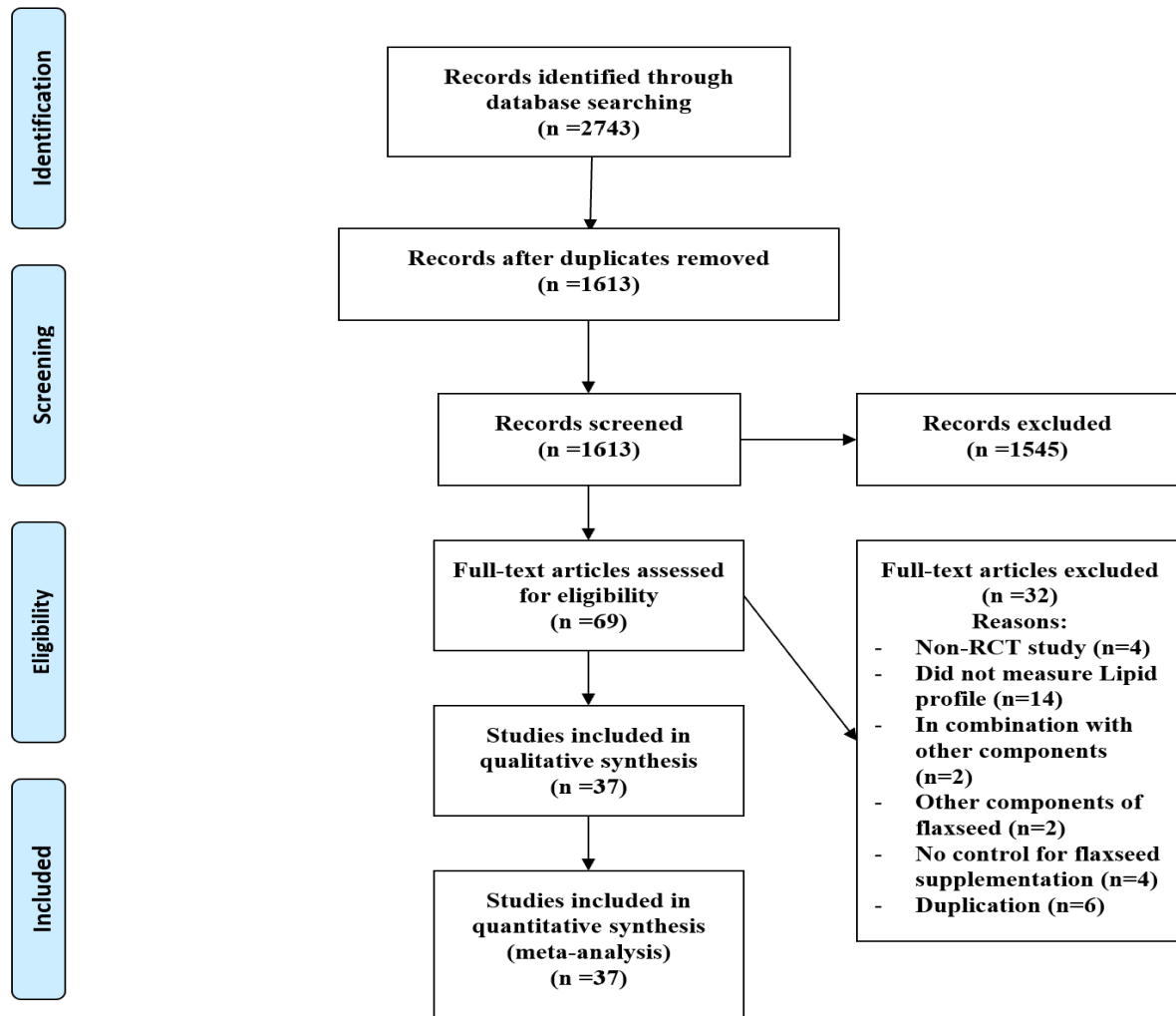


Figure 1. Flow diagram of the literature search process. Abbreviation: RCT, randomized controlled trial

Characteristics of included studies

The features of the studies outlined in the 37 included articles are summarized in Table 2.

Information was gathered from 37 included studies encompassing 41 treatment groups, involving a total of 1959 participants assigned randomly. (Akrami et al. 2018; Avelino et al. 2015; Babajafari et al. 2018; Barden et al. 2009; Blackwood et al. 2015; Dittrich et al. 2015; Ghanbari et al. 2023a; Gillingham et al. 2011; Gomes et al. 2015; Harper et al. 2006b; Jamilian et al. 2020b; Joris et al. 2020; Karakas et al. 2016; Kaul et al. 2008b; Kawakami et al. 2015c; Kelley et al. 1993; Kontogianni et al. 2013; Kuhnt et al. 2016; Layne et al. 1996; Lemos et al. 2012a; Mantzioris et al. 1994; McManus et al. 1996a; Mirfatahi et

al. 2016a; Mirmasoumi et al. 2018; Pang et al. 1998; Paschos et al. 2007; Rallidis et al. 2003; Raygan et al. 2019a; Rezaei et al. 2020a; Saleh-Ghadimi et al. 2019b; Schwab et al. 2006; Soleimani et al. 2017b; Soleimani et al. 2017c; Vargas et al. 2011b; Yang et al. 2019b; Zheng et al. 2018; Zheng et al. 2016). The sample sizes of these individual studies varied from 11 (McManus et al. 1996a) to 118 (Kuhnt et al. 2016). These studies, published from 1993 to 2023, took place in various countries including Iran (Akrami et al. 2018; Babajafari et al. 2018; Ghanbari et al. 2023a; Jamilian et al. 2020b; Mirfatahi et al. 2016a; Mirmasoumi et al. 2018; Raygan et al. 2019a; Rezaei et al. 2020a; Saleh-Ghadimi et al. 2019b; Soleimani et al. 2017b; Soleimani et al. 2017c), Canada

(Blackwood et al. 2015; Gillingham et al. 2011; Kaul et al. 2008b; Layne et al. 1996; McManus et al. 1996a), Brazil (Avelino et al. 2015; Gomes et al. 2015; Lemos et al. 2012a), Greece (Kontogianni et al. 2013; Paschos et al. 2007; Rallidis et al. 2003), Finland (Schwab et al. 2006), the United States (Karakas et al. 2016; Kelley et al. 1993; Layne et al. 1996; Vargas et al. 2011b), Germany (Dittrich et al. 2015; Kuhnt et al. 2016), USA (Harper et al. 2006b), Japan (Kawakami et al. 2015c), China (Yang et al. 2019b; Zheng et al. 2018; Zheng et al. 2016), the Netherlands (Joris et al. 2020), and Australia (Barden et al. 2009; Mantzioris et al. 1994; Pang et al. 1998).

Participants' average ages spanned from 25 to 68 years. Four studies focused solely on women (Jamilian et al. 2020b; Karakas et al. 2016; Mirmasoumi et al. 2018; Vargas et al. 2011b), seven included only men (Barden et al. 2009; Kawakami et al. 2015c; Kelley et al. 1993; Mantzioris et al. 1994; Pang et al. 1998; Paschos et al. 2007; Rallidis et al. 2003), while the rest involved both genders (Akrami et al. 2018; Avelino et al. 2015; Blackwood et al. 2015; Dittrich et al. 2015; Ghanbari et al. 2023a; Gillingham et al. 2011; Gomes et al. 2015; Harper et al. 2006b; Joris et al. 2020; Kaul et al. 2008b; Kontogianni et al. 2013; Kuhnt et al. 2016; Lemos et al. 2012a; McManus et al. 1996a; Mirfatahi et al. 2016a; Raygan et al. 2019a; Rezaei et al. 2020a; Saleh-Ghadimi et al. 2019b; Schwab et al. 2006; Soleimani et al. 2017b; Soleimani et al. 2017c; Yang et al. 2019b; Zheng et al. 2018; Zheng et al. 2016).

Data quality

The evaluation of bias risk in the studies included, based on Cochrane criteria, is presented in Table 3 (Akrami et al. 2018; Avelino et al. 2015; Ghanbari et al. 2023a; Harper et al. 2006b; Jamilian et al. 2020b; Joris et al. 2020; Kaul et al. 2008b; Kawakami et al. 2015c; Kontogianni et al. 2013; Kuhnt et al. 2016; Lemos et al. 2012a; McManus et al. 1996a; Mirfatahi et

al. 2016a; Mirmasoumi et al. 2018; Rallidis et al. 2003; Raygan et al. 2019a; Rezaei et al. 2020a; Saleh-Ghadimi et al. 2019b; Schwab et al. 2006; Soleimani et al. 2017b; Vargas et al. 2011b; Yang et al. 2019b).

Nearly all of the 36 trials assessed demonstrated a low risk of bias in terms of random sequence generation. The data quality review revealed varying degrees of bias risk across the examined studies. According to Cochrane standards, the majority of studies exhibited a low to moderate risk of bias, with only a small number showing a high risk. Key elements influencing study quality included allocation concealment, blinding of outcome evaluation, and selective reporting.

Table 2. Demographic characteristics of the included studies

Author (Year)	Design	Country	Patient status	Gender	Sample size (intervention/ control)	Intervention group		Duration (weeks)	Intervention/control type	FXO(g)	ALA(g)
						Mean age (Years)	Mean BMI				
Ghanbari,2023	Db/Rn/Pa	Iran	Burn	B	28/28	44	25.6	3	FXO/Control	27.8	NR
Ghanbari,2023	Db/Rn/Pa	Iran	Burn	B	28/28	42.5	24.6	3	FXO+OO/OO	13.5	NR
Jamilian, 2020	Db/Rn/Pa	Iran	GDM	F	26/25	29.5	28.9	6	FXO/SFO	2	0.8
Rezaei, 2020	Db/Rn/Pa	Iran	NAFLD	B	34/34	45.5	30.1	12	FXO/SFO	18	NR
Ghadimi,2019	Db/Rn/Pa	Iran	CHD	B	21/19	55.67	30.36	10	FXO/Control	5	2.5
Joris, 2019	Db/Rn/Pa	Netherlands	Healthy Obese	B	29/30	60	28.3	12	FXO/SFO	10	4.7
Raygan, 2019	Db/Rn/Pa	Iran	T2DM	B	30/30	64.6	29.3	12	FXO/Placebo	2	0.8
Yang, 2019	Db/Rn/Pa	China	HTN	B	39/35	56.73	26.83	12	FXO/CO	4	2.5
Babajafari,2018	Db/Rn/Pa	Iran	Burn	B	25/24	32.5	18-30	3	FXO/CO	30	NR
Zheng, 2018 (CD36 genotype, A allele)	Db/Rn/Pa	China	T2DM	B	16/19	59.2	25.4	27	FXO/CO	NR	2.5
Zheng, 2018 (CD36 genotype, G allele)	Db/Rn/Pa	China	T2DM	B	26/31	60.6	24.2	27	FXO/CO	NR	2.5
Akrami,2017	Rn/Pa	Iran	MET	B	26/26	48.3	NA	7	FXO/SFSO	23.22	NR
Mirmasoumi,2017	Db/Rn/Pa	Iran	PCOS	F	30/30	28.4	26.9	12	FXO/Control	2	NR
soleimani.,2017	Db/Rn/Pa	Iran	T2DM	B	30/30	58.8	27	12	FXO/Control	NR	2
Karakas, 2016	Db/Rn/Pa	USA	PCOS	F	17/17	29.4	35	6	FXO/SBO	NR	3.5
Kuhnt, 2016	Db/Rn/Pa	Germany	Healthy	B	59/59	48.15	24.9	8	FXO/ECHO	17	5
Mirfatahi, 2016	Db/Rn/Pa	Iran	HD	B	17/17	68	26	8	FXO/MCT	6	3.45
Zheng, 2016	Db/Rn/Pa	China	T2DM	B	53/55	59.7	24.7	27	FXO/CO	NR	2.5
Avelino,2015	Db/Rn/Pa	Brazil	Healthy	B	57/53	67.6	28.6	12	FXO/Placebo	3	1.75
Blackwood,2015	Rn/Pa	Canada	CVD	B	8/9	58	30	6	FXO/Control	2	1
Dittrich, 2015	Db/Rn/Pa	Germany	HT	B	12/42	56	28.1	20	FXO/SFO	20	7.42
Gomes, 2015	Db/Rn/Pa	Brazil	T2DM	B	10/10	47	28.3	9	FXO/Placebo	6	3
Kawakami, 2015	Db/Rn/Co	Japan	Healthy	M	15/15	44.5	25.1	12	FXO/CO	10	5.49
Soleimani,2015	Db/Rn/Pa	Iran	T1DM/T2DM	B	30/30	62.9	30.5	12	FXO/Placebo	NR	1
Kontogianni,2013	Sb/Rn/Co	Greece	Healthy	B	37/37	25.6	21.9	6	FXO/OO	13.8	8
Lemos, 2012	Db/Rn/Pa	Brazil	HD	B	54/60	59.3	25.6	16	FXO/Mineral Oil	2	NR
Gillingham,2011	Sb/Rn/Co	Canada	HC	B	36/36	47.49	28.56	4	FXO+HOCO/HOCO	NR	21
Vargas, 2011	Db/Pa	USA	PCOS	F	17/17	29.4	35	6	FXO/SBO	NR	3.27
Barden, 2009	Rn/Pa	Australia	Healthy	M	18/18	51	26.1	4	FXO/OO	9	5.4
Kaul, 2008	Db/Rn/Pa	Canada	Healthy	B	22/22	34.7	24.2	12	FXO/SFO	2	1
Kaul, 2008	Db/Rn/Pa	Canada	Healthy	B	22/22	34.7	24.2	12	FXO/HO	2	1
Paschos, 2007	Sb/Rn/Pa	Greece	HC	M	18/17	49	28	12	FXO/SAO	13.5	8.1
Harper, 2006	Db/Rn/Pa	Atlanta	Healthy	B	27/22	49.4	35.9	26	FXO/OO	5.2	3
Schwab, 2006	Db/Rn/Co	Finland	Healthy	B	14/14	45	25.54	4	FXO/HO	27.8	15.9
Rallidis, 2003	Sb/Rn/Pa	Greece	HC	M	50/26	50.4	28.42	12	FXO/SAO	13.5	8
Pang.,1998	Sb/Rn/Pa	Australia	Healthy	M	15/14	25	22	6	FXO/SFO	NR	10.1
Layne, 1996 (Low dietary PFA/SFA)	Db/Rn/Co	Canada	Healthy	NR	15/15	33.7	NR	12	FXO/FO	NR	NR
Layne, 1996 (High dietary PFA/SFA)	Db/Rn/Co	Canada	Healthy	NR	11/11	27.1	NR	12	FXO/FO	NR	NR
MCMANUS,1996	Db/Rn/Co	Canada	T2DM	B	11/11	61.8	28	13.5	FXO/OO	NR	2.8
Mantzioris,1994	Sb/Rn/Pa	Australia	Healthy	M	15/15	34.5	25.1	4	FXO/ n-6 oil	NR	14.7
Kelley, 1993	Co	USA	Healthy	M	10/10	27.3	NR	8	FXO/SFO	NR	18.7

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Abbreviations: NR: Not Reported; Db: Double-blinded; Sb: Single-blinded; Rn: Randomized; Pa: Parallel; Co: Cross-over; B: Both; M: Male; F: Female; HTN: Hypertension; T2DM: Type 2 diabetes mellitus; T1DM: Type 1 diabetes mellitus; GDM: Gestational diabetes mellitus; CHF: Congestive heart failure; NAFLD: Nonalcoholic fatty liver disease; MET: Metabolic syndrome; PCOS: Polycystic ovary syndrome; HD: Hemodialysis; CVD: Cardiovascular diseases; HT: Hypertriglyceridemia; HC: Hypercholesterolemia; FO: Flaxseed oil; ALA: Alfa--linolenic acid; OO: Olive oil; SFO: Sunflower oil; CO: Corn oil; SFSO: Sunflower seed oil; HOCO: High oleic canola oil; SAO: Safflower oil; SBO: Soybean oil; HO: Hempseed oil.

Table 3. Quality assessment of clinical trials (according to the Cochrane guideline) investigating the associations between flaxseed oil and lipid profile.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity	General risk of bias
Ghanbari,2023	L	H	L	H	L	L	L	Moderate
Jamilian, 2020	L	L	L	H	L	L	L	Low
Rezaei, 2020	L	L	L	H	L	L	L	Low
Ghadimi,2019	L	L	L	H	L	L	L	High
Joris, 2019	U	H	L	H	L	L	L	Moderate
Raygan, 2019	L	L	L	H	L	L	L	low
Yang, 2019	L	H	L	L	L	L	L	Low
Babajafari,2018	L	L	L	U	L	H	L	Low
Zheng, 2018	L	U	L	U	L	L	L	Low
Akram,2017	L	H	U	H	L	L	H	High
Mirmasoumi,2017	U	H	L	H	L	L	L	Moderate
soleimani,2017	L	L	L	L	L	U	L	Low
Karakas, 2016	L	L	L	L	L	L	L	Low
Kuhnt, 2016	U	H	L	U	L	L	L	Low
Mirfatahi, 2016	L	H	L	U	L	L	L	Low
Zheng, 2016	L	U	L	H	L	L	L	Low
Avelino,2015	U	H	L	H	L	L	L	Moderate
Blackwood,2015	L	U	H	H	L	H	H	High
Dittrich, 2015	U	H	L	U	L	L	H	Moderate
Gomes, 2015	U	U	L	H	L	L	L	Low
Kawakami, 2015	U	H	L	H	L	L	L	Moderate
Soleimani,2015	L	H	L	L	L	L	L	Low
Kontogianni,2013	U	H	H	H	L	L	L	High
Lemos, 2012	U	H	L	H	L	L	L	Moderate
Gillingham,2011	L	H	H	H	L	L	L	High
Vargas, 2011	U	H	L	H	L	L	L	Moderate
Barden, 2009	U	U	U	H	L	L	H	Moderate
Kaul, 2008	L	H	L	H	L	L	L	Moderate
Paschos, 2007	L	L	H	H	L	H	H	High
Harper, 2006	L	L	L	H	L	L	L	Low
Schwab, 2006	U	H	L	H	L	L	L	Moderate
Rallidis, 2003	U	H	U	H	H	L	H	High
Pang ,1998	L	L	L	L	U	L	H	Low
Layne, 1996	U	H	L	U	L	L	L	Low
MCMANUS,1996	U	H	L	H	L	L	H	High
Mantzioris,1994	U	H	U	H	L	L	L	Moderate
Kelley, 1993	H	H	H	H	L	L	L	High

Abbreviations: L: low risk of bias; H: high risk of bias; U: unclear risk of bias

Meta-analysis results

Forest plots depicting data synthesis from trials related to each lipid profile parameter are presented in Figures 2A-D. Additionally, subgroup analyses were performed considering the following variables: duration, baseline, health status, and BMI.

The effect of flaxseed oil on TG level

TG levels were measured across 37 arms from 35 trials. Results from the random-effects model indicated that flaxseed consumption has a significant effect on TG levels (WMD: -8.04 mg/dl; 95% CI, -15.63 to -0.45; $p = 0.038$), showing considerable heterogeneity ($I^2 = 82.05\%$; $p < 0.001$) (Figure 2A). Additionally, in the subgroup analysis categorized by duration of intervention, we observed a significant reduction in TG in studies with a duration of <12 weeks (WMD: -16.86; 95% CI, -28.56 to -5.16; $p = 0.005$). However, this effect was not evident in studies with durations of ≥ 12 weeks (WMD: -1.26; 95% CI, -11.14 to 8.62; $p = 0.8$). When the analysis was categorized based on the health status of participants, a notable decrease in TG levels was observed in studies involving non-healthy individuals (WMD: -14.58 mg/dl, 95% CI: -26.79 to -2.38, $p = 0.01$). However, this reduction was not seen in studies with healthy subjects (WMD: 1.72 mg/dl, 95% CI: -3.31 to 6.71, $p = 0.5$). Additionally, a significant reduction in TG levels was seen in studies with the obese category of BMI (WMD: -18.29 mg/dl, 95% CI: -34.96 to -1.62, $p = 0.03$); in contrast, no such decrease was observed in studies with normal (WMD: -2.49 mg/dl, 95% CI: -8.09 to 3.09, $p = 0.38$) and overweight (WMD: -10.57 mg/dl, 95% CI: -25.67 to 4.52, $p = 0.17$) BMI (Appendix 2. Supplemental Tables S2).

The effect of flaxseed oil on TC level

TC levels were assessed in 39 groups from 37 trials. The findings from the random-effects model showed that the

intake of FO did not significantly influence TC levels (WMD: -1.15 mg/dl; 95% CI, -5.75 to 3.44; $p = 0.62$), with significant heterogeneity observed ($I^2 = 82.82\%$; $p < 0.001$) (Figure 2 B). In our subgroup analysis, based on the duration of the intervention, we found a considerable decrease in TC levels in studies lasting <12 weeks (WMD: -3.5; 95% CI, -6.82 to -0.26; $p = 0.03$). However, this reduction was not observed in studies that lasted ≥ 12 weeks (WMD: 0.31; 95% CI, -6.26 to 6.9; $p = 0.8$). (Appendix 2. Supplemental Tables S3).

The effect of FO on LDL-C

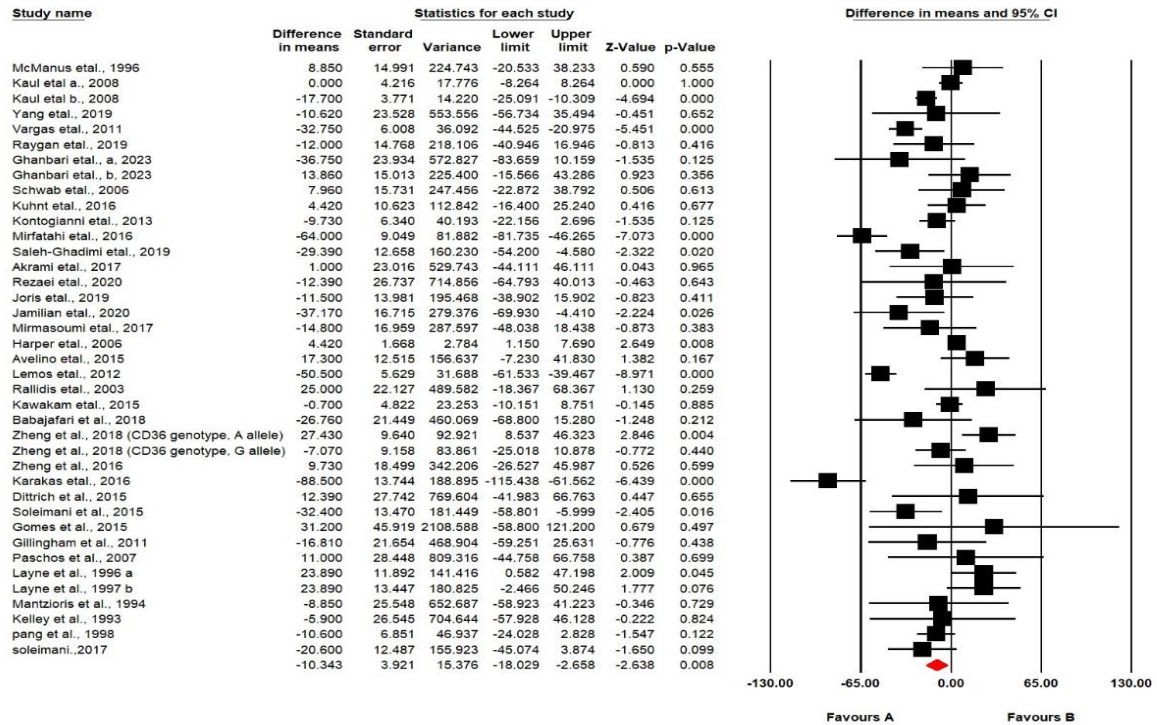
The results concerning LDL-C were derived from 35 groups across 33 studies. Flaxseed consumption did not lead to a significant change in LDL levels (WMD: 1.01 mg/dl; 95% CI: -1.35 to 3.41; $p = 0.41$), and there was moderate heterogeneity among the studies ($I^2 = 40.88\%$; $p = 0.007$) (Figure 2C). Statistical analyses of the subgroups showed no significant differences. (Appendix 2. Supplemental Tables S4).

The effect of flaxseed oil on HDL-C

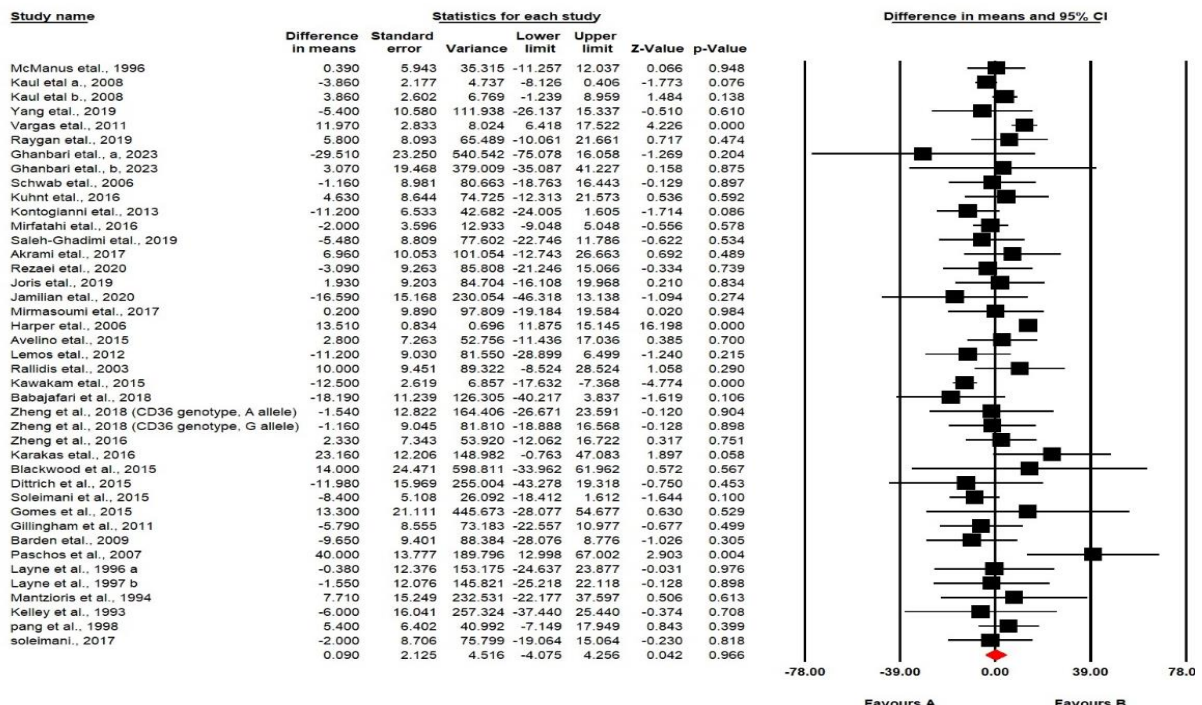
The findings related to HDL were derived from 48 groups across 36 studies. Flaxseed consumption did not lead to a significant change in HDL-C levels (WMD: 0.1 mg/dl; 95% CI: -1.26 to 1.47; $p = 0.88$). Additionally, substantial heterogeneity was observed among the studies ($I^2 = 76.99\%$; $p < 0.001$) (Figure 2D). Furthermore, when baseline HDL-C levels stratified the analysis, a significant increase was noted in participants with HDL-C ≤ 40 mg/dl (WMD: 1.35 mg/dl; 95% CI: 0.3 to 2.4; $p = 0.01$), but no significant change was observed in those with HDL-C > 40 mg/dl; 95% CI: -1.88 to 1.84; $p = 0.98$). (Appendix 2. Supplemental Tables S5).

Flaxseed oil and lipid profile: A meta-analysis

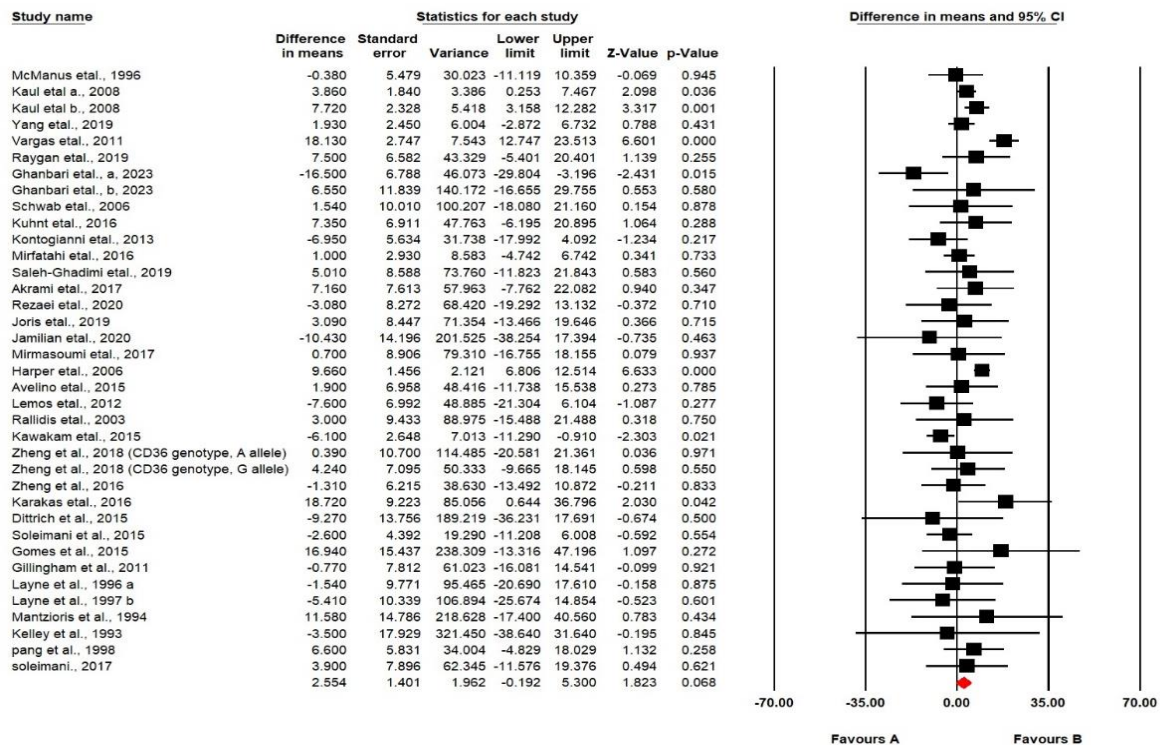
A. TG level



B. TC level



C. LDL level



D. HDL level

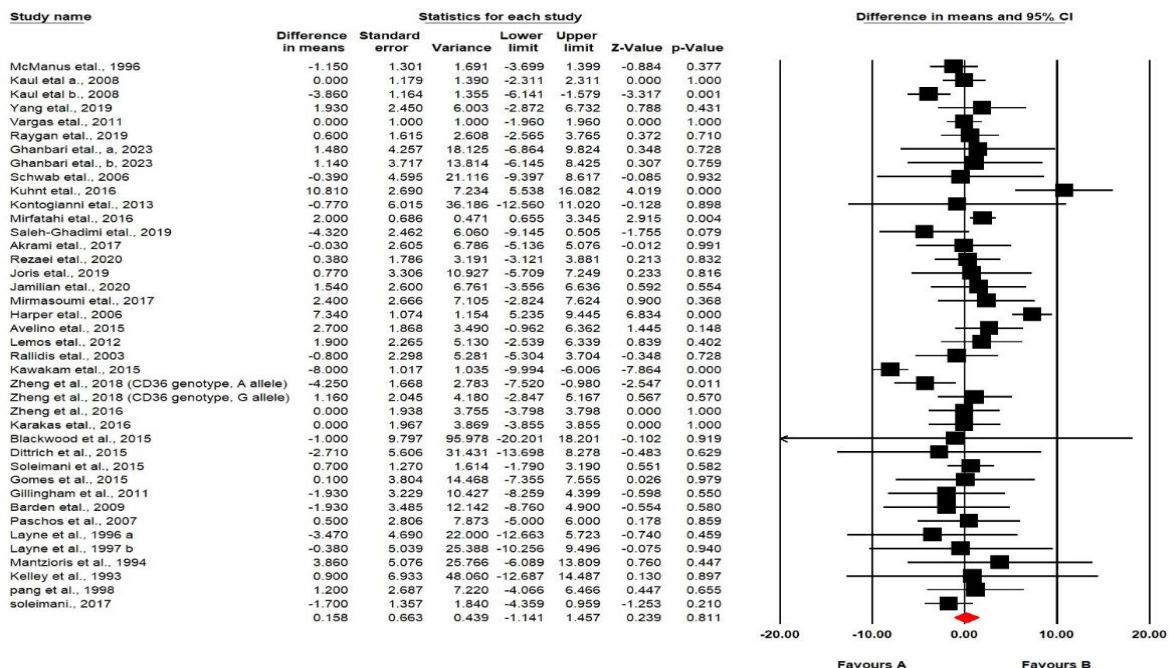
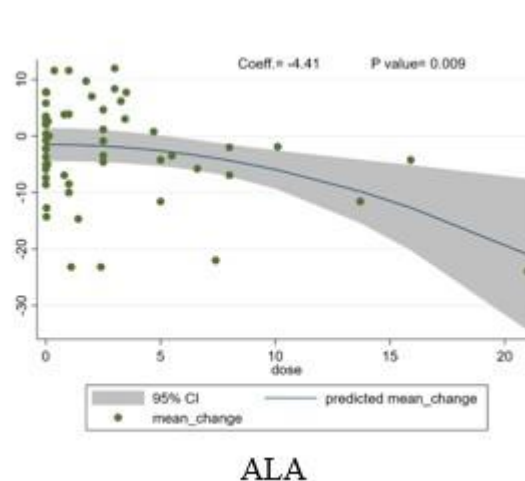
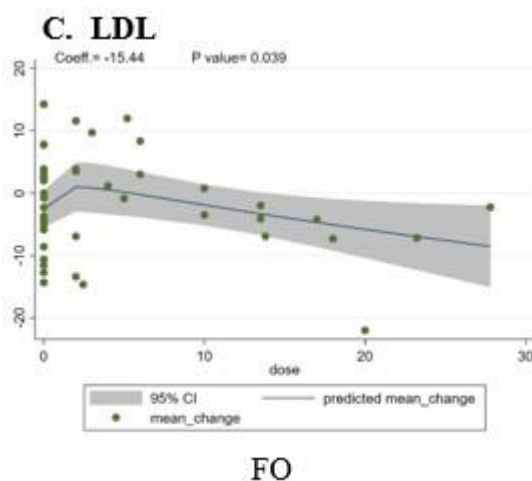
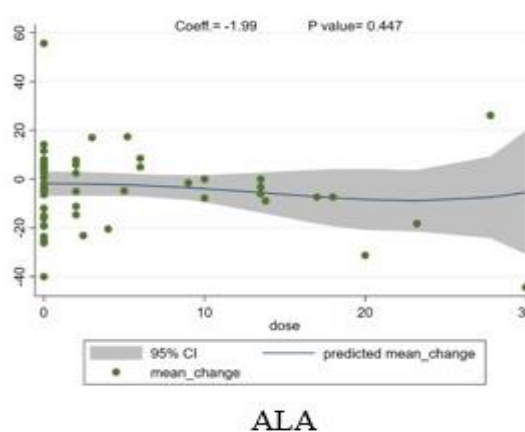
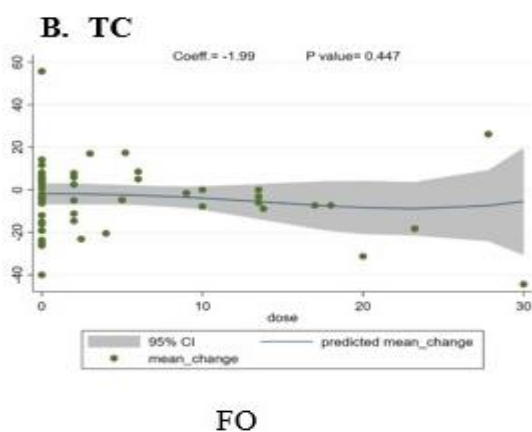
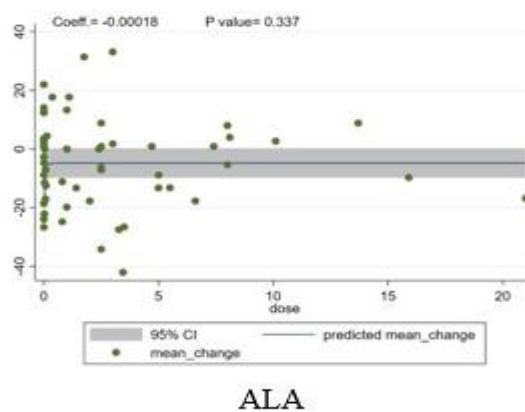
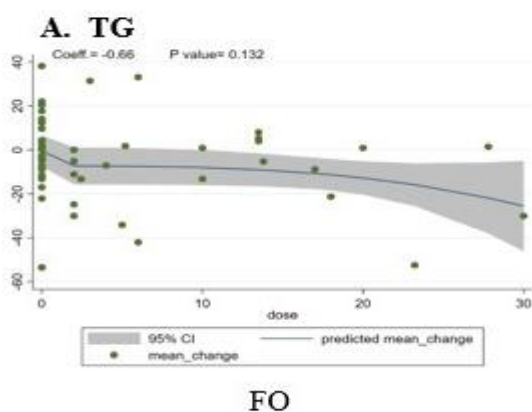


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the effect of flaxseed oil on blood lipids. (A) TG: Triglycerides, (B) TC: Total cholesterol, (C) LDL: Low-density lipoprotein and (D) HDL: high-density lipoprotein.

Non-linear dose-responses between dose and flaxseed intervention and lipid profile

The findings from the non-linear dose-response analysis (illustrated in multiple sections of Figure 3, panels A-D) indicated a notable link between flaxseed oil dosage and LDL-C levels (p non-linearity = 0.039). In contrast, this relationship was not statistically significant for TG (p non-

linearity = 0.132), total cholesterol (p non-linearity = 0.447), or HDL-C (p non-linearity = 0.538). Additionally, the impact of ALA intervention revealed a significant non-linear association with LDL-C (p non-linearity = 0.039) and total cholesterol (p non-linearity = 0.027). Still, this connection did not reach significance for TG (p non-linearity = 0.337) or HDL-C (p non-linearity = 0.157).



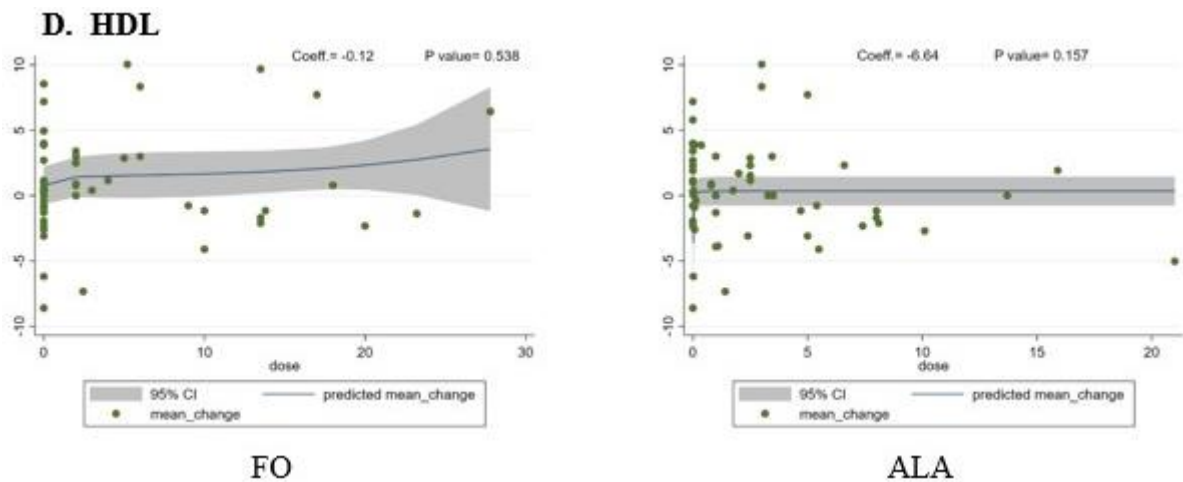


Figure 3. Non-linear dose-response effects of FO (Flaxseed oil) (g)/ ALA (α -Linolenic acid) (mg) dosages on A: TG: Triglycerides, B: TC: Total cholesterol, C: LDL: Low-density lipoprotein and D: HDL: high-density lipoprotein, in adults.

Sensitivity analysis

The sensitivity analysis indicates that removing any single trial did not significantly alter the analysis outcomes for LDL-C and HDL-C. However, the impact of flaxseed on TC levels was sensitive to the study conducted by Harper et al. (Harper et al. 2006a). Additionally, the TG level was sensitive to Soleimani et al. 2017 (Soleimani et al. 2017c), Soleimani et al., 2017 (Soleimani et al. 2017a), Karakas et al., 2016 (Karakas et al. 2016), Lemos et al., 2012 (Lemos et al. 2012b), Jamilian et al., 2020 (Jamilian et al. 2020c), Mirfatahi et al., 2016 (Mirfatahi et al. 2016b), and Ghanbari et al. 2023 (Ghanbari et al. 2023b).

Meta-regression

Meta-regression analysis revealed significant correlations between the duration of flaxseed oil intervention and changes in TG, TC, and LDL-C levels. However, no significant association was observed with HDL-C. Additionally, no significant associations were found between the dosage of supplementation and changes in TG, LDL-C, HDL-C, and TC (Appendix 2, Supplemental Table S6).

Publication bias

Following the execution of Egger's linear regression test and Begg's rank correlation test, we observed that the p-

values exceeded 0.05, except for the TC and LDL-C levels in Egger's linear regression test and the TC level in Begg's rank correlation test. Using the "trim and fill" technique, the analysis estimated that there were 8, 1, 3, and 14 potentially absent studies for TG, TC, LDL, and HDL, respectively (Appendix 4, Supplemental Table S7).

Discussion

In the current meta-analysis, we found that consumption of FO is associated with a significant inverse effect on TG levels, particularly in obese individuals and interventions lasting <12 weeks. However, the overall TG reduction is modest and of limited clinical significance, as reductions of ≥ 20 –30 mg/dl are typically required to impact cardiovascular risk meaningfully. FO consumption did not significantly affect other lipid parameters, except for HDL-C, where subgroup analyses revealed a significant increase in individuals with baseline HDL levels >40 mg/dl.

The mechanisms underlying the effects of FO on lipid profiles remain incompletely understood. However, FO is a rich source of ALA, which may influence HDL-C and TG levels. ALA exhibits anti-inflammatory properties that can effectively reduce TG levels (Hadi et al. 2020; Pan et al. 2009). Additionally, phytic acid, present in FO,

possesses antioxidant properties that may indirectly affect lipid metabolism by reducing oxidative stress (Torkan et al. 2015). FO also modulates key enzymes involved in lipid metabolism, such as fatty acid synthase (FAS) and hormone-sensitive lipase (HSL), which play critical roles in fat synthesis and breakdown (Liu et al. 2021). Furthermore, FO upregulates peroxisome proliferator-activated receptor- α (PPAR- α) which enhances fatty acid β -oxidation and reduces lipogenesis, ultimately leading to lower TG levels. Additionally, FO activates delta-5-desaturase (D5D) and delta-6-desaturase (D6D), enzymes that convert ALA into longer-chain omega-3 fatty acids, thereby further enhancing lipid metabolism (Devarshi et al. 2013). These mechanistic pathways suggest that FO's ALA content and its downstream effects on lipid metabolism, particularly via anti-inflammatory properties and β -oxidation, are central to its TG-lowering effects, especially in obese individuals or those with elevated baseline TG levels.

Variability in participant characteristics, such as health status and BMI, likely influences these outcomes. Subgroup analyses revealed that the reduction was particularly pronounced in interventions lasting 12 weeks and in obese individuals. These findings align with studies by Kaul et al. and several others, which reported a substantial reduction in TG levels following FO intervention (Kaul et al. 2008a; Lemos et al. 2012b; Vargas et al. 2011a). However, some studies did not observe a significant reduction in TG levels, likely due to limitations such as short intervention durations, small sample sizes, and the omission of potential confounders, including inflammatory markers and insulin resistance (Gomes et al. 2015; Pang et al. 1998; Raygan et al. 2019b; Rezaei et al. 2020b; Yang et al. 2019a).

FO intervention did not significantly reduce TC levels. However, the results became significant for intervention durations of less than 12 weeks. Most RCTs

have reported insignificant relationships, which may be attributed to limitations such as a small sample size, short intervention duration, and an uncontrolled dietary pattern (Gillingham et al. 2011; Gomes et al. 2015; Kelley et al. 1993; KS 1996; Pang et al. 1998). In contrast, Kawakami et al. and Harper et al. observed a significant reduction in TC levels in their studies (Harper et al. 2006a; Kawakami et al. 2015a). A dose-response effect of ALA intake on TC was observed, indicating that higher doses of ALA corresponded with a reduction in TC. Furthermore, an intake of more than 10 mg/day of ALA proved to be more effective, with the benefits increasing progressively with higher doses. This dose-response effect is supported by Kawakami et al. and Harper et al., suggesting that higher ALA doses (>10 mg/day) are required for meaningful TC reductions.

FO consumption did not demonstrate a significant relationship with LDL-C levels. Additionally, the creation of various subgroups did not affect the significance of this relationship. These findings contrast with those of Kawakami et al. and Harper et al., who reported an inverse relationship between FO consumption and LDL levels. This discrepancy may be attributed to limitations in their studies, such as the specific clinical conditions of burn patients, short intervention durations, and uncontrolled confounding factors, including caloric intake and inflammatory markers (Harper et al. 2006a; Kawakami et al. 2015a). In contrast, Ghanbari et al. did not find a significant association between FO consumption and LDL-C levels (Ghanbari et al. 2023b). Non-linear dose-response analysis revealed a slight increase in LDL-C at FO doses of 0 to <5 g/day, followed by a decrease at doses between 5 and <30 g/day. This suggests that higher FO doses (>5 g/day) and ALA intake (>10 mg/day) may be necessary to achieve meaningful LDL-C and TC reductions. These discrepancies may reflect variability in participant characteristics such as baseline lipid levels and health status, as

well as study limitations like inadequate FO doses or short intervention durations. Future research should prioritize standardized, higher-dose interventions to confirm these dose-dependent effects and optimize FO supplementation strategies for dyslipidemia management.

Most RCTs did not find a significant effect of FO on HDL-C levels, likely because they did not account for baseline HDL-C levels as a confounding variable (Karakas *et al.* 2016; Rezaei *et al.* 2020b; Zheng *et al.* 2018). However, subgroup analyses based on baseline HDL-C levels (>40 mg/dl) revealed a significant increase, consistent with findings by Kaul *et al.* and Kawakami *et al.* (Kaul *et al.* 2008a; Kawakami *et al.* 2015a).

While this meta-analysis consolidates the available evidence on the effects of FO on LDL-C, HDL-C, TC, and TG, certain limitations should be acknowledged when interpreting the findings. Significant heterogeneity was detected in the effects of FO on lipid parameters, even after subgroup analyses, likely due to variability in participant characteristics (e.g. health status, BMI, and baseline lipid profiles) and study designs (e.g. intervention duration, dosage, and sample size).

The included studies encompassed both healthy and unhealthy individuals, which may have contributed to variations in the results. Furthermore, individuals with different clinical conditions may exhibit diverse responses to FO interventions. For instance, insulin resistance levels are generally higher among individuals with type 2 diabetes mellitus (T2DM), potentially diminishing the effectiveness of FO supplementation. Regional dietary differences, particularly lower omega-6 fatty acid content in diets from Iran, Canada, and Brazil compared to Western diets, may limit the generalizability of findings to populations with higher baseline LDL-C. Subgroup analysis for studies with baseline LDL-C >130 mg/dl showed no significant reduction (WMD: -3.36 mg/dl, $p=0.1$; Appendix 2, Supplemental Table

S4), suggesting limited efficacy in such cohorts. Additionally, participant characteristics varied across studies, with some trials focusing on overweight individuals and others on obese populations.

Variability in intervention duration and dosage was also observed; for example, some studies administered 3 g/day of FO for 26 weeks, while others used 10 g/day for 12 weeks. Sample size discrepancies may have further influenced the outcomes. Subgroup analyses revealed significant reductions in TG and TC in interventions lasting <12 weeks, but not in trials ≥ 12 weeks (Appendix 2, Supplemental Tables S2–S3), possibly due to poor adherence, dietary non-compliance, or metabolic adaptation in longer trials. The lack of significant overall effects on LDL-C (WMD: 1.01 mg/dl, $p=0.41$) may be partly attributed to regional dietary differences among the included studies, predominantly conducted in Iran, Canada, and Brazil, where diets typically have lower omega-6 fatty acid content compared to Western diets rich in omega-6 and processed foods. Future RCTs should control for confounders such as physical activity, statin use, and dietary omega-3/6 ratios, while incorporating adherence monitoring to clarify the impact of intervention duration and dosage. Longitudinal studies exploring short- and long-term effects, as well as variations in FO extraction methods, are needed to optimize its therapeutic application for dyslipidemia management.

This systematic review and meta-analysis indicate that FO supplementation significantly reduces TG levels, particularly in obese individuals and interventions lasting less than 12 weeks. It also increases HDL-C in adults with baseline HDL-C levels ≤ 40 mg/dl. While no significant overall effects were observed on LDL-C or TC, non-linear dose-response analyses suggest that FO doses exceeding 5 g/day and ALA intake above 10 mg/day may influence LDL-C and TC levels. These findings support FO as a viable adjunctive

therapy for dyslipidemia management, particularly for TG reduction. However, variability in response across populations, intervention durations, and dosages highlights the need for further research to refine therapeutic strategies.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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