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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).

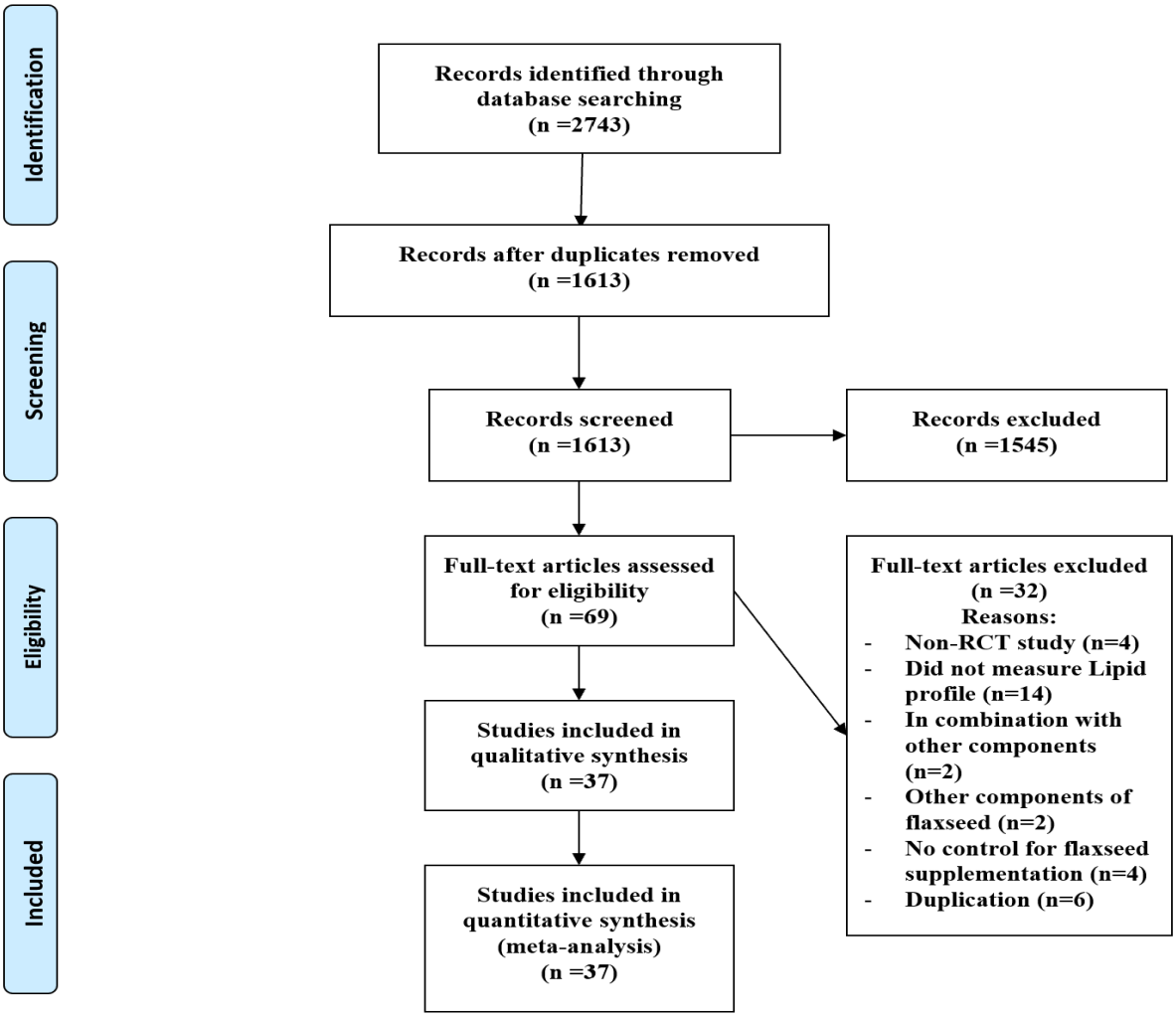


Figure 1. Flow diagram of the literature search process. Abbreviation: RCT, randomized controlled trial

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

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

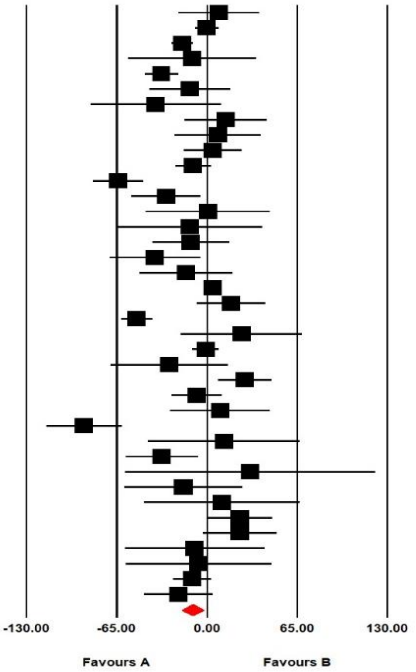
The results concerning LDL-C were derived from 35 groups across 33 studies. Flaxseed consumption did not lead to a significant change in LDL levels (WMD: 1.01 mg/dl; 95% CI: -1.35 to 3.41; p = 0.41), and there was moderate heterogeneity among the studies (I^2 = 40.88%; p = 0.007) (Figure 2C). Statistical 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).

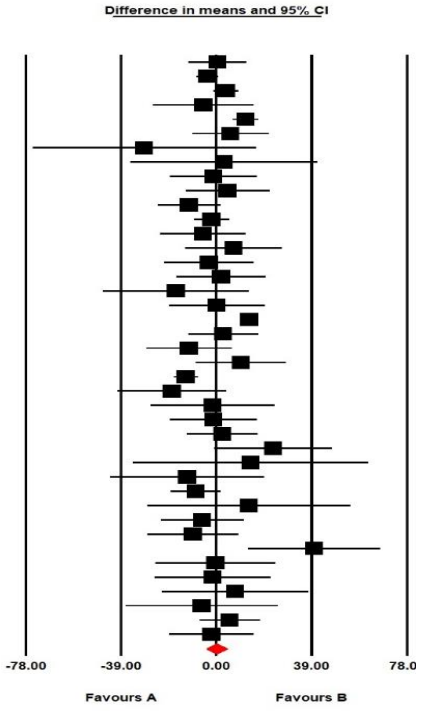
A. TG level

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McManus etal., 1996	8.850	14.991	224.743	-20.533	38.233	0.590	0.555
Kaul etal a., 2008	0.000	4.216	17.776	-8.264	8.264	0.000	1.000
Kaul etal b., 2008	-17.700	3.771	14.220	-25.091	-10.309	-4.694	0.000
Yang etal., 2019	-10.620	23.528	553.556	-56.734	35.494	-0.451	0.652
Vargas etal., 2011	-32.750	6.008	36.092	-44.525	-20.975	-5.451	0.000
Raygan etal., 2019	-12.000	14.768	218.106	-40.946	16.946	-0.813	0.416
Ghanbari etal., a, 2023	-36.750	23.934	572.827	-83.659	10.159	-1.535	0.125
Ghanbari etal., b, 2023	13.860	15.013	225.400	-15.566	43.286	0.923	0.356
Schwab etal., 2006	7.960	15.731	247.456	-22.872	38.792	0.506	0.613
Kuhnt etal., 2016	4.420	10.623	112.842	-16.400	25.240	0.416	0.677
Kontogianni etal., 2013	-9.730	6.340	40.193	-22.156	2.696	-1.535	0.125
Mirfatahi etal., 2016	-64.000	9.049	81.882	-81.735	-46.265	-7.073	0.000
Saleh-Ghadimi etal., 2019	-29.390	12.658	160.230	-54.200	-4.580	-2.322	0.020
Akrami etal., 2017	1.000	23.016	529.743	-44.111	46.111	0.043	0.965
Rezaei etal., 2020	-12.390	26.737	714.856	-64.793	40.013	-0.463	0.643
Joris etal., 2019	-11.500	13.981	195.468	-38.902	15.902	-0.823	0.411
Jamilian etal., 2020	-37.170	16.715	279.376	-69.930	-4.410	-2.224	0.026
Mirmasoumi etal., 2017	-14.800	16.959	287.597	-48.038	18.438	-0.873	0.383
Harper etal., 2006	4.420	1.668	2.784	1.150	7.690	2.649	0.008
Avelino etal., 2015	17.300	12.515	156.637	-7.230	41.830	1.382	0.167
Lemos etal., 2012	-50.500	5.629	31.688	-61.533	-39.467	-8.971	0.000
Rallidis etal., 2003	25.000	22.127	489.582	-18.367	68.367	1.130	0.259
Kawakam etal., 2015	-0.700	4.822	23.253	-10.151	8.751	-0.145	0.885
Babajafari et al., 2018	-26.760	21.449	460.069	-68.800	15.280	-1.248	0.212
Zheng et al., 2018 (CD36 genotype, A allele)	27.430	9.640	92.921	8.537	46.323	2.846	0.004
Zheng et al., 2018 (CD36 genotype, G allele)	-7.070	9.158	83.861	-25.018	10.878	-0.772	0.440
Zheng et al., 2016	9.730	18.499	342.206	-26.527	45.987	0.526	0.599
Karakas etal., 2016	-88.500	13.744	188.895	-115.438	-61.562	-6.439	0.000
Dittrich et al., 2015	12.390	27.742	769.604	-41.983	66.763	0.447	0.655
Soleimani et al., 2015	-32.400	13.470	181.449	-58.801	-5.999	-2.405	0.016
Gomes et al., 2015	31.200	45.919	2108.588	-58.800	121.200	0.679	0.497
Gillingham et al., 2011	-16.810	21.654	468.904	-59.251	25.631	-0.776	0.438
Paschos et al., 2007	11.000	28.448	809.316	-44.758	66.758	0.387	0.699
Layne et al., 1996 a	23.890	11.892	141.416	0.582	47.198	2.009	0.045
Layne et al., 1997 b	23.890	13.447	180.825	-2.466	50.246	1.777	0.076
Mantzioris et al., 1994	-8.850	25.548	652.687	-58.923	41.223	-0.346	0.729
Kelley et al., 1993	-5.900	26.545	704.644	-57.928	46.128	-0.222	0.824
pang et al., 1998	-10.600	6.851	46.937	-24.028	2.828	-1.547	0.122
soleimani.,2017	-20.600	12.487	155.923	-45.074	3.874	-1.650	0.099
	-10.343	3.921	15.376	-18.029	-2.658	-2.638	0.008

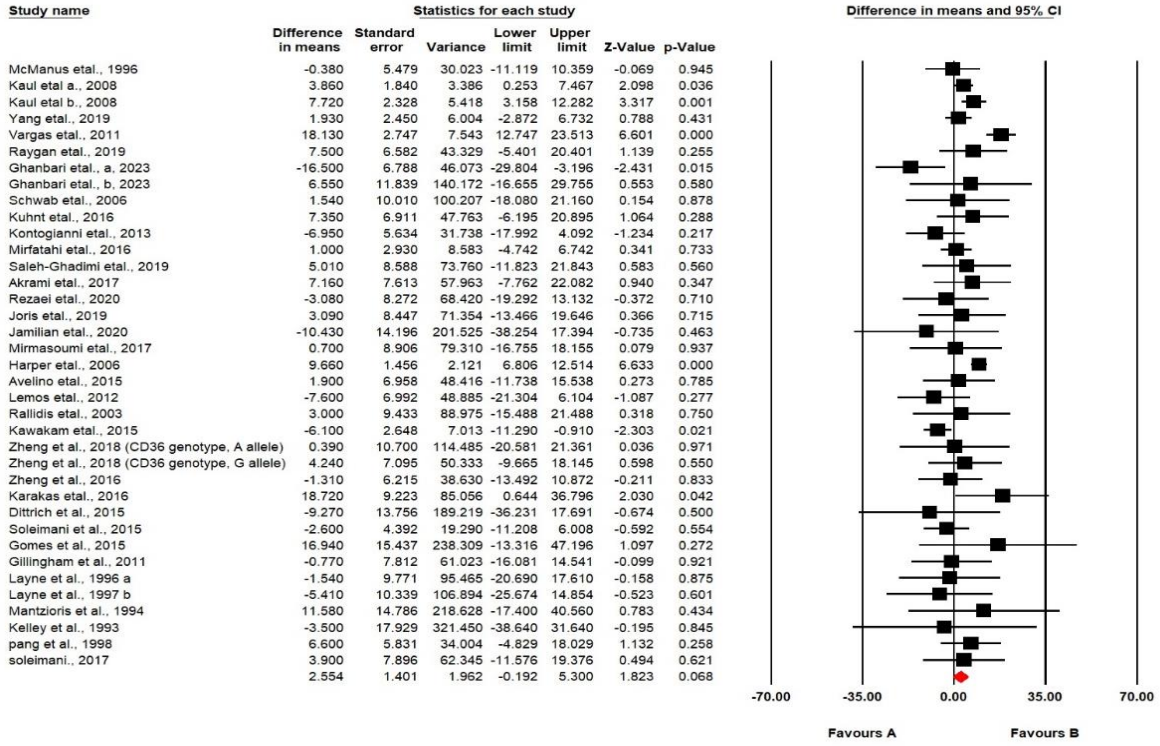


B. TC level

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McManus etal., 1996	0.390	5.943	35.315	-11.257	12.037	0.066	0.948
Kaul etal a., 2008	-3.860	2.177	4.737	-8.126	0.406	-1.773	0.076
Kaul etal b., 2008	3.860	2.602	6.769	-1.239	8.959	1.484	0.138
Yang etal., 2019	-5.400	10.580	111.938	-26.137	15.337	-0.510	0.610
Vargas etal., 2011	11.970	2.833	8.024	6.418	17.522	4.226	0.000
Raygan etal., 2019	5.800	8.093	65.489	-10.061	21.661	0.717	0.474
Ghanbari etal., a, 2023	-29.510	23.250	540.542	-75.078	16.058	-1.269	0.204
Ghanbari etal., b, 2023	3.070	19.468	379.009	-35.087	41.227	0.158	0.875
Schwab etal., 2006	-1.160	8.981	80.663	-18.763	16.443	-0.129	0.897
Kuhnt etal., 2016	4.630	8.644	74.725	-12.313	21.573	0.536	0.592
Kontogianni etal., 2013	-11.200	6.533	42.682	-24.005	1.605	-1.714	0.086
Mirfatahi etal., 2016	-2.000	3.596	12.933	-9.048	5.048	-0.556	0.578
Saleh-Ghadimi etal., 2019	-5.480	8.809	77.602	-22.746	11.786	-0.622	0.534
Akrami etal., 2017	6.960	10.053	101.054	-12.743	26.663	0.692	0.489
Rezaei etal., 2020	-3.090	9.263	85.808	-21.246	15.066	-0.334	0.739
Joris etal., 2019	1.930	9.203	84.704	-16.108	19.968	0.210	0.834
Jamilian etal., 2020	-16.590	15.168	230.054	-46.318	13.138	-1.094	0.274
Mirmasoumi etal., 2017	0.200	9.890	97.809	-19.184	19.584	0.020	0.984
Harper etal., 2006	13.510	0.834	0.696	11.875	15.145	16.198	0.000
Avelino etal., 2015	2.800	7.263	52.756	-11.436	17.036	0.385	0.700
Lemos etal., 2012	-11.200	9.030	81.550	-28.899	6.499	-1.240	0.215
Rallidis etal., 2003	10.000	9.451	89.322	-8.524	28.524	1.058	0.290
Kawakam etal., 2015	-12.500	2.619	6.857	-17.632	-7.368	-4.774	0.000
Babajafari et al., 2018	-18.190	11.239	126.305	-40.217	3.837	-1.619	0.106
Zheng et al., 2018 (CD36 genotype, A allele)	-1.540	12.822	164.406	-26.671	23.591	-0.120	0.904
Zheng et al., 2018 (CD36 genotype, G allele)	-1.160	9.045	81.810	-18.888	16.568	-0.128	0.898
Zheng et al., 2016	2.330	7.343	53.920	-12.062	16.722	0.317	0.751
Karakas etal., 2016	23.160	12.206	148.982	-0.763	47.083	1.897	0.058
Blackwood et al., 2015	14.000	24.471	598.811	-33.962	61.962	0.572	0.567
Dittrich et al., 2015	-11.980	15.969	255.004	-43.278	19.318	-0.750	0.453
Soleimani et al., 2015	-8.400	5.108	26.092	-18.412	1.612	-1.644	0.100
Gomes et al., 2015	13.300	21.111	445.673	-28.077	54.677	0.630	0.529
Gillingham et al., 2011	-5.790	8.555	73.183	-22.557	10.977	-0.677	0.499
Barden etal., 2009	-9.650	9.401	88.384	-28.076	8.776	-1.026	0.305
Paschos et al., 2007	40.000	13.777	189.796	12.998	67.002	2.903	0.004
Layne et al., 1996 a	-0.380	12.376	153.175	-24.637	23.877	-0.031	0.976
Layne et al., 1997 b	-1.550	12.076	145.821	-25.218	22.118	-0.128	0.898
Mantzioris et al., 1994	7.710	15.249	232.531	-22.177	37.597	0.506	0.613
Kelley et al., 1993	-6.000	16.041	257.324	-37.440	25.440	-0.374	0.708
pang et al., 1998	5.400	6.402	40.992	-7.149	17.949	0.843	0.399
soleimani., 2017	-2.000	8.706	75.799	-19.064	15.064	-0.230	0.818
	0.090	2.125	4.516	-4.075	4.256	0.042	0.966



C. LDL level



D. HDL level

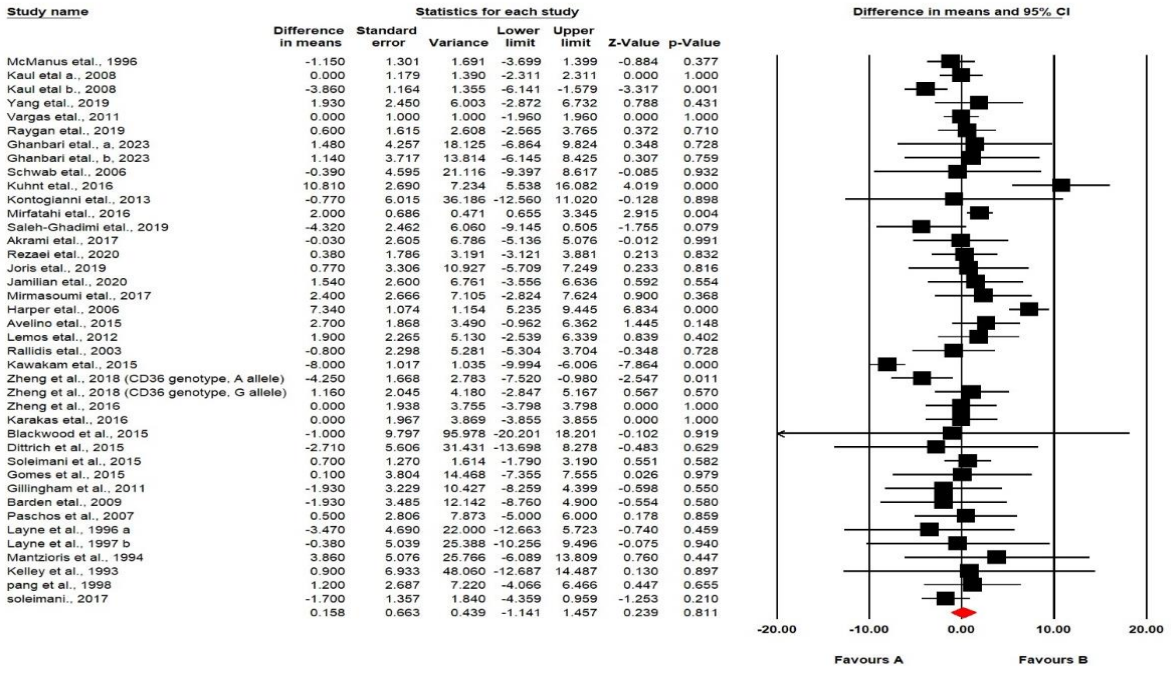
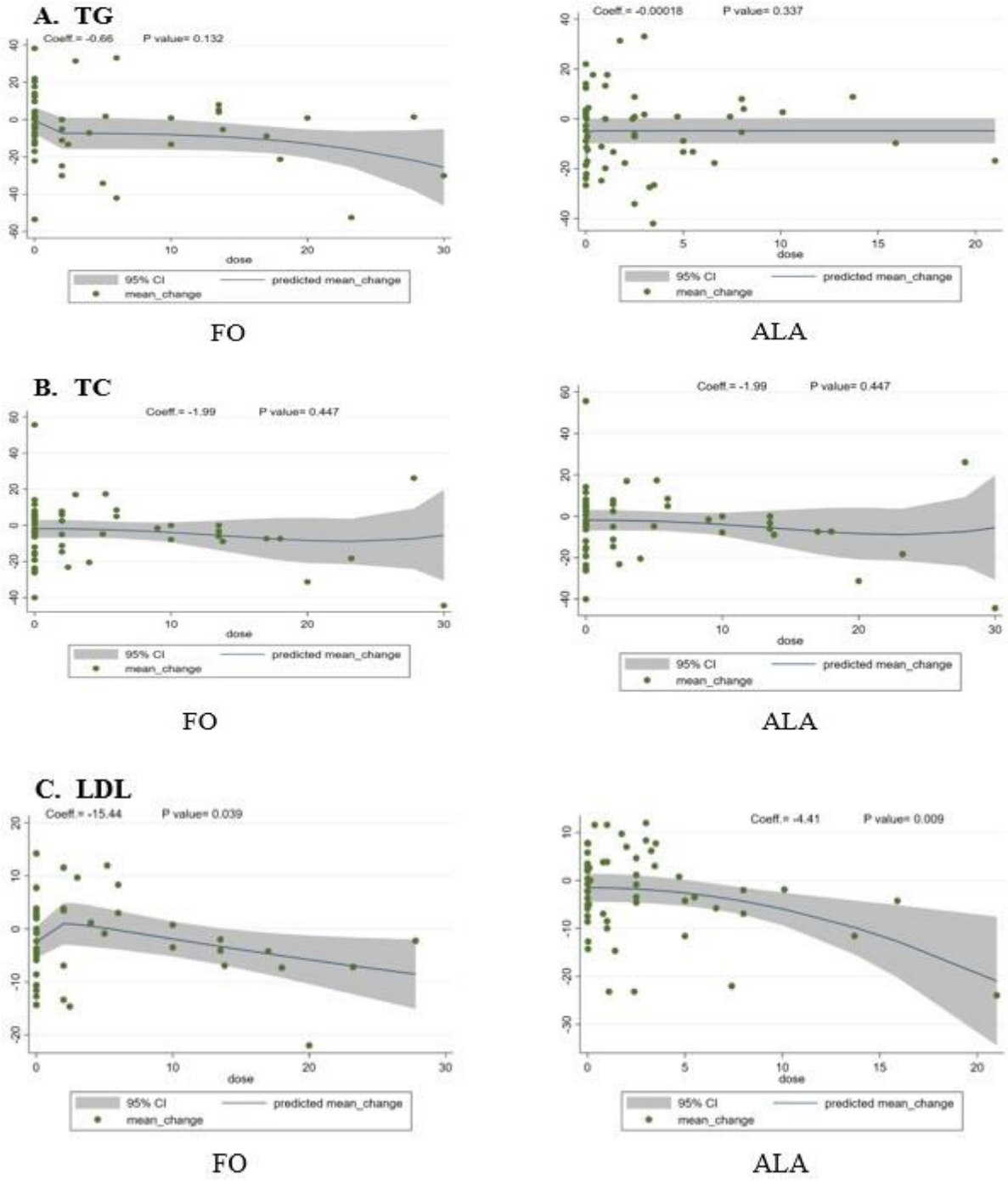


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the effect of flaxseed oil on blood lipids. (A) TG: Triglycerides, (B) TC: Total cholesterol, (C) LDL: Low-density lipoprotein and (D) HDL: high-density lipoprotein.

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).



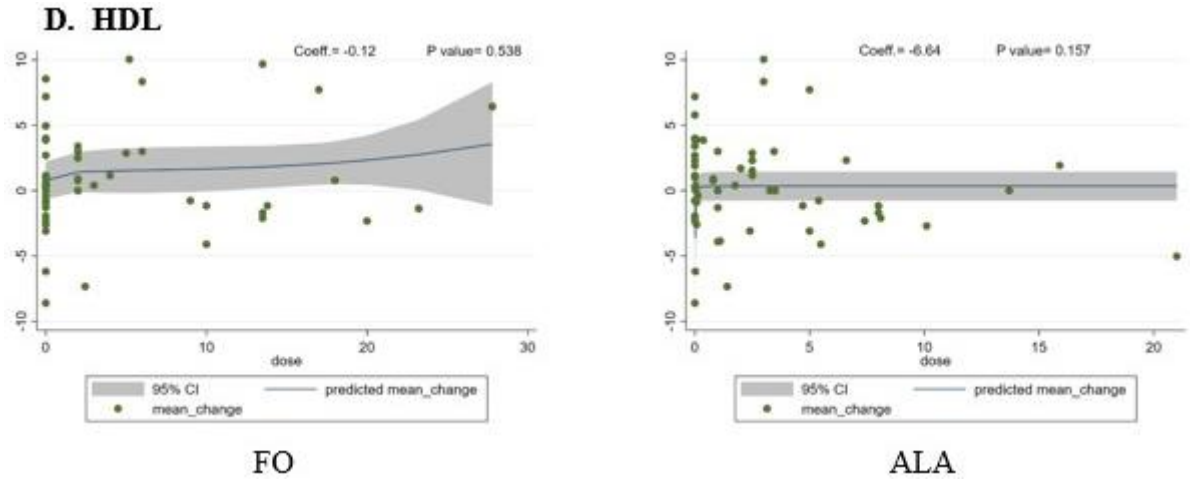


Figure 3. Non-linear dose-response effects of FO (Flaxseed oil) (g)/ ALA (α-Linolenic acid) (mg) dosages on A: TG: Triglycerides, B: TC: Total cholesterol, C: LDL: Low-density lipoprotein and D: HDL: high-density lipoprotein, in adults.

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-alpha (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.

References

Borenstein M, Hedges L, Higgins J, et al. Comprehensive Meta-Analysis Version 2.Englewood, NJ: Biostat. 2005.

Akrami A, Nikaein F, Babajafari S, Faghih S, Yarmohammadi H (2018) Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid profile, blood pressure, and lipid peroxidation in patients with metabolic syndrome. J Clin Lipidol 12(1):70-77 doi:10.1016/j.jacl.2017.11.004

Avelino AP, Oliveira GM, Ferreira CC, Luiz RR, Rosa G (2015) Additive effect of linseed oil supplementation on the lipid profiles of older adults. Clin Interv Aging 10:1679-85 doi:10.2147/CIA.S75538

Babajafari S, Hojhabrimanesh A, Sohrabi Z, Ayaz M, Noorafshan A, Akrami A (2018) Comparing isolated soy protein with flaxseed oil vs isolated soy protein with corn oil and wheat flour with corn oil consumption on muscle catabolism, liver function, blood lipid, and sugar in burn patients: a randomized clinical trial. Trials 19(1):1-10

Barden AE, Croft KD, Durand T, Guy A, Mueller MJ, Mori TA (2009) Flaxseed oil supplementation increases plasma F1-phytoprostanes in healthy men. J Nutr 139(10):1890-1895

Blackwood D, LaVallée R, Al Busaidi A, Jassal D, Pierce G (2015) A randomized trial of the effects of ezetimibe on the absorption of omega-3 fatty acids in cardiac disease patients: A pilot study. Clin Nutr ESPEN 10(5):e155-e159

Brown CD, Higgins M, Donato KA, et al. (2000) Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res 8(9):605-619

Covington MB (2004) Omega-3 fatty acids. AFP 70(1):133-140

Devarshi PP, Jangale NM, Ghule AE, Bodhankar SL, Harsulkar AM (2013) Beneficial effects of flaxseed oil and fish oil diet are through modulation of different hepatic genes involved in lipid metabolism in streptozotocin–nicotinamide induced diabetic rats. Genes & nutrition 8:329-342

Dittrich M, Jahreis G, Bothor K, et al. (2015) Benefits of foods supplemented with vegetable oils rich in α-linolenic, stearidonic or docosahexaenoic acid in hypertriglyceridemic subjects: A double-blind, randomized, controlled trail. Eur J Nutr 54:881-893

Duval S, Tweedie R (2000) Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56(2):455-463 doi:https://doi.org/10.1111/j.0006-341x.2000.00455.x

Eslami Z, Joshaghani H, Eghbal Moghanlou A, Norouzi A, Mirghani SJ (2025) Atorvastatin and flaxseed dietary treatments improve dyslipidemia and liver injuries in a diet-induced rat model of non-alcoholic fatty liver disease. AJP 15(3):1102-1112 doi:10.22038/ajp.2024.25220

Ferrari CKB (2023) Antioxidant and anti-atherosclerotic potential of Banana (Musa spp): A review of biological mechanisms for prevention and protection against atherosclerosis. AJP 13(3):240-254 doi:10.22038/ajp.2022.20616

Ghanbari A, Masoumi S, Kazemnezhad Leyli E, Mahdavi-Roshan M, Mobayen M (2023a) Effects of Flaxseed Oil and Olive Oil on Markers of Inflammation and Wound Healing in Burn Patients: A Randomized Clinical Trial. Bull Emerg Trauma 11(1):32-40 doi:10.30476/BEAT.2022.97070.1399

Ghanbari A, Masoumi S, Leyli EK, Mahdavi-Roshan M, Mobayen M (2023b) Effects of flaxseed oil and olive oil on markers of inflammation and wound healing in burn patients: A randomized clinical trial. Bulletin of Emergency & Trauma 11(1):32

Ghersi D, Berlin J, Askie L (2008) Prospective Meta-Analysis Cochrane Handbook for Systematic Reviews of Interventions. p 559-570

Gillingham LG, Gustafson JA, Han S-Y, Jassal DS, Jones PJ (2011) High-oleic rapeseed (canola) and flaxseed oils modulate serum lipids and inflammatory biomarkers in hypercholesterolaemic subjects. BJN 105(3):417-427

Gomes PM, Hollanda-Miranda WR, Beraldo RA, et al. (2015) Supplementation of α-linolenic acid improves serum adiponectin levels and insulin sensitivity in patients with type 2 diabetes. Nutrition 31(6):853-857

Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M (2020) Effect of flaxseed supplementation on lipid profile: An updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. Pharmacol Res 152:104622

Harper CR, Edwards MC, Jacobson TA (2006a) Flaxseed oil supplementation does not affect plasma lipoprotein concentration or particle size in human subjects. J Nutr 136(11):2844-2848

Harper CR, Edwards MC, Jacobson TA (2006b) Flaxseed oil supplementation does not affect plasma lipoprotein concentration or particle size in human subjects. J Nutr 136(11):2844-8 doi:10.1093/jn/136.11.2844

Hedayatnia M, Asadi Z, Zare-Feyzabadi R, et al. (2020) Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids in Health and Disease 19(1):42 doi:10.1186/s12944-020-01204-y

Higgins JP, Green S (2011) Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration. London, UK

Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5(1):1-10

Jamilian M, Tabassi Z, Reiner Ž, et al. (2020a) The effects of n-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus: A randomised, double-blind, placebo-controlled trial. BJN 123(7):792-799

Jamilian M, Tabassi Z, Reiner Z, et al. (2020b) The effects of n-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus: a randomised, double-blind, placebo-controlled trial. Br J Nutr 123(7):792-799 doi:10.1017/S0007114519003416

Jamilian M, Tabassi Z, Reiner Ž, et al. (2020c) The effects of n-3 fatty acids from flaxseed oil on genetic and metabolic profiles in patients with gestational diabetes mellitus: a randomised, double-blind, placebo-controlled trial. Br J Nutr 123(7):792-799 doi:10.1017/s0007114519003416

Jiang W, Liang J, Xiong M, Dong Y (2022) Efficacy of flaxseed oil compared with fish oil supplementation in the treatment of coronary heart disease: a retrospective study. J Thorac Dis 14(2):396-404 doi:10.21037/jtd-22-26

Joris PJ, Draijer R, Fuchs D, Mensink RP (2020) Effect of alpha-linolenic acid on vascular function and metabolic risk markers during the fasting and postprandial phase: A randomized placebo-controlled trial in untreated (pre-)hypertensive individuals. Clin Nutr 39(8):2413-2419 doi:10.1016/j.clnu.2019.11.032

Joshi SR, Anjana RM, Deepa M, et al. (2014) Prevalence of dyslipidemia in urban and rural India: the ICMR–INDIAB study. PloS one 9(5):e96808

Karakas SE, Perroud B, Kind T, Palazoglu M, Fiehn O (2016) Changes in plasma metabolites and glucose homeostasis during omega-3 polyunsaturated fatty acid supplementation in women with polycystic ovary syndrome. BBA clinical 5:179-185

Kaul N, Kreml R, Austria JA, et al. (2008a) A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers. Journal of the American College of Nutrition 27(1):51-58

Kaul N, Kreml R, Austria JA, et al. (2008b) A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers. J Am Coll Nutr 27(1):51-8 doi:10.1080/07315724.2008.10719674

Kawakami Y, Yamanaka-Okumura H, Naniwa-Kuroki Y, Sakuma M, Taketani Y, Takeda E (2015a) Flaxseed oil intake reduces serum small dense low-density lipoprotein concentrations in Japanese men: a randomized, double blind, crossover study. Nutrition journal 14:1-9

Kawakami Y, Yamanaka-Okumura H, Naniwa-Kuroki Y, Sakuma M, Taketani Y, Takeda

E (2015b) Flaxseed oil intake reduces serum small dense low-density lipoprotein concentrations in Japanese men: a randomized, double blind, crossover study. Nutr J 14(1):1-9

Kawakami Y, Yamanaka-Okumura H, Naniwa-Kuroki Y, Sakuma M, Taketani Y, Takeda E (2015c) Flaxseed oil intake reduces serum small dense low-density lipoprotein concentrations in Japanese men: a randomized, double blind, crossover study. Nutr J 14:39 doi:10.1186/s12937-015-0023-2

Kelley DS, Nelson GJ, Love JE, et al. (1993) Dietary α-linolenic acid alters tissue fatty acid composition, but not blood lipids, lipoproteins or coagulation status in humans. Lipids 28:533-537

Kontogianni MD, Vlassopoulos A, Gatzieva A, et al. (2013) Flaxseed oil does not affect inflammatory markers and lipid profile compared to olive oil, in young, healthy, normal weight adults. Metabolism 62(5):686-93 doi:10.1016/j.metabol.2012.11.007

KS L (1996) Normal subject consuming physiological levels of 18: 3 n-3 and 20: 5 n-3 from flaxseed or fish oils have characteristic differences in plasma lipid and lipoprotein fatty acid levels. J Nutr 126:2130-2140

Kuhnt K, Weiss S, Kiehntopf M, Jahreis G (2016) Consumption of echium oil increases EPA and DPA in blood fractions more efficiently compared to linseed oil in humans. Lipids Health Dis 15:32 doi:10.1186/s12944-016-0199-2

Layne KS, Goh YK, Jumpsen JA, Ryan EA, Chow P, Clandinin MT (1996) Normal subjects consuming physiological levels of 18: 3 (n-3) and 20: 5 (n-3) from flaxseed or fish oils have characteristic differences in plasma lipid and lipoprotein fatty acid levels. J Nutr 126(9):2130-2140

Lee P, Prasad K (2003) Effects of flaxseed oil on serum lipids and atherosclerosis in hypercholesterolemic rabbits. J CARDIOVASC PHARM T 8(3):227-235

Lemos JR, Alencastro MG, Konrath AV, Cargnin M, Manfro RC (2012a) Flaxseed oil supplementation decreases C-reactive protein levels in chronic hemodialysis patients. Nutr Res 32(12):921-7 doi:10.1016/j.nutres.2012.08.007

Lemos JR, de Alencastro MG, Konrath AV, Cargnin M, Manfro RC (2012b) Flaxseed oil supplementation decreases C-reactive protein levels in chronic hemodialysis patients. Nutr Res 32(12):921-927

Liu S, Wang X, Li Y, et al. (2021) Flaxseed oil and heated flaxseed supplements have different effects on lipid deposition and ileal microbiota in Albas cashmere goats. Animals 11(3):790

Liu YX, Yu JH, Sun JH, Ma WQ, Wang JJ, Sun GJ (2023) Effects of Omega-3 Fatty Acids Supplementation on Serum Lipid Profile and Blood Pressure in Patients with Metabolic Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Foods 12(4) doi:10.3390/foods12040725

Mantzioris E, James MJ, Gibson RA, Cleland LG (1994) Dietary substitution with an α-linolenic acid-rich vegetable oil increases eicosapentaenoic acid concentrations in tissues. AJCN 59(6):1304-1309

McManus RM, Jumpson J, Finegood DT, Clandinin MT, Ryan EA (1996a) A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. Diabetes Care 19(5):463-7 doi:10.2337/diacare.19.5.463

McManus RM, Jumpson J, Finegood DT, Clandinin MT, Ryan EA (1996b) A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. Diabetes care 19(5):463-467

Mirfatahi M, Tabibi H, Nasrollahi A, Hedayati M (2016a) Effects of Flaxseed Oil on Serum Lipids and Lipoproteins in Hemodialysis Patients: a Randomized Controlled Trial. Iran J Kidney Dis 10(6):405-412

Mirfatahi M, Tabibi H, Nasrollahi A, Hedayati M (2016b) Effects of flaxseed oil on serum lipids and lipoproteins in hemodialysis patients: A randomized controlled trial. Iranian journal of kidney diseases 10(6):405

Mirmasoumi G, Fazilati M, Foroozanfard F, et al. (2018) The Effects of Flaxseed Oil Omega-3 Fatty Acids Supplementation on Metabolic Status of Patients with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Exp Clin Endocrinol

Diabetes 126(4):222-228 doi:10.1055/s-0043-119751

Mohammadi-Sartang M, Mazloom Z, Sherafatmanesh S, Ghorbani M, Firoozi D (2017a) Effects of supplementation with quercetin on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr 71(9):1033-1039 doi:https://doi.org/10.1038/ejcn.2017.55

Mohammadi-Sartang M, Mazloom Z, Sohrabi Z, Sherafatmanesh S, Barati-Boldaji R (2017b) Resveratrol supplementation and plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 117:394-405 doi:10.1016/j.phrs.2017.01.012

Mohammadi-Sartang M, Sohrabi Z, Barati-Boldaji R, Raeisi-Dehkordi H, Mazloom Z (2018) Flaxseed supplementation on glucose control and insulin sensitivity: a systematic review and meta-analysis of 25 randomized, placebo-controlled trials. Nutr Rev 76(2):125-139 doi:https://doi.org/10.1093/nutrit/nux052

O'Meara JG, Kardia SL, Armon JJ, Brown CA, Boerwinkle E, Turner ST (2004) Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. Arch Intern Med 164(12):1313-1318

Page MJ, Moher D, Bossuyt PM, et al. (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. bmj 372

Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X (2009) Meta-analysis of the effects of flaxseed interventions on blood lipids. Am J Clin Nutr 90(2):288-97 doi:10.3945/ajcn.2009.27469

Pang D, Allman-Farinelli M, Wong T, Barnes R, Kingham K (1998) Replacement of linoleic acid with α-linolenic acid does not alter blood lipids in normolipidaemic men. BJN 80(2):163-167

Paschos GK, Zampelas A, Panagiotakos DB, et al. (2007) Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. Eur J Nutr 46:315-320

Prasad K (2009) Flaxseed and cardiovascular health. J Cardiovasc Pharmacol 54(5):369-377

Rallidis LS, Paschos G, Liakos GK, Velissaridou AH, Anastasiadis G, Zampelas A (2003) Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. Atherosclerosis 167(2):237-42 doi:10.1016/s0021-9150(02)00427-6

Raygan F, Taghizadeh M, Mirhosseini N, et al. (2019a) A comparison between the effects of flaxseed oil and fish oil supplementation on cardiovascular health in type 2 diabetic patients with coronary heart disease: A randomized, double-blinded, placebo-controlled trial. Phytother Res 33(7):1943-1951 doi:10.1002/ptr.6393

Raygan F, Taghizadeh M, Mirhosseini N, et al. (2019b) A comparison between the effects of flaxseed oil and fish oil supplementation on cardiovascular health in type 2 diabetic patients with coronary heart disease: a randomized, double-blinded, placebo-controlled trial. Phytother Res 33(7):1943-1951

Rezaei S, Sasani MR, Akhlaghi M, Kohanmoo A (2020a) Flaxseed oil in the context of a weight loss programme ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease: a randomised double-blind controlled trial. Br J Nutr 123(9):994-1002 doi:10.1017/s0007114520000318

Rezaei S, Sasani MR, Akhlaghi M, Kohanmoo A (2020b) Flaxseed oil in the context of a weight loss programme ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease: a randomised double-blind controlled trial. BJN 123(9):994-1002

Sadeghi M, Haghdoost AA, Bahrampour A, Dehghani M (2017) Modeling the burden of cardiovascular diseases in Iran from 2005 to 2025: the impact of demographic changes. Iran J Public Health 46(4):506

Saleh-Ghadimi S, Kheirouri S, Golmohammadi A, Moludi J, Jafari-Vayghan H, Alizadeh M (2019a) Effect of flaxseed oil supplementation on anthropometric and metabolic indices in patients with coronary artery disease: a double-blinded randomized controlled trial. JCVTR 11(2):152

Saleh-Ghadimi S, Kheirouri S, Golmohammadi A, Moludi J, Jafari-Vayghan H, Alizadeh M (2019b) Effect of flaxseed oil supplementation on anthropometric and

metabolic indices in patients with coronary artery disease: A double-blinded randomized controlled trial. J Cardiovasc Thorac Res 11(2):152-160 doi:10.15171/jcvtr.2019.26

Schwab US, Callaway JC, Erkkila AT, Gynther J, Uusitupa MI, Jarvinen T (2006) Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors. Eur J Nutr 45(8):470-7 doi:10.1007/s00394-006-0621-z

Simic I, Reiner Z (2015) Adverse effects of statins-myths and reality. Curr Pharm Des 21(9):1220-1226

Soleimani A, Taghizadeh M, Bahmani F, Badroj N, Asemi Z (2017a) Metabolic response to omega-3 fatty acid supplementation in patients with diabetic nephropathy: A randomized, double-blind, placebo-controlled trial. Clin Nutr 36(1):79-84

Soleimani A, Taghizadeh M, Bahmani F, Badroj N, Asemi Z (2017b) Metabolic response to omega-3 fatty acid supplementation in patients with diabetic nephropathy: A randomized, double-blind, placebo-controlled trial. Clin Nutr 36(1):79-84 doi:10.1016/j.clnu.2015.11.003

Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z (2017c) Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. JDC 31(9):1394-1400

Tavakkoli-Kakhki M, Motavasselian M, Mosaddegh M, et al. (2014) Omega-3 and omega-6 content of medicinal foods for depressed patients: implications from the Iranian Traditional Medicine. AJP 4(4):225-230 doi:10.22038/ajp.2014.2163

Thompson Paul D, Panza G, Zaleski A, Taylor B (2016) Statin-Associated Side Effects. J Am Coll Cardiol 67(20):2395-2410 doi:10.1016/j.jacc.2016.02.071

Torkan M, Hassan Entezari M, Siavash M (2015) Effect of flaxseed on blood lipid level in hyperlipidemic patients. REV RECENT CLIN TRIA 10(1):61-67

Vargas ML, Almario RU, Buchan W, Kim K, Karakas SE (2011a) Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. Metabolism 60(12):1711-1718

Vargas ML, Almario RU, Buchan W, Kim K, Karakas SE (2011b) Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. Metabolism 60(12):1711-8 doi:10.1016/j.metabol.2011.04.007

Villani AM, Crotty M, Cleland LG, et al. (2013) Fish oil administration in older adults: is there potential for adverse events? A systematic review of the literature. BMC geriatrics 13(1):1-9

Yang B, Shi M-q, Li Z-h, et al. (2019a) Effects of n-3 fatty acid supplements on cardiometabolic profiles in hypertensive patients with abdominal obesity in Inner Mongolia: a randomized controlled trial. Food & function 10(3):1661-1670

Yang B, Shi MQ, Li ZH, et al. (2019b) Effects of n-3 fatty acid supplements on cardiometabolic profiles in hypertensive patients with abdominal obesity in Inner Mongolia: a randomized controlled trial. Food Funct 10(3):1661-1670 doi:10.1039/c8fo01707g

Zheng J-S, Chen J, Wang L, et al. (2018) Replication of a gene-diet interaction at CD36, NOS3 and PPARG in response to omega-3 fatty acid supplements on blood lipids: a double-blind randomized controlled trial. EBioMedicine 31:150-156

Zheng JS, Lin M, Fang L, et al. (2016) Effects of n-3 fatty acid supplements on glycemic traits in Chinese type 2 diabetic patients: A double-blind randomized controlled trial. Mol Nutr Food Res 60(10):2176-2184