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Review Article

Effect of pomegranate seed supplementation on cardiometabolic parameters: A systematic review and meta-analysis of interventional studies

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Abstract

Objective: This systematic review and meta-analysis of interventional studies aimed to investigate cardiometabolic protective effects of pomegranate (Punica granatum) seed supplementation in adults.

Materials and Methods: PubMed, Embase, Scopus, and Web of Science ISI databases were systematically searched until February 2025. Pooled effect sizes were estimated using mean change and standard deviation (SD) of outcomes in each included trial and presented as standard mean differences (SMD) with a 95% confidence interval (95% CI). Also, heterogeneity among the included studies was measured using the I^2 statistic.

Results: Seven studies were included in the meta-analysis. Pomegranate seed supplementation led to a significant decrease in total cholesterol (TC) (SMD: -0.30; 95%CI, -0.55 to -0.05; p=0.01), triglycerides (TG) (SMD: -0.40; 95%CI, -0.65 to -0.15; p=0.002), Low-density lipoprotein to high-density lipoprotein ratio (LDL-C to HDL-C ratio) (SMD, -0.71; 95%CI, -1.12 to -0.30; p=0.001), and TG-HDL ratio (SMD, -0.49; 95%CI, -0.90 to -0.09; p=0.01) ratios, and tumor necrosis factor-alpha (TNF-a) levels (SMD: -0.94; 95%CI, -1.36 to -0.52; p<0.001). However, no significant changes were observed in LDL-C, HDL-C, fasting blood sugar (FBG), insulin, hemoglobin A1C (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), body mass index (BMI), and body weight.

Conclusion: This meta-analysis revealed that pomegranate seed supplementation may have a beneficial effect on cardiometabolic health. However, given the limited number of included trials, the findings of this review should be interpreted with caution and are not yet generalizable to clinical practice. Therefore, it seems that more trials are needed to reach a firm conclusion.

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Introduction

Cardiometabolic diseases are a cluster of conditions, such as cardiovascular disease (CVD), obesity, diabetes, and metabolic syndrome, that share common risk factors and pathophysiological mechanisms (Ash-Bernal and Peterson 2006; Srivastava 2012). These diseases are associated with increased morbidity and mortality rates and pose a significant public health challenge (Srivastava 2012). Academic research focuses on understanding the underlying mechanisms, risk factors, prevention, and treatment strategies for these diseases (Ash-Bernal and Peterson 2006; Srivastava 2012). CVDs, despite being preventable, are the main cause of death in the world, and have led to a significant financial burden (Ghayour-Mobarhan et al. 2015; Gohari-Kahou et al. 2020; Roth et al. 2015). Elevated levels of low-density lipoprotein (LDL) and cholesterol are implicated as predictors of CVD due to their connection to atherosclerosis (Ference et al. 2017). Dietary and lifestyle interventions can modify CVD risk factors (Ash-Bernal and Peterson 2006; Rippe 2019).

Dietary fats play a critical role in CVD risk (Steinberg 2005). Saturated fat is linked to an increase in LDL and the occurrence of CVD (Mensink and Katan 1992), while consumption of polyunsaturated fats reduces CVD risk by lowering cholesterol and LDL levels (Hodson et al. 2001). Numerous studies have found that increased intake of saturated fat, trans fat, and refined grains is significantly associated with an elevated risk of CVD. Conversely, consuming more fruits, vegetables, whole grains, and fatty fish protects against the development of CVD (Jayawardena et al. 2020).

Pomegranate (*Punica granatum*), native to Asia, including Iran, India, Pakistan, and China (Modaresi et al. 2011), has been utilized in traditional medicine for its anti-diabetic, antioxidant, and anti-inflammatory properties (Mollazadeh et al. 2016). Also, recent evidence showed that different components of pomegranate, including bark, seeds, juice, flowers, roots, and peels, may lead to cardioprotective, anti-obesity, antidiabetic, antioxidant, and anti-inflammatory impacts due to their bioactive compounds (Laurindo et al. 2024). The rich content of polyphenols, tocopherols, alkaloids, terpenoids, and sterols in pomegranate fruit can be responsible for its anti-diabetic, anti-inflammatory, anti-oxidant, anti-microbial, anti-hypertension, and antineoplastic effects that have been observed in animal and human studies (Barghchi et al. 2023). Approximately 3% of the weight of each pomegranate consists of its seeds, with 12-20% of each seed containing seed oil (Boroushaki et al. 2016). Pomegranate seed oil (PSO) composition varies depending on environmental factors, agricultural practices, and other related factors (Carvalho Filho 2014). The composition of pomegranate seed oil includes stearic acid, oleic acid, palmitic acid, and linoleic acid (Khoddami et al. 2014).

Punicic acid (PA), an isomer of linolenic acid, accounts for 30-80% of pomegranate seed oil (Harzallah et al. 2016). PA, classified as a conjugated linolenic acid (cis9,trans11,cis13 isomers of CLnA), has exhibited cytotoxic effects on cultured cancer cells in cell studies (Yuan et al. 2009), and improved glucose and lipid metabolism in animal studies (Harzallah et al. 2016; Mollazadeh et al. 2016). Although there is available evidence regarding anti-inflammatory, anti-oxidant activity of PA as well as its favorable impacts on body composition but the findings are not consistent (Putera et al. 2023). So far, no serious side effects have been reported for PA, and its action resembles thiazolidinediones (TZDs) (Khajebishak et al. 2019a). Furthermore, bioactive components of pomegranate seed may be related to the potential improvements in cardiometabolic parameters, as shown in Table 1 (Laurindo et al. 2024). While the beneficial effects of pomegranate seed (PS) have been observed in animal studies (Auerbach et al. 2012), the impacts of PS

supplementation in human interventional studies are conflicting.

To the best of our knowledge, no comprehensive systematic review and meta-analysis has been conducted to resolve this conflict by investigating the cardiometabolic protective properties of exclusively PS, independent of other components of the fruit. Therefore, our study aimed to assess the impacts of PS supplementation on cardiometabolic risk factors in adults by performing a meta-analysis.

Table 1. Bioactive components of pomegranate seed with potential cardiometabolic improvement features (Laurindo et al. 2022).

Bioactive components	anti-oxidant	anti-inflammatory	Anti-diabetic	Anti-obesity
Gallic acid	✓	✓	✓	
Ellagic acid	✓	✓	✓	✓
Quercetin		✓	✓	
Punicalagin	✓	✓	✓	

Materials and Methods

This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2015). The protocol for conducting this review has been registered in the PROSPERO database with the registration code CRD42023444596.

Search strategy

A comprehensive search was conducted on online databases up to February 2025, including PubMed, Scopus, Web of Science ISI, and Embase, in order to find interventional studies investigating the effect of supplementation with pomegranate seed in the adult population. This search was conducted without any limitations on date or language.

The design of the objectives of this study was based on The Participant, Intervention, Comparison/Control, Outcome (PICOS) approach (Participant: adults (aged ≥ 18 years); Intervention: Pomegranate seed (PS); Comparison: placebo group; Outcome: lipid profile, glycemic control; body mass index (BMI) and weight as anthropometric outcomes, and tumor necrosis factor alpha (TNF-α) as an inflammation marker; Study: interventional studies) (Amir-Behghadami and Janati 2020). The search strategy included mesh and non-mesh keywords related to the objective of this review, which included the following terms: ("Pomegranate seed" OR "Punicaceae seed" OR "Punica seed") AND ("Interventional" OR "clinical trial" OR "placebo" OR "randomized" OR "randomized controlled trial" OR "RCT"). The performed search strategy in each database is provided in Supplementary Table 1.

Study selection

The studies identified during the initial search were evaluated independently by two researchers (M.Sh.J and M.Sh.F.M), who screened them based on their titles and abstracts. The aim was to identify interventional studies that investigated the impact of pomegranate seed supplementation on cardiometabolic risk factors in human populations.

The selection of studies for this review was based on the following eligibility criteria: a) human studies, b) intervention group receiving pomegranate seed (powder or oil) c) there was an appropriate control group, d) study participants were adults (18 years or older), and e) studies reported changes in the mean and standard deviation of changes in outcomes during the intervention. Exclusion criteria included observational studies, animal studies, trials with combination treatments, studies without a suitable control group, letters to the editors, review studies, and short communication studies.

Data extraction

Two researchers performed data extraction from the selected studies independently (M.Sh.J and M.Sh.F.M). The extracted information included the first author's name, publication year, country of origin, intervention types, dose and

duration of pomegranate seed supplementation, sample size of each study and number of participants in each group, characteristics of the study population (mean age, mean BMI, and health status), and mean and standard deviation of changes in each outcome.

Quality assessment of studies

The quality assessment of the included studies was conducted using the Cochrane quality assessment tool (ROB 2) by two authors (H.B and M.Sh.J) independently (Cumpston et al. 2019). This assessment tool assessed the risk of bias in the studies across five domains, including risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, risk of bias in measurement of the outcome, risk of bias in missing outcome data, and risk of bias in selection of the reported result. Any disagreement was resolved by consulting the third author (M.Sh.F.M)

Data synthesis and statistical analysis

In this meta-analysis, the overall effect sizes are presented as SMD and 95% CI. The pooled effect sizes were calculated by using the extracted mean changes and standard deviation (SD) for each outcome. If the mean difference was not reported directly in the study, we calculated it by subtracting the cardiometabolic marker levels at the beginning of the intervention from those recorded at the end. If a change in standard deviations (SDs) was not reported, the change was calculated using the formula:

SD = square root [(SD at baseline)^2 + (SD at the end of study)^2 − (2R × SDbaseline × SDfinal) (Borenstein et al. 2021).

If the standard error of the mean (SEM) or medians and interquartile ranges were reported instead of the standard deviation, they were converted to SD (Hozo et al. 2005).

To determine the heterogeneity between studies, Cochrane's Q test was used and measured using I square (I^2) statistic (Higgins and Thompson 2002). I^2 value > 50% and P < 0.05 were interpreted as significant heterogeneity among the pooled trials. In order to find the source of heterogeneity, the subgroup analysis was performed based on the following pre-defined criteria: Sexes (Both genders, males, and not reported), baseline mean age of participants (≤ 50 and > 50 years), baseline BMI of participants (normal, overweight and obese), types of intervention (pomegranate seed oil (PSO) and pomegranate seed powder (PSP)), the dosage of PSO (≤800 and >800 mg/day), duration of PSO supplementation (≤ 4 and >4 weeks), and health status of the participants (type 2 diabetes, hyperlipidemic and healthy subjects). To investigate the susceptibility of the overall effect size from a specific study, a sensitivity analysis was performed with the leave-one-out approach (Duval 2005). Publication bias was evaluated by Egger's test and visual interpretation of funnel plots (Vandenbroucke 1998). All analyses of this meta-analysis were performed using Stata software version 17 (Stata Corp, College Station, TX). The p-values <0.05 were considered statistically significant in all analyses.

Results

Study selection

An initial search in the databases yielded 227 papers, of which 121 were identified as duplicates and subsequently excluded. The titles and abstracts of the remaining 106 studies were screened, which led to excluding 81 papers. Following this, the full text of 25 studies was reviewed, resulting in the exclusion of 18 studies that did not meeting the inclusion criteria of this review, due to being review articles (5), not reporting desired data (2), being animal research (7), and combination intervention (4). Finally, seven studies met the eligibility criteria and were included in this review (Figure 1).

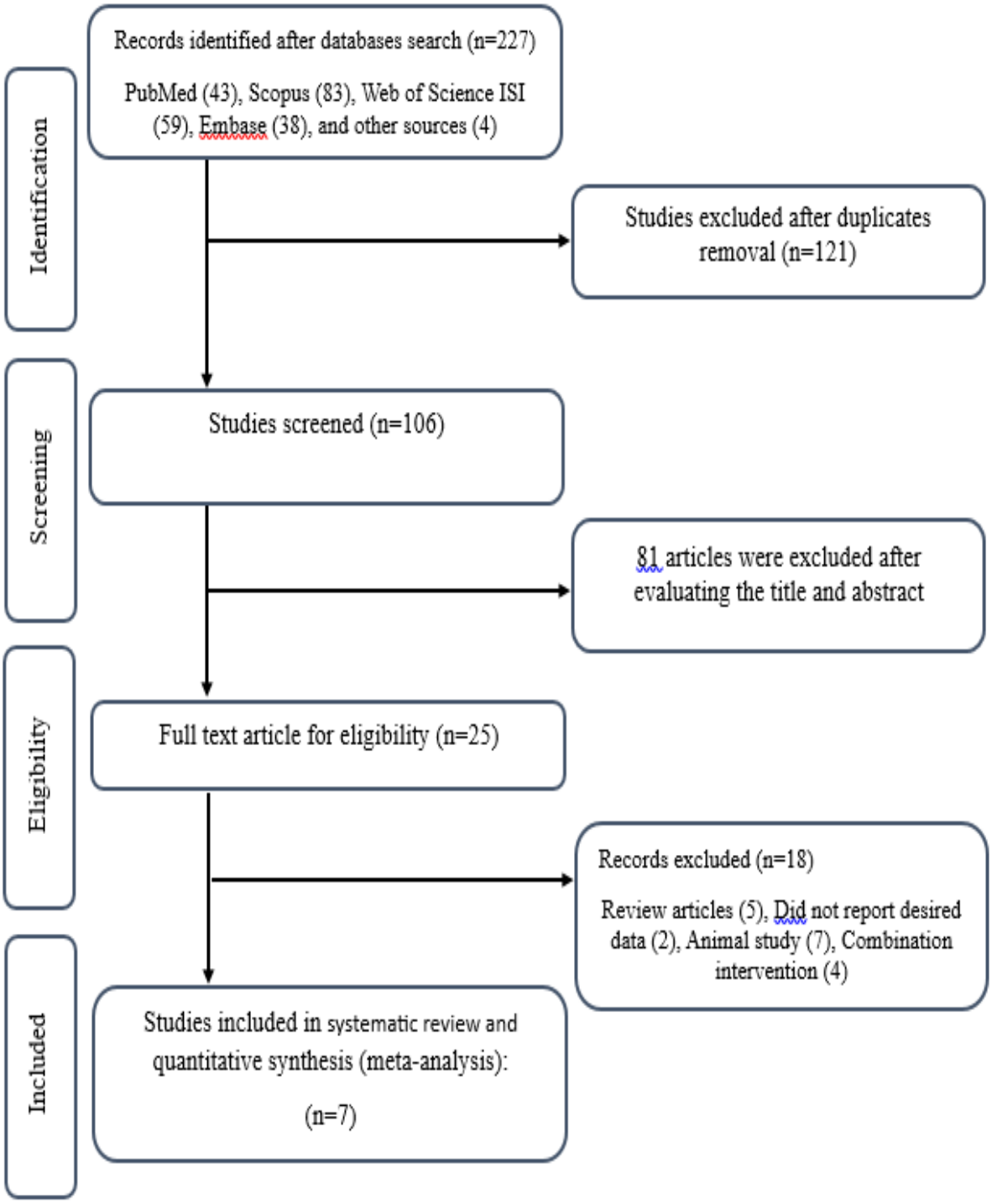


Figure 1. Flowchart of study selection for inclusion trials in the meta-analysis

Findings of systematic review

The studies included in this review were published between 2010 (Mirmiran et al. 2010), and 2021 (Seyed Hashemi et al. 2021). All of the studies were conducted in Iran and employed a parallel design, with the control groups receiving a placebo. The mean age of the participants was 22.52 (Shahidi and Moonikh 2017), to 62.10 years (Seyed Hashemi et al. 2021), and the sample size of the studies ranged from 14 (Shahidi and Moonikh 2017), to 74 participants (Faghihimani et al. 2016). The study durations were from 4 (Asghari et al. 2012; Mirmiran et al. 2010; Shahidi and Moonikh 2017) to 8 weeks (Faghihimani et

al. 2016; Khajebishak et al. 2019a; Khajebishak et al. 2019b; Seyed Hashemi et al. 2021). Intervention types were in two types of PS supplementation (Asghari et al. 2012; Faghihimani et al. 2016; Khajebishak et al. 2019a; Khajebishak et al. 2019b; Mirmiran et al. 2010; Shahidi and Moonikh 2017), and PSP supplementation (Seyed Hashemi et al. 2021). Supplemental dosage of PSO ranged from 800 (Asghari et al. 2012; Mirmiran et al. 2010; Shahidi and Moonikh 2017), to 3000 mg/d (Khajebishak et al. 2019a; Khajebishak et al. 2019b). The studied populations included individuals with diabetes (Faghihimani et al. 2016; Khajebishak et al. 2019a; Khajebishak et al. 2019b; Seyed Hashemi et al. 2021), non-athletic men (Shahidi and Moonikh 2017), and hyperlipidemia (Asghari et al. 2012; Mirmiran et al. 2010). The characteristics of the included studies are summarized in Table 2. Risk of bias assessment by using the ROB 2 tool identified the general risk of bias for 4 trials as low (Faghihimani et al. 2016; Khajebishak et al. 2019a; Khajebishak et al. 2019b; Mirmiran et al. 2010), some concerns for 1 (Shahidi and Moonikh 2017), and high for 2 included trials (Asghari et al. 2012; Seyed Hashemi et al. 2021). Details of the risk of bias assessment are presented in Figure 2.

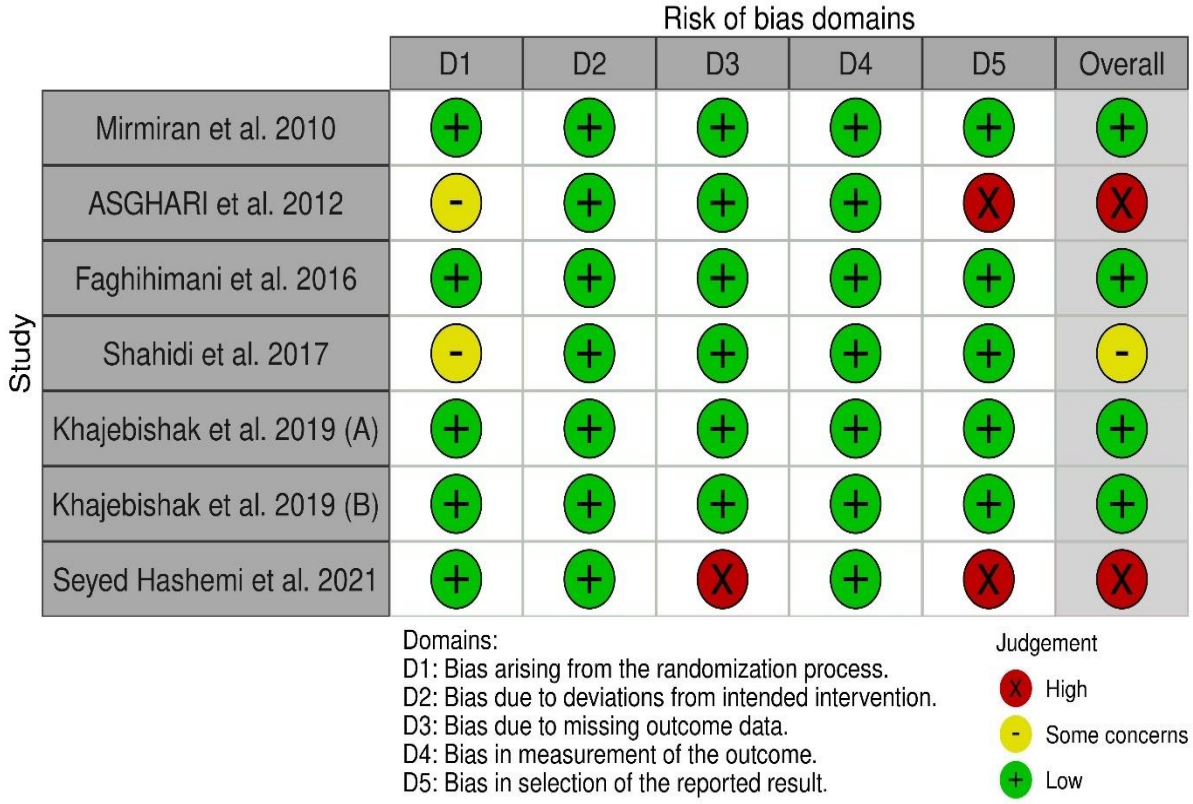


Figure 2. Risk of bias assessment plot

Table 2. Characteristic of the included studies in meta-analysis

Studies/year/ Country	Study design	Participant	Sample size and gender	Sample size		Trial duration (Week)	Means Age		Means BMI		Intervention	
				IG	**CG**		**IG**	**CG**	**IG**	**CG**	**Intervention type and dosage (mg/d)**	**Control group**
Mirmiran et al. 2010 Iran	Parallel, R, PC, DB	Hyperlipidemic subjects	45 B	23	22	4	51.0±9.0	55.0±9.0	27.2 ± 3.1	28.3 ± 3.7	PSO Supplementation 800 mg/d	Placebo
Asghari et al. 2012 Iran	Parallel, R, PC, DB	Hyperlipidemic subjects	45 B	23	22	4	51.0±9.0	55.00±9.00	27.2 ± 3.1	28.3 ± 3.7	PSO Supplementation 800 mg/d	Placebo
Faghihimani et al. 2017 Iran	Parallel, R, PC, DB	Patients with Type 2 Diabetes Mellitus	74 B	37	37	8	52 ± 6.8	48 ± 85	27 ± 2.4	26 ± 2.7	PSO Supplementation 2000 mg/d	Placebo
Shahidi et al. 2017 Iran	Parallel, R (semi-experimental), PC, DB	Non-athletic men	14 M	7	7	4	22.7±0.91	22.3 ± 1.13	23.0 ± 2.9	22.6 ± 3.7	PSO Supplementation 800 mg/d + Exercise	Placebo + Exercise
Khajebishak et al. 2019 (a) Iran	Parallel, R, PC, DB	Obese people with T2DM	52 B	26	26	8	44.6±5.1	44.9±5.2	33.9±4.8	33.4±3.0	PSO Supplementation 3000 mg/d	Placebo
Khajebishak et al. 2019 (b) Iran	Parallel, R, PC, DB	Obese people with T2DM	52 B	26	26	8	44.6±5.1	45.0±5.2	33.9±4.9	33.5±3.1	PSO Supplementation 3000 mg/d	Placebo
Seyed Hashemi et al. 2021 Iran	Parallel, R, PC, DB	Patients with Type 2 Diabetes Mellitus	60 B	30	30	8	62.5±6.1	61.6±4.82	NR	NR	PSP Supplementation 10000 mg/d	Placebo

Abbreviations: IG, intervention group; CG, control group; DB, double-blinded; PC, placebo-controlled; CO, controlled; RA, randomized; NR, not reported; NR, not reported, PSO, pomegranate seed oil; PSP, pomegranate seed powder.

Effect of PS supplementation on lipid profile and total cholesterol levels

A meta-analysis of five effect sizes involving 245 participants revealed that supplementation with PS led to a significant decrease in total cholesterol levels compared to the control groups. The heterogeneity among the studies was not significant (SMD: -0.30; 95% CI, (-0.55 to -0.05); p = 0.01, I^2 = 0.0%, p = 0.46; 245 participants) (Figure 3A). Subgroup analysis conducted to investigate the source of heterogeneity indicated a significant decrease in total cholesterol levels in the population that received PSP, trials with a duration of longer than 4 weeks, studies on both genders, or in individuals with type 2 diabetes followed by PS supplementation (Table 3).

Effect of PS supplementation on TG levels

After combining five effect sizes involving 245 participants, it was found that supplementation with PS, compared to control groups, significantly reduced TG levels. The heterogeneity among the studies was not significant (SMD: -0.40; 95% CI, -0.65 to -0.15; p = 0.002, I^2 = 0.0%, p = 0.53; 245 participants) (Figure 3B). Subgroup analysis demonstrated that PS supplementation led to a significant reduction in TG levels in individuals aged older than 50 or with type 2 diabetes. Also, significant decreases in TG levels were reported in trials longer than 4 weeks, conducted on both sexes, or those that performed intervention with PSP (Table 3).

Effect of PS supplementation on LDL-C levels

After combining four effect sizes involving 185 participants, it was found that supplementation with PS did not result in a significant change in LDL-C levels compared to the control groups. The heterogeneity among the studies was also not significant (SMD: -0.08; 95%CI, (-0.37 to 0.20); p = 0.55, I^2 = 0.0%, p= 0.41; 185 participants) (Figure 3C). Subgroup analysis showed that PS supplementation did not lead to a significant reduction of LDL-C levels in any of the determined subgroups (Table 3).

Effect of PS supplementation on HDL-C levels

After pooling four effect sizes involving 185 participants, it was observed that supplementation with PS did not result in a significant change in HDL-C levels, although the heterogeneity among the studies was significant (SMD: 0.39; 95%CI, -0.12 to 0.90; p = 0.13, I^2 = 63.2%, p= 0.04; 185 participants) (Figure 3D). Subgroup analysis indicated that PS supplementation in durations less than or equal to 4 weeks, with PSO dosage less than or equal to 800 mg/d, among individuals aged 50 years or less, in people with hyperlipidemia, or individuals with obesity led to a significant increase in HDL-C levels (Table 3).

Effect of PS supplementation on LDL-HDL ratio

After combining two effect sizes involving 97 participants, it was observed that supplementation with PS significantly reduced the LDL-HDL ratio in comparison to control groups (SMD: -0.71; 95% CI, -1.12 to -0.30; p = 0.001, I^2 = 0.0%, p = 0.35; 97 participants) (Figure 3E).

Effect of PS supplementation on TG-HDL ratio

After combining two effect sizes involving 97 participants, it was found that supplementation with PS significantly reduced the TG-HDL ratio compared to the control groups (SMD: -0.49; 95% CI, -0.90 to -0.09; p = 0.01, I^2 = 0.0%, p = 0.39; 97 participants) (Figure 3F).

Table 3. Subgroup analyses of pomegranate seed supplementation on cardiometabolic parameters in adults.

	NO	SMD (95%CI)	p-value	heterogeneity		
				p heterogeneity	I^2	p between sub-groups
Subgroup analyses of Pomegranate seed supplementation on TC						
Overall effect	5	-0.30 (-0.55, -0.05)	**0.01**	0.46	0.0%	
Gender						
N.R	1	-0.07 (-0.65, 0.51)	0.80	-	-	
Both	2	-0.35 (-0.68, -0.01)	**0.04**	0.26	25.0%	0.63
Male	1	-0.560 (-1.63, 0.51)	0.30	-	-	
Intervention types						
PSO	4	-0.19 (-0.48, 0.09)	0.18	0.75	0.0%	0.12
PSP	1	-0.66 (-1.18, -0.14)	**0.01**	-	-	
PSO Dosage (mg/day)						
X≤800	2	-0.18 (-0.69, 0.32)	0.47	0.43	0.0%	0.96
X>800	2	-0.20 (-0.55, 0.15)	0.26	0.45	0.0%	
Trial duration (week)						
x≤4	2	-0.18 (-0.69, 0.32)	0.47	0.43	0.0%	0.59
x>4	2	-0.35 (-0.68, -0.01)	**0.04**	0.26	25.0%	
Health status						
Type 2 diabetes	3	-0.35 (-0.68, -0.01)	**0.04**	0.26	25.0%	
HLP	1	-0.07 (-0.65, 0.51)	0.80	-	-	0.63
Healthy	1	-0.15(-0.43, 0.13)	0.30	-	-	
Age						
≤50	2	-0.40 (-0.89, 0.08)	0.10	0.74	0.0%	
>50	3	-0.27 (-0.65, 0.10)	0.15	0.19	38.4%	
Baseline BMI						
Normal	1	-0.56 (-1.63, 0.51)	0.30	-	-	
Overweight	2	-0.08 (-0.44, 0.27)	0.65	0.96	0.0%	0.31
Obesity	1	-0.36 (-0.91, 0.18)	0.19	-	-	
NR	1	-0.66 (-1.18, -0.14	**0.01**	-	-	
Subgroup analyses of Pomegranate seed supplementation on TG						
Overall effect	5	-0.40 (-0.65, -0.15)	**0.002**	0.53	0.0%	
Gender						
N.R	1	-0.18 (-0.77, 0.39)	0.53	-	-	
Both	3	-0.46 (-0.78, -0.13)	**0.006**	0.29	19.3%	0.72
Male	1	-0.46 (-1.52, 0.60)	0.39	-	-	
Intervention types						
PSO	4	-0.29 (-0.58, -0.005)	**0.04**	0.84	0.0%	0.13
PSP	1	-0.75 (-1.28, -0.23)	**0.005**	-	-	
PSO Dosage (mg/day)						
X≤800	2	-0.25 (-0.76, 0.26)	0.33	0.65	0.0%	0.83
X>800	2	-0.31 (-0.66, 0.03)	0.07	0.44	0.0%	
Trial duration (week)						
x≤4	2	-0.25 (-0.76, 0.26)	0.33	0.65	0.0%	0.50
x>4	3	-0.46 (-0.78, -0.13)	**0.006**	0.29	19.3%	
Health status						
Type 2 diabetes	3	-0.46 (-0.78, -0.13)	**0.006**	0.29	19.3%	
HLP	1	-0.18 (-0.77, 0.39)	0.53	-	-	0.72
Healthy	1	-0.46 (-1.52, 0.60)	0.394	-	-	
Age						
x≤50	2	-0.47 (-0.96, 0.01)	0.05	0.97	0.0%	0.75
x>50	3	-0.38 (-0.74, -0.01)	**0.04**	0.22	33.5%	
Baseline BMI						
Normal	1	-0.46 (-1.52, 0.60)	0.39	-	-	
Over weight	2	-0.19 (-0.55, 0.16)	0.28	0.96	0.0%	
Obesity	1	-0.48 (-1.03, 0.06)	0.08	-	-	0.37
NR	1	-0.75 (-1.28, -0.23)	**0.005**	-	-	

Table 3. Continued

Subgroup analyses of Pomegranate seed supplementation on LDL-C						
Overall effect	4	-0.08 (-0.37, 0.20)	0.55	0.41	0.0%	
Sex						
N.R	1	0.14 (-0.43, 0.73)	0.62	-	-	
Both	2	-0.18 (-0.68, 0.32)	0.48	0.15	49.6%	0.66
Male	1	-0.23 (-1.28, 0.82)	0.66	-	-	
PSO Dosage (mg/day)						
X≤800	2	0.05 (-0.45, 0.57)	0.82	0.53	0.0%	0.51
X>800	2	-0.18 (-0.68, 0.32)	0.48	0.15	49.6%	
Trial duration (week)						
x≤4	2	0.05 (-0.45, 0.57)	0.82	0.53	0.0%	0.51
x>4	2	-0.18 (-0.68, 0.32)	0.48	0.15	49.6%	
Health status						
Type 2 diabetes	2	-0.18 (-0.68, 0.32)	0.48	0.15	49.6%	
HLP	1	0.14 (-0.43, 0.73)	0.62	-	-	0.66
Healthy	1	-0.23 (-1.28, 0.82)	0.66	-	-	
Age						
≤50	2	-0.41 (-0.90, 0.07)	0.09	0.70	0.0%	0.10
>50	2	0.08 (-0.27, 0.44)	0.63	0.80	0.0%	
Baseline BMI						
Normal	1	-0.23 (-1.28, 0.82)	0.66	-	-	
Overweight	2	0.08 (-0.27, 0.44)	0.63	0.80	0.0%	0.25
Obesity	1	-0.46 (-1.01, 0.08)	0.10	-	-	
Subgroup analyses of Pomegranate seed supplementation on HDL-C						
Overall effect	4	0.39 (-0.12, 0.90)	0.13	**0.04**	63.2%	
Sex						
NR	1	0.68 (0.07, 1.28)	**0.02**	-	-	
both	2	0.25 (-0.63, 1.15)	0.57	**0.01**	83.6%	0.73
male	1	0.47 (-0.59, 1.53)	0.38	-	-	
PSO Dosage (mg/day)						
X≤800	2	0.63 (0.10, 1.15)	**0.01**	0.73	0.0%	0.48
X>800	2	0.25 (-0.63, 1.15)	0.57	**0.01**	83.6%	
Trial duration (week)						
x≤4	2	0.63 (0.10, 1.15)	**0.01**	0.73	0.0%	0.48
x>4	2	0.25 (-0.63, 1.15	0.57	**0.01**	83.6%	
Health status						
Type 2 diabetes	2	0.25 (-0.63, 1.15)	0.57	**0.01**	83.6%	
HLP	1	0.68 (0.07, 1.28)	**0.02**	-	-	0.73
Healthy	1	0.47 (-0.59, 1.53)	0.38	-	-	
Age						
≤50	2	0.67 (0.17, 1.17)	**0.008**	0.67	0.0%	0.37
>50	2	0.22 (-0.61, 1.07)	0.60	**0.02**	80.1%	
Baseline BMI						
Normal	1	0.47 (-0.59, 1.53)	0.38	-	-	
Overweight	2	0.22 (-0.61, 1.07)	0.60	**0.02**	80.1%	0.61
Obesity	1	0.73 (0.16, 1.29)	**0.01**	-	-	
Subgroup analyses of Pomegranate seed supplementation on LDL-HDL ratio						
Overall effect	2	-0.71 (-1.12, -0.30)	**0.001**	0.35	0.0%	
Subgroup analyses of Pomegranate seed supplementation on TG-HDL ratio						
Overall effect	2	-0.49 (-0.90, -0.09)	0.01	0.39	0.0%	
Subgroup analyses of Pomegranate seed supplementation on FBG						
Overall effect	4	-0.39 (-0.88, 0.09)	0.11	**0.04**	62.5%	
Gender						
Both	3	-0.37 (-0.96, 0.20)	0.20	**0.02**	74.5%	0.78
Male	1	-0.54 (-1.61, 0.52)	0.31	-	-	
Intervention types						
PSO	3	-0.34 (-1.04, 0.34)	0.32	**0.03**	71.1%	0.61
PSP	1	-0.56 (-1.08, -0.05)	**0.03**	-	-	

Table 3. Continued

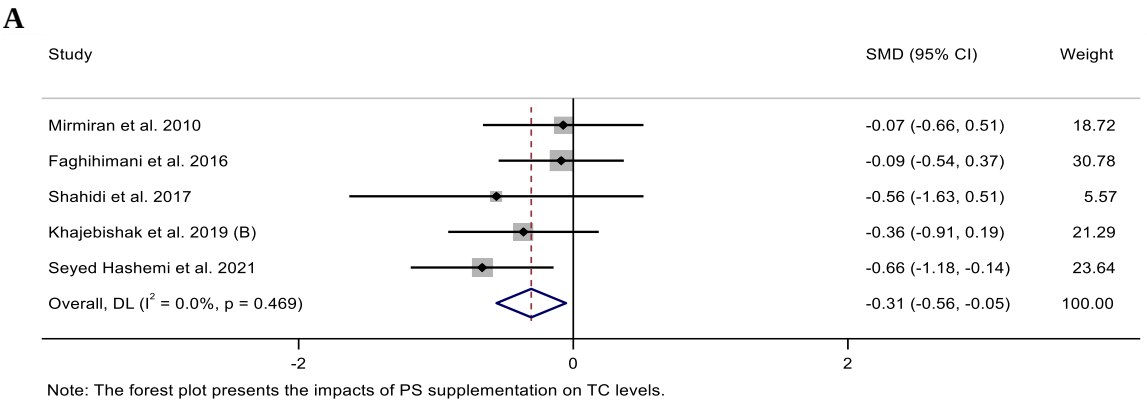
PSO dosage (mg/day)						
X≤800	1	-0.54 (|-1.61, 0.52)	0.31	-	-	0.72
X>800	2	-0.29 (-1.22, 0.63)	0.53	**0.01**	84.8%	
Trial duration (week)						
x≤4	1	-0.54 (-1.61, 0.52)	0.31	-	-	0.78
x>4	3	-0.37 (-0.96, 0.20)	0.20	**0.02**	74.5%	
Health status						
Type 2 diabetes	3	-0.37 (-0.96, 0.20)	0.20	**0.02**	74.5%	0.78
Healthy	1	-0.54 (-1.61, 0.52)	0.31	-	-	
Age						
≤50	2	-0.73 (-1.23, -0.23)	**0.004**	0.70	0.0%	
>50	2	-0.19 (-0.91, 0.52)	0.60	**0.03**	77.1%	
Subgroup analyses of Pomegranate seed supplementation on HOMA-IR						
Overall effect	4	-0.10 (-0.56, 0.36)	0.67	0.07	56.5%	
Sex						
Both	2	-0.25 (-0.97, 0.45)	0.47	0.04	74.6%	
Male	1	-0.34 (|-1.40, 0.70)	0.51	-	-	0.30
N.R	1	0.37 (-0.21, 0.96)	0.21	-	-	
PSO Dosage (mg/day)						
X≤800	2	0.15 (-0.50, 0.80)	0.65	0.24	26.4%	0.40
X>800	2	-0.25 (-0.97, 0.45)	0.47	**0.04**	74.6%	
Trial duration (week)						
x≤4	2	0.15 (-0.50, 0.80)	0.65	0.24	26.4%	0.40
x>4	2	-0.25 (-0.97, 0.45)	0.47	**0.04**	74.6%	
Health status						
Type 2 diabetes	2	-0.25 (-0.97, 0.45)	0.47	**0.04**	74.6%	
HLP	1	0.37 (-0.21, 0.96)	0.21	-	-	0.30
Healthy	1	-0.34 (-1.40, 0.70)	0.51	-	-	
Age						
≤50	2	-0.57 (-1.07, -0.08)	**0.02**	0.63	0.0%	**0.01**
>50	2	0.19 (-0.16, 0.55)	0.29	0.45	0.0%	
Baseline BMI						
Normal	1	-0.34 (-1.40, 0.70)	0.51	-	-	
Overweight	2	0.19 (-0.16, 0.55)	0.29	0.45	0.0%	**0.04**
Obese	1	-0.64 (-1.19, -0.08)	**0.02**	-	-	
Subgroup analyses of Pomegranate seed supplementation on insulin						
Overall effect	4	-0.004 (-0.29, 0.29)	0.97	0.37	2.8%	
Sex						
Both	2	-0.10 (-0.48, 0.27)	0.59	0.28	13.9%	
Male	1	-0.27 (-1.32, 0.78)	0.61	-	-	0.38
N.R	1	0.35 (-0.23, 0.94)	0.24	-	-	
PSO Dosage (mg/day)						
X≤800	2	0.20 (-0.32, 0.72)	0.45	0.31	1.8%	0.35
X>800	2	-0.10 (-0.48, 0.27)	0.59	0.28	13.9%	
Trial duration (week)						
x>4	2	0.20 (-0.32, 0.72)	0.45	0.31	1.8%	0.35
x≤4	2	-0.10 (-0.48, 0.27)	0.59	0.28	13.9%	
Health status						
Type 2 diabetes	2	-0.10 (-0.48, 0.27)	0.59	0.28	13.9%	
HLP	1	0.35 (-0.23, 0.94)	0.24	-	-	0.38
Healthy	1	-0.27 (-1.32, 0.78)	0.61	-	-	
Age						
≤50	2	-0.31 (-0.80, 0.16)	0.20	0.92	0.0%	0.11
>50	2	0.17 (-0.19, 0.53)	0.35	0.44	0.0%	
Baseline BMI						
Normal	1	-0.27 (-1.32, 0.78)	0.61	-	-	
Overweight	2	0.17 (-0.19, 0.53)	0.35	0.44	0.0%	0.28
Obese	1	-0.33 (-0.87, 0.21)	0.23	-	-	
Subgroup analyses of Pomegranate seed supplementation on HbA1c						
Overall effect	3	-0.43 (-1.22, 0.34)	0.27	**0.001**	85.6%	

Table 3. Continued

Intervention type						
PSO	2	-0.02 (-0.38, 0.32)	0.87	0.31	1.7%	**<0.001**
PSP	1	-1.22 (-1.77, -0.67)	**<0.001**	-	-	
Age						
≤50	1	-0.24 (-0.79, 0.30)	0.38	-	-	0.68
>50	2	-0.54 (-1.86, 0.77)	0.42	**<0.001**	92.6%	
Subgroup analyses of Pomegranate seed supplementation on BMI						
Overall effect	3	-0.32 (-0.94, 0.29)	0.30	0.07	61.8%	
PSO Dosage (mg/day)						
X≤800	2	-0.58 (-1.34, 0.17)	0.13	0.18	42.0%	0.19
X>800	1	0.00 (-0.45, 0.45)	1.00	-	-	
Trial duration (week)						
x≤4	2	-0.58 (-1.34, 0.17)	0.13	0.18	42.0%	0.19
x>4	1	0.00 (-0.45, 0.45)	1.00	-	-	
Age						
≤50	1	-0.06 (-1.11, 0.98)	0.90	-	-	0.61
>50	2	-0.41 (-1.26, 0.44)	0.34	**0.02**	80.2%	
Baseline BMI						
Normal	1	-0.06 (-1.11, 0.98)	0.90	-	-	0.61
Overweight	2	-0.41 (-1.26, 0.44)	0.34	**0.02**	80.2%	
Subgroup analyses of Pomegranate seed oil supplementation on weight						
Overall effect	2	-0.28 (-0.70, 0.13)	0.18	0.68	0.0%	
Subgroup analyses of Pomegranate seed supplementation on TNF-α						
Overall effect	2	-0.94 (-1.36, -0.52)	**<0.001**	0.87	0.0%	

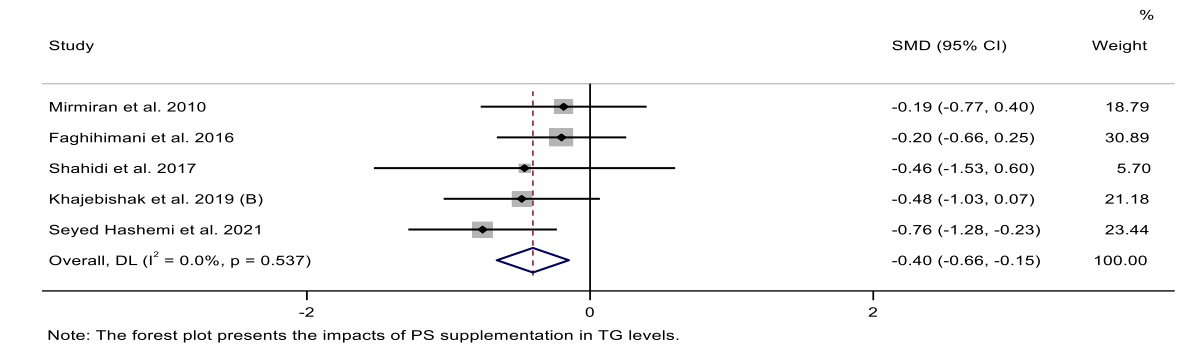
Abbreviations: CI, confidence interval; SMD, standard mean differences; NR, not reported; PS, pomegranate seed; PSO, pomegranate seed oil; PSP, pomegranate seed powder; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting Blood Glucose; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1c, hemoglobin A1C; TNF-α, tumor necrosis factor-α. HLP, hyperlipidemia. **Bold** indicates statistically significant (p<0.05)

A



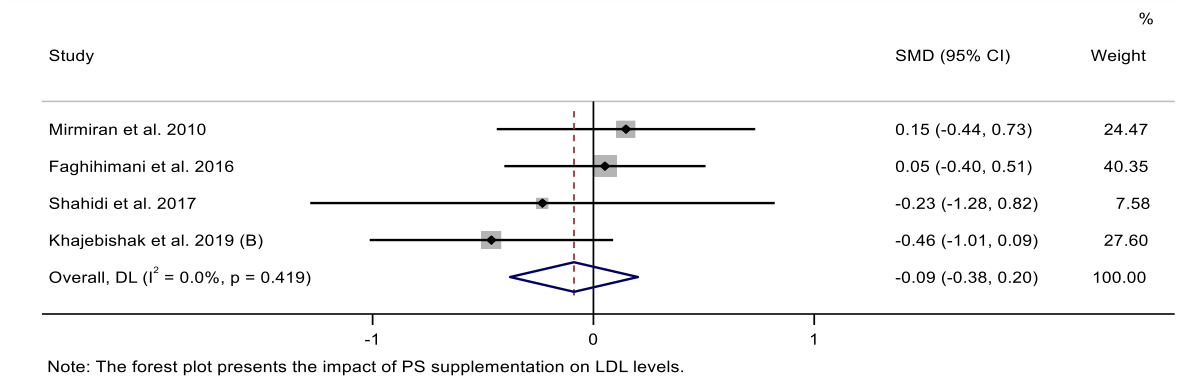
Note: The forest plot presents the impacts of PS supplementation on TC levels.

B



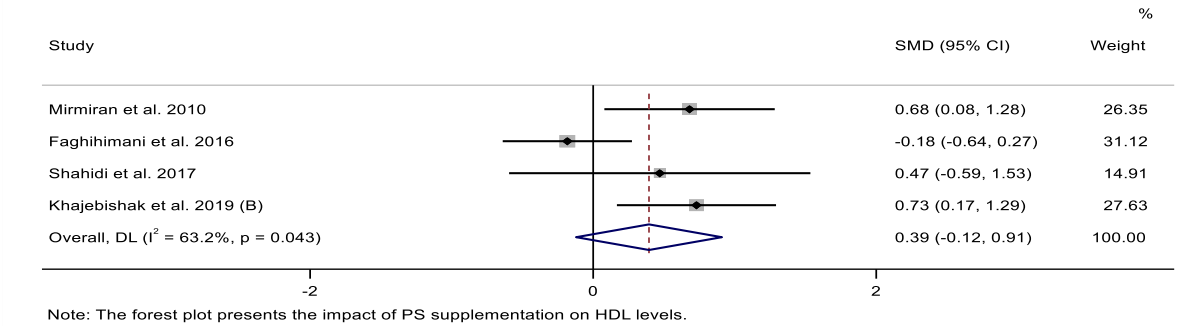
Note: The forest plot presents the impacts of PS supplementation in TG levels.

C



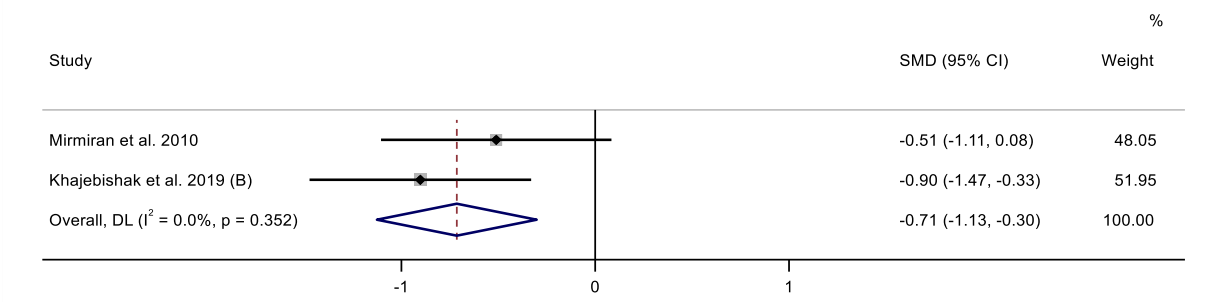
Note: The forest plot presents the impact of PS supplementation on LDL levels.

D



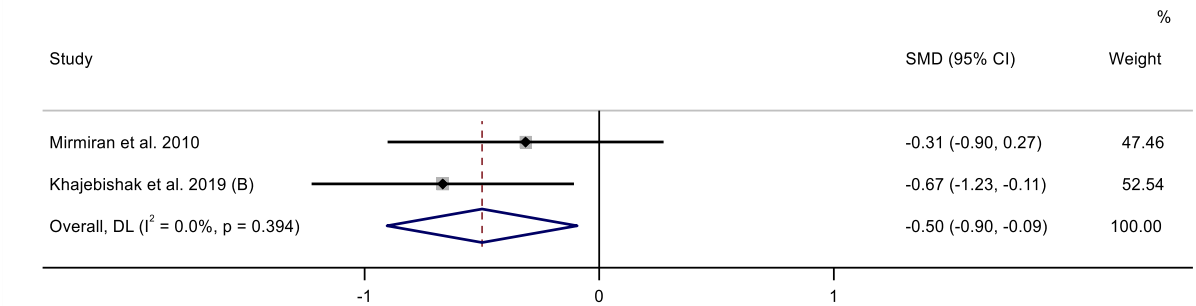
Note: The forest plot presents the impact of PS supplementation on HDL levels.

E



Note: The forest plot presents the impact of PS supplementation on LDL-HDL ratio.

F



Note: The forest plot presents the impact of PS supplementation on TG-HDL ratio.

Figure 3. Forest plot detailing standard mean difference and 95% confidence intervals (CIs) for the effect of Pomegranate Seed Supplementation on lipid profile; A) Total cholesterol (TC), B) Triglycerides (TG), C) Low-density lipoprotein (LDL), D) High-density lipoprotein (HDL), E) Low-density lipoprotein to high-density lipoprotein ratio (LDL-HDL ratio), F) Triglyceride to high-density lipoprotein ratio (TG-HDL ratio)

Effect of PS supplementation on glycemic control and FBG levels

A meta-analysis was conducted on four studies involving 200 participants to examine the effect of PS supplementation on FBG levels. The results showed that there were no significant changes in FBS levels following PS supplementation in comparison to control groups. However, a significant heterogeneity was detected among the pooled effect sizes (SMD: -0.39; 95% CI, -0.88 to 0.09; p = 0.11, I^2 = 62.5%, p=0.04; 200 participants) (Figure 4A). Subgroup analysis based on predefined criteria showed that PS supplementation significantly decreased FBS levels in participants aged ≤50 years or in those who consumed PSP (Table 3).

Effect of PS supplementation on Insulin levels

Four studies involving 185 participants were included in this meta-analysis to evaluate the effect of PS supplementation on insulin levels. The findings revealed that there were no significant changes in insulin levels following PS supplementation compared to the control groups. In addition, there was no significant heterogeneity among the combined trials (SMD: -0.004; 95% CI, -0.29 to 0.29; p = 0.97, I^2 = 2.8%, p=0.37; 185 participants) (Figure 4B). Subgroup analysis showed that PS supplementation did not lead to significant changes in insulin levels within any of the pre-defined subgroups (Table 3).

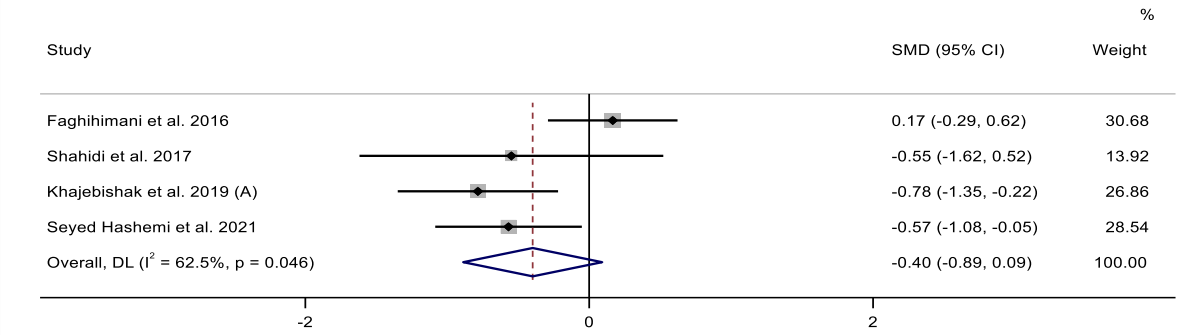
Effect of PS supplementation on hemoglobin A1C

A total of three studies, encompassing 186 participants, were included in this meta-analysis to examine the effect of PS supplementation on HbA1C levels. The results revealed that PS supplementation had no significant impact on HbA1C levels compared to the control groups. A significant heterogeneity was observed among included effect size (SMD: -0.43; 95%CI, -1.22 to 0.34; p = 0.27, I^2 = 85.6%, p=0.001; 186 participants) (Figure 4C). Subgroup analysis revealed that supplementation with PSP led to a significant decrease in HbA1C levels (Table 3).

Effect of PS supplementation on HOMA-IR

Four studies with 185 participants were included in this meta-analysis to examine the effect of PS supplementation on HOMA-IR. The results demonstrated that there were no significant changes in HOMA-IR following PS supplementation. In addition, no significant heterogeneity was detected between pooled effect sizes (SMD: -0.10; 95%CI, -0.56 to 0.36; p = 0.67, I^2 = 56.5%, p= 0.07; 185 participants) (Figure 4D). However, subgroup analysis showed that PS supplementation led to a significant decrease in HOMA-IR in individuals aged ≤50 years old, or with obesity (Table 3).

A



Note: The forest plot presents the impacts of PS supplementation in FBG levels.

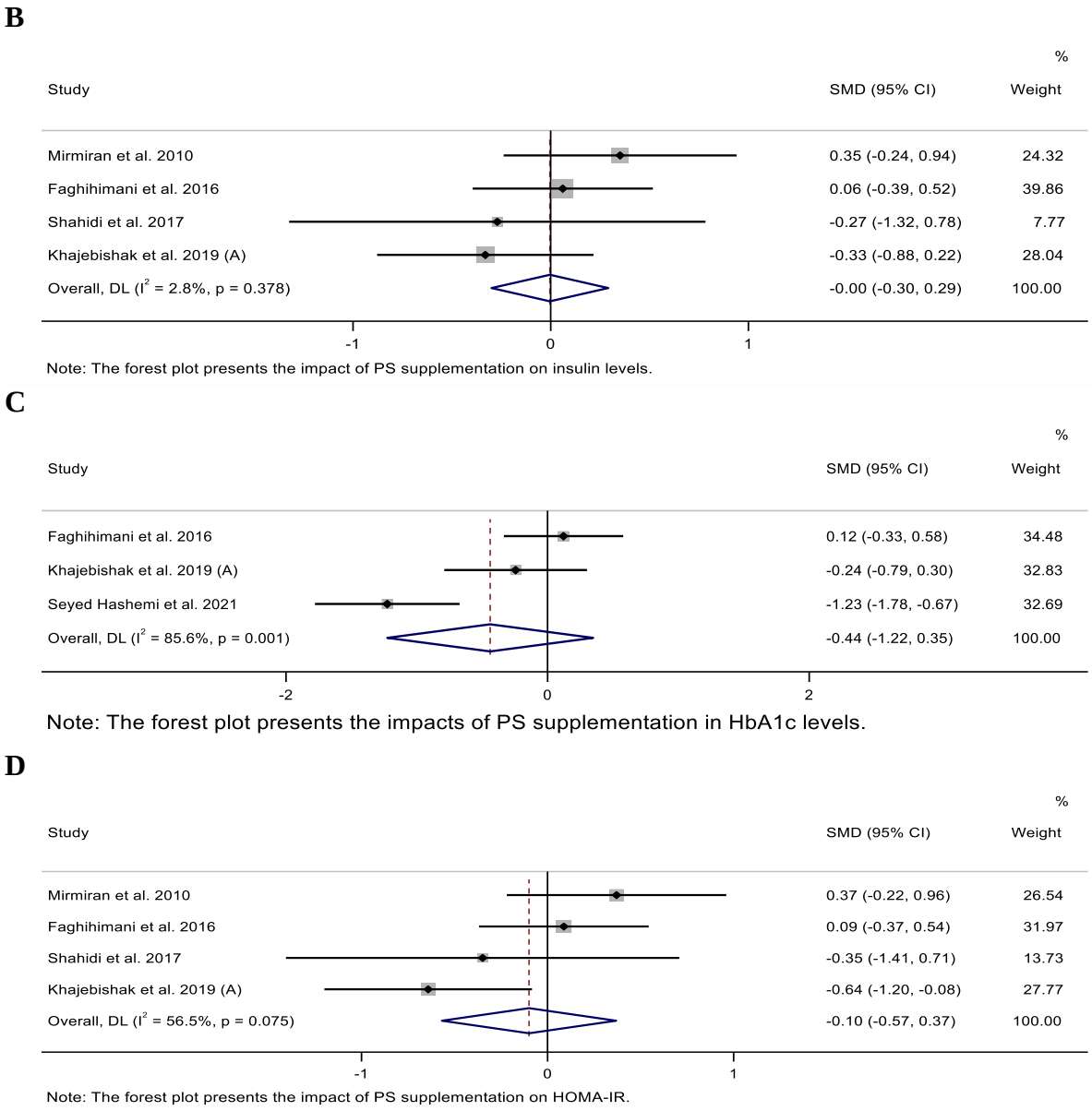


Figure 4. Forest plot detailing standard mean difference and 95% confidence intervals (CIs) for the effect of pomegranate seed supplementation on glucose metabolism and glycemic indices; A) Fasting blood glucose (FBG), B) Insulin, C) Hemoglobin A1C (HbA1C), D) Homeostatic model assessment of insulin resistance (HOMA-IR)

Effect of pomegranate seed supplementation on anthropometric indices and inflammation markers

Effect of PS supplementation on BMI

A meta-analysis including three studies with 133 participants was conducted to assess the effect of PS supplementation on BMI. The findings showed that there were no significant changes in BMI following PS supplementation compared to control groups. Also, there was no significant heterogeneity among included trials (SMD: -0.32; 95% CI, -0.94 to 0.29; p = 0.30, I^2 = 61.8%, p = 0.07; 133 participants) (Figure 5A). Furthermore, PS supplementation could not change the BMI in any of the pre-defined subgroups (Table 3).

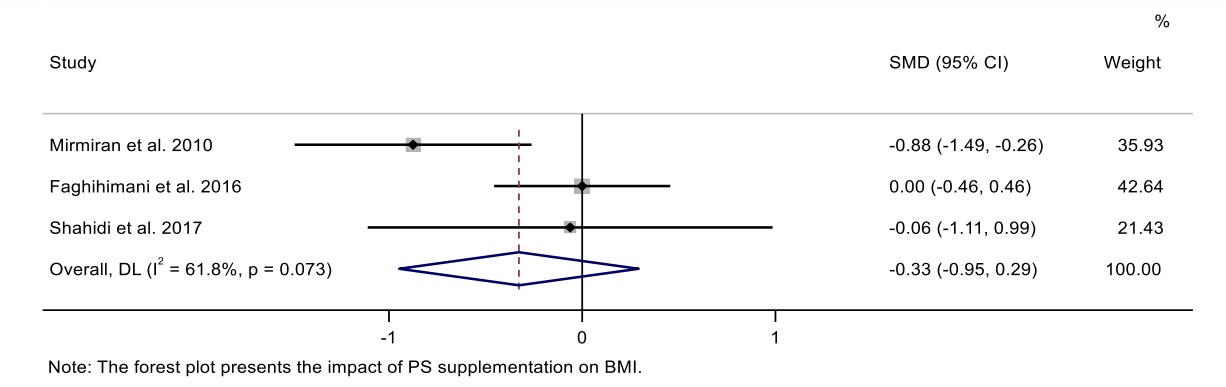
Effect of PS supplementation on weight

Meta-analyzing 2 effect sizes with 88 participants showed that there were no significant changes in weight following PS supplementation in comparison to the control groups. In addition, no significant (SMD: -0.28; 95%CI, -0.70 to 0.13; p=0.18, I^2 = 0.0%, p = 0.68; 88 participants) (Figure 5B).

Effect of PS supplementation on tumor necrosis factor-alpha (TNF-α)

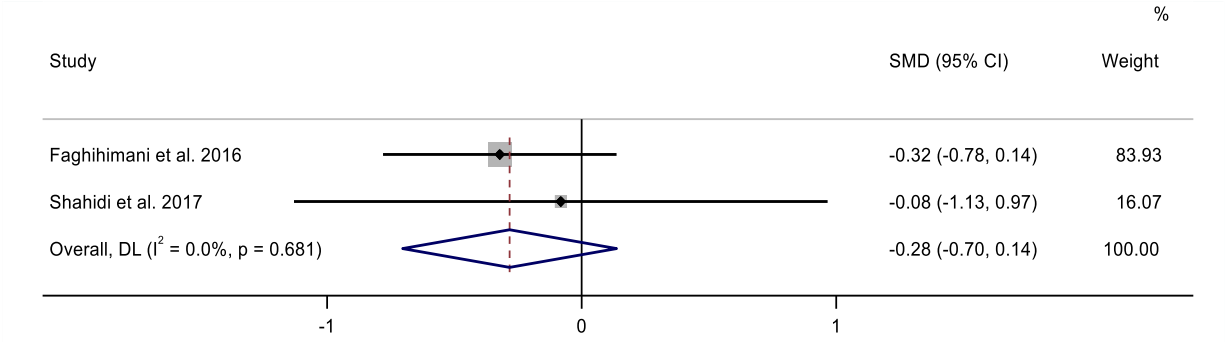
A meta-analysis of two studies involving 97 participants demonstrated that PS supplementation significantly reduced TNF-a levels compared to the control groups (SMD: -0.94; 95%CI, -1.36 to -0.52; p<0.001, I^2 = 0.0%, p=0.87; 97 participants) (Figure 5C).

A



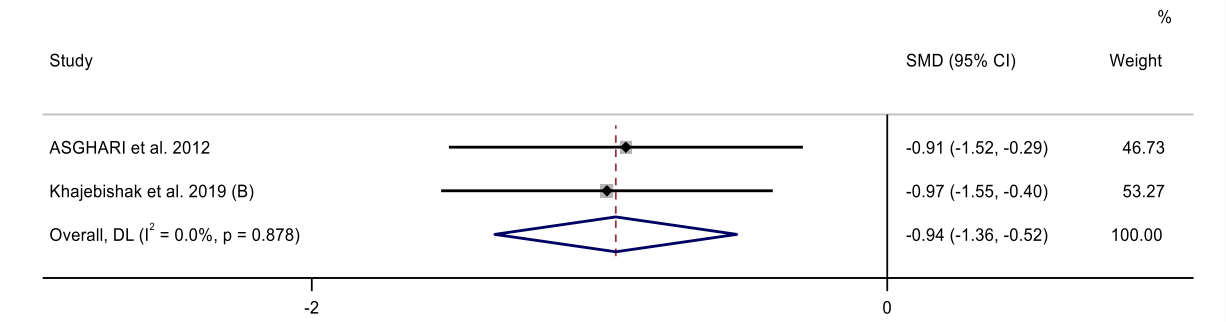
Note: The forest plot presents the impact of PS supplementation on BMI.

B



Note: The forest plot presents the impact of PS supplementation on weight.

C



Note: The forest plot presents the impact of PS supplementation on TNF-a levels.

Figure 5. Forest plot detailing standard mean difference and 95% confidence intervals (CIs) for the effect of pomegranate seed supplementation on anthropometric indices and inflammation markers; A) Body mass index (BMI); B) Weight; C) Tumor necrosis factor-alpha (TNF-α).

Sensitivity analysis

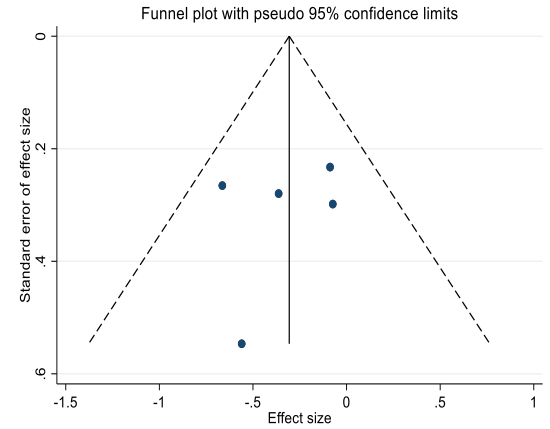
Sensitivity analysis was performed on markers with three or more included effect sizes, and it was found that the final results of PS effects on total cholesterol (TC) significantly changed after omitting the Khajebishak et al. 2019 (B) SMD: -0.29; 95%CI, -0.61 to 0.01) (Khajebishak et al. 2019b), or Seyed Hashemi et al. 2020 (SMD: -0.19; 95%CI, -0.48 to 0.09) (Seyed Hashemi et al. 2021). Also, after removing Faghihimani et al. 2016 (SMD: 0.67; 95%CI, 0.29 to 1.05) (Faghihimani et al. 2016), the overall effect size of FBG

changed significantly. However, the findings about the impacts of PS supplementation on TG, LDL-C, HDL-C, insulin, HbA1c, HOMA-IR, and BMI did not significantly change following omitting of each pooled effect size.

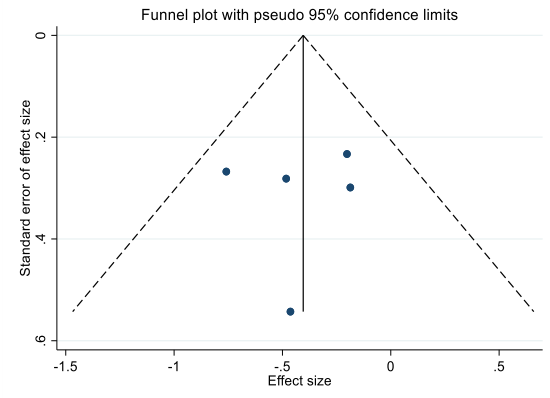
Publication bias

The visual interpretation of funnel plots and performing the Egger's test indicated no significant publication bias among the pooled effect sizes for meta-analyzing the effect of PS supplementation on TC (p =0.63), TG (p =0.83), LDL (p =0.76), HDL (p =0.53), FBG (p =0.59), insulin (p =0.77), HbA1c (p =0.42), HOMA-IR (p =0.77), and BMI (p =0.86) (Figure 6A-I). Investigation of the publication bias for LDL-HDL ratio, TG-HDL ratio, weight, and TNF-α was not possible due to the lack of enough included effect sizes.

A



B



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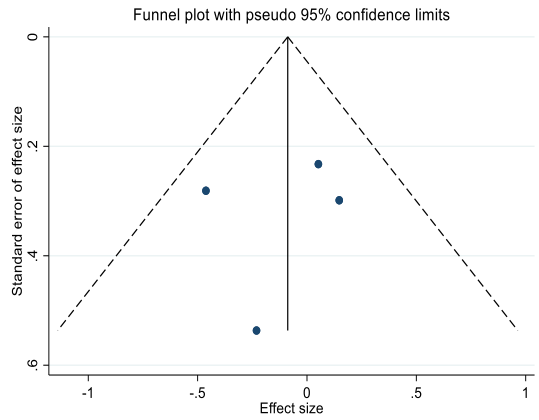

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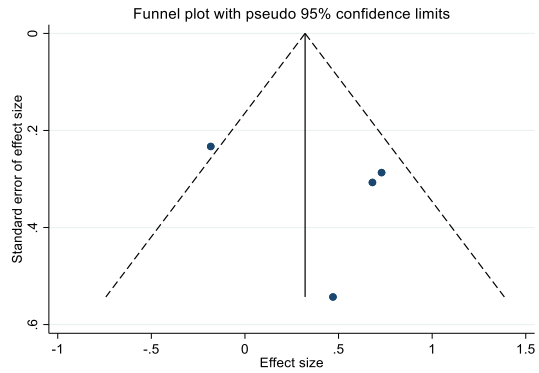

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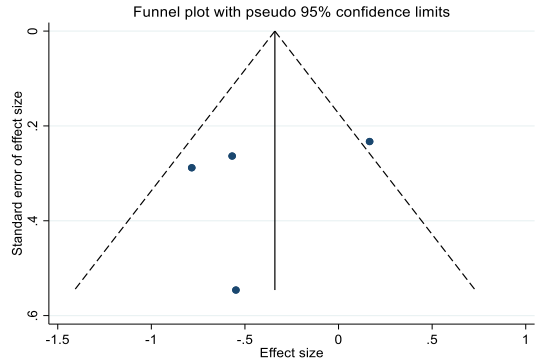
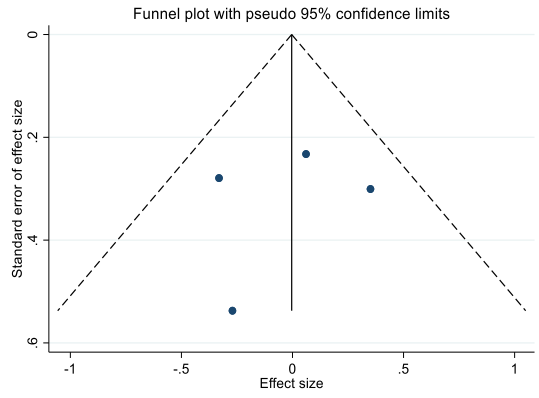


F



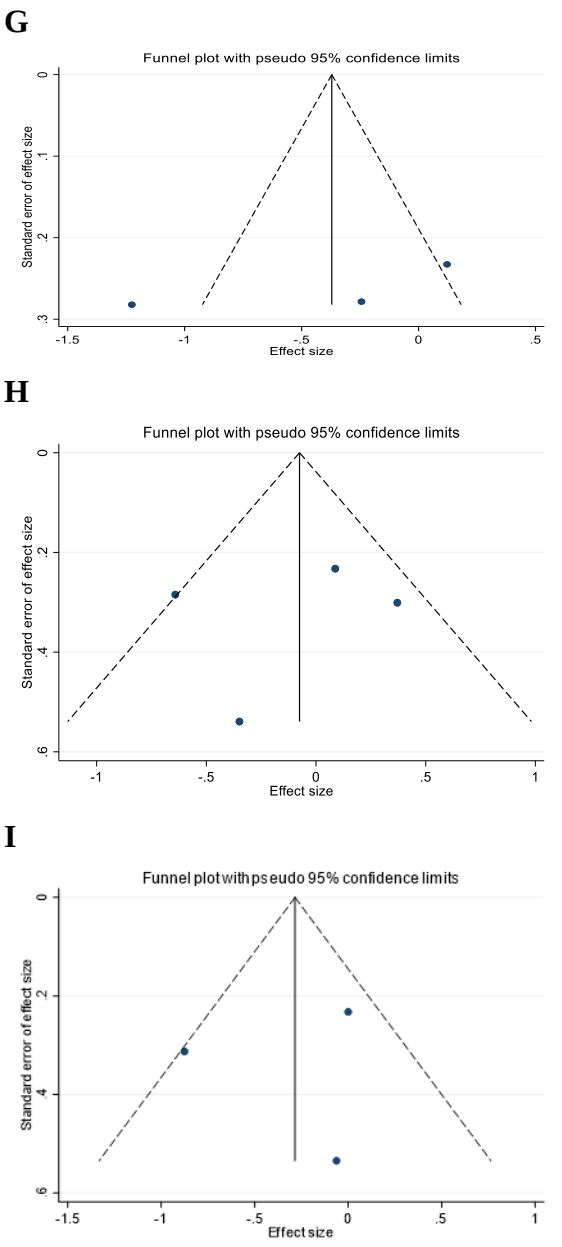


Figure 6. Funnel plots for the effect of Pomegranate seed intake on: A) Total cholesterol (TC), B) Triglycerides (TG), C) Low-density lipoprotein cholesterol (LDL-C), D) High-density lipoprotein cholesterol (HDL-C), E) Fasting blood glucose (FBG), F) Insulin, G) Hemoglobin A1C (HbA1C), H) Homeostatic model assessment of insulin resistance (HOMA-IR), and I) Body mass index (BMI).

Discussion

Our meta-analysis revealed that PS supplementation led to a significant improvement in lipid profile and inflammation status. This review revealed that PS supplementation significantly decreased TC and TG levels compared to the control groups. this finding was along with the results of a study conducted by Elbandy and Ashoush on hypercholesterolemic rats (Elbandy and Ashoush 2012). However, in this animal study, a significant reduction in LDL-C, unlike HDL-C levels, was reported, while in our meta-analysis, neither of these changes was significant. Furthermore, in another study on diabetic rats, no changes in TG, LDL-C, or HDL-C were observed following PS supplementation (Nekooeian et al. 2014). Our meta-analysis showed that PS supplementation significantly decreased LDL-C to HDL-C and TG to HDL-C ratios. In a study conducted by Koba et al., the impacts of punicic acid (PA), as the main bioactive component of pomegranate seed oil, on mice were investigated; no significant changes in the lipid profile were detected (Koba et al. 2007). However, in the study conducted by Taheri et al. PSP intake led to a significant rise in TC, LDL-C, and HDL-C levels among type 2 diabetic rats compared to the diabetic control group (Taheri Rouhi et al. 2017). Therefore, it seems that evidence for the impacts of PS supplementation on lipid profile is still contradictory. The effects of PSO supplementation on lipid profiles may be attributed to its role in enhancing lipid metabolism (Franczyk-Żarów et al. 2023; Raffaele et al. 2020).

Despite to existence of bioactive components with potential anti-diabetic effects such as gallic acid, ellagic acid, quercetin, and punicalagin in pomegranate seeds (Laurindo et al. 2022), another finding of our review was no changes in glycemic control markers, following PS supplementation compared to the control groups. Subgroup analysis showed that PSP, unlike PSO, could lead to a significant reduction in FBG and HbA1c. However, since only one trial used PSP as an intervention, these findings should be interpreted with caution. Taheri Rouhi et al. reported that PSP supplementation had no

significant impact on plasma glucose and fasting insulin concentration in type 2 diabetic rats compared to the diabetic control group (Taheri Rouhi et al. 2017).

Furthermore, our meta-analysis showed no significant alteration in weight or BMI following PS supplementation. However, in the meta-analysis that conducted by Asbaghi et al., they reported that conjugated linoleic acid (which is present in pomegranate seed oil) supplementation led to a significant reduction in weight (WMD, -0.34 Kg; 95%CI, (-0.54 to -0.15); $p<0.001$, $I^2 = 74.1\%$, $p<0.001$; 83 effect sizes), and BMI (WMD, -0.15 Kg/m^2; 95%CI, (-0.24 to -0.06); $p=0.001$, $I^2 = 70.6\%$, $p<0.001$; 77 effect sizes) (Asbaghi et al. 2024).

A significant reduction in TNF-α levels in comparison to control groups, following PS supplementation, was another finding of our meta-analysis. In this regard, in an experiment on 7–8 weeks-old male C57Bl/6 diabetic mice that received PSO with the dosage of 2 mL/kg/day for six weeks, a significant decrease in proinflammatory cytokines, including interleukin-6 (IL-6) and TNF-α levels, was observed (Harzallah et al. 2016). Also, in the study conducted by Taheri Rouhi et al, a significant reduction was observed in nuclear factor kappa B (NF-κB) and interleukin 6 (IL-6), following PSP consumption in type 2 diabetic rats compared to the diabetic control group. However, in comparison to the diabetic control group, changes in TNF-α level were not significant (Taheri Rouhi et al. 2017). This improvement in inflammation status could be linked to anti-inflammatory properties of punicic acid through limiting neutrophil activation by inhibiting the release of myeloperoxidase (MPO) and reactive oxygen species (ROS), and consequently lipid peroxidation (Boussetta et al. 2009). In addition, the anti-inflammatory activity of bioactive components of PS, such as quercetin, punicalagin, gallic acid, and ellagic acid, could be related to the improvements in inflammation status, which was demonstrated by a reduction in TNF-α levels (Laurindo et al. 2022).

To the best of our knowledge, this study is the first meta-analysis investigating the effect of pomegranate seeds on cardiometabolic parameters. The use of a placebo in the control groups and performing a comprehensive subgroup analysis to detect any sources of heterogeneity were other strengths of our meta-analysis.

However, this review included limitations such as the limited number of included studies, the impossibility of assessing publication bias and sensitivity analysis for some markers, including LDL-HDL ratio, TG-HDL ratio, Weight, and TNF-α. In addition, the general risk of bias for the two included trials was identified as high (Asghari et al. 2012; Seyed Hashemi et al. 2021). Also, it seems that conducting all the included studies in Iran limits the interpretation and generalization of the results of this meta-analysis to other populations and regions. Furthermore, due to a limited number of eligible studies, which made it impossible to perform certainty assessment, meta-regression, and dose-response analysis, as well as to study non-homogeneous populations, it was not possible to discuss the clinical applicability of this intervention. So, it is necessary to interpret the findings of this review with caution, and any clinical application of this intervention should be deferred until more high-quality randomized controlled trials become available.

Overall, the findings of this study suggest that PS supplementation may have beneficial effects on cardiometabolic health, as indicated by reductions in TC, TG, LDL-HDL ratio, and TG-HDL ratio. Additionally, PS supplementation may have anti-inflammatory effects, as evidenced by reduced TNF-α levels. However, due to insufficiently included studies, findings of this study should be interpreted with caution. Further high-quality trials are required to establish a firm

conclusion regarding the effects of PS on cardiometabolic parameters.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

Data will be made available on request

Author contribution

M.S and M.Sh.J designed the study. M.Sh.J formulated the search strategy. Screening and data collection conducted by M.Sh.J and M.Sh.F.M. M.Sh.J and H.B evaluated the risk of bias. M.Sh.F.M and M.Sh.J drafted the manuscript. Statistical analysis and interpretation of data performed by M.Sh.J. H.B revised manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Statement of Ethics

The protocol of this review has been registered in the PROSPERO database with the registration code: CRD42023444596.

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Supplementary

Supplementary Table 1. Last search date: February 2025.

PubMed	((((((((("interventional"[Title/Abstract]) OR ("randomized" [Title/Abstract])) OR (placebo[Title/Abstract])) OR (clinical trials[Title/Abstract])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (randomized controlled trial[Title/Abstract])) OR (RCT[Title/Abstract])) OR (("Clinical Trials as Topic"[Mesh]) OR ("Clinical Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type])))))) AND (((((((("Pomegranate seed" [Title/Abstract]))))) OR (Punicaceae seed"[Title/Abstract])) OR ("Punica seed"[Title/Abstract]))))	41
Scopus	((TITLE-ABS-KEY ("Pomegranate seed") OR TITLE-ABS-KEY ("Punicaceae seed") OR TITLE-ABS-KEY ("Punica seed"))) AND ((((TITLE-ABS-KEY (randomized) OR TITLE-ABS-KEY (placebo) OR TITLE-ABS-KEY (clinical AND trials) OR TITLE-ABS-KEY (randomly) OR TITLE-ABS-KEY (trial) OR TITLE-ABS-KEY (randomized AND controlled AND trial) OR TITLE-ABS-KEY ('RCT') OR TITLE-ABS-KEY ('interventional')))))	83
Web of Science	Query #1 ((((((TS=("randomized")) OR TS=("placebo")) OR TS=("clinical trials")) OR TS=("randomly")) OR TS=("trial")) OR TS=("randomized controlled trial")) OR TS=("RCT") OR TS=("interventional") Query #2 ((TS=("Pomegranate seed")) OR TS=("Punicaceae seed")) OR TS=("Punica seed") Query #3 #1 AND #2	69
Embase	('pomegranate seed' OR 'punicaceae seed' OR 'punica seed') AND ('clinical trial'/exp OR 'clinical trial' OR 'placebo'/exp OR 'placebo' OR 'randomized' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'RCT' OR 'interventional')	38