Sesame fractions and lipid profiles: a systematic review and meta-analysis of controlled trials

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Abstract

Increased plasma lipid profiles are among the most important risk factors of coronary heart disease and stroke. Sesame contains considerable amounts of vitamin E**,** monounsaturated fatty acids, fiber, and lignans, which are thought to be associated with its plasma lipid lowering properties. This study aimed to systematically review the evidence and clarify the effect of sesame consumption on blood lipid profile using a meta-analysis of controlled trials. PubMed (MEDLINE), CINAHL and Cochrane Library databases were searched (from 1960 to May 2015). A total of ten controlled trials were identified based on the eligibility criteria. The Cochrane Collaboration's tool for assessing risk of bias and the Rosendal scale were used to assess the risk of bias of the included studies. RevMan software was used to perform meta-analysis of the data. Meta-analysis showed that consumption of sesame did not significantly change the total blood cholesterol (-0.32 mmol/L, 95% CI: -0.75 to 0.11; p=0.14, I^2 =96 %), low density lipoprotein cholesterol (-0.15 mmol/L, 95 % CI: -0.50 to 0.19; p = 0.39, I^2 = 96 %) or high density lipoprotein cholesterol levels (0.01 mmol/L, 95% CI:-0.00 to 0.02; p = 0.16, I^2 = 0 %). However, a significant reduction was observed in serum triglyceride levels (-0.24 mmol/L, 95 % CI: -0.32 to -0.15; p < 0.001, I^2 = 84 %) after consumption of sesame. We conclude that consumption of sesame can significantly reduce blood triglyceride level but there is not enough evidence to support its hypocholesterolemic effects. Further studies are required to determine the potential effect of sesame consumption on lipid profile and cardiovascular risk.

Introduction

Coronary heart disease (CHD) is one of the major causes of death worldwide [1]. Increased plasma cholesterol levels and low-density lipoprotein cholesterol (LDL-C) concentrations are among the most important risk factors of CHD and stroke [2]. Oxidation of LDL-C triggers the generation of a series of oxidative reactions, promoting the initiation of atherosclerosis [3]. Literature indicates that antioxidants, and oils rich in polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), such as sesame oil, have cardiovascular protective characteristics [4]. Antioxidants (such as vitamin E) are known to protect LDL-C against oxidative modification [5; 6]. In addition the consumption of PUFA and MUFA rich oils may help decrease the fractions of circulating lipids levels, and the risk of CHD [7; 8].

For thousands of years sesame has been used as an important ingredient in cooking worldwide, especially in Asian countries. However, only recently it attracted research attention for its medicinal and physiological effects [9]. Sesame oil contains considerable amounts of vitamin E (40 mg/100 g oil), PUFA (43 percent of oil), and MUFA (40 percent of oil) [10]. The seeds also contain sesame lignans including sesamin, episesamin, and sesamolin which are effective antioxidants [11; 12] (Mean amount of lignans in sesame oil is 11.51 mg/g [13] and 5.81 mg/g in sesame seeds [14]). The high amounts of α-tocopherol and lignans in sesame oil underlie its capacity as naturally stable edible oil with strong radical scavenging properties [15]. Further, high linoleic acid and dietary fiber contents of sesame seed may be responsible for its plasma cholesterol lowering properties[16]. Studies conducted on the biological activities of sesamin showed the effect on inhibition of lipid metabolism, intestinal cholesterol absorption and desaturation in PUFA biosynthesis, and inhibition of the activity of acyl-CoA reductase [17]. Several animal studies also confirmed that the intake of sesame seeds or sesamin has cholesterol lowering effects [18; 19]. Literature also reports that sesame lignans improve lipid profiles, lipid peroxidation, serum lipoprotein metabolism, increase

apolipoprotein A, and decrease atherogenic apo-lipoprotein B [19; 20; 21; 22]. However, in human studies, the evidence of the effect of sesame or sesame oil on lipid profiles and cardiovascular risk factors is inconsistent [10; 23; 24; 25]. Therefore, this systematic review and meta-analysis of randomized clinical trials was conducted to summarize the available evidence and increase statistical ability to detect the effect of sesame consumption on lipid profiles in humans.

Methods

Literature search

Two researchers searched online databases including PubMed (MEDLINE), CINAHL and Cochrane Library (Central) to identify potentially relevant studies that evaluated the effect of sesame on lipid profile, dating from 1960 to May 2015. The following terms (including MeSH terms) and their combinations were used to search for publications: Sesame, Sesamin, Sesamum, Lipid, Cholesterol, Chol, Triglyceride, TG, Lipoprotein, LDL, LDL-C, HDL, and HDL-C (High Density Lipoprotein Cholesterol). Two researchers screened the title, abstract, and full text of the identified literature independently and made decisions regarding inclusion or exclusion of the articles. A third researcher was involved in the decision making in case of any disagreement. Selection of studies was based on pre-determined inclusion and exclusion criteria. Studies were included if they 1) were randomized or non-randomized controlled trials, 2) included adults (≥18 years of age) in their intervention, 3) used sesame seed or its extract (such as oil, and powder), 4) had accessible full text articles in English. Studies using sesame (or its extract) in mixture with other dietary components (e.g. mixture of sesame oil and fish oil) were included if the other component could be controlled. Studies were excluded if the duration of sesame consumption was <2 weeks; or the dose of sesame (or its extracts) consumption was not reported.

In screening the literature and presenting results The 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA statement' was followed [26]. A summary of the review and the reasons for excluding studies is presented in the PRISMA flow chart (see figure 1). This systematic review is registered at the International Prospective Register for Systematic Review (PROSPERO) with the registration number CRD42014013244.

Quality assessment and data extraction

The Cochrane Collaboration's tool for assessing risk of bias and the Rosendal scale [27] were used to assess the methodology quality and risk of bias of the included studies. Studies that scored 60% or more based on Rosendal scale were classified as excellent methodological quality study [27]. A Rosendal score of less than 50% was chosen as a cut-off point for the exclusion of studies. Studies were also excluded if they were ranked as high risk of bias based on Cochrane quality assessment tool. To extract relevant data from the included studies the "Checklist of items to consider in data collection" from the *Cochrane Handbook for Systematic Review of Interventions* [28] was followed. In the process of data collection, the following information was extracted from each study: study design, location, characteristics of participants, intervention/control characteristics (supplementation, duration, and dose), baseline and final measures, body weight changes, dietary measures and side effects.

Data synthesis and analysis

RevMan software (Cochrane Review Manager version 5.2) was used to perform meta-analysis of the data. The mean difference of changes between the intervention groups and control groups was defined as the effect of nutrition intervention. Statistical analysis was

performed following the *Cochrane Handbook for Systematic Review of Interventions* [28] guidelines. A correlation coefficient (r) of 0.5 was chosen to impute the SD of change for all interventions [28]. Considering differences in the design of included studies DerSimonian and Laird random effect model was selected to conduct the meta-analysis [29]. The I^2 index was evaluated to assess the heterogeneity. Low, moderate and high heterogeneity were defined as I^2 index equal to 25%, 50%, and 75%, respectively [28]. Statistically significant difference was defined as effect with a *p*-value of less than 0.05.

Sensitivity and subgroup analysis

A one-by-one sensitivity analysis was performed to assess the effect of individual studies on the overall meta-analysis results. The robustness of meta-analysis was assessed using alternative correlation coefficients (r = 0.2 and 0.8), and comparing the results with imputed correlation coefficient chosen for the meta-analysis (r = 0.5). Subgroup analysis of interventions with sesame consumption ≥ 8 weeks was compared with those with intervention duration of less than 8 weeks. Sources of sesame (whole or ground vs. oil) were chosen for another subgroup analysis. The influence of the intervention design was assessed by comparing the difference in the meta-analysis results of parallel against cross-over design trials. Finally, the influence of body weight on meta-analysis results was assessed by comparing the subgroup of studies with participants with mean baseline body mass index (BMI) of ≥30 kg/m^2 against those with BMI less than 30 kg/m^2.

Results

Overview of the studies and their quality

A total of ten trials (908 participants) that examined the effect of sesame consumption on blood lipid profile were included in the systematic review and meta-analysis. Of these, three studies [10; 24; 30] had the lowest Rosendal score of 50% (Supplemental Table 1). The highest Rosendal score of 93% was calculated for the studies conducted by Wu et al., 2009 [31] and Helli et al., 2015 [32]. Four of the studies had a cross-over design [10; 31; 32; 33] and the rest used a parallel design. Three studies reported using a double-blind [31; 32; 34] and one a single-blind designs [35]. The remaining studies did not mention blinding of the participants or the intervention.

Characteristics of participants and studies

Table 1 presents the characteristics of the included trials. Changes in total cholesterol, triglyceride, LDL-C and HDL-C were reported in all studies. Of the ten trials, two included hypertensive participants [10; 30], one diabetic patient [34] and one hypertensive and diabetic patients [10]. One trial recruited hyperlipidemia patients [36], one included hemodialysis participants [37], one rheumatoid arthritis patients [32] and one overweight and obese individuals [31]. Among all included trials, three studies included only female participants [32; 33; 35]. Five studies used sesame oil for the intervention [10; 24; 30; 35; 37] and the remaining trials used the seed or ground powdered sesame or its extracts [31; 32; 33; 34; 36]. Three studies reported a significant reduction of body weight after consuming sesame [10; 24; 32], and one reported a significant increase in body weight in the intervention group [33]. The remainder of the studies did not report significant changes in the body weight in any of the groups.

Majority of trials did not report measuring dietary intake of participants with only four studies [31; 32; 35; 38] using a 3-day food record method to measure dietary intake at the baseline and post intervention to determine any potential dietary changes. No significant differences were reported between control and intervention group at baseline in any of these studies.

Lemcke-Norajarvi et al. [35] reported significantly lower intake of polyunsaturated fatty acids as the difference between the oil consumed between control and intervention group. Mirmiran et al. [34] also reported that the sesame group had a higher intake of total fat as a result of intervention. Three studies reported that participants received the advice to maintain their usual diet [32; 33; 35] or avoid adding foods to their diet that contain sesame during the intervention [34].

Information on supplement protocol

Three of the trials reported using capsules as the vehicle for sesame supplementation [32; 33; 37], one used breakfast bars [31] and the remaining studies used sesame oil replacement of all oils consumed or a mixture of ground sesame in a variety of foods. A wide variation in daily dose of sesame consumption was observed between the studies. Daily sesame oil consumption varied from using capsules of 3.5 g oil [37] to 35 gram of sesame oil replacing the common oil used by participants daily [10; 24; 30]. The whole sesame (ground, powdered, or whole seed) consumption varied from 25 [31] to 50 gram per day [33]. Study duration varied from four [35] to 10 weeks [33]. None of the studies reported any significant side effects.

Meta-analysis results

The forest plots of the meta-analysis effect of sesame consumption on blood lipid profile are presented in Figures 2-5. Consumption of sesame did not significantly reduce the total blood cholesterol levels (-0.32 mmol/L, 95% CI: -0.75 to 0.11; p=0.14, I^2 =96 %) (Figure 2). However, a significant meta-analysis effect of sesame consumption was observed for the mean difference in triglyceride levels (-0.24 mmol/L, 95 % CI: -0.32 to -0.15; $p < 0.001$, I^2 = 84 %) (Figure 3). The meta-analysis for the effect of sesame consumption on the mean difference of LDL-C was not significant (-0.15 mmol/L, 95 % CI: -0.50 to 0.19; $p = 0.39$, I^2 =

96 %) (Figure 4). No significant change in the mean difference of HDL-C after consumption of sesame was observed (0.01 mmol/L, 95% CI:-0.00 to 0.02; $p = 0.16$, $I^2 = 0$ %) (Figure 5).

Sensitivity and subgroup analysis

The one-by-one sensitivity analysis did not show a significant effect of individual studies on the overall meta-analysis of the effect of sesame consumption on lipid profiles. Sensitivity analysis of alternative correlation coefficient (r = 0.2 and 0.8) showed agreement between the direction of the effect with the chosen correlation coefficient. These results showed the robustness of the meta-analysis results using chosen correlation coefficient of 0.5.

Subgroup analyses of the effect of sesame consumption on total cholesterol did not identify any study characteristics that could have moderated the results of the meta-analyses (Table 2). The duration of intervention, source of sesame (seed or oil) or baseline BMI of participants did not have significant influence on the subgroup analysis results. Subgroup analysis of the design of the studies (parallel or cross-over) also did not significantly affect the mean difference of the total cholesterol. The test of the difference between subgroups also did not report any significant results (Table 2).

A number of study characteristics seem to influence the effect of sesame consumption on blood triglyceride. Subgroup analysis by the duration of intervention showed significant reduction in triglyceride in both durations ≥ 8 weeks and < 8 weeks. The reduction observed in the subgroup of interventions with duration of < 8 weeks (n=4) was slightly more pronounced compared to the duration of ≥ 8 weeks (n=4) (-0.26 mmol/L vs -0.16 mmol/L). Nevertheless, the test for subgroup difference was not significant (I^2=7%, p=0.30) (Table 2). Subgroup analysis of the effect of the source of sesame showed a significant reduction in triglyceride when sesame was consumed as oil (n=5) (-0.27 mmol/L, 95% CI -0.36 to -0.17;

p<0.001). No meaningful effect of sesame consumption on triglyceride was observed in subgroup of sesame as whole or ground seed (n=5). Although the test for subgroup difference of source of sesame did not reach the statistical significant level, a trend was observed (I^2=71%, p=0.06) (Table 2). The baseline BMI of participants had an influence on triglyceride changes following sesame consumption. The subgroup of baseline BMI <30 kg/m^2 (n=7) had a significant reduction in triglyceride (-0.25 mmol/L 95% CI: -0.35 to -0.15; ρ<0.001). However, no significant effect was observed in the subgroup of studies with BMI ≥ 30 kg/m^2 (n=7). The test for subgroup analysis did not show significant difference between baseline BMI subgroups (I^2=0%, p=0.40). Both parallel and cross-over design subgroups showed significant reduction in triglyceride. The reduction was more pronounced in the subgroup of cross-over design compared to parallel design studies (-0.23 vs. -0.16 mmol/L). No significant subgroup difference was observed between the subgroups of study design (Table 2).

The subgroup analyses of the effect of duration of intervention on LDL-C did not result in significant differences (Table 2). The source of sesame consumption (oil or seed) also did not have any significant influence on LDL-C changes. Similar results were observed for the effect of the design of the studies. However, baseline BMI of participants had a more pronounced effect on the subgroup meta-analysis of the effect of sesame consumption on LDL-C. A 0.32 reduction in LDL-C was observed in the subgroup of studies with baseline BMI ≥ 30 kg/m^2, but the reduction did not reach the statistical significant level (Table 2).

No characteristics of studies were found to have a significant influence on the subgroup analysis of the effect of sesame consumption on blood HDL-C (Table 2). It appears that the different duration of sesame consumption, the source of sesame or the design of studies do not have any moderating influence on the meta-analysis of the effect of sesame on HDL-C.

Similar result was observed with regard to the different baseline BMI of participants (Table 2).

Discussion

To our knowledge the present meta-analysis is the first quantitative review of controlled trials on the effect of sesame consumption on serum lipid profiles. The current meta-analysis showed that sesame consumption significantly reduced triglyceride concentration, but not total cholesterol, HDL-C or LDL-C concentrations. While a neutral effect of sesame consumption on total cholesterol, HDL-C, and LDL-C was observed, the significant triglyceride reduction reported by the meta-analysis of this study may have pivotal clinical and public health implications.

Although the association between increased total cholesterol, and LDL-C and reduced HDL-C and the risk of cardiovascular diseases (CVD) is well studied, elevated triglyceride level has been recently considered as a single important risk factor of CVD and its incidents [(39)]. The management of dyslipidemia (characterized by elevated total cholesterol, LDL-C, triglyceride, and reduced HDL-C) involves a variety of approaches such as pharmacotherapy and lifestyle modification that can be adapted to control the lipid levels. However, many patients treated with anti-dyslipidemic drugs do not achieve the satisfactory results and still remain at high risk for CVD [(40)]. For instance statins which are the most commonly used lipid lowering drugs, at maximum dosage can reduce LDL-C only by 50-55% [(41)]. However, such dosages are often not well tolerated and 10-15% of patients reporting statin intolerance [(42)]. Considering the limitation of the anti-dyslipidemic drugs, there is a great interest in nutraceuticals that may possibly complement the pharmaceutical treatments. Food and dietary supplementation and nutraceuticals may affect lipid through complicated mechanisms which affect the absorption and metabolism of lipids [(41)].

Sesame as one of these potential dietary factors, contains several lignans such as sesamolin, sesaminol and sesamin which can be absorbed in intestines and reach the liver through the portal vein and metabolize into catechol derivatives [43]. The catechol metabolites from sesamin have a strong anti-oxidative activity on the liver [44], and can affect the metabolism and production of lipids [17; 19]. Its potential cholesterol lowering effects may be occurring due to the inhibition of the HMG-CoA reductase activity which is the enzyme involved in the synthesis of cholesterol [17]. Additionally, triglyceride lowering properties of sesame can be partially explained by its high MUFA contents (40% in sesame oil) [10]. American Heart Association reported that high dietary MUFA intake are likely to decrease blood triglyceride concentrations [8]. Evidence from the meta-analysis shows that a short-term interventions with MUFA rich diet can reduce the serum levels of triglyceride and HDL-C [45]. In addition, the high content of fiber, vitamin E and PUFA in sesame seeds, and the antioxidant activity of its lignans can affect the triglyceride generation and metabolism [10]. It is described that PUFA consumption reduces the risk of CVD by decreasing the serum triglyceride levels and modestly increasing the serum HDL-C concentrations [46]. Furthermore, the biological effectiveness of nutrients such as antioxidant activity, can be enhanced by their interaction with other components in the diet [47]. Sesame lignans in combination with α-tocopherol (precursor of vitamin E) were more effective on lipid peroxidation than a single compound [48]. Literature also reports that certain lignans in sesame seed and oil can elevate plasma and tissues levels of vitamin E precursors (alpha- and gama-tocopherol) [49; 50]. Dietary sesame lignans may also influence gene expression for various lipid metabolism enzymes involved in lipogenesis, beta-oxidation, and proteins involved in transportation of fatty acids [43].

This meta-analysis found that sesame consumption significantly decreased the triglyceride levels. The result of subgroup analysis showed that the source of sesame intake moderates the effect of sesame intake on triglyceride. Consuming sesame as oil (but not as whole or ground

seed) has significant reducing effect on triglyceride. A more pronounced effect of sesame on triglyceride was also observed in the subgroup with BMI < 30 kg/m^2. There is no logical explanation for the observed findings. However, the difference observed in subgroup of BMI can be due to the lower number of trials included in the subgroup of BMI ≥30 kg/m^2. Further interventions with a focus on higher BMI need to confirm the effect of sesame observed in this study. Subgroup analysis for duration and design of intervention did not affect the results. A neutral effect of sesame consumption on the total cholesterol, LDL-C, and HDL-C was observed in the current meta-analysis. Subgroup analysis of the effect of sesame intake on cholesterol or lipoprotein levels did not moderate the outcome. These findings are generally in line with the majority of the individual studies selected for this review. Only one study showed a significant change in cholesterol level [10] and others failed to find such a relationship.

In vitro studies showed that sesaminol inhibits peroxidation of LDL-C [51; 52] and therefore, sesame consumption may have a protective role in atherogenesis [53]. Animal studies also reported that sesamin decreases the synthesis of fatty acids in liver, down-regulates transcriptional factor [54], increases the activity of beta-oxidation associated enzyme, and decreases hepatic arachidonic and eicosapentaenoic acid concentration [55]. The suggested mechanisms for the effect of sesame on human lipid profiles are not entirely similar to those of animal studies. For instance, peroxisome proliferation which corresponds to increase peroxisomal fatty acid beta-oxidation activity can be activated in rodents but not in humans [56]. In addition, the dose of sesame consumption can have influence on the effect of sesame on lipid profile. There is a dose-dependent association between gene expression of hepatic beta-oxidation enzymes and sesamin intake [19]. Therefore, higher amount of sesame intake may have different results on cholesterol levels in humans. However, the dose-dependency

effect analysis was not applicable in this meta-analysis as the difference between the sesame sources (oil, lignans) and difficulties in accurate dose conversions.

The current meta-analysis has a number of limitations that need to be considered. Firstly, a small number of controlled trials was included in this review. The characteristics of included studies varied widely in terms of health status, gender and age of participants, study duration, sources and the dosage of sesame. Also, a significant heterogeneity was detected between the studies in meta-analysis. Sensitivity analyses attempted to highlight the influence of study characteristics on the heterogeneity and overall meta-analysis results. However, the wide variation in the characteristics of included studies limited the subgroup analysis. The limited number of studies also raises the heterogeneity of analyses. Furthermore, the majority of the trials did not control the dietary changes of participants during the intervention, which may have influenced the accuracy of the results. Moreover, one study with low quality assessment scores was excluded from the quantitative synthesis, which could have skewed the meta-analysis results [57]. Finally, only studies published in English language were included in this study. This may have resulted it the exclusion of quality studies that were published in other languages. Nevertheless, this study systematically reviewed the effects of sesame on lipid profile and increased the power of conclusion by using meta-analysis of controlled trials.

Conclusion

Consumption of sesame can significantly reduce blood triglyceride levels. Despite not having adequate evidence to support the hypocholesterolemic effects of sesame, the question whether the higher dosage or longer duration of sesame consumption would have such effects remains unanswered. Therefore, there is a need for further investigation of sesame consumption as a complementary dietary constituent to determine its potential effects on improving lipid profile and in turn reducing the CVD risks.

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Authors' contributions

S.K. and H.K designed the study; S.K., H.K., E.P and E.N. conducted research; E.P and E.N. conducted the quality assessment of studies. S.K. analyzed data, S.K. and H.K. drafted manuscript; S.K., H.K., E.P and E.N. finalized the paper. All authors read and approved the final manuscript.

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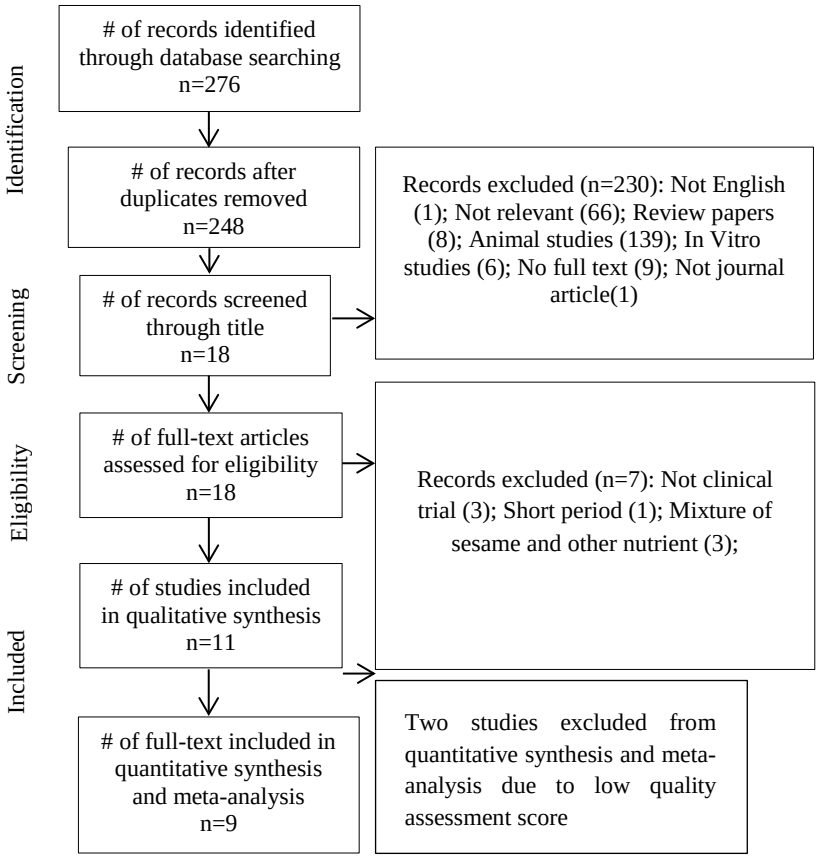


Figure.1 PRISMA flowchart

Table.1 Characteristics of studies evaluating the effect of Sesame on blood lipid profile

Study (year)	Design, Location	Intervention/ Control	Duration, weeks	Source	Dose (per day)	Participants,	Age, y	Participants intervention; control n (M/F)	Intervention Baseline (SD)	Changes from baseline	Control Baseline (mmol/L)	Changes from baseline
Alipoor 2012	R, C; Iran	Sesame seed/ control placebo	8	Seeds	40 g	Hyper Lipid	50-70	19; 19 (30/8)	TC: 6.23 (1.06) TG: 1.9 (0.83) LDL:4.13 (0.97) HDL:1.2 (0.21)	-0.51 (1.11) -0.14 (0.81) -0.41 (1.05) -0.01 (0.2)	TC: 5.92 (0.81) TG: 1.99 (0.97) LDL:3.74 (0.92) HDL:1.27 (0.25)	0.06 (0.79) 0.21 (1.04) -0.04 (0.88) -0.03 (0.24)
Khajehdehi 2000	R, PC, Iran	Sesame oil/ Corn oil	8	Capsule	4.5 g	Hemodialysis	32.3 (6.8)	15; 15 (16/14)	TC: 4.45(0.42) TG: 5.03(0.05) LDL:2.53(0.29) HDL:1.02(0.56)	-0.23 (2.8) -0.34 (0.04) 0.03 (2.01) 0.26 (0.52)	TC: 4.93(1.39) TG: 4.46(0.01) LDL: 3.19(1.24) HDL:0.88(0.19)	-0.09 (1.25) -0.18 (0.01) -0.61 (1.11) 0.54 (0.28)
Helli 2015	R, PC, CO, DB, Iran	Sesamin/ Starch	6	Capsule	200 mg	RA female	55.5 (6.0)	22 (0/22)	TC: 5.33 (0.85) TG: 1.92 (0.66) HDL: 1.53 (0.27) LDL: 2.71 (0.69)	-0.36 (0.76) -0.11 (0.84) 0.02 (0.24) -0.29 (0.62)	TC: 5.13 (1.22) TG: 2.00 (0.81) HDL: 1.47 (0.27) LDL: 2.62 (0.79)	-0.06 (1.12) -0.09 (1.12) -0.10 (0.19) -0.27 (0.83)
Lemcke-norajarvi 2001	R, PC, P, SB, Sweden	Sesame/ corn oil	4	Buns	22.5	Healthy female	27.6 (6.5)	10; 13 (0/23)	TC: 4.2 (0.80) TG: 0.80 (0.36) LDL:2.49 (0.60) HDL:1.40 (0.23)	-0.15 (0.74) -0.08 (0.33) -0.01 (0.59) -0.02 (0.24)	TC: 4.52 (0.72) TG: 0.87 (0.34) LDL:2.88 (0.58) HDL:1.33 (0.29)	-0.02 (0.68) 0.06 (0.31) -0.06 (0.56) 0.02 (0.27)
Mirmiran 2013	R, C, P, DB Iran	Sesame/ Control	6 w	Ground seeds	28 g	DM	18-60	20; 16 (8/28)	TC: 5.17 (0.48) TG: 1.85 (1.0) LDL:3.12 (1.3) HDL:1.30 (0.42)	-0.29 (1.51) -0.23 (0.99) -0.31 (1.28) 0.02 (0.41)	TC: 4.62 (0.53) TG: 1.7 (0.6) LDL: 2.58 (1.06) HDL:1.24 (0.25)	0.24 (1.98) 0.27 (0.58) 0.1 (1.04) -0.03 (0.24)
Sankar 2005	C; India	Sesame oil/ sunflowe	8 w	Oil in food	35 g	HTN	Middle age	356; 87*	TC: 5.34(0.47) TG: 2.07(0.1) LDL:3.25(0.33)	-0.85 (0.42) -0.39 (0.14) -0.78 (0.31)	TC: 5.34(0.47) TG: 2.07(0.1) LDL: 3.25(0.33)	-0.77 (0.47) -0.22 (0.14) -0.77 (0.29)

		r oil						HDL:1.14(0.09)	0.1 (0.08)	HDL:1.14(0.09)	0.09 (0.08)
Sankar 2006a	CO; India	Sesame/ Regular oil	6 w	Oil in food	35 g	HTN + DM	45-65	40 (22/18)	TC: 6.48 (0.19) TG: 2.66 (0.1) LDL:4.11 (0.22) HDL:1.23 (0.02)	-1.16 (0.34) -0.62 (0.13) -0.98 (0.29) 0.01 (0.02)	TC: 6.48 (0.19) TG: 2.66 (0.1) LDL:4.11 (0.22) HDL:1.23 (0.02)	0.03 (0.16) -0.33 (0.1) 0.02 (0.19) 0.02 (0.02)
Sankar 2006b	R, SO India	Sesame/ regular oil	6	Oil in food	35 g	HTN	35-60	50; 50 (32/18)	TC: 5.68 (0.4) TG: 5.03 (0.21) LDL:3.51 (0.18) HDL:1.18 (0.06)	-0.07 (0.43) -0.92 (0.22) 0.05 (0.24) 0.03 (0.05)	TC: 5.68 (0.4) TG: 5.03 (0.21) LDL:3.51 (0.18) HDL:1.18 (0.06)	0.08 (0.46) -0.38 (0.25) 0.08 (0.36) 0.02 (0.06)
Wu 2006	R, PC, CO, Taiwan	Sesame/ rice powder	10	Capsule	50 g	PM female	59 (7)	24 (0/24)	TC: 5.37 (0.93) TG: 1.07 (0.30) LDL:3.03 (0.97) HDL:1.33 (0.33)	-0.32 (0.89) 0.04 (0.40) -0.31 (0.90) -0.02 (0.33)	TC: 5.41(0.91) TG: 1.03 (0.34) LDL:3.19 (0.70) HDL:1.35 (0.29)	-0.06 (0.87) 0.14 (0.39) -0.05 (0.28) -0.02 (0.30)
Wu 2009	R, PC, CO, DB, AUS	Sesame seed bars/ Plain bars	5 w	Breakfast bars	25 g	OW, OB	54.7 (8.6)	33 (17/16)	TC: 5.84 (0.84) TG: 1.47 (0.47) LDL:3.75 (0.76) HDL:1.37 (0.38)	0 (0.84) -0.12 (0.45) 0.07 (0.80) 0 (0.38)	TC: 5.94 (0.82) TG: 1.51(0.38) LDL: 3.84 (0.75) HDL:1.36 (0.38)	-0.11 (0.81) -0.16 (0.41) -0.03 (0.73) -0.01 (0.37)

1- Values are presented as Mean (SD) or Mean of Change (SD of change).

2- Abbreviation used in this table: **CO**: Crossover; **DB**: Double Blind; **DM**: Diabetes Mellitus; **HTN**: Hypertension; **MetS**: Metabolic Syndrome; **OB**: Obesity; **OW**: Over Weight; **P**: Parallel; **PC**: Placebo Control; **PM**: Postmenopausal; **R**: Randomized; **RA**: Rheumatoid Arthritis.

Table.2 Results of subgroup analysis of included randomized controlled trials in meta-analysis of sesame consumption and blood lipid profile.

Group	*Subgroups*	Trials, n	Mean difference (95% CI) of lipid profile mmol/L	Test for subgroup difference
TC	Intervention duration ≥ 8 weeks	*n=4*	-0.10 (-0.21, 0.00; ρ=0.05; I^2=0%)	I^2=0%, ρ=0.43
	Intervention duration < 8 weeks	*n=6*	-0.35 (-0.97, 0.26; ρ=0.30; I^2=96%)	
	Source of sesame: oil	*n=5*	-0.37 (-1.00, 0.25; ρ=0.24; I^2=98%)	I^2=0%, ρ=0.58
	Source of sesame: whole, ground seed or supplement	*n=5*	-0.18 (-0.48, 0.12; ρ=0.24; I^2=34%)	
	Baseline BMI ≥ 30 kg/m^2	*n=3*	-0.45 (-1.45, 0.54; ρ= 0.37; I^2=97%)	I^2=0%, ρ=0.82
	Baseline BMI < 30 kg/m^2	*n=7*	-0.12 (-0.20, -0.03; ρ= 0.09; I^2=0%)	
	Design: Parallel	*n=4*	-0.34 [-0.74, 0.05; ρ=0.09; I^2=0%)	I^2=0%, ρ=0.92
	Design: Cross-over	*n=6*	-0.31 (-0.84, 0.22; ρ=0.25; I^2=98%)	
	Overall effect	*n=10*	-0.32 (-0.75, 0.11; ρ=0.14; I^2=96%)	
TG	Intervention duration ≥ 8 weeks	*n=4*	-0.16 (-0.18, -0.15; ρ<0.001; I^2=0%)	I^2=7%, ρ=0.30
	Intervention duration < 8 weeks	*n=6*	-0.26 (-0.44, -0.08; ρ<0.001; I^2=87%)	
	Source of sesame: oil	*n=5*	-0.27 (-0.36, -0.17; ρ<0.001; I^2=95%)	I^2=71%, ρ=0.06
	Source of sesame: whole, ground seed or supplement	*n=5*	-0.09 (-0.25, 0.07; ρ=0.25; I^2=14%)	
	Baseline BMI ≥ 30 kg/m^2	*n=3*	-0.12 (-0.40, 0.15; ρ=0.38; I^2=80%)	I^2=0%, ρ=0.40
	Baseline BMI < 30 kg/m^2	*n=7*	-0.25 (-0.35, -0.15; ρ<0.001; I^2=91%)	
	Design: Parallel	*n=4*	-0.16 (-0.18, -0.14; ρ<0.001; I^2=0%)	I^2=0%, ρ=0.36
	Design: Cross-over	*n=6*	-0.23 (-0.36, -0.09; ρ=0.001; I^2=93%)	
	Overall effect	*n=10*	-0.23 (-0.31, -0.15; ρ<0.001; I^2=90%)	
LDL-C	Intervention duration ≥ 8 weeks	*n=4*	-0.01 (-0.08, 0.05; ρ=0.68; I^2=0%)	I^2=0%, ρ=0.44
	Intervention duration < 8 weeks	*n=6*	-0.22 (-0.75, 0.30; ρ=0.38; I^2=97%)	
	Source of sesame: oil	*n=5*	-0.16 (-0.67, 0.35; ρ=0.53; I^2=98%)	I^2=0%, ρ=0.74
	Source of sesame: whole, ground seed or supplement	*n=5*	-0.07 (-0.27, 0.14; ρ=0.49; I^2=0%)	

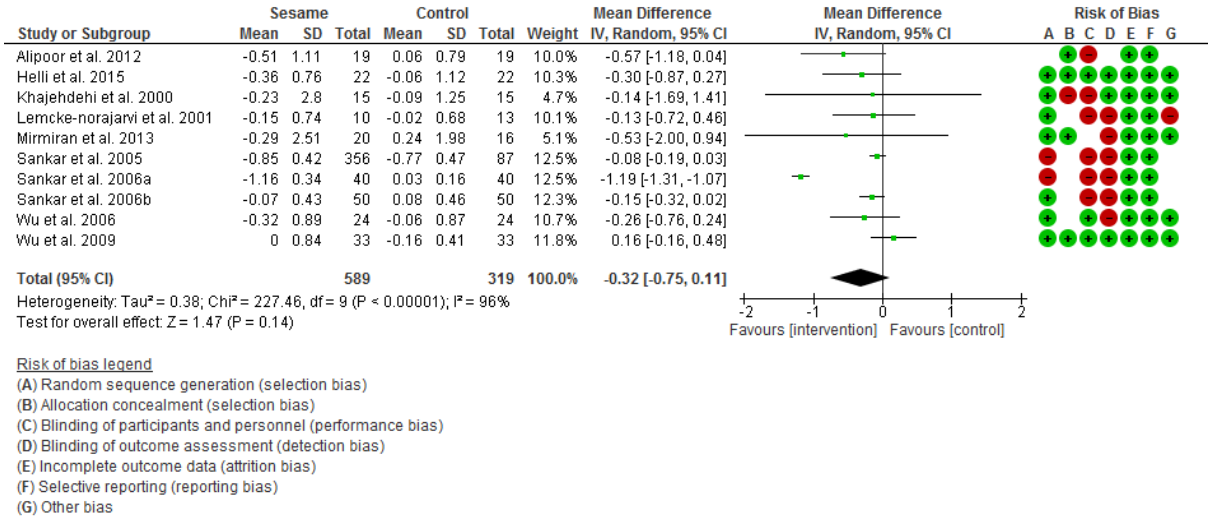
	Baseline BMI ≥ 30 kg/m^2	*n=3*	-0.32 (-1.15, 0.51; ρ=0.45; I^2=96%)	I^2=0%, ρ=0.45
	Baseline BMI < 30 kg/m^2	*n=7*	-0.02 (-0.08, 0.04; ρ=0.52; I^2=0%)	
	Design: Parallel	*n=4*	-0.09 (-0.42, 0.25; ρ=0.60; I^2=13%)	I^2=0%, ρ=0.68
	Design: Cross-over	*n=6*	-0.18 (-0.61, 0.25; ρ=0.38; I^2=98%)	
	Overall effect	*n=10*	-0.15 (-0.50, 0.19; ρ=0.39; I^2=96%)	
HDL-C	Intervention duration ≥ 8 weeks	*n=4*	0.00 (-0.05, 0.06; ρ=0.96; I^2=17%)	I^2=0%, ρ=0.76
	Intervention duration < 8 weeks	*n=6*	0.01 (-0.01, 0.03; ρ=0.31; I^2=0%)	
	Source of sesame: oil	*n=5*	0.01 (-0.01, 0.02; ρ=0.30; I^2=5%)	I^2=0%, ρ=0.82
	Source of sesame: whole, ground seed or supplement	*n=5*	0.05 (-0.02, 0.12; ρ=0.17; I^2=0%)	
	Baseline BMI ≥ 30 kg/m^2	*n=3*	0.03 (-0.05, 0.11; ρ=0.78; I^2=39%)	I^2=0%, ρ=0.65
	Baseline BMI < 30 kg/m^2	*n=7*	0.01 (-0.00, 0.02; ρ=0.19; I^2=0%)	
	Design: Parallel	*n=4*	-0.02 (-0.14, 0.09; ρ=0.66; I^2=18%)	I^2=0%, ρ=0.54
	Design: Cross-over	*n=6*	0.01 9-0.00, 0.02; ρ=0.56; I^2=0%)	
	Overall effect	*n=10*	0.01 (-0.01, 0.02; ρ=0.16; I^2=0%)	

1- Abbreviations used in this table: **BMI**: Body mass index

2- Changes in blood glucose are presented as mean difference and 95% confidence interval. Heterogeneity (I^2) is presented by %. A p-value <0.05 is considered significant.

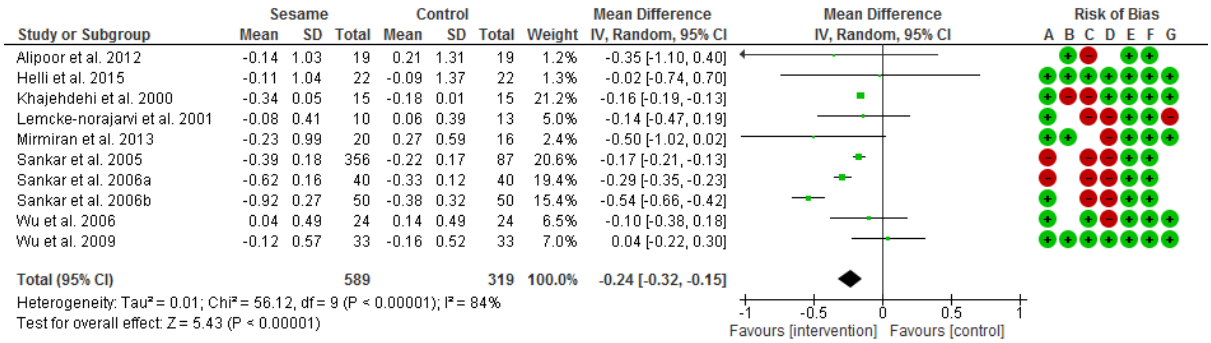
* Removing two studied without the complete cross-over design (Sankar et al. 2006a, and Sankar et al. 2006b), changed the subgroup analysis to non-significant effect

Figure.2 Forest plot and risk of bias of the effect of sesame consumption on blood total cholesterol. A random effect model was used to analysis the effectiveness of intervention. Effect of each trial was presented as weight (%), and mean difference and 95% CI.



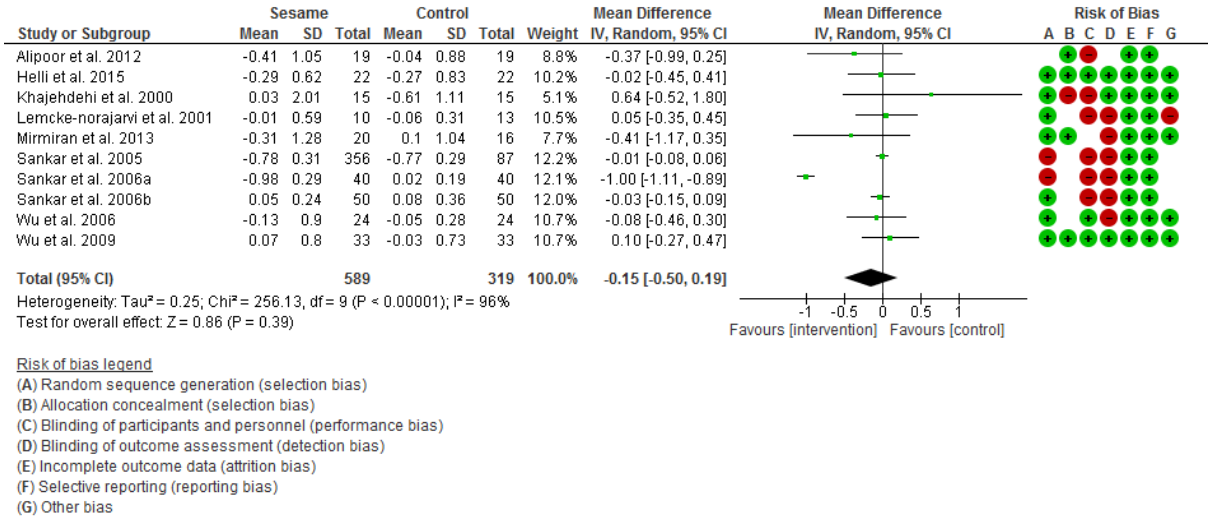
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure.3 Forest plot and risk of bias of the effect of sesame consumption on blood triglyceride. A random effect model was used to analysis the effectiveness of intervention. Effect of each trial was presented as weight (%), and mean difference and 95% CI.



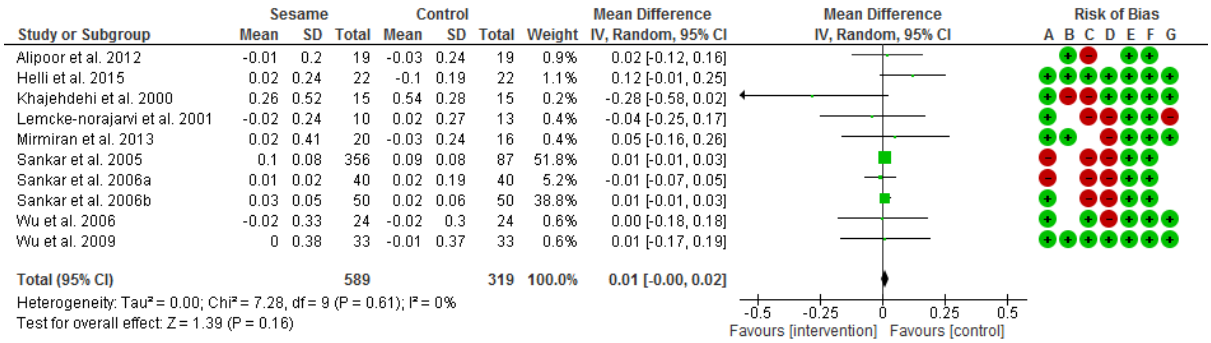
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure.4 Forest plot and risk of bias of the effect of sesame consumption on blood LDL-C. A random effect model was used to analysis the effectiveness of intervention. Effect of each trial was presented as weight (%), and mean difference and 95% CI.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure.5 Forest plot and risk of bias of the effect of sesame consumption on blood HDL-C,. A random effect model was used to analysis the effectiveness of intervention. Effect of each trial was presented as weight (%), and mean difference and 95% CI.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplemental Table 2. Results of sensitivity analysis using alternative levels of correlation coefficient (r) associated with sesame consumption analysis

Sensitivity analysis	r	Outcome	Mean difference (95% CI), mmol/l	p value	I^2	I^2 of main analysis (with r=0.50)
Using alternative correlation coefficient	0.2	TC	-0.33 (-0.77, 0.11)	0.15	94%	96%
		TG	-0.24 (-0.32, -0.15)	<0.001	84%	90%
		LDL-C	-0.16 (-0.52, 0.20)	0.38	95%	96%
		HDL-C	-0.01 (-0.01, 0.00)	0.16	0%	0%
	0.8	TC	-0.32 (-0.71, 0.060	0.10	98%	96%
		TG	-0.22 (-0.34, -0.10)	<0.001	96%	91%
		LDL-C	-0.14 (-0.49, 0.20)	0.41	98%	96%
		HDL-C	0.01 (-0.01, 0.02)	0.54	74%	0%

Supplemental Table 1. Methodology assessment summary and Rosendal score of studies included in systematic review for the effect of sesame consumption on blood lipid profile

Study	Eligibility	Randomisation	Method for Randomisation	Sample Size Calculated	Pre-trial Conditions	Baseline Measures	Blinding of Subjects	Blinding of Investigators	Method and Evaluation of Blinding	Non Completers Described	Stats Described	Measures and Variability Described	Between Group Stats Comparisons	Adverse Effects Described	Reproducibility Reported	Familiarisation Performance Test	% Score
Alipoor et al. (2012)	1	1	0	1	0	1	0	0	0	0	1	1	1	1	0	NA	53
Helli et al. (2015)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	NA	93
Khajehdehi et al. (2000)	1	1	0	0	0	1	1	0	0	NA	1	1	1	1	0	NA	57
Lemche-norajarvi et al. (2001)	1	1	0	0	1	1	0	0	0	1	1	1	1	0	0	NA	53
Mirmiran et al. (2013)	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	NA	80
Sankar et al. (2005)	1	0	NA	0	0	1	0	0	0	NA	1	1	1	0	1	NA	50
Sankar et al. (2006 a)	1	0	NA	0	0	1	0	0	0	1	1	1	1	0	1	NA	50
Sankar et al. (2006b)	1	1	0	0	0	1	0	0	0	NA	1	1	1	0	1	NA	50
Wu et al. (2006)	1	1	0	0	0	1	1	0	0	1	1	1	1	0	0	NA	53
Wu et al. (2009)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	NA	93