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Flaxseed Consumption May Reduce Blood Pressure: A Systematic Review and Meta-Analysis of Controlled Trials[1–3]

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Abstract

Background: High blood pressure is a major health burden positively associated with the risk of cardiovascular disease and other chronic diseases. Flaxseed is a rich dietary source of α-linolenic acid, lignans, and fiber, with a number of positive health benefits on blood pressure.

Objective: The purpose of this study was to clarify the effect of flaxseed consumption on blood pressure. Further, the influence of baseline blood pressure, type of flaxseed supplementation, and duration of flaxseed supplementation on blood pressure was explored.

Method: PubMed (MEDLINE), Cumulative Index to Nursing and Allied Health Literature, and Cochrane Library (Central) were searched through July 2014 for studies in which humans supplemented their habitual diet with flaxseed or its extracts (i.e., oil, lignans, fiber) for ≥2 wk.

Results: A total of 11 studies (14 trials) were included in the analysis. Random-effects meta-analyses were conducted for the mean difference in blood pressure. Results indicated that flaxseed supplementation reduced systolic blood pressure (−1.77 mm Hg; 95% CI: −3.45, −0.09 mm Hg; $P = 0.04$) and diastolic blood pressure (−1.58 mm Hg; 95% CI: −2.64, −0.52 mm Hg; $P = 0.003$). These results were not influenced by categorization of participants into higher baseline blood pressure (≥130 mm Hg). An improvement in diastolic blood pressure was observed in subgroup analysis for consuming whole flaxseed (−1.93 mm Hg; 95% CI: −3.65, −0.21 mm Hg; $P < 0.05$) and duration of consumption ≥12 wk (−2.17 mm Hg; 95% CI: −3.44, −0.89 mm Hg; $P < 0.05$).

Conclusion: The present meta-analysis suggests that consumption of flaxseed may lower blood pressure slightly. The beneficial potential of flaxseed to reduce blood pressure (especially diastolic blood pressure) may be greater when it is consumed as a whole seed and for a duration of >12 wk. *J Nutr* 2015;145:758–65.

Keywords: flaxseed, linseed, blood pressure, hypertension, systematic review, meta-analysis

Introduction

High blood pressure (BP)[7] is strongly and positively associated with increased risk of developing chronic diseases, including ischemic heart disease, heart failure, stroke, and kidney disease (1, 2). High BP or hypertension, as it is commonly known, is defined as systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg (3). Hypertension is a chronic noncommunicable disease, responsible for 13% of all global mortality (4). Given the increased risk of chronic disease associated with hypertension, it is a major cause of morbidity and has a great economic burden on society (5). BP can be controlled through diet and lifestyle modification to prevent hypertension or related complications (3). Evidence suggests that low-fat diets rich in fruits and vegetables can improve BP (6–8). Previous studies have also found that dietary constituents and supplements such as omega-3 (ω-3) FAs (9), garlic (10), and green tea (11) can improve BP.

Flaxseed or linseed is the seed of *Linum usitatissimum* L., with yellow or reddish brown seeds and nutty flavor (12). Flaxseed is one of the richest sources of the dietary ω-3 FA α-linolenic acid (ALA; 18:3n–3), which has anti-inflammatory characteristics (13, 14), potent antioxidant phytoestrogen lignans (15, 16), and dietary fiber (17, 18). The cardiovascular protective effect of flaxseed consumption, via an improvement of lipid profile and reduction in inflammatory markers, was studied extensively in both animals and

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[7] Abbreviation used: ALA, α-linolenic acid; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
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humans (19–23). Some studies have also addressed the potential BP-lowering characteristics of flaxseed consumption (12, 24), whereas others have not reported any improvement (20, 25). Because of these inconclusive results, a systematic review and meta-analysis of controlled trials was conducted. The findings from this meta-analysis may provide further information on effective interventions that involve dietary flaxseed consumption, including appropriate duration and flaxseed consumption type, to provide BP and health benefits.

Methods

Literature search. The online databases PubMed (MEDLINE) (http://www.ncbi.nlm.nih.gov/pubmed), Cumulative Index to Nursing and Allied Health Literature (http://health.ebsco.com/products/the-cinahl-database/allied-health-nursing), and Cochrane Library (Central) (http://www.cochranelibrary.com/) were searched until July 2014 for relevant studies. Combinations of the following terms (including MeSH terms) were used to search for relevant publications: flaxseed, linseed, BP, and hypertension.

Studies were included if they met the following inclusion criteria: *1*) were randomized controlled trials or quasi-experimental (non-randomized controlled trial), *2*) included adults older than 18 y of age, *3*) used whole flaxseed or flaxseed extracts (oil, lignin, fiber), and *4*) had accessible full-text articles in English. Studies were excluded if flaxseed (or its extracts) was combined in a mixture with other substances (if there was not a control arm to compare flaxseed intervention with), flaxseed consumption duration was <2 wk, or the daily dose of flaxseed (or supplement) consumption was not reported. Publications were discarded if they were duplicated or did not meet the review's initial objective.

Two researchers (SK, CI) conducted the literature search and screening process independently. The screening process involved review of the title, abstract, and full text of the article on the basis of the eligibility criteria. The decision about inclusion or exclusion of articles was made through agreement between the 2 researchers. In the case of any dissension, a third author (MS) was involved. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed during the preparation of this review and presentation of the results (26). The methodology of this systematic review is registered at the International Prospective Register for Systematic Reviews (CRD42014010248). A summary of the review study procedures is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow chart (**Supplemental Figure 1**).

Data extraction and quality assessment. The Rosendal scale (27), which is a combination of the PEDro scale (28), Jadad scoring system (29), and Delphi List (30), was used to assess the study quality and associated bias. A cutoff of 60% for overall Rosendal score is classified as an excellent methodology quality study (29). Studies were included if they had a Rosendal score of ≥50%. Included articles were reviewed to extract relevant data, following the checklist of items to consider in data collection from the Cochrane Handbook for Systematic Review of Interventions (31).

Data synthesis and analysis. RevMan 5.2 (Cochrane Review Manager) was used to perform meta-analysis of data. Mean difference of BP changes between the intervention groups and control groups were defined as the effect of nutrition intervention. The Cochrane Handbook for Systematic Review of Interventions (31) was used as the guideline to perform statistical analysis. Two studies reported the SD of change (12, 32). The missing SD of change for the remainder of studies was imputed. A correlation coefficient (r) of 0.5 was calculated on the basis of the 2 studies with reported SD of change. The SD of net change for cross-over trials was imputed with the use of $r = 0.5$ (31). Meta-analysis was conducted with the DerSimonian and Laird random-effect model (33). Heterogeneity was assessed with the I^2 index. Values of 25%, 50%, and 75% were used for the I^2 analysis and correspond to low, moderate, and high heterogeneity, respectively (31). $P < 0.05$ was considered a statistically significant effect, differing from zero by using a Z-test analysis.

Sensitivity and subgroup analysis. Sensitivity analysis was performed by excluding individual studies and assessing the effect of those studies on overall results of meta-analysis. Sensitivity analysis of different correlation coefficients (r = 0.2 and 0.8) was also performed to assess the robustness of using the imputed correlation coefficient (r = 0.05). Subgroup analysis of parallel trials was compared with cross-over trials to analyze the influence of the design on meta-analysis results. Subgroup analysis was limited to trials with participants' mean baseline BP of <130/85 mm Hg compared with participants with mean baseline BP of ≥130/85 mm Hg. Subgroup analysis of different sources of flax (whole, oil, lignan) and different duration of supplementation were also performed. A subgroup of studies with participants' mean baseline BMI (in kg/m^2) ≥30 was also performed to assess the influence of obesity on the meta-analysis results.

Results

Overview of studies and study quality. Twelve studies were included in the systematic review for the effect of flaxseed consumption on BP. Of these, 11 studies (14 trials), with a total of 1004 participants, were included in the final meta-analysis. The study by Singer et al. (34) was excluded from the meta-analysis on the basis of a Rosendal score of 33% (**Supplemental Table 1**). The included studies were all randomized controlled trials, with 5 using cross-over design (32, 35–38) and 6 using parallel design (12, 20, 24, 39–41). Seven studies reported using a double-blind design (12, 24, 32, 35, 36, 38, 40). Two studies mentioned flaxseed bread and muffins that could be differentiated by their appearances (37, 41). All included studies had a Rosendal score of >50% (Supplemental Table 1). The highest Rosendal score of 93% was for the study by Pan et al. (32), followed by the study by Dodin et al. (24) (Supplemental Table 1).

Participant and study characteristics. The characteristics of the included studies are presented in **Table 1**. All studies reported changes in SBP and DBP. Of the 11 studies, 2 included participants with metabolic syndrome (20, 41), 2 had participants with type 2 diabetes (32, 35), 1 included participants with hyperlipidemia (37), 1 included participants with peripheral artery disease (12), and 3 included menopausal and postmenopausal women (24, 36, 37, 40). One study reported a significant reduction of body weight in both the treatment and control groups (41), and another reported a significant increase in body weight in the flaxseed group (32). Significant changes in body weight were not reported in the remainder of the studies.

All trials, except one (12), reported a method of dietary intake measurement (diet records or FFQs) at baseline and the end of the study to determine whether dietary changes occurred. Schwab et al. (38) reported higher energy intake during flaxseed intervention, and Wu et al. (41) reported a reduction of energy intake in both the flaxseed and control groups. The remaining studies did not report significant changes in dietary intake of participants from the baseline. Five studies reported that participants received instructions and guidelines to maintain their usual diet (20, 32, 35, 37, 41).

Information on supplement protocol. Four studies used whole or ground flaxseed for the intervention (12, 24, 37, 41), 3 studies used flaxseed oil (20, 38, 39), and 3 studies used flaxseed lignan (32, 36, 40). All flaxseed oil and lignan interventions used capsules and supplements as the vehicle for flaxseed supplementation, except for the study by Schwab et al. (38), which used a mixture of flaxseed oil in a variety of foods. Whole or ground flaxseed was used as an additive to breads, muffins, and other foods (12, 24, 36, 37, 41). The daily dose of flaxseed consumption

TABLE 1 Characteristics of studies that evaluated the effect of flaxseed consumption on BP[1]

Reference	Design, location	Intervention/control	Duration,[2] wk	Source of flax	Dose per day	Participants	Age, y	Intervention, *n* (M/F)	SBP, mmHg Baseline	SBP, mmHg Change from baseline	DBP, mmHg Baseline	DBP, mmHg Change from baseline
Barceló-Coblijn et al. (39)	R, PC, P; Canada	Flax oil/ sunflower oil	12	Capsule	1.2 g flax oil	Firefighters	27–54	12 (12/0)	Int: 123.0 ± 8.3[3]	1 ± 8.8	Int: 80.0 ± 7.6	−1.5 ± 8.0
									Con: 118.0 ± 9.2	0.0 ± 8.3	Con: 75.6 ± 5.4	1.4 ± 7.2
Barceló-Coblijn et al. (39)	R, PC, P; Canada	Flax oil/ sunflower oil	12	Capsule	2.4 g flax oil	Firefighters	27–54	10 (9/1)	Int: 127.8 ± 10.5	−2.7 ± 11.6	Int: 85.4 ± 8.6	−1.3 ± 7.5
									Con: 118.0 ± 9.2	0.0 ± 8.3	Con: 75.6 ± 5.4	1.4 ± 7.2
Barceló-Coblijn et al. (39)	R, PC, P; Canada	Flax oil/ sunflower oil	12	Capsule	3.6 g flax oil	Firefighters	27–54	10 (10/0)	Int: 127.0 ± 13.5	1 ± 15.3	Int: 81.3 ± 13.3	−0.5 ± 11.6
									Con: 118.0 ± 9.2	0 ± 8.3	Con: 75.6 ± 5.4	1.4 ± 7.2
Barre et al. (35)	DB, PC, R, CO; Canada	Flax lignan/ placebo	12 (WO = 12)	Capsule	600 mg SDG	Type 2 DM, PM woman	≥55	16 (0/16)	Int: 133.6 ± 19.2	−9.2 ± 17.1	Int: 82.1 ± 7.6	−7.2 ± 11.3
									Con: 135.8 ± 17.2	−12 ± 17.1	Con: 84.5 ± 8.8	−6.2 ± 11.3
Cornish et al. (40)	DB, PC, R, P; Canada	Flax lignan/ maltodextrin	24	Tablet	543 mg lignan	Healthy	≥50	48 (20/28)	Int: 128.9 ± 14.8	0.0 ± 14.7	Int: 88.7 ± 14.0	−6.7 ± 14.0
									Con: 125.5 ± 14.3	−1.4 ± 14.4	Con: 82.7 ± 14.0	1.1 ± 14.0
Dewell et al. (20)	R, PC, P; USA	Flax oil/ soybean oil	8	Capsule	2.2 g ALA	MetS	40–60	20 (13/7)	Int: 128.0 ± 10.0	−2.0 ± 10.0	Int: 76.0 ± 6.6	2.0 ± 6.6
									Con: 124.0 ± 10.0	2.0 ± 8.8	Con: 76.0 ± 10.0	1.0 ± 8.8
Dewell et al. (20)	R, PC, P; USA	Flax oil/ soybean oil	8	Capsule	6.6 g ALA	MetS	40–60	20 (12/8)	Int: 124.0 ± 10.0	2 ± 10.0	Int: 73.0 ± 6.6	2 ± 5.7
									Con: 124.0 ± 10.0	2 ± 8.8	Con: 76.0 ± 10.0	1 ± 8.8
Dodin et al. (24)	DB, R, PC, P; Canada	Ground flax/ wheat germ	48	Bread + ground flax	40 g	Menopausal woman	50–79	85 (0/85)	Int: 125.4 ± 14.5	−5 ± 14.8	Int: 79.7 ± 9.4	−4.1 ± 9.8
									Con: 122.4 ± 15.5	−1.5 ± 14.7	Con: 77.7 ± 9.4	−1.5 ± 10.5
Hallund et al. (36)	DB, PC, CO; Denmark	Flax lignan muffin/ control muffin	6 (WO = 6)	Muffin	500 mg lignan	PM woman	54–68	22 (0/22)	Int: 124.0 ± 13.0	−2.0 ± 13.8	Int: 75.0 ± 8.0	−2.0 ± 9.2
									Con: 124.0 ± 13.0	−1.0 ± 13.8	Con: 75.0 ± 8.0	−1.0 ± 9.2
Jenkins et al. (37)	R, PC, CO; Canada	Defatted flax/ wheat barn	3 (WO = 2)	Muffin	50 g	HL	41–73	28 (22/6)	Int: 128.0 ± 21.2	−4.0 ± 14.0	Int: 81.0 ± 5.3	−2.0 ± 5.3
									Con: 129.0 ± 15.9	−4.0 ± 14.0	Con: 81.0 ± 10.6	−1.0 ± 5.3
Pan et al. (32)	DB, PC, CO; China	Flax lignan/ rice flour	12 (WO = 8)	Supplement	360 mg lignan	Type 2 DM	50–79	68 (25/43)	Int: 139.3 ± 21.4	−0.4 ± 15.1	Int: 79.2 ± 10.7	−1.5 ± 6.7
									Con: 138.0 ± 18.6	0.7 ± 11.6	Con: 79.36 ± 10.3	−0.3 ± 6.9
Rodriguez-Leyva et al. (12)	DB, PC, R, P; Cuba	Mild flax/ Wheat	24	Variety of foods	30 g	PAD	18–74	58[4]	Int: 143.3 ± 22.2	−7.3 ± 22.0	Int: 77.0 ± 9.5	−5.0 ± 11.0
									Con: 142.4 ± 17.5	3.6 ± 21.0	Con: 79.0 ± 15.6	0.0 ± 10.0
Schwab et al. (38)	DB, R, CO; Finland	Flax oil/ hempseed oil	4 (WO = 4)	Variety of foods	30 mL	Healthy	25–60	14 (8/6)	Int: 114.0 ± 12.0	−2.0 ± 13.1	Int: 74.0 ± 8.0	1.0 ± 9.1
									Con: 114.0 ± 12.0	1.0 ± 13.1	Con: 74.0 ± 8.0	1.0 ± 9.1
Wu et al. (41)	RC, P; China	Flax + lifestyle/ lifestyle	12	Bread	30 g	MetS	25–65	94 (53/41)	Int: 133.0 ± 17.1	−8.8 ± 15.0	Int: 85.6 ± 11.6	−5.0 ± 10.1
									Con: 133.7 ± 14.6	−7.0 ± 13.6	Con: 85.4 ± 9.0	−4.4 ± 8.1

[1] ALA, α-linolenic acid; BP, blood pressure; CO, crossover; Con, control; DB, double blind; DBP, diastolic blood pressure; DM, diabetes mellitus; HL, hyperlipidemia; Int, intervention; MetS, metabolic syndrome; P, parallel; PAD, peripheral artery disease; PC, placebo control; PM, postmenopausal; R, randomized; SBP, systolic blood pressure; SDG, secoisolariciresinol diglucoside; WO, washout.

[2] Duration reported for CO trials is duration of intervention, excluding WO period.

[3] Mean ± SD (all such values).

[4] Percentage or number of males or females is not mentioned in the study.

varied widely among different sources. Whole flaxseed doses varied from 30 g (12, 41) to 50 g (37) of flaxseed per day. Flaxseed oil consumption varied from as low as 1.2 g (39) to as high as 28 g (38) of oil per day. The daily dose of flaxseed lignan also varied from 360 mg (32) to 600 mg (35) of lignan. The duration of the studies varied from 3 wk (37) to 48 wk (24). Studies reported good compliance with no major side effects of consuming flaxseed. Two studies reported mild cases of constipation and other gastrointestinal problems (32, 40).

Meta-analysis results. The meta-analysis for the mean difference in SBP indicated that flaxseed significantly reduced SBP by −1.77 mm Hg (95% CI: −3.34, −0.09 mm Hg; $P = 0.04$). No heterogeneity was observed ($I^2 = 0\%$, $P = 0.74$) (**Figure 1**). The meta-analysis for the mean difference in DBP also indicated that flaxseed supplementation significantly reduced DBP by −1.16 mm Hg (95% CI: −2.64, −0.52 mm Hg; $P < 0.003$). No levels of heterogeneity were detected for the DBP analysis ($I^2 = 0\%$, $P = 0.56$) (**Figure 2**).

Sensitivity and subgroup analysis. Sensitivity analysis was performed by excluding individual studies and assessing the effect on overall results of the meta-analysis. Excluding 4 studies (12, 20, 24, 41) slightly reduced the significance of the meta-analysis for the effect of flaxseed on SBP (with the *P* value changes between 0.05 and –0.09). Excluding 4 studies (12, 24, 39, 40) also reduced the significance of the meta-analysis for the effect of flaxseed on DBP (with the *P* value changes between 0.07 and –0.11). Excluding 1 study (20) increased the significance of the meta-analysis for the effect of flaxseed on DBP (with the *P* value changes to 0.002).

Sensitivity analyses that used different levels of correlation coefficient ($r = 0.2$ and 0.8) were conducted (**Supplemental Table 2**). The sensitivity analysis of alternative correlation coefficients showed that all the results are in the same direction of effect. Therefore, the overall meta-analysis result is robust to use the imputed $r = 0.5$.

Subgroup analyses revealed a number of study characteristics that moderated the results of the meta-analyses. The test for subgroup analysis of the difference between parallel design trials and cross-over trials showed a significant reduction of both SBP and DBP when the trials had parallel design (**Table 2**). However, meaningful reduction of BP was not observed in the subgroup of studies with cross-over design. Subgroup analysis of the effect of flaxseed on DBP was significant in studies in which supplement duration was longer than 12 wk ($n = 10$; Table 2), compared with studies with duration of intervention shorter than 12 wk. The effect of flaxseed on SBP was slightly greater (but not significant, $P = 0.07$) in the subgroup with duration of intervention ≥12 wk compared with studies with shorter duration (Table 2). Subgroup analysis of whole flaxseed also reported a slightly more pronounced effect in reducing SBP (−3.39 mm Hg; 95% CI: −6.86, 0.07 mm Hg; $n = 4$) compared with other types, although this effect was not significant ($P = 0.05$). The analysis of whole flaxseed group showed a significant effect on DBP (−1.93 mm Hg; 95% CI: −3.65, −0.21 mm Hg; $P < 0.05$). The test for subgroup difference did not result in a difference between sources of flaxseed consumption (Table 2). Baseline SBP of participants appeared not to have any effect on the results of subgroup analysis; however, reduction in DBP was significant in subgroup analysis of participants with baseline BP < 130 mm Hg (−1.59 mm Hg; 95% CI: −3.03, −0.14 mm Hg). Baseline BMI ≥ 30 of study participants did not influence the effectiveness of flaxseed on BP ($n = 4$). The subgroup analysis of the effect of flaxseed on DBP reported a significant effect in the subgroup of participants with BMI < 30 (−1.86 mm Hg; 95% CI: −3.00, −0.72 mm Hg; $n = 10$; Table 2). The test for subgroup difference was not significant for the effect on DPB of this group.

Discussion

This systematic review and meta-analysis present evidence that dietary supplementation with whole flaxseed may reduce both

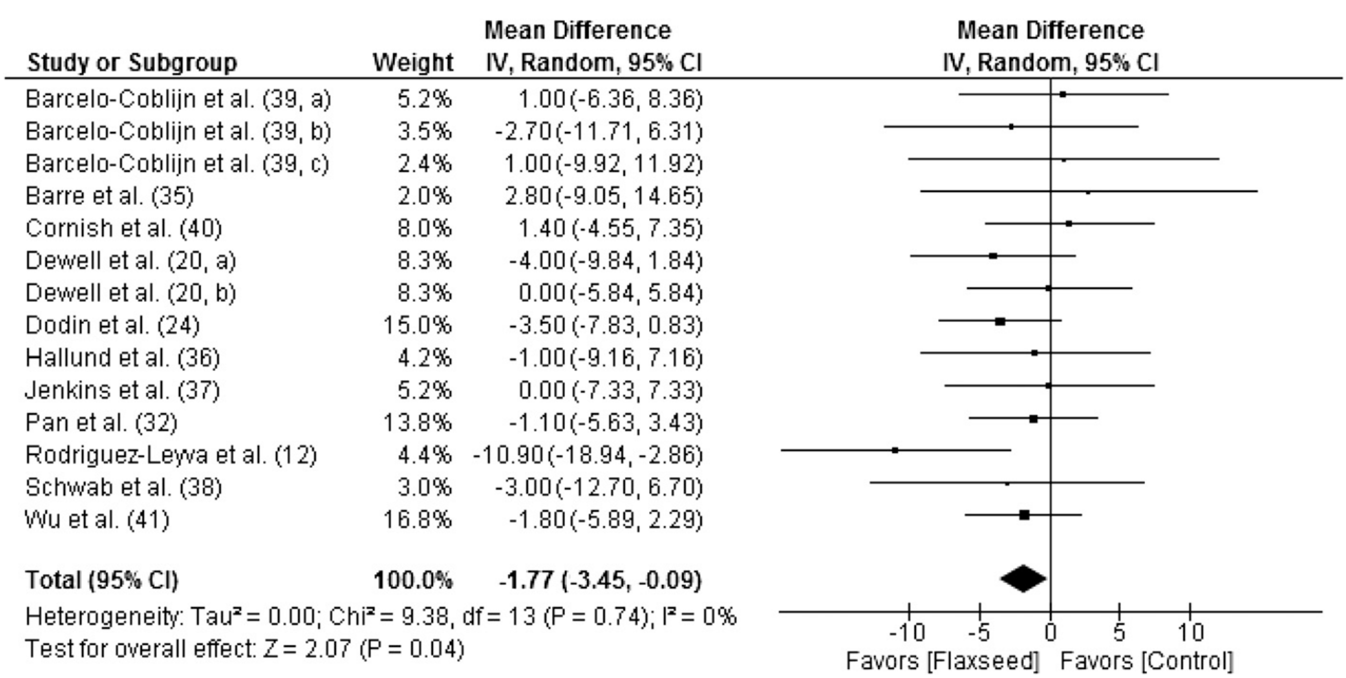

FIGURE 1 Forest plot of the effect of flaxseed consumption on systolic blood pressure. A random effect model was used to analyze the effectiveness of flaxseed consumption. Effect of each trial was presented as weight (%) and mean difference (95% CI). The weight of each study is represented by the size of the box; individual variance is represented by the length of the horizontal line. Random, random effect model; IV, inverse variance.

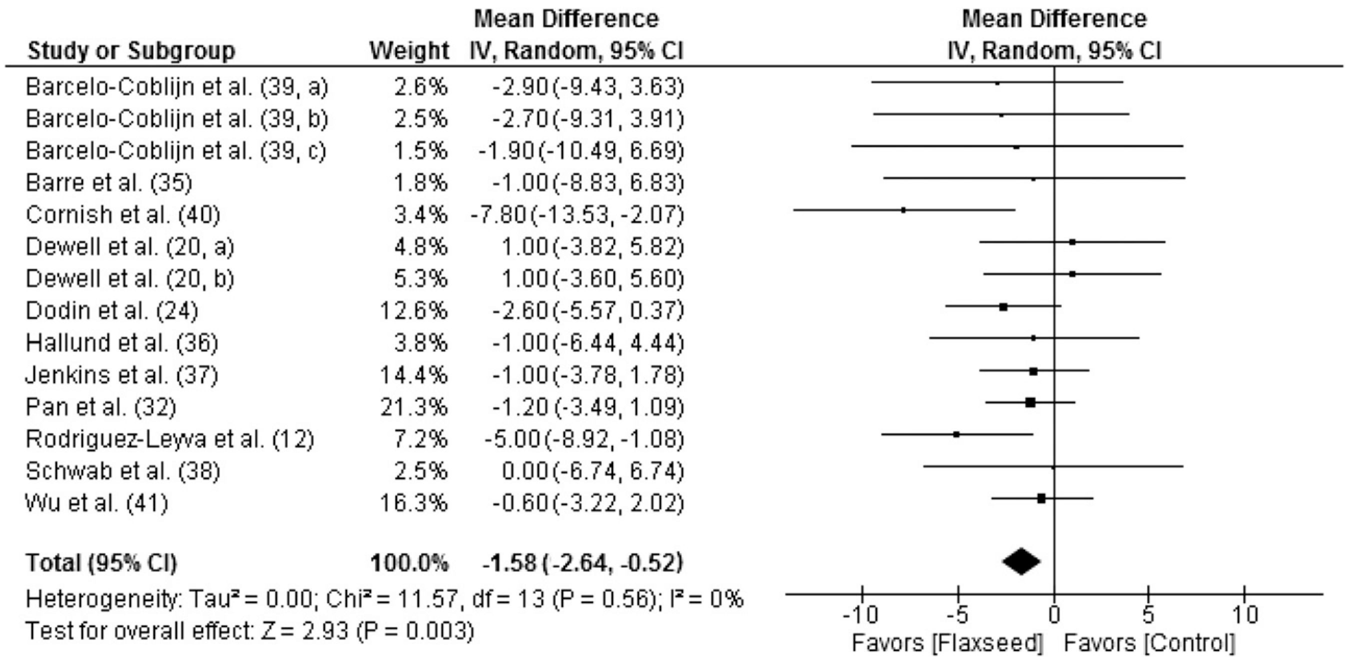

FIGURE 2 Forest plot of the effect of flaxseed consumption on diastolic blood pressure. A random effect model was used to analyze the effectiveness of flaxseed consumption. Effect of each trial was presented as weight (%) and mean difference (95% CI). The weight of each study is represented by the size of the box; individual variance is represented by the length of the horizontal line. Random, random effect model; IV, inverse variance.

SBP and DBP. Overall, this study showed that consuming flaxseed could significantly reduce SBP by 1.77 mm Hg and DBP by 1.16 mm Hg. The magnitude of reduction in BP reported by this meta-analysis is small; however, important public health and cardiovascular benefits can be expected from small reductions in BP (42). Even a 2-mm Hg reduction in SBP may lower stroke mortality by 10% and lower the mortality from ischemic heart disease by 7% (43). The magnitude of BP reduction reported in this meta-analysis is in consensus with the results of a meta-analysis on daily consumption of black tea reported by Greyling et al. (44). The findings are also slightly greater than the results of a meta-analysis based on per kilogram of body weight loss on BP (45). Although greater reduction of BP may be expected from continuous weight loss, a greater reduction of BP may also be expected from prolonged consumption of flaxseed. The results of subgroup analysis of this study also suggest more pronounced

TABLE 2 Results of subgroup analysis of included randomized controlled trials in meta-analysis of flaxseed and BP[1]

		SBP				DBP			
		Difference of SBP, mm Hg		Heterogeneity test for subgroup difference		Difference of DBP, mm Hg		Heterogeneity test for subgroup difference	
Subgroups	Trials, *n*	Mean (95% CI)	*P*	I^2, %	*P*	Mean (95% CI)	*P*	I^2, %	*P*
Intervention duration				0	0.74			62	0.10
≥12 wk	9	−1.84 (−3.86, 0.18)	0.07			−2.17 (−3.44, −0.89)	<0.05		
<12 wk	5	−1.60 (−4.71, 1.52)	0.87			−0.27 (−2.17, 1.64)	0.78		
Source of flax				0	0.39			35	0.11
Whole	4	−3.39 (−6.86, 0.07)	0.05			−1.93 (−3.65, −0.21)	<0.05		
Oil	6	−1.44 (−4.47, 1.60)	0.33			−0.38 (−2.79, 2.03)	0.76		
Lignan	3	−0.09 (−3.27, 3.08)	0.95			−2.39 (−5.32, 0.54)	0.11		
Baseline mean BP of participants				0	0.57			0	0.95
≥130 mm Hg	4	−2.75 (−6.89, 1.38	0.19			−1.66 (−3.43, 0.17)	0.07		
<130 mm Hg	10	−1.42 (−3.54, 0.69)	0.19			−1.59 (−3.03, −0.14)	<0.05		
Baseline BMI				0	0.95			39	0.20
≥30 kg/m²	4	−1.67 (−5.25, 1.90)	0.36			0.10 (−2.68, 2.87)	0.95		
<30 kg/m²	10	−1.80 (−3.70, 0.10)	0.06			−1.86 (−3.00, −0.72)	<0.05		
Design				0	0.48			0	0.37
Parallel	9	−2.15 (−4.17, −0.12)	<0.05			−2.12 (−3.85, −0.39)	<0.05		
Cross-over	10	−0.80 (−3.96, 2.35)	0.62			−1.04 (−2.64, 0.55)	0.20		
All trials (meta-analysis result)	14	−1.77 (−3.45, −0.09)	<0.05			−1.58 (−2.64, −0.52)	<0.05		

[1] BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

reduction of DBP can be anticipated by longer (≥12 wk) consumption of flaxseed. The results of the present study suggest that flaxseed be a dietary constituent considered for BP control and prevention.

Subgroup analysis of studies showed that flaxseed source was an important factor to influence reductions in BP. Consumption as a whole or ground seed as opposed to oil or lignin provided more pronounced reductions in SBP than did other sources and a significant reduction in DBP. The seeds of flax are the richest source of ALA– and are one of the best sources of phytoestrogens (lignans) and dietary fiber (17, 18). Although these findings might be influenced by the low number of trials in each subgroup, it appears that flaxseed consumption as whole or ground seed has the potential to produce greater benefit in reducing BP.

ALA in the human body can be converted to EPA (20:5n–3) and DHA (22:6n–3) by enzymatic mechanisms (46). Although this conversion rate is typically <0.5% (46), consumption of ALA can increase the blood concentration of EPA and DHA (47, 48). ALA, along with EPA and DHA, is reported to have anti-inflammatory and cardiovascular protective properties (49–51) and may improve BP (52). As a possible anti-inflammatory mechanism of ALA, reduction of oxylipins (oxygenated derivate of polyunsaturated FAs) associated with inflammation and vasoconstriction (series 2 eicosanoids) is proposed (52). The results of this action may be an increase in systemic vasodilation and reduction in BP (52, 53).

Lignans are diphenolic compounds, and one of the major phytoestrogens that have antioxidant and anti-inflammatory properties (54). Secoisolariciresinol diglucoside and secoisolariciresinol are the main lignans found in flaxseed (55). These plant lignans can be converted to mammalian lignans entreodiol and entrolactone by the action of gut microbiota (55, 56). Mammalian lignans have higher antioxidant and anti-inflammatory activities (16). Moreover, ~30% of flaxseed is dietary fiber, one-third of which is soluble polysaccharides (57). Dietary fiber, especially soluble fiber, can reduce blood cholesterol (58, 59) and BP (58). The BP-improving effect of dietary fiber is proposed through different mechanisms such as improving lipid profile (59), reducing insulin resistance (60), improving the gut flora of the intestine (61), and having antioxidant characteristics (62). A meta-analysis of 25 randomized controlled trials showed a significant reduction in BP from consuming dietary fiber (6). Another mechanism of the effect of dietary fiber on BP can be because of improving body weight (63); however, with the exception of 1 study (41), trials included in the present meta-analysis did not report significant reductions in body weight with flaxseed consumption. Moreover, subgroup analysis of trials with baseline BMI ≥ 30 of participants did not result in meaningful effect on SBP or DBP.

Another subgroup analysis of the present study showed that the reduction in DBP was significant with mean baseline BP of <130 mm Hg. Although the magnitude of BP reduction was slightly higher among participants with mean baseline SBP ≥ 130 mm Hg compared with participants with mean SBP < 130 mm Hg, the reduction did not reach statistical significance (P = 0.07). The nonsignificant result may be because of the low number of included trials (n = 4) that involved the subgroup of participants with mean baseline SBP ≥ 130 mm Hg. However, 3 of 4 studies reported a significant reduction of 7–9 mm Hg for SBP after flaxseed intervention (12, 35, 41). Subgroup analysis on the basis of the baseline BMI of participants may present a more pronounced reduction in DBP of nonobese participants. However, the low number of trials in the obese subgroup compared with the nonobese subgroup makes it difficult to draw a conclusion about BMI. Further interventions with obese participants need to be done to confirm the effect of flaxseed on BP of obese individuals.

Another important finding of the present meta-analysis was the influence of intervention duration on the magnitude of BP reduction. The magnitude of reduction in SBP was also greater in the subgroup of studies with duration of flaxseed consumption ≥12 wk, but the reduction did not reach statistical significance (P = 0.07). The subgroup analysis indicated that longer consumption of flaxseed (intervention duration ≥ 12 wk) can significantly reduce DBP to a greater extent than interventions with durations of <12 wk. These findings may be explained by the subsequent increase in ALA, EPA, DHA, and the antioxidant pool of blood (55, 56) or the gradual increase in intestinal gut flora, which may improve lignan absorption (56) and consequently reduce BP. A recent meta-analysis of 9 randomized trials reported that consumption of beneficial gut bacteria (probiotics) can significantly reduce both SBP and DBP (64).

To our knowledge, the present systematic review of the literature is the only study to have pooled the results of several controlled trials to investigate the effect of flaxseed on BP. However, as with all systematic reviews and meta-analyses, the present study had some limitations. For example, only studies published in the English language were included in the systematic review. In addition, the design of studies and the bias of included studies may have influenced the overall result of the meta-analysis. For instance, the washout period of cross-over trials varied from 2 wk (37) to 12 wk (32, 35). An inadequate washout period may increase the possibility of a carry-over effect from one treatment period to another and may affect the overall results. This may, to some extent, explain the greater meta-analysis effect observed in the subgroup analysis of parallel designs compared with cross-over trials. Moreover, cross-over studies included in this meta-analysis have a shorter duration of intervention than the parallel studies. This may explain the slightly greater effect of flaxseed on SBP in the subgroup of studies with duration of intervention ≥ 12 wk. Furthermore, 2 of the included studies (39, 41) did not report blinding of included subjects, and only 2 studies reported the method and an evaluation of the successfulness of blinding (12, 32). Four studies did not report attempts to control or monitor pretrial conditions (diet and exercise) (12, 35, 39, 40). Sample size calculation and justification were not reported in 5 studies (12, 35, 38–40).

The use of subgroup analyses also had some limitations. The dose-dependency analysis of the effect of flaxseed on BP was not applicable because of the variation in the flaxseed sources used. Several studies used concentrated flaxseed extract (oil or lignans supplements), which made it inappropriate to convert their daily dose to whole flaxseed dose. Moreover, the low number of trials in the subgroups that used different dietary sources of flaxseed may have affected the result of subgroup analysis.

Overall this meta-analysis suggests that consumption of flaxseed for a duration of 3–48 wk may reduce BP. The magnitude of improvement is greater if flaxseed is consumed as a whole seed for ≥12 wk. Although some studies have investigated the influence of flaxseed consumption on BP, there is a need for more research in this area. Future interventions that use different sources and doses of flaxseed, different durations of consumption, and participants with different BMIs are required to confirm the positive benefits of flaxseed consumption on BP. Additional studies should also be conducted to explore the mechanisms of how flaxseed influences changes in BP.

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SK designed the research; SK, CI, and MS conducted the research; SK and CI conducted the quality assessment of studies;

SK analyzed data and drafted the manuscript; SK, CI, and MS finalized the paper. SK had primary responsibility for final content. All authors read and approved the final manuscript.

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Update

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Erratum for Khalesi et al. Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials. J Nutr 2015;145:758–65.

In the above-mentioned article, the characteristics (for location, duration, and participants' age) of the study by Rodriguez-Leyva et al. (12) in Table 1 should read as follows: Canada, 52 wk, >40 y. In 1 instance, "wheat barn" should read "wheat bran," and in another instance, "Wheat" should read "wheat bran." In column 1 of Table 2, "Baseline mean BP of participants" should read "Baseline mean SBP of participants." The word "lignin" should be "lignan" on page 759 in the fourth line of the second paragraph of Methods and on page 763 in the third line of the first full paragraph. These changes do not alter the results or conclusion of the article.

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