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Review article

Effect of flaxseed supplementation on markers of inflammation and endothelial function: A systematic review and meta-analysis

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ABSTRACT

Objectives: The rationale for the current study was to evaluate the efficacy of flaxseed supplementation on important adhesion molecules and inflammatory cytokines in adults.

Methods: We conducted searches of published literature in PubMed, Scopus, Web of Science, and Google Scholar databases from inception until May 2019. All randomized controlled trials (RCTs) which investigated the effects of flaxseed supplementation on the circulating concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), vascular cell adhesion protein 1 (VCAM-1), E-selectin, and intercellular adhesion molecule 1 (ICAM-1) were included in our analysis. Results were summarized using weighted mean differences (WMDs) by random-effects model.

Results: Forty eligible RCTs, including 2520 participants were identified. The results of the meta-analysis revealed flaxseed supplementation reduced the concentrations of CRP (WMD = −0.387 mg/L; 95% CI: −0.653, −0.121, p = 0.004), IL-6 (WMD = −0.154 pg/Ml; 95% CI: −0.299, −0.010, p = 0.036), and VCAM-1 (WMD = –22.809 ng/ml; 95% CI: −41.498, −4.120, p = 0.017) but had no significant effect on TNF-α (WMD = -0.077 pg/mL; 95% CI: −0.317, 0.163, p = 0.530), ICAM-1 (WMD = −8.610 ng/ml; 95% CI: −21.936, 4.716, p = 0.205), and E-selectin (WMD = −1.427 ng/ml; 95% CI: −4.074, 1.22, p = 0.291).

Conclusions: These findings showed that flaxseed supplementation may improve some circulating concentrations of specific adhesion molecules and inflammatory cytokines. However, well-designed trials are needed to confirm the range of non-significant and/or equivocal findings.

1. Introduction

The rates of cardiovascular disease (CVDs) and subsequent mortality are rising to such an extent that it remains the leading cause of death around the world [1–3]. According to the World Health Organization, CVDs are responsible for one third of all global deaths, i.e about 17.7 million people, a number that is expected to grow [2]. This has major costs to the economy and health care systems and it is critical that effective interventions are implemented to prevent CVD and its-related complications. The onset of CVD is influenced by endothelial dysfunction which is associated with increased expression of adhesion molecules and inflammatory cytokines [4], factors that contribute to plaque formation and ultimately plaque rupture [5].

Established nutritional strategies such as the consumption of herbs as medicine to modify adhesion molecules and inflammatory cytokines have been developed [6–9]. These complementary therapies are the

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oldest form of healthcare known to humanity and are becoming increasingly popular as people seek out natural and safe natural remedies to prevent or treat disease [10–13]. One typical example is flaxseed [14] that can help optimize the supply of α-linolenic acid, phenolic compounds, phytoestrogen, and lignans, as well as being a good source of high quality protein and soluble fiber [15,16] which can also modify serum lipid concentrations [16]. It is also important to evaluate the impact of flaxseed supplementation on adhesion molecules and inflammatory cytokines. Currently, not all studies reported the same results, with some showing beneficial on inflammation and some do not [17–33]. Given the current lack of robust evidence based research, the current study was conducted to investigate the effects of flaxseed and flaxseed-derived products supplementation on specific adhesion molecules and inflammatory cytokines in adults through a *meta*-analysis. We aimed to include all randomized controlled trials (RCTs) on this topic.

Ultimately our review can summaries current evidence of the impact of flaxseed supplementation on CVDs risk factors and thereby help inform policy makers, investors, and health professionals.

2. Method

All procedures mentioned in this review were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [34].

2.1. Search strategy

The following databases were electronically searched from inception to May 2019: PubMed, Scopus, Web of Science, and Google Scholar. There were no language or year of publication restrictions. We used two groups of search terms to retrieve potentially relevant articles: (1) (flax OR flaxseed OR flaxseed OR linseed OR lignan OR whole flaxseed OR ground flaxseed OR flaxseed oil OR *Linum Usitatissimum*); (2) (Intervention Studies OR intervention OR controlled trial OR randomized OR randomised OR random OR randomly OR placebo OR assignment OR randomized controlled trial OR randomized clinical trial OR RCT OR double blinded OR trial OR controlled clinical trial OR Pragmatic clinical trial OR crossover procedure OR Cross-Over trial OR Double-Blind Method OR equivalence trial). Furthermore, we searched relevant reviews and reference lists of included trials for additional eligible studies that were missed by our electronic search.

2.2. Study selection

Initially, duplicates were removed using the reference manager software Endnote (Version X6, Thomson Reuters, New York). Then the remaining citations were screened by title and abstract for relevance. Following the initial screening, the full-text articles of potentially relevant publications were evaluated for inclusion in the review. Studies were included if they were human RCTs that measured the effects of flaxseed supplementation on at least one of the following outcomes: changes in C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), vascular cell adhesion protein 1 (VCAM-1), E-selectin, and intercellular adhesion molecule 1 (ICAM-1). Exclusion criteria included child/adolescent participants, combined interventions (flaxseed plus other active substances), duplications, and studies without outcomes of interest. Study selection and screening were done by two researchers (E.Gh and M.A) separately. All disagreements in the study selection process were resolved by consensus through discussion.

2.3. Data extraction

The key information of all eligible studies were independently extracted by two reviewers (E.Gh and M.A). The following data were collected with a standardized data collection form: (1) first author's last name; (2) year of publication; (3) country were the study was performed; (4) study design; (5) number of participants in the intervention and control groups; (6) type and dose of flaxseed; (7) intervention duration; (8) age, gender, body mass index (BMI) and health status of participants; and (9) data regarding baseline and follow-up plasma concentrations of CRP, IL-6, TNF-α, VCAM-1, E-Selectin, and ICAM-1. We resolved disagreements through discussions until a consensus was reached. When multiple articles were published from the same dataset, to avoid duplication of information, we selected the study with the largest sample. Moreover, the authors of some article were contacted via email if extra data were required.

2.4. Quality assessment

Two investigators (E.Gh and M.A) independently assessed the quality of each included study, discrepancies were discussed, and if consensus was not reached a third investigator was consulted (A.H). Quality was mainly assessed using the Cochrane Collaboration tool [35], based on the following three criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. We rated each domain of the trials as low risk, unclear, or high risk.

2.5. Statistical analysis

We used STATA 11.2 software (StataCorp, College Station, Texas, USA) for statistical analysis. Differences were expressed as weighted mean differences (WMD) with the 95% confidence interval (CI). To calculate WMDs, means and mean change scores and their standard deviations (SD) were employed. If only the SD for the baseline and final values were provided, SD for the net changes were imputed according to the method of Follmann [36]. A random-effects *meta*-analysis was employed a priori throughout this study because of inherent variations between study characteristics. We calculated heterogeneity across studies using the I^2 statistic. $I^2 > 50\%$ indicated significant heterogeneity. To find the possible source of heterogeneity, subgroup analysis and *meta*-regression were performed according to the following indicators: baseline BMI, participants' health condition, study duration, and type of supplement. In addition, the non-linear potential effects of flaxseed dosage and treatment duration were examined using fractional polynominal modeling. The influence of a single study was checked by a leave-one-out sensitivity analysis. Publication bias was assessed graphically through funnel plot asymmetry and statistically by Begg's test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection

A total of 6666 studies were yielded from the initial search (1082 from PubMed, 2120 from ISI, 522 from Cochrane, and 2942 from Scopus). After removing duplicates (n = 1262), 5404 articles remained of which 5335 were excluded after careful evaluation of the titles and abstracts based on PICOS criteria: (1) Unrelated title (n = 3441), (2) were animal studies (n = 1456), (3) editorial (n = 49) (4) conference paper (n = 54) (5) review (n = 268) (6) book section (n = 15) (7) other reason (letter, short survey and note) (n = 52).

Consequently, 69 potentially relevant articles were retrieved for full-text assessment and detailed examination. Twenty nine full-text articles were excluded, due to following reasons: without a control group (n = 3), did not report data of interest (n = 17), performed on children and adolescent (n = 2), the same study population (n = 2), combined intervention along with flaxseed (n = 5). Finally, a total of 40 eligible RCTs met all inclusion criteria. The PRISMA flow diagram is depicted in Supplemental Fig. 1.

Table 1
Characteristics of the 40 included studies, with 46 comparisons.

Author, Publication Year and Reference Number	Location	Intervention			Gender	Intervention/Control	WFX (g/d)	ALA (g/d)	LIG (mg/d)	Duration (week)	Patient features	Design	Diet Type	Outcomes
		Number (c)	Mean (range) age	Mean BMI (kg/m^2)										
Almario et al., 2013–1	USA	13	54.7	28.4	M/F	LIG/SBO	NA	3	150	6	Healthy	RP	Usual	CRP
Almario et al., 2013–2	USA	12	52.9	29.2	M/F	LIG/SBO	NA	3	410	6	Healthy	RP	Usual	CRP
Babajafari et al., 2018 moderate burn	Iran RP	25 Usual + ISP	36.8 CRP	(18–30)	M/F	FXO/CO	NA	NR	NA	3	mild to			
Barre et al., 2012	Canada	16	66.2	31.2	M/F	LIG/PB	NA	NR	600	13.5	T2DM	RC	Usual	TNF-α, ILK-6, CRP
Bloedon et al., 2008	Canada	29	56.8	27.4	M/F	GFX/Wheat barn	40	3.8	640	10	HC	RP	Usual	ILK-6, CRP
Caligiuri et al., 2015	Canada	45	(40 = <)	NR	M/F	WFX/PB	30	NR	NR	27	PAD	RP	Usual	TNF-α, CRP
Caughey et al., 1996	Australia	13	(24–44)	(16–36)	M	FXO/SFO	NA	13.7	NA	8	Healthy	RP	Usual	TNF-α
Cornish et al., 2009–1	Canada	20	62.2	28.4	M	LIG/PB	NA	NA	543	24	NR	RP	Usual + Exercise	TNF-α, ILK-6
Cornish et al., 2009–2	Canada	27	59.7	27.1	F	LIG/PB	NA	NA	543	24	NR	RP	Usual + Exercise	TNF-α, ILK-6
De oliveira et al., 2017	Brazil	26	66.3	34.4	M/F	FXO/SAO	NA	16	NA	13.5	MS	RP	Usual	CRP
Demark-Wahnefried et al., 2008–1	USA	40	59.3	28.5	M	WFX/Control	30	NR	NR	4.5	PC	RP	Low Fat	CRP
Demark-Wahnefried et al., 2008–2	USA	40	60.2	28.5	M	WFX/Control	30	NR	NR	4.5	PC	RP	Usual	CRP
Dewell et al., 2011–1	USA	20	50	30	M/F	FXO/SBO	NA	6.6	NA	8	MS	RP	Usual	I-CAM, ILK-6
Dewell et al., 2011–2	USA	20	50	30	M/F	FXO/SBO	NA	2.2	NA	8	MS	RP	Usual	I-CAM, ILK-6
Dittrich et al., 2014	Germany	46	56	28.1	M/F	FXO/SFO	NA	7.42	NA	10	HT	RC	Usual	CRP
Dodin et al., 2008	Canada	85	54	25.5	F	WFX/wheat germ	40	9.1	21	54	Healthy	RP	Usual	CRP
Faintuch et al., 2007	Brazil	24	40.8	47.1	M/F	WFX/Manioc flour	30	5	NR	2	OB	RC	Usual	CRP
Faintuch et al., 2011	Brazil	11	47.8	44	M/F	WFX/Cassava powder	60	10	NR	12	OB	RP	Usual	CRP
Foster et al., 2013–1	Australia	10	65	28.6	F	FXO/OO	NA	1.2	NA	12	T2DM	RP	Usual	TNF-α, ILK-6, CRP
Foster et al., 2013–2	Australia	11	65	28.6	F	FXO/ Control	NA	1.2	NA	12	T2DM	RP	Usual + Zinc supplement	TNF-α, ILK-6, CRP
Gillingham et al., 2010	Canada	36	47.4	28.5	M/F	FXO + HOCO/ HOCO	NA	21	NA	4	HC	RC	Usual	I-CAM, V-CAM, E-Selectin , ILK-6, CRP
Gomes et al., 2015	Brazil	10	47	28.9	M/F	FXO/PB	NA	3	NA	9	T2DM	RP	Usual	TNF-α, ILK-6, CRP
Hallund et al., 2008	Denmark	22	61	24.1	F	LIG/PB	NA	NR	500	6	Healthy	RC	Usual	I-CAM, V-CAM, TNF-α, ILK-6, CRP
Hutchins et al., 2013–1	Canada	25	58.6	30.4	M/F	GFX/ Control	13	2.9	59	12	OW/OB	RC	Usual	ILK-6, CRP
Hutchins et al., 2013–2	Canada	25	58.6	30.4	M/F	GFX/ Control	26	5.8	118	12	OW/OB	RC	Usual	ILK-6, CRP
Kaul et al., 2008	Canada	22	34.7	24.2	M/F	FXO/SFO	NA	1	NA	12	Healthy	RP	Usual	TNF-α, CRP
Khalatbari et al., 2012	Iran	15	54	25.5	M/F	GFX/Control	40	NR	NR	8	HM	RP	Usual	CRP
Khandouzi et al., 2018	Iran	21	56.6	26.5	M/F	WFX/Control	30	NR	NR	12	CVD	RP	DR	TNF-α, ILK-6, CRP
Kontogianni et al., 2013	Greece	37	25.6	21.9	M/F	FXO/OO	NA	8	NA	6	Healthy	RC	Usual	TNF-α, CRP
Lemos et al., 2012	Brazil	70	55.7	25.1	M/F	FXO/Mineral Oil	NA	2	NA	18	RF	RP	Usual	CRP
Mirfatahi et al., 2016	Iran	17	68	26	M/F	FXO/MCT	NA	3.5	NA	8	HM	RP	Usual	I-CAM, V-CAM, E-Selectin , CRP
Mirhashemi et al., 2016	Iran	30	63.5	NR	M/F	FXO/PB	NA	NR	NA	12	Diabetic nephropathy	RP	Usual	TNF-α
Mirmasoumi et al., 2017	Iran	30	28.4	26.9	F	FXO/PB	NA	NR	NA	12	PCOS	RP	Usual	CRP
Nelson et al., 2007	USA	27	37.7	29.31	M/F	FXO/Control	NA	11.6	NA	8	Healthy	RP	Usual	TNF-α, ILK-6, CRP
Nordstrom et al., 1995	Finland	11	51	NR	M/F	FXO/SFO	NA	9.6	NA	13.5	RA	RP	Usual	CRP
Pan et al., 2008	USA	70	62.9	25	M/F	LIG/PB	NA	NA	361	12	T2DM	RC	Usual	ILK-6, CRP
Paschos et al., 2007	Greece	18	49	28	M	FXO/SAO	NA	8.1	NA	12	HC	RP	Usual	TNF-α, CRP
Patade et al., 2008	USA	17	(47–63)	NR	F	WFX/Control	30	6	NR	12	HC	RP	Usual	CRP
Rallidis et al., 2003	Greece	50	50.4	28.4	M	FXO/SAO	NA	8	NA	12	HC	RP	Usual	I-CAM, V-CAM, E-Selectin, ILK-6, CRP
Rhee et al., 2011	USA	9	54.7	32.4	M/F	GFX/wheat barn	40	NR	NR	12	GI	RC	Usual	TNF-α, ILK-6, CRP
Soleimani et al., 2015	Iran	30	62.9	30.5	M/F	FXO/PB	NA	1	NA	12	Diabetic nephropathy	RP	Usual	CRP

(*continued on next page*)

Table 1 (*continued*)

Author, Publication Year and Reference Number	Location	Intervention			Gender	Intervention/Control	WFX (g/d)	ALA (g/d)	LIG (mg/d)	Duration (week)	Patient features	Design	Diet Type	Outcomes
		Number (c)	Mean (range) age	Mean BMI (kg/m^2)										
Soleimani et al., 2017	Iran	30	58.8	27	M/F	FXO/PB	NA	NR	NA	12	Diabetic			
foot ulcer	RP	Usual	CRP											
Thies et al., 2001	UK	8	66	25.5	M/F	FXO + SFO + PO/ SFO + PO	NA	2	NA	12	Healthy	RP	Usual	I-CAM, V-CAM, E-Selectin, TNF-α, ILK-6
Vargas et al., 2011	USA	17	29.4	35	F	FXO/SBO	NA	3.27	NA	6	PCOS	RP	Usual	CRP
Yari et al., 2016	Iran	25	45	29.9	M/F	WFX/Control	30	NR	NR	12	NAFD	RP	Usual + LC	TNF-α, CRP
Zong et al., 2012	China	83	48.9	25.1	M/F	GFX/Control	30	7	NR	12	MS	RP	Usual + LC	I-CAM, V-CAM, E-Selectin, TNF-α, ILK-6, CRP

ALA, a-linolenic acid; C, number of intervention group participants who completed the study; CO, corn oil; CRP,C-reactive protein; CVD, cardio vascular disease; DR, dietary recommendation; F, female; FXO, flaxseed oil; GFX, ground flaxseed; GI, glucose intolerant HC, hypercholesterolemia; HM, hemodialysis patients; HO, hempseed oil; HOCO, high oleic canola oil; HT, hypertriglyceridemia; I-CAM, Intercellular Adhesion Molecule 1; ISP, isolated soy protein; LC, Lifestyle counseling; LIG, lignans; M, male; MCT, medium-chain triglycerides oil; MS, Metabolic syndrome NA, not applicable; NAFD, non-alcoholic fatty liver disease; NR, not reported; OB, obese; OO, olive oil; OW, overweight; PAD, peripheral arterial disease; PB, placebo; PC, prostate cancer; PCOS, polycystic ovary syndrome; PO, palm oil; RA, Rheumatoid arthritis; RC, randomized crossover design; RF, Renal failure; RP, randomized parallel design; SAO, safflower oil; SBO, soybean oil; SFO, sunflower oil; T2DM, type2 diabetes mellitus; TNF-α, tumor necrosis factor alpha; ILK-6, Interleukin 6; V-CAM, vascular cell adhesion molecule; WFX, whole flaxseed.

3.2. Characteristics of the studies

The primary characteristics of these 40 trials are outlined in Table 1. Overall, 2520 participants were randomly assigned and completed the studies. CRP has been reported in 35 trails [17,18,21–26, 28–30,32,33,37–58], TNF-α in 17 trials [17–33], IL6 has been indicated in 16 trials [17,20–23,25,28,30,31,33,39,46,47,53,55,59], I-CAM in 7 trials [23,31,33,46,50,55,59], V-CAM in 6 trials [23,31,33,46,50,55] and E-selectin in 5 trials [31,33,46,50,55].

Of the 40 trials used in the present *meta*-analysis, 6 were conducted only on women (4 in post-menopausal women [21,23,43,54] and 2 in premenopausal women [51,58], 4 were conducted only in men [19,29,41,55], 1 trial reported results separately by sex [20], and 29 trials were conducted on both sexes [17,18,22,24–28,30–33, 37–40,42,44–50,52,53,56,57,59]. The included trials varied in the range from 2 to 54 weeks and the study design of most trials (31/40) was parallel [18–22,24,25,27–29,31–33,37–41,43,44,48–52,54–59], while crossover designs were used in 9 [17,23,26,30,42,45–47,53].

Whole flaxseed [18,25,32,41,43–45,54] or ground flaxseed [30,33,39,47,48] were used in 13 studies with doses from 13 to 60 g, wheat bran [30,39], wheat germ [43], manioc flour [45], or Cassava powder [44], placebo [18] were chosen as the control regimen in these studies. However, some studies received no intervention as a control group [25,32,33,41,47,48,54]. More than half of the trials (21/40) used flaxseed oil [19,21,22,24,26–28,31,38,40,42,46,49–52,55–59], with doses of 1–36 g. The control regimens included sunflower oil alone [19,24,42,52] or palm oil [31], soybean oil [58,59], olive oil [21,26], corn oil [38], safflower oil [29,40,55] or mineral oil [49]. Although, in some trials a placebo has been replaced oil [22,27,51,56,57]. Moreover, in one trial, no intervention in the control group was reported [21,28]. A flaxseed lignan supplement was tested in the remaining 5 trials [17,20,23,37,53], with doses from 150 to 600 mg. The control group in these trials was assigned to placebo [17,20,23,53] or soybean oil [37]. Moreover, in some trails participants the flaxseed intervention adhered to nutritional guidance [25], or included a low fat diet [41], exercise training[20], consuming supplements [21,38] or Lifestyle counseling [32,33].

Studies were performed in patients with different baseline conditions: four studies were performed in patients with type 2 diabetes mellitus [17,21,22,53], two on patients with diabetic nephropathy [27,56], and one in patents with diabetic foot ulcer [57], or with glucose intolerance [30]; two studies enrolled participants with polycystic ovary syndrome [51,58], three were carried out on patients with the metabolic syndrome [33,40,59], one with non-alcoholic fatty liver disease [32]; six investigated dyslipidemia subjects [29,39,42, 46,54,55], one on rheumatoid arthritis [52]; or hemodialysis patients [48,50], or renal failure [49] or CVD [25], or peripheral arterial disease [18], or prostate cancer [41] ornpatients with mild to moderate burn [38]. The remaining studies were conducted on metabolically healthy subjects; three on patients who were either overweight or obese [44,45,47], and seven in healthy participants [19,23,26,28,31,37,43]. Moreover, in one study patient features were not reported [20].

Trials also were performed in different countries as follows: USA [28,30,37,41,53,54,58,59], Canada [17,18,20,24,39,43,46,47] Brazil [22,40,44,45,49], Iran [25,27,32,38,48,50,51,56,57] Germany [42] Australia [19,21] Greece [26,29,55] Denmark [23] UK[31] Finland [52] and China [33].

3.3. Quality assessment

The quality of the selected trials varied, with random group allocation of participants in them all, with the method of random sequence generation described in 12 trials [20,21,24,25,27,38,41,43,50, 53,56,57], whereas the remainder have an unclear risk of bias. Allocation concealment was reported in 16 trials [20,21,24,26, 27,38,39,41,43,45,50–53,56,57] and remaining indicated unclear risk

Table 2
Cochrane risk of bias of included studies.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Almario et al., 2013	U	U	L	L	L	L	U
Babajafari et al., 2017	L	L	L	L	L	L	U
Barre et al., 2012	U	U	U	U	L	L	U
Bloedon et al., 2008	U	L	L	U	L	L	U
Caligiuri et al., 2015	U	U	L	L	L	L	U
Caughey et al., 1996	U	U	U	U	L	L	U
Cornish et al., 2009	L	L	L	L	L	L	U
De Oliveira et al., 2017	U	U	L	L	L	L	U
Demark-Wahnefried et al., 2008	L	L	L	L	L	L	U
Dewell et al., 2011	U	U	U	U	L	L	U
Dittrich et al., 2014	U	U	L	L	L	L	U
Dodin et al., 2008	L	L	L	L	L	L	U
Faintuch et al., 2007	U	L	L	U	L	L	U
Faintuch et al., 2011	U	U	L	L	L	L	U
Foster et al., 2013	L	L	L	L	L	L	U
Gillingham et al., 2010	U	U	L	U	L	L	U
Gomes et al., 2015	U	U	L	L	L	L	U
Hallund et al., 2008	U	U	L	L	L	L	U
Hutchins et al., 2013	U	U	U	U	L	L	U
Kaul et al., 2008	L	L	L	L	L	L	U
Khalatbari et al., 2012	U	U	H	H	L	L	U
Khandouzi et al., 2018	L	U	U	U	L	L	U
Kontogianni et al., 2012	U	L	L	L	L	L	U
Lemos et al., 2012	U	U	L	L	L	L	U
Mirfatahi et al., 2016	L	L	L	L	L	L	U
Mirhashemi et al., 2016	L	L	L	L	L	L	U
Mirmasoumi et al., 2017	U	L	L	L	L	L	U
Nelson et al., 2007	U	U	U	U	L	L	U
Nordstrom et al., 1994	U	L	L	L	L	L	U
Pan et al., 2008	L	L	L	L	L	L	U
Paschos et al., 2007	U	U	L	U	L	L	U
Patade et al., 2008	U	U	L	U	L	L	U
Rallidis et al., 2003	U	U	U	U	L	L	U
Rhee et al., 2011	U	U	H	H	L	L	U
Soleimani et al., 2015	L	L	L	L	L	L	U
Soleimani et al., 2017	L	L	L	L	L	L	U
Thies et al., 2001	U	U	L	U	L	L	U
Vargas et al., 2011	U	U	L	L	L	L	U
Yari et al., 2016	U	U	H	H	L	L	U
Zong et al., 2012	U	U	L	U	L	L	U

L, low risk of bias; H, high risk of bias; U, unknown risk of bias.

of bias with the lack of blinding of participants and personnel [17,19,25,28,29,31,33,39,45–47,54,55,59]. Seven described an unclear risk of bias [17,19,25,28,47,55,59] and 3 demonstrated a high risk of bias [30,32,48] and the rest had low risk of bias. All of the studies showed low risk of bias based on incomplete outcome data and selective reporting, as well as other potential threats to validity as described in Table 2.

4. Meta-analysis results

4.1. Effect of flaxseed supplementation on C-reactive protein

The pooled effect size of 39 trials (1151 intervention and 1134 control subjects) indicated that there was a significant reduction in CRP (WMD $-$**0.387** mg/L; 95% CI: $-$**0.653, −0.121**, $p = 0.004$), following flaxseed supplementation with considerable heterogeneity between studies ($p < 0.001$, $I^2 = 82.9\%$) (Fig. 1). To find any source of heterogeneity, subgroup analyses were performed based on baseline BMI (normal/overweight/obese), participants' health condition (healthy/unhealthy), study duration (< 12/≥12 weeks) and type of supplement (flaxseed oil/lignan supplement/whole flaxseed). Subgroup analysis revealed a significant CRP-lowering effect of flaxseed in RCTs carried-out in unhealthy, or overweight subjects, in trials which administered whole flaxseed and lignan supplement and performed for more than 12 weeks (Table 3).

4.2. Effect of flaxseed supplementation on Interleukin-6

The effect of the flaxseed supplementation on IL-6 was evaluated in twenty trials (518 intervention and 504 control subjects) and overall estimate of effect size showed a significant reduction in IL-6 of $-$**0.154** pg/mL (95% CI: $-$**0.299, −0.010**, $p = 0.036$) with considerable between-study heterogeneity ($p < 0.001$, $I^2 = 67.6$) (Fig. 2). Subgroup analysis indicated that IL-6 was only decreased in RCTs conducted in unhealthy, or overweight subjects, in trials that administered flaxseed oil and were conducted for < 12 weeks (Table 3).

4.3. Effect of flaxseed supplementation on tumor necrosis factor-alpha

Overall, 19 clinical trials (432 intervention and 437 control subjects) investigated the effect of flaxseed supplementation on TNF-α concentration, and pooled effect size showed no significant effect (WMD = $-$**0.077** pg/mL; 95% CI: $-$**0.317, 0.163**, p = 0.530), with between-study heterogeneity ($P < 0.001$, $I^2 = 67$) (Fig. 3). Subgroup analysis similarly revealed no effect on TNF-α (Table 3).

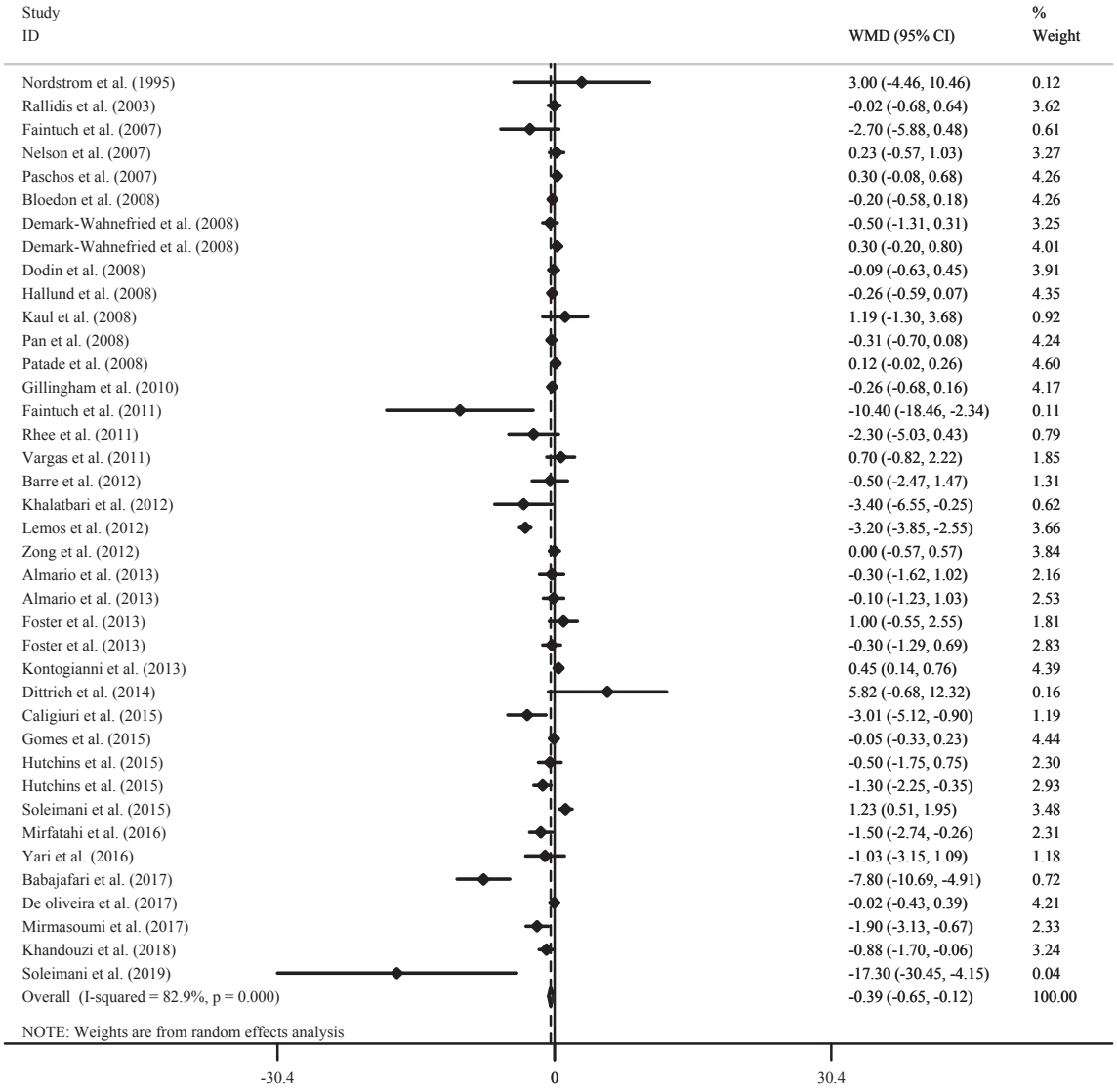

Fig. 1. Forest plot of the effect of flaxseed supplementation on C-reactive protein.

4.4. Effect of flaxseed supplementation on markers of endothelial function

Six RCTs (216 intervention and 199 control subjects) reported the effect of flaxseed supplementation on circulating VCAM-1, and combining effect sizes revealed a significant reduction (WMD = –22.809 ng/ml; 95% CI: −41.498, −4.120, $p = 0.017$), without any significant between-study heterogeneity ($p = 0.180$, $I^2 = 34.2$) (Fig. 4).

Eight trials (256 intervention and 239 control subjects) reported serum ICAM-1 as an outcome measure. Overall estimate of effect size revealed no significant effect of flaxseed supplementation on ICAM-1 (WMD = -8.610 ng/ml; 95% CI: −21.936, 4.716, $p = 0.205$), with a significant between-study heterogeneity ($p < 0.001$, $I^2 = 82.6$) (Fig. 5).

Overall five RCTs (194 intervention and 177 control subjects) reported the effect of flaxseed supplementation on circulating E-selectin and pooled effect size did not show any significant effect (WMD = -1.427 ng/ml; 95% CI: −4.074, 1.22, $p = 0.291$), with no heterogeneity between studies ($p = 0.138$, $I^2 = 42.5$) (Fig. 6).

4.5. Sensitivity analysis

Sensitivity analysis for IL-6 showed that pooled effect size were influenced by elimination of studies conducted by Rhee *et al.* (-0.12 ng/ml, 95%CI: −0.27, 0.01), Rallidis *et al.* (-0.08 ng/ml, 95%CI: −0.203, 0.026), Gillingham *et al.* (-0.15 ng/ml, 95% CI: −0.317, 0.004), Dewell *et al.* (-0.143 ng/ml, 95% CI: −0.295, 0.009) and Bloedon *et al.* (-0.147 ng/ml, 95% CI: −0.301, 0.006) which resulted in non-significance. Exclusion of studies carried-out by Mirfatahi *et al.* (-15.1 ng/ml, 95% CI: −36.46, 6.24) and Rallidis *et al.* −18.7 ng/ml, 95% CI: −40.1, 2.69) also changed the overall effect size for VCAM-1 to non-significant. Sensitivity analysis did not show any significance for any other parameters.

4.6. Publication bias, trim and fill sensitivity analysis

There was no evidence of publication bias for studies examining the effect of flaxseed supplementation on IL-6 ($p = 0.399$, Begg's test), TNF-α ($p = 0.552$, Begg's test), ICAM-1 ($p = 0.322$, Begg's test), VCAM-1 ($p = 0.188$, Begg's test) and E-selectin ($p = 0.327$, Begg's test). Visual

Table 3
Subgroup analysis to assess the effect of flaxseed supplementation on inflammatory factors.

Subgrouped by	No. of trials	WMD (95% CI)			P Value	P for heterogeneity	I^2 (%)	P for between subgroup heterogeneity
CRP								
Total	**39**	**−0.387**	**−0.653**	**−0.121**	**0.004**	**0.000**	**82.9**	
Baseline BMI								0.009
< 25 kg/m2	5	−0.424	−1.232	0.385	0.304	0.000	90.4	
25–30 kg/m2	22	−0.442	−0.827	−0.058	0.024	0.000	83.6	
> 30 kg/m2	9	−0.424	−1.266	0.418	0.324	0.000	75	
Intervention Duration (Weeks)								0.872
< 12 weeks	16	−0.236	−0.582	0.110	0.181	0.000	75.4	
≥ 12 weeks	23	−0.498	−0.914	−0.082	0.019	0.000	86.4	
Health Status								0.355
Healthy	10	−0.078	−0.387	0.231	0.621	0.018	54.9	
Unhealthy	29	−0.556	−0.916	−0.196	0.002	0.000	86.1	
Type of Intervention								0.140
Flaxseed Oil	19	−0.348	−0.871	0.174	0.191	0.000	89.7	
Lignan Supplement	5	−0.277	−0.518	−0.035	0.025	0.996	0	
Whole Flaxseed	15	−0.439	−0.791	−0.087	0.015	0.000	68.3	
Interleukin-6								
Total	**20**	**−0.154**	**−0.299**	**−0.010**	**0.036**	**0.000**	**67.6**	
Baseline BMI								0.044
< 25 kg/m2	2	−0.026	−0.163	0.111	0.712	0.784	0	
25–30 kg/m2	10	−0.218	−0.334	−0.102	0.000	0.001	66.7	
> 30 kg/m2	6	−0.015	−0.107	0.076	0.744	0.018	63.2	
Intervention Duration (Weeks)								0.098
< 12 weeks	7	−0.153	−0.261	−0.045	0.006	0.754	0	
≥ 12 weeks	12	−0.040	−0.118	0.038	0.316	0.000	77.1	
Health Status								0.000
Healthy	7	0.038	−0.052	0.129	0.409	0.060	50.4	
Unhealthy	13	−0.192	−0.281	−0.103	0.000	0.001	64.6	
Type of Intervention								0.003
Flaxseed Oil	11	−0.268	−0.393	−0.143	0.000	0.001	65.9	
Lignan Supplement	3	−0.029	−0.166	0.107	0.673	0.530	0	
Whole Flaxseed	6	−0.007	−0.094	0.081	0.884	0.007	68.9	
TNF-alpha								
Total	**19**	**−0.077**	**−0.317**	**0.163**	**0.530**	**0.000**	**67.0**	
Baseline BMI								0.627
< 25 kg/m2	3	0.060	−0.129	0.248	0.536	0.277	22.1	
25–30 kg/m2	9	−0.212	−0.783	0.359	0.466	0.000	80.1	
> 30 kg/m2	3	−0.130	−0.397	0.136	0.337	0.316	13.3	
Intervention Duration (Weeks)						0.374		
< 12 weeks	5	−0.063	−0.219	0.093	0.428	0.346	10.6	
≥ 12 weeks	14	−0.111	−0.495	0.273	0.571	0.000	73.6	
Health Status								0.922
Healthy	8	−0.010	−0.230	0.211	0.933	0.113	39.9	
Unhealthy	11	−0.197	−0.680	0.286	0.424	0.000	76.7	
Type of Intervention								0.42
Flaxseed Oil	12	0.070	−0.219	0.359	0.530	0.140	31.4	
Lignan Supplement	2	−0.009	−0.143	0.126	0.90	0.960	0	
Whole Flaxseed	5	−0.716	−1.608	0.177	0.116	0.000	89.1	

inspection of funnel plots also showed no publication bias. However, there were significant publication bias for CRP ($p = 0.041$, Begg's test), that was unchanged after trim and fill sensitivity analysis from hypothesized negative unpublished studies. The corrected effect size of "publication bias" unchanged; trim and fill analysis were statistically significant ($p < 0.001$), indicating the results would not be changed if new studies publish regarding flaxseed effects on CRP.

4.7. Non-linear dose-responses between dose and duration of flaxseed supplementation and C-reactive protein

Dose-response analysis showed that flaxseed supplementation changed CRP (r = -0.41, P-nonlinearity = 0.007) significantly based on dose in non-linear fashion (Fig. 7). Significant associations were not observed for other outcomes in non-linear dose-responses.

5. Discussion

The vascular endothelium exhibits a diverse range of roles and activities including the regulation of vascular tone and maintenance of blood circulation, fluidity, coagulation, and inflammatory responses, all of which contribute to the overall health and function of the cardiovascular system [5]. Cardiovascular risk factors such as raised circulation of adhesion molecules and inflammatory cytokines compromise endothelial function and thus contribute to CVD [4]. The potential of flaxseed and flaxseed products [60,61] to reduce the concentration of inflammatory and adhesion molecules [62] could reduce CVD. Therefore, the purpose of this review is critically assess the scientific evidence regarding their efficacy in improving the circulatory status of inflammatory and adhesion molecules in adults.

A previous *meta*-analysis in 2016 of 20 studies [63] assessed the effects of flaxseed and flaxseed-derived products (flaxseed oil or lignans) on CRP, but found no effect and did not include any other inflammation or adhesion markers. The present *meta*-analysis included additional randomized trials as well other markers (CRP (n = 35), TNF-α (n = 17), IL-6 (n = 16), I-CAM (n = 7), V-CAM (n = 6), E-selectin (n = 5)) and found indicated that supplementation significantly decreased CRP, IL-6, and VCAM-1. With respect to CRP, this was only affected in RCTs with unhealthy or overweight participants in trials administered whole flaxseed and lignan supplement or for > 12 weeks

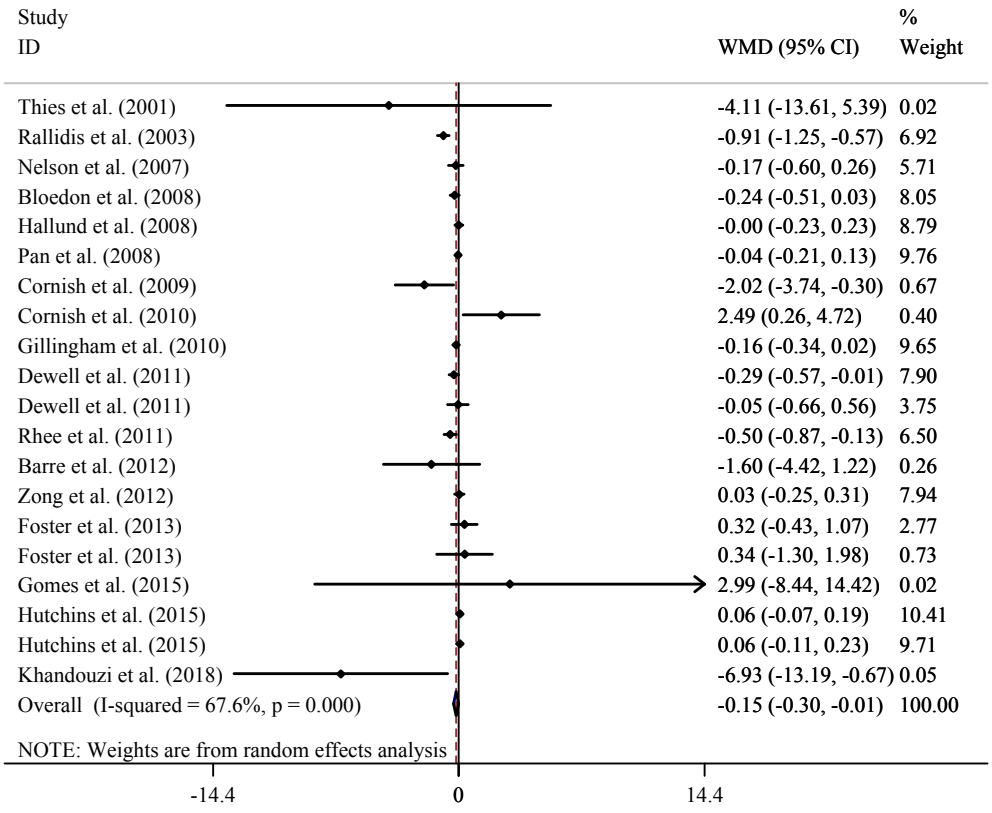

Fig. 2. Forest plot of the effect flaxseed supplementation on Interleukin-6.

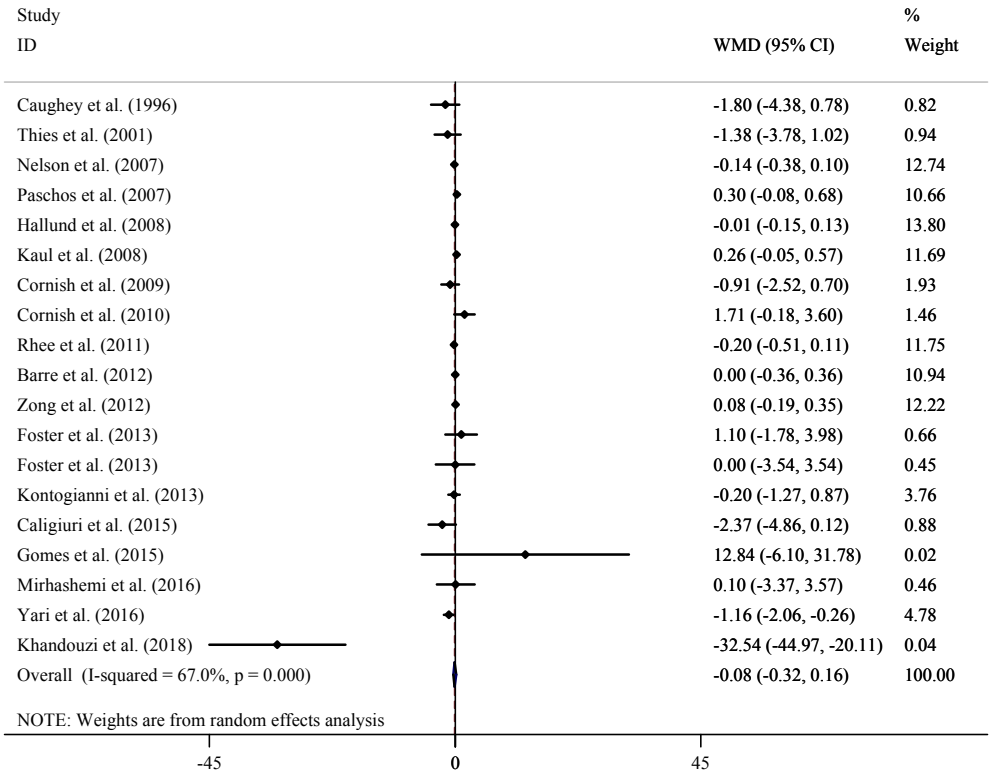

Fig. 3. Forest plot of the effect of flaxseed supplementation on Tumor necrosis factor-alpha.

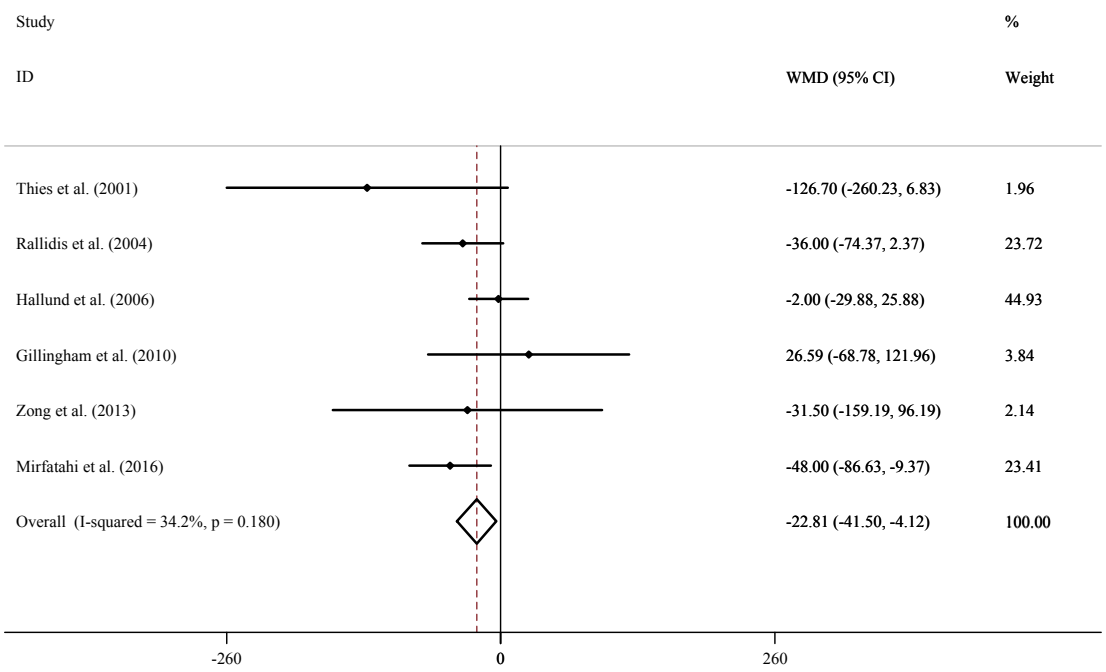

Fig. 4. Forest plot of the effect of flaxseed supplementation on VCAM-1.

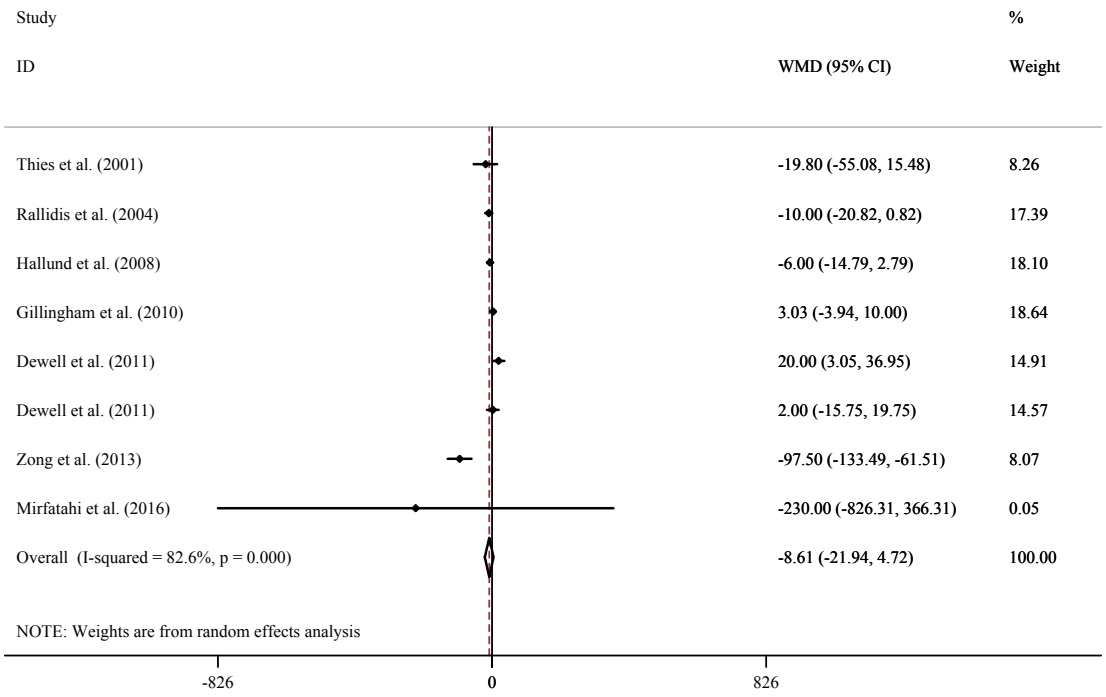

Fig. 5. Forest plot of the effect of flaxseed supplementation on ICAM-1.

and in a nonlinear fashion based on flaxseed dosage. Comparable results were obtained for IL6 except supplementation was required for < 12 weeks or flaxseed oil.

Obese [63] and unhealthy subjects [64,65] tend to have higher blood levels of inflammatory factors, and these people [63] or patients with metabolic disorders [66] may benefit most from the intervention [66]. Nutrient deficiency that can accompany metabolic disorders [67,68] could thus be overcome in part by flaxseed administration.

There were mixed findings regarding the duration of studies and type of supplement, that may depend on the mechanism of action of flaxseed and its bioactive components as different inflammatory pathways can be affected by dietary components [69]. Overall, the divergence in the results we describe might be due to other dietary components [70,71], life style factors [72] or genetic factors such as single nucleotide polymorphisms of subjects [73]. Interactions between diet, inflammation, and the microbiota should also be considered [74]. For example, flaxseed is the richest non bioactive source of lignan precursors and is converted in the colon by gut microbiota into its primary metabolites which possess antioxidants action [75], and could be thus modified by the microbiota profile [74]. Furthermore, different bioactive components in flaxseed and flaxseed-derived products [75,76], plus the type of production, storage, compound stability, and

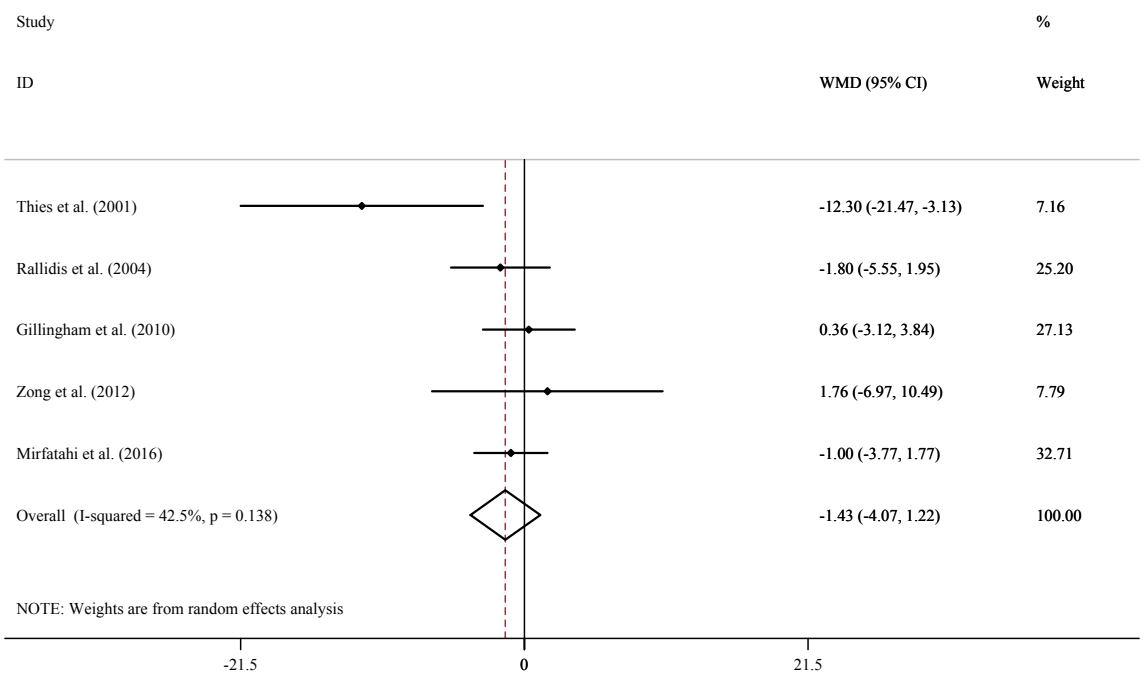

Fig. 6. Forest plot of the effect of flaxseed supplementation on E-selectin.

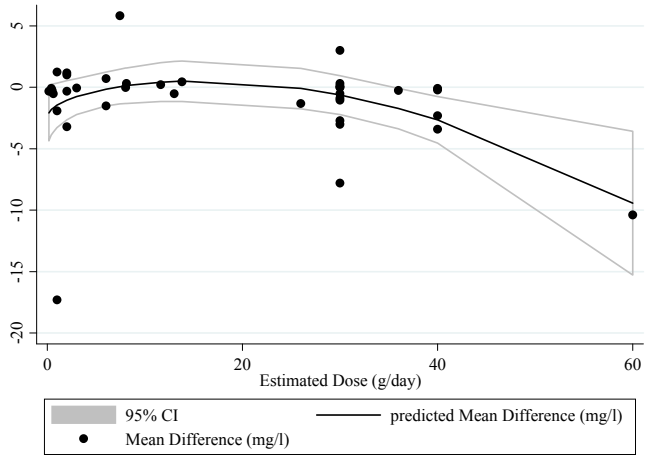

Fig. 7. Non-linear dose-responses between dose and duration of flaxseed supplementation and C-reactive protein.

use of whole flaxseed or its derivatives [77] could influence bioavailability and thus adhesion molecules and inflammatory cytokines responses.

Several mechanisms have been proposed for the effect of flaxseed on inflammation and adhesion markers. It is one of the richest sources of alpha-linolenic acid (ALA) as PUFA-omega-3 fatty acid [78], an essential fatty acid that can be converted to long-chain-omega-3 fatty acid, which is anti-inflammatory. Omega-3 fatty acids inhibit the formation of omega-6 fatty acids-derived pro-inflammatory eicosanoids (e.g. PGE2 and LTB4) and can form several potent anti-inflammatory mediators (e.g. resolvins and protectins). Together these provide a mechanism to suppress the activity of nuclear transcription factors including NFκB, and thus decrease the production of pro-inflammatory enzymes and cytokines, such as COX-2, TNF-α, and interleukin (IL)-1β [79]. It should be noted ALA, as a plant-based source of *PUFA-omega-3 fatty acid*, might not have the same effects on inflammation [63]. The fibre content of flaxseed could also determine whether it protects against inflammation by creating short chain fatty acids such as acetate, propionate, and butyrate [63] that can downregulate some pro-inflammatory cytokines in adipose tissue [63].

The present *meta*-analysis had several limitations, including the effects of confounding variables such as genetic background and lifestyle factors on the efficacy of flaxseed supplements, together with their formulation. Its strengths were evaluating dose–responses for the first time using a *meta*-analysis, together with subgroup analysis and assessment of the impact of baseline BMI, the participants health, study duration, and type of supplement on the overall effect sizes. In addition, our method for analyzing depended on between-group's mean changes that are more accurate than within-group changes, thereby enabling us to assess greater effect sizes. In addition, we tried to minimize any biases in the review process by performing a comprehensive search of the literature and also by adhering to the PRISMA guidelines.

6. Safety

Although the positive effects of flaxseed on health have been reported, there is a particular concern in some populations including pregnant women. Furthermore, the exact effect of flaxseed phytoestrogens on the male reproductive system are not known, however, animal studies showed neonatal exposure to estrogens resulted in the reduction of the sperm production [80]. Therefore, utilization of flaxseed in the diet, especially long term should be performed with caution for pregnant women and men in their reproductive ages especially in chronic use [80].

7. Implications for practice

Our current *meta*-analysis strongly suggested that giving flaxseed supplements to subjects that are overweight and/or with an unhealthy metabolic status could have beneficial effects. Furthermore, flaxseed is considered as an alternative source of marine-derived omega-3 fatty acid due to it's readily availability and it is inexpensive compare to fish oil [63].

8. Implications for research

Future large, long duration and high-quality trials should be designed to ensure low risk of bias and to meet current reporting

standards for clinical trials. Another outcome to consider is whether any beneficial effects are maintained.

9. Conclusion

Consuming flaxseed and its products have a beneficial effect on lowering CRP, IL-6, and VCAM-1 in humans and could provide an important alternative strategy to control endothelial dysfunction and CVD.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Each author acknowledges he/she has participated in the work in a substantive way and is prepared to take full responsibility for the work.

Author contribution

The authors' contribution was as follows: E.G.: contributed to the design and statistical analysis, A.H and M.A. conducted the systematic search, screening and data extraction, E.G. prepared the primary manuscript, E.G. and M.M. finalized the manuscript, and; MES and M.M. proofread the manuscript for native English writing; all authors read and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.154922.

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