1-s2.0-S2405457722002285-main.pdf

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Submission date: 24-Oct-2022 04:15PM (UTC+0700)
Submission ID: 1933839998
File name: 1-s2.0-S2405457722002285-main.pdf (1.02M)
Word count: 5721
Character count: 30968

The effect of conjugated linoleic acid supplementation on oxidative stress markers: A systematic review and meta-analysis of randomized controlled trials

Article *in* Clinical Nutrition ESPEN · April 2022

DOI: 10.1016/j.clnesp.2022.04.004

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Clinical Nutrition ESPEN 49 (2022) 121–128

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Meta-analysis

The effect of conjugated linoleic acid supplementation on oxidative stress markers: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 4 January 2022
Accepted 3 April 2022

Keywords:
Conjugated linoleic acid
Oxidative stress
Meta-analysis
Systematic review

SUMMARY

Background & aims: Recent trial studies have found that conjugated linoleic acid (CLA) supplementation beneficially reduces oxidative stress markers but, there is no definitive consensus on this context. The present systematic review and meta-analysis aimed to investigate the effect of CLA supplementation on oxidative stress parameters.

Methods: We searched PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases until September 2021 to identify randomized controlled trials (RCTs) assessing CLA supplementation effects on oxidative markers including malondialdehyde (MDA), 8-isoprostanesF2α (8-iso-PGF2α), and glutathione peroxidase (GPx). Summary estimates and corresponding 95% confidence intervals (CI) were derived via the DerSimonian and Laird method using a random-effects model.

Results: A total of 11 RCTs were included. The obtained results show that CLA supplementation caused a significant decrease in MDA concentrations (Hedges's: −0.35; 95% CI: −0.70 to −0.01, P = 0.04, I^2 = 62.1%, n = 7), and also significantly increased 8-iso-PGF2α levels (Hedges's: 1.45; 95% CI: 0.98 to 1.91, P<0.001, I^2 = 42.9%, n = 4). However, the results showed that supplementation with CLA did not significantly change the concentrations of GPx (Hedges's: 0.30; 95% CI: −0.04 to 0.64, P = 0.08, I^2 = 0.0%, n = 3).

Conclusion: It seems this supplement can be used as a dietary supplement to improve oxidative stress parameters. However, further studies are required to demonstrate present results.

1. Introduction

Oxidative stress reflects an imbalance between the production of free radicals and the body's ability to detoxify the toxic effects through antioxidants [1]. This condition is known to affect the progression of chronic diseases like obesity, cancer, cardiovascular diseases, diabetes, and neurological disorders [2–6]. Under the physiologic condition, the antioxidant defense systems maintain the oxidant-antioxidant balance by adjusting the altering levels of oxidants [7]. Since antioxidants degenerate during this action, there is a perennial need to reload their stores [8]. Oxidative stress could be measured by several oxidative stress markers such as malondialdehyde (MDA), total antioxidant capacity (TAC), xanthine oxidase (XO), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [9]. Exogenous antioxidants are found in a variety of foods

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https://doi.org/10.1016/j.clnesp.2022.04.004
2405-4577/

such as fruits, vegetables, spices, cereals, and extra virgin olive oil that are effective in protection against oxidative stress and postprandial oxidative stress [10–12]. Recently, the role of dietary supplements in the prevention of oxidative stress has been discussed [13,14].

Conjugated linoleic acid (CLA) consists of a group of positional and geometrical isomers of conjugated dienoic octadecadienoate (18:2) which is found predominantly in dairy and meat products [15,16]. Cis-9, trans-11 CLA, and trans-10, cis-12 CLA is most important isomers [17]. The beneficial effects of CLA supplementation on improving lipid profile [18], glycemic indices [18,19], blood pressure [20], liver function [21], anthropometric indices [22] and inflammation [23] have been well established. During the past decades, several clinical trials have been carried out to evaluate the role of CLA against oxidative stress [24–35]. Some studies indicated positive effects of CLA on antioxidant status [26,29,35], while others did not show such beneficial effects [28,34]. Since there is a controversy over this claim, we conducted a systematic review and meta-analysis on randomized controlled trials (RCTs) to evaluate the effects of CLA supplementation on antioxidant indices, including MDA, 8-isoprostanesF2α (8-iso-PGF2α), and GPx, to determine whether CLA has a protective role against oxidative stress or not.

2. Methods

The present meta-analysis was reported based on the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline [36].

2.1. Search strategies

We carried out a systematic literature search of PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases to extract the randomized controlled trials (RCTs) published until September 2021. No language restriction or other filters were applied when searching the literature. The following search strategy was run in the aforesaid databases: ("trans-10, cis-12-conjugated linoleic acid" OR "cis-9, trans-11-conjugated linoleic acid" OR "CLA fatty acid" OR "CLA" OR "conjugated linoleic acid" OR "trans fatty acid" OR "TFA") AND ("Oxidative stress" OR "TAC" OR "Total antioxidant capacity" OR "Malondialdehyde" OR "MDA" OR "Glutathione peroxidase" OR GPx OR GSH OR "Catalase" OR "Superoxide dismutase" OR SOD OR "Total Oxidant Status" OR TOS OR "lipid peroxidation" OR TBARS OR "Thiobarbituric acid reactive substances" OR "Glutathione reductase" OR GR OR "Nitric oxide" OR "reactive oxygen species" OR ROS) AND ("Intervention Studies" OR "Intervention" OR "Controlled trial" OR "Randomized" OR "Randomised" OR "Random" OR "Randomly" OR "Placebo" OR "Assignment"). In addition, to ensure we collected any other relevant papers, all reference lists of eligible studies, previous review articles, and trial registry platforms were searched.

2.2. Study selection

All studies found from electronic databases and reference lists were entered into endnote software (EndNote X6, Thomson Corporation, Stamford, USA) and duplicate studies were removed. Then, two authors independently read the titles and abstracts of studies to exclude those that were not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria. To identify eligible studies the following criteria were used: (1) RCTs (either parallel or cross-over design), (2) adult individuals (over 18 years old), (3) studies in which the participants were treated with CLA supplementation in comparison to a control group whose participants received placebo or no supplementation at all, (4) reported antioxidant indices (MDA, 8-iso-PGF2α, and GPx) in both CLA and control groups before and after the intervention. Exclusion criteria were (1) studies with CLA supplementation in combination with other nutrients, (2) studies with insufficient data at baseline and final level of selected outcomes in the control and intervention groups, (3) animal studies, reviews, and letters to editors, and (4) trials with follow up less than 2 weeks. When multiple publications for the same study were found, the most recent publication was used. Any discrepancies raised between reviewers were resolved by a panel discussion.

2.3. Data extraction and quality assessment

All eligible studies were reviewed, and the following data were extracted using a predefined, standardized, electronic data extraction form: first author's name, year of publication, study location, study duration, gender, mean age, and mean body mass index (BMI) of participants, study design, the health status of participants, total sample size, the dose of CLA supplementation and baseline and endpoint levels of oxidative stress parameters. When our interest data were not reported in the papers, we contacted the authors via email to obtain missing data.

Study quality was assessed by the Cochrane collaboration modified tool [37]. This scale assesses the risk of bias in the trials according to random sequence generation and allocation concealment, blinding of the participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was considered "Low risk of bias" when the true effect of the outcome is not likely to be affected, "Unclear risk of bias" when the study did not report enough information to permit judgment, and "High risk of bias" when the true effect of the outcome is likely affected. Two of the authors independently performed the data extraction, and quality assessment, with disagreements resolved by discussion.

2.4. Statistical analysis

Statistical analyses were carried out using the STATA software (version 11.0; Stata Corporation). All data were collected as means ± standard deviation (SD) for each variable to estimate the pooled effects. In studies that mean changes were not directly reported in intervention and control groups, it was calculated by the difference of the post-intervention data from the baseline values. In this case, the SD of the mean difference was calculated based on the Follmann method [38], using a correlation coefficient of 0.5. When standard error (SE) was reported in place of SD, we converted it to SD as SD = SE × sqrt (n) where n = number of subjects in each group. Weighted mean difference (WMD) with 95% CI was used for pooling data to determine effect sizes. The random-effect model was used to report the pooled effect sizes using 95% CI. Heterogeneity among studies was assessed by the I^2 statistic (I^2 0–30%, <30%–60%, and more than 60% indicated low, moderate, and high heterogeneity, respectively). To find possible sources of heterogeneity, subgroup analysis was conducted according to participant mean age, CLA dosage, and duration of intervention. To investigate whether the results of the meta-analysis were dependent on a particular trial or group of trials, we recomputed the meta-analysis statistic after omitting one study at a time (sensitivity analysis). The possibility of publication bias was also explored using Egger's linear regression [39] and Begg's rank-correlation methods [40]. All tests were two-tailed and $p < 0.05$ indicated statistical significance.

3. Results

3.1. Flow and characteristics of included studies

A flow chart showing the study extraction is presented in Fig. 1. Throughout the initial search strategy, we identified 2301 articles but finally, eleven RCTs [26–35,41] met the inclusion criteria and were included in the final meta-analysis.

3.2. Population and study characteristics

The included studies were published between 2000 and 2017 and reported data on 485 subjects. The design of all the included studies was parallel, and all were performed in Iran, Germany, Sweden, Finland, and Korea. The participants' mean age ranged from 33 to 60 years. All studies were conducted on both genders, except for two studies performed exclusively on women and men. The CLA does range from 2 g to 4.5 g/day, and the intervention duration ranged from 4 to 12 weeks. The target population for three of the studies was overweight, obese, or healthy subjects, and for the other studies patients with non-alcoholic fatty liver disease, metabolic syndrome, rheumatoid arthritis, atherosclerotic disease, chronic obstructive pulmonary disease, birch pollen allergy, type 2 diabetes, and rectal cancer. The basic characteristics of these trials are summarized in Table 1.

3.3. Risk of bias and quality of evidence

According to the Cochrane risk of bias tool, seven trials were classified as good quality and four as fair quality. Table 2 presents details of the study quality assessment of the included studies.

3.4. Effect of CLA supplementation on concentration of MDA

The effect of CLA supplementation on serum CLA levels was investigated in seven trials [26–29,31,34,41]. Using the random-effects model, the pooling of the effect sizes reveal a significant reduction in serum MDA levels after CLA supplementation compared to the placebo (Hedges's: −0.35; 95% CI: −0.70 to −0.01, P = 0.04), with high heterogeneity (I^2 = 62.1%, P = 0.01) (Fig. 2). Subgroup analysis based on CLA dosage, and participants' age reduced the heterogeneity. However, the effect of CLA supplementation on MDA was not significant in all subsets (Table 3).

3.5. Effect of CLA supplementation on concentration of 8-iso-PGF2α

Combining findings from 4 studies [27,32,33,35], a significant increase in the 8-iso-PGF2α levels (Hedges's: 1.45; 95% CI: 0.98 to 1.91, P<0.001) was detected after CLA supplementation than placebo consumption, with a moderate between-study heterogeneity (I^2 = 42.9%, P = 0.15) (Fig. 3). Subgroup analysis by the participants'

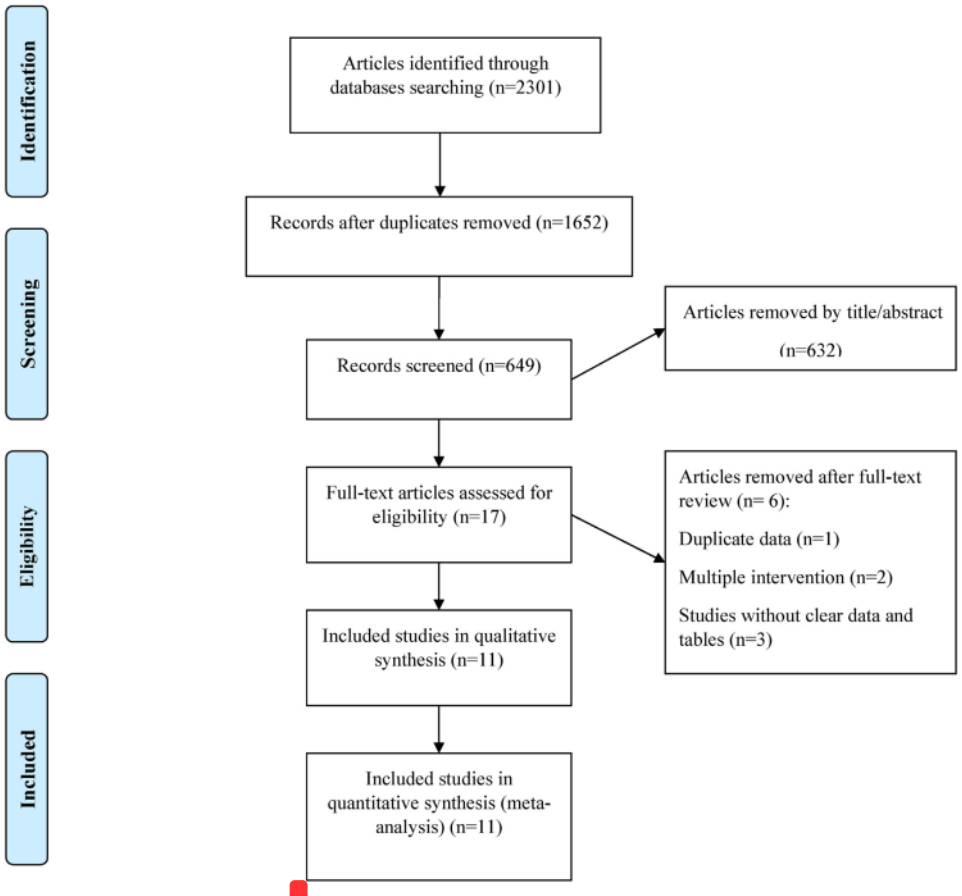

Fig. 1. PRISMA flow diagram of study selection process.

Table 1
Characteristics of included trials.

First author (publication year)	Country	Total Sample size	Gender	Age (mean)	BMI (mean)	RCT design	Follow-up	Health status	Intervention of experimental group	Intervention of control group	Investigated outcomes
Basu et al. (2000)	Sweden	53	Both	45.4	25.1	parallel	12 weeks	Healthy subjects	4.2 gr CLA	placebo	MDA, u-8-iso-$PGF_{2\alpha}$
Risérus (2004)	Sweden	25	Both	55	30	parallel	12 weeks	Patients with metabolic syndrome	3gr CLA	placebo	u-8-iso-$PGF_{2\alpha}$
Shadman (2013)	Iran	37	Both	46	28	parallel	8 weeks	Type 2 diabetes patients	3gr CLA	placebo	MDA
Aryaeian (2009)	Iran	44	Both	47	28	parallel	12 weeks	Patients with rheumatoid Arthritis	2.5gr CLA	placebo	MDA,GPX
Eftekhari (2013)	Iran	57	both	54	24	parallel	8 weeks	Atherosclerotic patients	3 gr CLA	placebo	MDA,GPX
Pfeuffer (2011)	Germany	42	men	57	28	parallel	4 weeks	Overweight and obese participants	4.5gr CLA	placebo	u-8-iso-$PGF_{2\alpha}$
Ebrahimi-Mameghani (2016)	Iran	38	female	35	33	parallel	8 weeks	Obese patients with non-alcoholic fatty liver disease	3gr CLA	placebo	MDA
Matin (2018)	Iran	90	Both	60	NR	parallel	6 weeks	patients with Chronic obstructive pulmonary disease	3.2gr CLA	placebo	MDA
Kim (2012)	Korea	29	Both	40	25.5	parallel	8 weeks	Healthy overweight/ obese individuals	2.4gr CLA	placebo	GPX
Faramarzi (2017)	Iran	32	Both	60	24	parallel	6 weeks	Rectal cancer patients	3 gr CLA	placebo	MDA
Turpeinen (2008)	Finland	38	Both	33	NR	parallel	12 weeks	Subjects with birch pollen allergy	2 gr CLA	placebo	u-8-iso-$PGF_{2\alpha}$

Abbreviations: RCT, randomized controlled trial; BMI, body mass index; MDA, Malondialdehyde; u-8-iso-$PGF_{2\alpha}$, Urinary 8-Iso-Prostaglandin F2α; GPX, Glutathione peroxidase, NR, not reported.

Table 2
Quality assessment of included studies based on Cochrane guidelines.

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Score	Overall quality
Basu (2000)	L	U	L	H	L	U	L	4	Good
Risérus (2004)	L	U	L	H	L	U	L	4	Good
Shadman (2013)	L	U	L	H	L	U	L	4	Good
Aryaeian (2009)	L	L	L	H	L	U	U	4	Good
Eftekhari (2013)	L	L	H	H	L	U	U	3	Fair
Pfeuffer (2011)	L	U	L	H	L	U	L	4	Good
Ebrahimi-Mameghani (2016)	L	L	H	H	L	U	L	4	Good
Matin (2018)	H	U	L	H	L	U	L	3	Fair
Kim (2012)	L	U	L	H	U	U	L	3	Fair
Faramarzi (2017)	L	L	L	H	L	U	L	5	Good
Turpeinen (2008)	L	U	U	H	L	U	L	3	Fair

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

age, CLA dosage, and duration of intervention removed between-study heterogeneity. Significant increases in the 8-iso-PGF2α levels were observed in all subgroups (Table 3).

3.6. Effect of CLA supplementation on concentration of GPx

The effect of CLA supplementation on the GPx level was examined in three clinical trials [26,29,30]. Meta-analysis could not show any beneficial effect of CLA supplementation on GPx levels (Hedges's: 0.30; 95% CI: −0.04 to 0.64, P = 0.08), with no heterogeneity (I^2 = 0.0%, P = 0.90) (Fig. 4). We could not perform subgroup analysis due to a lack of sufficient study.

3.7. Sensitivity analysis

The sensitivity analysis, in which one study at a time was omitted, demonstrated that with the removal of the study by Aryaeian et al. [26] (Hedges's: −0.27; 95% CI: −0.64 to 0.09), Eftekhari et al. [29](Hedges's: −0.36; 95% CI: −0.78 to 0.04), Ebrahimi-Mameghani et al. [28] (Hedges's: −0.36; 95% CI: −0.76 to 0.04), Faramarzi et al. [41](Hedges's: −0.37; 95% CI: −0.76 to 0.02) and Matin et al. [31](Hedges's: −0.23; 95% CI: −0.53 to 0.07), the effect of CLA on MDA became non-significant. The removal of the remaining studies, one by one, did not substantially change the effect of CLA supplementation on 8-iso-PGF2α, and GPx levels.

3.8. Publication bias

No evidence of publication bias was shown for the meta-analysis of the MDA (Begg's test, P = 0.29 and Egger's test, P = 0.18), 8-iso-PGF2α (Begg's test, P = 0.49 and Egger's test, P = 0.48), and GPx (Begg's test, P = 0.60 and Egger's test, P = 0.44), using asymmetry tests.

4. Discussion

According to electronic database search results, our systematic review and meta-analysis is the first one which summarized CLA effect on selected oxidative stress mediators. In the present meta-analysis, we clarified that CLA supplementation

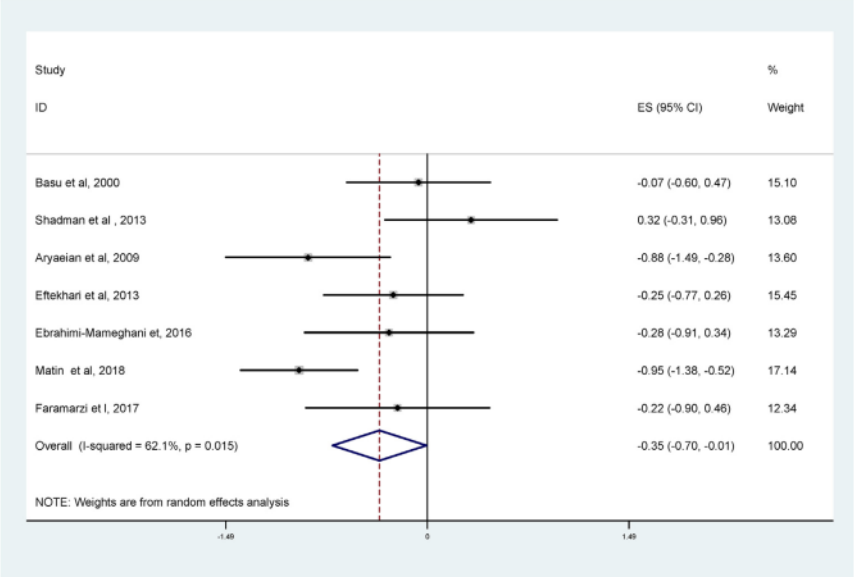

Fig. 2. Forest plot of the effects of conjugated linoleic acid supplementation on malondialdehyde.

significantly improved MDA and 8-iso-PGF2α levels, but did not affect GPx levels in adults. The subgroup analysis shows that the results of the current meta-analysis about the MDA is conclusive. These conflicting results may be due to the small number of studies. In addition, given that the biological activities of CLA probably need a certain serum concentration, it can be inferred that sufficient duration of intervention might be necessary to observe its effects.

Oxidative stress is outlined as an alteration in the pro-oxidant–antioxidant balance in favor of ROS overload that leads to cellular damage. It has been proposed that pro-oxidative status is a critical driver in the pathogenesis and progression of many chronic diseases, including cancer, cardiovascular disease, lung disease, and chronic kidney disease [42–44]. Thus oxidative stress bring major cost to the economy and health care systems, especially in developing countries [45,46]. In recent years dietary supplements have been proposed to manage oxidative stress [47–49]. In this regard, CLA has attracted significant attention, both in the scientific and consumer societies [31,50,51].

Table 3
Subgroup analyses of the effects of conjugated linoleic acid consumption on malondialdehyde, and 8-isoprostanesF2α concentrations.

Sub-grouped by	Number of trials	WMD	95% CI	Heterogeneity (I^2%)	P value[a]
MDA					
Duration of treatment					
≤8 weeks	5	−0.31	−0.75 to 0.13	66.3%	0.16
>8 weeks	2	−0.46	−1.26 to 0.34	74.6%	0.26
Dosage					
≤3 g/day	5	−0.27	−0.64 to 0.10	44.9%	0.15
>3 g/day	2	−0.52	−1.39 to 0.34	84.4%	0.23
Age					
≤45	2	−0.16	−0.56 to 0.25	0.0%	0.07
>45	5	−0.42	−0.89 to 0.04	70.7%	0.44
u-8-iso-$PGF_{2\alpha}$					
Duration of treatment					
≤8 weeks	2	1.75	0.87 to 2.63	59.0%	<0.001
>8 weeks	2	1.20	0.76 to 1.64	0.0%	<0.001
Dosage					
≤3 g/day	2	1.31	0.78 to 1.85	0.0%	<0.001
>3 g/day	2	1.61	0.56 to 2.67	79.9%	<0.001
Age					
≤45	2	1.20	0.76 to 1.64	0.0%	<0.001
>45	2	1.75	0.87 to 2.63	59.0%	<0.001

Abbreviations: MDA, Malondialdehyde; u-8-iso-$PGF_{2\alpha}$, Urinary 8-Iso-Prostaglandin F2α.
[a] P effect size, calculated by Random-effects model.

Precise biological mechanisms for the antioxidant effects of CLA have not yet been established. However, several possible mechanisms have been suggested. Nuclear factor-κb (NFκb) is a transcription factor which is modified by the redox state of the cell and is involved in cellular responses to oxidative stress status and ROS-producing agents such as tumor necrosis factor-α (TNF-α). CLA inhibits TNF-α induced activation of human T cell NF- Kb which explains its potent antioxidant activity. Inhibition of NF- Kb could prevent oxidative modification of LDL, which postpone the progression of atherogenesis. Also, the mechanism of the antioxidative action of CLA might be involved with the regulation of the Nrf 2-ARE pathway and the enhancement of antioxidant enzyme activities. Nrf2 trans-activation promotes the up-regulation of antioxidant genes responsible for the expression of antioxidant enzymes. Therefore, CLA increases the total antioxidant capacity by increasing the intracellular antioxidants such as glutathione, uric acid, and improving the expression of intracellular antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [26,28,29,52].

CLA is likely safe when taken by mouth in amounts found in foods and is possibly safe when taken by mouth in medicinal amounts (larger amounts than those found in food). However, it might cause side effects such as stomach upset, diarrhea, nausea, and fatigue. In addition, The dietary intake of CLA could enhance immune responses, as well as reduce the adverse effects of mediated catabolism [53].

This meta-analysis has some limitations. The number of eligible RCTs included was low, and most of them included a modest number of participants. Various doses of CLA were

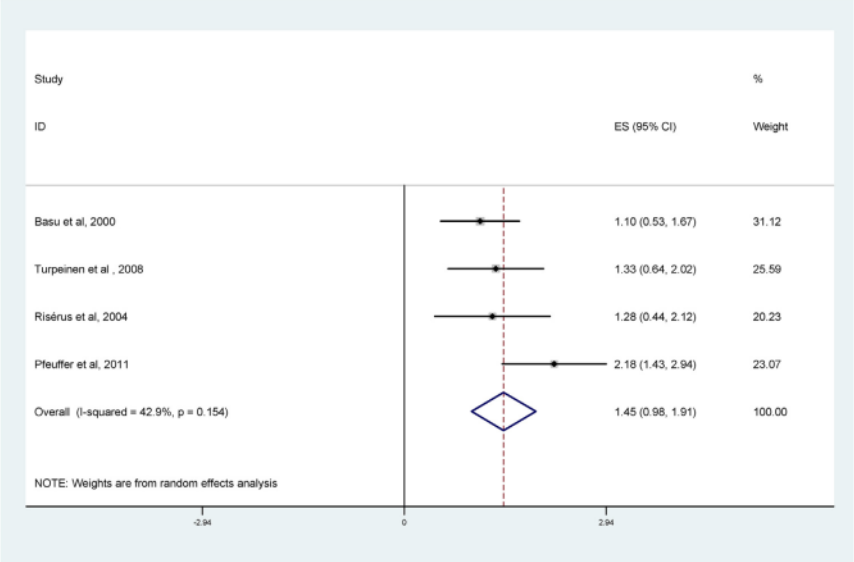

Fig. 3. Forest plot of the effects of conjugated linoleic acid supplementation on 8-isoprostanesF2α.

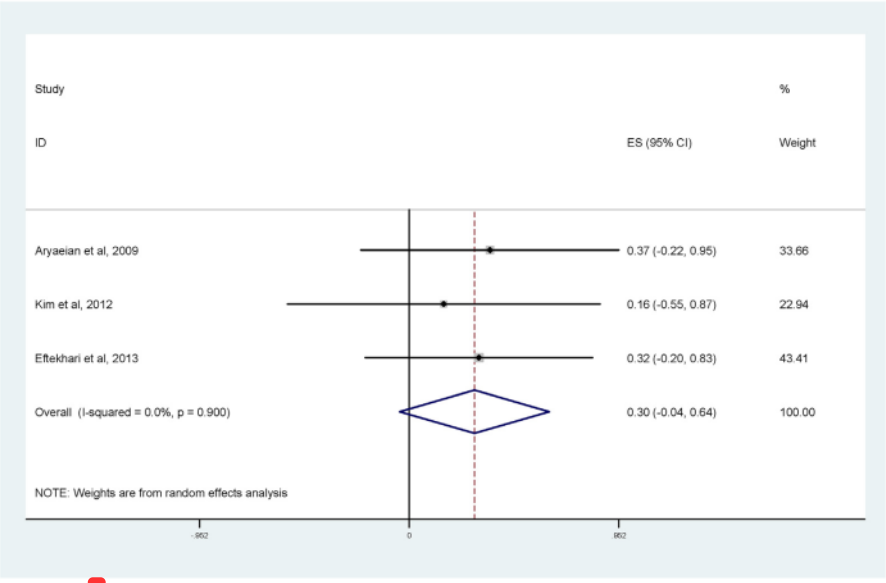

Fig. 4. Forest plot of the effects of conjugated linoleic acid supplementation on glutathione peroxidase.

administered for intervention in the included studies. Various methods were also applied to determine the levels of oxidative stress markers and activity of enzymes, which may affect the results. Finally, confounding factors and their influence were not reported and analyzed in the majority of trials, precluding their analysis in our study. We suggest that future suggest should consider the influence of confounding factors such as physical activity and smoking status.

5. Conclusion

In summary, the current meta-analysis showed a promising action of CLA supplementation for improving MDA and 8-iso-PGF2α levels in adults We Suggest more clinical trials with various durations and dosages in subjects with different health statuses to clarify the efficacy of CLA on markers of oxidative stress and ant oxidative capacity.

Grants and funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

F.I and P.R carried out the concept, design, and drafting of this study. F.I searched databases, screened articles and extracted data. P.R performed the acquisition, analysis, and interpretation of data. F.I., P.R., and W.S critically revised the manuscript. All authors approved the final version of the manuscript. F.I and P.R are the guarantors of this study.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

None.

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