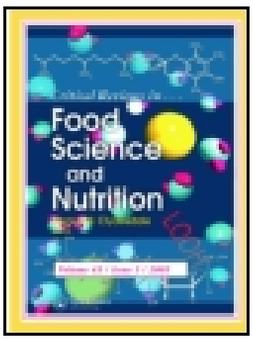

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The effects of supplementation with conjugated linoleic acid on anthropometric indices and body composition in overweight and obese subjects: A systematic review and meta-analysis

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ABSTRACT

Clinical trials have indicated conflicting results on the effects of conjugated linoleic acid (CLA) on obesity. The present study aimed to systematically review controlled clinical trials examining the effects of CLA on anthropometric indices and body composition in overweight and obese subjects. Pubmed, Scopus, Web of science, and Cochrane databases were searched between 2000 and December 2017 with no language restriction. Placebo-controlled clinical trials that reported anthropometric indices and body composition in overweight and obese subjects were included. Random-effect model was used to pool the effect estimates. Of 4032 publications, 13 trials were included for the meta-analysis. Pooled effect sizes indicated that CLA significantly reduced body weight (WMD: -0.52 kg, 95% CI: -0.83, -0.21; I^2: 48.0%, p=0.01), BMI (WMD: -0.23 kg/m^2, 95% CI: -0.39, - 0.06; I^2: 64.7%, p=0.0001), FM (WMD: -0.61 kg, 95% CI: -0.98, -0.24; I^2: 53.8%, p=0.01) and increased LBM (WMD: 0.19 kg, 95% CI: 0.04, 0.34; I^2: 81.4%, p=0.0001) compared to the placebo group. However, the effects of CLA on WC (WMD: 0.05 cm, 95% CI: -0.01, 0.1; I^2: 0%, p=0.93) was not significant. Additionally, its impact on body weight in subjects older than 44 year (WMD: -1.05 kg, 95% CI: -1.75, -0.35; I^2: 57.0%, p=0.01), with longer duration (more than 12 weeks) (WMD: -1.29 kg, 95% CI: -2.29, -0.29; I^2: 70.3%, p=0.003) and dosage more than 3.4 g/day (WMD: -0.77 kg, 95% CI: -1.28, -0.25; I^2: 62.7%, p=0.004) were

greater than comparative groups. Supplementation with CLA can slightly reduce body weight and FM and increase LBM in overweight and obese subjects. However, its efficacy was not clinically relevant. Further studies with high methodological quality are needed to shed light on the effects of CLA on anthropometric indices in overweight and obese subjects.

Keywords: CLA, Obesity, WC, body composition

INTRODUCTION

Obesity is one of main public health problem that is growing dramatically across the world (1). Different weight management strategies including adherence to weight loss diets, increasing physical activity levels, changing in dietary habits and other lifestyle modifications have been introduced (2). However, a demand to identify an anti-obesity agent to reduce dietary restrictions with minimum changes in usual life style has been existed (3). A wide range of supplements and medications are available with the claim of slimming effects; Nevertheless, the efficacy for numbers of them has not been proven yet (4). One of such supplements is conjugated linoleic acid (CLA) (5).

CLA is a group of positional and geometrical isomers of linoleic acid (C18:2, n-6), which are linked by the presence of conjugated dienes (5). Cis-9, trans-11 CLA and trans-10, cis-12 CLA are examples of the main active isomers (6). CLA is produced naturally and is found in fat, milk and meat of ruminant animals (7). Based on prior studies, CLA posses beneficial properties such as anti-carcinogenic effects, improving insulin resistance, glucose levels, lipid profile, blood pressure, body composition and weight (8, 9). However, anti-obesity effects of CLA are controversial.

Several possible mechanisms have been suggested for anti-obesity effects of CLA in animal models (10-15) and human studies (16-20). For instance, it can decrease the size of adipocytes, modify adipocyte differentiation, stimulate apoptotic pathways and regulate lipid metabolism (5). Several narrative reviews and meta-analysis have been published earlier in this regard (5, 21-23). The meta-analysis by Kim et al., revealed that supplementation with CLA could reduce body weight and body mass index (BMI) significantly, whereas its effects were not clinically relevant (5). In the study by Kim et al., the efficacy of CLA on body composition and other anthropometric indices including waist and hip circumferences were not examined. Additionally, they only included studies on metabolic syndrome (MetS) and its efficacy on subjects without chronic diseases remained unclear. Another meta-analysis by Onakpoya et al., evaluated only long-term (more than 6 months) effects of CLA in overweight and obese subjects (24). Although they found a significant reduction in body weight and fat mass (FM), they stated that due to differences in the methodology of the included studies more clinical trials are needed to clarify its effects on obesity. They also did not compare short- and long-term effects of CLA on obesity. Currently, there is no convincing evidence for nutritionists to recommend CLA as a complementary therapy along with a low-calorie diet for overweight and obese individuals. Accordingly, we aimed to summarize the short- and long-term effects of CLA on anthropometric indices and body composition in overweight and obese subjects as a systematic review and meta-analysis.

METHOD

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for the present systematic review and meta-analysis (25).

Literature search and study identification: A systematic search was conducted using PubMed, Scopus, Web of Sciences and Cochrane electronic databases to identify clinical trials that examined the effects of CLA supplement on anthropometric indices and body composition from January 2000 to December 2017 without language restriction. Additionally, hand-searching from reference lists of all relevant papers, previous reviews and meta-analyses was performed to cover all relevant publications. The primary outcome was body weight and other outcomes of interest included BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WtHR), fat mass (FM), and lean body mass (LBM).

To create a strategy search, a combination of the MeSH (Medical Subject Headings) terms from the PubMed database and free text words were used. For each electronic database, search strategy was adopted. For example, the search strategy for the PubMed were as follows: ("conjugated linoleic acid" [tiab] OR "conjugated fatty acid" [tiab] OR "bovic acid" [tiab] OR "rumenic acid" [tiab] OR "CLA" [tiab]) AND ("weight"[tiab] OR "obes*" [tiab] OR "body composition" [tiab] OR "adiposity" [tiab] OR "slim" [tiab] OR "waist" [tiab] OR "abdomen" [tiab] OR "BMI" [tiab] OR "body mass index" [tiab]). PubMed's e-mail alert service was activated to identify any new publication in this regard after the search. Details of the search strategy for other databases are presented in **Appendix 1**.

The protocol of the study was registered in the international prospective register of systematic reviews (PROSPERO) database (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42018085447).

***Inclusion and exclusion criteria*:** To be included in the systematic review and meta-analysis, a publication had to meet the following criteria: (i) placebo-controlled clinical trials (both parallel

and cross-over studies); (ii) CLA as a supplement; (iii) adult subjects (older than 18 years); (iv) reporting at least body weight before and after the study; (v) providing sufficient information on anthropometric indices (body weight, BMI, WC) and body composition (FM, FFM) with standard deviations (SDs), standard errors of the means (SEMs), or 95% confidence intervals (CIs) at baseline and at the end of intervention in the intervention and placebo group.

We did not include (i) before-after studies or any other human models except clinical trial; (ii) animal or *in vitro* studies; (iii) CLA-enriched food; (4) CLA in combination with other ingredients; (iv) subjects with any disease and (v) children. Grey literature including conference abstract, thesis, and reports due to problems in access and insufficient data were excluded as well. PICOS criteria are presented in **Table 1**.

Two independent reviewers (N.N, L.A) searched the databases and screened the publications to reach possible relevant papers. Any disagreement was solved by discussion.

Data extraction: The following data based on a pre-designed form were extracted from each paper by two reviewers (N.N, P.I) independently: name of first author, publication year, country, individual's characteristics including mean age, sex, randomization, blinding (open label, single or double blind), sample size (enrollment, completion), dosage, duration of intervention, other intervention, and outcome values at the beginning and at the end of study. When more than one paper from the same study individuals was published, data from the publications with the largest and the longest duration of the intervention were extracted. If there were more than two study groups, only the data for CLA group (s) and placebo were extracted. Studies in which the interest outcomes were reported in more than two intervals, only data at baseline and at the end of the intervention were extracted. Some studies examined different dosages of CLA; in such studies

each dosage considered as an independent study by dividing sample size into numbers of assessed dosages to avoid multiple counting. As in most studies, FM and LBM were reported in gram, this type of reporting data were included in the meta-analysis. When our necessary data were not reported in the papers, we contacted the authors by emails for three times in reasonable intervals. When we did not receive any answer, we excluded the whole of the paper or variable with insufficient information.

Risk of bias assessment: Two reviewers (N.N, P.I) independently examined the risk of bias for the included studies using the Cochrane quality assessment tool for RCTs (26). This checklist has 7 criteria for quality assessment including: (i) random sequence generation, (ii) allocation sequence concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data, (vi) selective outcome reporting, and (vii) other potential sources of bias. Low risk of bias, high risk of bias, or being unclear for each aforesaid item was determined. Any disagreement in the all aforementioned processes which were not resolved through consultation was referred to the principal reviewer (L.A) in order to reach a consensus.

Quantitative data synthesis and statistical analysis: Effect sizes for all interest outcomes were expressed as weighted mean differences (WMDs) and 95% CI. The effect sizes were pooled using a random effects model with DerSimonian and Laird method (27). Wherever within-group changes did not report, mean value at the end of the study was subtracted from the mean at the baseline in each group. To calculate the SD, the following formula was used: SD= square root [(SD pre-treatment) ^{2} + (SD post-treatment) ^{2} – (2R × SD pre-treatment × SD post-treatment)]. In this formula, R=0.5 was assumed as a correlation coefficient which ranges between 0 and 1 (28). When an SEM was reported instead of SD, based on the following formula, SD was calculated:

SD= SEM× square root (n), that 'n' was sample size in each group. If the outcome values were reported in medians and ranges or 95% CIs, means and SD values were estimated using the method by Hozo et al., (29). Plot digitizer software was used to obtain the data when the outcome was presented only in the graphic form.

Heterogeneity was assessed by the I^2 index; I^2 greater than 50% was considered as the existence of substantial heterogeneity among the studies (30). To identify factors for high heterogeneity, whenever possible (at least two studies in each subgroup), subgroup analysis was performed.

A pre-defined subgroup analysis was based on the following parameters: mean age, sex, dosage, duration of supplementation, and quality assessment. Less or more than median was considered as cut off values for each aforementioned quantitative parameter for subgroup analysis.

The sensitivity analysis was performed using the leave-one-out method (removing a single clinical trial in each time and repeating the analysis) to examine the impact of each trial on the pooled effect size. Any potential publication bias was identified using the funnel plot, either Egger's regression test (number of studies less than 10) or Begg's rank correlation (number of studies more than 10). When a publication bias was existed, "trim and fill" method was used to correct the overall effect size. All statistical analyses were carried out using STATA version 11.0 (Stata Corp, College Station, TX). P values that were less than 0.05 were considered statistically signifcant.

Results

Selection and characteristics of the included studies: As presented in **Figure 1**, a total of 4032 publication (including 1855 duplications) were initially identified after searching Pubmed, Scopus, Web of science, and Cochrane electronic databases. Of 2177 publications, 2130 were excluded after screening based on title and abstract. They were irrelevant to the current meta-

analysis according to our criteria. In the next step, 47 possible relevant papers were selected for the evaluation of full-texts. After detailed examination, 31 papers were excluded due to the following reasons: Irrelevant (n=3), unhealthy patients (n=8), children (n=1), did not report body weight or other necessary data (n=2), repeated data (n=3), studies on athletes (n=2), not supplement (n= 6), do not have placebo (n= 4), in combination with other components (n=2).

In the last procedure, a total of 16 eligible RCTs were included. As the authors of three studies did not provide us necessary data (not answered our emails (n=2), not access of authors to data (n=1)), they were excluded. Finally, 13 clinical trials were included for the meta-analysis.

Characteristics of the included studies: Characteristics of the 13 randomized clinical trials (6, 16-20, 31-37) are reported in **Table 2**. The sample size in the included trials ranged from 18 (16) to 394 (19). The included studies were published between 2000 and 2016 and were conducted in the USA (n=3) (6, 17, 18), Europe (n= 8) (16, 19, 20, 31-33, 35, 37), and Asia (n=2) (34, 36). The mean age of the participants ranged from 23 (20) to 58 (19) years. Trials included men (n=2) (35, 36), women (n=3) (20, 34, 37) and both genders (n=9) (6, 16-19, 31-33).

In four studies (16, 20, 32, 36), either a special diet or physical activity program were recommended along with CLA supplementation. The dosage of CLA was between 1.5 (35) and 6.8 g/day (16) and it was consumed from 8 (20, 36) to 52 (32) weeks. In the all included studies (6, 16-20, 31-37), a mixture of CLA isomers (particularly cis 9, trans 11 isomer in combination with trans 10, cis 12) was recommended.

Most studies (n=7) (16, 17, 20, 31-33, 35) used olive oil as a placebo. The remaining papers used safflower oil (n=3) (6, 18, 19), sunflower (n=2) (34, 37), soybean (n=1) (36). All studies except two (used body impedance analyzer), used dual-energy X-ray absorptiometry (DEXA) for measurement of body compositions.

Gastrointestinal problems including nausea, stomachache, burning and frequent bowel movement, bloating, soft stool, constipation and other side effects such as headache, eczema and backache were also reported. They were mild to moderate. However, in 5 studies drop out was reported due to the side effects following CLA supplementation (16, 17, 20, 31, 34). In the all mentioned studies except one (34), the drop out was 1 due to adverse effects. However, Darestani et al., reported 4 drop outs following taking CLA with dosage of 3.2 g/day. All studies except one (37) had high risk of bias based on the Cochrane criteria. Therefore, all findings should be declared with more caution.

Systematic review: Limited studies reported the effects of CLA on hip circumference (HC) (n=3) (17, 32, 37) and WtHR (n=2) (17, 19). Madry et al indicated that daily 3gr CLA reduced HC significantly (-2cm) after 12 weeks of supplementation (37). However, based on Larsen et al., 3.4 g/day CLA did not change HC after 8 weeks (32). In the study by Gaullier et al., although a reduction in HC and WtHR was observed in the intervention group, the changes were not significant between two groups (38). Besides, Slujis et al found that CLA did not have positive effect on reduction in WtHR in overweight and obese subjects (19). Due to limited studies on HC and WtHR, meta-analysis was not performed on this regard.

Meta-analysis for the effects of supplementation with CLA on anthropometric indices: Forest plots for the effects of CLA on anthropometric indices (body weight, BMI and WC) are presented in **Figures 2-4**.

Body weight: As our primary outcome was body weight, all the 13 included studies (6, 16-20, 31-37) reported weight changes following the CLA supplementation. Pooled effect sizes indicated that CLA significantly reduced body weight (WMD: -0.52 kg, 95% CI: -0.83, -0.21; I^2: 48.0%, p=0.01) compared to placebo **(Figure 2)**. Subgroup analysis indicated that reduction in

body weight in older individuals (more than 44 year old) (WMD: -1.05 kg, 95% CI: -1.75, -0.35; I^2: 57.0%, p=0.01) was significantly greater that the younger one (less than 44 years old) (WMD: -0.07 kg, 95% CI: -0.29, 0.15; I^2: 0%, p=0.84). Dosage more than 3.4 g/day WMD: -0.77 kg, 95% CI: -1.28, -0.25; I^2: 62.7%, p=0.004) reduced body weight significantly more than the lower one (WMD: -0.16 kg, 95% CI: -0.43, 0.12; I^2: 0%, p=0.59). However, it also did not attenuate the heterogeneity. Reduction in body weight after longer duration (more than 12 weeks) (WMD: -1.29 kg, 95% CI: -2.29, -0.29; I^2: 70.3%, p=0.003) of the intervention was significantly greater than the shorter duration (less than 12 weeks) (WMD: -0.09 kg, 95% CI: -0.30, 0.12 I^2: 0%, p=0.96) of the supplementation. Stratification by risk of bias, life style interventions, and sex did not reduce the between-study heterogeneity. However, subgroup analysis based on control group (olive oil, sunflower oil) considerably removed the heterogeneity (I^2:0%) (**Table 3**). Among the included studies, only one recommended a low-calorie diet along with CLA, after removing this study, no considerable changes were observed in body weight (WMD: -0.53 kg, 95% CI: -0.85, -0.22, I^2: 50.8%, p=0.007).

BMI: Twelve trials (6, 16. 17, 19, 20, 31, 33-37) provided data on the effects of CLA on BMI **(Figure 3)**. The pooled estimates demonstrates that supplementation with CLA significantly reduced BMI in healthy subjects (WMD: -0.23 kg/m^2, 95% CI: -0.39, - 0.06), while the heterogeneity was high (I^2: 64.7%, p=0.0001). Stratification by duration showed a greater reduction in BMI following longer duration (WMD: -0.51 kg/m2, 95% CI: -0.92, -0.09; I^2: 80.5%, p=0.0001), while it was not significant after the shorter one (WMD: 0.05 kg, 95% CI: -0.05, 0.15; I^2: 0%, p=0.73). After excluding one study with high risk of bias no considerable changes in the pooled estimate was observed (WMD: -0.29 kg, 95% CI: -0.45, -0.12; I^2: 70.1%, p=0.0001). After removing one study (37) with high risk of bias, the pooled estimates did not

change notably (WSD: -0.23 kg/m2, 95% CI: -0.39, -0.06; I2:64.7%, p=0.0001). The results of other stratifications by sex, placebo type and dosage were presented in **Table 3**.

Waist circumference: The results for WC were shown in 7 RCTs (19, 20, 32, 34-37) including 8 effect sizes. Overall, supplementation with CLA did not significantly change WC compared to placebo group (WMD: -0.05 kg, 95% CI: -0.01, 0.1; I^2: 0%, p=0.93) **(Figure 4).** As no heterogeneity was existed, we did not perform subgroup analysis for WC.

Meta-analysis for the effects of supplementation with CLA on body composition

Fat mass: The pooled estimates of FM (7 studies, 12 effect sizes) (6, 16-18, 31, 32, 34) showed that in subjects who consumed CLA, FM decreased significantly compared to those in placebo group (WMD: -0.61 kg, 95% CI: -0.98, -0.24; I^2: 53.8%, p=0.01) **(Figure 5)**. Longer intervention by CLA resulted in greater reduction in FM (WMD: -1.94 kg, 95% CI: -2.74, -1.15; I^2: 0%, p=0.58), while FM changes was -0.23 kg (95% CI: -0.25, -0.21; I^2: 0%, p=0.77) after shorter supplementation. Stratification by duration removed the heterogeneity considerably compared to other parameters. Additionally, CLA reduced FM in older subjects (WMD: -1.79 kg, 95% CI: -2.72, -0.86; I^2: 0%, p=0.49) significantly more than younger ones (WMD: -0.32 kg, 95% CI: -0.56, -0.08; I^2: 46.9 %, p=0.11) **(Table 3).** After removing one study (32) that recommended CLA along with diet, the reduction in FM remained significant (WMD: -0.62 kg, 95% CI: -1.01, -0.24; I^2: 57.9 %, p=0.008).

Lean body mass: The pooled estimate (containing 9 effect sizes extracted from 5 RCTs) (6, 16, 17, 31, 34) for LBM is presented in **Figure 6.** Based on findings, significant changes were observed in LBM following the CLA supplementation (WMD: 0.19 kg, 95% CI: 0.04, 0.34; I^2: 81.4%, p=0.0001). After removing one study (17) which examined long-term effects of CLA, the heterogeneity was reduced considerably (WMD: 0.32 kg, 95% CI: 0.16, 0.48; I^2: 0%, p=0.99).

Stratification by mean age revealed that LBM in younger can significantly enhance LBM (WMD: 0.31 kg, 95% CI: 0.16, 0.47; I^2: 0%, p=0.97), while the changes were not significant in older one (WMD: -0.28 kg, 95% CI: -2.20, 1.64; I^2: 46.8%, p=0.09) **(Table 3).**

In three trials (6, 16, 35) more than one dosage of CLA was examined. After considering only the highest dosage of each study in the meta-analysis, we found that CLA reduced body weight (WMD: -0.72 kg, 95% CI: -1.13, -0.31; I^2: 52.4%, p=0.01), BMI (WMD: -0.30 kg, 95% CI: -0.49, -0.11; I^2: 64.5%, p=0.01), FM (WMD: -0.36 kg, 95% CI: -0.67, -0.05; I^2: 0%, p=0.49) with no changes in LBM (WMD: -0.15 kg, 95% CI: -1.17, 1.44; I^2: 90.3%, p=0.0001) and WC (WMD: 0.05 kg, 95% CI: -0.01, 0.10; I^2: 0%, p=0.87) in overweight and obese subjects.

Publication bias

Based on visual inspection of funnel plots, there was no publication bias in the effects of CLA on anthropometric indices and body composition that were confirmed by complementary analyses. Begg's test indicated no publication bias for body weight (p=0.75), BMI (p=0.99), FM (p=0.10), and LBM (p=0.11). Egger test also confirmed no publication bias for WC (p=0.17).

Sensitivity analysis: According to sensitivity analysis, excluding none of the trials had a considerable change on body weight (range= -0.23 to -0.36), BMI (range= -0.21, -0.33), WC (-0.05, 0.09), and FM (range= -0.21, -0.25). However, leave-one-out method did not show the robustness in findings of LBM (range= -1.16, 0.09)".

Discussion

Based on the current systematic review and meta-analysis, supplementation with CLA can significantly but slightly reduce body weight, BMI and FM and increase LBM in overweight and obese subjects. However, its effects on WC were not statistically significant.

Our findings were in line with earlier meta-analysis (24) which examined the long-term (more than 6 months) effects of CLA in overweight and obese subjects. Based on pooling effect estimates of 6 RCTs, they found that CLA can reduce body weight (-0.7 kg) and FM (-1.3 kg) without changes in WC (-0.12 cm). In our study, we included all available studies (n=13) in this regard without any limitation in the duration of intervention. In our meta-analysis, the mean period of supplementation was 3 months. Observing similar findings with Onakpoya et al., study (24) can show no considerable differences in the efficacy of CLA in different duration of supplementation. Hence, limited studies (n=7) were included in the meta-analysis by Onakpoya et al, subgroup analysis based on study and participants' characteristic were not possible.

Another meta-analysis is the study by Kim et al (5). Our findings were in parallel with Kim et al., study. They reported that CLA reduced body weight (-0.5 kg) and BMI (-0.18 kg/m2) (5). However, they did not examine either WC or body composition. In contrary to our study that only healthy subjects (without any disease except obesity) were included, they examined subjects with MetS. Similar results can show that the efficacy of CLA is not affected by metabolic status and disease background. Due to limited studies in Kim et al.'s meta-analysis (5), subgroup analysis were not performed. Our findings were also similar to Rahbar et al.'s study. They indicated that neither CLA supplement nor foods enriched with CLA changed WC in healthy adults (39).

Our findings revealed that CLA with 3.4 g/day or greater, in subjects older than 44 years for minimum 12 weeks had the highest effect on body weight. However, supplementation for the mean duration of 12 weeks resulted in only 1.3 kg reduction in body weight that it was too slight from clinical point of view. Although BMI reduction following receiving CLA was statistically significant, it was not clinically relevant. Based on our findings, short-term supplementation did

not lower BMI value. Most included studies did not recommend subjects to increase their physical activity or reduce their energy intake. However, findings indicated no significant differences between studies with and without other weight management strategies.

We found that CLA is not considerably helpful for improving body size and body composition. Although more than 12- week supplementation reduced FM by 2 kg, it is moderate from clinical point. Besides, CLA is not much effective in increasing LBM and only in younger subjects a slight increase was observed. In the present study, we did not include RCTs on athletes due to their different physiological and metabolic characteristics. Therefore, the efficacy of CLA on body composition of this group remained unclear. Hence, reduction in LBM may result in a reduction in basal metabolic rate; LBM maintenance can be helpful for preventing weight regain (40). However, in the present meta-analysis, weight reduction following CLA was small and observing no changes in LBM might be due to this issue. Overall, due to limited studies on WC, FM, LBM, findings of the aforesaid variables and their stratifications by parameters that may affect the results should be declared with caution.

Based on prior clinical trials on weight management (41-43), weight-loss diet with even a moderate physical activity is more effective than CLA supplementation. Based on findings, CLA did not reduce at least 5% of body weight at the end of the trial compared to the baseline. In our meta-analysis, most included studies recommended CLA alone not with low-calorie diets or exercise; Therefore, CLA concurrent with other common weight-loss treatment can be more helpful. However, more evidence is needed to confirm this hypothesis.

Several possible mechanisms are suggested for CLA on anthropometric indices and body composition. CLA can impact upon lipoprotein lipase, stearoyl coenzyme A desaturase, activate Peroxisome proliferator-activated receptor gamma (PPAR-γ) receptors and pro-inflammatory

cytokines (6, 44). Accordingly, it can reduce fat accumulation (24). In addition, animal studies showed that CLA particularly trans-10, cis-12 isomer can reduce energy intake, inhibit lipogenesis, and increase fat oxidation (44). Some studies demonstrated that CLA can cause insulin resistance (45, 46) and this adverse effect is more probable in older obese individuals (47); however, this issue is conflicting. Different isomers of CLA had different effects. Therefore, observing different findings on the effects of CLA can be partially interpreted by this matter. For instance, trans-10, cis-12 showed catabolic effects, increase in lipolysis and fat oxidation, while cis-9, trans-11 plays an anabolic role (33).

Another plausible mechanism of CLA on obesity is related to its impacts on hormones. Based on evidence, CLA can decrease leptin hormone following a reduction in FM (17). It also can increase serum levels of adiponectin, a hormone with anti-inflammatory properties (46, 48). In the present meta-analysis, limited studies examined the effects of CLA on serum levels of leptin (17, 18, 33). Serum levels of leptin in Macredmond et al., decreased with no considerable changes in adiponectin levels (33). However, Gauiller et al., found no changes in leptin and adiponectin concentrations following the CLA intervention (38). Additionally, based on Watras et al., changes in leptin levels were not significant after 6 months of the intervention (18). Increasing energy expenditure through changes in gene expression (ex. encoding uncoupling proteins), reduction in adipocyte size, inhibiting pre-adipocyte differentiation and increasing adipocyte apoptosis are reported for CLA (6).

It is notable that the type of placebo is the main parameter in RCTs. Apart from its appearance (color, size) that is recommended to be similar to the intervention; it should have minimum effect on interest outcomes. In our meta-analysis, the included studies reported different materials as a placebo including olive, sunflower, soybean, palm oil, oleic acid and safflower oil. Stratification

by the type of placebo revealed different findings. For instance, reduction in body weight following CLA compare to olive oil showed the greatest value compare to other placebo groups.

Another important point in RCTs is related to the side effects of the intervention. In our meta-analysis, a few studies reported drop out due to severe gastrointestinal disorders or other complications following CLA supplementations (16, 17, 20, 31, 34). Although CLA is not an effective anti-obesity supplement, no serious side effects at least in the reported ranges of dosage were observed. However, gastrointestinal disorders were reported in most studies in a few participants.

The findings of the present meta-analysis can be helpful for nutritionists and researchers. However, it had some limitations. First, we could not compare the pure effects of CLA verses its concurrent use with a low-calorie diet due to limited studies. Second, as most studies recommended a mixture of CLA isomers, the most effective one or a suitable isomer combination remained unclear. The strength of the current meta-analysis was as follows: (i) examining CLA on overweight and obese subjects without any disease background that might affect the results, (ii) pooling suitable numbers of RCTs made it possible to do subgroup analysis, and (iii) examining the risk of bias that can affect the effect estimates. However, as most studies had a high risk of bias, making decision on the efficacy of CLA on obesity should be declared with caution.

In conclusion, supplementation with CLA can slightly reduce body weight, BMI and FM and increase LBM in overweight and obese subjects. However, its efficacy was not clinically relevant. More studies with high methodological quality are required to clarify the efficacy of CLA on obesity management. Due to the lack of robustness in the effects of CLA on LBM, drawing a decisive conclusion needs further investigations in this regard. For future studies,

examining the efficacy of CLA on body composition in athletes and weight maintenance is suggested.

Author Contribution statement: The authors' responsibilities were as follows: B.L, L.A designed the research; N.N and P.I: conducted systematic research; P.I, N.N: extracted data; N.N, L.A, B.L: analyzed data; N.N, B.L and L.A: wrote manuscript; N.N, L.A: had primary responsibility for the final content of the manuscript; and all authors read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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Legends to figures:

Figure 1- Flowchart for study identification and selection

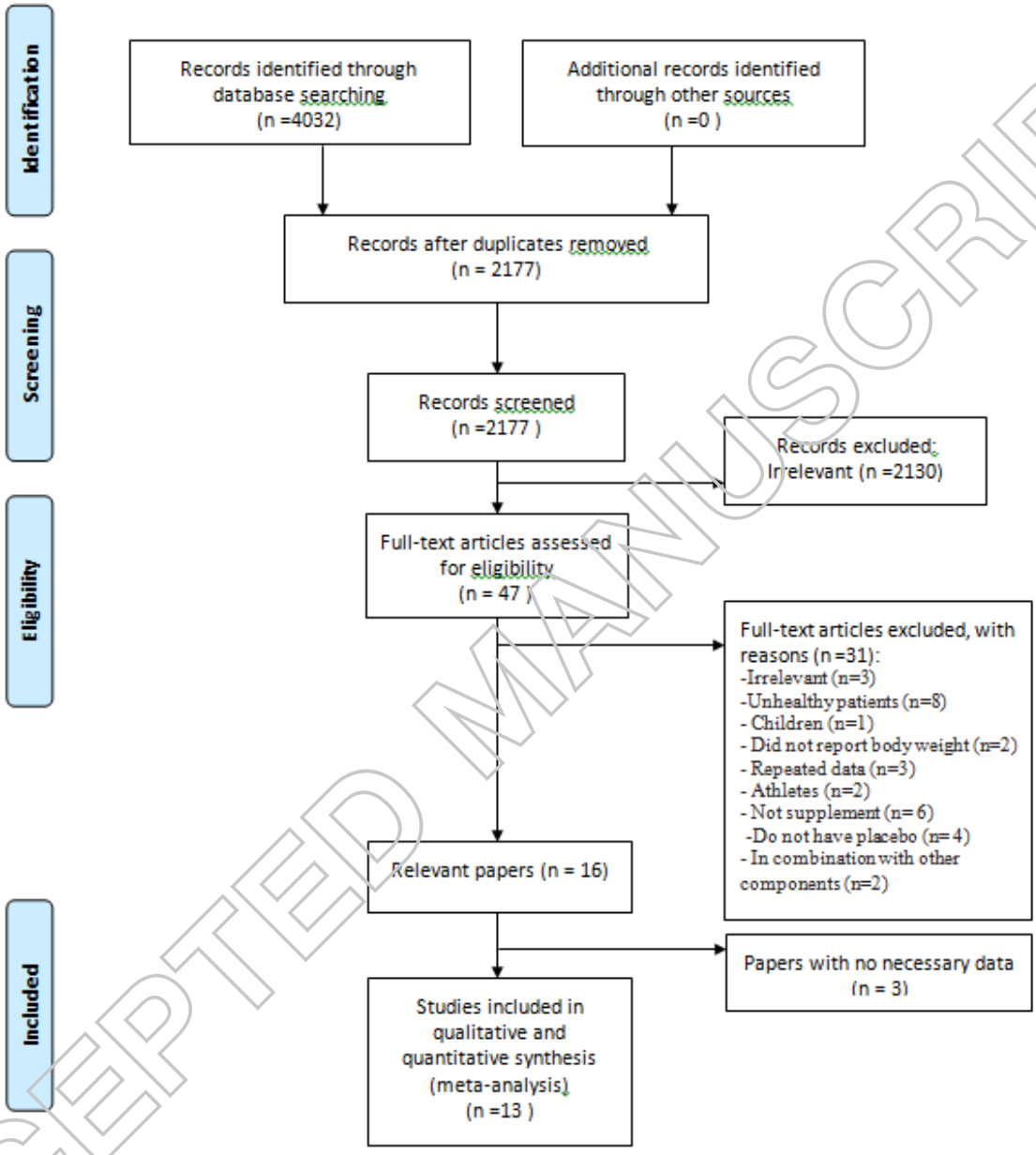

Figure 2- Forest plot of weighted mean difference (WMD) in body weight between supplementation with CLA and placebo group

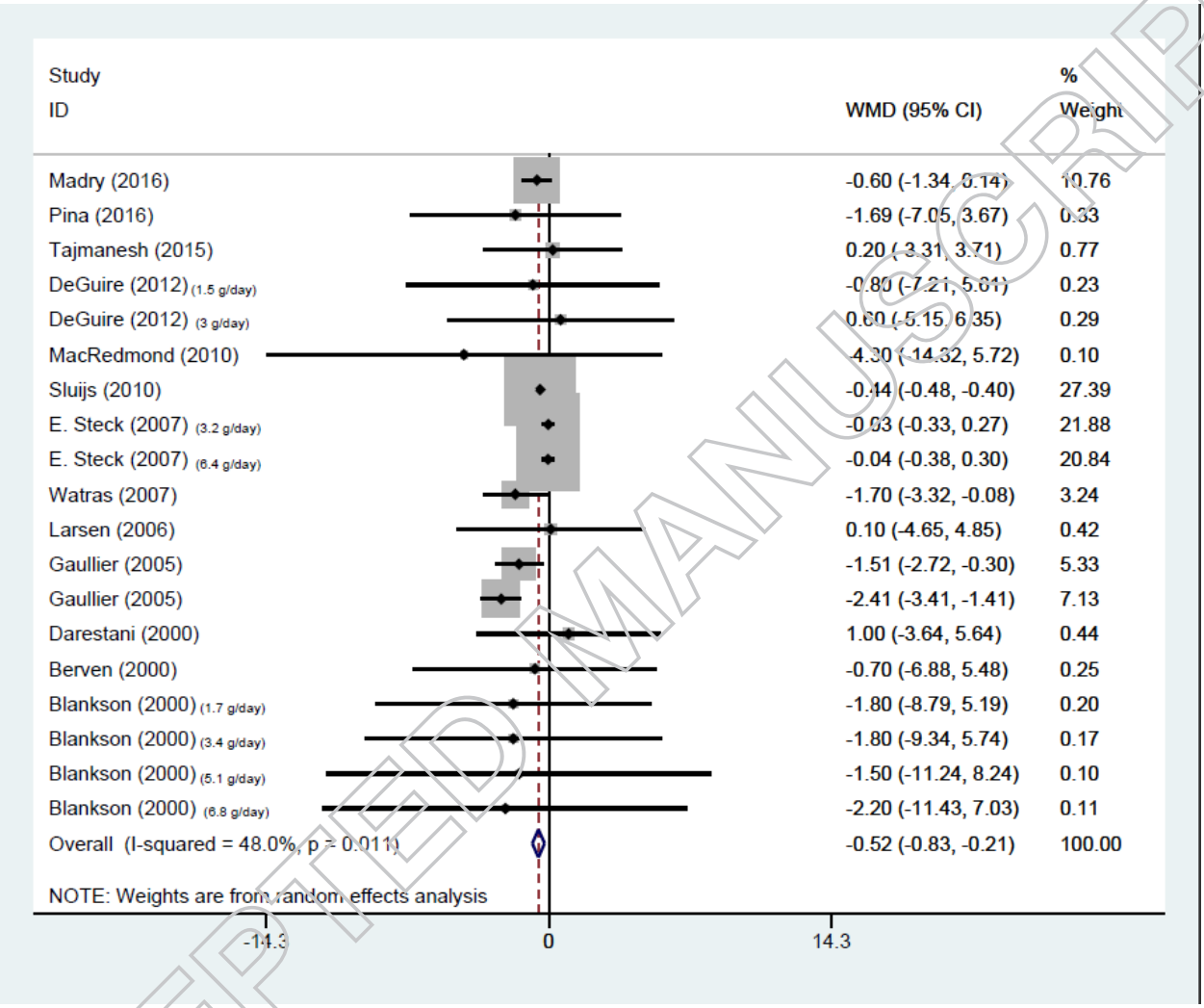

Figure 3- Forest plot of weighted mean difference (WMD) in body mass index between supplementation with CLA and placebo group

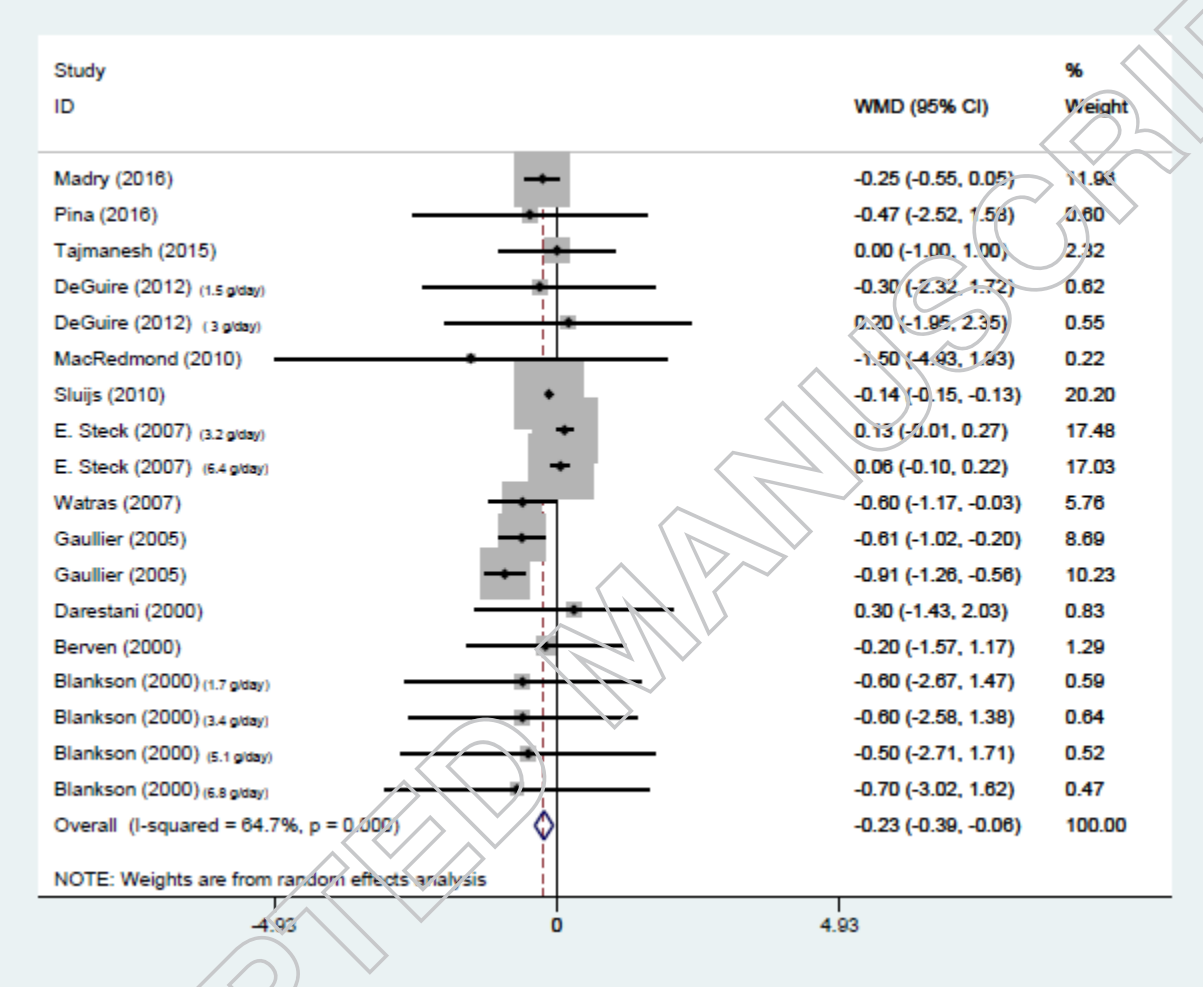

Figure 4- Forest plot of weighted mean difference (WMD) in waist circumference between supplementation with CLA and placebo group

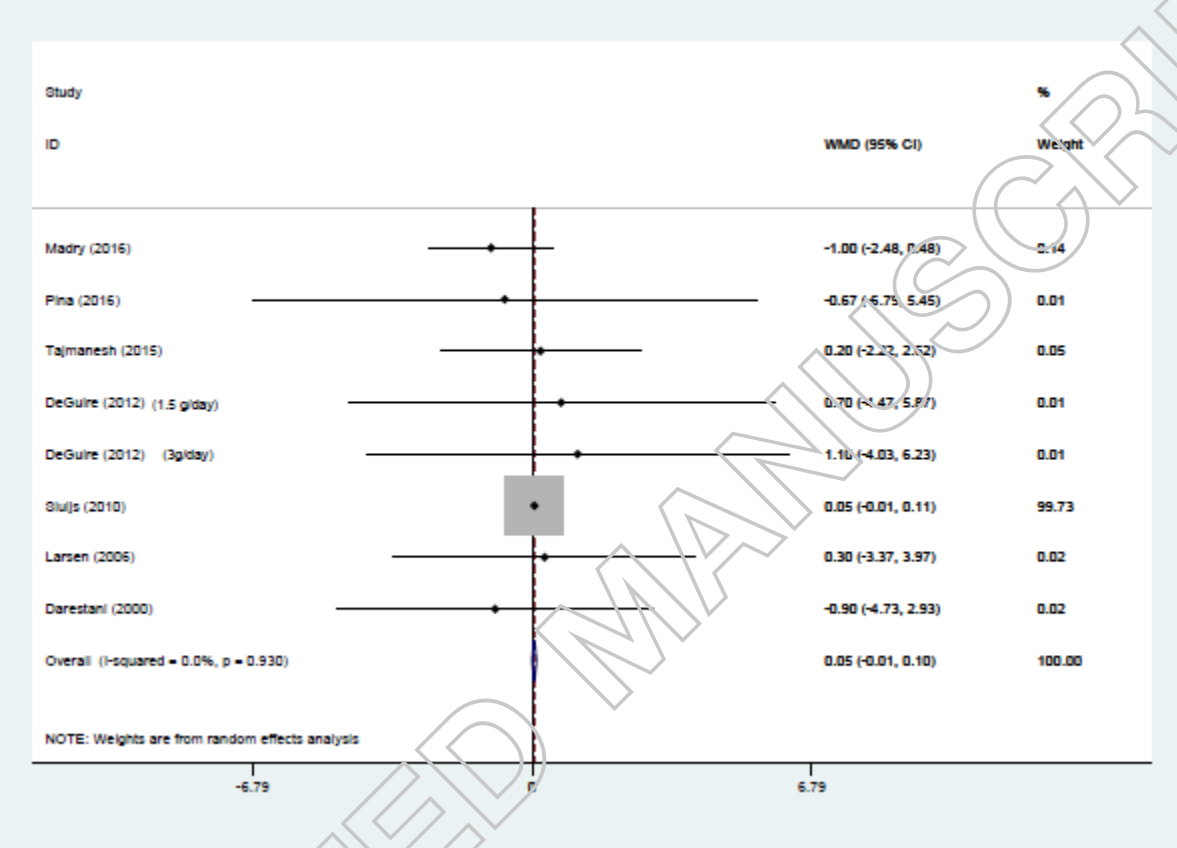

Figure 5- Forest plot of weighted mean difference (WMD) in fat mass between supplementation with CLA and placebo group

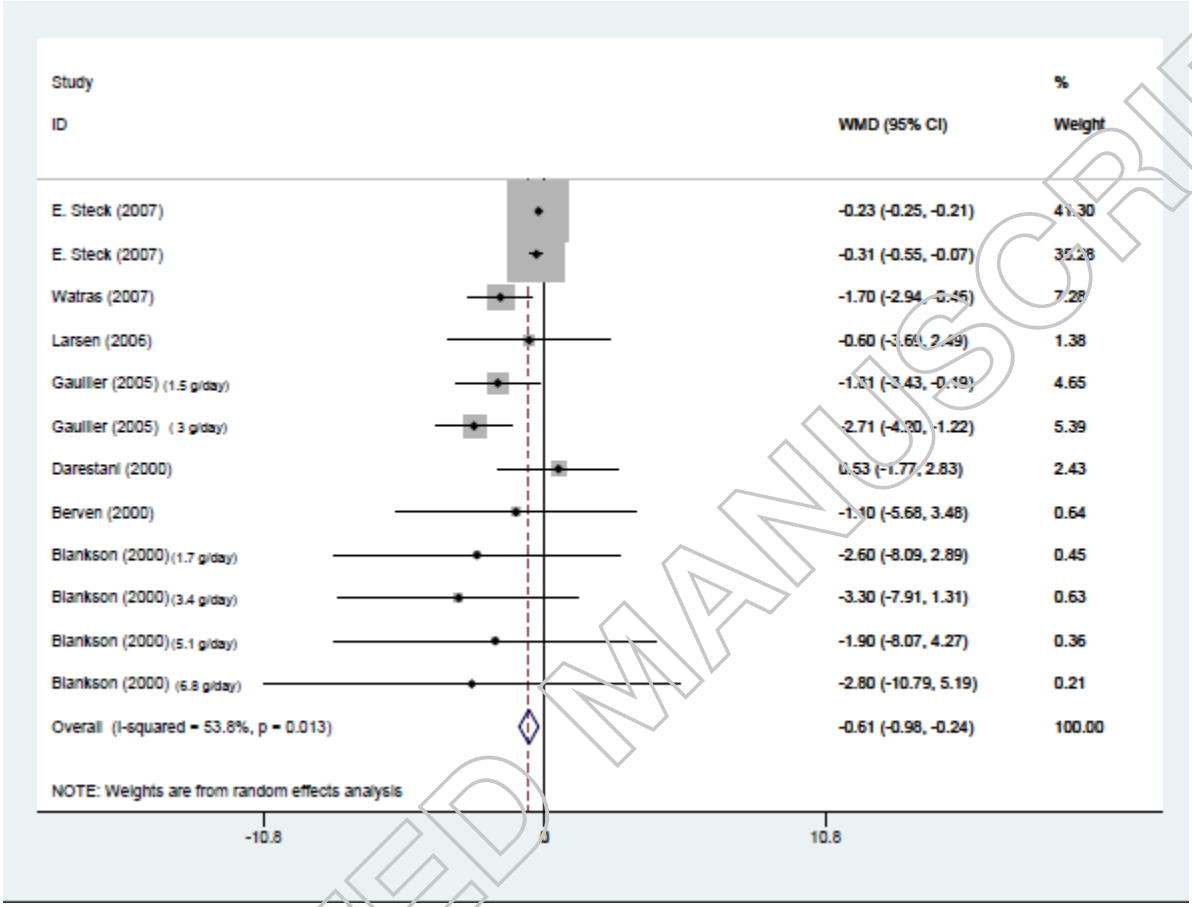

Figure 6- Forest plot of weighted mean difference (WMD) in lean body mass between supplementation with CLA and placebo group

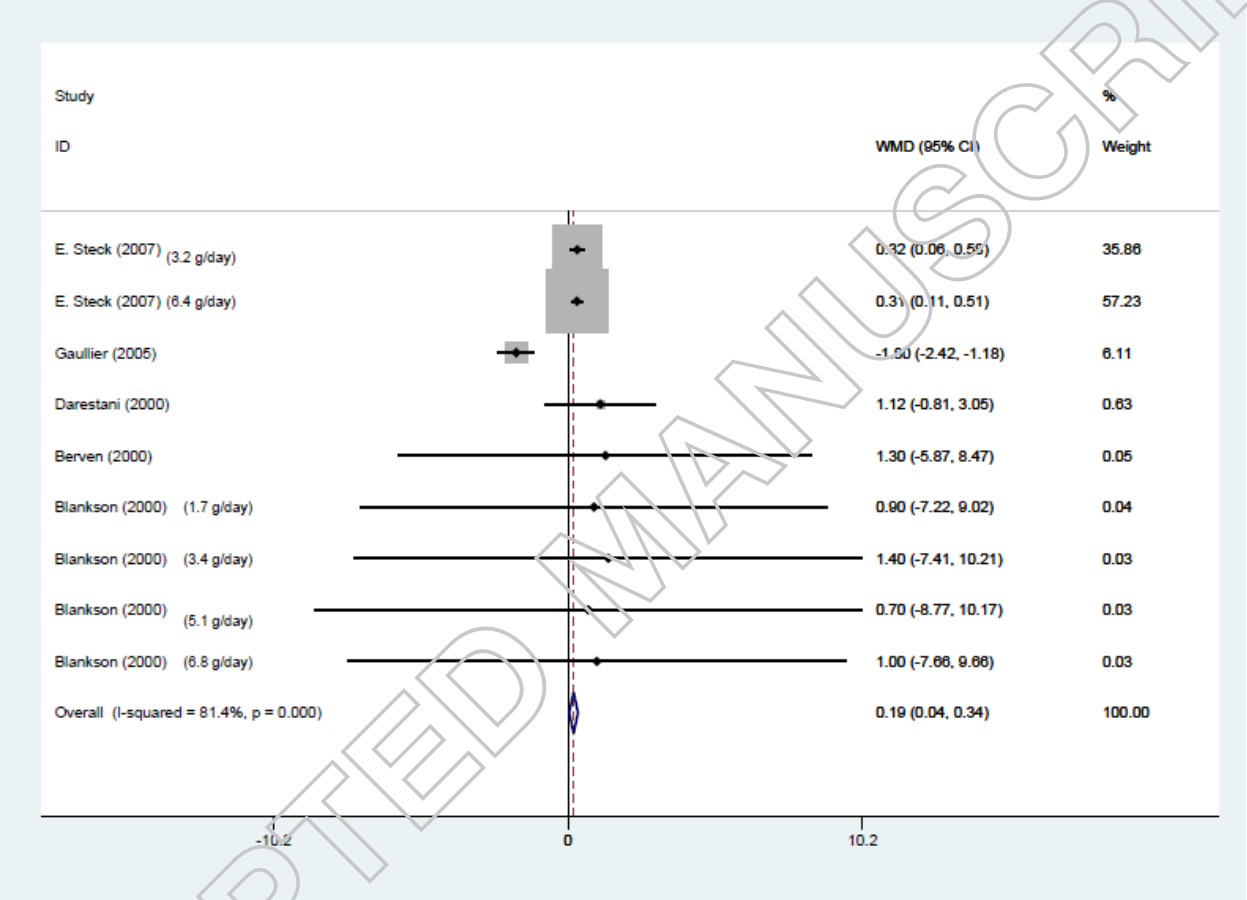

Table 1- The PICO criteria used for the present systematic review

PICO criteria	Description
Patients	Overweight OR obese subjects
Exposure	"conjugated linoleic acid" OR "conjugated fatty acid" OR "bovic acid" OR "rumenic acid" OR "CLA"
Comparison	Placebo
Outcome	"Weight" OR "BMI" OR "body mass index" OR "waist circumference" OR "fat mass" OR "FM" OR "lean body mass" OR "LBM"

Table 2- Characteristics of the included studies in the meta-analysis

Author/ Year	Country	Subject (gender)	Mean age (year)	Sample size	Study design (Blinding)	Other intervention	Dosage (g/day)	Duration (wk)	Side effects (withdrawal due to side effects)	Quality
Madry et al, 2016 (37)	Poland	Female	54	62	R/P Double	No	3	12	Nausea (n=0)	High
Pina et al, 2016 (20)	Brazil	Female	23	28	R/P Double	Aerobic training program	3.2	8	Gastrointestinal discomfort, stomach ache, burning and more frequent bowel movements (n=1)	Low
Tajmanesh et al, 2015 (36)	Iran	Male	24.8	66	R/P Double	Physical activity program	3.2	8	Not reported (n=0)	Low
DeGuire et al, 2012 (35)	Canada	Male	37.5	21	R/P Double	No	Two different dosages: 1.5 3	16	Gastrointestinal discomfort (n=0)	Low
MacRedmond et al, 2010	Canada	Male & Female	31	26	R/P Double	No	4.5	12	Headache, Backache Gastrointe	Low

(33)									stinal upset (n=0)	
Sluijs et al, 2010 (19)	Netherlands	Male & Female	58.4	346	R/P Double	No	4	24	Gastrointestinal discomfort, Eczema, Transpiration, Heart complaints (n=0)	Low
Darestani et al, 2010 (34)	Iran	Menopause female	55.1	67	R/P Double	No	3.2	12	Gastrointestinal discomfort (n=4)	Low
E. Steck et al, 2007 (6)	U.S	Male & Female	35.1	48	R/P Double	No	Two different dosages: 3.2 6.4	12	Mild gastrointestinal adverse events Gas, Bloating, Indigestion, Diarrhea, or Heartburn (increase in higher dose) (n=0)	Low
Watras et al, 2007 (18)	U.S	Male & Female	33.1	40	R/P Double	No	3.2	24	Not reported	Low
Gaullier et al,	Norway	Male &	47.1	105	R/P		3.4	24	Constipation	Low

2007 (38)		Female	8		Double	No			(n=0)	
Larsen et al, 2006 (32)	Norway	Male & Female	42.51	77	R/P Double	Modest hypocaloric diet	3.4	52	Soft stools, Depression, Air in the stomach, or Stomach pain (n=0)	Low
Berven et al, 2000 (31)	Norway	Male & Female	47.08	47	R/P Double	No	3.4	12	Diarrhea, Bad oral smell, Bad smell of perspiration (n=1)	Low
Blankson et al, 2000 (16)	Norway	Male & Female	45.47	47	R/P Double	Standard training program	<u>Four different dosages:</u> 1.7 3.4 5.1 6.8	12	Gastrointestinal discomfort (n=1):dose 6.8g/day	Low
						Replace their habitual lunch by one meal of a protein-				

						rich, low-energy supplement				

*Randomized placebo

Table 3- Subgroup analysis for the effects of CLA on anthropometric indices and body composition

Outcome	No.study	Pooled effect size (95% CI)	I^2 (%)	$P_{heterogeneity}$	$P_{between}$
Body weight					
Age					
> 44 years	6	-1.05 (-1.75, -0.35)	57	0.01	0.001
≤ 44 years	7	-0.07 (-0.29, 0.15)	0	0.8	
Sex					
Men	2	0.11 (-2.60, 2.82)	0	0.94	0.85
Women	3	-0.58 (-1.31, 0.14)	0	0.73	
Both	8	-0.59 (-0.96, -0.21)	64.3	0.001	
Duration					
>12 weeks	5	-1.29 (-2.29, -0.29)	70.3	0.003	0.001
≤ 12 weeks	8	-0.09 (-0.30, 0.12)	0	0.96	
Dose					
> 3.4 g/day	7	-0.77 (-1.28, -0.25)	62.7	0.004	0.04
≤ 3.4 g/day	8	-0.16 (-0.43, 0.12)	0	0.59	
Physical activity program					
Yes	3	-0.87 (-3.25, 1.51)	0	0.98	0.72
No	10	-0.56 (-0.90, -0.21)	64.5	0.001	
Type of Control					
Olive oil		-1.92 (-2.64, -1.19)	0	0.98	

Sunflower oil		-0.56 (-1.29, 0.17)	0	0.50	0.001
Safflower oil		-0.26 (-0.59, 0.08)	79.4	0.002	
BMI					
Age					
> 44 years	6	-0.42 (-0.71, -0.12)	67.1	0.002	0.001
≤ 44 years	7	0.07 (-0.03, 0.17)	0	0.46	
Sex					
Men	2	-0.02 (-0.85, 0.81)	0	0.94	0.76
Women	3	-0.24 (-0.53, 0.05)	0	0.80	
Both	7	-0.25 (-0.45, -0.06)	76.6	0.0001	
Duration					
>12 weeks	5	-0.51 (-0.92, -0.009)	80.5	0.0001	0.0001
≤ 12 weeks	8	0.05 (-0.05, 0.15)	0	0.73	
Dose					
> 3.4 g/day	6	-0.33 (-0.58, -0.09)	73.8	0.0001	0.009
≤ 3.4 g/day	8	-0.10 (-0.34, 0.13)	25.9	0.21	
Physical activity program					
Yes	3	-0.30 (-0.99, 0.39)	0	0.98	0.64
No	10	-0.23 (-0.41, -0.05)	76.7	0.0001	
Type of Control					
Olive Oil	6	-0.73 (-0.98, -0.48)	0	0.97	0.001
Sunflower oil	3	-0.23 (-0.53, 0.06)	0	0.54	
FM					

Age					
> 44 years	4	-1.79 (-2.72, -0.86)	0	0.49	0.001
≤ 44 years	4	-0.32 (-0.56, -0.08)	46.9	0.11	
Duration					
>12 weeks	4	-1.94 (-2.74, -1.15)	0	0.58	0.0001
≤ 12 weeks	3	-0.23 (-0.25, -0.21)	0	0.77	
Dose					
> 3.4 g/day	5	-1.45 (-2.59, -0.31)	53.1	0.03	0.12
≤ 3.4 g/day	4	-0.63 (-1.69, 0.39)	53.8	0.09	
Type of Control					
Olive oil	4	-2.14 (-3.09, -1.19)	0	0.94	0.0001
Safflower oil	2	-0.31 (-0.56, -0.07)	65.4	0.05	
LBM					
Age					
> 44 years	2	-0.28 (-2.20, 1.64)	46.8	0.09	0.0001
≤ 44 years	5	0.31 (0.16, 0.47)	0	0.97	

Appendix 1- Search strategies and the number of publications in each electronic database		
Database	**Search strategy**	**Number of publications**
PubMed	("conjugated linoleic acid"[tiab] OR "conjugated fatty acid"[tiab] OR "rumenic acid"[tiab] OR "CLA"[tiab]) AND ("weight"[tiab] OR "obes*"[tiab] OR "body composition"[tiab] OR "adiposity"[tiab] OR "slim"[tiab] OR "waist"[tiab] OR "abdomen"[tiab] OR "BMI"[tiab] OR "body mass index"[tiab]) AND 2000/01/01:2017/12/31 [dp]	740
Web of Science	((TS= (“conjugated linoleic acid”) OR TS= (“conjugated fatty acid”) OR TS= (“bovic acid”) OR TS= (“rumenic acid”) OR TS= (“CLA”)) AND (TS= (weight) OR TS= (obesity) OR TS= (obese) OR TS= (“body composition”) OR TS= (“adiposity”) OR TS= (“slim”) OR TS= (waist) OR TS= (“abdomen”) OR TS= (“BMI”) OR TS= (“body mass index”)) AND (PY= (1990-2017))) AND DOCUMENT TYPES: (Article)	1845
Scopus	TITLE-ABS ("conjugated linoleic acid") OR TITLE-ABS ("conjugated fatty acid") OR TITLE-ABS ("rumenic acid") OR TITLE-ABS ("CLA") AND (TITLE-ABS ("weight") OR TITLE-ABS ("obese") OR TITLE-ABS (obesity) OR TITLE-ABS ("body composition") OR TITLE-ABS ("adiposity") OR TITLE-ABS ("slim") OR TITLE-ABS ("waist") OR TITLE-ABS ("abdomen") OR TITLE-ABS ("BMI") OR TITLE-ABS ("body mass index")) AND ((PUBYEAR > 1999 AND PUBYEAR < 2018)) AND (LIMIT-TO (SRCTYPE , "j ")) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , " re ")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re"))	1322
Cochrane	("conjugated linoleic acid" OR "conjugated fatty acid" OR "rumenic acid" OR "CLA") AND ("weight" OR "obese" OR “obesity” OR "body composition" OR "adiposity" OR "slim" OR "waist" OR "abdomen" OR "BMI" OR "body mass index") AND ([2000-2017]/py)	125