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The effects of conjugated linoleic acid supplementation on anthropometrics and body composition indices in adults: a systematic review and dose–response meta-analysis

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Abstract

Prior meta-analytic investigations over a decade ago rather inconclusively indicated that conjugated linoleic acid (CLA) supplementation could improve anthropometric and body composition indices in the general adult population. More recent investigations have emerged, and an up-to-date systematic review and meta-analysis on this topic must be improved. Therefore, this investigation provides a comprehensive systematic review and meta-analysis of randomised controlled trials (RCT) on the impact of CLA supplementation on anthropometric and body composition (body mass (BM), BMI, waist circumference (WC), fat mass (FM), body fat percentage (BFP) and fat-free mass (FFM)) markers in adults. Online databases search, including PubMed, Scopus, the Cochrane Library and Web of Science up to March 2022, were utilised to retrieve RCT examining the effect of CLA supplementation on anthropometric and body composition markers in adults. Meta-analysis was carried out using a random-effects model. The I^2 index was used as an index of statistical heterogeneity of RCT. Among the initial 8351 studies identified from electronic databases search, seventy RCT with ninety-six effect sizes involving 4159 participants were included for data analyses. The results of random-effects modelling demonstrated that CLA supplementation significantly reduced BM (weighted mean difference (WMD): −0·35, 95 % CI (−0·54, −0·15), $P < 0·001$), BMI (WMD: −0·15, 95 % CI (−0·24, −0·06), $P = 0·001$), WC (WMD: −0·62, 95% CI (−1·04, −0·20), $P = 0·004$), FM (WMD: −0·44, 95 % CI (−0·66, −0·23), $P < 0·001$), BFP (WMD: −0·77 %, 95 % CI (−1·09, −0·45), $P < 0·001$) and increased FFM (WMD: 0·27, 95 % CI (0·09, 0·45), $P = 0·003$). The high-quality subgroup showed that CLA supplementation fails to change FM and BFP. However, according to high-quality studies, CLA intake resulted in small but significant increases in FFM and decreases in BM and BMI. This meta-analysis study suggests that CLA supplementation may result in a small but significant improvement in anthropometric and body composition markers in an adult population. However, data from high-quality studies failed to show CLA's body fat-lowering properties. Moreover, it should be noted that the weight-loss properties of CLA were small and may not reach clinical importance.

Keywords: **Conjugated linoleic acid: Anthropometrics: Body composition indices: Systematic review: Meta-analysis**

Abbreviations: BM, body mass; BFP, body fat percentage; CLA, conjugated linoleic acid; FM, fat mass; FFM, fat-free mass; RCT, randomised controlled trial; WC, waist circumference; WMD, weighted mean difference.

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Obesity negatively influences overall health, adds significantly to societal and economic burdens, and shows no signs of slowing[1]. Globally, millions of individuals maintain a sedentary lifestyle and adhere to nutrient-poor and energy-dense diets, which contributes to overweightness/obesity and increases the risk for many non-communicable chronic diseases[2,3]. Therefore, the identification of alternative adiposity-reducing strategies with the potential to prevent or alleviate the negative consequences of obesity is warranted. Apart from lifestyle modification, often considered the cornerstone of a weight management programme[4–6], a wide range of supplements are now available touting anti-obesity properties[7–10]. Among those, conjugated linoleic acid (CLA) has shown promise as a food supplement to reduce adiposity in preventing overweightness and obesity[11,12].

CLA have been investigated for various beneficial effects, including cancer, atherosclerosis and obesity[13–16]. Major isomers of CLA are cis-9, trans-11 CLA (9, 11 CLA) and trans-10, cis-12 CLA (10, 12 CLA)[17], which are found naturally in ruminant animal food products[18] and are primary components of widely consumed CLA weight-loss supplements[19,20]. Although humans can produce endogenous CLA, the blood and tissue levels of CLA in non-supplemented individuals are less[21,22]. According to prior investigations, isomer 10, 12 CLA seems to elicit the greatest beneficial effect on promoting weight loss in animals and humans[23–25]. One proposed explanation behind CLA action may be stimulating apoptotic mechanisms and regulating lipolytic pathways, both of which positively affect body composition and weight loss in humans[26]. A substantial body of evidence also indicates that CLA promotes weight loss by reducing fat cells' size and altering fat cells' evolution[27]. While future research needs to elucidate further the physiological or other mechanisms behind CLA-induced altered fat cells, the vast majority of literature on the role of CLA in managing obesity utilises common measures for anthropometrics and body composition, including body mass (BM), BMI, waist circumference (WC) and body fat percentage (BFP)[28,29]. To this, a series of recent well-controlled pharmacological investigations have demonstrated conflicting results on the effectiveness of CLA supplementation on these outcomes in adults[11,30].

As noted, investigations on the association between CLA supplementation with anthropometric and body composition outcomes have sometimes been in agreement, which may be due to various factors, including supplementation dosages, the length of intervention and the health status of participants. Although prior meta-analyses exist, such investigations targeted special populations, including overweight and obese individuals[31,32] and those with metabolic syndrome[33]. To the best of our knowledge, two prior meta-analyses have been conducted to determine the pooled effects of CLA supplementation on fat and fat-free mass (FFM) in the general adult population[34,35]. However, these meta-analytic investigations, in particular, were performed over a decade ago, and numerous relevant randomised controlled trials (RCT) have been published since. Therefore, we performed a comprehensive systematic review and meta-analysis of the literature to date on the effects of CLA supplementation on anthropometric and body composition markers in adults.

Methods

This investigation was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol[36].

Search strategy

A comprehensive literature search was performed for RCT that investigated the efficacy of CLA supplementation on anthropometric measurements and body composition indicators using online databases, including PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library up to March 2022. The following MeSH and non-MeSH terms were applied in the search strategy: ('Conjugated linoleic acid' OR 'conjugated fatty acid' OR 'bovic acid' OR 'rumenic acid' OR 'CLA' AND Intervention OR 'Intervention Study' OR 'Intervention Studies' OR 'controlled trial' OR 'randomized' OR 'randomized' OR 'random' OR 'randomly' OR 'placebo' OR 'clinical trial' OR 'Trial' OR 'randomized controlled trial' OR 'randomized clinical trial' OR 'RCT' OR 'blinded' OR 'double blind' OR 'double blinded' OR 'trial' OR 'clinical trial' OR 'trials' OR 'Pragmatic Clinical Trial' OR 'Cross-Over Studies' OR 'Cross-Over' OR 'Cross-Over Study' OR 'parallel' OR 'parallel study' OR 'parallel trial').

No restrictions were placed in database searches for the date of publication. Reference lists of all relevant studies were cross-checked against database search results for overlooked publications. All references were included in the Endnote software (EndNote X21, Thomson Reuters, New York) for screening, and duplicate citations and unpublished manuscripts were removed.

Study selection and eligibility criteria

Titles and abstracts of all records from the initial search were evaluated independently by two investigators. Studies were selected for further analysis if they met the following criteria: (a) original RCT with either parallel or crossover designs; (b) studies that were done on adult participants (≥18 years old); (c) trials investigating the impact of CLA supplementation on anthropometric measurements (BM, BMI and WC) and body composition indicators (fat mass (FM), BFP and FFM) in both intervention and placebo groups; (d) studies that reported means and standard deviations for each outcome or any other effect sizes by which the calculation of means and standard deviation was possible. Conversely, studies were excluded if: (a) the duration of intervention was less than 4 weeks; (b) inadequate data on the selected outcomes in intervention or control groups was presented; (c) they were observational, case reports, reviews, letters to an editor, editorial articles, and *in vitro* studies and animal experiments; (d) children or adolescents were enrolled; and (e) no control group was apparent.

Data extraction

The data extraction was independently performed using a pre-designed standardised electronic form (Excel, Microsoft Office). The following information from each study were extracted: first author's name, year of publication, study location, total sample size, numbers of cases (those who received CLA) and controls,

participant's demographic data (sex, mean age and BMI), the health status of participants, study design, the intervention dose, length of follow-up, and outcomes measured as mean and standard deviation of selected end points at study baseline, post-intervention, and/or changes between baseline and post-intervention.

Quality and certainty assessment

A systematic bias assessment of the included studies was performed using the Cochrane criteria[37]. The quality of all eligible studies was evaluated based on the following items: random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias and other possible causes of bias. Based on the Cochrane Handbook recommendation, studies were ranked as low (L), high risk of bias (H) or unclear (U) regarding each field of bias[37]. In addition, the overall certainty of evidence across the studies was evaluated based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group guidelines. Subsequently, the quality of evidence was classified into four categories: high, moderate, low and very low[38].

Data synthesis and statistical analysis

Data analysis was performed using STATA® version 14.0 (StataCorp.), and mean (SD) changes of outcomes were used to estimate the overall effect size. Effect sizes for all variables are reported as weighted mean differences (WMD) and 95 % CI derived from random-effects models. A random-effects model was selected to address significant heterogeneity between studies for methodology, outcome measures and participant characteristics. The I^2 index was used as an index of statistical heterogeneity of RCT. If the SD change following intervention was not reported in studies, it was calculated based on the formula provided by the Cochrane Collaboration[39] such that: SD = square root [(SD baseline) ^{2} + (SD final) ^{2} – (2R × SD baseline × SD final)], where the correlation coefficient (R) = 0·8. Statistical heterogeneity between studies was assessed by Cochrane's Q test (significance point at $P < 0{\cdot}1$) and the I^2 index (significance point at $I^2 > 40$ %).

The publication bias was assessed using visual inspection of funnel plots and statistically using Egger's regression and Begg's tests[40]. Subgroup analyses were performed to find probable sources of heterogeneity based on several predefined variables, including duration of follow-up (≥12 *v.* <12 weeks), intervention dosage (≥3 *v.* <3 g/d), participants' health condition (healthy *v.* unhealthy), baseline values of BMI (normal *v.* overweight *v.* and obese), sex (female *v.* male *v.* combined) and the quality of studies (high *v.* moderate, *v.* high quality). Sensitivity analysis was applied to detect if an overall effect size relied on the outcomes of a particular RCT. To determine the non-linear dose–response and linear meta-regression effects of CLA dosage (g/d) as well as the duration of intervention on each marker, fractional polynomial modelling was used. A P-value ≤ 0·05 was considered to be a statistically significant outcome.

Results

Study selection

The study selection process is illustrated in Fig. 1. A total of 8351 publications were found in the initial search. Of those, 2419 were duplicates and thus removed from further consideration. After a review of the remaining 5932 titles and abstracts, 104 publications were advanced for full-text examination. An additional thirty-four studies were removed following full-text scrutiny according to inclusion/exclusion criteria. Finally, sixty-nine RCT with ninety-five effect sizes and 4159 participants met the inclusion criteria for quantitative and qualitative analyses.

Study characteristics

The characteristics of the included RCT are outlined in Table 1. Investigations were published between 2000 and 2020 and were carried out in Europe[25,41–68], Asia[23,30,69–87], America[88–103], Africa[104–106] and Oceania[107]. Of the sixty-nine RCT, six were randomised crossover design[63,65,92,93,98,103], and the remaining were of parallel design. Intervention dosages of CLA varied between 1·0 and 6·8 g/d, and follow-up durations ranged from 4 to 104 weeks. Selected studies enrolled participants with different health conditions; three studies enrolled patients with diabetes[55,78,87]; three investigated the effects of CLA supplementation in individuals with hyperlipidemia[93,98,103], two recruited patients with metabolic syndrome[59,90], and individual studies investigated the following health conditions: rheumatoid arthritis[69], hypertension[80], atherosclerosis[76], chronic obstetric pulmonary disease[75] and benign breast disease[84]. All remaining studies were performed on apparently healthy individuals. The vast majority of RCT were performed on both sexes, except sixteen investigations that were conducted exclusively on females[25,50,55,72,82,84–86,89,90,95,97,100–102,106] and seventeen on males[57–63,65,70,79,88,91–93,103,105,106]. The mean age of individuals was between 18 and 63·3 years, with BMI ranging from 19 to 37·1 kg/m^2. All sixty-nine included trials had an appropriately controlled design, with the sole difference between control and treatment groups being the CLA intervention.

Risk of bias assessment

Cochrane risk of bias results of included studies is shown in Supplementary 1 and indicated that thirty-three[25,30,41,44,46,47,51,53,57,59–62,65–70,72,80,81,89–93,95,98–100,103,106] trials were considered to be at high risk for bias, nineteen[42,43,50,52,54,56,58,63,76–79,82,83,94,96,102,104,105] were deemed the moderate risk of bias and the remaining eighteen[23,45,48,49,55,64,71,73–75,84–88,97,101,107] were at low risk of bias.

Meta-analysis results

Effects of conjugated linoleic acid supplementation on anthropometric measurements. Combining eighty-three effect sizes where CLA supplementation was compared with a placebo control revealed a significant lowering effect of CLA supplementation on BM (WMD: −0·34 kg, 95 % CI (−0·54, −0·15), $P < 0{\cdot}001$). However, there was a significant between-study

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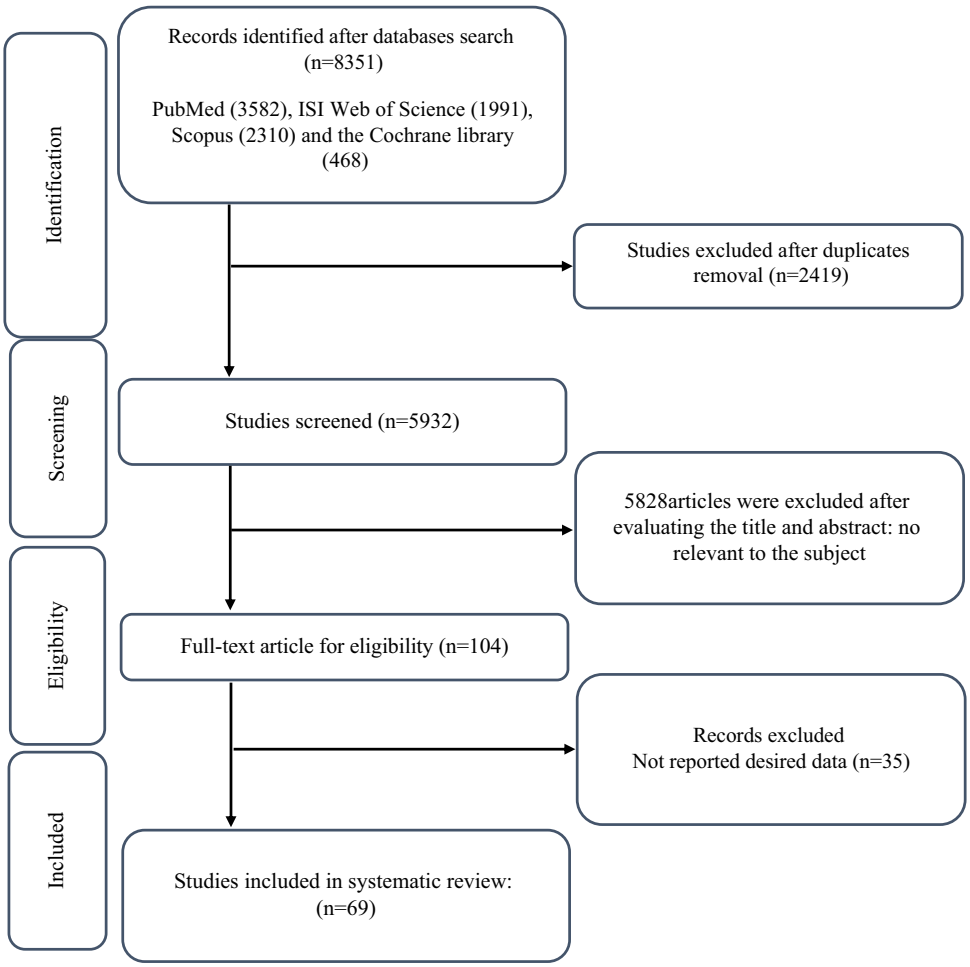

Fig. 1. Flow chart of study selection for inclusion trials in the systematic review.

heterogeneity ($I^2 = 42{\cdot}7\,\%$, $P < 0{\cdot}001$) (Fig. 2(a)). The findings from subgroup analyses showed that CLA consumption was associated with decreased BM irrespective of the health condition of participants and follow-up length. In addition, BM was only reduced in overweight and obese individuals (as defined by BMI) and female and both sexes and in those who ingested 3 g/d or more of CLA. Weight-lowering effects of CLA were shown in both high- and low-quality studies but not in low-quality studies (Table 2).

Eighty effect sizes from seventy-seven included RCT reported the effect of CLA supplementation on BMI and revealed a significant reduction in BMI (WMD: $-0{\cdot}15$ kg/m^2, 95 % CI ($-0{\cdot}24$, $-0{\cdot}06$), $P = 0{\cdot}001$) albeit with a significant between-study heterogeneity ($I^2 = 70{\cdot}6\,\%$, $P < 0{\cdot}001$) (Fig. 2(b)). Subgroup analyses demonstrated BMI values were significantly reduced following CLA supplementation regardless of participant health status and follow-up duration. As with BM, BMI was only reduced in overweight and obese individuals and those who ingested 3 g/d or more CLA. However, BMI only decreased in high-quality studies subgroups (Table 2).

Overall, thirty-nine arms of included clinical trials investigated the effect of CLA supplementation on WC, and pooled effect size showed a significant reduction in WC (WMD: $-0{\cdot}67$ cm, 95 % CI ($-1{\cdot}10$, $-0{\cdot}23$), $P = 0{\cdot}002$) with significant between-study heterogeneity ($I^2 = 76{\cdot}0\,\%$, $P < 0{\cdot}001$) (Fig. 2(c)). Subgroup analyses revealed that CLA supplementation resulted in a significant reduction in WC among healthy participants, in those with baseline BMI > 30 kg/m^2, upon supplementing with 3 g/d or more of CLA, and in cases where follow-up length was less than 12 weeks. Regarding the quality of studies, CLA was the cause of the WC decrease in moderate-quality studies (Table 2).

Effects of conjugated linoleic acid supplementation on body composition indicators. Meta-analysis of forty-nine effect sizes revealed a significant change in FM values after CLA intervention (WMD: $-0{\cdot}46$ kg, 95 % CI ($-0{\cdot}68$, $-0{\cdot}23$), $P < 0{\cdot}001$) despite a significant heterogeneity between studies ($I^2 = 51{\cdot}6\,\%$, $P < 0{\cdot}001$) (Fig. 2(d)). The findings of the subgroup analyses showed that CLA consumption reduced FM regardless of the intervention dosage and duration. However, CLA supplementation was associated with decreased FM only in healthy individuals and those with a baseline BMI categorised as overweight or obese. Furthermore, FM decreased in low- and moderate-quality subgroups (Table 2).

A total of forty-three effect sizes (835 cases and 808 controls) investigated the effect of CLA supplementation on BFP. Pooled data analysis indicated that BFP was significantly reduced following CLA supplementation compared with

Table 1. Characteristics of the included studies

Studies	Country	Study design	Participant	Sex	Sample size		Trial Duration (week)	Means age				Means BMI				Intervention	
					IG	CG		IG		CG		IG		CG		CLA dose (g/d)	Control group
Zambell et al. 2000	USA	Parallel, R, PC, B	Healthy	F: 17	10	7	8	20–41		20–41		NR		NR		3	Placebo
Berven et al. 2000	Norway	Parallel, R, PC, DB	Obese human volunteers	M/F (F:17, M:30)	25	22	12	47·6	7·1	46·5	7	29·4	2·6	30·1	2·2	3·4	Placebo
Blankson et al. 2000 (a)	Norway	Parallel, R, PC, DB	Overweight and obese human	M/F (F:16, M:6)	12	10	12	47·2	13·5	44·4	13·2	29·7	2·5	28	2·4	1·7	Placebo
Blankson et al. 2000 (b)	Norway	Parallel, R, PC, DB	Overweight and obese human	M/F (F:13, M:5)	8	10	12	42·8	10·4	44·4	13·2	27·7	2·1	28	2·4	3·4	Placebo
Blankson et al. 2000 (c)	Norway	Parallel, R, PC, DB	Overweight and obese human	M/F (F:15, M:6)	11	10	12	47·7	11·3	44·4	13·2	29·4	2·8	28	2·4	5·1	Placebo
Blankson et al. 2000 (d)	Norway	Parallel, R, PC, DB	Overweight and obese human	M/F (F:15, M:6)	11	10	12	44·3	12·7	44·4	13·2	30·3	2·9	28	2·4	6·8	Placebo
Medina et al. 2000	USA	Parallel, R, PC, B	Healthy	F: 17	10	7	9	20–41		20–41		23·2	1·5	22·2	3·9	3	Placebo
Thom et al. 2001	Norway	Parallel, R, PC, DB	Healthy exercising humans	M/F: 20	10	10	12	27·5	3	28	3·2	23·2	2·4	23·3	2·5	1·8	Placebo
Mougios et al. 2001	Greece	Parallel, R, PC, DB	Healthy	M/F (F:10, M:14)	10	12	8	22·4	1·7	22	1·3	23·8	2·7	22·7	3·3	1·4	Placebo
Riserus et al. 2001	Sweden	Parallel, R, PC, DB	Obese middle-aged men	M: 24	14	10	4	54	5·7	52	7·8	32·2	3·4	31·7	1·9	4·2	Placebo
Riserus et al. 2002 (A)	Sweden	Parallel, R, PC, DB	Obese men with the metabolic syndrome	M: 38	19	19	12	51	7·1	53	10·1	30·1	1·8	30·2	1·8	3·4	Placebo
Riserus et al. 2002 (B)	Sweden	Parallel, R, PC, DB	Obese men with the metabolic syndrome	M: 38	19	19	12	55	7·1	53	10·1	31·2	2·5	30·2	1·8	3·4	Placebo
Kreider et al. 2002	Egypt	Parallel, R, PC, DB	Resistance training	M: 23	12	11	4	23	3·7	23	3·7	NR		NR		6	Placebo
Noone et al. 2002 (a)	Ireland	Parallel, R, PC, DB	Healthy human subjects	M/F (F:21, M:13)	16	18	8	33·22	11·78	32·31	10·86	23·51	3·1	23·35	3·35	3	Control diet
Noone et al. 2002 (b)	Ireland	Parallel, R, PC, DB	Healthy human subjects	M/F (F:18, M:17)	17	18	8	28·58	6·08	32·31	10·86	24·08	7·08	23·35	3·35	3	Control diet
Kamphuis et al. 2003 (a)	The Netherlands	Parallel, R, PC, DB	Overweight subjects	M/F (F:14, M:13)	14	13	13	40·9	5	39·5	7·7	25·6	1·1	26·1	1·4	1·8	Placebo
Kamphuis et al. 2003 (b)	The Netherlands	Parallel, R, PC, DB	Overweight subjects	M/F (F:14, M:13)	13	14	13	36·2	7·6	34	9·1	26·2	1·7	25·7	1·4	3·6	Placebo
Kamphuis et al. 2003	The Netherlands	Parallel, R, PC, DB	Overweight subjects	M/F (F:28, M:26)	27	27	13	39	7	37	9	27·8	1·6	27·8	1·4	3·6	Placebo
Malpuech-Brugère et al. 2004 (a)	France	Parallel, R, PC, DB	Overweight	M/F: 33	18	15	6	47·5	7·7	48·3	9·7	27·9	1·7	27·7	1·6	1·5	Placebo
Malpuech-Brugère et al. 2004 (b)	France	Parallel, R, PC, DB	Overweight	M/F: 33	18	15	6	49·9	8·1	48·3	9·7	27·7	1·2	27·7	1·6	3	Placebo
Malpuech-Brugère et al. 2004 (c)	France	Parallel, R, PC, DB	Overweight	M/F: 30	15	15	6	48·1	6·8	48·3	9·7	28·4	2·1	27·7	1·6	1·5	Placebo

Table 1. (*Continued*)

Studies	Country	Study design	Participant	Sex	Sample size		Trial Duration (week)	Means age				Means BMI				Intervention	
					IG	CG		IG		CG		IG		CG		CLA dose (g/d)	Control group
Malpuech-Brugère et al. 2004 (d)	France	Parallel, R, PC, DB	Overweight	M/F: 30	15	15	6	48·2	8·6	48·3	9·7	27·1	1·3	27·7	1·6	3	Placebo
Riserus et al. 2004	Sweden	Parallel, R, PC, DB	Obese men	M: 25	13	12	12	54	5·5	56	6	30·6	2	30·4	2·5	3	Placebo
Gaullier et al. 2004 (a)	Norway	Parallel, R, PC, DB	Healthy overweight humans	M/F (F:98, M:22)	61	59	52	44·5	10·7	45	9·5	28·1	1·5	27·7	1·7	4·5	Placebo
Gaullier et al. 2004 (b)	Norway	Parallel, R, PC, DB	Healthy overweight humans	M/F (F:98, M:21)	60	59	52	48	10·7	45	9·5	28·3	1·6	27·7	1·7	4·5	Placebo
Riserus et al. 2004 (a)	Sweden	Parallel, R, PC, DB	Obese men	M: 38	19	19	12	51	7·1	53	10·1	30·1	1·8	30·2	1·8	3·4	Control diet
Riserus et al. 2004 (b)	Sweden	Parallel, R, PC, DB	Obese men	M: 38	19	19	12	55	7·1	53	10·1	31·2	2·5	30·2	1·8	3·4	Control diet
Gaullier et al. 2005 (a)	Norway	Parallel, R, PC, DB	Healthy overweight humans	M/F (F:69, M:18)	46	41	104	45·1	10·5	45·1	8·8	28·1	1·4	27·4	1·7	3·4	Placebo
Gaullier et al. 2005 (b)	Norway	Parallel, R, PC, DB	Healthy overweight humans	M/F (F: 74, M:14)	47	41	104	48·6	10·6	45·1	8·8	28·3	1·5	27·4	1·7	3·4	Placebo
Desroches et al. 2005	Canada	Crossover, R, PC, B	Overweight and obese	M: 17	17	17	4	36·6	12·4	36·6	12·4	31·2	4·4	31·2	4·4	4·22	Control diet
Nugent et al. 2005 (a)	Ireland	Parallel, R, PC, DB	Healthy	M/F:38	19	19	8	33·83	2·75	32·23	2·42	23·2	2·68	23·3	2·56	3	Control diet
Nugent et al. 2005 (b)	Ireland	Parallel, R, PC, DB	Healthy	M/F: 36	17	19	8	28·44	1·42	32·23	2·42	24·1	2·52	23·3	2·56	3	Control diet
Colakoglu et al. 2006 (a)	Turkey	Parallel, R, PC, SB	Healthy	F: 26	12	14	6	21·7	2	20·4	2·5	22·5	1·7	21·6	1·6	3·6	Control diet-exercise
Colakoglu et al. 2006 (b)	Turkey	Parallel, R, PC, SB	Healthy	F: 18	11	7	6	20·4	1·7	21·9	2	23·3	1·2	20·8	1·6	3·6	Control diet
Pinkoski et al. 2006	Canada	Parallel, R, PC, DB	Resistance training	M/F (F: 40, M:36)	38	38	7	25·2	5·95	25·15	6·65	NR		NR		5	Placebo
Larsen et al. 2006	Norway	Parallel, R, PC, DB	Obese healthy subjects	M/F (F:47, M:36)	40	43	52	43·4	8·4	41·7	8·2	28–35		28–35		3·4	Placebo
Taylor et al. 2006	UK	Parallel, R, PC, DB	Healthy	M/F: 40	21	19	12	45	6	47	8	33	3	33	3	4·5	Control diet
Adams et al. 2006	USA	Parallel, R, PC, DB	Resistance-trained men	M: 28	15	13	4	43·4	6	43·8	4·2	30·3	4·4	30·4	4·6	3·2	Placebo
Steck et al. 2007 (a)	UK	Parallel, R, PC, DB	Healthy obese humans	M/F (F:23, M:9)	16	16	12	36·3	8·9	34·9	8	32·7	1·8	32·7	1·9	3·2	Placebo
Steck et al. 2007 (b)	UK	Parallel, R, PC, DB	Healthy obese humans	M/F (F:24, M:8)	16	16	12	34·1	8·9	34·9	8	32·7	1·7	32·7	1·9	6·4	Placebo
Watras et al. 2007	Canada	Parallel, R, PC, DB	Healthy	M/F (F:32, M:8)	22	18	24	34	8	32	7	27·6	1·8	28	2·2	3·2	Placebo
Lambert et al. 2007 (a)	South Africa	Parallel, R, PC, DB	Regularly exercising	M: 25	13	12	12	32	7	32	7	22·5	2·5	22·5	2·5	3·9	Control diet
Lambert et al. 2007 (b)	South Africa	Parallel, R, PC, DB	Regularly exercising	F: 37	14	13	12	32	7	32	7	24·2	2·1	24·2	2·1	3·9	Control diet
Nazare et al. 2007	France	Parallel, R, PC, DB	Healthy subjects	M/F: 44	21	23	14	29·4	6·75	28·5	5·7	25·2	1·45	25·1	1·48	3·76	Placebo

Table 1. (*Continued*)

Studies	Country	Study design	Participant	Sex	Sample size		Trial Duration (week)	Means age				Means BMI				Intervention	
					IG	CG		IG		CG		IG		CG		CLA dose (g/d)	Control group
Gaullier et al. 2007	Norway	Parallel, R, PC, DB	Overweight and obese	M/F (F:84, M:21)	55	50	24	45·8	10	48·7	9·2	30·5	10·4	30·2	10·4	3·4	Placebo
Attar-Bashi etval. 2007	Australia	Parallel, R, PC	Healthy	M/F: 16	8	8	8	33·1	8·2	37·4	12·2	24	4·3	25	3·8	3·2	Placebo
Sneddon et al. 2008 (a)	UK	Crossover, R, PC, DB	Young lean	M: 13	13	13	12	30·5	4·9	30·5	4·9	23·6	1·5	23·6	1·5	3	Placebo
Sneddon et al. 2008 (b)	UK	Crossover, R, PC, DB	Young obese	M: 12	12	12	12	32·4	2·3	32·4	2·4	32·3	1·9	32·3	1·9	3	Placebo
Sneddon et al. 2008 (c)	UK	Crossover, R, PC, DB	Older lean	M: 20	20	20	12	56·3	4·2	56·3	4·2	23·6	1·5	23·6	1·5	3	Placebo
Sneddon et al. 2008 (d)	UK	Crossover, R, PC, DB	Older obese	M: 14	14	14	12	56·9	5·4	56·4	5·4	32	1·6	32	1·6	3	Placebo
Kim et al. 2008	Korea	Parallel, R, PC, DB	Healthy overweight women	F: 27	15	12	12	26·33	9·4	29·5	10·8	25·23	2·16	26·47	1·8	3	Control diet
Park et al. 2008	Korea	Parallel, R, PC, DB	Overweight and obese human	M/F (F:27, M:3)	15	15	8	38·7	4·2	40·7	4	25·5	2	26·3	2·5	2·4	Placebo
Aryaeian et al. 2008	Iran	Parallel, R, PC, DB	Rheumatoid arthritis	M/F (F:38, M:6)	22	22	12	46·23	13·07	47·95	11·14	27·18	0·99	28·48	0·84	2·5	Placebo
Raff et al. 2008	Denmark	Parallel, R, PC, DB	Healthy young men	M: 38	18	20	5	25·7	4·2	26·1	3·6	22	1·9	22·5	2·1	5·5	Control diet
Goedecke et al. 2009	South Africa	Parallel, R, PC, DB	Healthy	M/F (F:15, M:10)	14	11	12	21–45		21–45		24·2	2·2	24·5	2·4	3·9	Placebo
Son et al. 2009 (a)	China	Parallel, R, PC, DB	Women with high body fat mass	F: 29	16	13	12	21·9	2·7	21·9	2·7	22·6	1·9	22·8	1·9	4·5	Placebo
Son et al. 2009 (b)	China	Parallel, R, PC, DB	Women with high body fat mass	F: 32	16	16	12	21·9	2·7	21·9	2·7	21·8	1·1	22·5	1·7	4·5	Placebo- exercise
Norris et al. 2009	Germany	Parallel, R, PC, DB	Postmenopausal women with type 2 diabetes mellitus	F: 55	22	33	16	59·4	7·3	60·1	7·3	37·1	7·2	36·3	6·1	6·4	Control diet
Zhao et al. 2009	China	Parallel, R, PC, DB	Obesity-related hypertension	M/F (F:36, M:44)	40	40	8	62·3	3·5	59·4	2·4	32·3	2·3	31·2	1·4	4·5	Control diet
Tavakkoli Darestani et al. 2010	Iran	Parallel, R, PC, DB	Postmenopausal	F: 76	38	38	12	55·1	6·4	54·9	6·9	27·6	3·4	27	3·4	3·2	Placebo
Michishita et al. 2010	japan	Parallel, R, PC, DB	Healthy overweight humans	M/F: 30	15	15	16	34·9	1·4	39·4	3·2	26·1	1·6	25·6	2	1·6	Amino acids
Venkatramanan et al. 2010	Canada	Crossover, R, PC, SB	Overweight, borderline hyperlipidemic individuals	M/F (F:5, M:10)	15	15	8	46·6	2	46·6	2	NR		NR		1·3	Control diet
Sluijs et al. 2010	Netherlands	Parallel, R, PC, DB	Overweight and obese adults	M/F (F:179, M:167)	173	173	24	58	0·4	58·8	0·5	28	9·45	27·7	12·75	4	Placebo
MacRedmond et al. 2010	Canada	Parallel, R, PC, DB	Overweight mild asthmatics	M/F (F:15, M:13)	15	13	12	32·2	8·7	29·9	3·8	27·8	4·5	27·3	3·6	4·5	Placebo
Brown et al. 2011	USA	Paralrell, R, PC	Health in young women	F: 18	9	9	8	20–40		20–40		19–30		19–30		1·17	Control diet
Joseph et al. 2011 (a)	Canada	Crossover, R, PC, DB	Overweight, hyperlipidemic	M: 27	27	27	8	18–60		18–60		31·5	4	31·3	4	3·5	Placebo
Joseph et al. 2011 (b)	Canada	Crossover, R, PC, DB	Overweight, hyperlipidemic	M: 27	27	27	8	18–60		18–60		31·4	4	31·3	4	3·5	Placebo
Plourde et al. 2011 (a)	Canada	Crossover, R, PC, DB	Overweight, hyperlipidemic men	M:27	27	27	8	44·8	7·8	44·8	7·8	30·9	4·7	30·9	4·7	3·5	Placebo

Table 1. (*Continued*)

Studies	Country	Study design	Participant	Sex	Sample size		Trial Duration (week)	Means age				Means BMI				Intervention	
					IG	CG		IG		CG		IG		CG		CLA dose (g/d)	Control group
Plourde et al. 2011 (b)	Canada	Crossover, R, PC, DB	Overweight, hyperlipidemic men	M:27	27	27	8	44·8	7·8	44·8	7·8	30·9	4·7	30·9	4·7	3·5	Placebo
Pfeuffer et al. 2011	Germany	Parallel, R, PC, DB	Obese male subjects	M: 40	21	19	4	45–68		45–68		28·3	2·3	27·8	1·3	4·5	Control diet
Chen et al. 2012	Taiwan	Parallel, R, PC, DB	Healthy	M/F (F:42, M:21)	30	33	12	33·1	1·1	32·5	1·1	27·56	2·45	28·04	2·94	1·7	Placebo
DeGuire et al. 2012 (a)	Canada	Parallel, R, PC, DB	Healthy	M:21	11	10	16	39	3	36	3	24·7	0·6	24·3	0·8	1·5	Placebo
DeGuire et al. 2012 (b)	Canada	Parallel, R, PC, DB	Healthy	M: 20	10	10	16	35	4	36	3	25·8	0·7	24·3	0·8	3	Control diet
Rubin et al. 2012 (a)	Germany	Crossover, R, PC, DB	Middle-aged men	M: 35	35	35	4	45–68		45–68		26	2·6	26·1	3	4·25	Control diet
Rubin et al. 2012 (b)	Germany	Crossover, R, PC, DB	Middle-aged men	M:35	35	35	4	45–68		45–68		26	3·5	26·1	3	4·25	Control diet
Bulut et al. 2013	Turkey	Parallel, R, PC, DB	Young men	M: 18	9	9	4	19–31		19–31		27·5	2·6	26·8	1·9	3	Placebo
Lopes et al. 2013	Brazil	Parallel, R, PC, DB	Healthy	F: 28	14	14	16	29·37	7·8	27·86	4·74	28·72	3·93	27·1	4·12	4	Placebo
Shadman et al. 2013	Iran	Parallel, R, PC, DB	Overweight type2 diabetics	M/F (F:21, M:18)	19	20	8	45·1	5·7	45·5	4·3	27·4	0·5	27·1	1·8	3	Placebo
Lopez-Plaza et al. 2013	Spain	Parallel, R, PC, DB	Healthy overweight people	M/F (F:29, M:9)	22	16	24	43	8·3	44·35	7·79	28·44	1·08	28·56	0·95	3	Placebo
Carvalho et al. 2013	Brazil	Parallel, R, PC, DB	Metabolic syndrome	F: 14	7	7	12	40	14·12	42	5·16	32·53	2·1	32·3	2·16	3	Placebo
Eftekhari et al. 2013	Iran	Parallel, R, PC	Atherosclerotic patients	M/F: 57	29	28	8	52·79	14·11	55·85	14·13	24·02	2·76	24·66	2·34	3	Control diet
Tajmanesh et al. 2015	Iran	Parallel, R, PC, DB	Healthy young men	M: 80	40	40	8	24·6	2·04	25	1·6	23·2	2·3	23·3	2·3	3·2	Placebo
Ebrahimi-Mameghani et al. 2016	Iran	Parallel, R, PC, B	Non-alcoholic fatty liver disease	M/F (F:33, M:5)	19	19	8	36·74	6·87	38·58	8·24	32·72	4·63	35·27	3·46	3	Placebo
Pina et al. 2016	Brasil	Parallel, R, PC, DB	Aerobic training in overweight women	F: 28	15	13	8	18–30		18–30		29·1	3·5	31·2	4·2	3·2	Placebo
Madry et al. 2016	Poland	Parallel, R, PC, DB	Obese	F: 74	37	37	12	54	4	54	4	34	3·6	35·36	4	3	Placebo
Ghobadi et al. 2016	Iran	Parallel, R, PC, DB	Patients with chronic obstructive pulmonary disease	M: 93	45	45	6	63·6	10·94	61·64	10·6	24·91	3·54	24·84	2·96	3·2	Placebo
Ribeiro et al. 2016	Brasil	Parallel, R, PC, DB	Obese women	F: 28	15	13	8	23·1	2·8	23·2	2·6	28·9	2·6	30·1	3·2	3·2	Placebo
Abedi et al. 2018	Iran	Parallel, R, PC, SB	Non-alcoholic fatty liver disease	M/F (F:32, M: 6)	19	19	8	36·74	6·87	38·58	8·24	32·72	4·63	35·27	3·46	3	Control diet
Rezvani et al. 2018	Iran	Parallel, R, PC, DB	Benign breast disease	F: 46	23	23	13	32·86	6·89	31·91	6·42	25·77	4·68	25·75	5·37	1	Placebo
Fouladi et al. 2018 (a)	Iran	Parallel, R, PC	Overweight	M/F (F:62, M:52)	58	56	12	36·5	30	35	29	27·6	2·9	27·7	2·98	3	Control diet
Fouladi et al. 2018 (b)	Iran	Parallel, R, PC	Overweight	M/F (F:62, M:51)	57	56	12	35	30	35	29	27·6	2·74	27·7	2·98	3	Control diet

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Table 1. (*Continued*)

Studies	Country	Study design	Participant	Sex	Sample size		Trial Duration (week)	Means age		Means BMI		Intervention	
					IG	CG		IG	CG	IG	CG	CLA dose (g/d)	Control group
Shahmirzadi et al. 2019	Iran	Parallel, R, PC, DB	Obese	M/F (F:29, M:25)	27	27	12	38·22	7·74	36·72	5·78	32·87	1·58	32·52	1·27	3	Placebo
Chang et al. 2020	China	Parallel, R, PC, DB	Healthy adults	M/F (F:40, M:25)	32	33	12	25·3	4·3	25·2	4·4	26·4	4·1	26·4	3·2	3·2	Placebo
Madry et al. 2020	Poland	Parallel, R, PC, DB	Obese or overweight	F: 62	32	30	12	54	4	54	4	34	3·5	35·36	7·58	3	Placebo

R, randomised; PC, placebo-control; DB, double-blind; M, male; F, female.

placebo (WMD: −0·76 %, 95 % CI (−1·08, −0·44), $P < 0·001$) albeit with a significant degree of heterogeneity between RCT ($I^2 = 66·6$ %, $P < 0·001$) (Fig. 2(e)). Subgroup analyses revealed that CLA supplementation significantly reduced BFP irrespective of participants' health condition, baseline BMI values, and intervention dosages and duration. BFP-lowering effects of CLA are only seen in low-quality studies (Table 2).

Forty-five effect sizes (975 cases and 939 controls) were assessed for the effect of CLA supplementation on FFM. Meta-analysis indicated that CLA supplementation significantly increased FFM values in study participants (WMD: 0·27 kg, 95 % CI (0·09, 0·45), $P = 0·003$). A significant between-studies degree of heterogeneity was observed ($I^2 = 47·6$ %, $P < 0·001$) (Fig. 2(f)). Findings from subgroup analyses showed that CLA consumption was associated with increased FFM in healthy participants and in those with normal baseline BMI values upon supplementing with 3 g/d or more of CLA and when the trial duration was 12 weeks or more. Finally, FFM increases in high- and low-quality studies (Table 2).

Publication bias. There was no evidence of publication bias in RCT examining the effect of CLA supplementation for all outcomes, including BM ($P = 0·142$ Egger's test), BMI ($P = 0·201$ Egger's test), WC ($P = 0·107$ Egger's test), FM ($P = 0·055$ Egger's test), BFP ($P = 0·059$ Egger's test) and FFM ($P = 0·601$ Egger's test). Funnel plots further indicated no evidence of asymmetry for the effects of CLA consumption on each outcome analysed in this meta-analysis (online Supplementary 2).

Dose–response and meta-regression analyses. Dose–response analyses showed that CLA supplementation significantly altered BFP based on the intervention duration ($r = −1·41$, P-non-linearity = 0·04) in a non-linear manner. No other significant non-linear dose–response associations were observed for the remaining outcomes (online Supplementary 3 and 4). A meta-regression analysis was performed to assess the presence of any correlation between intervention duration (weeks) and dose of CLA supplementation with BM, BMI, WC, FM, BFP and FFM values. However, the meta-regression results demonstrated no significant linear relationship between changes in BM, BMI, WC, FM, BFP and FFM with the dose and duration of the intervention (online Supplementary 5 and 6).

Grading of evidence. An evaluation of the quality of evidence using the GRADE approach is presented in Table 3. For BM and FFM, the quality of evidence was high since included RCT had a low to moderate risk of bias with low statistical and clinical heterogeneity and narrow CI. Moreover, moderate quality of evidence was detected for BMI, WC, FM and BFP because of existing very serious limitations for inconsistency ($I^2 = 69·5$ %, $I^2 = 75·0$ %, $I^2 = 51·8$ %, and $I^2 = 66·6$ % for heterogeneity, respectively).

(a)

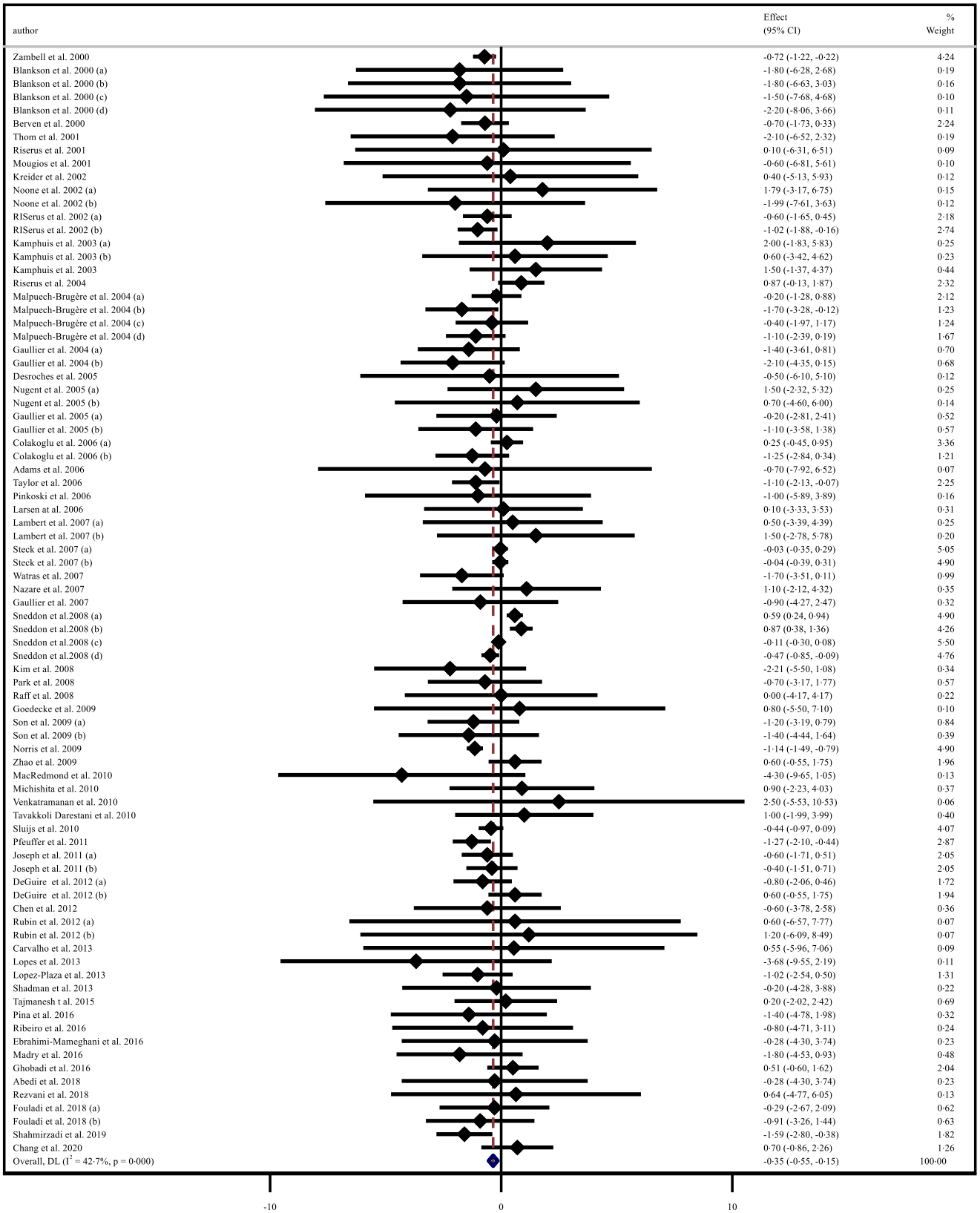

Fig. 2. Forest plot detailing weighted mean difference and 95 % CI for the effect of CLA supplementation on: (a) body weight (kg); (b) BMI (kg/m^2); (c) WC (cm); (d) FM (kg); (e) BFP (%); and (f) FFM (kg). CLA, conjugated linoleic acid; WC, waist circumference; FM, fat mas; BFP, body fat percentage; FFM, fat-free mass.

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(b)

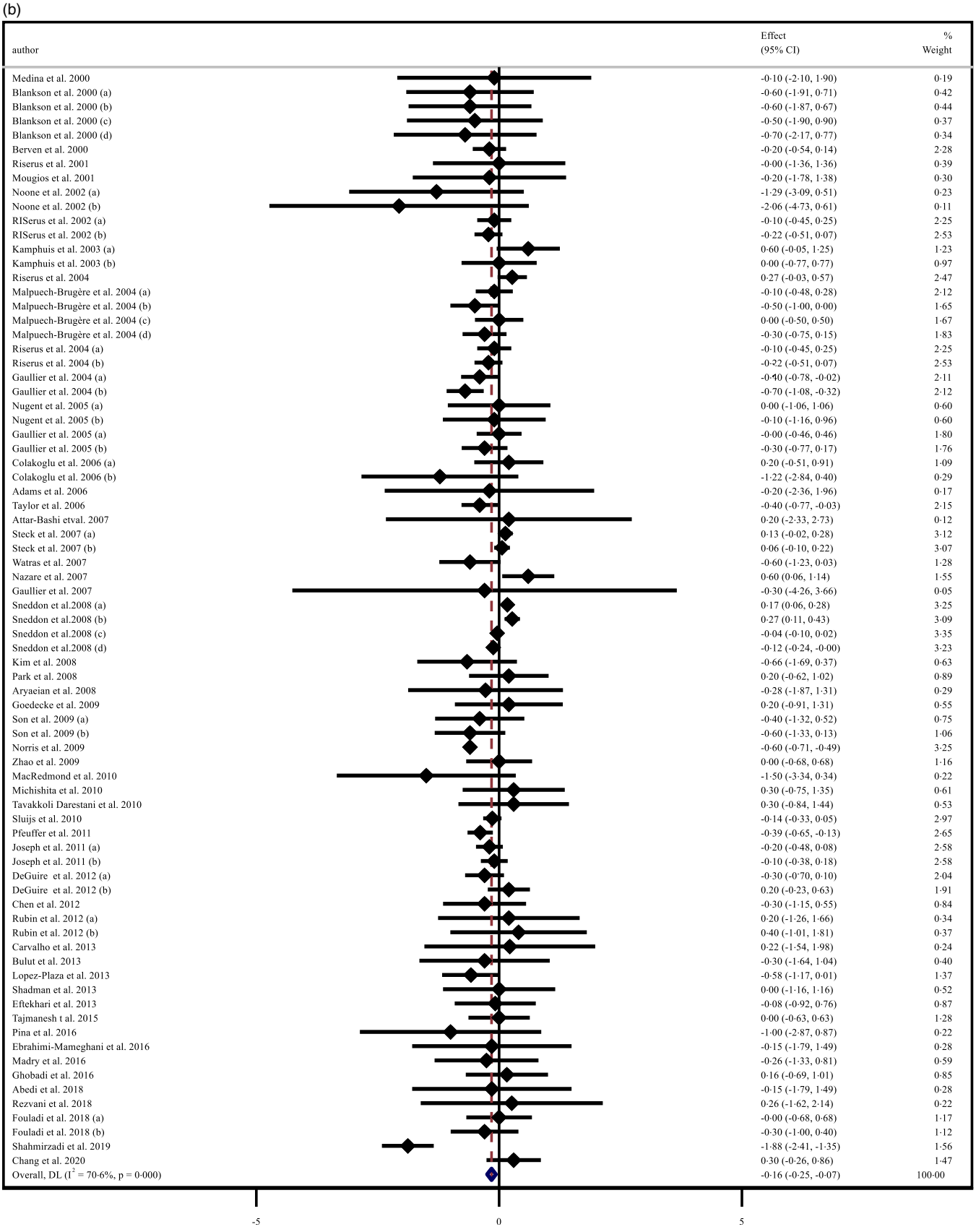

Fig. 2. (Continued)

(c)

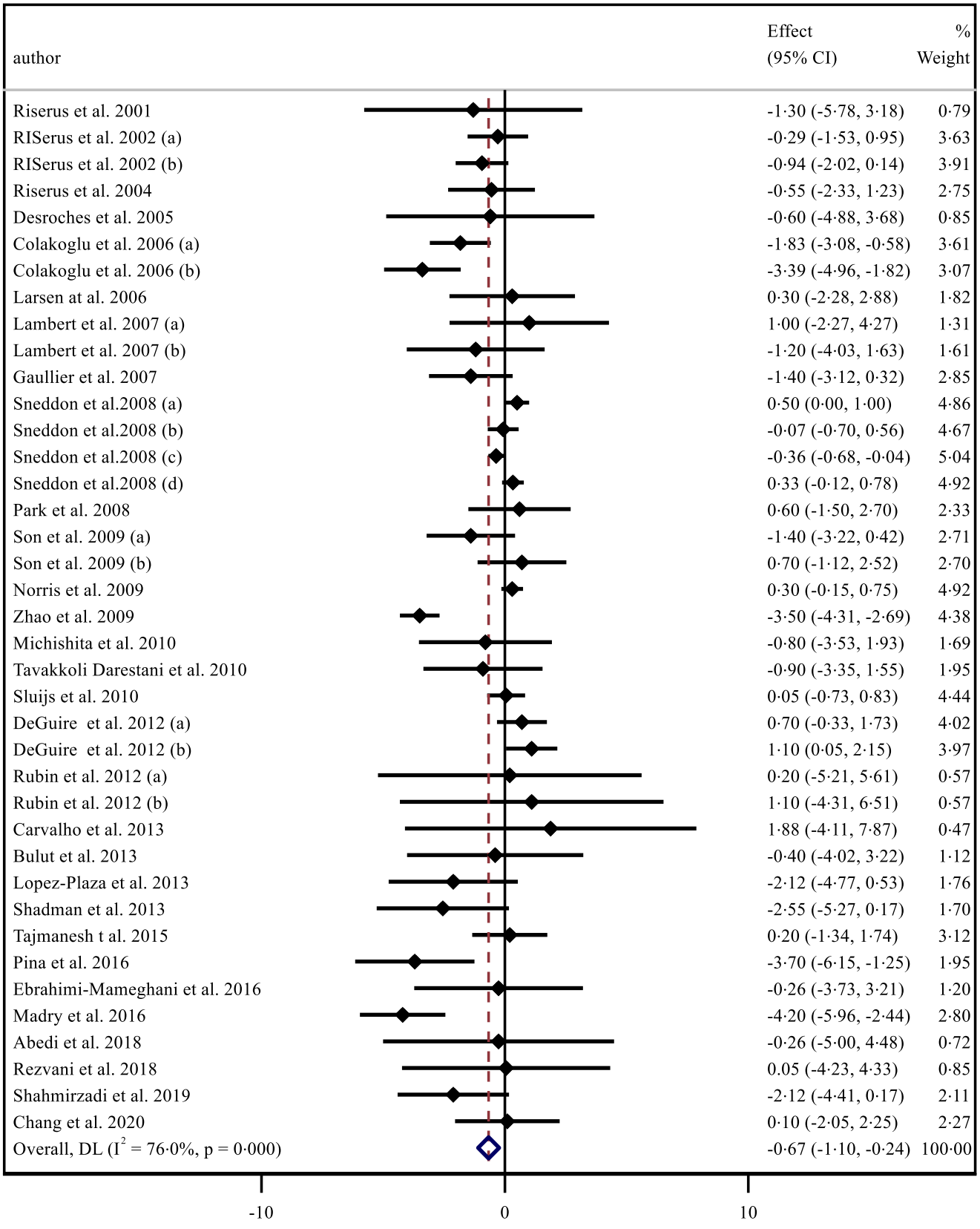

Fig. 2. (Continued)

(d)

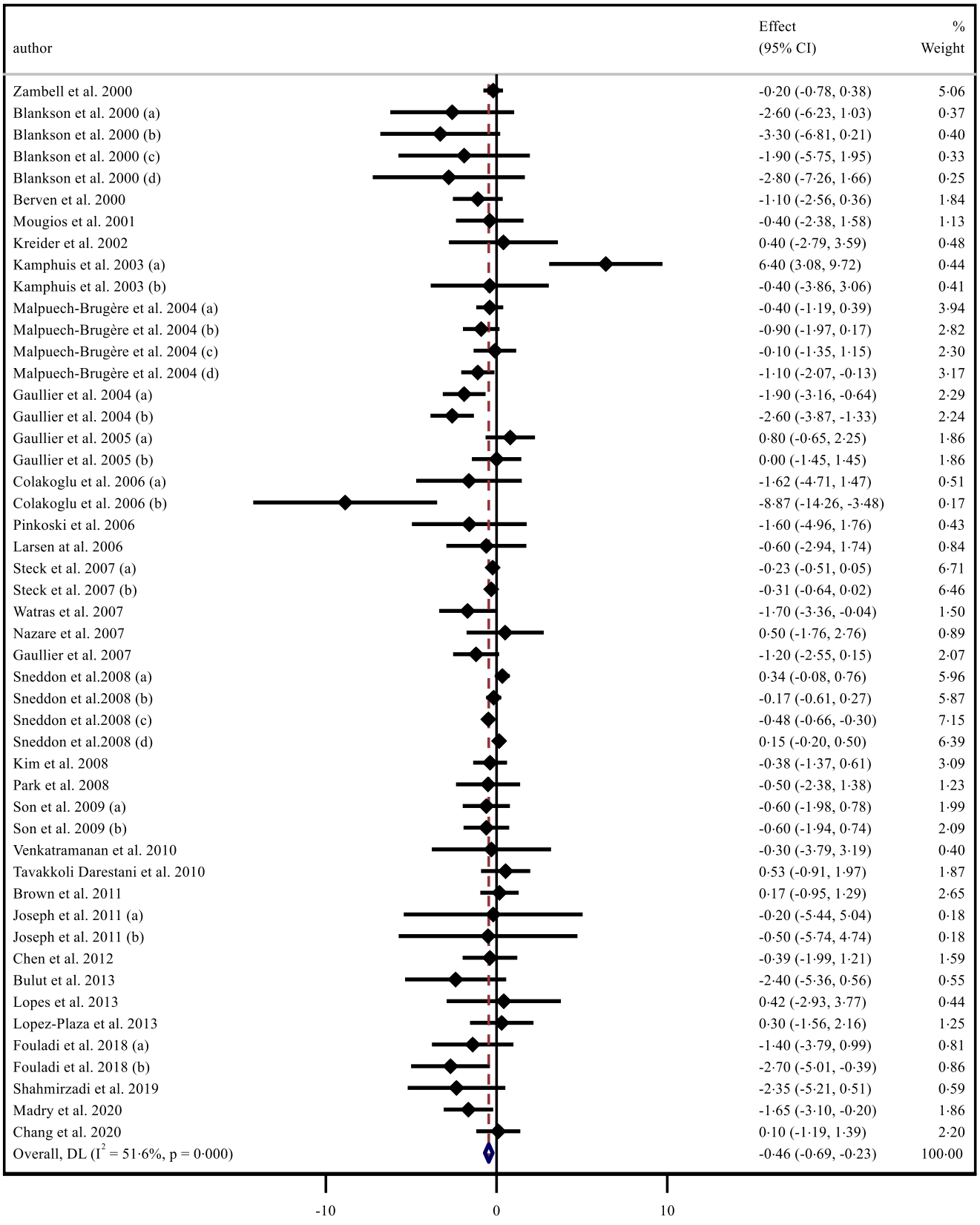

Fig. 2. (Continued)

(e)

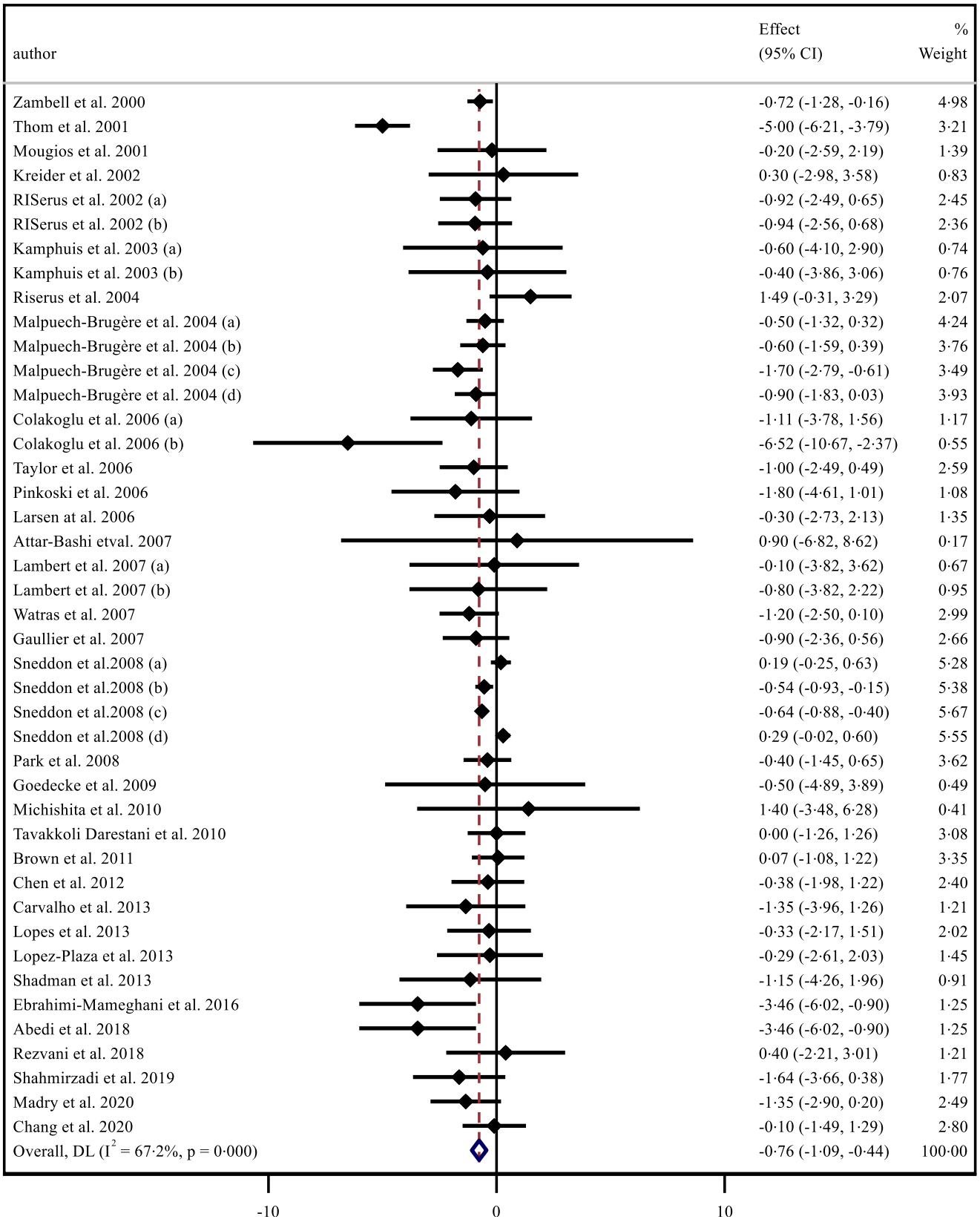

Fig. 2. (Continued)

(f)

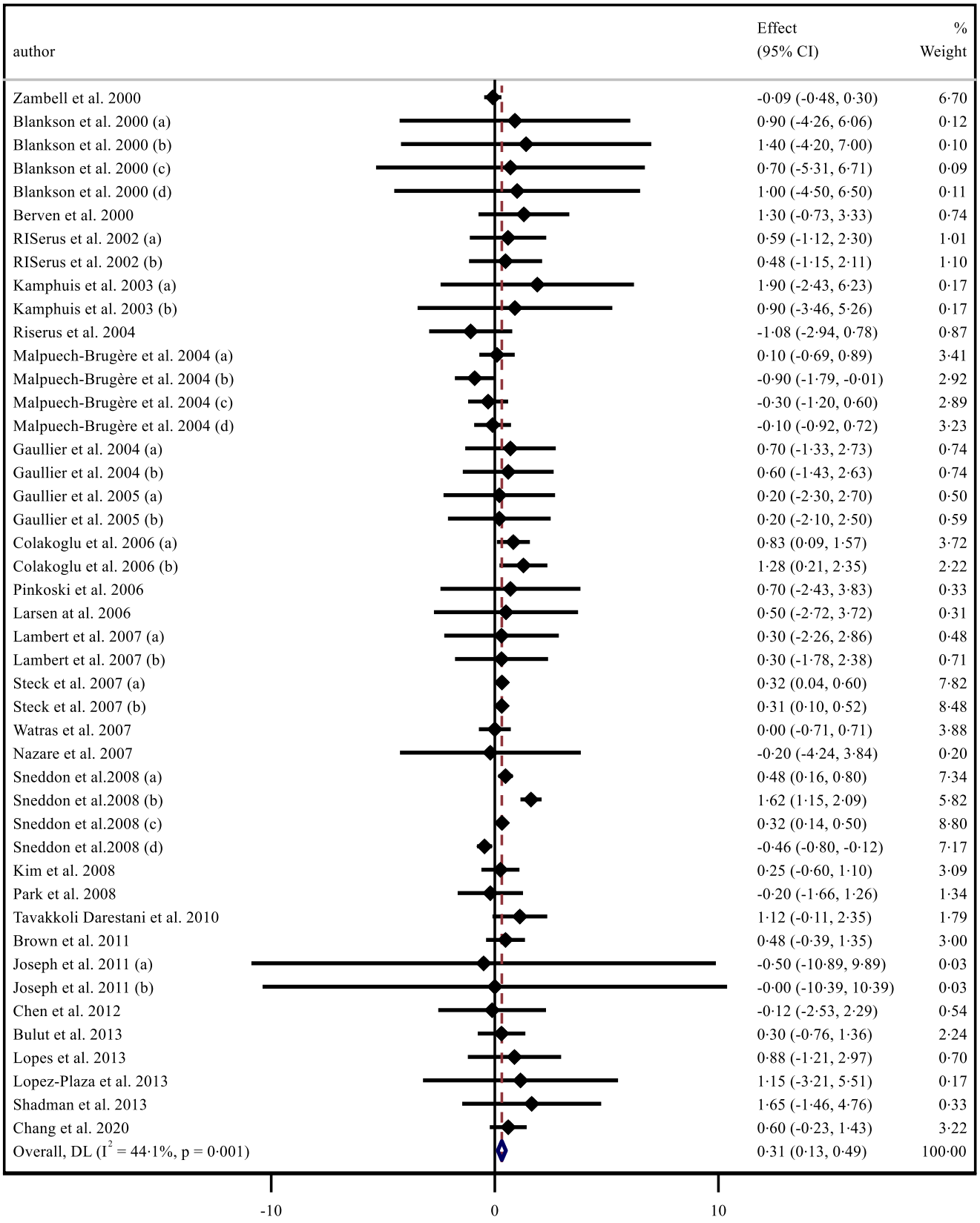

Fig. 2. (Continued)

Table 2. Subgroup analyses of CLA supplementation on anthropometric indices and body composition

					Heterogeneity	
	Number of studies	WMD	95 %CI	P	P heterogeneity	I2
Subgroup analyses of CLA supplementation on body weight (kg).						
Overall effect	83	-0·34	-0·54, −0·15	**<0·001**	<0·001	42·7
Trial duration (week)						
<12	33	-0·45	-0·70, −0·20	**<0·001**	0·927	0·0
≥12	50	-0·33	-0·59, −0·08	**0·010**	<0·001	57·8
Health status						
Healthy	72	-0·28	-0·47, −0·08	**0·005**	0·005	32·6
Unhealthy	11	-0·55	-0·94, −0·16	**<0·001**	0·184	25·1
Supplementation dose (g/d)						
<3	35	-0·21	-0·51, 0·09	0·178	0·001	48·6
≥3	48	-0·46	-0·68, −0·23	**<0·001**	0·081	22·7
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	22	-0·07	-0·39, 0·24	0·642	0·077	31·9
Overweight (25–29·9)	39	-0·57	-0·86, −0·29	**<0·001**	0·841	0·0
Obese (>30)	20	-0·36	-0·71, −0·01	**0·041**	<0·001	66·7
Sex						
Female	15	-0·73	-1·15, −0·32	**<0·001**	0·202	22·7
Both	46	-0·26	-0·43, −0·08	**0·004**	0·738	0·0
Male	22	-0·09	-0·41, 0·21	0·535	<0·001	58·3
Study quality (based on risk of bias)						
Moderate quality	24	-0·60	-1·41, 0·20	0·144	0·995	0·0
Low quality	41	-0·25	-0·48, −0·02	**0·029**	<0·001	54·7
High quality	18	-0·69	-1·05, −0·33	**<0·001**	0·304	12·6
Subgroup analyses of CLA supplementation on BMI (kg/m2).						
Overall effect	77	-0·15	-0·24, −0·06	**0·001**	<0·001	70·6
Trial duration (week)						
<12	30	-0·17	-0·27, −0·07	**0·001**	0·987	0·0
≥12	47	-0·16	-0·27, −0·04	**0·005**	<0·001	80·8
Health status						
Healthy	65	-0·13	-0·22, −0·04	**0·002**	<0·001	60·4
Unhealthy	12	-0·18	-0·37, 0·00	**0·060**	0·001	61·4
Supplementation dose (g/d)						
<3	36	-0·11	-0·23, 0·01	0·088	<0·001	64·7
≥3	41	-0·17	-0·29, −0·06	**0·003**	<0·001	65·1
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	18	-0·02	-0·15, 0·10	0·728	0·126	28·4
Overweight (25–29·9)	36	-0·17	-0·28, −0·06	**0·002**	0·120	21·9
Obese (>30)	21	-0·17	-0·34, −0·00	**0·042**	<0·001	85·6
Sex						
Female	12	-0·56	-0·67, −0·46	**<0·001**	0·522	0·0
Both	44	-0·20	-0·33, −0·06	**0·003**	<0·001	57·2
Male	21	-0·04	-0·13, 0·04	0·354	<0·001	57·1
Study quality (based on risk of bias)						
Moderate quality	22	-0·17	-0·42, 0·07	0·165	0·939	0·0
Low quality	39	-0·07	-0·16, 0·00	0·056	<0·001	59·8
High quality	16	-0·35	-0·62, −0·08	**0·010**	<0·001	75·5
Subgroup analyses of CLA supplementation on WC (cm).						
Overall effect	39	-0·67	-1·10, −0·23	**0·002**	<0·001	76·0
Trial duration (week)						
<12	14	-1·19	-2·20, −0·18	**0·021**	<0·001	70·3
≥12	25	-0·19	-0·53, 0·16	0·288	<0·001	58·3
Health status						
Healthy	32	-0·50	-0·92, −0·08	**0·018**	<0·001	63·8
Unhealthy	7	-0·75	-2·03, 0·51	0·244	<0·001	87·9
Supplementation dose (g/d)						
<3	18	-0·30	-0·79, 0·19	0·231	<0·001	65·7
≥3	21	-0·75	-1·46, −0·05	**0·035**	<0·001	78·3
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	10	-0·46	-1·16, 0·23	0·190	<0·001	76·1
Overweight (25–29·9)	14	-0·49	-1·25, 0·26	0·198	0·058	39·5
Obese (>30)	15	-0·77	-1·54, −0·00	**0·048**	<0·001	84·4
Sex						
Female	11	-1·48	-2·71, −0·24	**0·019**	<0·001	82·4
Both	12	-1·18	-2·25, −0·10	**0·031**	<0·001	75·4
Male	16	0·12	-0·16, 0·40	0·407	0·149	26·1

Table 2. (*Continued*)

	Number of studies	WMD	95 %CI	P	Heterogeneity	
					P heterogeneity	I2
Study quality (based on risk of bias)						
Moderate quality	9	-1·43	-2·79, −0·07	**0·038**	0·004	64·9
Low quality	19	-0·56	-1·17, 0·04	0·067	<0·001	83·9
High quality	11	-0·01	-0·44, 0·40	0·935	0·373	7·4
Subgroup analyses of CLA supplementation on FM (kg).						
Overall effect	49	-0·46	-0·68, −0·23	<**0·001**	<0·001	51·6
Trial duration (week)						
<12	16	-0·45	-0·77, −0·14	**0·004**	0·290	14·3
≥12	33	-0·44	-0·71, −0·16	**0·002**	<0·001	60·7
Health status						
Healthy	46	-0·46	-0·69, −0·23	<**0·001**	<0·001	54·6
Unhealthy	3	-0·34	-0·79, 0·10	0·127	0·810	0·0
Supplementation dose (g/d)						
<3	23	-0·33	-0·63, −0·03	**0·028**	<0·001	59·1
≥3	26	-0·60	-0·93, −0·26	<**0·001**	0·009	44·4
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	11	-0·29	-0·74, 0·16	0·210	0·006	59·1
Overweight (25–29·9)	28	-0·63	-1·09, −0·18	**0·006**	0·002	50·0
Obese (>30)	10	-0·27	-0·50, −0·03	**0·024**	0·102	38·5
Sex						
Female	10	-0·47	-1·06, 0·12	0·122	0·060	44·9
Both	31	-0·67	-1·03, −0·32	<**0·001**	0·001	49·5
Male	8	-0·15	-0·47, 0·15	0·332	0·003	67·3
Study quality (based on risk of bias)						
Moderate quality	10	-0·82	-1·45, −0·20	**0·009**	0·739	0·0
Low quality	28	-0·50	-0·78, −0·22	<**0·001**	<0·001	67·7
High quality	11	-0·09	-0·57, 0·39	0·718	0·788	0·0
Subgroup analyses of CLA supplementation on BFP (%).						
Overall effect	43	-0·76	-1·08, −0·44	<**0·001**	<0·001	67·2
Trial duration (week)						
<12	17	-0·91	-1·35, −0·47	<**0·001**	0·102	31·8
≥12	27	-0·65	-1·06, −0·23	**0·002**	<0·001	73·7
Health status						
Healthy	38	-0·76	-1·10, −0·42	<**0·001**	<0·001	70·7
Unhealthy	5	-0·90	-1·78, −0·02	**0·044**	0·932	0·0
Supplementation dose (g/d)						
<3	25	-0·78	-1·18, −0·38	<**0·001**	<0·001	78·3
≥3	18	-0·72	-1·19, −0·26	**0·002**	0·801	0·0
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	14	-1·08	-1·84, −0·32	**0·005**	<0·001	82·5
Overweight (25–29·9)	17	-0·63	-0·97, −0·29	<**0·001**	0·949	0·0
Obese (>30)	12	-0·80	-1·40, −0·20	**0·009**	<0·001	70·1
Sex						
Female	10	-0·63	-1·22, −0·04	**0·035**	0·204	26·0
Both	24	-1·18	-1·73, −0·62	<**0·001**	<0·001	59·5
Male	9	-0·18	-0·62, 0·26	0·428	<0·001	76·0
Study quality (based on risk of bias)						
Moderate quality	8	-0·56	-1·27, 0·15	0·122	0·951	0·0
Low quality	25	-0·87	-1·28, −0·46	<**0·001**	<0·001	79·6
High quality	10	-0·45	-1·06, 0·14	0·137	0·539	0·0
Subgroup analyses of CLA supplementation on FFM (kg).						
Overall effect	45	0·27	0·09, 0·45	**0·003**	<0·001	47·6
Trial duration (week)						
<12	14	0·07	-0·21, 0·35	0·630	0·094	34·3
≥12	31	0·39	0·17, 0·61	<**0·001**	0·002	48·2
Health status						
Healthy	40	0·30	0·11, 0·49	**0·002**	<0·001	49·8
Unhealthy	5	-0·07	-0·50, 0·36	0·747	0·396	3·2
Supplementation dose (g/d)						
<3	19	0·17	-0·13, 0·49	0·274	<0·001	72·2
≥3	26	0·31	0·17, 0·45	<**0·001**	0·882	0·0
Baseline BMI (kg/m2)						
Normal (18·5–24·9)	9	0·35	0·15, 0·56	**0·001**	0·241	22·8
Overweight (25–29·9)	26	0·15	-0·11, 0·41	0·256	0·933	0·0
Obese (>30)	10	0·20	-0·24, 0·65	0·365	<0·001	84·4
Sex						
Female	8	0·49	0·08, 0·91	**0·019**	0·125	38·2

Table 2. (*Continued*)

	Number of studies	WMD	95 %CI	P	Heterogeneity	
					P heterogeneity	I2
Both	26	0·25	0·10, 0·39	**0·001**	0·956	0·0
Male	11	0·23	-0·18, 0·65	0·273	<0·001	83·1
Study quality (based on risk of bias)						
Moderate quality	8	0·28	-0·39, 0·96	0·408	0·981	0·0
Low quality	29	0·28	0·06, 0·50	**0·011**	<0·001	62·3
High quality	8	0·65	0·08, 1·22	**0·026**	0·987	0·0

CLA, conjugated linoleic acid; WMD, weighted mean differences; WC, waist circumferenc; FM, fat mass; BFP, body fat percentage; FFM, fat-free mass.
Bold value: significant effect (p<0.05).

Table 3. GRADE profile of CLA supplementation for on anthropometric indices and body composition

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Body weight	No serious limitation	No serious limitation	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕⊕ High
BMI	No serious limitation	Serious limitation*	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕◯ Moderate
WC	No serious limitation	Serious limitation*	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕◯ Moderate
FM	No serious limitation	Serious limitation*	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕◯ Moderate
BFP	No serious limitation	Serious limitation*	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕◯ Moderate
FFM	No serious limitation	No serious limitation	No serious limitation	No serious limitation	No serious limitation	⊕⊕⊕⊕ High

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CLA, conjugated linoleic acid; WC, waist circumference; FM, fat mass; BFP, body fat percentage; FFM, fat-free mass.
* There is significant heterogeneity for BMI ($I^2 = 70{\cdot}6$ %), WC ($I^2 = 76{\cdot}0$ %), FM ($I^2 = 51{\cdot}6$ %) and BFP ($I^2 = 67{\cdot}2$ %).

Sensitivity analysis

Sensitivity analysis revealed that no particular RCT significantly influenced outcomes (BM, BMI, WC, FM, BFP and FFM) compared with others in a given data set (pooled effect).

Discussion

This meta-analysis showed that CLA supplementation decreased BM, BMI, WC, FM and BFP and increased FFM. It should be noted that the weight-loss properties of CLA were small and may not reach clinical importance. Based on subgroup analysis, CLA supplementation reduced BM and BMI only in overweight/obese individuals and those consuming more than 3 g/d of CLA. Moreover, CLA supplementation decreased WC in obese participants, dose ≥ 3 g/d and duration < 12 weeks. Regarding body composition indices, CLA supplementation only reduced FM in overweight/obese and in healthy participants. CLA intake as a dietary supplement increased FFM in healthy participants, normal BMI, dose ≥ 3 g/d and duration ≥ 12 weeks. Body composition improvement seems to be only statistically significant in females, not men. Meanwhile, a subgroup based on the quality of studies showed that high-quality studies failed to show the fat loss effects of CLA supplementation. However, high-quality studies showed a small but significant decrease in BM and BMI and an increase in FFM. The time–response model revealed that the optimal duration of CLA supplementation for reducing BFP was around 6 to 7 weeks. Variability in body fat distribution and susceptibility to obesity may explain this study's failure to show a similar dose–response relationship of CLA supplementation with BFP, BM, BMI, WC, FM and FFM.

Numerous mechanisms of action in regulating body anthropometrics and composition following ingestion of CLA have been suggested, resulting from animal and human studies. For example, CLA seems to enhance fat mobilisation and oxidation, reduce the size of adipocytes, regulate lipolysis by adipocytes, increase apoptosis in preadipocytes and adipocytes, reduce adipocyte differentiation through interaction with PPAR-γ, and modulate cytokines-/adipokines-associated mechanisms[108]. Despite promising results in animal studies regarding an inverse relationship between CLA and obesity, evidence in humans supporting the role of CLA in reducing BM and improving repartitioning of body fat and FFM is limited.

As noted, early meta-analytic work by Whigham *et al.* (2007), having focused on the effects of CLA supplementation on body composition in the general adult population, indicated that by pooling effect estimates of eighteen RCT, CLA ingestion promoted moderate alterations in BF[34]. Moreover, Schoeller *et al.* (2009) conducted a meta-analytic study focused on eighteen trials, illustrating a small increase in FFM following CLA treatment[35]. Subsequent meta-analyses have focused on specific population outcomes, such as those who are overweight and/or obese, individuals with metabolic syndrome and postmenopausal women. For instance, Onakpoya *et al.* (2012)

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performed a meta-analysis on a select number of studies (*n* 7) and reported that consuming CLA for more than 6 months resulted in small yet significant reductions in BM, BMI and FM, along with no change in WC in overweight and obese and individuals[32]. Namazi *et al.* study (2019), working with thirteen trials utilising overweight and obese participants, showed that CLA slightly reduced BM, BMI, and FM and slightly increased lean body mass. Yet, these authors similarly reported no influence of CLA on WC measurements[31]. A meta-analysis by Kim *et al.* (2016) conducted on nine RCT in metabolic syndrome patients showed BM and BMI improvements following CLA consumption. However, neither body composition nor WC was considered, thus limiting any direct comparisons between body composition and anthropometric alterations[33]. Lastly, a recent meta-analysis (*n* 8) involving female participants performed by Hamdallah *et al.* (2020) illustrated that consuming CLA for between 6 and 16 weeks had moderate effects on BM, BMI and total body fat, particularly in those classified as overweight/obese and postmenopausal status[109].

In contrast with the meta-analyses mentioned above, the present study's findings analysing an accumulation of seventy RCT demonstrated a small but significant efficacy for CLA supplementation to reduce WC. Moreover, some previous studies revealed that CLA could be a moderate anti-obesity agent without generating clinically relevant effects. This effect owes to CLA's relatively limited reductions in BM (upwards of 5 %) and FM (approaching 8 %), as noted in prior investigations[108,110]. Further, CLA administration might aid in targeted FM reduction (e.g. central abdominal fat pattern) rather than a more evenly distributed reduction of whole-body fat. Such modest effects of CLA in addressing obesity may also be advantageous when the risk of weight gain is heightened at particular times of the year (e.g. social occasions, holidays, etc.).

It should be noted that RCT in this study frequently used various types of vegetable oils as a placebo, including sunflower, olive, soyabean, paraffin, rapeseed and safflower. These oils are rich in MUFA and PUFA, like oleic acid, linoleic acid and α-linolenic acid. Biohydrogenation of linoleic acid into CLA may occur through the bacteria in the digestive tract and via the mediation of vaccenic acid. While it is assumed that these oils have supplementary or complementary effects which can influence human health[111], overall effect size differences between CLA supplementation *v.* placebo may be muted in certain RCT, and care should be taken in future investigations to avoid such confounding variables. It is also worth noting that type of CLA supplement (isomer or mixture) as well varies in RCT where the trans-10 and cis-12 isomers of CLA are suggested to induce catabolic effects, including enhanced lipolysis and fat oxidation, while cis-9 and trans-11 are considered anabolic agent[94].

Furthermore, applying different body composition measurement methodologies in clinical trials (e.g. bioelectrical impedance analysis *v.* dual-energy X-ray absorptiometry *v.* skinfold calipers) may influence the interpretation and accuracy of results. To alleviate such concerns, further clinical trials comparing CLA supplement types and selecting gold standard body composition methodologies should be undertaken.

While rare, a few RCT analysed in this meta-analysis reported complications during or following CLA intervention, amongst which gastrointestinal disorders were the most common. However, such unwanted side effects were not serious in the CLA dosage range reported in RCT, and generally, CLA appears to be safe and well tolerated.

Of other note, CLA taken with other supplements, dietary restriction and increased physical activity may further promote the correction of anthropometric indices and body composition in obese individuals[112]. For example, combining CLA with γ-oryzanol significantly reduced body fat in overweight Korean female participants[82]. Another investigation on well-trained young adults indicated that CLA along with creatine and whey protein consumption enhanced strength gains and lean mass following heavy resistance training[113]. Therefore, CLA intake and other weight-reducing or body composition-modulating treatments may provide additional benefits.

Although there is evidence outlining the small but significant effects of CLA supplementations on body composition, little is known about the impact of gender differences on body composition changes induced following CLA consumption. The gender-specific effect of different dietary interventions is important because it is generally more difficult for females to lose BM[114]. Females are also likely to lose less BM than males during a dietary intervention[114], although they are more likely to adopt and adhere to a diet initially[115]. Although the findings of the gender differences in body composition changes induced by CLA supplementation in humans are limited, our study showed that CLA supplementation may be more beneficial in women than men. Further studies are needed to evaluate the gender-specific effects of CLA supplementation on body composition.

Strengths of this meta-analysis include a relatively large number of RCT containing no observable publication bias, suggesting overestimation of the relationship between CLA and body composition indicators and/or anthropometric measurements were avoided. Moreover, findings from sensitivity analyses support the robustness of the results. Finally, the quality of evidence was moderate to high. Limitations that should be acknowledged include identifying the sources of heterogeneity for BFP needed to be elucidated, and individuals with varying degrees of health status and other characteristics were pooled for overall effect size analyses, thus contributing to a rather heterogeneous sample. Heterogeneity was encountered, perhaps due to various regimens, doses, types, duration, centre settings and populations enrolled. Significant heterogeneity is a serious limitation and should be included because it may significantly undermine the validity of the result. Subgroup analyses were performed to find probable sources of heterogeneity based on the duration of studies, intervention dosage, participants' health condition, obesity status and sex. However, significant heterogeneity in all included variables remains a main limitation in our findings. Moreover, the varying risk of bias in the pool of studies is another main limitation of our analysis. Although we conducted a subgroup analysis based on the quality of studies to minimise the limitation, another drawback is the devices used for body composition analysis in the included studies. Different body composition assessment methods do not always similarly reflect changes in body composition associated

with weight loss. Finally, the present study has not been registered in the PROSPERO; this could also be considered a limitation.

In conclusion, CLA supplementation significantly, albeit mildly, reduces obesity markers, including BM, BMI, WC and FM, while enhancing FFM in an adult population. More specifically, anthropometric measures (BM, BMI and WC) improved following 3 g/d or more of CLA regardless of intervention duration (except for WC, which favoured shorter dosage durations of <12 weeks). In contrast, body composition alterations (FM, FFM and BFP) improved regardless of intervention dosage or duration (except for FFM, which favoured CLA dosages 3 g/d or more and longer duration trials lasting >12 weeks). Certain additional participant characteristics such as being overweight/obese (BM, BMI, WC and FM), noted as having healthy status (FM and FFM) and having normal BMI (FFM) further delineated the significance of overall effect size results. It should be noted that the data from high-quality studies failed to show the body fat-lowering properties of CLA. Also, both overall effects and high-quality studies showed that CLA supplementation resulted in weight loss. However, it should be noted that the weight-loss properties of CLA were small and may not reach clinical importance. It has been mentioned that the minimal clinically important difference is classified as clinically important and is considered the smallest effect required to produce clinically important results[116]. The data for minimal clinically important difference regarding body composition are limited; however, a wide range of studies have confirmed that the risk of metabolic disorders could be decreased whenever they saw reductions of 5 % of initial weight[117,118]. Warkentin *et al.* showed that weight reductions to achieve minimal clinically important difference for most health-related quality-of-life instruments are markedly higher than the conventional threshold of 5 % to 10 %. Future investigations should also determine the best combination of CLA with other anti-obesity agents to promote additional benefits of health-related BM parameters. Finally, to improve the continuity of results, the composition of fatty acids in a placebo should be carefully considered when investigating the effects of CLA in various populations.

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Supplementary material

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