*Public Health Nutrition: 18(11), 2041–2054* doi:10.1017/S1368980014002262

Review Article

# Association of foods enriched in conjugated linoleic acid (CLA) and CLA supplements with lipid profile in human studies: a systematic review and meta-analysis

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Submitted 29 April 2014: Final revision received 29 August 2014: Accepted 1 September 2014: First published online 7 November 2014

## Abstract

*Objective:* The present study aimed to review the association of conjugated linoleic acid (CLA) consumption in two forms, foods enriched in CLA and CLA supplements, with serum lipid profile in human studies.

*Design:* Systematic review and meta-analysis.

*Setting:* Search process was conducted in PubMed, Cochrane Library, Google Scholar, Scopus and Science Direct. Clinical trials that investigated the association of CLA intakes either in the form of supplements or enriched foods with lipid profile in healthy adults were included. All outcomes were recorded as continuous variables, and the effect size was measured by analysis of the mean and standard deviation before and after the intervention for case and control groups.

*Subjects:* Healthy adult population.

*Results:* CLA supplementation was associated with a significant decrease in LDL cholesterol (mean difference = −0·218; 95 % CI −0·358, −0·077; $P$ = 0·002), a non-significant decrease in HDL cholesterol (mean difference = −0·051; 95 % CI −0·188, 0·086; $P$ = 0·468), a non-significant increase in total cholesterol (mean difference = 0·009; 95 % CI −0·128, 0·146; $P$ = 0·896) and a non-significant decrease in TAG (mean difference = −0·065; 95 % CI −0·20, 0·07; $P$ = 0·344). Foods enriched with CLA were associated with significantly decreased LDL cholesterol (mean difference = −0·231; 95 % CI −0·438, −0·024; $P$ = 0·028), non-significantly increased HDL-C (mean difference = 0·075; 95 % CI −0·121, 0·270; $P$ = 0·455), non-significantly decreased total cholesterol (mean difference = −0·158; 95 % CI −0·349, 0·042; $P$ = 0·124) and non-significantly decreased TAG (mean difference = −0·078; 95 % CI −0·274, 0·117; $P$ = 0·433).

*Conclusions:* According to our analysis, consumption of foods enriched with CLA or CLA supplements has favourable effects on LDL cholesterol levels.

**Keywords**
Conjugated linoleic acid
TAG
Total cholesterol
HDL cholesterol
LDL cholesterol

Dyslipidaemia consists of different abnormalities in lipid profile and is one of the main risk factors for several diseases such as CVD, diabetes mellitus, hypertension, stroke and acute pancreatitis[1]. The prevalence of dyslipidaemia depends on socio-economic status and ethnicity[2]. It is increasing in most developed[3] and developing countries owing to unhealthy diets and lifestyle changes[4,5]. The main factors for dyslipidaemia are genetic, diet and lifestyle. According to previous studies, *trans*-fatty acids (TFA) play an important role in lipid profile disorders[6].

There are two sources of dietary TFA: (i) industrial TFA, which are produced technologically during the partial hydrogenation of vegetable oils; and (ii) ruminant TFA, such as vaccenic acid and conjugated linoleic acid (CLA) that are synthesized by rumen bacteria via the metabolism of MUFA and PUFA[7–9]. Clinical studies have reported that dietary

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intake of industrial TFA has a deleterious effect on lipoprotein concentrations; however, ruminant TFA may be less detrimental to blood lipid levels than industrial TFA[10]. Two isomers of CLA are *cis*-9, *trans*-11 (*c*9,*t*11) and *trans*-10, *cis*-12 (*t*10,*c*12)[11–17]. The abundance of these isomers is different in foods and industrial supplements[11–13,18–22].

CLA is produced naturally by the rumen bacteria of ruminants[14,19,23–27] or by bioconversion of vaccenic acid in the ruminant mammary gland[26,28]. Moreover, it can even be produced synthetically by partial hydrogenation of linoleic acid[20,25]. The main dietary sources of CLA are ruminant meats such as beef and lamb, and dairy products such as milk and cheese[11,14–16,19,20,23,24,29]. The mean CLA intake is estimated at 0·3–2·6 g/d and daily intake of CLA through natural sources is 160 mg/d approximately[22,30].

Animal studies have shown that CLA might have various beneficial effects, e.g. prevention of carcinogenesis, decrease body fat, enhancement of lean body mass, empowering the immune system and prevention of diabetes and CVD[14,15,21,31–33]. However, the findings of human studies are controversial[17,25,26,30,34]. These differences may be related to the different forms and doses of CLA, study populations and duration of trials[25].

Some human studies have reported that CLA supplementation had no significant effect on plasma lipid concentrations[18,21]; whereas another study found that CLA supplementation could significantly reduce total cholesterol (TC) and LDL cholesterol (LDL-C) in both genders and HDL cholesterol (HDL-C) only in women[12]. Moreover, there are inconsistent findings on foods enriched in CLA. Some studies have claimed that CLA-rich dairy products significantly increased TC and LDL-C and decreased HDL-C; however, they had no significant effect on TAG concentration[34]. On the other hand, another study indicated that the consumption of skimmed milk enriched with CLA had no significant effect on plasma lipid variables such as TAG, TC, LDL-C and HDL-C levels[22].

Studies on different forms of CLA, i.e. commercial natural products enriched in CLA or supplement forms, showed various findings; therefore it is necessary to summarize the controversial findings. The present study aimed to review the association of CLA consumption in two forms, foods enriched in CLA or CLA supplements, with serum lipid profile in human studies.

## Methods

### *Literature search*

The search was conducted in the following databases: PubMed, Cochrane Library, Google Scholar, Scopus and Science Direct, from 1 June to 23 November 2013. Keywords such as '*trans*-10 *cis*-12-conjugated linoleic acid', '*cis*-9 *trans*-11-conjugated linoleic acid', 'CLA fatty acid', 'CLA', 'conjugated linoleic acid', 'trans fatty acid', 'TFA', 'Triglycerides', 'lipoprotein triglyceride', 'Lipoproteins, HDL', 'Cholesterol, HDL', 'Cholesterol, LDL', 'Lipoproteins, LDL', 'LDL', 'HDL', 'Total cholesterol', 'TG', 'triglyceride', 'triacylglycerol', 'TAG', 'lipid profile', 'low density lipoprotein' and 'high density lipoprotein' were used. Keywords and medical subject heading (MeSH) terms are presented in Table 1. Age, gender and language were not limited during the search. Clinical trials that investigated the association of CLA intakes either in the form of supplements or enriched foods with lipid profile in healthy adults were included. Animal studies, studies on unhealthy individuals, study designs other than clinical trial, studies that investigated the effect of TFA other than CLA and studies that investigated outcomes other than lipid profile were excluded. Inappropriate forms of CLA, such as CLA plus *n*-3 fatty acid, CLA plus amino acid, CLA plus chromium picolinate, CLA plus creatine monohydrate or CLA plus exercise were excluded because these forms did not permit us to isolate the precise effect of CLA. Articles without complete data or placebo and articles on participants with metabolic and genetic disorders were excluded. Title and abstract of papers were screened and relevant papers were selected. Then, full texts of relevant papers were read and findings were re-screened. A flowchart of the literature search is shown in Fig. 1.

**Table 1** Search strategy for PubMed, Cochrane Library, Google Scholar, Scopus and Science Direct databases

| No. | |
|---|---|
| 1 | '*trans*-10, *cis*-12-conjugated linoleic acid' (Supplementary Concept) OR '*cis*-9, *trans*-11-conjugated linoleic acid' (Supplementary Concept) OR 'CLA fatty acid' (Supplementary Concept) OR 'CLA' (tiab) OR 'conjugated linoleic acid' (tiab) OR 'trans fatty acid' (tiab) OR 'TFA' (tiab) |
| 2 | 'Triglycerides' (MeSH) OR 'lipoprotein triglyceride' (tiab) OR 'Lipoproteins, HDL' (MeSH) OR 'Cholesterol, HDL' (MeSH) OR 'Cholesterol, LDL' (MeSH) OR 'Lipoproteins, LDL' (MeSH) OR 'LDL' (tiab) OR 'HDL' (tiab) OR 'Total cholesterol' (tiab) OR 'TG' (tiab) OR 'triglyceride' (tiab) OR 'triacylglycerol' (tiab) OR 'TAG' (tiab) OR 'lipid profile' (tiab) OR 'low density lipoprotein' (tiab) OR 'high density lipoprotein' (tiab) |
| 3 | 1 AND 2 |

Relevant papers were selected according to the title and abstract by three authors (S.-M.D.-R. and M.H.-B., R.K.). Two independent reviewers (S.-M.D.-R. and M.H.-B.) screened papers and read full texts of relevant papers. They assessed full texts for inclusion criteria and extracted data. Statistical analysis was done (M.M.) and cases of disagreement were resolved in consultation with a fourth arbitrating investigator (R.K.). Summaries of the clinical trials that investigated the association of CLA supplementation and foods enriched in CLA with lipid profile in human studies are shown in Tables 2 and 3, respectively.

### *Data extraction*

Data of thirty-three articles that investigated the effect of CLA intake in either supplement form or enriched foods

https://doi.org/10.1017/S1368980014002262 Published online by Cambridge University Press

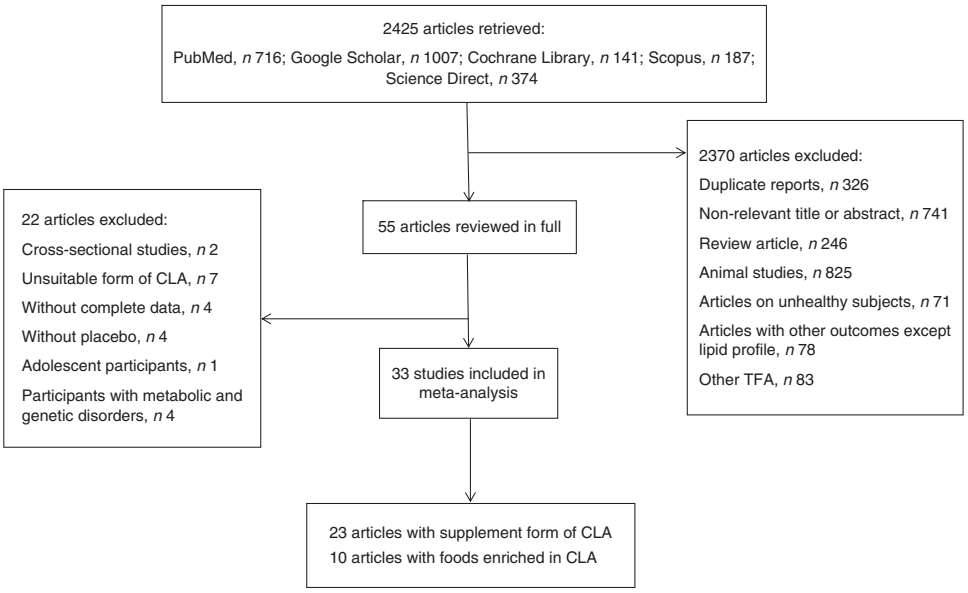


**Fig. 1** Flowchart of the literature search

on lipid profile in healthy adult populations were entered into meta-analysis. Mean and standard deviation for TC, HDL-C, LDL-C and TAG before and after placebo or CLA consumption were extracted. Data from the following studies were not extracted: four studies without complete data for analysis[35–38], four studies without a placebo group[32,39–41], one study that considered special polymorphisms (PPARγ2, Pro12Ala) of healthy adults[42], one study done on adolescents[43] and participants of three studies had signs of metabolic syndrome or borderline hyperlipidaemia[44–46]. Complete information about excluded studies is shown in Fig. 1.

Two structural forms of CLA, i.e. TAG and NEFA, and two isomeric forms, i.e. *cis*-9, *trans*-11 isomer (*c*9,*t*11) and *trans*-10, *cis*-12 isomer (*t*10,*c*12), were used as intervention groups[47,48]. There were different proportions (approximately 50:50 or 80:20; all proportions stated in the paper are by weight) of these isomers and we extracted results of all of them[17,23]. Two studies reported their results stratified by gender or BMI[12,22]. We entered their results into meta-analysis separately.

### *Statistical analysis*

All outcomes were recorded as continuous variables, and the effect size was measured by analysis of the mean and standard deviation before and after the intervention for the case and control groups. Pooled meta-analyses were completed on studies that reported the same outcomes. The $I^2$ statistic was used to test for heterogeneity; if there was significant heterogeneity, the random-effects model was used. $I^2$ values of 25 %, 50 % and 75 % were used as evidence of low, moderate and high heterogeneity, respectively. Sensitivity analysis was done by successively removing a particular study that had the highest impact on the heterogeneity test. Comprehensive Meta-Analysis (CMA) software version 2 was used to carry out the data analysis. $P$ values <0·05 were considered statistically significant. All reported $P$ values resulted from two-sided versions of the respective tests. Potential publication bias was evaluated by Egger's regression test[49]. The trim and fill method was used to assess the potential effect of any publication bias on the meta-analysis results[50].

## Results

### *Conjugated linoleic acid supplementation and LDL cholesterol*

The summary mean difference and 95 % confidence interval for all fifteen clinical trial studies that investigated the effects of CLA supplementation on LDL-C are shown in Fig. 2. Heterogeneity among studies was significant ($I^2 = 52\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}040$). The clinical trial studies[11,13,18,21,29,51–53] contributed most to heterogeneity. In an analysis excluding these studies, CLA supplementation led to a significant decrease in LDL-C level (mean difference = −0·218; 95 % CI −0·358, −0·077; $P = 0{\cdot}002$); the test for heterogeneity was not statistically significant ($I^2 = 0\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}934$). Publication bias was not significant (Egger's test $P$ value = 0·17).

### *Conjugated linoleic acid supplementation and HDL cholesterol*

The summary mean difference and 95 % confidence interval for all seventeen clinical trial studies that investigated the effects of CLA supplementation on HDL-C are shown in Fig. 3. Heterogeneity among studies was significant ($I^2 = 50\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}030$). The

https://doi.org/10.1017/S1368980014002262 Published online by Cambridge University Press

**Table 2** Summary of clinical trials on the association of conjugated linoleic acid (CLA) supplementation and lipid profile in human studies

| Reference | Population | Age (years) | | Duration (weeks) | CLA dose and form (g/d) | Isomers | Placebo dose and form (g/d) | Results |
|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | | | | | |
| Iwata *et al.* (2007)[57] | Sixty males, healthy overweight and obese | 41·5 | 9·6 | 12 | 3·4 g/d, CLA-TAG<br>6·8 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 10·8 g/d, high-linoleic safflower oil | TAG, HDL-C, LDL-C and TC levels did not change significantly among three groups |
| Watras *et al.* (2007)[51] | Forty males and females, healthy overweight | 33 | 7·5 | 24 | 3·2 g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 (39·2:38·5) | 4 g/d, safflower oil | No significant changes in TC, LDL-C, HDL-C or TAG concentrations were observed between groups |
| Gaullier *et al.* (2004)[47] | 180 males and females, healthy overweight | 45·83 | 10·3 | 48 | 3·4 g/d, CLA-TAG<br>3·6 g/d, CLA-NEFA | *c*9,*t*11–*t*10,*c*12 (50:50)<br>*c*9,*t*11–*t*10,*c*12 (50:50) | 4·5 g/d, olive oil | No effect on TC or TAG concentrations; CLA-TAG group had lower HDL-C concentrations and CLA-NEFA group had higher LDL-C concentrations than at baseline of the study |
| Gaullier *et al.* (2005)[32] | 134 males and females, healthy overweight | 46·26 | 9·96 | 96 | 3·4 g/d, CLA-TAG<br>3·4 g/d, CLA-NEFA | *c*9,*t*11–*t*10,*c*12 (50:50)<br>*c*9,*t*11–*t*10,*c*12 (50:50) | 3·4 g/d, placebo | Plasma TC and LDL-C were reduced, whereas HDL-C and TAG were unchanged |
| Blankson *et al.* (2000)[13] | Sixty males and females, healthy overweight and obese | 44·35 | 12·95 | 12 | 1·7 g/d, CLA-TAG<br>3·4 g/d, CLA-TAG<br>5·1 g/d, CLA-TAG<br>6·8 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 9 g/d, olive oil | No significant differences were observed in blood lipids among the groups |
| Steck *et al.* (2007)[33] | Forty-eight males and females, healthy obese | 34·50 | 4·85 | 12 | 3·2 g/d, CLA-TAG<br>6·4 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 8 g/d, safflower oil | HDL-C decreased significantly in placebo and 6·4 g CLA/d groups; other clinical laboratory values did not change across all groups |
| Noone *et al.* (2002)[23] | Fifty-one males and females, healthy normal-weight and overweight | 31·37 | 6·31 | 8 | 3 g/d, CLA-TAG<br>3 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50)<br>*c*9,*t*11–*t*10,*c*12 (80:20) | 3 g/d, linoleic acid | Plasma TAG concentrations were significantly decreased in the 50:50 CLA supplement group but not in the 80:20 CLA or control groups; TC had no changes in all supplementation groups; HDL-C concentrations increased non-significantly in the control group; LDL-C concentrations decreased non-significantly in both CLA supplementation groups |
| Lambert *et al.* (2007)[12] | Sixty-two males and females, healthy regularly exercising non-obese | 32 | 7 | 12 | 3·9 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–other isomers (29·7:30·9:2·9) | 3·9 g/d, high-oleic-acid sunflower oil | TC and LDL-C reduced significantly in both genders; HDL-C decreased significantly only in women; TAG did not change significantly |
| Gaullier *et al.* (2007)[31] | 118 males and females, healthy overweight and obese | 47·25 | 9·6 | 24 | 3·4 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (37·5:38·0) | 4·5 g/d, olive oil | HDL-C decreased slightly in the CLA group; other blood lipids were not significantly changed in either group |
| Berven *et al.* (2000)[14] | Sixty males and females, healthy overweight and obese | 47·05 | 3·9 | 12 | 3·4 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 4·5 g/d, olive oil | No significant changes were observed in blood lipid parameters |
| Mougios *et al.* (2001)[15] | Twenty-four males and females, healthy normal-weight and overweight | 22·2 | 1·5 | 4–8 | (0·7–1·4) g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 (50:50) | 0·7–1·4 g/d, soyabean oil | HDL-C significantly reduced in all groups of CLA; TAG and TC tended to decrease in the CLA group during the low CLA intake but not during the high CLA intake |
| Petridou *et al.* (2003)[16] | Sixteen females, healthy sedentary normal-weight and overweight | 22·30 | 1·80 | 6·5 | 2·1 g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 (50:50) | 2·1 g/d, soyabean oil | CLA supplementation had no significant effect on TAG, TC, HDL-C and TC:HDL-C |
| Kamphuis *et al.* (2003)[19] | Sixty males and females, healthy overweight | 35·1 | 8·35 | 13 | 1·8 g/d, CLA-TAG<br>3·6 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 1·8 g/d, oleic acid<br>3·6 g/d, oleic acid | CLA supplementation did not have any significant effect on plasma TAG concentrations |
| Pfeuffer *et al.* (2011)[21] | Eighty-five males, healthy overweight and obese | 45–68 | – | 4 | 3·4 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 4·5 g/d, safflower oil | CLA decreased TC and LDL-C concentrations not significantly more than safflower oil. HDL-C, fasting and postprandial TAG did not change |

**Table 2** *Continued*

| Reference | Population | Age (years) Mean | Age (years) SD | Duration (weeks) | CLA dose and form (g/d) | Isomers | Placebo dose and form (g/d) | Results |
|---|---|---|---|---|---|---|---|---|
| Colakoglu *et al.* (2006)[29] | Forty-four females, healthy exercising normal-weight | 21·15 | 1·85 | 6 | 3·6 g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 | Control | CLA supplementation with or without exercise did not change serum lipid profile (TC, LDL-C, HDL-C, TAG) |
| Benito *et al.* (2001)[58] | Seventeen females, healthy normal-weight | 28·15 | 6·2 | 9 | 3·9 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–*c*11, *t*13–*t*8,*c*10–*cc*–*tt* (11·4:14·7:15·3:10·8: 6·74:5·99) | 3·9 g/d, high-linoleic sunflower oil | CLA supplementation did not change the levels of plasma TC, LDL-C, HDL-C and TAG |
| Tavakoli-Darestani *et al.*[59] | Seventy-six females, healthy menopausal overweight women | 55 | 6·65 | 12 | 3·2 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 4 g/d, high-oleic-acid sunflower oil | CLA supplementation had no significant effect on TC, TAG, LDL-C and HDL-C |
| Risérus *et al.* (2004)[11] | Twenty-five males, healthy overweight and obese | 55 | 5·75 | 12 | 3 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–*c*9, *c*11–*c*10,*c*12–*t*9, *t*11 + *t*10,*t*12 (83·3:7·3:0·46:0·2:1·4) | 3 g/d, olive oil | CLA had no significant effects on lipoprotein or TAG concentrations compared with placebo |
| Sluijs *et al.* (2010)[18] | 401 males and females, healthy overweight and obese | 58·4 | 0·45 | 24 | 3·1 g/d, CLA | *c*9,*t*11–*t*10,*c*12 (80:20) | 4 g/d, 80 % palm oil + 20 % soyabean oil | There was no effect of CLA supplementation on concentrations of lipids such as TAG, LDL-C, HDL-C and TC |
| Whigham *et al.* (2004)[20] | Sixty-four males and females, healthy overweight and obese | 42·3 | 5·35 | 24 | 6 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–*tt* (37·3:37·6:1·3) | 7·5 g/d, high-oleic acid sunflower oil | CLA increased TAG. Other lipids did not change |
| Song *et al.* (2005)[54] | Twenty-eight males and females, healthy normal-weight | 31·35 | 7·01 | 12 | 3 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50) | 3 g/d, high-oleic-acid sunflower oil | CLA supplementation did not change TC level. HDL-C level decreased significantly after 12 weeks of supplementation. LDL-C did not alter. Plasma TAG levels were increased in the two groups, however; significantly in the CLA group |
| Taylor *et al.* (2006)[52] | Forty males, healthy overweight and obese | 46 | 7 | 12 | 4·5 g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 (35:36) *c*9,*c*11–*c*10,*c*12 (1–2 %) *t*9,*t*11–*t*10,*t*11 (1·5 %) *t*8,*c*10–*c*11,*t*13 (<1 %) | 4·5 g/d, olive oil | There was no change in TC, TAG, LDL-C and HDL-C |
| Smedman and Vessby (2001)[53] | Fifty-three males and females, healthy | 45·2 | 11·65 | 12 | 4·2 g/d, CLA-mix | *c*9,*t*11–*t*10,*c*12 (50:50) | 4·2 g/d, olive oil | TC, LDL-C, HDL-C increased and TAG decreased |
| Kim (2008)[48] | Fifty-one females, healthy overweight Korean women | 28·24 | 20·39 | 12 | 2·25 g/d, CLA-NEFA 2·25 g/d, CLA-TAG | *c*9,*t*11-CLA–*t*10, *c*12-CLA–*c*9,*c*11-CLA–*t*9, *t*11-CLA (37·95:38·84:0·96:1·35) *c*9,*t*11–CLA–*t*10, *c*12–CLA–*c*9,*c*11-CLA–*t*9,*t*11-CLA (37·83:38·55:0·98:1·86) | 3 g/d, olive oil | No significant changes were observed within and between treatment groups in blood lipid parameters (TAG, TC, LDL-C or HDL-C) |
| Tholstrup *et al.* (2008)[35] | Seventy-five females, healthy postmenopausal women | 60·16 | 4·46 | 16 | 4·6 g/d, CLA-mix 5·1 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–other CLA (41·17:39·90:1·79) *c*9,*t*11–*t*10,*c*12–other CLA (85·03:7·11:0·47) | 5·5 g/d, olive oil | CLA mixture decreased HDL-C, increased TC: HDL-C compared with other groups and increased TAG levels compared with control. Plasma LDL-C concentrations did not differ among the three groups |

**Table 2** *Continued*

| Reference | Population | Age (years) | | Duration (weeks) | CLA dose and form (g/d) | Isomers | Placebo dose and form (g/d) | Results |
|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | | | | | |
| Sahin *et al.* (2008)[39] | Twenty females, healthy overweight or obese premenopausal | 22–48 (range) | | 8 | 1·8 g/d, CLA-NEFA | *c*9,*t*11–*t*10,*c*12 (80–84:37–42) | Without placebo | CLA reduced TC, TAG and LDL-C significantly and non-significantly increased HDL-C level |
| Tricon *et al.* (2004)[41] | Forty-nine males, healthy normal-weight | 30·95 | 1·7 | 8 | 0·59, 1·19, 2·38 g/d, CLA-TAG<br>0·63, 1·26, 2·52 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (79·3:7·8)<br>*c*9,*t*11–*t*10,*c*12 (10·6:84·1) | Without placebo | CLA supplementation had significant effects on TC, LDL-C and no effect on HDL-C in all isomers and doses |
| von Loeffelholz *et al.* (2003)[40] | Fourteen males and females, healthy bodybuilders | 26 | 4 | 24 | 3·78 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12–*t*8, *c*10–*c*11,*t*13–*cc*–*tt* (8·3:7·9:6·0:7·1:4·7:17·7) | Without placebo | CLA supplementation significantly increased LDL-C and TC concentration only in the beginners, not in the advanced athletes, and had no significant effect on TAG or HDL-C levels in either intervention group |
| Albers *et al.* (2003)[36] | Seventy-one men, healthy overweight or obese | 52·33 | 9 | 12 | 1·7 g/d, CLA-NEFA<br>1·6 g/d, CLA-TAG | *c*9,*t*11–*t*10,*c*12 (50:50)<br>*c*9,*t*11–*t*10,*c*12 (80:20) | Sunflower oil fatty acids | CLA supplementation did not affect fasting serum lipids |

clinical trial studies[11,13,18,21,29,51–53] contributed most to heterogeneity. In an analysis excluding these studies, CLA supplementation led to a slight and non-significant decrease in HDL-C level (mean difference = −0·051; 95 % CI −0·188, 0·086; $P = 0·468$); the test for heterogeneity was not statistically significant ($I^2 = 0$ %; $P_{\text{heterogeneity}} = 0·649$). Publication bias was not significant (Egger's test $P$ value = 0·94).

### *Conjugated linoleic acid supplementation and total cholesterol*

The summary mean difference and 95 % confidence interval for all seventeen clinical trial studies that investigated the effects of CLA supplementation on TC are shown in Fig. 4. Heterogeneity among studies was significant ($I^2 = 55$ %; $P_{\text{heterogeneity}} = 0·034$). The clinical trial studies[11,13,18,21,29,51–54] contributed most to heterogeneity. In an analysis excluding these studies, CLA supplementation led to a slight and non-significant increase in TC level (mean difference = 0·009; 95 % CI −0·128, 0·146; $P = 0·896$); the test for heterogeneity was not statistically significant ($I^2 = 0$ %; $P_{\text{heterogeneity}} = 0·956$). Since publication bias existed, we tried to evaluate the effect of publication bias by the trim and fill method. After eliminating the effect of publication bias, the combined mean difference was 0·0089 (95 % CI −0·125, 0·152), which remained consistent with previous results.

### *Conjugated linoleic acid supplementation and TAG*

The summary mean difference and 95 % confidence interval for all eighteen clinical trial studies that investigated the effects of CLA supplementation on TAG are shown in Fig. 5. Heterogeneity among studies was significant ($I^2 = 54$ %; $P_{\text{heterogeneity}} = 0·041$). The clinical trial studies[11,13,18,21,29,51–53] contributed most to heterogeneity. In an analysis excluding these studies, CLA supplementation led to a non-significant decrease in TAG level (mean difference = −0·065; 95 % CI −0·200, 0·070; $P = 0·344$) and the test for heterogeneity was not statistically significant ($I^2 = 0$ %; $P_{\text{heterogeneity}} = 0·954$). Publication bias was not significant (Egger's test $P$ value = 0·08).

### *Foods enriched in conjugated linoleic acid and LDL cholesterol*

The summary mean difference and 95 % confidence interval for all ten clinical trial studies that investigated the effects of foods enriched in CLA on LDL-C are shown in Fig. 6. Heterogeneity among studies was significant ($I^2 = 51$ %; $P_{\text{heterogeneity}} = 0·023$). One clinical trial study[26] contributed most to heterogeneity. In an analysis excluding that study, we found that foods enriched in CLA led to a significant decrease in LDL-C level (mean difference = −0·231; 95 % CI −0·438, −0·024; $P = 0·028$); the test for heterogeneity was not statistically significant ($I^2 = 1$ %; $P_{\text{heterogeneity}} = 0·965$). Publication bias was not significant (Egger's test $P$ value = 0·18).

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**Table 3** Summary of clinical trials on the association of enriched foods with conjugated linoleic acid (CLA) and lipid profile in human studies

| Reference | Population | Age (years) | | Duration (weeks) | CLA form and dose | Isomers | Placebo form and dose | Results |
|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | | | | | |
| Desroches *et al.* (2005)[27] | Sixteen males, healthy overweight and obese | 36·6 | 12·4 | 8 | Butter–CLA (4·22 g CLA/100 g fat) | *c*9,*t*11–other isomers (80:20) | Butter (0·38 g CLA/100 g fat) | Butter–CLA diet reduced TC significantly more than control. LDL-C, HDL-C and TAG levels did not change significantly between the two groups |
| Tricon *et al.* (2006)[55] | Thirty-two males, healthy | 45·5 | 8·7 | 6 | (Butter + cheese + milk)–CLA (1·421 g CLA/d) | *c*9,*t*11 | Butter + cheese + milk (0·151 g CLA/d) | Dairy products enriched with CLA did not significantly affect TAG, TC, LDL-C and HDL-C. They slightly increased LDL-C: HDL-C |
| Wanders *et al.* (2010)[34] | Sixty-one males and females, healthy normal weight | 30·9 | 13·7 | 9 | (Margarine + yoghurt drinks)–CLA (73·7 (SD 0·6) g CLA/100 g fat) | *c*9,*t*11–*t*10,*c*12 (80:20) | (Margarine + yoghurt drinks)–oleic acid | TAG level did not change, LDL-C and TC: HDL-C increased, whereas HDL-C decreased in CLA group compared to control |
| Brown *et al.* (2011)[26] | Eighteen females, healthy normal-weight and overweight | 20–40 (range) | | 8 | Beef + dairy (ice cream, cheese, butter)–CLA (1·17 g CLA/d) | *c*9,*t*11–other isomers (87·5:12·5) | Beef + dairy (ice cream, cheese, butter) (0·35 g CLA/d) | No significant differences were observed in TC, TAG, LDL-C, HDL-C levels between treatment groups |
| Sofi *et al.* (2010)[24] | Ten males and females, healthy normal-weight and over weight | 51·5 | | 20 | Pecorino cheese (1·56 g CLA/100 g lipid) | *c*9,*t*11 | Placebo cheese (0·19 g CLA/100 g lipid) | TC, TAG, LDL-C and HDL-C did not change during either intervention phases |
| Raff *et al.* (2008)[30] | Thirty-eight males, healthy normal-weight | 25·9 | 3·9 | 5 | Butter–CLA (4·6 g/d CLA) | c9,*t*11–*t*10,*c*12 (39·4:38·5) | Butter (0·3 g CLA/d) | TC, TAG, LDL-C, HDL-C and TC:HDL-C did not differ during either intervention phase |
| Chen *et al.* (2012)[25] | Eighty males and females, healthy overweight and obese | 32·8 | 0·8 | 12 | Milk–CLA (1·7 g/d CLA) | *c*9,*t*11–*t*10,*c*12 (50:50) | Milk | CLA treatment increased levels of TC, TAG and LDL-C, decreased HDL-C concentration. None of these changes were significant |
| Naumann *et al.* (2006)[17] | Ninety-two males and females, healthy overweight and obese with LDL phenotype B | 52·33 | 7·66 | 13 | Drinkable dairy product–CLA (3 g CLA/d) Drinkable dairy product –CLA (3 g CLA/d) | *c*9,*t*11–*t*10,*c*12 (>80: <5) *t*10,*c*12–*c*9,*t*11 (>80: <5) | Drinkable dairy product (3 g high-oleic-acid sunflower oil/d) | LDL-C, HDL-C, TAG, TC:HDL-C, LDL-C: HDL-C did not change in CLA-enriched groups |
| Laso *et al.* (2007)[22] | Sixty males and females, healthy overweight and obese | 53·85 | 7·73 | 12 | Skimmed milk–CLA (3 g CLA/d) | *c*9,*t*11–*t*10,*c*12 | Skimmed milk | Plasma TAG, TC and LDL-C increased slightly in all CLA groups, however these changes were not significant |
| Nazare *et al.* (2007)[56] | Forty-four males and females, healthy normal-weight and overweight | 28·9 | 1·14 | 14 | Yoghurt–CLA (3·76 g CLA/d) | *c*9,*t*11–*t*10,*c*12–*tt* (35:35: <1) | Yoghurt | CLA-enriched yoghurt did not alter any of the TAG, TC and HDL-C concentrations |

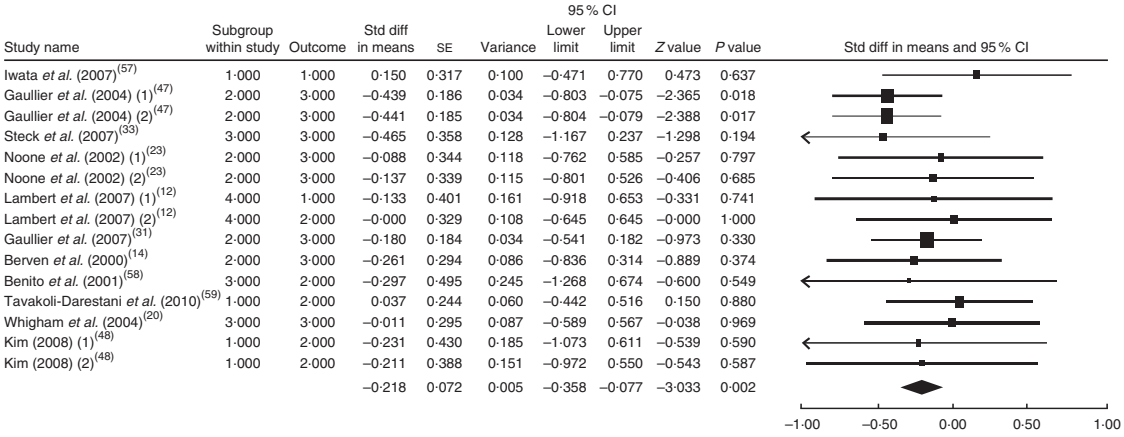


**Fig. 2** Meta-analysis of the effect of conjugated linoleic acid supplementation on LDL cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

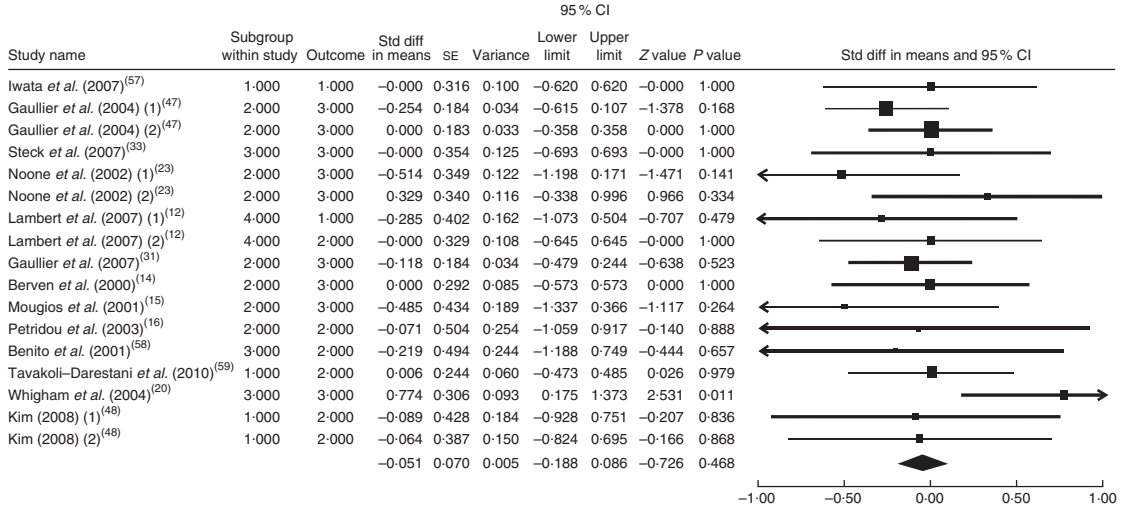


**Fig. 3** Meta-analysis of the effect of conjugated linoleic acid supplementation on HDL cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

### *Foods enriched in conjugated linoleic acid and HDL cholesterol*

The summary mean difference and 95 % confidence interval for all eleven clinical trial studies that investigated the effects of foods enriched in CLA on HDL-C are shown in Fig. 7. Heterogeneity among studies was significant ($I^2 = 50\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}045$). One clinical trial study[26] contributed most to heterogeneity. In an analysis excluding that study, foods enriched in CLA led to a non-significant increase in HDL-C level (mean difference = 0·075; 95 % CI −0·121, 0·270; $P = 0{\cdot}455$) and the test for heterogeneity was not statistically significant ($I^2 = 19\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}262$). Publication bias was not significant (Egger's test $P$ value = 0·07).

### *Foods enriched in conjugated linoleic acid and total cholesterol*

The summary mean difference and 95 % confidence interval for all eleven clinical trial studies that investigated the effects of foods enriched in CLA on TC are shown in Fig. 8. Heterogeneity among studies was significant ($I^2 = 58\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}018$). One clinical trial study[26] contributed most to heterogeneity. In an analysis excluding that study, we found that foods enriched in CLA led to a non-significant decrease in TC level (mean difference = −0·158; 95 % CI −0·349, 0·042; $P = 0{\cdot}124$) and the test for heterogeneity was not statistically significant ($I^2 = 10\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}345$). Publication bias was not significant (Egger's test $P$ value = 0·84).

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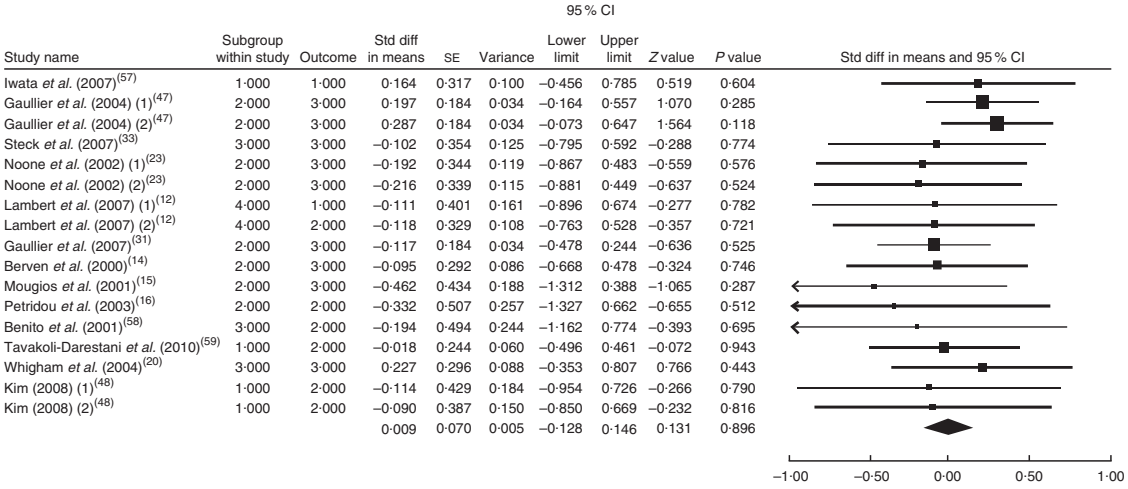


**Fig. 4** Meta-analysis of the effect of conjugated linoleic acid supplementation on total cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

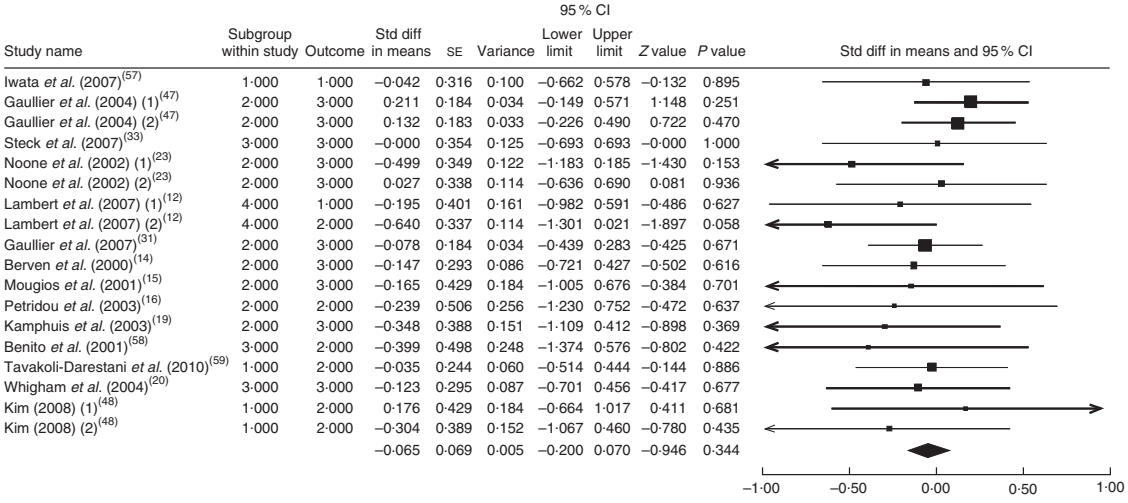


**Fig. 5** Meta-analysis of the effect of conjugated linoleic acid supplementation on TAG in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

### *Foods enriched in conjugated linoleic acid and TAG*

The summary mean difference and 95 % confidence interval for all eleven clinical trial studies that investigated the effects of foods enriched in CLA on TAG are shown in Fig. 9. Heterogeneity among studies was significant ($I^2 = 56\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}033$). One clinical trial study[26] contributed most to heterogeneity. In an analysis excluding that study, we documented that foods enriched in CLA led to a non-significant decrease in TAG level (mean difference = −0·078; 95 % CI −0·274, 0·117; $P = 0{\cdot}433$); the test for heterogeneity was not statistically significant ($I^2 = 6\,\%$; $P_{\text{heterogeneity}} = 0{\cdot}384$). Publication bias was not significant (Egger's test $P$ value = 0·71).

### *Sensitivity analyses*

To identify the source of the heterogeneity between studies, we performed sensitivity analyses by including and excluding some studies. Sensitivity analyses were done sequentially for all of the lipids and all of the studies. In a sensitivity analysis excluding one study at a time, we consistently found statistically the same results. Ranges of summary mean differences were (−0·242, −0·178), (−0·097, −0·016), (0·001, 0·017) and (−0·110, −0·040) for

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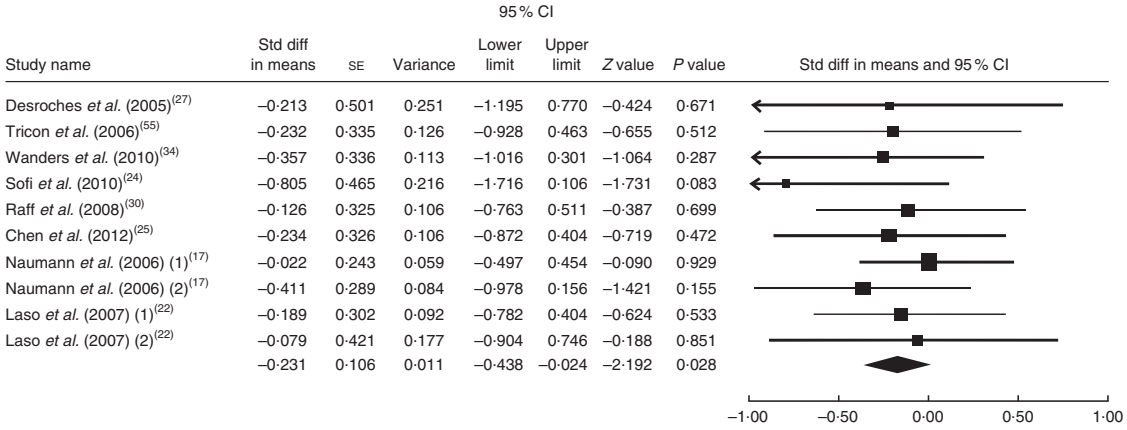


**Fig. 6** Meta-analysis of the effect of natural foods enriched with conjugated linoleic acid on LDL cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

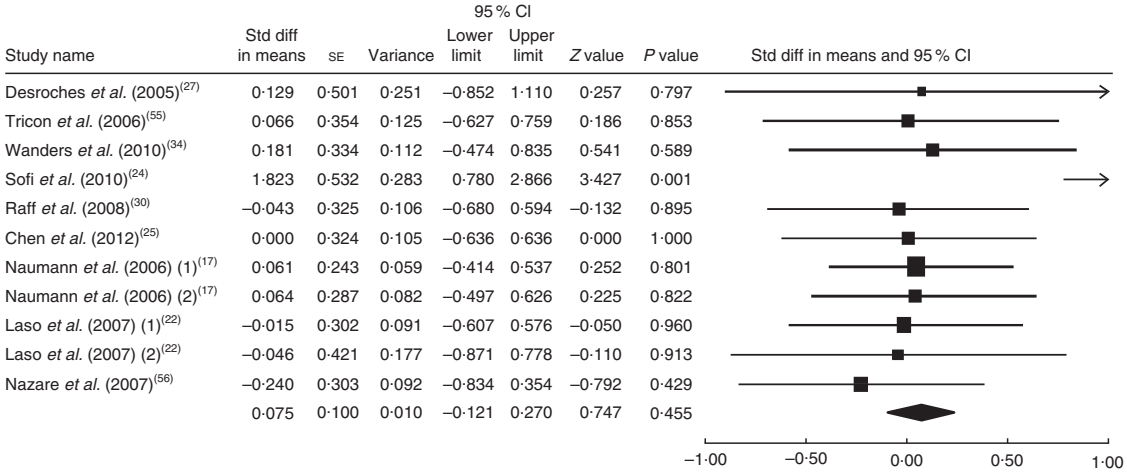


**Fig. 7** Meta-analysis of the effect of natural foods enriched with conjugated linoleic acid on HDL cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

the effect of CLA supplementation on LDL-C, HDL-C, TC and TAG, respectively. Also the sensitivity analysis results based on the effect of enriched foods with CLA for different lipids according to summary mean differences were (–0·280, – 0·200), (–0·082, – 0·641), (–0·460, – 0·222) and (–0·156, – 0·047) for LDL-C, HDL-C, TC and TAG, respectively.

## Discussion

The present meta-analysis is the first quantitative review of thirty-three randomized controlled clinical studies investigating the effect of CLA supplements and foods enriched in CLA on serum lipids separately. Our meta-analysis showed that intake of foods enriched in CLA decreased LDL-C levels significantly, decreased TC and TAG concentrations non-significantly and increased HDL-C levels non-significantly. CLA supplements decreased LDL-C, HDL-C and TAG levels and increased TC level; however, only the effect on LDL-C level was statistically significant. According to our analysis, consumption of foods enriched in CLA and CLA supplements has favourable effects on LDL-C level.

Some studies, in agreement with our results, showed that a mixture of CLA isomers decreased LDL-C level significantly in healthy adults[12,34,39,41]. Noone *et al.*[23] observed that the daily intake of 3 g CLA supplement (50:50 and 80:20) decreased LDL-C levels non-significantly in CLA groups. However, von Loeffelholz[40] claimed that CLA supplementation for 6 months increased LDL-C and

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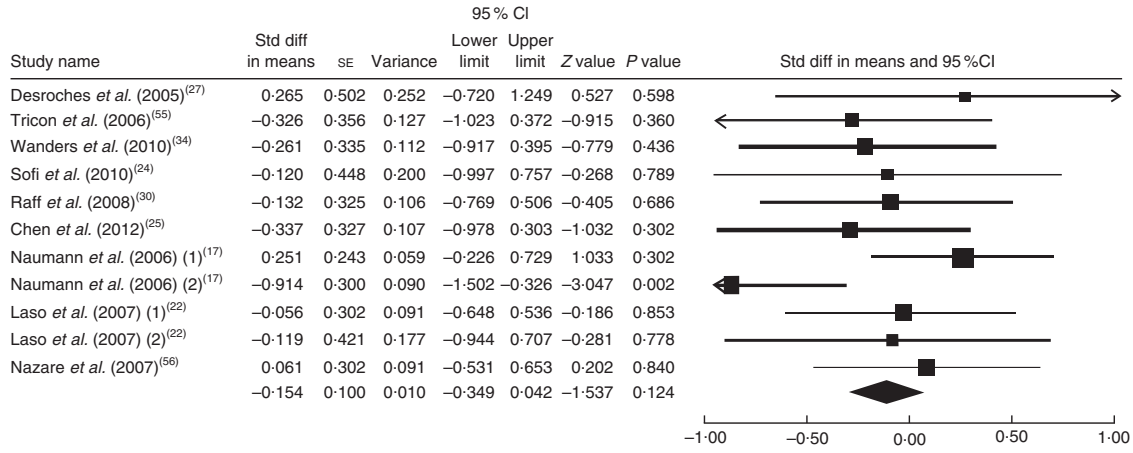


**Fig. 8** Meta-analysis of the effect of natural foods enriched with conjugated linoleic acid on total cholesterol in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

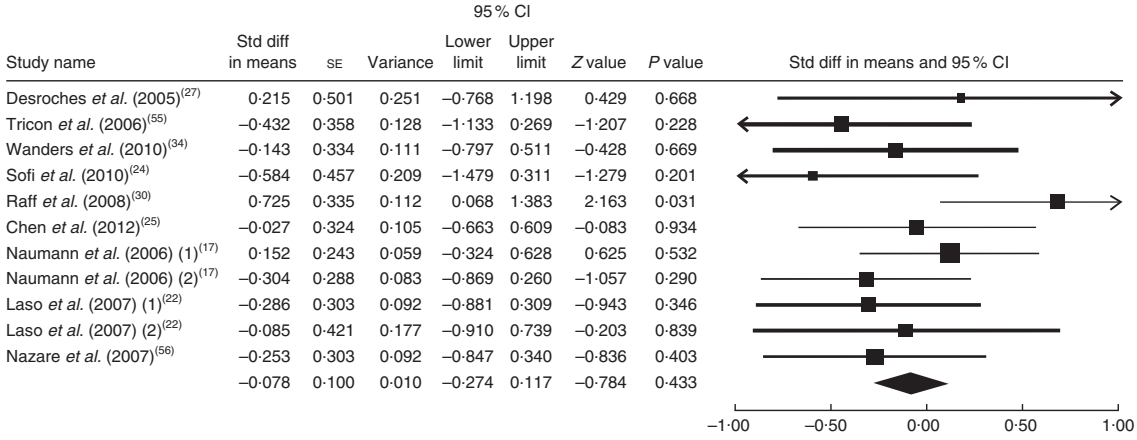


**Fig. 9** Meta-analysis of the effect of natural foods enriched with conjugated linoleic acid on TAG in published clinical trials. The study-specific standardized difference (Std diff) in means and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the black diamond presents the pooled standardized difference in means and its width represents the pooled 95 % CI

TC concentrations significantly. Some studies showed that CLA supplementation[47,53] or foods enriched in CLA[22,25] led to a slight, non-significant increase in LDL-C level.

We found that TC level decreased and HDL-C level increased non-significantly after intake of foods enriched in CLA and our findings are in accordance with other studies[17,22,27]. According to our meta-analysis, CLA supplementation led to an adverse non-significant effect on TC or HDL-C level, which is in agreement with some studies on CLA supplements[12,15,31,33,35,40,47,53,54] and is in disagreement with other studies[21,39,41].

Our analysis showed that TAG level decreased non-significantly after intake of either CLA supplements or CLA-enriched foods, similar to previous studies on either enriched foods or CLA supplements. Some findings suggested that CLA had no significant effect on TAG concentration[11–19,21,22,24–27,29–34,36,40,47–53,55–59].

However, Chen *et al.*[25] reported that TAG level increased in individuals who consumed foods enriched in CLA. Some trials reported a significant increase in TAG concentration after consuming CLA supplements[20,35,41,54].

The proportion of CLA isomers and their dosage may be important to determine the effect of CLA on lipid profile. Noone *et al.*[23] showed that CLA supplementation with the 50:50 proportions of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers caused a significant reduction in plasma TAG concentrations; however, this effect disappeared with the 80:20 proportion of CLA isomers. Mougios *et al.*[15] investigated the effect of CLA capsules that included 0·7–1·4 g CLA mixture for 4–8 weeks. They showed that low-dose CLA intake decreased TAG and TC and high CLA intake did not change TAG and TC levels.

Findings from human studies that investigated the effects of CLA mixtures or *cis*-9, *trans*-11 and *trans*-10,

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*cis*-12 CLA isomers separately on lipid profile in either enriched foods or supplement forms are controversial. This may be related to differences in the CLA forms (TAG or NEFA), doses of CLA (0·59–6·8 g in supplement forms and 1·17–73·7 g in enriched foods), variation in isomers and their proportions, duration of studies (from 4 weeks to 2 years in supplement forms and from 5 weeks to 5 months in enriched foods), variation in subjects' body weight and different control groups. As placebo, most of the studies used olive oil or oleic acid extracts; some of them used safflower oil, sunflower oil or linoleic acid extracts; and a few studies used soyabean oil solely or in combination with palm oil. Studies enriched different kinds of dairy products such as cheese, milk, yoghurt, butter and ice cream with CLA. Furthermore, the CLA content of milk and other dairy products ranged from 0·34 % to 1·07 % of total fat, which is influenced by the diet of cows. In European countries, where cows are traditionally pasture grazed, their milk contains higher CLA levels than in countries where cows are mainly fed corn, such as the USA. These can lead to different results in studies[60].

The mechanism of lowering cholesterol level by CLA remains to be determined[28]. It was suggested that CLA could decrease LDL-C particles by forbidding the secretion of apo B or by increasing the clearance rate of circulating LDL-C through increasing activity of the LDL receptor[61,62]. According to evidence, dietary CLA enhances the fecal excretion of total neutral sterols[63] and inhibits cholesterol absorption through down-regulation of intestinal acyl-CoA cholesterol acyltransferase[28]. CLA can decrease TAG level by inhibiting the expression and activity of hepatic stearoyl-CoA desaturase. This enzyme is involved in the desaturation of substrate for the synthesis of TAG[64].

According to our meta-analysis, foods enriched in CLA and CLA supplements have beneficial effect on LDL-C concentration. CLA did not affect other lipids in the profile. Foods enriched in CLA increased HDL-C and tended to decrease TC non-significantly. Nutrients such as calcium, potassium, vitamin D and vitamin B, or bioactive peptides in dairy products, have been shown to be associated with beneficial outcomes. These nutrients and CLA can influence the lipid profile synergistically[60].

There are some concerns about the potential safety of CLA for human subjects. Studies have shown that supplementation with CLA or *trans*-10, *cis*-12 isomer could induce insulin resistance, lipodystrophy in animals, fatty liver, C-reactive protein enhancement and undesirable changes in lipid profile in man[65,66].

There is no consensus on the recommended dosage of CLA; however, according to evidence, 3 g/d seems to be most desirable. Consumption of CLA supplements is not recommended in pregnancy[67,68].

## Conclusion

The present review showed that both CLA supplements and foods enriched in CLA caused a significant reduction in LDL-C level. Foods enriched in CLA, in comparison with CLA supplementation, had a beneficial effect on the whole lipid profile although only the effect on LDL-C level was statistically significant.

## Acknowledgements

*Financial support:* This research received no specific grant from any funding agency in the public, private or not-for-profit sectors. *Conflict of interest:* None. *Authorship:* Relevant papers were selected according to the title and abstract by three authors (S.-M.D.-R., M.H.-B. and R.K.). Two independent reviewers (S.-M.D.-R. and M.H.-B.) screened papers and read the full text of relevant papers. They assessed full texts for inclusion criteria and extracted data. Statistical analysis was done (M.M.) and cases of disagreement were resolved in consultation with a fourth arbitrating investigator (R.K.). *Ethics of human subject participation:* Ethical approval was not required.

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