Systematic Review with Meta-Analysis

Effect of dietary lipids on circulating adiponectin: a systematic review with meta-analysis of randomised controlled trials

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Abstract

Different dietary interventions have been identified as potential modifiers of adiponectin concentrations, and they may be influenced by lipid intake. We identified studies investigating the effect of dietary lipids (type/amount) on adiponectin concentrations in a systematic review with meta-analysis. A literature search was conducted until July 2013 using databases such as Medline, Embase and Scopus (MeSH terms: ‘adiponectin’, ‘dietary lipid’, ‘randomized controlled trials (RCT)’). Inclusion criteria were RCT in adults analysing adiponectin concentrations with modification of dietary lipids. Among the 4930 studies retrieved, fifty-three fulfilled the inclusion criteria and were grouped as follows: (1) total dietary lipid intake; (2) dietary/supplementary n-3 PUFA; (3) conjugated linoleic acid (CLA) supplementation; (4) other dietary lipid interventions. Diets with a low fat content in comparison to diets with a high-fat content were not associated with positive changes in adiponectin concentrations (twelve studies; pooled estimate of the difference in means: 20.04 (95% CI 20.82, 0.74) mg/ml). A modest increase in adiponectin concentrations with n-3 PUFA supplementation was observed (thirteen studies; 0.27 (95% CI 0.07, 0.47) mg/ml). Publication bias was found by using Egger’s test (P = 0.01) and funnel plot asymmetry. In contrast, CLA supplementation reduced the circulating concentrations of adiponectin compared with unsaturated fat supplementation (seven studies; 20.74 (95% CI 21.38, 20.10) mg/ml). However, important sources of heterogeneity were found as revealed by the meta-regression analyses of both n-3 PUFA and CLA supplementation. Results of new RCT would be necessary to confirm these findings.

Key words: Adiponectin; Dietary lipids; n-3 PUFA; Conjugated linoleic acid

Adiponectin, a hormone expressed mostly in adipose tissue and encoded by the APM1 gene (chromosome 3q27), plays an important role in regulating insulin sensitivity, glucose and lipid metabolism besides its anti-inflammatory and anti-atherogenic properties. It has been suggested that the synthesis and secretion of adiponectin are influenced by body fat distribution, sex and ethnicity. Low levels of adiponectin are found in patients with obesity, type 2 diabetes mellitus and coronary artery disease. More recently, we also found that the presence of the metabolic syndrome and the increasing number of its components are associated with decreased adiponectin concentrations. Therapeutic strategies that target the metabolic syndrome and its components have been shown to increase adiponectin concentrations, such as lifestyle modification involving moderate- or high-intensity physical activities and weight loss.
Although different nutrients may affect adiponectin concentrations, it is not clear how changes in the amount and quality of macronutrients affect its concentrations." In one study, where subjects were randomised to receive hypocaloric moderate-fat/moderate-carbohydrate v. low-fat/high-carbohydrate diets, no changes in adiponectin concentrations were observed over 10 weeks of dietary intervention. In other intervention studies, the comparison between diets with low and high fat content showed conflicting results. While adiponectin concentrations were not affected in one study, intake of a low-fat diet was associated with a 30% increase in the concentrations of adiponectin in another study. These differences probably suggest that the quality rather than the amount of fat may have a significant influence on adiponectin concentrations. This may be exemplified by analysing the effect of a Mediterranean diet on adiponectin concentrations. Close adherence to a Mediterranean diet has been associated with higher adiponectin concentrations. This may be explained not only by its low glycaemic load and moderate alcohol consumption, but also by its composition that is rich in nuts, olive oil and fish, all of which are dietary sources of unsaturated fatty acids. As a result, these data pointed out that lipids are outstanding among potential dietary modulators of circulating adiponectin.

Other dietary lipids such as conjugated linoleic acid (CLA), dietary cholesterol and long-chain n-3 PUFA have been associated with a variable response to adiponectin concentrations. Regarding n-3 PUFA, a well-conducted systematic review and meta-analysis showed that its intake was associated with a significant increase in adiponectin concentrations. However, the results of that meta-analysis need to be interpreted with caution as a significant and unexplained heterogeneity was present between studies included in its results. Therefore, the present meta-analysis aimed to systematically review and analyse randomised controlled trials (RCT) investigating the effects of dietary lipids on circulating adiponectin concentrations in adults.

**Methods**

A systematic review was conducted using a predetermined protocol established according to the Cochrane Handbook's recommendations. Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

**Search strategy**

A literature review was conducted by searching the electronic databases Medline, Embase and Scopus until July 2013 to identify RCT that reported the effect of dietary lipids on adiponectin concentrations in adults. The initial search included the key search terms ‘dietary lipid’ and ‘adiponectin’. It also included the entry terms associated with a high-sensitivity strategy for the search of RCT (available at http://www.sign.ac.uk/methodology/filters.html#random). The complete ‘Medline’ search strategy is described in the online supplementary material.

**Inclusion and exclusion criteria**

We included only those RCT that analysed the effect of dietary lipids on fasting concentrations of circulating total adiponectin. The outcome was changes in adiponectin concentrations from baseline to the end of the study. Studies that met the initial criteria were identified, regardless of language or publication date.

We excluded the studies that did not report the outcome, were not randomised, or included children or pregnant women. Controlled trials that analysed the interaction between dietary interventions and changes in adiponectin concentrations corresponding to different polymorphisms were also excluded if they did not report the overall outcome regardless of polymorphisms. Although studies that did not report means and standard deviations for the outcome (separately for each group at baseline and at the end of the intervention, or changes from baseline for each group) were included in the review, these studies were not included in the meta-analysis. If data necessary for the review were missing, we contacted the authors by e-mail and/or telephone. The study was excluded if the reply was not received within 4 weeks. Of the thirteen authors who were contacted, nine replied back. Of these nine authors, three provided the requested data to be included in the present meta-analysis.

**Study selection and data extraction**

For the present meta-analysis, two reviewers (A. D. v. F. and F. M. S.) independently analysed the titles and abstracts of the articles retrieved from the literature search, reviewed the full text of the published articles, and extracted the data using a standard data extraction protocol. Any disagreements between the reviewers regarding study inclusion were resolved by a third investigator (J. C. d. A. or F. G.).

The extracted data included the number of participants, study design, trial duration, and patients’ demographic and anthropometric characteristics (age, sex, height, weight, BMI, presence of obesity, the metabolic syndrome, hypertension, and dyslipidaemia). Data on total energy, macronutrients (type and amount) and dietary compliance were collected from the description of the intervention and control diets. Data extracted for dietary fat composition included the following: total, saturated, monounsaturated and polyunsaturated fats (g or percentage of total energy intake); n-3 PUFA (g); n-6 PUFA (g); cholesterol (mg). However, data for n-3 and n-6 PUFA were not available in most of the included studies. Data on means and statistical dispersion for adiponectin concentrations at baseline and at the end of the study were extracted. Percentage changes in adiponectin concentrations at the end of each study were calculated for all studies that presented baseline adiponectin values.

The included studies were grouped according to the following interventions: (1) total dietary lipid intake; (2) dietary/supplementary n-3 PUFA; (3) CLA supplementation; (4) other dietary lipid interventions.
Assessment of bias and quality of studies

The quality of the studies was assessed independently by two reviewers (A. D. v. F. and F. M. S.), and any disparity was resolved by a third reviewer (J. C. d. A. or F. G.). Biases were classified into six domains: selection; performance; detection; attrition; reporting; other. The ‘other’ domain included the assessment of dietary compliance. The risk of bias in each domain was classified as high, low or unclear. Regarding dietary compliance, the risk of bias was classified as ‘low’ if the study described the method for the assessment of dietary compliance.

Statistical analyses

Changes in adiponectin concentrations were reported as absolute differences between the values of arithmetic means and standard deviations at baseline and at the end of the study. Heterogeneity between studies was assessed by Cochran’s Q test, and a P for trend ≤0.10 was considered statistically significant. The I² test was also performed to evaluate the magnitude of heterogeneity, which was considered high if I² ≥ 50%. Pooled estimates of the weighted mean differences (WMD) between dietary intervention and control groups were calculated using a random-effects model of DerSimonian & Laird because a significant heterogeneity between the included studies was identified in preliminary models. Furthermore, this approach provides a more conservative assessment of the average effect size.

Potential sources of heterogeneity between trials were assessed by meta-regression analyses. Variables were chosen based on biological relevance before the meta-analysis was conducted. All meta-regression models included the following variables: age (less than the mean value, or equal to or greater than the mean value); sex (male, %); study location (Europe/North America v. others); time of the follow-up (equal to or less than the mean value, or greater than the mean value); BMI (<30 and ≥30 kg/m²); differences in weight change between groups. Blinding of participants/personnel was included in the n-3 PUFA meta-analysis as a meta-regression variable. This variable was neither included in the total dietary lipid meta-analysis as blinding was not clear in all studies, nor in the CLA supplementation meta-analysis as the risk of bias was low in all the studies. Additionally, specific variables were included in the three different meta-analyses according to relevance and availability. For total dietary lipid intake, a cut-off point for the amount of lipid intake was not defined as exclusion criteria. The difference in total energy intake, total dietary lipid intake between groups (difference in total energy intake <1256 kJ/d >1256 kJ/d (300 kcal/d), median percentage point difference in lipid intake between groups (≤10 v. >10% of lipid intake), and mean carbohydrate content in control groups (<30 v. >30% of total energy intake) were included in the meta-regression models. Mean carbohydrate content was analysed only in the control group because it is expected to be dependent on the differences in the amount of lipid intake between groups. For n-3 PUFA and CLA supplementation, the amount of supplementation and the type of oil used as a placebo were also considered in the meta-regression models.

Subsequently, sensitivity (subgroup) analyses were conducted by including the variables with a positive adjusted R² value in meta-regression analyses, to determine how much of the between-study difference could be explained by these variables.

Publication bias was assessed by funnel plot asymmetry and Begg’s or Egger’s tests. The bias was considered significant if P<0.10. The non-parametric trim-and-fill method was used to assess the potential influence of publication bias on sensitivity analyses, and provided a theoretical pooled estimate accounting for estimated missing studies.

All statistical analyses were performed using Stata 11.0 software (Stata). Significance was set at P<0.05, and 95% CI are quoted throughout.

Results

A total of 4930 studies were identified from the literature search (Fig. 1). On the basis of the titles and abstracts, ninety-one studies were selected for the full-text review, of which fifty-three fulfilled the final inclusion criteria. The included studies were grouped according to the following interventions: (1) total dietary lipid intake; (2) n-3 PUFA intake; (3) CLA supplementation; (4) other dietary lipid interventions. The main results of the studies included in the meta-analysis are presented in Tables 1–3, whereas those included only in qualitative analyses are presented in online supplementary Table S2.

Total dietary lipid intake

Of the total selected studies, fifteen investigated the effects of a diet with a low-fat content (20–37% of energy from lipids) on the circulating concentrations of adiponectin compared with a control diet with a high fat content (35–61% of energy from lipids), as shown in Table 1. To test how differences in lipid quantity (expressed as the percentage of daily energy) may affect adiponectin concentrations, the diet with the lowest fat content was classified as an intervention diet in each study.

The median follow-up time was 14 weeks (5 d–144 weeks). These studies included seventeen to 322 participants (mean age 50 years). Most (71±4%) of the studies included both sexes. The mean difference in total dietary lipid intake between the intervention and control groups was 12.0% of the total energy intake. Of these studies, seven (16,31,32,35–37–39) did not describe the lipid type and four (38,39,40,41) had no information about energy consumption. Differences in energy intake were not found to be significant in most of the studies, but were statistically significant only in one study. Among all the other studies that did not report a statistical difference in energy intake between the intervention and control groups, two studies were found to have an energy intake difference of 2173 and 1382 kJ (519 and 330 kcal). In the first study, there were no changes and differences in adiponectin concentrations between the groups throughout...
the study, while in the other study, there was an increase in adiponectin concentrations within the groups, but not between the groups.

The risk of bias in the studies included in the quantitative analysis is summarised in online supplementary Table S1. The risk of selection bias was unclear in the majority of the studies, taking into account the lack of information about random sequence generation and allocation concealment. Performance bias was also unclear in all studies. Information about the blinding of outcome assessors was described in only one study. Regarding attrition bias, the rates of dropouts and/or withdrawals were less than 20% in nine studies. Reporting bias was low in all studies. Dietary compliance was assessed in most studies.

Among the fifteen selected studies, twelve reported sufficient data and were thus included in the meta-analysis. The remaining three studies were excluded due to the lack of sufficient data for quantitative analysis. Among these three studies that were excluded from the quantitative analysis, one showed a greater increase in adiponectin concentrations in the control group than in the intervention group, another showed an increase in the concentrations of adiponectin in the control group than in the intervention group, and in the last one it was not possible to...
Table 1. Characteristics of the studies investigating changes in adiponectin concentrations by modifying the amount of total dietary lipid intake

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design; follow-up</th>
<th>Sample</th>
<th>Dietary I and C groups</th>
<th>Dietary composition (%): fat:carbohydrate: protein; total energy intake</th>
<th>Difference in the percentage points of lipid intake between groups</th>
<th>Changes in adiponectin concentrations (µg/ml; % of change)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvidsson (2004)(37)</td>
<td>Parallel; 10 weeks</td>
<td>Eighty obese women 21–49 years BMI 30.9–47.7 kg/m²</td>
<td>I: low-fat diet C: high-fat diet</td>
<td>I: 27:52:21 C: 41:39:20 Hypoenergetic diets (2092 kJ/d (~ 500 kcal/d)) without any difference between the I and C groups SFA:MUFA:PUFA ratio 2:2:1</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 2.3 ± 2.18 (12.6%) C: 0.8 ± 1.67 (13.1%)</td>
</tr>
<tr>
<td>Cardillo (2006)(31)</td>
<td>Parallel; 144 weeks</td>
<td>132 subjects 55 ± 10 years BMI ≥ 35 kg/m²</td>
<td>I: low-fat diet C: low-carbohydrate diet</td>
<td>I: 32:47:20; 8117 kJ (1940 kcal)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: −1.1 ± 12.5 C: −6.68 ± 34.8 (% of change NA)</td>
</tr>
<tr>
<td>Ng (2007)(32)</td>
<td>Parallel; 16 weeks</td>
<td>Thirty-five males with the MetS Age not reported</td>
<td>I: low-fat diet C: weight-maintenance diet</td>
<td>I: 25:55:20; 6979 kJ (1668 kcal)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 0.7 ± 0.3* (17.9%)</td>
</tr>
<tr>
<td>Keogh (2008)(38)</td>
<td>Parallel; 8 weeks</td>
<td>Sex not reported</td>
<td>I: low-fat, low-SFA diet C: high-fat, high-SFA diet</td>
<td>I: 21.4:35; 5966 kJ (1433 kcal; 20.0% SFA)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 0.4 ± 0.26 (7.6%) C: 0.3 ± 2.16 (15.0%)</td>
</tr>
<tr>
<td>Al-Sarraj (2009)(34)</td>
<td>Parallel; 6 weeks</td>
<td>Thirty-nine subjects with the MetS 18–50 years</td>
<td>I: lower fat diet (AHA) C: low-carbohydrate diet</td>
<td>C: 35:40:20; 9736 kJ (2327 kcal) (mainly MUFA and PUFA, with restriction of SFA)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>C: 0.1 ± 0.4 (12.9%)</td>
</tr>
<tr>
<td>Brons (2009)(18)</td>
<td>Cross-over; 5d</td>
<td>Twenty-six males 30–31 years BMI 23.4–24.0 kg/m²</td>
<td>I: low-fat diet C: high-fat, high-energy diet</td>
<td>I: 30:46:24; 6427 kJ (1536 kcal; 8.0% SFA)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 4.6 ± 1.9* (129.9%)</td>
</tr>
<tr>
<td>Wycherley (2010)(39)</td>
<td>Parallel; 52 weeks</td>
<td>Forty-nine subjects with the MetS 50 ± 11 years BMI 34.7–50.0 kg/m²</td>
<td>I: low-fat diet C: high-fat diet</td>
<td>I: 30:46:24; 6427 kJ (1536 kcal; 8.0% SFA)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>C: 2.8 ± 2.8* (17.8%)</td>
</tr>
<tr>
<td>Vetter (2010)(35)</td>
<td>Parallel; 24 weeks</td>
<td>144 patients with type 2 DM 60–84 ± 10–13 years BMI 28.2–46.0 kg/m²</td>
<td>I: low-fat, energy-restricted diet C: high-fat, high-energy diet</td>
<td>I: 37:44:22; 6640 kJ (1587 kcal)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 2.6 ± 8.4* (163%) C: 4.3 ± 14.6* (321%)</td>
</tr>
<tr>
<td>Summer (2011)(37)</td>
<td>Parallel; 24 weeks</td>
<td>Eighty-one females 35–50 years</td>
<td>I: low-fat diet (AHA) C: low-carbohydrate ad libitum diet (Atkins)</td>
<td>I: 31:50:19; 5615 kJ (1342 kcal)</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 2.9 ± 1.4* (19.8%)</td>
</tr>
<tr>
<td>Blüher (2012)(16)</td>
<td>Parallel; 48 weeks</td>
<td>BMI 30–35 kg/m² 322 subjects</td>
<td>I: low-fat diet (AHA) C: low-carbohydrate diet</td>
<td>I: 30:51:19; 6276 kJ (1500 kcal) for males and 7531 kJ (1800 kcal) for females</td>
<td>Total energy intake did not differ between the I and C groups</td>
<td>I: 0.8 ± 2.9 (11.0%) C: 1.5 ± 3.5 (20.8%)</td>
</tr>
</tbody>
</table>
describe the differences between intervention and control groups because the results were not described separately by groups\(^\text{53}\).

Overall, the intervention diet (28–37% of the total energy intake from fat) did not increase adiponectin concentrations compared with the control diet (39–61% of the total energy intake from fat) (WMD = −0.04 (95% CI −0.82, 0.74) µg/ml; \(I^2 = 83.7\%\), \(P\) for heterogeneity <0.001; Fig. 2(a)). Given the significant heterogeneity between the included studies, we performed a meta-regression analysis by including one variable per model: age (adjusted \(R^2 = 9.6\%\), \(P = 0.63\)); sex (adjusted \(R^2 = 16.5\%\), \(P = 0.90\)); study location (adjusted \(R^2 = 9.8\%\), \(P = 0.61\)); follow-up time (adjusted \(R^2 = 12.7\%\), \(P = 0.87\)); BMI (adjusted \(R^2 = 10.3\%\), \(P = 0.91\)); weight-loss difference between the intervention and control groups (adjusted \(R^2 = 11.1\%\), \(P = 0.66\)); energy intake differences between the intervention and control groups (adjusted \(R^2 = 5.7\%\), \(P = 0.41\)); percentage point difference in total dietary lipid intake between the intervention and control groups (adjusted \(R^2 = 15.1\%\), \(P = 0.65\)); carbohydrate content in the control group (adjusted \(R^2 = 16.4\%\), \(P = 0.88\)). In three studies\(^\text{32,34,37}\), a significant change in body weight between the intervention and control groups was observed at the end of each trial. We also performed a sensitivity analysis with body weight used as a variable, which showed no significant change in the results. Publication bias was not observed in the present meta-analysis (Begg’s test, \(P = 0.89\); Egger’s test, \(P = 0.21\)), and asymmetry was also not detected, as shown in the funnel plot (Fig. 3(a)).

### n-3 PUFA intake

Of the total selected studies, nineteen analysed the effect of n-3 PUFA intake on adiponectin concentrations: sixteen\(^\text{21,22,24,40–42,45–52,54,55}\) with n-3 PUFA supplementation and three\(^\text{43,44,53}\) with diets composed of n-3 PUFA-rich foods. The details of these studies are summarised in Table 2. The median follow-up time was 10 weeks (3–24 weeks). These studies included twenty-six to 324 participants, and most studies (54%) included both sexes.

Dietary composition was described in ten studies\(^\text{21,22,24,40–42,45–52,54,55}\). Comparisons between intervention (diet or supplementation) and fatty acid intake from different sources (placebo) were made in twelve studies\(^\text{21,22,24,40–42,45–48,51,52,55}\). Among the dietary intervention studies, one\(^\text{43}\) used different amounts of n-3 PUFA from plant and marine sources, while two\(^\text{44,53}\) used different types of fish.

The risk of selection bias was unclear in the majority of the studies, taking into account the lack of information about random sequence generation and allocation concealment. In general, performance bias was low in most studies. Information about the blinding of outcome assessors was described in only three studies\(^\text{24,42,53}\). Attrition bias was low in ten studies\(^\text{21,22,41,42,46–50,55}\). Reporting bias was low in all studies. Dietary compliance was analysed in the majority of the studies (online supplementary Table S1).

Of these nineteen studies, thirteen\(^\text{21,22,24,40–42,46–51,55}\) presented the data that could be pooled and used in a
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design; follow-up</th>
<th>Sample</th>
<th>Dietary I and C groups</th>
<th>n-3 PUFA dose (EPA + DHA)</th>
<th>Dietary composition (%): fat:carbohydrate:protein; total energy intake</th>
<th>Changes in adiponectin concentrations (% of change)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krebs (2006)(40)</td>
<td>Parallel; 24 weeks</td>
<td>116 hyperinsulinaemic females 44.7 ± 13.2 years</td>
<td>I: 5.0 g/d of fish oil with dietary and physical activity advice C&quot;: 5.0 g/d of placebo oil (each capsule with 2.8 g linoleic and 1.4 g oleic) with dietary and physical activity advice</td>
<td>I: 4.2 g/d (1.3 g EPA + 2.9 g DHA)</td>
<td>I: 35:50:15; 10 460 kJ (2500 kcal) C&quot;: 35:50:15; 10 460 kJ (2500 kcal)</td>
<td>C&quot;: 2.33 ± 2.61† (1 22.2 %)</td>
</tr>
<tr>
<td>Kabir (2007)(41)</td>
<td>Parallel; 8 weeks</td>
<td>Twenty-six postmenopausal females with type 2 DM 40–60 years BMI 27–40 kg/m²</td>
<td>C: 3.0 g/d of fish oil</td>
<td>I: 1.8 g/d (1.08 g EPA + 0.72 g DHA)</td>
<td>Not reported</td>
<td>C: 0.5 ± 5.3 (18.5 %)</td>
</tr>
<tr>
<td>Damsgaard (2008)(42)</td>
<td>Parallel; 8 weeks</td>
<td>Sixty-four males 24.9 ± 3.9 years</td>
<td>I¹: 5.0 ml fish oil, sunflower oil and Becel® margarine</td>
<td>I²: 3.1 g/d (1.8 g EPA + 1.3 g DHA)</td>
<td>Not reported</td>
<td>I²: 1.3 ± 1.03 (18.6 %)</td>
</tr>
<tr>
<td>Micallef (2009)(46)</td>
<td>Parallel; 3 weeks</td>
<td>Sixty hyperlipidaemic subjects 55.4 ± 1.0 years 45.0 % males</td>
<td>I¹: 4.0 g/d of tuna oil + 2.0 g/d of plant sterols</td>
<td>I¹: 1.4 g/d (0.3 g EPA + 1.1 g DHA)</td>
<td>Not reported</td>
<td>I¹: 0.2 ± 0.19† (11.8 %)</td>
</tr>
<tr>
<td>Rizza (2009)(47)</td>
<td>Parallel; 12 weeks</td>
<td>Fifty subjects 29.9 ± 6.2 years 50.0 % males</td>
<td>C: 2.0 g/d of fish oil</td>
<td>I: 1.7 g/d (EPA:DHA ratio 0.9–1.5:1)</td>
<td>Not reported</td>
<td>C: 0.5 ± 0.2 (23.8 %)</td>
</tr>
<tr>
<td>Troseid (2009)(22)</td>
<td>Factorial; 144 weeks</td>
<td>563 men with a high risk of CVD 64–76 years</td>
<td>I: n-3 PUFA supplementation (2.4 g/d)</td>
<td>I: 1.3 g/d (0.84 g EPA + 0.48 g DHA)</td>
<td>Not reported</td>
<td>I: ± 0.72 ± 3.3 (18.0 %)</td>
</tr>
<tr>
<td>Sofi (2010)(21)</td>
<td>Parallel; 48 weeks</td>
<td>Eleven subjects with non-alcoholic fatty liver disease &gt; 18 years 80.0 % males BMI 29.3 ± 4.1 kg/m²</td>
<td>I: 6.5 ml/d of olive oil (0.83 g n-3 PUFA) + dietary recommendations</td>
<td>I: 0.71 g/d (0.47 g EPA + 0.24 g DHA)</td>
<td>C: 29.51:18; 8933 KJ (2135 kcal)</td>
<td>C: 0.08 ± 0.08 (16.9 %)</td>
</tr>
<tr>
<td>Vargas (2010)(22)</td>
<td>Parallel; 6 weeks</td>
<td>Fifty-one patients with PCOS 20–45 years</td>
<td>I¹: six capsules of fish oil</td>
<td>I¹: 3.6 g/d (2.2 g EPA + 1.5 g DHA)</td>
<td>All groups were analysed together</td>
<td>I¹: ± 0.1 ± 0.2° (1.3 %)§</td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of the studies investigating changes in adiponectin concentrations by n-3 PUFA intake

- **Study design; follow-up**: Parallel; 24 weeks, Parallel; 8 weeks, Parallel; 8 weeks, Parallel; 3 weeks, Parallel; 12 weeks, Factorial; 144 weeks, Parallel; 48 weeks, Parallel; 6 weeks.
- **Sample**: Hyperinsulinaemic females, postmenopausal females with type 2 DM, Sixty-four males, Sixty hyperlipidaemic subjects, Fifty subjects, Fifty subjects, Fifty-one patients with PCOS.
- **Dietary I and C groups**: Fish oil with dietary and physical activity advice, 3.0 g/d of fish oil, fish oil, sunflower oil and Becel® margarine, 4.0 g/d of tuna oil, sunflower oil and Becel® margarine, 2.0 g/d of fish oil, n-3 PUFA supplementation, fish oil, sunflower oil and Becel® margarine, 6.5 ml/d of olive oil (0.83 g n-3 PUFA) + dietary recommendations.
- **n-3 PUFA dose (EPA + DHA)**: 7.0 g/d, 7.0 g/d, 6.5 ml/d, 3.6 g/d, 6.5 ml/d, 2.0 g/d, 6.5 ml/d.
- **Dietary composition (%): fat:carbohydrate:protein; total energy intake**: 35:50:15; 10 460 kJ, 30:55:15; 6109 KJ, Not reported, Not reported, Not reported, Not reported, Not reported.
- **Changes in adiponectin concentrations (% of change)‡**: ± 2.33 ± 2.61† (1 22.2 %), ± 0.5 ± 5.3 (18.5 %), Not reported, Not reported, Not reported, Not reported, Not reported.

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[1](https://www.cambridge.org/core/terms) Downloaded from Cambridge Core, on 16 Apr 2018 at 16:40:07, subject to the Cambridge Core terms of use, available at [http://doi.org/10.107/bj00731151402013](http://doi.org/10.107/bj00731151402013)
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design; follow-up</th>
<th>Sample</th>
<th>Dietary I and C groups</th>
<th>n-3 PUFA dose (EPA + DHA)</th>
<th>Dietary composition (%): fat:carbohydrate:protein; total energy intake</th>
<th>Changes in adiponectin concentrations (% of change)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammelmark (2012)(^{(48)})</td>
<td>Parallel; 6 weeks</td>
<td>Forty-nine subjects</td>
<td>I: 2·0 g/d of fish oil C: 2·0 g/d of olive oil</td>
<td>I: 1·1 g/d (0·64 g EPA + 0·48 g DHA)</td>
<td>Not reported</td>
<td>$\pm$ 0·52 ± 5·3 (17·3 %) C: 0·02 ± 5·32 (10·22 %)</td>
</tr>
<tr>
<td>Koh (2012)(^{(49)})</td>
<td>Parallel; 8 weeks</td>
<td>150 subjects</td>
<td>I(^1): 2·0 g/d of fish oil I(^2): 160·0 mg/d of fenofibrate</td>
<td>I(^1): 1·7 g/d (0·93 g EPA + 0·75 g DHA)</td>
<td>Low-fat diet for all groups Dietary information not reported</td>
<td>I(^1): $-0·3 \pm 0·1$ (12·2 %) I(^2): $0·2 \pm 0·1^* \dagger$ (18·4 %)</td>
</tr>
<tr>
<td>Mohammadi (2012)(^{(50)})</td>
<td>Parallel; 8 weeks</td>
<td>Thirty-one females with PCOS</td>
<td>I: 4 g/d of fish oil</td>
<td>I: 1·2 g/d (720 g EPA + 480 g DHA)</td>
<td></td>
<td>I: $35·50:15; 6979$ kJ (1668 kcal) C: $35·50:15; 7029$ kJ (1680 kcal)</td>
</tr>
<tr>
<td>Munro (2012)(^{(51)})</td>
<td>Parallel; 14 weeks</td>
<td>Thirty-two subjects</td>
<td>I: 6 g/d of fish oil</td>
<td>I: 2·04 g/d (0·42 g EPA + 1·62 g DHA)</td>
<td></td>
<td>I: $16·40:40; 3000$ kJ (717 kcal) for 4 weeks C: $16·40:40; 3000$ kJ (717 kcal) for 4 weeks After 4 weeks approximately 6694 kJ/d (1600 kcal/d)</td>
</tr>
<tr>
<td>Spencer (2013)(^{(55)})</td>
<td>Parallel; 12 weeks</td>
<td>Thirty-three subjects with insulin resistance</td>
<td>I: 4 g/d of fish oil</td>
<td>I: 3·32 g/d (1·86 g EPA + 1·46 g DHA)</td>
<td>Not reported</td>
<td>$-0·2 \pm 0·71$ (10·2 %) C: $-0·1 \pm 0·8$ (2·5 %)</td>
</tr>
</tbody>
</table>

I, intervention; C\(^1\), control 1; C\(^2\), control 2; I\(^1\), intervention 1; C, control; I\(^2\), intervention 2; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

* Significant change from baseline ($P<0·05$).
† Significant difference between the intervention and control groups ($P<0·05$).
‡ Adiponectin concentrations expressed as means and standard deviations.
§ Adiponectin concentrations expressed as ng/ml.
Table 3. Characteristics of the studies investigating changes in adiponectin concentrations by conjugated linoleic acid (CLA) intake

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Study design; follow-up</th>
<th>Sample</th>
<th>Dietary I and C groups</th>
<th>Dietary composition (%): fat:carbohydrate:protein; total energy intake</th>
<th>Changes in adiponectin concentrations (µg/ml; % of change)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riserus (2004)³⁵⁶</td>
<td>Parallel; 12 weeks</td>
<td>Fifty-seven males</td>
<td>I: 3.4 g/d of CLA</td>
<td>Dietary information not reported</td>
<td>I: 0.26 ± 1.50 (±3.5%)</td>
</tr>
<tr>
<td>Syvertsen (2007)³⁵⁷</td>
<td>Parallel; 24 weeks</td>
<td>Forty-nine subjects</td>
<td>I: 3.4 g/d (37.5% cis-9, trans-11-CLA and 38.0% trans-10, cis-12-CLA)</td>
<td>Dietary information not reported</td>
<td>I: 0.01 ± 2.50 (±0.13%)</td>
</tr>
<tr>
<td>Norris (2009)³⁵⁸</td>
<td>Cross-over; 16 weeks (4-week washout)</td>
<td>Fifty-five postmenopausal females with type 2 DM</td>
<td>I: 6.4 g/d (CLA isomers)</td>
<td>I: 38:44:33; 6402 kJ (1530 kcal)</td>
<td>I: 0.80 ± 0.6 (±25.3%)</td>
</tr>
<tr>
<td>Zhao (2009)³⁵⁹</td>
<td>Parallel; 8 weeks</td>
<td>Eighty hypertensive subjects</td>
<td>I: 4.5 g/d of CLA (50:50 of cis-9, trans-11-CLA and trans-10, cis-12-CLA)</td>
<td>I: 22:64:14; 10 222 kJ (2443 kcal)</td>
<td>I: 2.5 ± 1.35 (±37.3%)</td>
</tr>
<tr>
<td>MacRedmond (2010)³⁶⁰</td>
<td>Parallel; 12 weeks</td>
<td>Twenty-eight mild asthmatic subjects</td>
<td>I: 4.5 g/d of CLA (36.4% of cis-9, trans-11-CLA and 37.0% of trans-10, cis-12-CLA)</td>
<td>Dietary information not reported</td>
<td>I: 0.8 ± 1.5 (±14.6%)</td>
</tr>
<tr>
<td>Joseph (2011)³⁶¹</td>
<td>Cross-over; 8 weeks (4-week washout)</td>
<td>Thirty-six overweight males</td>
<td>I: 3.5 g/d (50:50 of trans-10, cis-12-CLA and cis-9, trans-11-CLA)</td>
<td>Dietary information not reported</td>
<td>I: −0.8 ± 0.7 (±6.5%)</td>
</tr>
<tr>
<td>Shademan (2011)³¹⁷</td>
<td>Parallel; 8 weeks</td>
<td>Forty-two patients with type 2 diabetes</td>
<td>I: 3.5 g/d (cis-9, trans-11-CLA)</td>
<td>Dietary information not reported</td>
<td>I: −0.5 ± 0.3 (±4.1%)</td>
</tr>
</tbody>
</table>

I, intervention; C, control; DM, diabetes mellitus.
* Significant change from baseline (P<0.05).
† Significant difference between the intervention and control groups (P<0.05).
‡ Adiponectin concentrations expressed in as means and standard deviations.
Favours diet with a high fat content
Favours diet with a low fat content

(a)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Difference in lipid intake between groups (% EI)</th>
<th>Adiponectin changes (µg/ml)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer (2011)</td>
<td>81</td>
<td>18-0</td>
<td>-1.60, -2.21, -0.39</td>
<td>12.69</td>
</tr>
<tr>
<td>Cardillo (2008)</td>
<td>53</td>
<td>10-0</td>
<td>-1.29, -7.47, 6.01</td>
<td>1.41</td>
</tr>
<tr>
<td>Rajee (2012)</td>
<td>30</td>
<td>15-0</td>
<td>-1.20, -2.34, -0.06</td>
<td>10.62</td>
</tr>
<tr>
<td>Heggen (2012)</td>
<td>181</td>
<td>5-0</td>
<td>-1.12, -4.10, 1.88</td>
<td>4.56</td>
</tr>
<tr>
<td>Brons (2009)</td>
<td>26</td>
<td>8-0</td>
<td>-1.02, -3.25, 1.21</td>
<td>6.46</td>
</tr>
<tr>
<td>Blührer (2012)</td>
<td>180</td>
<td>0-0</td>
<td>-0.70, -1.84, 0.24</td>
<td>11.43</td>
</tr>
<tr>
<td>Keoghe (2008)</td>
<td>99</td>
<td>31-0</td>
<td>0.10, -0.77, 0.97</td>
<td>11.72</td>
</tr>
<tr>
<td>Al-Sarra (2009)</td>
<td>39</td>
<td>20-0</td>
<td>0.46, -2.10, 3.02</td>
<td>5.51</td>
</tr>
<tr>
<td>Ng (2007)</td>
<td>35</td>
<td>10-0</td>
<td>0.56, 0.34, 0.78</td>
<td>13.80</td>
</tr>
<tr>
<td>Vetter (2010)</td>
<td>79</td>
<td>7-0</td>
<td>1.70, -3.48, 6.88</td>
<td>1.94</td>
</tr>
<tr>
<td>Arvidsson (2004)</td>
<td>80</td>
<td>14-0</td>
<td>1.80, 0.60, 3.00</td>
<td>10.34</td>
</tr>
<tr>
<td>Wycherley (2010)</td>
<td>49</td>
<td>31-0</td>
<td>1.80, 0.45, 5.15</td>
<td>9.72</td>
</tr>
</tbody>
</table>

Overall (I² = 83.7%, P < 0.001)

-0.04, -0.82, 0.74

(b)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>n-3 PUFA (g/d)</th>
<th>Adiponectin changes (µg/ml)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer (2013)</td>
<td>33</td>
<td>3.3</td>
<td>-0.10, -0.50, 0.30</td>
<td>11.63</td>
</tr>
<tr>
<td>Troseid (2009)</td>
<td>236</td>
<td>1.3</td>
<td>-0.09, -1.01, 0.83</td>
<td>3.90</td>
</tr>
<tr>
<td>Munro (2012)</td>
<td>29</td>
<td>2.0</td>
<td>-0.06, -2.62, 2.46</td>
<td>0.61</td>
</tr>
<tr>
<td>Koh (2012)</td>
<td>99</td>
<td>1.7</td>
<td>-0.03, -0.56, 0.01</td>
<td>21.69</td>
</tr>
<tr>
<td>Mituliel (2009)</td>
<td>30</td>
<td>1.4</td>
<td>0.21, 0.10, 0.31</td>
<td>20.56</td>
</tr>
<tr>
<td>Solf (2010)</td>
<td>11</td>
<td>0.4</td>
<td>0.26, 0.09, 0.43</td>
<td>10.96</td>
</tr>
<tr>
<td>Dammagard (2008)</td>
<td>33</td>
<td>2.1</td>
<td>0.20, -0.22, 0.92</td>
<td>8.86</td>
</tr>
<tr>
<td>Gammelmark (2012)</td>
<td>49</td>
<td>1.1</td>
<td>0.50, -2.47, 3.47</td>
<td>0.46</td>
</tr>
<tr>
<td>Kaito (2007)</td>
<td>26</td>
<td>1.8</td>
<td>-0.00, 0.36, 1.44</td>
<td>8.53</td>
</tr>
<tr>
<td>Vargae (2011)</td>
<td>34</td>
<td>3.6</td>
<td>1.30, 0.07, 2.53</td>
<td>2.39</td>
</tr>
<tr>
<td>Mohammadi (2012)</td>
<td>61</td>
<td>1.2</td>
<td>2.00, 0.41, 3.59</td>
<td>1.50</td>
</tr>
<tr>
<td>Krebs (2006)</td>
<td>87</td>
<td>4.2</td>
<td>2.51, -0.55, 5.69</td>
<td>0.40</td>
</tr>
<tr>
<td>Rizza (2009)</td>
<td>50</td>
<td>1.7</td>
<td>3.00, 1.10, 6.70</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Overall (I² = 79.6%, P < 0.001)

-0.07, 0.07, 0.47

(c)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>CLA (g/d)</th>
<th>Adiponectin changes (µg/ml)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norris (2009)</td>
<td>35</td>
<td>0.0</td>
<td>-1.35, -1.06, -1.02</td>
<td>15.63</td>
</tr>
<tr>
<td>Syvertsen (2007)</td>
<td>41</td>
<td>3.4</td>
<td>-0.87, -1.66, -0.66</td>
<td>15.77</td>
</tr>
<tr>
<td>Joseph (2011)</td>
<td>27</td>
<td>3.5</td>
<td>-0.80, -1.12, -0.48</td>
<td>15.46</td>
</tr>
<tr>
<td>MacRedmond (2010)</td>
<td>26</td>
<td>4.5</td>
<td>-0.40, -1.84, 0.94</td>
<td>10.28</td>
</tr>
<tr>
<td>Rosen (2004)</td>
<td>38</td>
<td>3.4</td>
<td>-0.23, -1.18, 0.72</td>
<td>12.05</td>
</tr>
<tr>
<td>Shademan (2011)</td>
<td>39</td>
<td>3.0</td>
<td>-0.00, -0.02, 0.02</td>
<td>16.04</td>
</tr>
<tr>
<td>Zhao (2009)</td>
<td>80</td>
<td>4.5</td>
<td>2.40, 1.06, 2.84</td>
<td>14.97</td>
</tr>
</tbody>
</table>

Overall (I² = 37.7%, P < 0.001)

-0.18, -0.84, 0.48

Note: Weights are from random-effects analysis

Fig. 2. Forest plots (meta-analyses, random-effects models) of the effect of fatty acid interventions on circulating adiponectin concentrations (µg/ml): (a) diet with a low fat content; (b) n-3 PUFA supplementation; (c) conjugated linoleic acid (CLA) supplementation. % EI, percentage of energy intake. For the Troseid et al. (24) study, data for the main effect of fish oil intake on adiponectin concentrations were obtained directly from the authors and used in the pooled meta-analysis. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)
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meta-analysis. Different oils were used as a placebo: four studies\(^{22,42,47,48}\) used olive oil; three\(^{24,46,51}\) used sunola oil; one\(^{22}\) used soybean oil; one\(^{55}\) used maize oil; two\(^{41,50}\) used paraffin oil; one study\(^{40}\) used a mixture of linoleic and oleic oil; one study\(^{49}\) did not describe the oil type. Of these thirteen studies, only five\(^{22,40,41,50,51}\) reported the dietary composition in both intervention and control groups. None of these studies showed any differences in total energy or in the proportion of macronutrient intake between the two groups. Furthermore, no studies described the consumption of n-3 and n-6 PUFA.

Studies that had analysed the effects of n-3 PUFA-rich foods on adiponectin concentrations\(^{43,44,53}\) were not included in the quantitative analysis. In addition, one study\(^{45}\) that combined n-3 PUFA intake with CLA supplementation in the intervention group, as well as two studies\(^{52,54}\) in which data extraction was not available were excluded from the analysis. Among these six excluded studies\(^{43–45,52–54}\) four did not show any significant change in adiponectin concentrations at the end of the intervention\(^{43–45,54}\). However, in two studies\(^{52,53}\), an increase in adiponectin concentrations was observed at the end of the trial.

The pooled data from thirteen studies did show a modest and significant effect of n-3 PUFA supplementation on adiponectin concentrations (WMD 0.27 (95% CI 0.07, 0.47) µg/ml; \(I^2\) 79.6%, \(P\) for heterogeneity < 0.001; Fig. 2(b)). Given the high heterogeneity between the included studies, we performed a meta-regression analysis by including one variable per model. The independent variables were as follows: age (adjusted \(R^2 = 24.2, P = 0.10\)); sex (adjusted \(R^2 = 11.2, P = 0.01\)); study location (adjusted \(R^2 = 28.8\%\), \(P = 0.59\)); follow-up time (adjusted \(R^2 = 47.0\%\), \(P = 0.58\)); BMI (adjusted \(R^2 = 39.5\%\), \(P = 0.42\)); blinding of participants/personnel (adjusted \(R^2 = 10.3\%\), \(P = 0.71\)); amount of n-3 PUFA (g/d); adjusted \(R^2 = 64.8\%\), \(P = 0.85\)); EPA (adjusted \(R^2 = 65.9\%\), \(P = 0.83\)); docosapentaenoic acid (adjusted \(R^2 = 87.0\%\), \(P = 0.60\)); fat type used as a placebo (vegetable oil v. paraffin oil; adjusted \(R^2 = 100\%\), \(P = 0.04\)); change in body weight over the study period between the intervention and control groups (adjusted \(R^2 = 21.9\%\), \(P = 0.60\)).

Subsequently, we performed a sensitivity analysis with fat type as placebo (unsaturated oil or paraffin oil), which revealed that n-3 PUFA supplementation was still associated with an increase in adiponectin concentrations. Studies that had used unsaturated oil as placebo showed an effect of n-3 PUFA supplementation on adiponectin concentrations (WMD 0.23 (95% CI 0.04, 0.42) µg/ml; \(I^2\) 40.2%, \(P\) for heterogeneity = 0.09) as well as those that had used paraffin oil as placebo (WMD 1.19 (95% CI 0.24, 2.13)µg/ml; \(I^2\) 39.5%, \(P\) for heterogeneity = 0.20). Studies that had used paraffin oil as placebo showed a greater increase (0.96 µg/ml) in adiponectin concentrations than those that had used vegetable oils as placebo.

Significant evidence of publication bias was found by Egger’s test (\(P = 0.01\)) but not by Begg’s test (\(P = 0.95\)). Visual inspection of the funnel plot confirmed the existence of asymmetry (Fig. 3(b)). In fact, a theoretical pooled estimate of 0.08 (95% CI -0.13, 0.30) µg/ml (\(P = 0.46\)) was obtained by using the trim-and-fill correction method after the addition of six theoretically unreported studies.

**Conjugated linoleic acid supplementation**

Of the total selected studies, seven\(^{17,56–61}\) assessed the effect of CLA (mixture containing cis-9, trans-11 and trans-10, cis-12) supplementation on adiponectin concentrations. The median follow-up time was 13.0 weeks (8–24 weeks). These studies included twenty-eight to eighty participants, aged 18 to 80 years. The details of these studies are summarised in Table 3.

In most studies, CLA supplementation (intervention) was compared with unsaturated fatty acid supplementation (placebo) such as olive oil\(^{56,57,60}\), safflower oil\(^{58,61}\) or soyabean oil\(^{17}\). Only one study\(^{59}\) compared CLA supplementation with saturated fatty acid intake (placebo, mixture of fatty acids in capsules). The median CLA supplementation was 4.1 (range 3.0–8.0) g/d, with an equal mix of the two predominant isomers. Only two studies\(^{58,59}\) described the dietary composition.

The risk of selection bias was unclear in the majority of the studies, taking into account the lack of information about random sequence generation and allocation concealment. Performance bias was low in most studies. Information about the blinding of outcome assessors was described in only two studies\(^{58,61}\). Attrition bias was low in five\(^{17,56,57,59,60}\) out of seven studies\(^{17,56–61}\). Reporting bias was low in all
Discussions

The present systematic review with meta-analysis analysed how different types or amounts of dietary lipids affect circulating adiponectin concentrations. Intervention studies that compared diets with low and high fat content were not associated with any differences in adiponectin concentrations. However, it was observed that n-3 PUFA supplementation modestly increased the circulating concentrations of adiponectin, whereas CLA supplementation reduced the concentrations when compared with unsaturated fatty acid supplementation used as an active placebo.

In the present meta-analysis, a difference of 18-0% of energy intake from total lipids between the intervention and control groups was not associated with changes in adiponectin concentrations, corroborating the idea that the quality of fat, rather than its amount, might have a more important role in modulating the concentrations of adiponectin. Although we found a high level of heterogeneity between the studies included in the present meta-analysis, this could not be explained by any factor in the exploratory analysis. Differences in carbohydrate content between the low-fat and high-fat dietary arms could also have an impact on adiponectin concentrations. We also performed a meta-regression analysis by including the differences in carbohydrate content between the study arms; however, this could not explain the high level of heterogeneity found between the included studies. In addition, differences in carbohydrate content may affect insulin resistance, which is a potential modifier of adiponectin concentrations(535). However, it was unlikely to explore the aspects associated with insulin resistance due to the lack of data in most studies.

The protective effect of high intake of oily fish on the risk of type 2 diabetes has been demonstrated in a recent meta-analysis(535). Improvement in insulin sensitivity resulting from the intake of n-3 PUFA has been shown to be strongly associated with the increase in adiponectin concentrations. In fact, the utilisation of EPA and DHA in the culture medium of human and rat adipocytes increased the synthesis and secretion of adiponectin by the activation of PPARy that acts as an insulin sensitiser(724). In the present meta-analysis, n-3 PUFA supplementation modestly increased the circulating concentrations of adiponectin, suggesting the beneficial effect of this supplementation on adipocyte metabolism. Additionally, the well-known effect of n-3 PUFA intake on reducing TAG and increasing HDL-cholesterol levels(735) may be partially associated with its effect on adiponectin secretion, which also improves lipid metabolism through the modulation of insulin sensitivity and fatty acid oxidation(740).

In contrast to the study of Wu et al(135), we found a possible explanation for the heterogeneity identified in the meta-analysis of n-3 PUFA supplementation. While updating the results published by Wu et al(135) by the addition of three studies(50,51,55), we showed using the meta-regression analysis that the type of the placebo oil (vegetable oil or paraffin oil) could explain part of the heterogeneity found between the studies included in the meta-analysis. Studies that had used paraffin oil as placebo showed a greater increase in adiponectin concentrations.

Other dietary lipids interventions

Among the total selected studies, three analysed the effect of fatty acid intake on adiponectin concentrations (saturated fat(683), α-lipoic acid(699) and n-6 PUFA(688)) and nine analysed the effect of the food source of lipids on adiponectin concentrations (eggs(643), partially-hydrogenated oil(20,65), nuts(66,67,71) and flaxseed(25,62,70)). The details of these studies are summarised in online supplementary Table S2. The median follow-up time was 9 weeks (4-48 weeks). These studies included fifteen to 160 participants, aged 20 to 80 years. However, these studies were not included in the meta-analysis due to the variability in dietary intervention.

A high consumption of saturated fat(683), n-6 PUFA(688) and α-lipoic acid(699) did not show a significant effect on adiponectin concentrations. In contrast, intake of eggs increased the circulating concentrations of adiponectin(643). Flaxseed intake reduced adiponectin concentrations in one study(622), but did not change its concentrations in other two studies(25,703). Intake of nuts increased adiponectin concentrations in two studies(66,671), with no effect being found in one study(71).
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concentrations than those that had used vegetable oils as placebo. We believe that the biological effect promoted by vegetable oils used as a placebo could reduce the difference in adiponectin concentrations between the intervention and control groups. Interestingly, even after grouping only those studies that used vegetable oils as placebo, the effect of n-3 PUFA intake remains to be significantly associated with an increase in adiponectin concentrations. However, it is likely that studies with negative results were not published. The inclusion of the studies that were not published would probably reduce the effect of n-3 PUFA intake on adiponectin concentrations, as we have already found. Therefore, caution needs to be exercised in the interpretation of the effect of n-3 PUFA intake on adiponectin concentrations.

CLA fatty acids are lipids derived from fatty tissues of ruminant animals. Some studies suggested that either the trans-10, cis-12 or cis-9, trans-11 isomer increased insulin resistance, but not a mixture of both isomers. Additionally, it was found that supplementation of the trans-10, cis-12 isomer increases C-reactive protein, a well-defined marker of subchronic inflammation associated with insulin resistance, but not the supplementation of isometric mixture. A commercially prepared oil contains a 50:50 mixture of the trans-10, cis-12 and cis-9, trans-11 isomers. All studies included in the present meta-analysis assessed the effect of CLA oil as a mixture containing the cis-9, trans-11 and trans-10, cis-12 isomers compared with placebo. Although we showed no changes in adiponectin concentrations with CLA vs. placebo supplementation, data from the sensitivity analysis suggested that CLA supplementation resulted in a reduction of circulating adiponectin concentrations when compared with unsaturated fat supplementation. This result could be attributed to the antioxidant properties of unsaturated fatty acids that might be more effective in modulating the concentrations of adiponectin. The high level of heterogeneity found between these studies could not be explained by BMI, the amount of CLA supplementation, and the change in body weight over the study period between the intervention and control groups. However, we found the role of blinding of subjects/personnel to be significant in explaining this heterogeneity. As a result, we should be cautious in concluding that there is no effect of CLA supplementation on adiponectin concentrations. Further intervention studies should address the role of CLA as a dietary supplement as well as the mechanisms by which CLA acts to regulate vital steps in the modulation of insulin sensitivity and adiponectin metabolism.

Although other types of fatty acid interventions (diet or supplementation) were identified, they were not included in the meta-analysis due to the lack of sufficient studies. Our data suggest that the consumption of nuts, but not flaxseed, is associated with increasing adiponectin concentrations; however, this effect needs to be further explored in RCT.

Although the literature search was conducted using multiple databases and was not restricted to the English language, the present meta-analysis has some limitations. First, despite several attempts to contact the authors of the published articles that had missing data by e-mail or telephone, some studies were excluded from the meta-analysis due to the delay in response. Second, funnel plot asymmetry was apparent with n-3 PUFA and CLA supplementation and may, in part, explain the heterogeneity found between the studies included in the present meta-analysis. To better understand this issue, we performed meta-regression and sensitivity analyses. These analyses revealed the type of oil used as a placebo (paraffin oil or vegetable oil) in the studies that had used n-3 PUFA supplementation could explain part of the heterogeneity found in the present meta-analysis. Third, the lack of data on the actual consumption of n-3 PUFA has to be taken into account because it may have an influence on adiponectin concentrations. Fourth, differences in dietary composition between the control and intervention groups were not analysed because most of the included studies had limited data, hindering the analysis of the content of other dietary components, such as n-3 PUFA, n-6 PUFA, fibre and whole grains, that have been shown to affect adiponectin concentrations. Fifth, as complete data about the presence of diabetes and the metabolic syndrome, being associated with decreased adiponectin concentrations, were not identified in most of the studies included in the meta-analysis, the results of dietary intervention on subjects with and without them may distinctly affect its concentrations. Lastly, none of the studies included in the meta-analysis presented intention-to-treat analysis, a statistical approach that is usually associated with more conservative results.

In conclusion, the present systematic review with meta-analysis of RCT suggests that, among the different interventions on dietary lipid intake, intake of low-fat diets were not associated with differences in adiponectin concentrations. n-3 PUFA supplementation was associated with moderate increases in adiponectin concentrations, whereas CLA supplementation seemed to be associated with a decrease in adiponectin concentrations compared with unsaturated fat intake. Caution needs to be exercised in interpreting these results because important sources of heterogeneity were found in the meta-analyses of n-3 PUFA and CLA supplementation. Therefore, future RCT are necessary to confirm these findings.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114514002013

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