



Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms



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ABSTRACT

Background and aims: The effect of statin therapy on plasma adiponectin levels has not been conclusively studied. Therefore, we aimed to evaluate this effect through a systematic review and meta-analysis of available randomized controlled trials (RCTs).

Methods: Quantitative data synthesis was performed using a random-effects model with weighted mean difference (WMD) and 95% confidence interval (CI) as summary statistics.

Results: In 30 studies (43 study arms) with 2953 participants, a significant increase in plasma adiponectin levels was observed after statin therapy (WMD: 0.57 µg/mL, 95% CI: 0.18, 0.95, $p = 0.004$). In subgroup analysis, atorvastatin, simvastatin, rosuvastatin, pravastatin and pitavastatin were found to change plasma adiponectin concentrations by 0.70 µg/mL (95% CI: -0.26, 1.65), 0.50 µg/mL (95% CI: -0.44, 1.45), -0.70 µg/mL (95% CI: -1.08, -0.33), 0.62 µg/mL (95% CI: -0.12, 1.35), and 0.51 µg/mL (95% CI: 0.30, 0.72), respectively. With respect to duration of treatment, there was a significant increase in the subset of trials lasting ≥ 12 weeks (WMD: 0.88 µg/mL, 95% CI: 0.19, 1.57, $p = 0.012$) but not in the subset of < 12 weeks of duration (WMD: 0.18 µg/mL, 95% CI: -0.23, 0.58, $p = 0.390$). Random-effects meta-regression suggested a significant association between statin-induced elevation of plasma adiponectin and changes in plasma low density lipoprotein cholesterol levels (slope: 0.04; 95% CI: 0.01, 0.06; $p = 0.002$).

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Conclusions: The meta-analysis showed a significant increase in plasma adiponectin levels following statin therapy. Although statins are known to increase the risk for new onset diabetes mellitus, our data might suggest that the mechanism for this is unlikely to be due to a reduction in adiponectin expression.

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1. Introduction

Adiponectin is an adipocyte-derived plasma protein secreted mainly by white adipose tissue [1]. It impacts metabolism of carbohydrates and fatty acids in the liver cells and muscles, indirectly influencing the insulin resistance *via* decreasing hepatic gluconeogenesis, increasing glucose uptake and beta-oxidation in the muscles [2]. In the circulation, adiponectin exists in three oligomeric forms: a low-molecular weight trimer, a medium molecular weight hexamer and a larger High-Molecular Weight (HMW) adiponectin form [3]. The HMW adiponectin is in particular the major active form of protein, which is primarily associated with insulin resistance and the presence of metabolic syndrome [4]. The adiponectin gene (*ADIPOQ*) located at position 3q27 is considered the most important genetic factor regulating plasma adiponectin levels [5]. The levels of plasma adiponectin are higher in women than in men and vary by ethnicity, being lower in African-Americans than in Caucasians [6,7]. Several single nucleotide polymorphism (SNPs) of the adiponectin gene such as SNP45, SNP276, SNP11377 and SNP11391 were associated with low plasma concentrations of adiponectin and type 2 diabetes mellitus (DM) [8]. Moreover, a sedentary life and high fat diet seems to be associated with disturbances of plasma adiponectin concentrations [9]. Indeed, it has been recently shown that obesity induces a DNA hypermethylation of *ADIPOQ* gene [10]. Low plasma concentrations of adiponectin have been observed in patients with metabolic syndrome, DM, obesity, hypertension, and coronary artery disease (CAD) [11–14]. Nevertheless, increased plasma levels of adiponectin have been found to be associated with increased values of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), suggesting a role of adiponectin in inflammatory processes [15]. Adiponectin also stimulates endothelial production of nitric oxide (NO) and endothelin-1 (ET-1), inhibits monocyte adhesion to endothelial cells and macrophage-derived foam cell transformation, stimulates angiogenesis through promotion of cross-talk between Akt signaling and AMP-activated protein kinase and attenuates TNF- α -induced expression of adhesion molecules in endothelial cells [16]. Plasma adiponectin levels were negatively correlated with triglyceride and low-density lipoprotein cholesterol (LDL-C), but positively correlated with high-density lipoprotein cholesterol (HDL-C) levels in clinical trials [17,18]. Similarly to HDL-C its level increases after physical exertion [19].

Statins have been shown to have pleiotropic effects, influencing endothelial function, platelet adhesion, thrombosis, plaque stability, and inflammation, however there have been recently a discussion whether this effect is not only related to potent LDL-C reduction [20,21]. Available data also suggest that statins may have an impact on the adiponectin levels and hence the use of statins should be recorded, as can be a potential confounder. On the other hand statin therapy increases the risk of new onset diabetes (NOD), and one of the investigated hypotheses of this mechanism might be adipokines related [22].

Taking into account that statin therapy might modulate plasma adiponectin concentrations, and the exact effects are not completely known, we evaluated the impact of statin therapy on plasma adiponectin concentrations in the systematic review and

meta-analysis of randomized controlled trials (RCTs).

2. Materials and methods

The analysis was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. Due to the study design (meta-analysis of randomized controlled trials) no Institutional Review Board (IRB) approval, as well as no patients' informed consents was obtained.

2.1. Search strategy

The analysis was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. PubMed, Medline and SCOPUS databases were searched using the following search terms in titles and abstracts: (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR) AND (adiponectin). Additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses: scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), the American College of Cardiology (ACC), European Society of Atherosclerosis (EAS) and National Lipid Association (NLA). The wild-card term "*" was used to increase the sensitivity of the search strategy. All searches were limited to studies in human. The literature was searched from inception to March 1, 2015. Two reviewers (CS and AS) examined every article separately to minimize the possibility of duplication, investigating reviews, case studies and experimental studies. Disagreements were resolved by discussion with a third party (MB).

2.2. Study selection

Original studies were included if they met the following *inclusion criteria*: (i) having a randomized controlled design in either parallel or cross-over form, (ii) investigating the impact of statin therapy (in monotherapy or in the combined therapy) on plasma/serum concentrations of adiponectin, (iii) treatment duration of at least two weeks, (iv) presentation of sufficient information on plasma/serum adiponectin concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were (i) non-clinical studies, (ii) lack of a control group in the study design, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up adiponectin concentrations.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) study design; 5) number of participants in the statin and control groups; 5) type, dose and duration of statin therapy; 6) age, gender and body mass index (BMI) of study participants; 7)

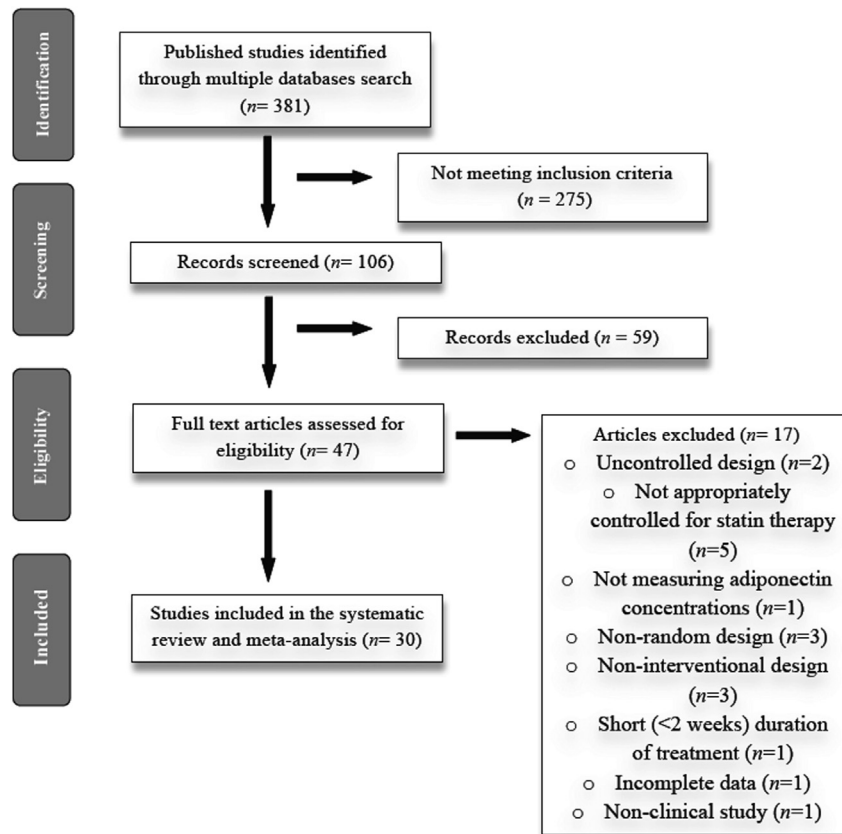


Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

baseline levels of total cholesterol, LDL-C, HDL-C, triglycerides, hs-CRP and glucose; 8) systolic and diastolic blood pressures; and 9) data regarding baseline and follow-up concentrations of adiponectin. Data extraction was performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [24]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding of subjects and personnel, blinding of outcome assessment, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias. Risk-of-bias assessment was performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

2.5. Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [25]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up – measure at baseline. For single-arm cross-over trials, net change in plasma concentrations of adiponectin were calculated by subtracting the value after control intervention from that reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula:

$SD = \text{square root} [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and inter-quartile range, mean and standard SD values were estimated using the method described by Hozo et al. [26]. To convert interquartile range into Min-Max range, the following equations were used: $A = \text{median} + 2 \times (Q_3 - \text{median})$ and $B = \text{median} - 2 \times (\text{median} - Q_1)$, where A, B, Q_1 and Q_3 are upper and lower ends of the range, upper and lower ends of the interquartile range, respectively. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects. In case the values were only presented as graph, the software GetData Graph Digitizer 2.24 (<http://getdata-graph-digitizer.com/>) was applied to digitize and extract the data.

A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and type of statin being studied [27]. Heterogeneity was quantitatively assessed using I^2 index. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Sensitivity analysis was performed using leave-one-out method. In this method, each study is iteratively removed at a time to confirm that the pooled estimate of effect size is not driven by any single study.

2.6. Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association

Table 1
Demographic characteristics and baseline parameters of the studies selected for analysis.

Study		Buldak et al. [51]	Chan et al. [52]	Devaraj et al. [53]	Doh et al. [54]	El-Barbery et al. [55]	Fichtenbaum et al. [56]	Forst et al. [57]
Year		2012	2008	2007	2012	2011	2010	2007
Location		Poland	Taiwan	USA	Korea	Egypt	USA	Germany
Design		Randomized simple-blind parallel group trial	Randomized parallel group trial	Randomized, double-blind, placebo-controlled parallel group trial	Randomized parallel group trial	Randomized parallel group trial	Multicenter randomized open label parallel group trial	Two center randomized double-blind parallel group trial
Duration of trial		90 days	6 months	8 weeks	6 months	6 months	48 weeks	12 weeks
Inclusion criteria		Patients with mixed hyperlipidemia (total cholesterol >200 mg/dL, LDL-C >130 mg/dL and triglycerides >200 mg/dL) fasting glucose (100–125 mg/dL), glycemia at 2 h of OGTT <140 mg/dL, BMI 25–35 kg/m ² , postmenopausal state or effective methods of mechanical contraception	CAD patients with stable angina and normal lipid profiles scheduled for PCI (balloon angioplasty and stenting), and who were not taking statins	Patients with MS as defined using the criteria of the National Cholesterol Education Panel Adult Treatment Panel III	Patients who were 20 yrs of age or older and had been maintained on PD > 3 months	Patients with RA fulfilling the 1987 American College of Rheumatology revised criteria, with disease duration <1 year with no prior use of disease-modifying antirheumatic drugs and/or systemic steroids	HIV-infected persons with combined hyperlipidemia	Patients with previous medical history of infarction, and/or coronary angiography with proven cardiovascular disease, and/or unstable angina pectoris, and/or duplex sonography of cervical or leg vessels with proven arteriosclerotic alterations, and/or electrocardiogram with ischemia, and/or stroke, and/or transient ischemic attack, and/or peripheral arterial occlusion, and/or vessel surgery, and/or hypertension
Statin form		Atorvastatin	Atorvastatin	Simvastatin	Rosuvastatin	Atorvastatin	Pravastatin	Simvastatin
Statin intervention		10 mg/day Combination: atorvastatin + fenofibrate (267 mg/day)	10 mg/day	40 mg/day	10 mg/day	40 mg/day	40 mg/day Combination: pravastatin + fenofibrate (200 mg/day)	40 mg/day** Combination: simvastatin + pioglitazone (45 mg/day)**
Participants	Statin group	16	30	25	35	15	37	43
	Control group	19					60	43
	Statin group	14	30	25	35	15	37	39
Age (years)	Statin group	52.9 ± 7.2	66.13 ± 11.50	51 ± 12	48.9 ± 11.7	54.8 ± 14.7	42 (31–57)	57.3 ± 8.4
	Control group	51.9 ± 9.1					44 (28–57)	59.0 ± 8.6
Male (%)	Statin group	49.1 ± 8.8	63.77 ± 12.73		48.5 ± 11.3	53.7 ± 15.4	46 (28–62)	59.5 ± 7.8
	Control group	56.25	80.0	28	45.7	20.0	91.89	37.21
BMI (kg/m ²)	Statin group	47.37					95.0	41.86
	Control group	50.0	63.3	39 ± 7	45.7	13.33	100.0	48.75
hs-CRP (mg/L)	Statin group	29.5 ± 3.6	25.86 ± 2.51		22.9 ± 3.1	25.8 ± 3.1	26.4 (24.0–30.9)*	30.5 ± 3.7
	Control group	27.8 ± 2.6					25.9 (22.6–28.3)*	31.2 ± 4.1
	Statin group	28.3 ± 2.2	25.12 ± 2.48	3.6 (3, 6.1)	22.7 ± 3.0	25.5 ± 3.3	25.4 (22.2–27.1)*	30.8 ± 4.8
	Control group	NS	0.89 ± 1.16		2.05 ± 1.57	31.46 ± 14.33	3.5 (2.1–6.0)*	NS
	Statin group	NS					2.7 (1.5–4.5)*	NS
Total cholesterol (mg/dL)	Statin group	NS	0.71 ± 0.88	5.3 (2.4, 6.6)	1.90 ± 1.33	33.06 ± 14.13	2.4 (1.2–3.9)*	NS
	Control group	257.9 ± 22.2	195.13 ± 36.32	NS	190.3 ± 25.47	228.13 ± 11.75	260 (249–289)*	221.18 ± 42.46
LDL-C (mg/dL)	Statin group	265.6 ± 28.8					269 (248.5–316)*	218.86 ± 48.63
	Control group	231.1 ± 40.7	193.57 ± 41.31	NS	190.68 ± 46.32	224.66 ± 31.12	281 (252–325)*	216.16 ± 38.21
HDL-C (mg/dL)	Statin group	152.1 ± 17.9	128.67 ± 28.80	NS	117.73 ± 28.56	142.66 ± 24.33	160 (145–179)*	138.96 ± 38.98
	Control group	165.3 ± 26.4					156.5 (139–179)*	142.05 ± 42.46
	Statin group	152.7 ± 41.6	123.93 ± 37.78	NS	115.8 ± 37.05	142.33 ± 24.41	148 (132–176)*	135.1 ± 36.28
	Control group	43.7 ± 11.1	40.97 ± 8.16	NS	52.88 ± 15.05	41.60 ± 10.85	35 (32–41)*	55.2 ± 15.82
Triglycerides (mg/dL)	Statin group	43.0 ± 10.1					35 (30–39)*	55.58 ± 17.37
	Control group	44.1 ± 10.7	38.77 ± 8.86	NS	52.88 ± 18.14	44.06 ± 9.12	34 (30–39)*	54.42 ± 15.82
	Statin group	240.1 ± 14.6	163.57 ± 123.48	NS	95.58 (71.68–152.22)	126.93 ± 31.97	307 (225–399)*	144.25 ± 145.14
	Control group	248.1 ± 39.6					355 (252.5–468.5)*	128.32 ± 52.21
Adiponectin (µg/mL)	Statin group	226.6 ± 35.5	168.80 ± 107.70	NS	107.08 (84.07–167.26)	137.33 ± 47.31	375 (262–457)*	132.75 ± 64.6
	Control group	17.5 ± 2.7	8.66 ± 3.79	7.7 ± 2.1	21.0 ± 6.1	19.21 ± 2.10	4.5 (3–7)*	15.49 ± 12.66
	Statin group	16.2 ± 2.7					4 (3–6)*	11.68 ± 9.96
	Control group	17.8 ± 3.4	8.80 ± 3.74	7.3 ± 1.9	21.3 ± 9.9	19.81 ± 1.95	4 (3–6)*	13.96 ± 8.16
Glucose (mg/dL)	Statin group	107.6 ± 6.0	NS	114 ± 55	93.06 ± 8.82	NS	NS	100.8 ± 11.16
	Control group	103.0 ± 8.0					NS	102.6 ± 11.88
	Statin group	110.3 ± 6.5	NS	109 ± 35	92.34 ± 26.64	NS	NS	101.34 ± 9.72
	Control group	NS	NS	NS	136.6 ± 19.7	NS	NS	NS
SBP (mmHg)	Statin group	NS	NS	NS	136.8 ± 17.2	NS	NS	NS
	Control group	NS	NS	NS	81.1 ± 7.7	NS	NS	NS
DBP (mmHg)	Statin group	NS	NS	NS	80.9 ± 10.5	NS	NS	NS
	Control group	NS	NS	NS			NS	NS

Study	Gamage-Vareed et al. [38]	Kim et al. [60]	Koh et al. [61]	Koh et al. [62]	Koh et al. [63]	Koh et al. [64]	Koh et al. [65]
Year	2005	2008	2005a	2005b	2009	2010	2011a
Location	Lebanon	Germany	Korea	Korea	Korea	Korea	Korea
Design	Randomized, double-blind, placebo-controlled parallel group trial	Randomized parallel group factorial randomized trial	Multicenter, double-blind, placebo-controlled crossover trial	Randomized, double-blind, controlled crossover trial	Randomized, double-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, crossover trial
Duration of trial	12 weeks	14 days	2 months	2 months	2 months	2 months	2 months
Inclusion criteria	Healthy volunteers	Male volunteers aged between 18 and 60 yrs, with BMI between 18.5 and 30 kg/m ² . LDL-C concentrations < 190 mg/dL, triglycerides < 250 mg/dL and normal blood pressure (< 140/90 mmHg)	Patients with a history of type 2 DM and hypercholesterolemia	Hypercholesterolemic patients with type 2 diabetes (LDL cholesterol levels > 100 mg/dL)	Patients with hypercholesterolemia (LDL cholesterol levels ≥ 130 mg/dL)	Patients with hypercholesterolemia (LDL cholesterol levels > 100 mg/dL)	Patients with mild-to-moderate hypertension (systolic blood pressure < 180 and diastolic blood pressure < 110 mm Hg)
Statin form	Pravastatin	Simvastatin	Atorvastatin	Simvastatin	Simvastatin	Atorvastatin	Atorvastatin
Statin intervention	40 mg/day	40 mg/day Combination: simvastatin + ezetimibe (10 mg/day)	10 mg/day Combination: atorvastatin + fenofibrate (200 mg/day)	20 mg/day Combination: simvastatin + ramipril (10 mg/day)	20 mg/day 40 mg/day	10 mg/day 20 mg/day 40 mg/day	20 mg/day Combination: atorvastatin + amlodipine (10 mg/day)
Participants	19	24	56	50	43	44	42
Age (years)	21 51.6 ± 13.0	24 31.9 ± 8.8 34.1 ± 11.2	56 ± 1**	59 ± 1**	42 58 ± 2** 56 ± 2**	44 56 ± 10 58 ± 9 59 ± 12	53 ± 2**
Male (%)	46.3 ± 9.7 52.63	28.6 ± 6.6 100.0	41.07	60.0	59 ± 1** 39.53	54 ± 11 50.0 47.72	52.38
BMI (kg/m ²)	57.14 26.8 ± 4.28	100.0 26.4 ± 3.2	25.46 ± 0.34**	25.5 ± 0.4**	35.71 38.09 25.25 ± 0.53**	51.16 52.27 24.8 ± 3.4 24.9 ± 3.4	25.45 ± 0.36**
hs-CRP (mg/L)	26.1 ± 4.20 NS	25.8 ± 3.1 25.0 ± 3.3 NS	25.47 ± 0.34** 25.45 ± 0.34** 1.20 (0.65–2.20)*	1.10 (0.60–2.90)*	24.52 ± 0.54** 1.00 (0.40–3.10)* 1.45 (0.60–2.10)*	24.9 ± 3.4 24.8 ± 2.4 0.95 (0.50–3.10)* 1.00 (0.45–2.00)* 1.00 (0.65–2.00)*	25.48 ± 0.37** 25.51 ± 0.35** 1.05 (0.80–2.40)* 1.40 (0.90–2.40)*
Total cholesterol (mg/dL)	224 ± 51.7	239.22 ± 19.3	234 ± 6**	227 ± 6**	254 ± 5**	242 ± 31 253 ± 41	227 ± 5**
LDL-C (mg/dL)	229.8 ± 48.9 159.6 ± 43.9	245.18 ± 34.74 154.4 ± 15.44	240 ± 6** 134 ± 7**	223 ± 7** 135 ± 6**	267 ± 5** 178 ± 5**	240 ± 32 156 ± 31 159 ± 33	211 ± 5** 132 ± 6**
HDL-C (mg/dL)	149.7 ± 43.8 44.1 ± 14.1	158.26 ± 27.02 50.18 ± 1.58	130 ± 7**	134 ± 5**	170 ± 5**	169 ± 38 154 ± 29	137 ± 5** 124 ± 5**
Triglycerides (mg/dL)	47.8 ± 13.5 146.6 ± 56.9	54.04 ± 3.86 54.04 ± 7.72 141.6 (70.8–300.9)	46 ± 2**	46 ± 2**	51 ± 2**	51 ± 12 54 ± 13	48 ± 2**
Adiponectin (µg/ml)	168.5 ± 100.7 7.30 ± 4.79	141.6 (88.5–345.15) 3.22 ± 1.27	44 ± 1**	47 ± 1**	54 ± 2**	51 ± 12 52 ± 11	51 ± 2**
Glucose (mg/dL)	7.36 ± 3.59 92.8 ± 15.1	13.17 ± 5.97 NS	322 ± 19** 3.5 (2.6–5.0)*	213 ± 18** 3.8 (2.7–5.2)*	147 ± 12** 5.8 ± 0.8**	172 ± 89 2.8 ± 2.4 3.1 ± 2.4	209 ± 18** 3.3 ± 0.3**
SBP (mmHg)	89.5 ± 9.2 NS	151.2 ± 39.6 126.8 ± 11.8	89 ± 3**	128 ± 6**	97 ± 3**	108 ± 21 109 ± 22 103 ± 17	106 ± 2** 104 ± 3** 154 ± 1**
DBP (mmHg)	NS	125.1 ± 21.8	NS	135 ± 2**	NS	NS	157 ± 1**
	NS	129.8 ± 7.7 76.4 ± 7.1	NS	131 ± 2** 80 ± 1**	NS	NS	156 ± 2** 94 ± 1**
	NS	76.3 ± 6.8	NS	80 ± 1**	NS	NS	96 ± 1**
	NS	81.2 ± 6.8	NS	78 ± 1**	NS	NS	95 ± 1**

Study	Roberto et al. [74]	Sawara et al. [75]	Shetty et al. [76]	Sugiyama et al. [77]	Van hoek et al. [78]	Yokoyama et al. [79]	Hu et al. [80]
Year	2010	2008	2004	2007	2009	2011	2009
Location	Italy	Japan	USA	Japan	Netherlands	Japan	China
Design	Randomized parallel group trial	Randomized parallel group trial	Randomized, double-blind, placebo-controlled, parallel group trial	Open-label, randomized parallel group trial	Randomized, double-blind, placebo-controlled, parallel group trial	Randomized parallel group trial	Randomized parallel group trial
Duration of trial	30 days	12 months	12 weeks	6 months	30 weeks	2 months	12 weeks
Inclusion criteria	Patients with polygenic hypercholesterolemia (patients, LDL-C > 160 mg/dL).	Patients with chronic kidney disease (stage 2–4) with an estimated GFR <90 mL/min and ≥15 mL/min.	Diabetic patients with no serious long-term complications (macroalbuminuria, severe neuropathy, and/or peripheral vascular disease associated with foot ulceration or other lower extremity amputations) or were considered at higher risk to develop type 2 diabetes than the general population	Non-hypercholesterolemic (total cholesterol <220 mg/dL); and non-diabetic (fasting glucose <126 mg/dL, 2 h post-loaded glucose <200 mg/dL and glycosylated hemoglobin A1c (HbA1c) < 6.4%) and without taking any lipid-lowering medications	Men and women aged 45–75 yrs, with a known duration of type 2 diabetes of at least 1 year and mild hypertriglyceridemia (total cholesterol levels between 4.0 and 8.0 mmol/L and fasting triglyceride levels between 1.5 and 6.0 mmol/L)	Patients with CAD, with serum LDL cholesterol level >100 mg/dL	Type 2 diabetic patients
Statin form	Atorvastatin	Rosuvastatin	Atorvastatin	Pravastatin	Atorvastatin	Pravastatin	Simvastatin
Statin intervention	10 mg/day	2.5 mg/day	20 mg/day	10–20 mg/day	10 mg/day	10 mg/day	40 mg/day
Participants	18	22	34	20	73	12	23
Age (years)	55.2 ± 4.1	63.8 ± 9.1	NS	68.2 ± 8.3	72	11	20
Male (%)	55.2 ± 3.8	67.0 ± 7.9	NS	65.7 ± 9.2	72	13	58.5 ± 1.6**
	44.44	50.0	55.84	65.0	59.7 ± 7.6**	65 ± 2**	55.2 ± 2.3**
					60.1 ± 7.7**	66 ± 3**	39.1
					58.5 ± 7.5**	69 ± 2**	
					60.0	83.33	
					53.0	81.81	
					46.0	100.0	
					30.0 ± 3.8**	23.7 ± 0.5**	
					30.4 ± 4.5**	24.8 ± 1.3**	
					32.2 ± 6.0**	24.2 ± 1.2**	
					NS	405 ± 309**	
					NS	389 ± 162**	
					NS	579 ± 165**	
					228.51 ± 35.51**	193 ± 17**	
					231.98 ± 34.35**	202 ± 10**	
					233.144 ± 31.26**	179 ± 9**	
					NS	124 ± 16**	
					NS	127 ± 8**	
					NS	93 ± 5**	
					40.53 ± 1.158**	45.7 ± 3.2**	
					40.14 ± 1.15**	51.0 ± 4.2**	
					40.53 ± 1.15**	42.5 ± 3.0**	
					235.41 ± 9.73**	166 ± 44**	
					260.19 ± 12.39**	112 ± 20**	
					249.57 ± 11.5**	174 ± 26**	
					7.69 ± 0.46**	3.28 ± 0.11**	
					8.20 ± 0.58**	2.95 ± 0.56**	
					7.44 ± 0.42**	3.51 ± 0.41**	
					189.0 ± 54.0**	145 ± 12**	
					190.8 ± 52.2**	139 ± 9**	
					189.0 ± 64.8**	131 ± 20**	
					146 ± 17**	NS	
					145 ± 17**	NS	
					144 ± 19**	NS	
					86 ± 10**	NS	
					85 ± 9**	NS	
					85 ± 9**	NS	

Values are expressed as mean ± SD or median (range); * median (25th–75th percentiles); ** mean ± SEM; [§]values of adiponectin levels, CRP levels and triglycerides levels are log-transformed.

BMI: body mass index; NS: not stated; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index; OGTT: oral glucose tolerance test; CAD: coronary artery disease; PCI: percutaneous coronary intervention; MS: metabolic syndrome; PD: peritoneal dialysis; RA: rheumatoid arthritis; DM: diabetes mellitus; GFR: glomerular filtration rate.

Table 2
Assessment of risk of bias in the included studies using Cochrane criteria.

Study	Ref	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Buldak et al.	[51]	U	U	L	U	L	L	L
Chan et al.	[52]	U	U	L	U	L	L	L
Devaraj et al.	[53]	U	U	L	U	L	L	L
Doh et al.	[54]	L	L	L	U	L	L	L
El-Barbery et al.	[55]	U	U	L	L	L	L	L
Fichtenbaum et al.	[56]	H	H	H	U	L	L	L
Forst et al.	[57]	U	U	L	L	L	L	L
Gannage-Yaredet et al.	[58]	U	U	L	U	L	L	L
Gouni-Berthold et al.	[59]	U	U	L	U	L	L	L
Kim et al.	[60]	U	U	L	U	L	L	L
Koh et al.	[61]	U	U	L	L	L	L	L
Koh et al.	[62]	U	U	L	L	L	L	L
Koh et al.	[63]	U	U	L	L	L	L	L
Koh et al.	[64]	L	L	L	U	L	L	L
Koh et al.	[65]	U	U	L	L	L	L	L
Koh et al.	[66]	U	U	L	U	L	L	L
Koh et al.	[67]	L	L	L	U	L	L	L
Koh et al.	[68]	U	U	L	L	L	L	L
Koh et al.	[69]	U	U	L	L	L	L	L
Krysiak et al.	[70]	H	H	H	L	L	L	L
Kwang et al.	[71]	U	U	L	L	L	L	L
Nakamura et al.	[72]	U	U	L	U	L	L	L
Nomura et al.	[73]	U	U	L	U	L	L	L
Roberto et al.	[74]	L	L	L	L	L	L	L
Sawara et al.	[75]	U	U	L	L	L	L	L
Shetty et al.	[76]	U	U	L	U	L	L	L
Sugiyama et al.	[77]	L	L	L	U	L	L	L
van Hoek et al.	[78]	U	U	L	U	L	L	L
Yokoyama et al.	[79]	U	U	L	U	L	L	L
Hu et al.	[80]	U	U	L	L	L	L	L

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

between calculated WMD and duration of statin therapy and changes in plasma LDL-C concentrations as potential moderator variables.

2.7. Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, classic "fail-safe N" methods and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias [28].

3. Results

3.1. Search results and trial flow

The initial screening for potential relevance removed the articles with titles and/or abstracts that were obviously irrelevant. Among the 47 full text articles assessed for eligibility, 17 studies were excluded because: uncontrolled design ($n = 2$), not appropriately controlled for statin therapy ($n = 5$), not measuring adiponectin concentrations ($n = 1$), non-random design ($n = 3$), non-interventional design ($n = 3$), short (<2 weeks) duration of treatment ($n = 1$), incomplete data ($n = 1$), non-clinical study ($n = 1$) (Fig. 1). After final assessment, 30 trials with 43 treatment arms achieved the inclusion criteria and were preferred for the final meta-analysis.

In total, 1470 participants were allocated to statin therapy groups, 482 to combined therapy groups and 1001 to control groups in the 30 selected studies. The number of participants in

these trials ranged from 30 to 217. Included studies were published between 2004 and 2014, and were conducted in Korea ($n = 12$), Japan ($n = 5$), USA ($n = 3$), Poland ($n = 2$), Germany ($n = 2$), Italy, Taiwan, Lebanon, Egypt, China, and the Netherlands. The following statin doses were administered in the included trials: 10 mg–40 mg/day simvastatin, 10 mg–80 mg/day atorvastatin, 10 mg–40 mg/day pravastatin, 2.5 mg–10 mg/day rosuvastatin, and 2 mg/day pitavastatin. Combined therapy was administered in 11 trials (statins plus fibrates or pioglitazone or ezetimibe or amlodipine or ramipril or sartans or eicosapentaenoic acid). Duration of statin intervention ranged between 14 days and 12 months. 25 trials were designed as parallel group and 5 as cross-over studies. All studies employed immunoassay methods for the quantification of adiponectin levels.

Two studies were multicenter. Demographic and baseline parameters of the included trials are shown in Table 1.

3.2. Risk of bias assessment

Some of the included studies were characterized by lack of information about the random sequence generation and allocation concealment. Details of the quality assessment are shown in Table 2.

3.3. Effect of statin therapy on plasma adiponectin concentrations

Changes in plasma adiponectin concentrations following statin therapy were reported in 43 treatment arms. A significant increase in plasma adiponectin concentrations was observed following statin therapy (WMD: 0.57 $\mu\text{g/mL}$, 95% CI: 0.18, 0.95, $p = 0.004$)

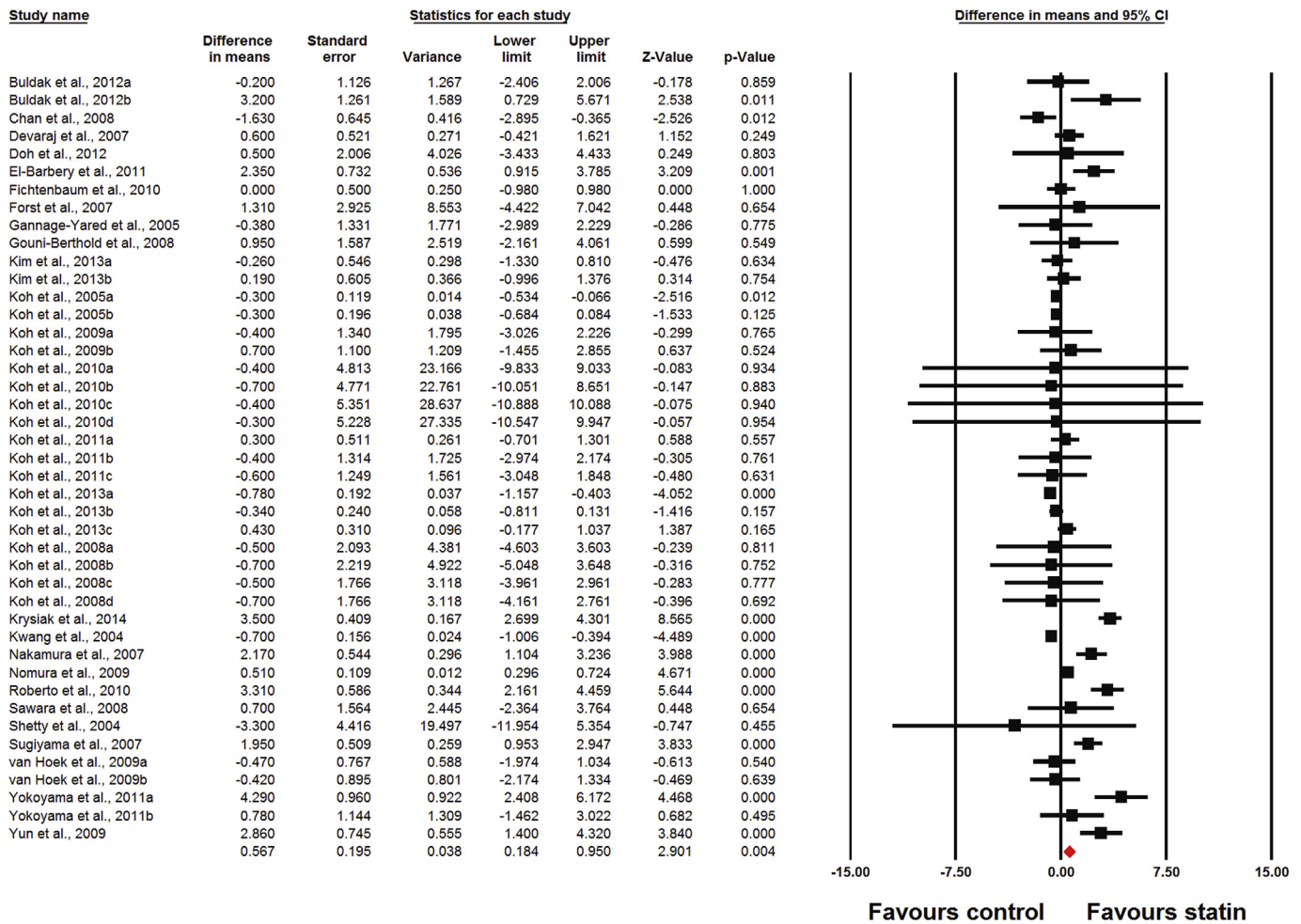


Fig. 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations.

(Fig. 2). This effect was robust in the sensitivity analysis (Fig. 3). In the subgroup analysis, atorvastatin, simvastatin, rosuvastatin, pravastatin and pitavastatin were found to change plasma adiponectin concentrations by 0.70 $\mu\text{g}/\text{mL}$ (95% CI: $-0.26, 1.65, p = 0.152$), 0.50 $\mu\text{g}/\text{mL}$ (95% CI: $-0.44, 1.45, p = 0.297$), $-0.70 \mu\text{g}/\text{mL}$ (95% CI: $-1.08, -0.33, p = 0.001$), 0.62 $\mu\text{g}/\text{mL}$ (95% CI: $-0.12, 1.35, p = 0.100$), and 0.51 $\mu\text{g}/\text{mL}$ (95% CI: $0.30, 0.72, p = 0.001$), respectively (Fig. 4). With respect to duration of treatment, there was a significant increase in the subset of trials lasting ≥ 12 weeks (WMD: 0.88 $\mu\text{g}/\text{mL}$, 95% CI: 0.19, 1.57, $p = 0.012$) but not in the subset with < 12 weeks of duration (WMD: 0.18 $\mu\text{g}/\text{mL}$, 95% CI: $-0.23, 0.58, p = 0.390$) (Fig. 5). There was a greater effect in the subset of trials in which statins were administered as monotherapy (WMD: 0.70 $\mu\text{g}/\text{mL}$, 95% CI: 0.02, 1.39, $p = 0.044$) versus the subset that used a combination therapy approach (WMD: 0.11 $\mu\text{g}/\text{mL}$, 95% CI: $-0.31, 0.54, p = 0.599$) (Fig. 6). With respect to diabetes, there was a significant increase in plasma adiponectin concentrations in the subsets of trials without diabetes as an inclusion criterion (WMD: 0.62 $\mu\text{g}/\text{mL}$, 95% CI: 0.15, 1.08, $p = 0.010$), and not in the subset of trials defining diabetes as an inclusion criterion (WMD: 0.34 $\mu\text{g}/\text{mL}$, 95% CI: $-0.41, 1.09, p = 0.373$).

3.4. Meta-regression

Random-effects meta-regression suggested a significant association between statin-induced elevation of plasma adiponectin

concentrations and changes in plasma LDL-C levels (slope: 0.04; 95% CI: 0.01, 0.06; $p = 0.002$) (Fig. 7). However, changes in plasma adiponectin concentrations were not found to be associated with treatment duration (slope: -0.01 ; 95% CI: $-0.05, 0.04$; $p = 0.816$) (Fig. 7).

3.5. Publication bias

The funnel plot of the study precision (inverse standard error) by effect size (WMD) was asymmetric and suggested potential publication bias. This asymmetry was addressed by imputing nine potentially missing studies on the right side of funnel plot using “trim and fill” correction (Fig. 8). The imputed effect size was 0.87 $\mu\text{g}/\text{mL}$ (95% CI: 0.41, 1.32). There was no sign of publication bias according to the results of Begg’s rank correlation (Kendall’s Tau with continuity correction = $-0.001, z = 0.01$, two-tailed p -value = 0.992) and Egger’s linear regression (intercept = 0.83, standard error = 0.50; 95% CI = $-0.19, 1.84, t = 1.64, df = 41$, two-tailed $p = 0.109$) tests. The “fail safe N” method indicated that 124 theoretically missing studies would be required to make the overall estimated effect size non-significant.

4. Discussion

To our best knowledge, the present study is the first meta-analysis to comprehensively assess the association between statin

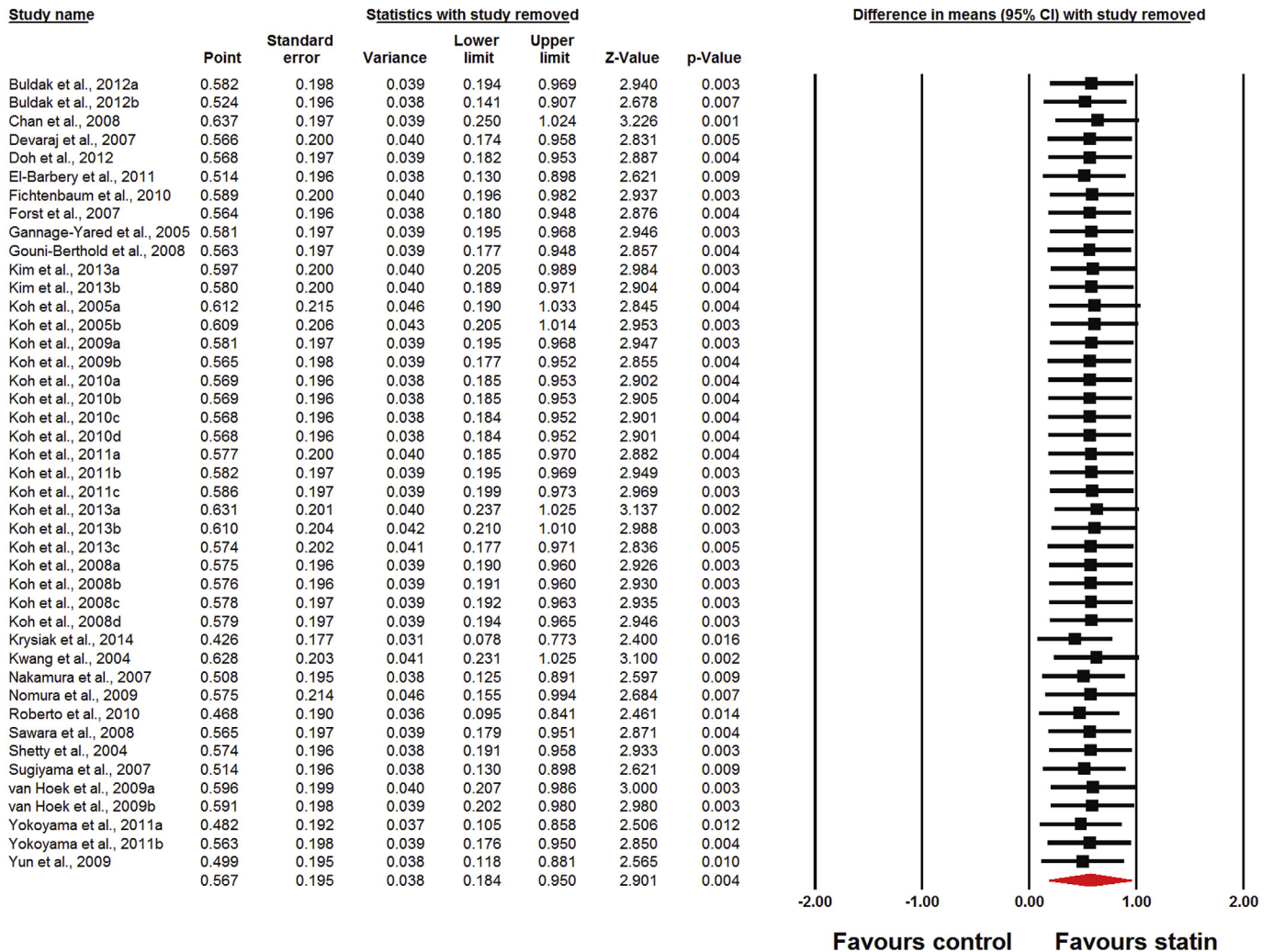


Fig. 3. Results of sensitivity analysis based on leave-one-out approach.

therapy and plasma adiponectin concentrations. The results showed that statins significantly increase, irrespective of the medication dose, the plasma adiponectin concentrations, especially in the subset of trials lasting ≥ 12 weeks, but not in the subset with < 12 weeks of duration. This effect was even greater in the subset of trials in which statins were administered as monotherapy compared with the subset that used a combination therapy. It is especially interesting as the studies included in this meta-analysis combined statins with various drugs, which can directly or indirectly stimulate PPAR α (e.g. fenofibrate) [29] or PPAR γ receptors (e.g. eicosapentaenoic acid, pioglitazone, ramipril) [30], and consequently increase the expression of adiponectin receptors in macrophages and increase plasma adiponectin concentrations in monotherapy.

This meta-analysis confirmed that statins may have an important impact on the adiponectin levels and hence the use of statins (in monotherapy or in the combination therapy) should be recorded, as can be a potential confounder. This analysis supports the results of our previous meta-analyses, in which we confirmed that statins have important out-of-lipid lowering properties, which might explain, at least in part, the potent effectiveness of these drugs in reducing cardiovascular risk [20,21,31,32]. The mechanism why statin therapy produces an increase of plasma adiponectin

concentrations seems not to be related to a reduction in adiponectin expression of these tissue-derived proteins [33]. Many available trials described the increased risk for NOD after statin therapy, addressing this complication as a possible side effect [34]. A meta-analysis of 6 trials comprising 57,593 patients showed a 13% higher NOD incidence in statin users compared to non-users [35]. Several mechanisms were described in NOD with statins, such as the modification of intracellular signal transduction pathways of insulin caused by inhibition of phosphorylation and inhibition of β -cell proliferation [36], differences in lipophilicity, inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, decrease of mevalonate synthesis, inhibition of isoprenoid biosynthesis, decrease of peroxisome proliferator activated receptor γ (PPAR- γ) and inhibition of adipocytes differentiation [37]. Nevertheless, the reduction of the action of small GTPase prevents proper transmission of the signals in pancreatic cells [38,39]. The secretion of insulin in statin-related NOD might be decreased through reduction of the ATP in the mitochondria of pancreatic cells, determined by reduced concentration of coenzyme Q10 [40, 41]. The decrease of glucose uptake by adipocytes seems to be a consequence of the reduction of glucose protein transporter type 4 (GLUT-4) on their surface [42,43], while the generation of non-specific inflammation conditions in pancreatic cells is a result

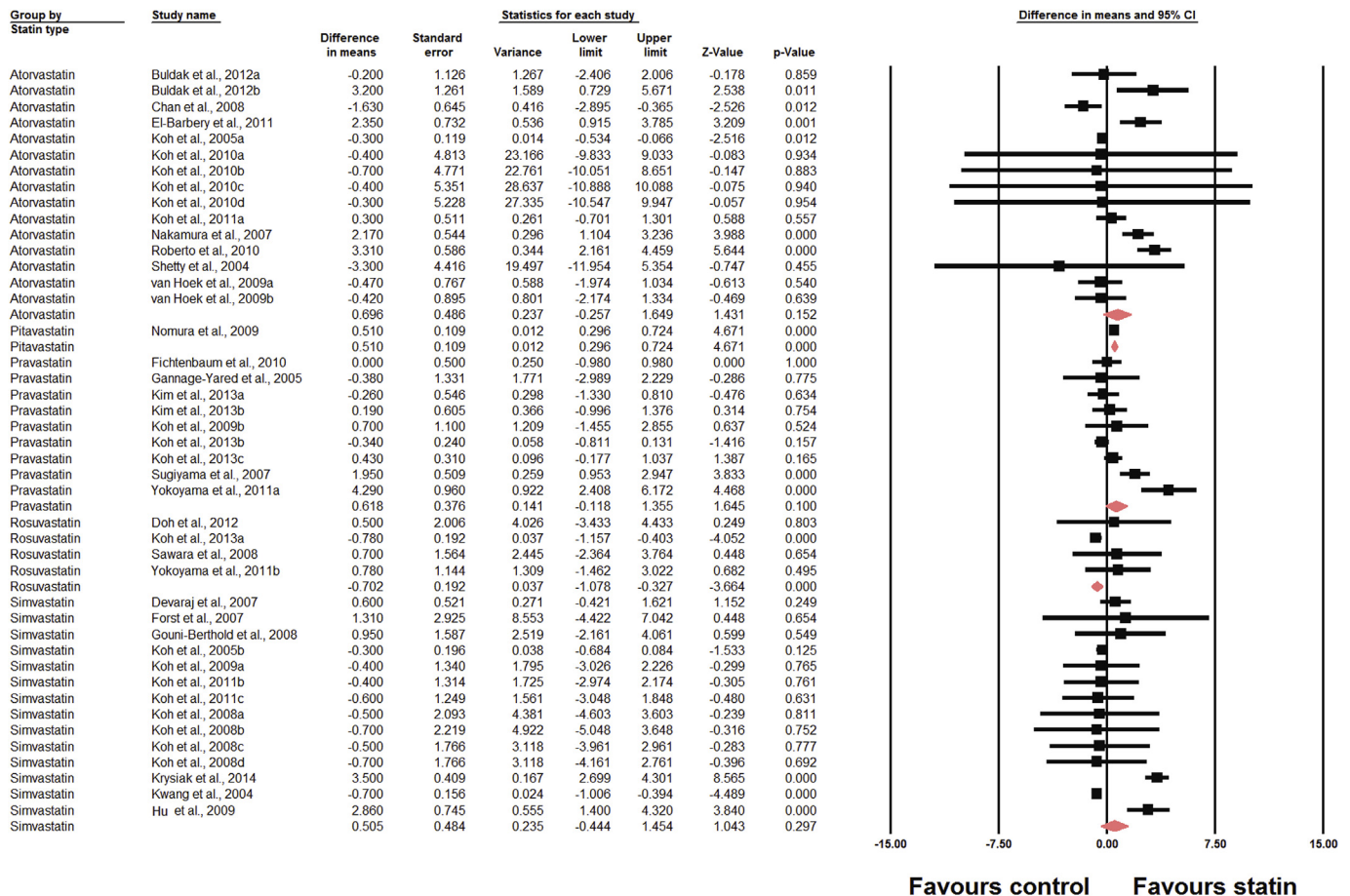


Fig. 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations in trials with different types of statins.

of increased compensating uptake of oxidized LDL particles [44] with consecutively decrease of plasma adiponectin concentrations. Some studies have shown the effects of statins on the level of secretion of adipokines; thus changing the secretory profile of adipose tissue might be another mechanism by which statins increase risk for DM [22]. However, the authors aware that there is still no convincing evidence that lower adiponectin levels are causally associated with diabetes, and the obtained results cannot explain the increase in diabetes risk in statin users, because this cannot be answered within the meta-analysis.

The association between statin therapy and adiponectin levels vary upon statin type and dose [47–50]. The results of our meta-analysis showed that both atorvastatin and pravastatin were more effective (numerically) than other statins in increasing plasma adiponectin concentrations. In contrast, rosuvastatin decreased plasma adiponectin concentrations. The main difference between strong hypolipemiant properties of rosuvastatin and the rest of statins is the increased affinity for hepatocytes with low systemic bioavailability [45,46] and consecutive lower effect on adiponectin secretion [47]. By all the statins, only pitavastatin did not show pro-diabetes effects in clinical trials [48], what might be in the line with the results of the meta-analysis, and significant increase of adiponectin concentrations after pitavastatin therapy observed.

The available studies have emphasized primarily a clear correlation between adiponectin concentration and HDL-C and inverse

correlation between adiponectin concentration and concentration of triglycerides [9], while the relationship between adiponectin and LDL-cholesterol levels is unclear. Interestingly, the results of the meta-analysis also confirm the relationship between plasma adiponectin concentration after statins and LDL-C levels.

Our meta-analysis has noteworthy limitations. The studies included had a relatively small population size and were heterogeneous, regarding the characteristics of patients and study design - inclusion criteria, statin dose and duration of the therapy. Different confounding factors like gender, the presence of chronic kidney disease or various inflammatory triggers might have also influenced the results of this meta-analysis. Smoking status is another factor, which might have modified our results since nicotine is known to decrease plasma adiponectin levels through changing KATP channels in adipocytes [49]. Furthermore, various changes of plasma adiponectin concentrations are dependent by different pharmacokinetic profiles of statins used (lipophilicity, metabolism, half-life, protein binding, and bioavailability, presence of active metabolites or excretion) [50].

In conclusion, the meta-analysis showed a significant increase in plasma adiponectin levels following statin therapy. Although statins are known to increase the risk for NOD, our data might suggest that the mechanism for this is unlikely to be due to a reduction in adiponectin expression. The pleiotropic adiponectin-elevating effect of statins may also explain, at least in part, the putative benefits of these drugs in reducing cardiovascular risk in diabetic patients.

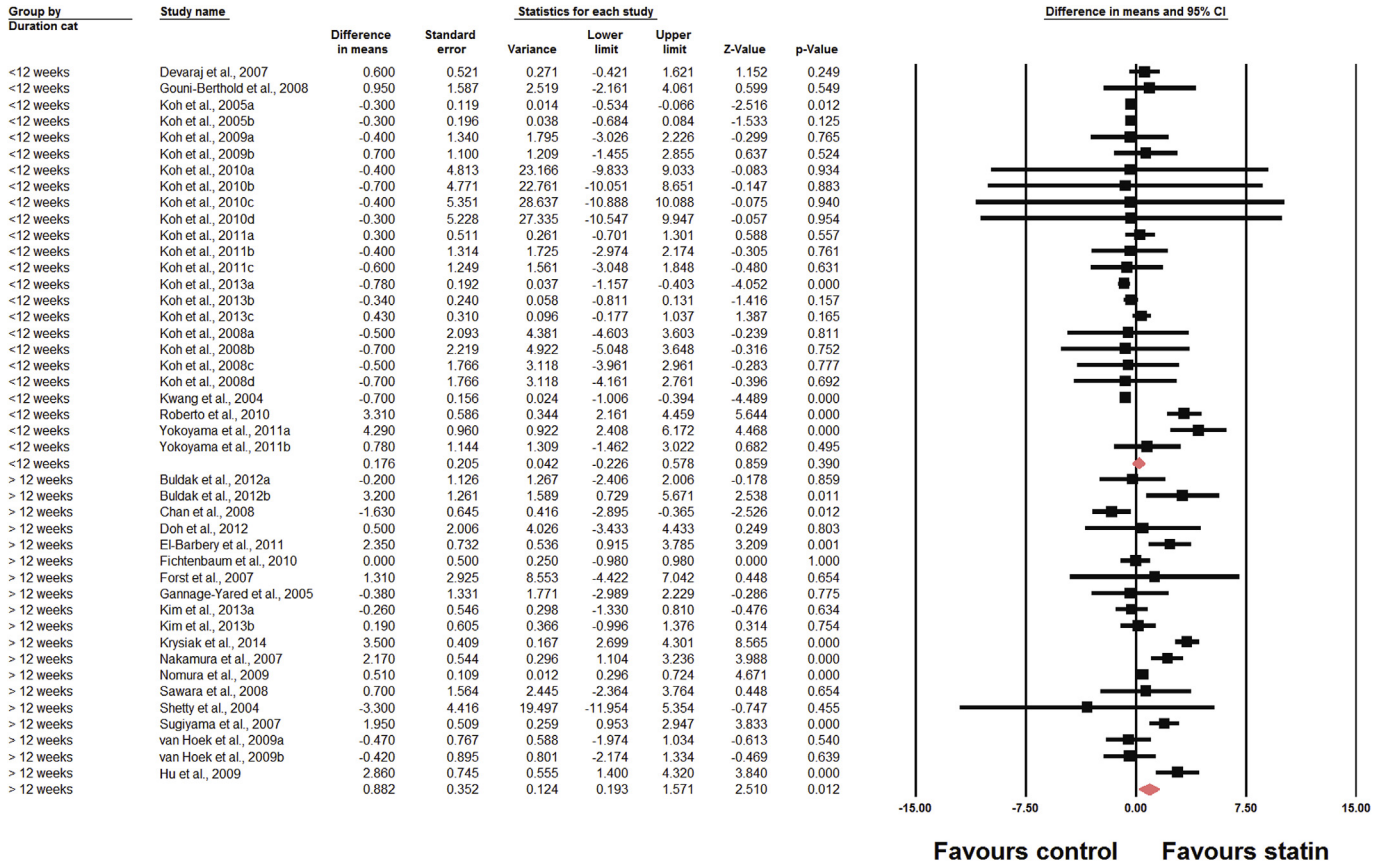


Fig. 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations in trials lasting <12 weeks and ≥12 weeks.

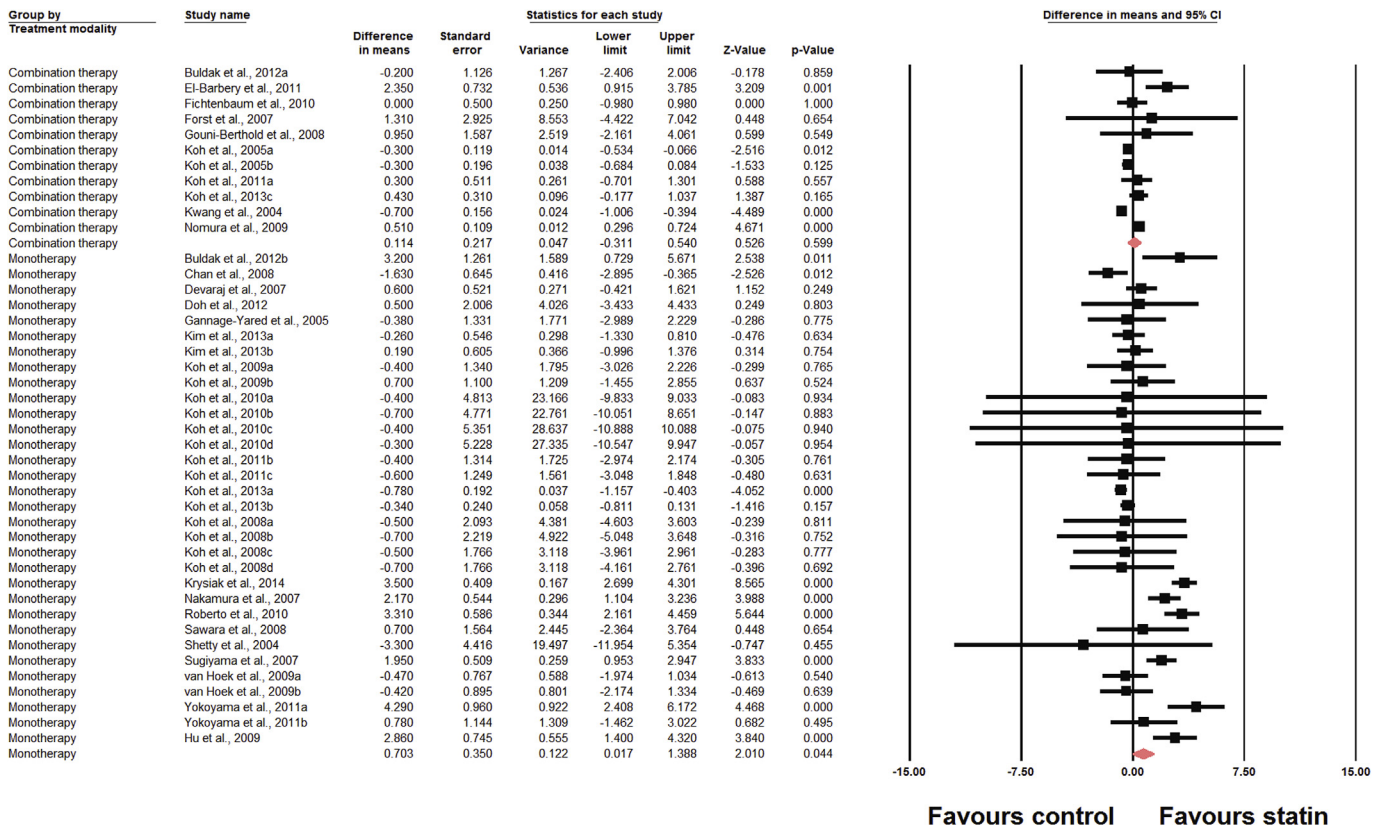


Fig. 6. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations in trials administering statins as monotherapy or in combination with other agents.

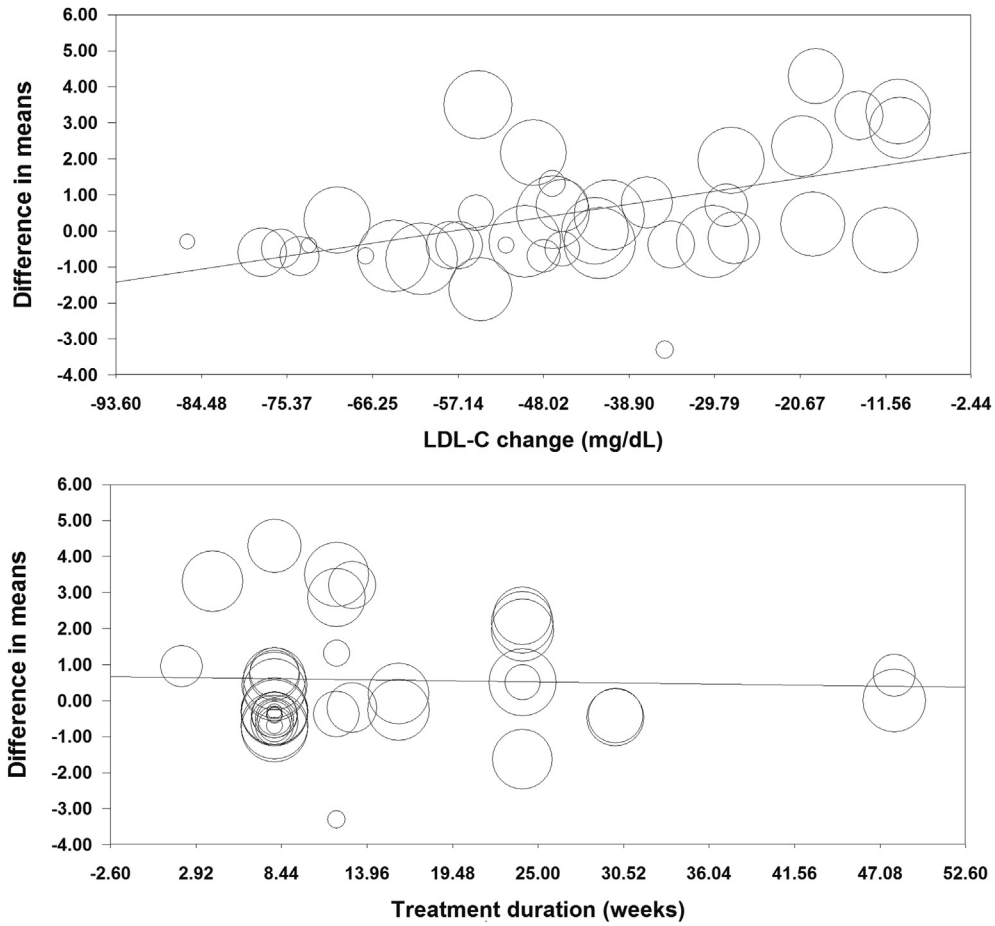


Fig. 7. Meta-regression bubble plots of the association between mean changes in plasma adiponectin concentrations with changes in plasma LDL-C concentrations (upper plot) and duration of treatment (lower plot). The size of each circle is inversely proportional to the size of the study.

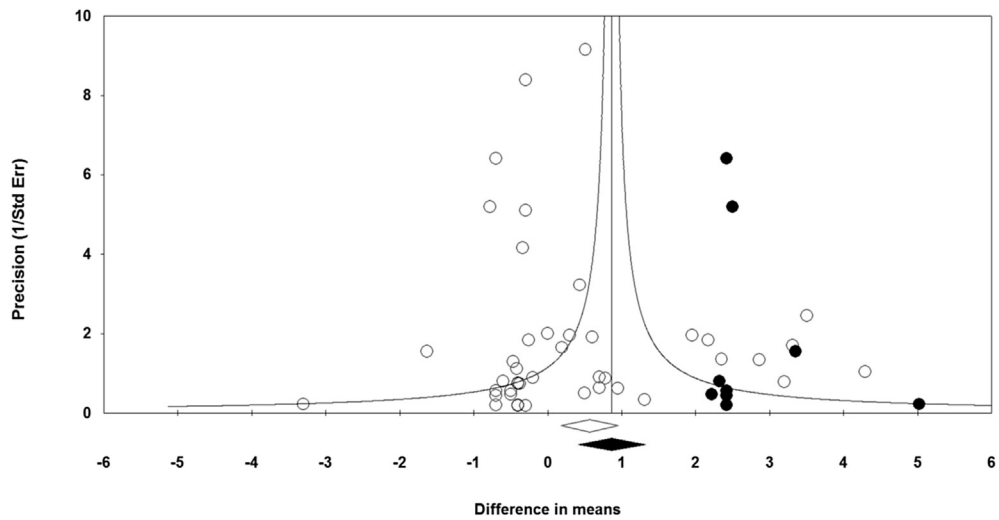


Fig. 8. Funnel plot detailing publication bias in the studies reporting the impact of statin therapy on plasma adiponectin concentrations. Open diamond represents observed effect size; closed diamond represents imputed effect size.

Conflict of interest

This meta-analysis was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

Author contributions

AS designed the study, made the statistical analysis, corrected the draft of the paper; PC, MR, CS made the literature search, drafted the manuscript; MB designed the study, made the literature search, drafted the manuscript, prepared the final version, submitted the paper; SU made the literature search, drafted the manuscript; DPM, SRJ, SM, MJB, SSM, JR, PPT, GYHL, MJP, KKR corrected the draft of the paper and prepared the final version of the manuscript. All authors read and approved the final manuscript.

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