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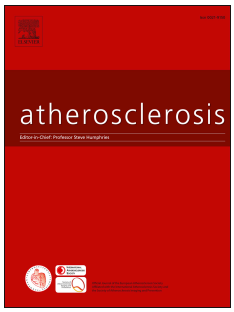

Impact of statin therapy on plasma adiponectin concentrations: A systematic review and meta-analysis of 43 randomized controlled trial arms

Piotr Chruściel, Amirhossein Sahebkar, Magdalena Rembek, Maria-Corina Serban, Sorin Ursoniu, Dimitri P. Mikhailidis, Steven R. Jones, Svetlana Mosteoru, Michael J. Blaha, Seth S. Martin, Jacek Rysz, Peter P. Toth, Gregory Y.H. Lip, Michael J. Pencina, Kausik K. Ray, Maciej Banach

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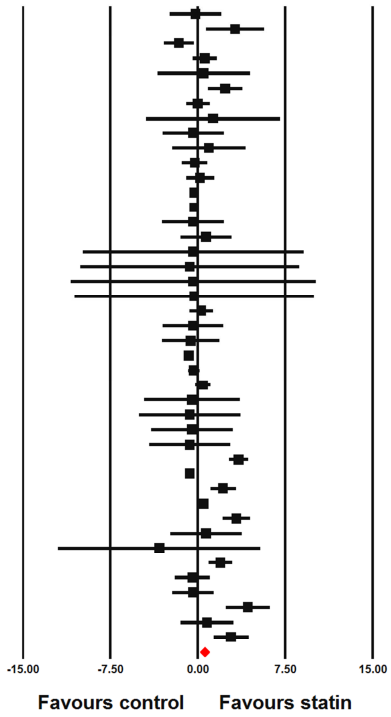
Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Buldak et al., 2012a	-0.200	1.126	1.267	-2.406	2.006	-0.178	0.859
Buldak et al., 2012b	3.200	1.261	1.589	0.729	5.671	2.538	0.011
Chan et al., 2008	-1.630	0.645	0.416	-2.895	-0.365	-2.526	0.012
Devaraj et al., 2007	0.600	0.521	0.271	-0.421	1.621	1.152	0.249
Doh et al., 2012	0.500	2.006	4.026	-3.433	4.433	0.249	0.803
El-Barbery et al., 2011	2.350	0.732	0.536	0.915	3.785	3.209	0.001
Fichtenbaum et al., 2010	0.000	0.500	0.250	-0.980	0.980	0.000	1.000
Forst et al., 2007	1.310	2.925	8.553	-4.422	7.042	0.448	0.654
Gannage-Yared et al., 2005	-0.380	1.331	1.771	-2.989	2.229	-0.286	0.775
Gouni-Berthold et al., 2008	0.950	1.587	2.519	-2.161	4.061	0.599	0.549
Kim et al., 2013a	-0.260	0.546	0.298	-1.330	0.810	-0.476	0.634
Kim et al., 2013b	0.190	0.605	0.366	-0.996	1.376	0.314	0.754
Koh et al., 2005a	-0.300	0.119	0.014	-0.534	-0.066	-2.516	0.012
Koh et al., 2005b	-0.300	0.196	0.038	-0.684	0.084	-1.533	0.125
Koh et al., 2009a	-0.400	1.340	1.795	-3.026	2.226	-0.299	0.765
Koh et al., 2009b	0.700	1.100	1.209	-1.455	2.855	0.637	0.524
Koh et al., 2010a	-0.400	4.813	23.166	-9.833	9.033	-0.083	0.934
Koh et al., 2010b	-0.700	4.771	22.761	-10.051	8.651	-0.147	0.883
Koh et al., 2010c	-0.400	5.351	28.637	-10.888	10.088	-0.075	0.940
Koh et al., 2010d	-0.300	5.228	27.335	-10.547	9.947	-0.057	0.954
Koh et al., 2011a	0.300	0.511	0.261	-0.701	1.301	0.588	0.557
Koh et al., 2011b	-0.400	1.314	1.725	-2.974	2.174	-0.305	0.761
Koh et al., 2011c	-0.600	1.249	1.561	-3.048	1.848	-0.480	0.631
Koh et al., 2013a	-0.780	0.192	0.037	-1.157	-0.403	-4.052	0.000
Koh et al., 2013b	-0.340	0.240	0.058	-0.811	0.131	-1.416	0.157
Koh et al., 2013c	0.430	0.310	0.096	-0.177	1.037	1.387	0.165
Koh et al., 2008a	-0.500	2.093	4.381	-4.603	3.603	-0.239	0.811
Koh et al., 2008b	-0.700	2.219	4.922	-5.048	3.648	-0.316	0.752
Koh et al., 2008c	-0.500	1.766	3.118	-3.961	2.961	-0.283	0.777
Koh et al., 2008d	-0.700	1.766	3.118	-4.161	2.761	-0.396	0.692
Krysiak et al., 2014	3.500	0.409	0.167	2.699	4.301	8.565	0.000
Kwang et al., 2004	-0.700	0.156	0.024	-1.006	-0.394	-4.489	0.000
Nakamura et al., 2007	2.170	0.544	0.296	1.104	3.236	3.988	0.000
Nomura et al., 2009	0.510	0.109	0.012	0.296	0.724	4.671	0.000
Roberto et al., 2010	3.310	0.586	0.344	2.161	4.459	5.644	0.000
Sawara et al., 2008	0.700	1.564	2.445	-2.364	3.764	0.448	0.654
Shetty et al., 2004	-3.300	4.416	19.497	-11.954	5.354	-0.747	0.455
Sugiyama et al., 2007	1.950	0.509	0.259	0.953	2.947	3.833	0.000
van Hoek et al., 2009a	-0.470	0.767	0.588	-1.974	1.034	-0.613	0.540
van Hoek et al., 2009b	-0.420	0.895	0.801	-2.174	1.334	-0.469	0.639
Yokoyama et al., 2011a	4.290	0.960	0.922	2.408	6.172	4.468	0.000
Yokoyama et al., 2011b	0.780	1.144	1.309	-1.462	3.022	0.682	0.495
Yun et al., 2009	2.860	0.745	0.555	1.400	4.320	3.840	0.000
	0.567	0.195	0.038	0.184	0.950	2.901	0.004



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).

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.

Keywords: adiponectin, statins, hydroxymethylglutaryl-CoA reductase inhibitors, meta-analysis.

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,

simulates 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).

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.

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).

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.

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) 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.

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.

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 = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, 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 = median + 2 × (Q_3 – median) and B = median – 2 × (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 × 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.

Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD and duration of statin therapy and changes in plasma LDL-C concentrations as potential moderator variables.

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].

RESULTS

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 to 40 mg/day simvastatin, 10 mg to 80 mg/day atorvastatin, 10 mg to 40 mg/day pravastatin, 2.5 mg to 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 crossover 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.**

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**.

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 µg/mL, 95% CI: 0.18, 0.95, p = 0.004) (**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 µg/mL (95% CI: -0.26, 1.65, p = 0.152), 0.50 µg/mL (95% CI: -0.44, 1.45, p = 0.297), -0.70 µg/mL (95% CI: -1.08, -0.33, p = 0.001), 0.62 µg/mL (95% CI: -0.12, 1.35, p = 0.100), and 0.51 µg/mL (95% CI: 0.30, 0.72, p = 0.001), respectively (**Figure 4**). 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 with <12 weeks of duration (WMD: 0.18 µg/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 µg/mL, 95% CI: 0.02, 1.39, p = 0.044) versus the subset that used a combination therapy approach (WMD: 0.11 µg/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 µg/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 µg/mL, 95% CI: -0.41, 1.09, p = 0.373).

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).**

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 µg/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.

DISCUSSION

To our best knowledge, the present study is the first meta-analysis to comprehensively assess the association between statin 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 alfa (e.g. fenofibrate) [29] or PPAR gamma 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 gamma (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 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.

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,

KKRcorrected 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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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]	Gannage-Yared *et al*[58]	Gouni-Berthold *et al.*[59]	Kim *et al.*[60]	Koh *et al.*[61]	Koh *et al.*[62]	Koh *et al.*[63]	Koh *et al.*[64]	Koh *et al.*[65]	Koh *et al.*[66]	Koh *et al.*[67]	Koh *et al.*[68]	Koh *et al.*[69]	Krysiak *et al.*[70]	Koh *et al.*[71]	Nakamura *et al.*[72]	Nomura *et al.*[73]	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		2012	2008	2007	2012	2011	2010	2007	2005	2008	2013	2005a	2005b	2009	2010	2011a	2011b	2013a	2013b	2008	2014	2004	2007	2009	2010	2008	2004	2007	2009	2011	2009
Location		Poland	Taiwan	USA	Korea	Egypt	USA	Germany	Lebanon	Germany	Korea	Korea	Korea	Korea	Korea	Korea	Korea	Korea	Korea	Korea	Poland	Korea	Japan	Japan	Italy	Japan	USA	Japan	Netherlands	Japan	China
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	Randomized, double-blind, placebo-controlled parallel group trial	Randomized parallel group trial	Multicenter, double-blind, placebo-controlled, factorial randomized trial	Randomized, double-blind, placebo-controlled crossover trial	Randomized, double-blind, placebo-controlled crossover trial	Randomized, single-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, crossover trial	Randomized, single-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, parallel group trial	Randomized, single-blind, placebo-controlled, crossover trial	Randomized, double-blind, placebo-controlled, parallel group trial	Open-label, parallel group trial	Randomized, double-blind, placebo-controlled crossover trial	Randomized parallel group trial	Randomized parallel group trial	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		90 days	6 months	8 weeks	6 months	6 months	48 weeks	12 weeks	12 weeks	14 days	16 weeks	2 months	2 months	2 months	2 months	2 months	2 months	2 months	2 months	2 months	12 weeks	2 months	6 months	6 months	30 days	12 months	12 weeks	6 months	30 weeks	2 months	12 weeks
Inclusion criteria		Patients with mixed hyperlipidemia (total cholesterol >200 mg/dL LDL-C >130 mg/dL and triglycerides >200mg/dL) fasting glucose (100-125 mg/dL), glycemia at 2 hours 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	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)	Female patients between 30 and 70 yrs of age with a less than 10-year recorded history of type 2 DM and hypercholesterolemia	Patients with combined hyperlipidemia (total cholesterol 200 mg/dl and triglycerides ranging from 200 mg/dl to 800 mg/dL)	Hypercholesterolemic patients with type 2 diabetes (LDL cholesterol levels >100 mg/dL)	Patients with hypercholesterolemia (LDL cholesterol levels ≥130mg/dL)	Patients with hypercholesterolemia (LDL cholesterol levels >100 mg/dL)	Patients with mild-to-moderate hypertension (systolic blood pressure <180 and diastolic blood pressure <110mm Hg)	Patients with hypercholesterolemia (LDL cholesterol levels ≥100 mg/dL and BMI≥23.0 kg/m^2)	Hypercholesterolemic patients (LDL cholesterol levels ≥130 mg/dL)	Hypercholesterolemic patients (LDL cholesterol levels ≥130 mg/dL)	Patients with hypercholesterolemia (LDL cholesterol levels ≥100 mg/dL and BMI ≥23.0 kg/m^2)	Patients with isolated hypercholesterolemia, defined as total plasma cholesterol above 200 mg/dL, LDL cholesterol above 130 mg/dL, and triglycerides below 150 mg/dL	Hypercholesterolemic, hypertensive patients (LDL cholesterol levels ≥100 mg/dL, systolic and diastolic blood pressure ≥140 or ≥90 mm Hg, respectively)	Patients with stable CAD (≥75% narrowing ≥1 major coronary artery) who had both hypercholesterolemia (180 mg/dL≤serum total cholesterol levels < 260 mg/dL) and hypertriglyceridemia (150 mg/dL≤serum triglycerides levels < 400 mg/dL)	Patients with diabetes and hyperlipidemia	Patients with polygenic hypercholesterolemia (patients, LDL-C > 160 mg/dL),	Patients with chronic kidney disease (stage 2 to 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-loadedglucose <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	atorvastatin	simvastatin	rosuvastatin	atorvastatin	pravastatin	simvastatin	pravastatin	simvastatin	pravastatin	atorvastatin	simvastatin	simvastatin pravastatin	atorvastatin	atorvastatin	simvastatin	rosuvastatin pravastatin	pravastatin	simvastatin	simvastatin	simvastatin	atorvastatin	pitavastatin	atorvastatin	rosuvastatin	atorvastatin	pravastatin	atorvastatin	pravastatin rosuvastatin	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)**	40 mg/day	40 mg/day combination: simvastatin+ezetimibe (10 mg/day)	20 mg/day 40 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 80 mg/day	20 mg/day combination: atorvastatin+amlodipine (10 mg/day)	20 mg/day 40 mg/day	10 mg/day 40 mg/day	40 mg/day combination: pravastatin+valsartan (160 mg/day)	10 mg/day 20 mg/day 40 mg/day	40 mg/day combination: simvastatin+ezetimibe (10 mg/day)	20 mg/day combination: simvastatin+losartan (100 mg/day)	10 mg/day	2 mg/day combination: pitavastatin+eicosapentaenoic acid (1800 mg/day)	10 mg/day	2.5 mg/day	20 mg/day	10-20 mg/day	10 mg/day 80 mg/day	10 mg/day 2.5 mg/day	40 mg/day
Participants	Statin group	16 19	30	25	35	15	37 60	43 43	19	24 24	28 25	56	50	43 42	42 44 43 40	42	45 45	52 53	48	30 32 31	23 21	47	16	64 72	18	22	34	20	73 72	12 11	23
	Control group	14	30	25	35	15	37	39	21	24	20			42	44	42	44	53		32	21		15	55	18	16	33	20	72	13	20
Age (years)	Statin group	52.9±7.2 51.9±9.1	66.13±11.50	51±12	48.9±11.7	54.8±14.7	42 (31–57) 44 (28–57)	57.3±8.4 59.0±8.6	51.6±13.0	31.9±8.8 34.1±11.2	60 (36-70) 60 (41-69)	56±1**	59±1**	58±2** 56±2**	56±10 58±9 59±12 57±11	53±2**	58±2** 61±2**	55±1** 54±1**	56±1**	57±2** 58±2** 60±2**	51.9±2.7 52.5±3.5	57±2**	60±7	65±3	55.2±4.1	63.8±9.1	NS	68.2±8.3	59.7±7.6** 60.1±7.7**	65±2** 66±3**	58.5±1.6**
	Control group	49.1±8.8	63.77±12.73		48.5±11.3	53.7±15.4	46 (28–62)	59.5±7.8	46.3±9.7	28.6±6.6	57 (34-70)			59±1**	54±11		57±2**	56±1**		59±2**	51.1±2.6		59±8		55.2±3.8	67.0±7.9	NS	65.7±9.2	58.5±7.5**	69±2**	55.2±2.3**
Male (%)	Statin group	56.25 47.37	80.0	28	45.7	20.0	91.89 95.0	37.21 41.86	52.63	100.0 100.0	0.0 0.0	41.07	60.0	39.53 35.71	50.0 47.72 51.16 50.0	52.38	44.44 42.22	42.31 39.62	60.42	46.67 46.87 45.16	61.0 57.0	42.55	63.0	52.88	44.44	50.0	55.84	65.0	60.0 53.0	83.33 81.81	39.1
	Control group	50.0	63.3		45.7	13.33	100.0	48.75	57.14	100.0	0.0			38.09	52.27		47.72	41.51		46.87	57.0		67.0		50.0	56.25		75.0	46.0	100.0	70.0
BMI (kg/m^2)	Statin group	29.5±3.6 27.8±2.6	25.86±2.51	39±7	22.9±3.1	25.8±3.1	26.4 (24.0–30.9)* 25.9 (22.6–28.3)*	30.5±3.7 31.2±4.1	26.8±4.28	26.4±3.2 25.8±3.1	26.2±2.6 26.2±3.4	25.46±0.34**	25.5±0.4**	25.25±0.53** 25.48±0.48**	24.8±3.4 24.9±3.4 25.1±3.0 24.9±3.4	25.45±0.36**	25.3±0.5** 25.4±0.4**	24.00±0.43** 23.75±0.40**	25.66±0.43** 25.50±0.46**	25.9±0.7** 27.0±0.5** 26.8±0.6**	26.5±2.6 26.9±2.2	25.2±0.5**	25±2	27.3±3.9	25.2±2.7	23.1±2.5	29.5±1.3	23.0±2.3	30.0±3.8** 30.4±4.5**	23.7±0.5** 24.8±1.3**	24.5±0.6**
	Control group	28.3±2.2	25.12±2.48		22.7±3.0	25.5±3.3	25.4 (22.2–27.1)*	30.8±4.8	26.1±4.20	25.0±3.3	26.0±3.5	25.45±0.34**		24.52±0.54**	24.8±2.4	25.51±0.35**	24.9±0.5**	23.95±0.35**	25.48±0.47***	25.7±0.6**	27.2±2.6		26±2		25.2±2.3	23.4±2.9	28.8±1.1	23.9±2.4	32.2±6.0**	24.2±1.2**	24.1±0.8**
hs-CRP (mg/L)	Statin group	NS	0.89±1.16	3.6 (3, 6.1)	2.05±1.57	31.46±14.33	3.5 (2.1–6.0)*	NS	NS	NS	0.12 (0.03-1.10)	1.20 (0.65–2.20)*	1.10 (0.60–2.90)*	1.00 (0.40–3.10)*	0.95 (0.50–3.10)* 1.00 (0.45–2.00)*	1.05 (0.80–2.40)*	1.10 (0.40–2.70)*	0.60 (0.40–1.27)*	0.85 (0.50–1.60)*	0.64 (0.27–2.91) 1.05 (0.40–2.35)	3.4±0.5	0.85(0.30–2.70)*	−1.20 ± 0.4[+]	NS	NS	0.89±0.89	0.32±0.05	1.4 (0.8–2.3)*	NS	405±309**	4.3±1.0**

		NS					2.7 (1.5–4.5)*	NS		NS	0.11 (0.03-1.43	0.80 (0.53–2.03)*	1.60 (0.60–3.50*	1.45 (0.60–2.10)*	1.00 (0.53–2.30)* 1.00 (0.65–2.00)*	1.40 (0.90–2.40)*	0.80 (0.44–1.75)*	0.70 (0.40–1.35)*	1.00 (0.63–1.80)*	0.73 (0.44–1.39)	3.7±0.7	0.85(0.50–2.00)*							NS	389±162**	
	Control 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	NS	NS	0.10 (0.03-0.63)	1.20 (0.70–2.35)*	1.30 (0.60–2.80)*	1.00 (0.70–2.20)*	1.00 (0.65–2.30)*	1.30 (0.80–2.50)*	1.00 (0.70–2.10)*	0.60 (0.30–1.20)*	1.10 (0.50–1.78)*	0.95 (0.46–2.10)	3.5±0.6	0.85(0.50–2.30)*	−1.27 ± 0.3†		NS	0.88±0.84	0.30±0.05	1.1 (0.5–2.0)*	NS	579±165**	3.8±1.4**
Total cholesterol(mg/dL)	Statin 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	234±51.7	NS	243.18±27.02	243±7**	229±6**	260±5**	238±34 245±37	219±6**	258±5**	246±3**	233±6**	246±3** 256±7**	258±16	247±5**	NS	254±24	279±47	228.5±47.6	199.8±7.0	188±16	228.51±35.51**	193±17**	185.28±7.72**
		265.6±28.8					269 (248.5–316)*	218.86±48.63		NS	239.22±19.3	234±6**	227±6**	254±5**	242±31 253±41	227±5**	263±4**	241±4**	234±5**	264±6**	256±15	242±4**		251±45					231.98±34.35**	202±10**	
	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	229.8±48.9	NS	243.18±34.74	240±6**	223±7**	267±5**	240±32	211±5**	268±5**	248±4**	229±6**	267±6**	246±14	238±5**	NS	229±37	280±29	205.6±28.1	211.9±7.0	183±21	233.144±31.26**	179±9**	173.7±7.72**
LDL-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	159.6±43.9	NS	154.4±15.44	134±7**	135±6**	178±5**	156±31 159±33	132±6**	176±5**	166±4**	151±5**	162±3** 174±7**	186±13	160±5**	136±25	169±21	188±17	130.3±24.3	120.4±5.9	122±15	NS	124±16**	100.36±3.86**
		165.3±26.4					156.5 (139–179)*	142.05±42.46		NS	146.68±15.44	130±7**	134±5**	170±5**	155±27 169 ±38	137±5**	177±5**	165±3**	148±4**	181±7**	184±11	154±5**		156±31					NS	127±8**	
	Control 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	149.7±43.8	NS	158.26±27.02	128±6**	134±7**	177±6**	154±29	124±5**	177±6**	166±4**	146±5**	179±6**	178±12	149±5**	130±23	128±32	187±7	128.3±16.2	127.0±5.6	118±20	NS	93±5**	96.5±7.72**
HDL-C (mg/dL)	Statin 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	44.1±14.1	NS	50.18±11.58	46±1**	46±2**	51±2**	51±12 54±13	48±2**	52±2**	53±2**	53±1**	54±1** 52±2**	46±4	53±2**	43±8	48±14	62±12	55.9±14.5	58.8±2.3	46±10	40.53±1.158**	45.7±3.2**	40.53±0.38**
		43.0±10.1					35 (30–39)*	55.58±17.37		NS	54.04±3.86	44±1**	47±1**	54±2**	51±12 52±11	51±2**	56±2**	51±1**	51±1**	54±2**	46±4	51±2**		46±17					40.14±1.15**	51.0±4.2**	
	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	47.8±13.5	NS	54.04±7.72	46±1**	47±2**	55±2**	50±11	47±2**	54±1**	54±1**	52±2**	57±2**	47±4	52±2**	44±6	43±15	61±11	54.9±10.6	61.9±3.3	49±10	40.53±1.15**	42.5±3.0**	42.46±3.86**
Triglycerides (mg/dL)	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	146.6±56.9	NS	141.6 (70.8-300.9)	301±23**	236±25**	143±13**	152±69 157±71	201±16**	142±13**	136±8**	151±9**	131±12** 147±18**	122±12	172±12**	5.4±0.3§	198±57	103±24	177.1±73.2	114.3±15.0	122 (92–162)*	235.41±9.73**	166±44**	221.25±26.55**
		248.1±39.6					355 (252.5–468.5)*	128.32±52.21		NS	141.6 (44.25-300.9)	337±24**	231±17**	162±9**	179±98 164±88	196±15**	155±14**	136±8**	164±10**	149±16**	126±11	179±13**		248±61					260.19±12.39**	112±20**	
	Control 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	168.5±100.7	NS	141.6 (8.85-345.15)	322±19**	213±18**	147±12**	172±89	203±18**	144±12**	138±10**	158±12**	146±15**	120±12	186±16**	5.3±0.2§	258±72	102±19	161.2±35.3	110.2±13.0	101 (85–129)*	249.57±11.5**	174±26**	177.0±44.25**

Adiponectin (μg/mL)	Statin 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	7.30±4.79	13.28±5.29	3.22±1.27	3.5 (2.6–5.0)*	3.8 (2.7–5.2)*	5.8±0.8**	2.8±2.4	3.3±0.3**	5.7±0.7**	2.05 (1.37–3.75)*	2.97 (2.09–4.80)*	6.4±1.0**	5.3±1.2	4.5 (3.4–7.0)*	1.4±0.5$	3.29±0.51	5.5 (4–8)*	9.7±5.3	21.7±2.3	5.2 (4.0–6.5)*	7.69±0.46**	3.28±0.11**	4.8±0.6**
															3.1±2.4					6.0±1.0**											
		16.2±2.7					4 (3–6)*	11.68±9.96		13.63±4.88	3.19±1.28	3.4 (2.3–4.7)*	3.8 (2.5–6.2)*	5.6±0.6**	3.4±2.5	3.2±0.3**	6.8±0.7**	2.00 (1.22–4.12)*	2.81 (1.96–5.03)*	6.2±0.8**	6.0±1.0	4.6 (3.3–6.4)*		3.24±0.41					8.20±0.58**	2.95±0.56**	
															3.2±2.4															
	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	7.36±3.59	13.17±5.97	3.76±2.31	3.2 (2.5–5.1)*	3.8 (2.6–6.7)*	6.2±0.7**	3.3±2.0	3.2±0.3**	6.8±0.8**	2.05 (1.32–6.07)*	2.96 (1.92–5.45)*	6.6±1.0**	5.7±1.1	4.2 (3.5–6.2)*	1.5±0.6$	3.03±0.57	NS	8.9±3.9	25.2±3.5	5.8 (4.1–6.7)*	7.44±0.42**	3.51±0.41**	4.5±0.4**
Glucose (mg/dL)	Statin group	107.6±6.0	NS	114±55	93.06±8.82	NS	NS	100.8±11.16	92.8±15.1	NS	144.0±37.8	92±3**	122±5**	97±2**	106±18	104±2**	85±2**	97±1**	102±1**	89±9**	95±4	82±2**	118±30	NS	84±11	97.1±10.9	NS	92±11	189.0±54.0**	145±12**	NS
															108±21					86±3**											
		103.0±8.0					NS	102.6±11.88		NS	140.4±25.2	89±3**	128±6**	99±3**	113±24	106±2**	91±3**	98±1**	105±2**	91±4**	96±4	82±2**		NS					190.8±52.2**	139±9**	
															109±22															
	Control group	110.3±6.5	NS	109±35	92.34±26.64	NS	NS	101.34±9.72	89.5±9.2	NS	151.2±39.6	91±4**	121±5**	94±3**	103±17	104±3**	94±3**	96±2**	103±2**	95±4**	95±5	83±2**	118±31	NS	85±13	98.2±18.6	NS	91±8	189.0±64.8**	131±20**	NS
SBP (mmHg)	Statin group	NS	NS	NS	136.6±19.7	NS	NS	NS	NS	NS	126.8±11.8	NS	134±2**	NS	NS	154±1**	NS	NS	138±2**	NS	NS	145±2**	NS	NS	124±12	126.7±9.3	NS	NS	146±17**	NS	NS
															NS					NS											
		NS					NS	NS		NS	125.1±21.8	NS	135±2**	NS	NS	157±1**	NS	NS	134±2**	NS	NS	147±3**		NS					145±17**	NS	
															NS															
	Control group	NS	NS	NS	136.8±17.2	NS	NS	NS	NS	NS	129.8±7.7	NS	131±2**	NS	NS	156±2**	NS	NS	138±2**	NS	NS	145±2**	NS	NS	125±12	128.3±8.1	NS	NS	144±19**	NS	NS
DBP (mmHg)	Statin group	NS	NS	NS	81.1±7.7	NS	NS	NS	NS	NS	76.4±7.1	NS	80±1**	NS	NS	94±1**	NS	NS	85±2**	NS	NS	90±1**	NS	NS	74±7	76.7±8.2	NS	NS	86±10**	NS	NS
															NS					NS											
		NS					NS	NS		NS	76.3±6.8	NS	80±1**	NS	NS	96±1**	NS	NS	82±2**	NS	NS	91±1**		NS					85±9**	NS	
															NS															
	Control group	NS	NS	NS	80.9±10.5	NS	NS	NS	NS	NS	81.2±6.8	NS	78±1**	NS	NS	95±1**	NS	NS	83±2**	NS	NS	89±1**	NS	NS	76±10	80.4±5.4	NS	NS	85±9**	NS	NS

Values are expressed as mean ± SD or median (range);* median (25^{th}–75^{th} 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.* 2012	[51]	U	U	L	U	L	L	L
Chan *et al.* 2008	[52]	U	U	L	U	L	L	L
Devaraj *et al.* 2007	[53]	U	U	L	U	L	L	L
Doh *et al.* 2012	[54]	L	L	L	U	L	L	L
El-Barbery *et al.* 2011	[55]	U	U	L	L	L	L	L
Fichtenbaum *et al.* 2010	[56]	H	H	H	U	L	L	L
Forst *et al.* 2007	[57]	U	U	L	L	L	L	L
Gannage-Yaredet *et al.* 2005	[58]	U	U	L	U	L	L	L
Gouni-Berthold *et al.* 2008	[59]	U	U	L	U	L	L	L
Kim *et al.* 2013	[60]	U	U	L	U	L	L	L
Koh *et al.* 2005a	[61]	U	U	L	L	L	L	L
Koh *et al.* 2005b	[62]	U	U	L	L	L	L	L
Koh *et al.* 2009	[63]	U	U	L	L	L	L	L
Koh *et al.* 2010	[64]	L	L	L	U	L	L	L
Koh *et al.* 2011a	[65]	U	U	L	L	L	L	L
Koh *et al.* 2011b	[66]	U	U	L	U	L	L	L

Koh *et al.* 2013a	[67]	L	L	L	U	L	L	L
Koh *et al.* 2013b	[68]	U	U	L	L	L	L	L
Koh *et al.* 2008	[69]	U	U	L	L	L	L	L
Krysiak *et al.* 2014	[70]	H	H	H	L	L	L	L
Kwang *et al.* 2004	[71]	U	U	L	L	L	L	L
Nakamura *et al.* 2007	[72]	U	U	L	U	L	L	L
Nomura *et al.* 2009	[73]	U	U	L	U	L	L	L
Roberto *et al.* 2010	[74]	L	L	L	L	L	L	L
Sawara *et al.* 2008	[75]	U	U	L	L	L	L	L
Shetty *et al.* 2004	[76]	U	U	L	U	L	L	L
Sugiyama *et al.* 2007	[77]	L	L	L	U	L	L	L
van Hoek *et al.* 2009	[78]	U	U	L	U	L	L	L
Yokoyama *et al.* 2011	[79]	U	U	L	U	L	L	L
Hu *et al.* 2009	[80]	U	U	L	L	L	L	L

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

FIGURE LEGENDS:

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

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

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

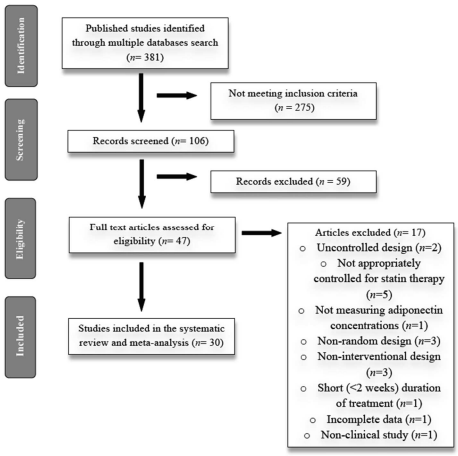
Fig. 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations in trials with different types of statins.

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.

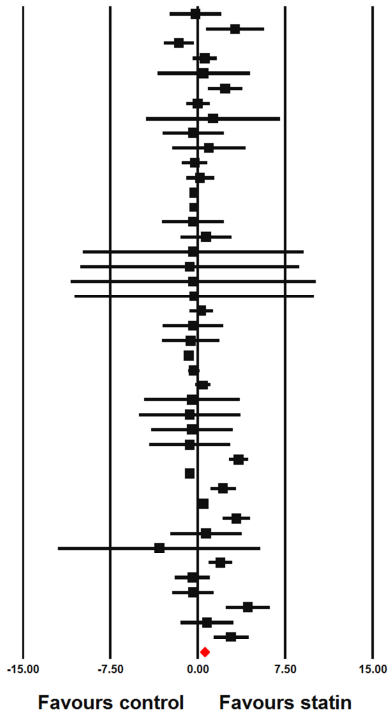
Fig. 6. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma adiponectin concentrations in trials administering statins as monotherapy or in combination with other agents.

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.



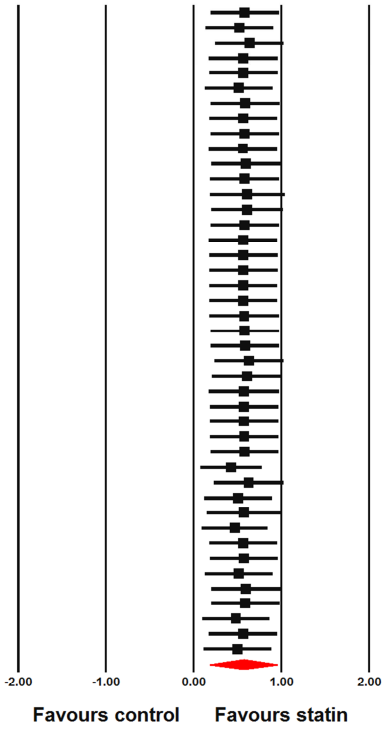
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Buldak et al., 2012a	-0.200	1.126	1.267	-2.406	2.006	-0.178	0.859
Buldak et al., 2012b	3.200	1.261	1.589	0.729	5.671	2.538	0.011
Chan et al., 2008	-1.630	0.645	0.416	-2.895	-0.365	-2.526	0.012
Devaraj et al., 2007	0.600	0.521	0.271	-0.421	1.621	1.152	0.249
Doh et al., 2012	0.500	2.006	4.026	-3.433	4.433	0.249	0.803
El-Barbery et al., 2011	2.350	0.732	0.536	0.915	3.785	3.209	0.001
Fichtenbaum et al., 2010	0.000	0.500	0.250	-0.980	0.980	0.000	1.000
Forst et al., 2007	1.310	2.925	8.553	-4.422	7.042	0.448	0.654
Gannage-Yared et al., 2005	-0.380	1.331	1.771	-2.989	2.229	-0.286	0.775
Gouni-Berthold et al., 2008	0.950	1.587	2.519	-2.161	4.061	0.599	0.549
Kim et al., 2013a	-0.260	0.546	0.298	-1.330	0.810	-0.476	0.634
Kim et al., 2013b	0.190	0.605	0.366	-0.996	1.376	0.314	0.754
Koh et al., 2005a	-0.300	0.119	0.014	-0.534	-0.066	-2.516	0.012
Koh et al., 2005b	-0.300	0.196	0.038	-0.684	0.084	-1.533	0.125
Koh et al., 2009a	-0.400	1.340	1.795	-3.026	2.226	-0.299	0.765
Koh et al., 2009b	0.700	1.100	1.209	-1.455	2.855	0.637	0.524
Koh et al., 2010a	-0.400	4.813	23.166	-9.833	9.033	-0.083	0.934
Koh et al., 2010b	-0.700	4.771	22.761	-10.051	8.651	-0.147	0.883
Koh et al., 2010c	-0.400	5.351	28.637	-10.888	10.088	-0.075	0.940
Koh et al., 2010d	-0.300	5.228	27.335	-10.547	9.947	-0.057	0.954
Koh et al., 2011a	0.300	0.511	0.261	-0.701	1.301	0.588	0.557
Koh et al., 2011b	-0.400	1.314	1.725	-2.974	2.174	-0.305	0.761
Koh et al., 2011c	-0.600	1.249	1.561	-3.048	1.848	-0.480	0.631
Koh et al., 2013a	-0.780	0.192	0.037	-1.157	-0.403	-4.052	0.000
Koh et al., 2013b	-0.340	0.240	0.058	-0.811	0.131	-1.416	0.157
Koh et al., 2013c	0.430	0.310	0.096	-0.177	1.037	1.387	0.165
Koh et al., 2008a	-0.500	2.093	4.381	-4.603	3.603	-0.239	0.811
Koh et al., 2008b	-0.700	2.219	4.922	-5.048	3.648	-0.316	0.752
Koh et al., 2008c	-0.500	1.766	3.118	-3.961	2.961	-0.283	0.777
Koh et al., 2008d	-0.700	1.766	3.118	-4.161	2.761	-0.396	0.692
Krysiak et al., 2014	3.500	0.409	0.167	2.699	4.301	8.565	0.000
Kwang et al., 2004	-0.700	0.156	0.024	-1.006	-0.394	-4.489	0.000
Nakamura et al., 2007	2.170	0.544	0.296	1.104	3.236	3.988	0.000
Nomura et al., 2009	0.510	0.109	0.012	0.296	0.724	4.671	0.000
Roberto et al., 2010	3.310	0.586	0.344	2.161	4.459	5.644	0.000
Sawara et al., 2008	0.700	1.564	2.445	-2.364	3.764	0.448	0.654
Shetty et al., 2004	-3.300	4.416	19.497	-11.954	5.354	-0.747	0.455
Sugiyama et al., 2007	1.950	0.509	0.259	0.953	2.947	3.833	0.000
van Hoek et al., 2009a	-0.470	0.767	0.588	-1.974	1.034	-0.613	0.540
van Hoek et al., 2009b	-0.420	0.895	0.801	-2.174	1.334	-0.469	0.639
Yokoyama et al., 2011a	4.290	0.960	0.922	2.408	6.172	4.468	0.000
Yokoyama et al., 2011b	0.780	1.144	1.309	-1.462	3.022	0.682	0.495
Yun et al., 2009	2.860	0.745	0.555	1.400	4.320	3.840	0.000
	0.567	0.195	0.038	0.184	0.950	2.901	0.004



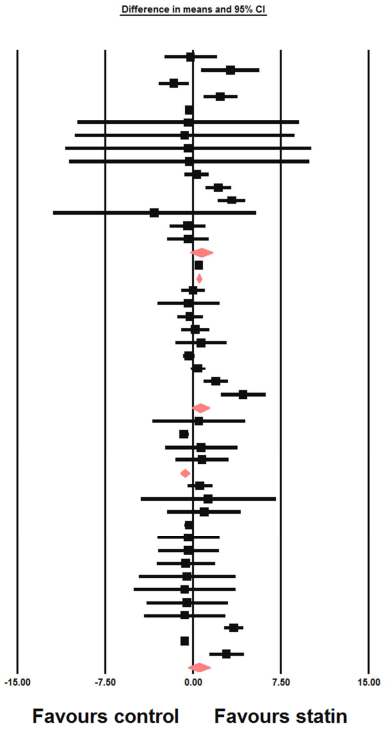
Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Buldak et al., 2012a	0.582	0.198	0.039	0.194	0.969	2.940	0.003
Buldak et al., 2012b	0.524	0.196	0.038	0.141	0.907	2.678	0.007
Chan et al., 2008	0.637	0.197	0.039	0.250	1.024	3.226	0.001
Devaraj et al., 2007	0.566	0.200	0.040	0.174	0.958	2.831	0.005
Doh et al., 2012	0.568	0.197	0.039	0.182	0.953	2.887	0.004
El-Barbery et al., 2011	0.514	0.196	0.038	0.130	0.898	2.621	0.009
Fichtenbaum et al., 2010	0.589	0.200	0.040	0.196	0.982	2.937	0.003
Forst et al., 2007	0.564	0.196	0.038	0.180	0.948	2.876	0.004
Gannage-Yared et al., 2005	0.581	0.197	0.039	0.195	0.968	2.946	0.003
Gouni-Berthold et al., 2008	0.563	0.197	0.039	0.177	0.948	2.857	0.004
Kim et al., 2013a	0.597	0.200	0.040	0.205	0.989	2.984	0.003
Kim et al., 2013b	0.580	0.200	0.040	0.189	0.971	2.904	0.004
Koh et al., 2005a	0.612	0.215	0.046	0.190	1.033	2.845	0.004
Koh et al., 2005b	0.609	0.206	0.043	0.205	1.014	2.953	0.003
Koh et al., 2009a	0.581	0.197	0.039	0.195	0.968	2.947	0.003
Koh et al., 2009b	0.565	0.198	0.039	0.177	0.952	2.855	0.004
Koh et al., 2010a	0.569	0.196	0.038	0.185	0.953	2.902	0.004
Koh et al., 2010b	0.569	0.196	0.038	0.185	0.953	2.905	0.004
Koh et al., 2010c	0.568	0.196	0.038	0.184	0.952	2.901	0.004
Koh et al., 2010d	0.568	0.196	0.038	0.184	0.952	2.901	0.004
Koh et al., 2011a	0.577	0.200	0.040	0.185	0.970	2.882	0.004
Koh et al., 2011b	0.582	0.197	0.039	0.195	0.969	2.949	0.003
Koh et al., 2011c	0.586	0.197	0.039	0.199	0.973	2.969	0.003
Koh et al., 2013a	0.631	0.201	0.040	0.237	1.025	3.137	0.002
Koh et al., 2013b	0.610	0.204	0.042	0.210	1.010	2.988	0.003
Koh et al., 2013c	0.574	0.202	0.041	0.177	0.971	2.836	0.005
Koh et al., 2008a	0.575	0.196	0.039	0.190	0.960	2.926	0.003
Koh et al., 2008b	0.576	0.196	0.039	0.191	0.960	2.930	0.003
Koh et al., 2008c	0.578	0.197	0.039	0.192	0.963	2.935	0.003
Koh et al., 2008d	0.579	0.197	0.039	0.194	0.965	2.946	0.003
Krysiak et al., 2014	0.426	0.177	0.031	0.078	0.773	2.400	0.016
Kwang et al., 2004	0.628	0.203	0.041	0.231	1.025	3.100	0.002
Nakamura et al., 2007	0.508	0.195	0.038	0.125	0.891	2.597	0.009
Nomura et al., 2009	0.575	0.214	0.046	0.155	0.994	2.684	0.007
Roberto et al., 2010	0.468	0.190	0.036	0.095	0.841	2.461	0.014
Sawara et al., 2008	0.565	0.197	0.039	0.179	0.951	2.871	0.004
Shetty et al., 2004	0.574	0.196	0.038	0.191	0.958	2.933	0.003
Sugiyama et al., 2007	0.514	0.196	0.038	0.130	0.898	2.621	0.009
van Hoek et al., 2009a	0.596	0.199	0.040	0.207	0.986	3.000	0.003
van Hoek et al., 2009b	0.591	0.198	0.039	0.202	0.980	2.980	0.003
Yokoyama et al., 2011a	0.482	0.192	0.037	0.105	0.858	2.506	0.012
Yokoyama et al., 2011b	0.563	0.198	0.039	0.176	0.950	2.850	0.004
Yun et al., 2009	0.499	0.195	0.038	0.118	0.881	2.565	0.010
	0.567	0.195	0.038	0.184	0.950	2.901	0.004

Statistics with study removed

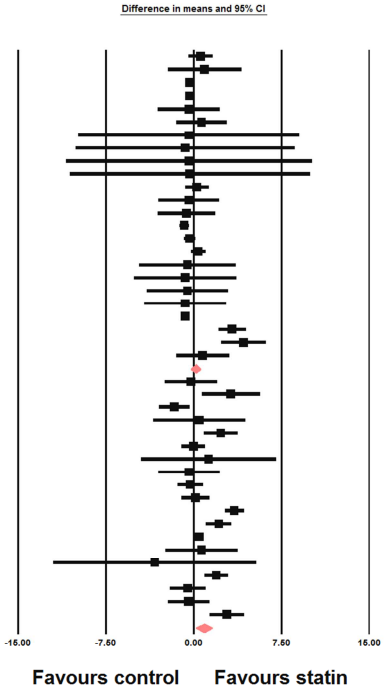
Difference in means (95% CI) with study removed



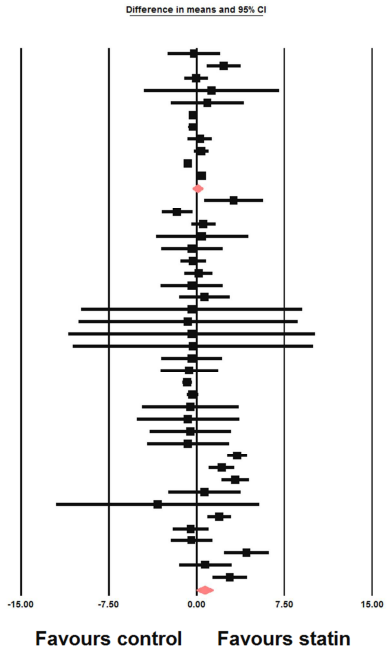
Group by Statin type	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Atorvastatin	Buldak et al., 2012a	-0.200	1.126	1.267	-2.406	2.006	-0.178	0.859
Atorvastatin	Buldak et al., 2012b	3.200	1.261	1.589	0.729	5.671	2.538	0.011
Atorvastatin	Chan et al., 2008	-1.630	0.645	0.416	-2.895	-0.365	-2.526	0.012
Atorvastatin	El-Barbery et al., 2011	2.350	0.732	0.536	0.915	3.785	3.209	0.001
Atorvastatin	Koh et al., 2005a	-0.300	0.119	0.014	-0.534	-0.066	-2.516	0.012
Atorvastatin	Koh et al., 2010a	-0.400	4.813	23.166	-9.833	9.033	-0.083	0.934
Atorvastatin	Koh et al., 2010b	-0.700	4.771	22.761	-10.051	8.651	-0.147	0.883
Atorvastatin	Koh et al., 2010c	-0.400	5.351	28.637	-10.888	10.088	-0.075	0.940
Atorvastatin	Koh et al., 2010d	-0.300	5.228	27.335	-10.547	9.947	-0.057	0.954
Atorvastatin	Koh et al., 2011a	0.300	0.511	0.261	-0.701	1.301	0.588	0.557
Atorvastatin	Nakamura et al., 2007	2.170	0.544	0.296	1.104	3.236	3.988	0.000
Atorvastatin	Roberto et al., 2010	3.310	0.586	0.344	2.161	4.459	5.644	0.000
Atorvastatin	Shetty et al., 2004	-3.300	4.416	19.497	-11.954	5.354	-0.747	0.455
Atorvastatin	van Hoek et al., 2009a	-0.470	0.767	0.588	-1.974	1.034	-0.613	0.540
Atorvastatin	van Hoek et al., 2009b	-0.420	0.895	0.801	-2.174	1.334	-0.469	0.639
Atorvastatin		0.696	0.486	0.237	-0.257	1.649	1.431	0.152
Pitavastatin	Nomura et al., 2009	0.510	0.109	0.012	0.296	0.724	4.671	0.000
Pitavastatin		0.510	0.109	0.012	0.296	0.724	4.671	0.000
Pravastatin	Fichtenbaum et al., 2010	0.000	0.500	0.250	-0.980	0.980	0.000	1.000
Pravastatin	Gannage-Yared et al., 2005	-0.380	1.331	1.771	-2.989	2.229	-0.286	0.775
Pravastatin	Kim et al., 2013a	-0.260	0.546	0.298	-1.330	0.810	-0.476	0.634
Pravastatin	Kim et al., 2013b	0.190	0.605	0.366	-0.996	1.376	0.314	0.754
Pravastatin	Koh et al., 2009b	0.700	1.100	1.209	-1.455	2.855	0.637	0.524
Pravastatin	Koh et al., 2013b	-0.340	0.240	0.058	-0.811	0.131	-1.416	0.157
Pravastatin	Koh et al., 2013c	0.430	0.310	0.096	-0.177	1.037	1.387	0.165
Pravastatin	Sugiyama et al., 2007	1.950	0.509	0.259	0.953	2.947	3.833	0.000
Pravastatin	Yokoyama et al., 2011a	4.290	0.960	0.922	2.408	6.172	4.468	0.000
Pravastatin		0.618	0.376	0.141	-0.118	1.355	1.645	0.100
Rosuvastatin	Doh et al., 2012	0.500	2.006	4.026	-3.433	4.433	0.249	0.803
Rosuvastatin	Koh et al., 2013a	-0.780	0.192	0.037	-1.157	-0.403	-4.052	0.000
Rosuvastatin	Sawara et al., 2008	0.700	1.564	2.445	-2.364	3.764	0.448	0.654
Rosuvastatin	Yokoyama et al., 2011b	0.780	1.144	1.309	-1.462	3.022	0.682	0.495
Rosuvastatin		-0.702	0.192	0.037	-1.078	-0.327	-3.664	0.000
Simvastatin	Devaraj et al., 2007	0.600	0.521	0.271	-0.421	1.621	1.152	0.249
Simvastatin	Forst et al., 2007	1.310	2.925	8.553	-4.422	7.042	0.448	0.654
Simvastatin	Gouni-Berthold et al., 2008	0.950	1.587	2.519	-2.161	4.061	0.599	0.549
Simvastatin	Koh et al., 2005b	-0.300	0.196	0.038	-0.684	0.084	-1.533	0.125
Simvastatin	Koh et al., 2009a	-0.400	1.340	1.795	-3.026	2.226	-0.299	0.765
Simvastatin	Koh et al., 2011b	-0.400	1.314	1.725	-2.974	2.174	-0.305	0.761
Simvastatin	Koh et al., 2011c	-0.600	1.249	1.561	-3.048	1.848	-0.480	0.631
Simvastatin	Koh et al., 2008a	-0.500	2.093	4.381	-4.603	3.603	-0.239	0.811
Simvastatin	Koh et al., 2008b	-0.700	2.219	4.922	-5.048	3.648	-0.316	0.752
Simvastatin	Koh et al., 2008c	-0.500	1.766	3.118	-3.961	2.961	-0.283	0.777
Simvastatin	Koh et al., 2008d	-0.700	1.766	3.118	-4.161	2.761	-0.396	0.692
Simvastatin	Krysiak et al., 2014	3.500	0.409	0.167	2.699	4.301	8.565	0.000
Simvastatin	Kwang et al., 2004	-0.700	0.156	0.024	-1.006	-0.394	-4.489	0.000
Simvastatin	Hu et al., 2009	2.860	0.745	0.555	1.400	4.320	3.840	0.000
Simvastatin		0.505	0.484	0.235	-0.444	1.454	1.043	0.297

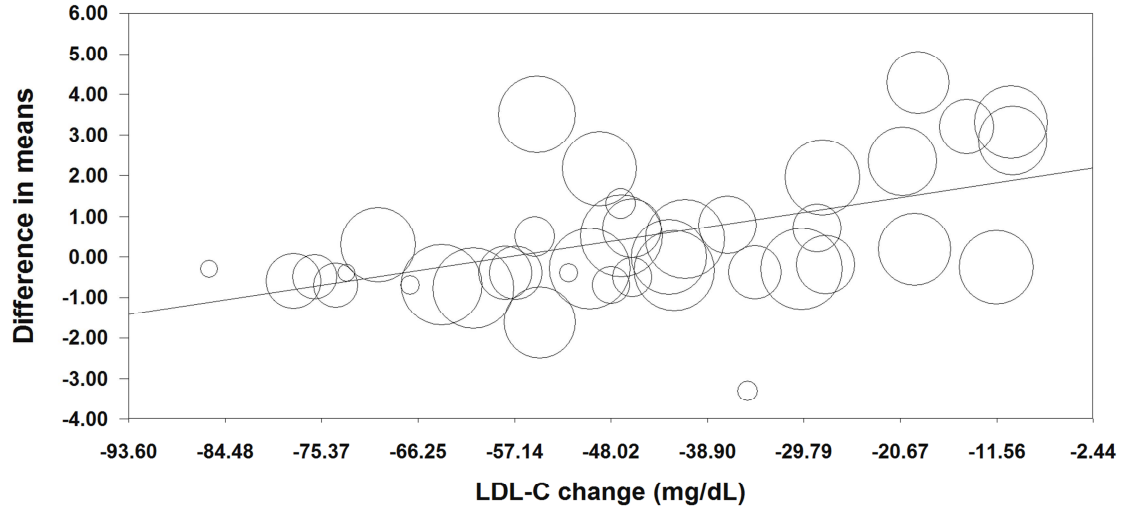


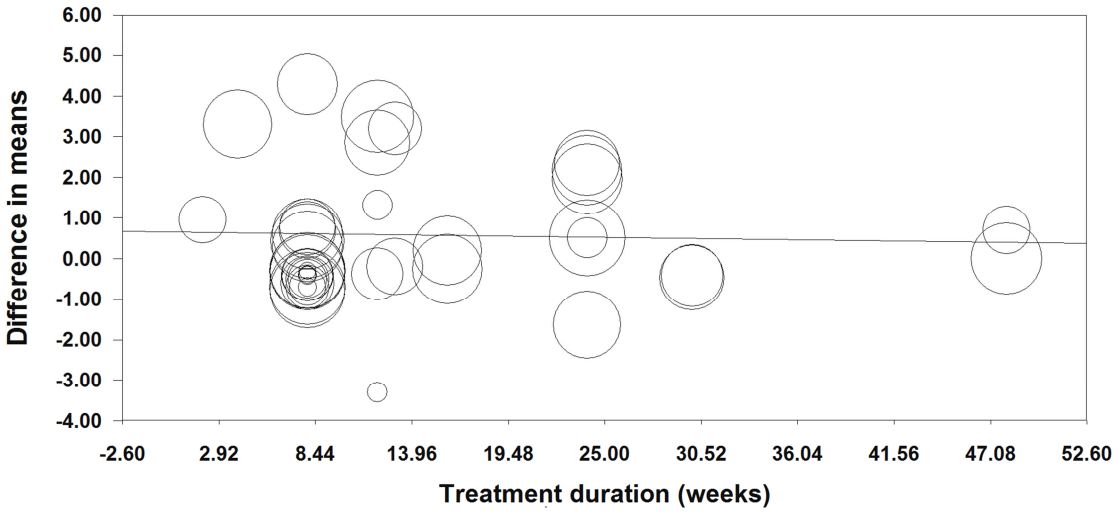
Group by Duration cat	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
<12 weeks	Devaraj et al., 2007	0.600	0.521	0.271	-0.421	1.621	1.152	0.249
<12 weeks	Gouni-Berthold et al., 2008	0.950	1.587	2.519	-2.161	4.061	0.599	0.549
<12 weeks	Koh et al., 2005a	-0.300	0.119	0.014	-0.534	-0.066	-2.516	0.012
<12 weeks	Koh et al., 2005b	-0.300	0.196	0.038	-0.684	0.084	-1.533	0.125
<12 weeks	Koh et al., 2009a	-0.400	1.340	1.795	-3.026	2.226	-0.299	0.765
<12 weeks	Koh et al., 2009b	0.700	1.100	1.209	-1.455	2.855	0.637	0.524
<12 weeks	Koh et al., 2010a	-0.400	4.813	23.166	-9.833	9.033	-0.083	0.934
<12 weeks	Koh et al., 2010b	-0.700	4.771	22.761	-10.051	8.651	-0.147	0.883
<12 weeks	Koh et al., 2010c	-0.400	5.351	28.637	-10.888	10.088	-0.075	0.940
<12 weeks	Koh et al., 2010d	-0.300	5.228	27.335	-10.547	9.947	-0.057	0.954
<12 weeks	Koh et al., 2011a	0.300	0.511	0.261	-0.701	1.301	0.588	0.557
<12 weeks	Koh et al., 2011b	-0.400	1.314	1.725	-2.974	2.174	-0.305	0.761
<12 weeks	Koh et al., 2011c	-0.600	1.249	1.561	-3.048	1.848	-0.480	0.631
<12 weeks	Koh et al., 2013a	-0.780	0.192	0.037	-1.157	-0.403	-4.052	0.000
<12 weeks	Koh et al., 2013b	-0.340	0.240	0.058	-0.811	0.131	-1.416	0.157
<12 weeks	Koh et al., 2013c	0.430	0.310	0.096	-0.177	1.037	1.387	0.165
<12 weeks	Koh et al., 2008a	-0.500	2.093	4.381	-4.603	3.603	-0.239	0.811
<12 weeks	Koh et al., 2008b	-0.700	2.219	4.922	-5.048	3.648	-0.316	0.752
<12 weeks	Koh et al., 2008c	-0.500	1.766	3.118	-3.961	2.961	-0.283	0.777
<12 weeks	Koh et al., 2008d	-0.700	1.760	3.118	-4.161	2.761	-0.396	0.692
<12 weeks	Kwang et al., 2004	-0.700	0.156	0.024	-1.006	-0.394	-4.489	0.000
<12 weeks	Roberto et al., 2010	3.310	0.586	0.344	2.161	4.459	5.644	0.000
<12 weeks	Yokoyama et al., 2011a	4.290	0.960	0.922	2.408	6.172	4.468	0.000
<12 weeks	Yokoyama et al., 2011b	0.780	1.144	1.309	-1.462	3.022	0.682	0.495
<12 weeks		0.176	0.205	0.042	-0.226	0.578	0.859	0.390
> 12 weeks	Buldak et al., 2012a	-0.200	1.126	1.267	-2.406	2.006	-0.178	0.859
> 12 weeks	Buldak et al., 2012b	3.200	1.261	1.589	0.729	5.671	2.538	0.011
> 12 weeks	Chan et al., 2008	-1.630	0.645	0.416	-2.895	-0.365	-2.526	0.012
> 12 weeks	Doh et al., 2012	0.500	2.006	4.026	-3.433	4.433	0.249	0.803
> 12 weeks	El-Barbery et al., 2011	2.350	0.732	0.536	0.915	3.785	3.209	0.001
> 12 weeks	Fichtenbaum et al., 2010	0.000	0.500	0.250	-0.980	0.980	0.000	1.000
> 12 weeks	Forst et al., 2007	1.310	2.925	8.553	-4.422	7.042	0.448	0.654
> 12 weeks	Gannage-Yared et al., 2005	-0.380	1.331	1.771	-2.989	2.229	-0.286	0.775
> 12 weeks	Kim et al., 2013a	-0.260	0.546	0.298	-1.330	0.810	-0.476	0.634
> 12 weeks	Kim et al., 2013b	0.190	0.605	0.366	-0.996	1.376	0.314	0.754
> 12 weeks	Krysiak et al., 2014	3.500	0.409	0.167	2.699	4.301	8.565	0.000
> 12 weeks	Nakamura et al., 2007	2.170	0.544	0.296	1.104	3.236	3.988	0.000
> 12 weeks	Nomura et al., 2009	0.510	0.109	0.012	0.296	0.724	4.671	0.000
> 12 weeks	Sawara et al., 2008	0.700	1.564	2.445	-2.364	3.764	0.448	0.654
> 12 weeks	Shetty et al., 2004	-3.300	4.416	19.497	-11.954	5.354	-0.747	0.455
> 12 weeks	Sugiyama et al., 2007	1.950	0.509	0.259	0.953	2.947	3.833	0.000
> 12 weeks	van Hoek et al., 2009a	-0.470	0.767	0.588	-1.974	1.034	-0.613	0.540
> 12 weeks	van Hoek et al., 2009b	-0.420	0.895	0.801	-2.174	1.334	-0.469	0.639
> 12 weeks	Hu et al., 2009	2.860	0.745	0.555	1.400	4.320	3.840	0.000
> 12 weeks		0.882	0.352	0.124	0.193	1.571	2.510	0.012



Group by Treatment modality	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Combination therapy	Buldak et al., 2012a	-0.200	1.126	1.267	-2.406	2.006	-0.178	0.859
Combination therapy	El-Barbery et al., 2011	2.350	0.732	0.536	0.915	3.785	3.209	0.001
Combination therapy	Fichtenbaum et al., 2010	0.000	0.500	0.250	-0.980	0.980	0.000	1.000
Combination therapy	Forst et al., 2007	1.310	2.925	8.553	-4.422	7.042	0.448	0.654
Combination therapy	Gouni-Berthold et al., 2008	0.950	1.587	2.519	-2.161	4.061	0.599	0.549
Combination therapy	Koh et al., 2005a	-0.300	0.119	0.014	-0.534	-0.066	-2.516	0.012
Combination therapy	Koh et al., 2005b	-0.300	0.196	0.038	-0.684	0.084	-1.533	0.125
Combination therapy	Koh et al., 2011a	0.300	0.511	0.261	-0.701	1.301	0.588	0.557
Combination therapy	Koh et al., 2013c	0.430	0.310	0.096	-0.177	1.037	1.387	0.165
Combination therapy	Kwang et al., 2004	-0.700	0.156	0.024	-1.006	-0.394	-4.489	0.000
Combination therapy	Nomura et al., 2009	0.510	0.109	0.012	0.296	0.724	4.671	0.000
Combination therapy		0.114	0.217	0.047	-0.311	0.540	0.526	0.599
Monotherapy	Buldak et al., 2012b	3.200	1.261	1.589	0.729	5.671	2.538	0.011
Monotherapy	Chan et al., 2008	-1.630	0.645	0.416	-2.895	-0.365	-2.526	0.012
Monotherapy	Devaraj et al., 2007	0.600	0.521	0.271	-0.421	1.621	1.152	0.249
Monotherapy	Doh et al., 2012	0.500	2.006	4.026	-3.433	4.433	0.249	0.803
Monotherapy	Gannage-Yared et al., 2005	-0.380	1.331	1.771	-2.989	2.229	-0.286	0.775
Monotherapy	Kim et al., 2013a	-0.260	0.546	0.298	-1.330	0.810	-0.476	0.634
Monotherapy	Kim et al., 2013b	0.190	0.605	0.366	-0.996	1.376	0.314	0.754
Monotherapy	Koh et al., 2009a	-0.400	1.340	1.795	-3.026	2.226	-0.299	0.765
Monotherapy	Koh et al., 2009b	0.700	1.100	1.209	-1.455	2.855	0.637	0.524
Monotherapy	Koh et al., 2010a	-0.400	4.813	23.166	-9.833	9.033	-0.083	0.934
Monotherapy	Koh et al., 2010b	-0.700	4.771	22.761	-10.051	8.651	-0.147	0.883
Monotherapy	Koh et al., 2010c	-0.400	5.351	28.637	-10.888	10.088	-0.075	0.940
Monotherapy	Koh et al., 2010d	-0.300	5.228	27.335	-10.547	9.947	-0.057	0.954
Monotherapy	Koh et al., 2011b	-0.400	1.314	1.725	-2.974	2.174	-0.305	0.761
Monotherapy	Koh et al., 2011c	0.600	1.249	1.561	-3.048	1.848	0.480	0.631
Monotherapy	Koh et al., 2013a	-0.780	0.192	0.037	-1.157	-0.403	-4.052	0.000
Monotherapy	Koh et al., 2013b	-0.340	0.240	0.058	-0.811	0.131	-1.416	0.157
Monotherapy	Koh et al., 2008a	-0.500	2.093	4.381	-4.603	3.603	-0.239	0.811
Monotherapy	Koh et al., 2008b	-0.700	2.219	4.922	-5.048	3.648	-0.316	0.752
Monotherapy	Koh et al., 2008c	-0.500	1.766	3.118	-3.961	2.961	-0.283	0.777
Monotherapy	Koh et al., 2008d	-0.700	1.766	3.118	-4.161	2.761	-0.396	0.692
Monotherapy	Krysiak et al., 2014	3.500	0.409	0.167	2.699	4.301	8.565	0.000
Monotherapy	Nakamura et al., 2007	2.170	0.544	0.296	1.104	3.236	3.988	0.000
Monotherapy	Roberto et al., 2010	3.310	0.586	0.344	2.161	4.459	5.644	0.000
Monotherapy	Sawara et al., 2008	0.700	1.564	2.445	-2.364	3.764	0.448	0.654
Monotherapy	Shetty et al., 2004	-3.300	4.416	19.497	-11.954	5.354	-0.747	0.455
Monotherapy	Sugiyama et al., 2007	1.950	0.509	0.259	0.953	2.947	3.833	0.000
Monotherapy	van Hoek et al., 2009a	-0.470	0.767	0.588	-1.974	1.034	-0.613	0.540
Monotherapy	van Hoek et al., 2009b	-0.420	0.895	0.801	-2.174	1.334	-0.469	0.639
Monotherapy	Yokoyama et al., 2011a	4.290	0.960	0.922	2.408	6.172	4.468	0.000
Monotherapy	Yokoyama et al., 2011b	0.780	1.144	1.309	-1.462	3.022	0.682	0.495
Monotherapy	Hu et al., 2009	2.860	0.745	0.555	1.400	4.320	3.840	0.000
Monotherapy		0.703	0.350	0.122	0.017	1.388	2.010	0.044




Difference in means
6.00
5.00
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-93.60
-84.48
-75.37
-66.25
-57.14
-48.02
-38.90
-29.79
-20.67
-11.56
-2.44
LDL-C change (mg/dL)


Difference in means
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5.00
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-2.60
2.92
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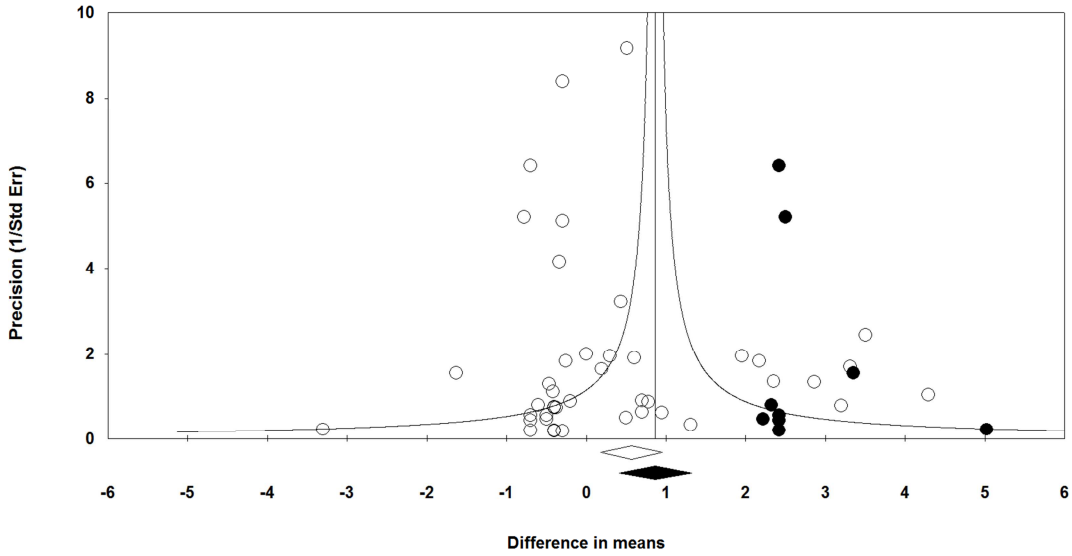
25.00
30.52
36.04
41.56
47.08
52.60
Treatment duration (weeks)



HIGHLIGHTS:

- The effect of statin therapy on plasma adiponectin levels has not been conclusively studied.
- The analysis shows a significant increase in plasma adiponectin levels after statin therapy (weighted mean difference (WMD): +0.57 µg/mL).
- The meta-analysis confirmed that statins may have an important impact on the adiponectin levels.
- The pleiotropic adiponectin-elevating effect of statins might explain the benefits of statins in reducing the cardiovascular risk.

AUTHOR DECLARATION TEMPLATE

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from: maciejbanach@aol.co.uk

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