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Statin therapy and plasma free fatty acids: a systematic review and meta-analysis of controlled clinical trials

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AIM

The aim of this meta-analysis was to evaluate the effect of statin therapy on plasma FFA concentrations in a systematic review and meta-analysis of controlled clinical trials.

METHODS

PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched (from inception to February 16 2015) to identify controlled trials evaluating the impact of statins on plasma FFA concentrations. A systematic assessment of bias in the included studies was performed using the Cochrane criteria. A random effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Random effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of potential moderators.

RESULTS

Meta-analysis of data from 14 treatment arms indicated a significant reduction in plasma FFA concentrations following treatment with statins (weighted mean difference (WMD) –19.42%, 95% CI –23.19, ––15.64, $P < 0.001$). Subgroup analysis confirmed the significance of the effect with both atorvastatin (WMD –20.56%, 95% CI –24.51, –16.61, $P < 0.01$) and simvastatin (WMD –18.05%, 95% CI –28.12, –7.99, $P < 0.001$). Changes in plasma FFA concentrations were independent of treatment duration (slope –0.10, 95% CI –0.30, 0.11, $P = 0.354$) and magnitude of reduction in plasma low density lipoprotein cholesterol concentrations (slope 0.55, 95% CI –0.17, 1.27, $P = 0.133$) by statins.

CONCLUSIONS

The results of the present study suggest that statin therapy may lower plasma FFA concentrations. The cardiovascular and metabolic significance of this finding requires further investigation.

Introduction

Inhibitors of 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA), are known for their established efficacy in decreasing cardiovascular outcomes and mortality in both primary and secondary prevention [1–4]. The main effect of statins is reducing plasma low density lipoprotein cholesterol (LDL-C) concentrations [5]. In addition, statin therapy can reduce triglycerides and increase high density lipoprotein (HDL) cholesterol concentrations plus a plethora of non-lipid pleiotropic actions [6–12].

FFAs are non-esterified fatty acids that are released from adipocyte triglyceride stores following lipolysis, and from phospholipids after hydrolysis by phospholipases [13]. FFAs promote the formation and release of triglycerides by the liver leading to an overproduction of very low density lipoprotein (VLDL) [14, 15] and consequent development of atherogenic dyslipidaemia. On the other hand, overproduction of VLDL and LDL can increase the flux of plasma FFAs to the liver causing hepatic insulin resistance and inflammation [16, 17].

Fatty acid metabolism was once considered to be unchanged by statin therapy [18–20]. However, mild elevations in fatty acid synthesis were subsequently reported in animal models [21] cultured cells [22], and after statin treatment in mice [23]. Moreover, statins may also inhibit hepatic synthesis of apolipoprotein B-100 and decrease the synthesis and secretion of triglyceride-rich lipoproteins [24, 25]. The molecular mechanism by which statins reduce triglycerides levels is not known with certainty. In this regard, statins could affect hepatic FFA metabolism [26]. However, studies evaluating the effects of statins on serum fatty acid metabolism in humans are lacking and published data are contradictory [27]. Therefore, the aim of this study was to evaluate the effect of statin therapy on plasma FFA concentrations and calculate the size of this effect using a systematic review and meta-analysis of controlled clinical trials.

Methods

Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [28]. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR 'statin therapy' OR statins) AND ('free fatty acid' OR 'free fatty acids' OR FFA OR FFAs). The wild-card term '*' was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in humans. The literature was searched from inception to February 16 2015.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being a controlled trial with either parallel or crossover design, (ii) investigating the impact of statin therapy, either as monotherapy or combination therapy, on plasma/serum concentrations of FFAs, (iii) treatment duration of at least 2 weeks and (iv) presentation of sufficient information on FFA concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-interventional trials, (ii) lack of an appropriate control group for statin therapy, (iii) observational studies with case–control, cross-sectional or cohort design and (iv) lack of sufficient information on baseline or follow-up FFA 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) age, gender and body mass index (BMI) of study participants, 6) baseline concentrations of total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides, 7) systolic and diastolic blood pressures and 8) data regarding baseline and follow-up concentrations of FFAs.

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [29]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, 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. Labelling an item as 'unclear' indicated an unclear or unknown risk of bias.

Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [30]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up − measure at baseline. For single arm crossover trials, net change in plasma concentrations of FFA were calculated by subtracting the value after control intervention from that reported after treatment. All values were collated as percent change from baseline in each group, or percent change in the statin group relative to control group. 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 range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by Hozo *et al*. [31]. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × square root (n), where n is the number of subjects. To avoid the problem of double-counting in randomized controlled trials with multiple treatment arms and a common control group, the number of subjects in the control group was divided by the required comparisons.

A random effects model (using the 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 [32]. Heterogeneity was quantitatively assessed using I^2 index. Effect sizes were expressed as weighed mean difference (WMD) and 95% confidence interval (CI). Subgroup analyses were carried out to explore the impact of statin type and treatment duration (< 12 weeks *vs.* ≥12 weeks) on plasma FFA concentrations. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method, i.e. removing one study each time and repeating the analysis [33-35].

Meta-regression

Random effects meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential moderators including duration of treatment with statins, dose of treatment (expressed as equivalent dose of atorvastatin) and magnitude of LDL-C reduction by statin therapy.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie 'trim and fill' and 'fail-safe N' methods were used to adjust the analysis for the effects of publication bias [36].

Results

Flow and characteristics of included studies

Firstly, 189 published studies were identified following the database search. After reviewing the titles and abstracts, 170 studies did not meet the inclusion criteria and were excluded. Then, 19 full text articles were carefully assessed and reviewed. Ten of these studies were excluded for the following reasons: non-interventional design (n = 1), being non-original (n = 1), presenting incomplete data (n = 2), not measuring plasma/serum FFA concentrations (n = 4) and not being controlled for statin therapy (n = 2). Finally, nine eligible studies with 14 treatment arms were included in the systematic review and meta-analysis. The study selection process is shown in Figure 1.

A total of 764 individuals were incorporated in the nine eligible controlled trials, including 462 and 302 subjects in the statin and control groups (participants from the cross-over trials were counted in both treatment and control groups), respectively. Included studies were published between 1991 and 2014. The clinical trials used only atorvastatin and simvastatin but with different doses. Two studies used atorvastatin 10 mg day^{-1} [37, 38], one study atorvastatin 20 mg day^{-1} [39], one study atorvastatin 80 mg day^{-1} [38], one study simvastatin 10 mg day^{-1} [40], one study simvastatin 20 mg day^{-1} [41], one study simvastatin 30 mg day^{-1} [42], three studies simvastatin 40 mg day^{-1} [41, 43, 44] and one study simvastatin 80 mg day^{-1} [45]. The range of intervention periods was from 3 weeks [42] to 2 years [41]. Study designs of included studies were parallel [38–41, 43–45] and crossover [37, 42]. Selected trials enrolled subjects with primary hypercholesterolaemia [41, 43, 44], type 2 diabetes [38, 42, 45], metabolic syndrome [37, 40] and mixed dyslipidaemia [39] (Table 1). Finally, most of the included studies measured FFA concentrations using an enzymatic assay method [38, 40, 41, 43–45], while three trials did not specify the method used [37, 39, 42].

Risk of bias assessment

Seven included studies were characterized by lack of information about the sequence generation, allocation

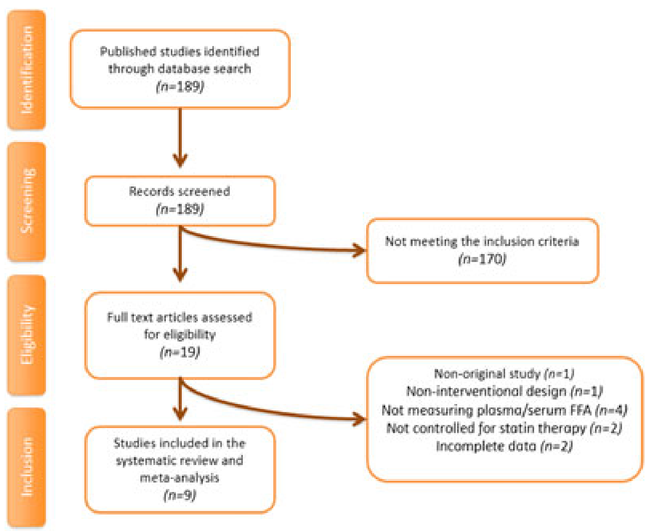


Figure 1

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

Table 1

Demographic characteristics of the included studies

Author	Study design	Target population	Treatment duration	n	Study groups	Age (years)s	Female (n, %)	BMI, (kg m^{-2})	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Total cholesterol (mgdl^{-1})	LDL cholesterol (mg dl^{-1})	HDL cholesterol (mg dl^{-1})	Triglycerides (mg dl^{-1})	FFA (mmol l^{-1})
Bays *et al.* [39]*	Randomized, double-blind, placebo-controlled Parallel group	Overweight and mixed dyslipidaemia	8 weeks	31	Control	54.9 ± 1.5	15 (48.0)	33.4 ± .08	ND	ND	251.7 ± 5.8	160.7 ± 4.3	43.6 ± 1.3	254.6 ± 22.5	0.6 ± 0.0
				28	MBX-8025, 50 mg day^{-1}	54.3 ± 2.2	11 (39.0)	33.5 ± 1.3	ND	ND	254.6 ± 6.1	169.3 ± 5.0	44.6 ± 1.2	214.8 ± 14.0	0.6 ± 0.0
				32	MBX-8025, 100 mg day^{-1}	54.6 ± 1.9	17 (53.0)	31.8 ± 0.6	ND	ND	250.6 ± 6.4	163.6 ± 6.3	44.3 ± 1.7	236.3 ± 16.3	0.6 ± 0.1
				31	Atorvastatin 20 mg day^{-1}	54.3 ± 1.9	18 (58.0)	34.0 ± 1.2	ND	ND	245.4 ± 5.5	165.1 ± 5.0	42.7 ± 1.5	199.8 ± 11.6	0.6 ± 0.0
				30	MBX-8025, 50 mg day^{-1} + atorvastatin 20 mg day^{-1}	54.6 ± 1.7	18 (60.0)	33.8 ± 1.1	ND	ND	258.4 ± 6.6	175.0 ± 5.3	44.8 ± 1.5	196.2 ± 13.5	0.5 ± 0.0
				29	MBX-8025, 100 mg day^{-1} + atorvastatin 20 mg day^{-1}	52.6 ± 1.7	16 (55.0)	35.2 ± 1.1	ND	ND	239.8 ± 4.8	157.6 ± 3.1	42.6 ± 1.2	211.6 ± 13.9	0.6 ± 0.1
Huptas *et al.* [37]	Randomized, double-blind, placebo-controlled Crossover	Metabolic syndrome	6 weeks	10		40 ± 12	0 (0.0)	33.6 ± 5.2	ND	ND					
					Control						208 ± 46	125 ± 43	45.0 ± 11.4	198 ± 122	0.96 ± 0.49
					Atorvastatin 10 mg day^{-1}						164 ± 41	85 ± 30	47.6 ± 10.5	192 ± 188	0.52 ± 0.17
Krysiak *et al.* [43]	Placebo-controlled Parallel	Primary hypercholesterolaemia	12 weeks												
				21	Control	51.1 ± 2.6	9 (43)	26.8 ± 2.7	ND	ND	250 ± 15	175 ± 13	47 ± 4	112 ± 13	0.34 ± 0.04
				23	Simvastatin 40 mg day^{-1}	51.9 ± 2.7	9 (39)	26.7 ± 2.3	ND	ND	192 ± 13	128 ± 11	49 ± 5	107 ± 14	0.24 ± 0.02
				21	Simvastatin 40 mg day^{-1}+ ezetimibe 10 mg day^{-1}	52.5 ± 3.5	9 (43)	26.5 ± 2.4	ND	ND	156 ± 12	98 ± 9	54 ± 4	105 ± 18	0.20 ± 0.02
Krysiak *et al.* [44]	Placebo-controlled Parallel	Primary hypercholesterolemia	30 days												
				17	Control	50.7 ± 2.6	8 (47)	27.2 ± 2.6	ND	ND	246 ± 14	175 ± 14	48 ± 5	119 ± 12	0.32 ± 0.05
				22	Simvastatin 40 mg day^{-1}	51.8 ± 2.6	9 (41)	26.3 ± 2.5	ND	ND	191 ± 13	128 ± 11	49 ± 5	113 ± 15	0.30 ± 0.03
Mitropoulos *et al.* [41]	Randomized, placebo-controlled	Primary hypercholesterolaemia	2 years	54	Simvastatin 40 mg/day	62.6 ± 6.7	6 (11.1)	26.0 ± 2.7	ND	ND	194.9 ± 34.8	95.5 ± 25.1	62.6 ± 15.1	146.1 ± 71.7	0.32 ± 0.21
				57	Simvastatin 20 mg day^{-1}	62.5 ± 7.6	8 (14.0)	25.8 ± 3.5	ND	ND	233.6 ± 64.2	ND	ND	131.1 ± 64.7	0.34 ± 0.21
				51	Control	64.0 ± 6.2	10 (19.6)	26.7 ± 4.2	ND	ND	273.0 ± 45.2	162.8 ± 35.2	58.4 ± 14.7	185.1 ± 94.8	0.41 ± 0.23
Paolisso *et al.* [42]	Randomized, double-blind, placebo-controlled cross-over	Type 2 diabetes and hypercholesterolaemia	3 weeks	12		72.3 ± 1.4	6 (50.0)	27.2 ± 0.6	ND	ND					
					Control						305.5 ± 11.6	278.4 ± 15.5	23.2 ± 7.7	256.9 ± 35.4	1.10 ± 0.21
					Simvastatin 30 mg day^{-1}						204.9 ± 7.7	166.3 ± 11.6	34.8 ± 11.6	186.0 ± 17.7	0.81 ± 0.10
Plat *et al.* [40]*	Randomized, double-blind, placebo-controlled parallel	Metabolic syndrome	8 weeks												
				9	Control	60 ± 7	4 (44.4)	30.2 ± 1.9	142 ± 14	92 ± 10	250.2 ± 57.6	ND	45.6 ± 7.7	174.5 ± 80.6	0.30 ± 0.10
				10	Simvastatin 10 mg day^{-1}	61 ± 8	4 (40.0)	29.2 ± 3.3	139 ± 7	89 ± 7	247.5 ± 43.7	ND	43.3 ± 8.9	203.7 ± 75.3	0.39 ± 0.14
				9	Plant stanols	60 ± 4	2 (22.2)	28.1 ± 2.6	138 ± 11	94 ± 8	288.1 ± 49.1	ND	44.9 ± 7.3	128.4 ± 44.3	0.29 ± 0.10
				8	Simvastatin 10 mg day^{-1} + plant stanols	60 ± 8	3 (37.5)	29.7 ± 7.5	150 ± 30	96 ± 21	280.4 ± 47.6	ND	45.2 ± 16.2	177.1 ± 81.5	0.29 ± 0.08
DALI Study Group [38]	Randomized, double-blind, placebo-controlled parallel	Type 2 diabetes and dyslipidaemia	30 weeks												
				72	Control	58.5 ± 7.5	26 (36.1)	32.2 ± 6.0	144 ± 19	85 ± 9	232.0 ± 3.9	139.2 ± 3.9	40.2 ± 1.2	255.1 ± 19.5	0.72 ± 0.04
				73	Atorvastatin 10 mg day^{-1}	59.7 ± 7.6	13 (17.8)	30.0 ± 3.8	146 ± 17	86 ± 10	158.5 ± 3.9	85.1 ± 3.9	42.5 ± 1.5	163.0 ± 8.9	0.57 ± 0.03
				72	Atorvastatin 80 mg day^{-1}	60.1 ± 7.7		30.4 ± 4.5	145 ± 17	85 ± 9	139.2 ± 3.9	65.7 ± 3.9	42.2 ± 1.5	157.7 ± 14.2	0.61 ± 0.03
Szendroedi *et al.* [45]	Randomized, double-blind, placebo-controlled parallel	Type 2 diabetes and hypercholesterolaemia	2 months												
				10	Simvastatin 80 mg day^{-1}	55 ± 6	3 (30.0)	28.9 ± 3.5	ND	ND	197.2 ± 38.7	108.3 ± 34.8	54.1 ± 11.6	132.9 ± 35.4	0.39 ± 0.13
				10	Control	58 ± 8	5 (50.0)	27.3 ± 3.7	ND	ND	255.2 ± 30.9	162.4 ± 19.3	54.1 ± 11.6	186.0 ± 70.9	0.60 ± 0.23

Values are expressed as mean ± SD. *Only basal conditions. ND, no data; BMI, body mass index; FFA, free fatty acids; DALI, Diabetes Atorvastatin Lipid Intervention.

concealment and blinding of participants, personnel and outcome assessors [37, 38, 41–45]. In addition, two studies had high risk of bias for sequence generation and allocation concealment [43, 44]. However, six evaluated studies showed low risk of bias with respect to selective outcome reporting and other sources of bias [38–41, 43, 45]. Finally, all trials had low risk of bias for incomplete outcome data. Details of the quality of bias assessment are shown in Table 2.

Effect of statin therapy on plasma FFA concentrations

Meta-analysis of data from 14 treatment arms revealed a significant reduction in plasma FFAs following treatment with statins (WMD −19.42%, 95% CI −23.19, −15.64, $P < 0.001$; I^2 65.27%). This effect was robust in the sensitivity analysis (Figure 2). In subgroup analysis, reductions in plasma FFA concentrations were observed in both subsets of trials with treatment durations <12 weeks (WMD −7.38%, 95% CI −13.36, −1.40, $P = 0.016$; I^2 0%) and ≥12 weeks (WMD −23.51%, 95% CI −25.88, −21.14, $P < 0.001$; I^2 52.41%), though the effect size was numerically greater in the latter group (Figure 3). With respect to the type of statin, there were significant reductions in plasma FFA concentrations with both atorvastatin (WMD −20.56%, 95% CI −24.51, −16.61, $P < 0.01$; I^2 71.91%) and simvastatin (WMD −18.05%, 95% CI −28.12, −7.99, $P < 0.001$; I^2 61.81%) (Figure 4).

Meta-regression

Random effects meta-regression was performed to evaluate the impact of potential moderators on the estimated effect size. Changes in plasma FFA concentrations were independent of treatment duration (slope −0.10, 95% CI −0.30, 0.11, P = 0.354), statin dose (slope −0.08, 95% CI −0.33, 0.16, P = 0.514) and magnitude of LDL-C reduction (slope 0.55, 95% CI −0.17, 1.27, P = 0.133) by statins (Figure 5).

Publication bias

The funnel plot of standard error *vs.* effect size (mean difference) was asymmetric and suggested potential publication bias. Presence of publication bias was also suggested by Egger's linear regression (intercept =1.05, standard error = 0.48; 95% CI = 0.004, 2.10, t = 2.19, df = 12.00, two-tailed P = 0.049) but not Begg's rank correlation test (Kendall's Tau with continuity correction =0, z = 0, two-tailed P value =1.000). After adjustment of effect size for potential publication bias using the 'trim and fill' correction, five potentially missing studies on the left side of the funnel plot were imputed leading to a corrected effect size that was greater than the initial estimate (WMD −21.54%, 95% CI −25.44, −17.64) (Figure 6). The 'fail-safe N' test showed that 1417 studies would be needed to bring the WMD down to a non-significant ($P > 0.05$) value.

Discussion

The findings of the present meta-analysis suggest that statins are associated with a significant reduction in the plasma concentrations of FFAs. This effect that was independent of statin type, treatment duration and dose and magnitude of changes in plasma LDL-C concentrations. It has been reported that high concentrations of FFAs induce oxidative stress, inflammation and insulin resistance by activating the nuclear factor-kappa B pathway and promoting increased reactive oxidant species [17]. Therefore, the decrease in FFA concentrations after statin therapy may have important clinical implications slowing the progression of atherogenesis and consequently a lower cardiovascular risk. However, these potential effects of statins as antioxidant and anti-inflammatory through the reduction of FFA concentrations are still uncertain and remain to be clarified in further studies. Although the effect of statins on FFA metabolism is unclear, there are several mechanisms which may be involved. In this regard, acetyl coenzyme A carboxylase and fatty acid synthase, two important regulatory enzymes in fatty acid biosynthesis, could be regulated simultaneously by HMG-CoA reductase enzyme at the genomic level. Therefore, activity of both enzymes could be influenced by statin therapy [46, 47]. Since HMG-CoA reductase and acetyl coenzyme A carboxylase are reversibly inactivated through phosphorylation by AMP-activated protein kinase [48], down regulation of this enzyme by sterol deficiency would increase acetyl coenzyme A carboxylase activity after statin therapy when regulatory sterols are absent [49]. In addition, a pleiotropic effect of statins on peroxisome proliferator-activated receptor-α (PPARα) expression has been described. Statins activate PPARα, which increases the hepatic fatty acid uptake and promotes the transformation of fatty acids to acyl-coenzyme A, resulting in increased β-oxidation and reduced availability of fatty acids [50]. However, available data on the effects of statins on plasma FFA concentrations in humans is still limited and is based on small scale studies. The aim of the present study was to obtain more robust evidence on the impact of statins on plasma FFA concentrations through combining individual studies and applying a random effects meta-analysis.

Circulating FFAs mainly derive from adipose tissue lipolysis by the action of lipase. Hepatic FFAs are available from *de novo* lipogenesis and uptake of triglyceride-rich lipoproteins, cholesteryl esters, and plasma FFAs. Fatty acid derivatives can serve as ligands for the peroxisome proliferator-activated receptors (PPARs) [51], particularly PPAR-α which is considered as the most important regulator of intra and extracellular fatty acid metabolism. In fact, PPAR-α activation decreases VLDL synthesis and secretion, increases plasma HDL, decreases triglyceride concentrations and enhances fatty acid oxidation [52]. Interestingly, lipid lowering drugs have shown a reduction of serum total fatty acid concentration while simultaneously increasing

Table 2

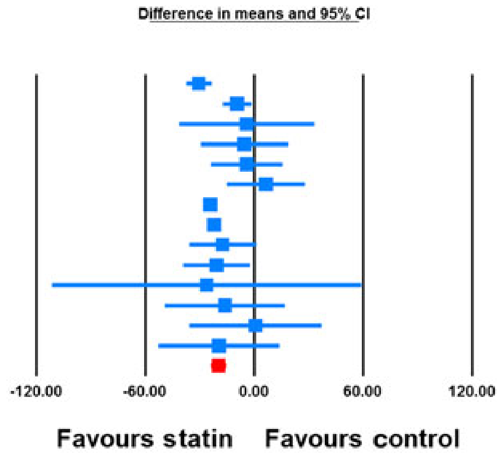
Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bays *et al.* [39]	L	L	U	L	L	L
Huptas *et al.* [37]	U	U	U	L	U	L
Krysiak *et al.* [43]	H	H	L	L	L	L
Krysiak *et al.* [44]	H	H	L	L	L	U
Mitropoulos *et al.* [41]	U	U	L	L	L	L
Paolisso *et al.* [42]	U	U	U	L	U	L
Plat *et al.* [40]	U	L	L	L	L	L
DALI Study Group [38]	U	U	U	L	L	L
Szendroedi *et al.* [45]	U	U	U	L	L	L

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

Statistics for each study

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	*P* value
Krysiak *et al.*, [43]	-30.300	3.472	12.053	-37.105	-23.495	-8.727	0.000
Krysiak *et al.*, [44]	-9.170	3.812	14.534	-16.642	-1.698	-2.405	0.016
Huptas *et al.*, [37]	-3.890	18.948	359.028	-41.027	33.247	-0.205	0.837
Bays *et al.*, [39]	-5.100	12.126	147.036	-28.866	18.666	-0.421	0.674
Bays *et al.*, [39]	-3.700	9.938	98.767	-23.178	15.778	-0.372	0.710
Bays *et al.*, [39]	6.600	10.873	118.217	-14.710	27.910	0.607	0.544
Stolk, [38]	-24.000	0.793	0.629	-25.555	-22.445	-30.251	0.000
Stolk, [38]	-21.800	0.849	0.722	-23.465	-20.135	-25.664	0.000
Mitropoulos *et al.*, [41]	-17.210	9.310	86.676	-35.457	1.037	-1.849	0.065
Mitropoulos *et al.*, [41]	-20.450	9.310	86.676	-38.697	-2.203	-2.197	0.028
Paolisso *et al.*, [42]	-26.040	43.360	1880.090	-111.024	58.944	-0.601	0.548
Plat *et al.*, [40]	-15.910	16.771	281.264	-48.780	16.960	-0.949	0.343
Plat *et al.*, [40]	1.010	18.518	342.933	-35.285	37.305	0.055	0.957
Szendroedi *et al.*, [45]	-19.160	16.813	282.692	-52.114	13.794	-1.140	0.254
	-19.419	1.927	3.712	-23.195	-15.643	-10.079	0.000



Statistics with study removed

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z Value	*P* Value
Krysiak *et al.*, [43]	-17.836	2.005	4.020	-21.766	-13.907	-8.896	0.000
Krysiak *et al.*, [44]	-21.787	1.683	2.833	-25.086	-18.488	-12.945	0.000
Huptas *et al.*, [37]	-19.570	1.938	3.757	-23.369	-15.771	-10.096	0.000
Bays *et al.*, [39]	-19.820	1.923	3.699	-23.589	-16.050	-10.305	0.000
Bays *et al.*, [39]	-20.109	1.891	3.575	-23.815	-16.404	-10.636	0.000
Bays *et al.*, [39]	-20.542	1.774	3.148	-24.019	-17.064	-11.577	0.000
Stolk, [38]	-15.492	3.229	10.426	-21.821	-9.164	-4.798	0.000
Stolk, [38]	-15.562	3.428	11.748	-22.280	-8.844	-4.540	0.000
Mitropoulos *et al.*, [41]	-19.441	1.987	3.949	-23.336	-15.546	-9.783	0.000
Mitropoulos *et al.*, [41]	-19.293	1.995	3.979	-23.203	-15.384	-9.672	0.000
Paolisso *et al.*, [42]	-19.336	1.954	3.819	-23.166	-15.506	-9.895	0.000
Plat *et al.*, [40]	-19.401	1.963	3.852	-23.247	-15.554	-9.885	0.000
Plat *et al.*, [40]	-19.671	1.922	3.692	-23.438	-15.905	-10.237	0.000
Szendroedi *et al.*, [45]	-19.350	1.965	3.863	-23.202	-15.498	-9.845	0.000
	-19.419	1.927	3.712	-23.195	-15.643	-10.079	0.000

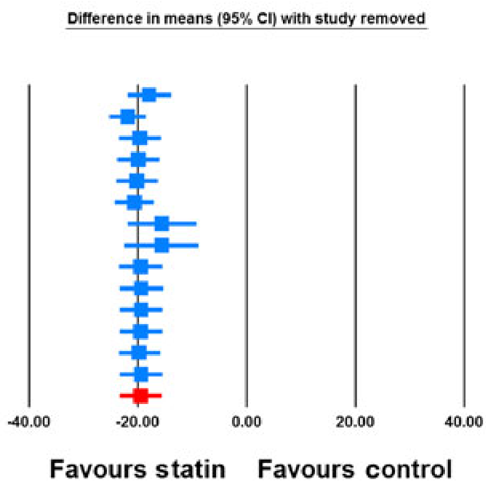
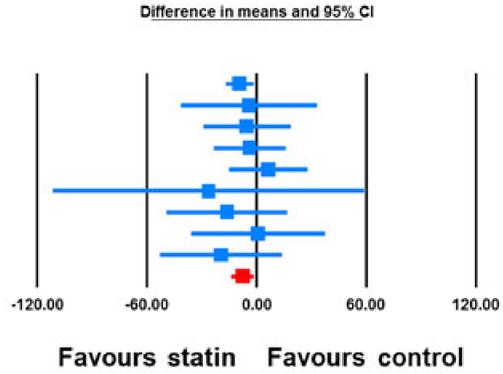


Figure 2

Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma FFA concentrations (I^2 65.27%). Lower plot shows leave-one-out sensitivity analysis

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	*P* value
Krysiak *et al.*, [44]	-9.170	3.812	14.534	-16.642	-1.698	-2.405	0.016
Huptas *et al.*, [37]	-3.890	18.948	359.028	-41.027	33.247	-0.205	0.837
Bays *et al.*, [39]	-5.100	12.126	147.036	-28.866	18.666	-0.421	0.674
Bays *et al.*, [39]	-3.700	9.938	98.767	-23.178	15.778	-0.372	0.710
Bays *et al.*, [39]	6.600	10.873	118.217	-14.710	27.910	0.607	0.544
Paolisso *et al.*, [42]	-26.040	43.360	1880.090	-111.024	58.944	-0.601	0.548
Plat *et al.*, [40]	-15.910	16.771	281.264	-48.780	16.960	-0.949	0.343
Plat *et al.*, [40]	1.010	18.518	342.933	-35.285	37.305	0.055	0.957
Szendroedi *et al.*, [45]	-19.160	16.813	282.692	-52.114	13.794	-1.140	0.254
	-7.379	3.050	9.301	-13.356	-1.401	-2.419	0.016



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	*P* value
Krysiak *et al.*, [43]	-30.300	3.472	12.053	-37.105	-23.495	-8.727	0.000
Stolk, [38]	-24.000	0.793	0.629	-25.555	-22.445	-30.251	0.000
Stolk, [38]	-21.800	0.849	0.722	-23.465	-20.135	-25.664	0.000
Mitropoulos *et al.*, [41]	-17.210	9.310	86.676	-35.457	1.037	-1.849	0.065
Mitropoulos *et al.*, [41]	-20.450	9.310	86.676	-38.697	-2.203	-2.197	0.028
	-23.514	1.209	1.462	-25.884	-21.144	-19.445	0.000

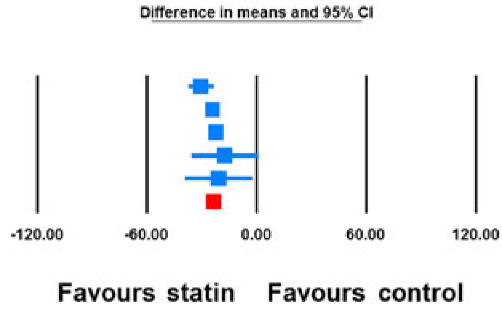
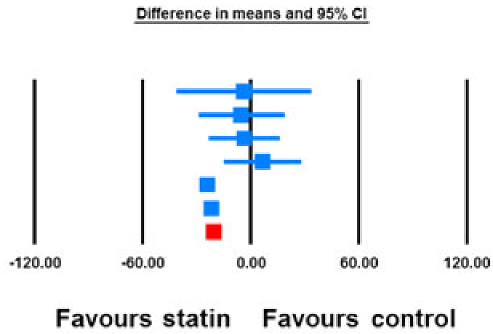


Figure 3

Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma FFA concentrations in trials with treatment durations of $<$12 weeks (upper plot) (I^2 0%) and $\geq$12 weeks (lower plot) (I^2 52.41%)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	*P* value
Huptas *et al.*, [37]	-3.890	18.948	359.028	-41.027	33.247	-0.205	0.837
Bays *et al.*, [39]	-5.100	12.126	147.036	-28.866	18.666	-0.421	0.674
Bays *et al.*, [39]	-3.700	9.938	98.767	-23.178	15.778	-0.372	0.710
Bays *et al.*, [39]	6.600	10.873	118.217	-14.710	27.910	0.607	0.544
Stolk, [38]	-24.000	0.793	0.629	-25.555	-22.445	-30.251	0.000
Stolk, [38]	-21.800	0.849	0.722	-23.465	-20.135	-25.664	0.000
	-20.559	2.014	4.056	-24.506	-16.612	-10.208	0.000



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z value	*P* value
Krysiak *et al.*, [43]	-30.300	3.472	12.053	-37.105	-23.495	-8.727	0.000
Krysiak *et al.*, [44]	-9.170	3.812	14.534	-16.642	-1.698	-2.405	0.016
Mitropoulos *et al.*, [41]	-17.210	9.310	86.676	-35.457	1.037	-1.849	0.065
Mitropoulos *et al.*, [41]	-20.450	9.310	86.676	-38.697	-2.203	-2.197	0.028
Paolisso *et al.*, [42]	-26.040	43.360	1880.090	-111.024	58.944	-0.601	0.548
Plat *et al.*, [40]	-15.910	16.771	281.264	-48.780	16.960	-0.949	0.343
Plat *et al.*, [40]	1.010	18.518	342.933	-35.285	37.305	0.055	0.957
Szendroedi *et al.*, [45]	-19.160	16.813	282.692	-52.114	13.794	-1.140	0.254
	-18.053	5.134	26.360	-28.116	-7.990	-3.516	0.000

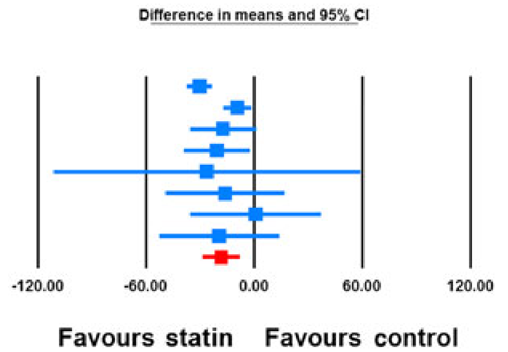


Figure 4

Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of atorvastatin (upper plot) (I^2 71.91%) and simvastatin (lower plot) (I^2 61.81%) on plasma FFA concentrations

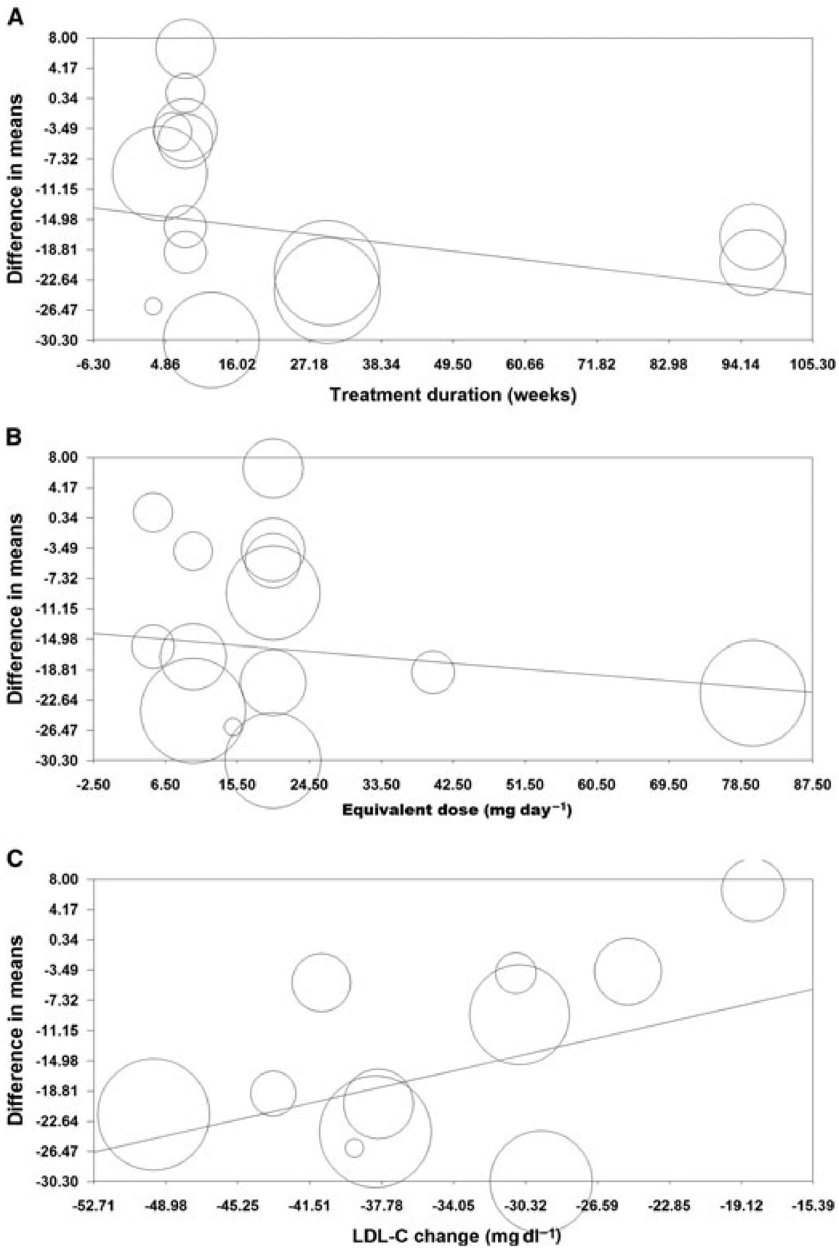


Figure 5

Meta-regression plots of the association between mean changes in plasma FFA concentrations with duration of statin therapy (A), statin dose (expressed as equivalent dose of atorvastatin; B) and magnitude of LDL-C reduction (C)

the proportion of long chain polyunsaturated fatty acids and precursor fatty acids for eicosanoid production [53]. Circulating total fatty acids are found in different forms: 45% in triacylglycerols, 15% in cholesteryl esters, 35% in phospholipids and about 5% as non-esterified free fatty acids [53]. Between 75% and 80% of serum cholesterol is esterified with fatty acids and only 20% to 25% is non-esterified cholesterol [53]. Nonetheless, statins appear to exert their effects on the metabolism and serum composition of FFAs through disturbing the biogenesis of isolated fatty acids independently of the mechanism that regulates lipoprotein synthesis and secretion. In this context, the results of meta-regression analysis revealed that changes in plasma FFA concentrations were independent of the magnitude of LDL-C reduction. This lack of dependence of FFA changes on the potency and duration of statin treatment is suggestive of a class effect that is independent of degree of inhibition of HMG-CoA reductase. As referred to above, it is likely that enhancement of PPAR-α expression and activity in liver and muscle tissues is responsible for the FFA-reducing effect through increasing FFA uptake, FFA conversion to acyl-CoA and β-oxidation of FFAs [54].

There is evidence indicating that treatment with statins is a risk factor for the development of new onset type 2 diabetes [55], though the causes of this negative effect remain unexplained. In this regard, it has been suggested

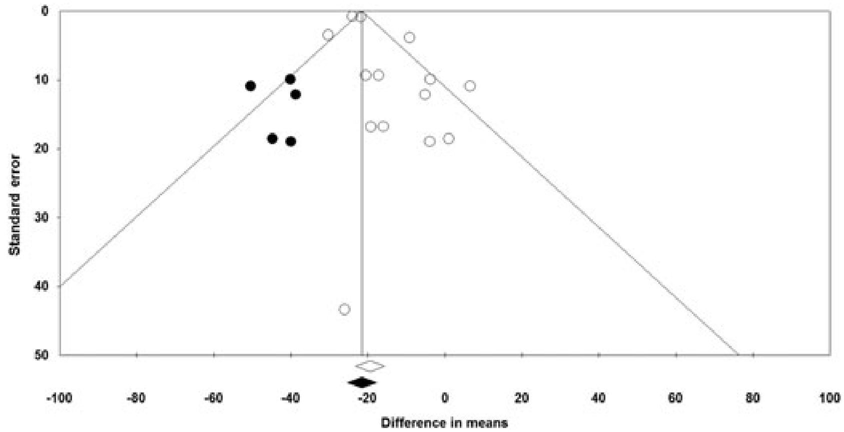


Figure 6

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

that statins may contribute to insulin resistance and impair β-cell function [56]. In animal models, long term treatment with statins increased insulin resistance in the adipose tissue [57]. There is evidence indicating that both increased efflux of FFAs from adipose tissue and impaired insulin-mediated skeletal muscle uptake of FFAs increase fatty acid flux to the liver promoting the development of peripheral insulin resistance [58, 59]. The association between plasma FFA concentrations and insulin resistance has been supported by epidemiological studies [60]. There is robust evidence from published meta-analyses indicating that although statin therapy increases the risk of new-onset diabetes, the risk is not equivalent for all statins. It has been reported that the diabetogenic effect of statins depends on the type (being highest with rosuvastatin) and dose of statins (a higher risk at higher doses) [61, 62]. In this context, it is important to note that none of the studies included in the present meta-analysis included a rosuvastatin arm, and except one trial, all other included studies used a mild to moderate intensity statin therapy regimen. Hence, the overall set of trials included in this meta-analysis may not fully represent the impact of a highly diabetogenic statin regimen on plasma concentrations of FFAs, and future studies are required to see if a similar or differential effect on plasma FFAs could be seen in trials with rosuvastatin and high intensity statin regimens. Moreover, in spite of some controversies, it has been shown that in diabetic subjects statin therapy is not associated with an adverse impact on glycaemic index and insulin resistance [63]. Therefore, since diabetes was either the main inclusion criteria or comorbidity in most of the studies included in the present meta-analysis, it is unlikely that the diabetogenic effect of statins has occurred predominantly in the overall population studied in our analysis. Hence, further evidence is required to clarify if the FFA-reducing effect of statins can be replicated in non-diabetic subjects receiving high intensity statins, particularly rosuvastatin.

Some limitations of this study should be mentioned. The most important one was the small sample size in several of the included studies. As another limitation, changes in plasma FFA concentrations were not among the primary objectives of the included studies. Thus, further studies are warranted to evaluate the effect of statin therapy on FFA concentrations as primary outcome to obtain more robust evidence about the effects of statins on circulating FFA status. Finally, the diversity of statin types in the included studies was low and administered statins were limited to atorvastatin and simvastatin. While this may reduce the inter-study heterogeneity, it limits the generalizability of findings to other statin types.

Conclusion

In conclusion, results of this meta-analysis, being the first of its kind, showed that statin therapy significantly reduces plasma FFA concentrations. Future investigations are required to clarify if this effect of statin therapy accounts, at least in part, for the established cardiovascular benefits of these drugs. Also, the association of this effect of statins with the hepatic content of FFAs and risk of hepatic insulin resistance needs to be elucidated in future studies. Finally, the magnitude of the FFA lowering effects of statins in comparison with other conventional and novel lipid lowering therapies [64–70] remains to be clarified.

Competing Interests

All authors have completed the Unified Competing Interest form and declare no support from any organization for the submitted work. GFW has received honoraria for lectures and commentaries, outside the submitted work, from Genfit, Pfizer, Astrazeneca, MSD, Novartis, Amgen and Sanofi-Aventis in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

Author Contributions

AM conceptualized and designed the study, carried out the statistical analyses and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted. LES-M drafted the initial manuscript, critically reviewed the manuscript and approved the final manuscript as submitted. CP critically reviewed the manuscript and approved the final manuscript as submitted. GF critically reviewed the manuscript and approved the final manuscript as submitted. PN critically reviewed the manuscript and approved the final manuscript as submitted. SB critically reviewed the manuscript and approved the final manuscript as submitted. GD critically reviewed the manuscript and approved the final manuscript as submitted. PM critically reviewed the manuscript and approved the final manuscript as submitted. GFW critically reviewed the manuscript, interpreted data and approved the final manuscript as submitted.

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