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Statins influence biomarkers of low grade inflammation in apparently healthy people or patients with chronic diseases: A systematic review and meta-analysis of randomized clinical trials

Alireza Milajerdi[a,b], Bagher Larijani[c], Ahmad Esmaillzadeh[d,a,e,*]

[a] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[b] Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[c] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[d] Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[e] Food Security Research Center, Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Background: No earlier study summarized findings on the effect of statins on inflammatory biomarkers in apparently healthy individuals or those with chronic diseases. This study was done to systematically review earlier publications on the effect of statins on serum concentrations of C-reactive protein (CRP) and Interleukin-6 (IL-6) in apparently healthy individuals or those with chronic diseases.

Methods: We searched relevant publications published up to December 2018 in PubMed, MEDLINE, SCOPUS, EMBASE, and Google Scholar databases. For this purpose, suitable MESH and non-MESH keywords were used. Randomized placebo-controlled clinical trials that examined the effect of statins on serum concentrations of CRP and IL-6 in apparently healthy adults or those with chronic diseases were included.

Results: Overall, 18 studies with 23 effect sizes, that enrolled 32,156 individuals (38% female and 62% male; mean age: 44.79 years) were included. When we combined 21 effect sizes from 16 studies, we observed a significant reduction in circulating levels of CRP following administration of statins [Weighted Mean Difference (WMD): −0.80; 95% CI: −1.05, −0.56]. Combining 12 effect sizes from 11 studies, a significant reduction was found in serum CRP concentrations following administration of Atorvastatin (WMD: −0.57; 95% CI: −0.78, −0.35). Pooling 5 effect sizes from 2 studies, we found a significant reduction in serum concentrations of CRP following administration of Simvastatin (WMD: −0.29; 95% CI: −0.49, −0.10; I^2 = 88.5%). Combining 6 effect sizes from 5 studies, we found a significant reduction in serum IL-6 concentrations after Atorvastatin therapy (WMD: −2.13; 95% CI: −3.96, −0.30; I^2 = 98.6%).

Conclusions: In conclusion, we found that statins administration in apparently healthy people or those with chronic diseases help reducing serum CRP concentrations. In addition, Atorvastatin administration resulted in reduced serum IL-6 concentrations in these people.

1. Introduction

Low-grade systematic inflammation is a chronic condition which is known by consistent high serum concentrations of pro-inflammatory cytokines [1]. It has been associated with a higher risk of several metabolic conditions, including diabetes, obesity, Metabolic Syndrome (MtS), Cardiovascular Disease (CVD) [2,3], and Non-alcoholic Fatty Liver Disease (NAFLD) [4].

Several strategies, including different medications, are used to reduce low grade inflammation [5]. Statins are a well-known class of cholesterol-lowering medicines [6] that their anti-inflammatory effects have been reported in some recent studies [7–9]. Combining statins with metformin in women with polycystic ovarian syndrome resulted in a significant reduction in inflammation [10]. Administration of statins in renal dialysis patients resulted in reduced inflammation as well [11]. Although several publications have summarized findings on the effect of statins on inflammation in different diseases [12,13], no study is available in apparently healthy individuals or those with chronic

* Corresponding author at: Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P.O. Box 14155-6117, Tehran, Iran.
E-mail address: a-esmaillzadeh@tums.ac.ir (A. Esmaillzadeh).

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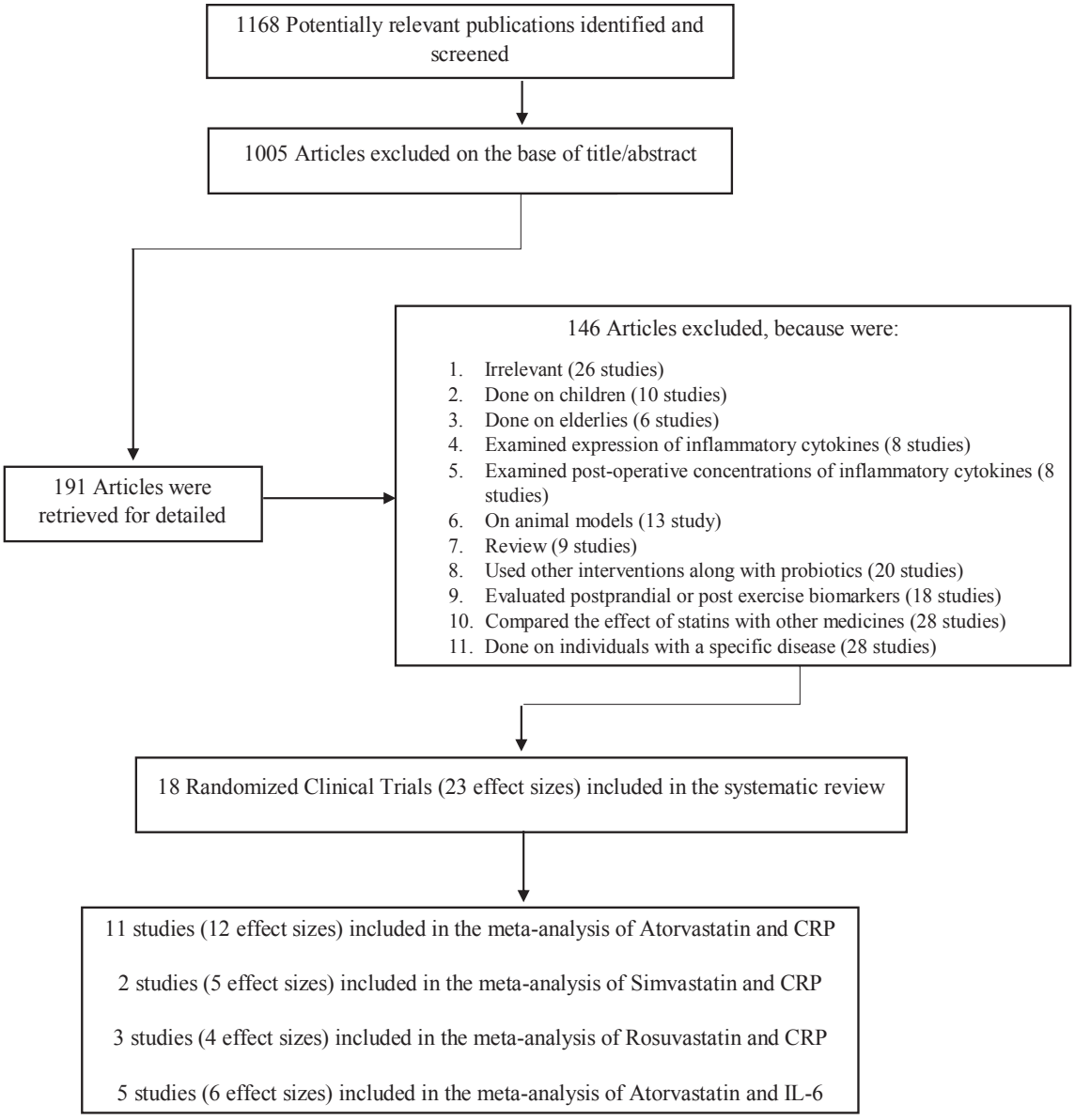

Fig. 1. Flow-diagram of study selection.

diseases. Beyond their cholesterol lowering effects, statins have modulatory effects in the stability of atherosclerotic plaques, the production of pro-inflammatory cytokines and reactive oxygen species, as well as in the reactivity of platelets [14]. Unlike disease situation, the effect of statins on inflammation in apparently healthy individuals is controversial. Administration of a high-dose of atorvastatin reduced inflammatory biomarkers in individuals with MetS [15]. Reduced serum C-reactive protein (CRP) concentrations in healthy individuals was reported following four weeks taking of Atorvastatin [16]. However, some studies did not find a significant effect of statins on serum concentrations of inflammatory cytokines in apparently healthy subjects [17,18].

To the best of our knowledge, there is no study available that systematically reviewed findings of earlier studies on the effect of statins on serum concentrations of inflammatory biomarkers in apparently healthy individuals or those with chronic diseases. Therefore, we conducted this study to systematically review previous publications on the effects of statins on inflammatory biomarkers in apparently healthy individuals or those with chronic diseases and to provide a summary estimate of this effect through the application of a meta-analysis.

2. Methods

2.1. Search strategy

We used following MESH and non-MESH keywords to find relevant articles published up to December 2018 in PubMed, MEDLINE, SCOPUS, EMBASE, and Google Scholar databases: ((“Atorvastatin”[tiab] OR “Atorvastatin”[MESH] OR “Rosuvastatin”[tiab] OR “Simvastatin”[tiab] OR “Simvastatin”[MESH]) AND (“Inflammation” OR ”Inflammatory biomarker” OR ”Interleukin-10” OR ”Interleukin-8” OR ”Interleukin-6” OR ”Tumor necrosis factor” OR ”C- Reactive protein” OR ”Transforming growth factor beta” OR “Cytokine” OR ”Acute phase reactant” OR ”Matrix metalloproteinase” OR ”e-selectin” OR ”p-selectin” OR ”Intercellular adhesion molecule-1” OR ”Monocyte chemotactic protein 1” OR ”Inflammation Mediator” OR ”Neurogenic Inflammation” OR “Myokine” OR “Adipokine” OR ”Interleukin-1B” OR “Interleukin” OR ”Systemic inflammation” OR ”Biological marker”)). Duplicate citations removed. We restricted our searches to RCTs published in English language. In addition, reference lists of all relevant review articles and other relevant publications were

Table 1
General characteristics of included studies.

Code/Author (yaer)	Subjects and gender	Age range (y) and mean	Design	Medication dosage (mg/day)	Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Any other intervention (from)	Notes about subjects	Adjustment or matching*
								Intervention mean ± SD and number	Control mean ± SD and number			
1. Chan et al. (2002)	F[1]: 0 M[2]: 25 Both: 25 ATOR[3]: 13 Plb[4]: 12	53.5 ± 9.0	Parallel	40	6	CRP[5], IL-6[6]	CRP: High-sensitivity monoclonal antibody assay IL-6: immunoassay	CRP (mean, 95% CI): Before (mg/L): 2.60 (1.90–4.20) After: 1.80 (1.30–3.20) IL-6 (mean, 95% CI): Before (pg/L): 363 (298–462) After: 301 (256–368)	CRP: Before: 2.04 (1.60–3.10) Aft: 1.97 (1.10–4.00) IL-6: Before: 303 (243–384) After: 324 (245–442)	Two other groups received fish oil or fish oil + Atorvastatin	25 obese men, aged 53.5 ± 9.0 years, BMI < 29 kg/m^2	1
2. Costa et al. (2003)	F: 11 M: 22 Both: 33 ATOR: 16 (6/10) Plb: 17 (5/12)	ATOR: 49.9 ± 4.9 Plb: 55.4 ± 8.87	Parallel	40	16	CRP	Not reported	CRP (Median, range): Before (mg/L): 0.19 (0.03, 0.50) After: 0.10 (0.01, 0.39)	CRP: Before: 0.28 (0.07, 0.82) After: 0.25 (0.04, 0.94)	No	33 subjects with impaired fasting glucose, age 49.9 ± 4.9 for ATOR and 55.4 ± 8.87 years for Plb groups, BMI 30.5 ± 3.47 for ATOR and 28.8 ± 2.72 kg/m^2 for Plb groups.	No
3. Economides et al. (2004)	F: 17 M: 20 Both: 37 ATOR: 15 Plb: 15	49 ± 12 ATOR: 48 ± 13 Plb: 49 ± 11	Parallel	20	12	CRP	Chemiluminescent immunoassay	CRP (Median, IQR): Before (mg/ml): 0.24 (0.07, 0.35) After: 0.12 (0.07, 0.27)	CRP: Before: 0.20 (0.06, 0.53) After: 0.23 (0.05, 0.43)	No	30 participants at risk of type 2 diabetes, age 21–80, BMI 29.5 ± 5.8 kg/m^2	No
4. Pleiner et al. (2004)	F: 0 M: 20 Both: 20 SIM[7]: 10 Plb: 10	SIM: 28 ± 2 Plb: 26 ± 1	Parallel	80	0.58	IL-6	ELISA	IL-6 (Mean, SEM): Before (mg/L): 0.9 ± 0.2 After: 0.8 ± 0.1	IL-6: Before: 1.1 ± 0.3 After: 1.0 ± 0.2	LPS in all participants	20 healthy volunteers, age 20–40 years, BMI 23.8 ± 1.0 and 23.4 ± 1.0 kg/m^2 in SIM and Plb groups, respectively.	No
5. Devaraj et al. (2006)	F: 18 M: 7 Both: 25 SIM: 25 (18/7) Plb: 25 (18/7)	SIM: 52 ± 11 Plb: 49 ± 13	Parallel	40	8	IL-6	Highly sensitive immunoassay	IL-6 (mean ± SD): Before (ng/ml): 0.43 ± 0.26 After: 0.24 ± 0.14	IL-6: Before: 0.41 ± 0.26 After: 0.39 ± 0.21	No	50 subjects with metabolic syndrome, age 52 ± 11 and 49 ± 13 years, BMI 39 ± 8 and 39 ± 6 kg/m^2 in SIM and Plb groups, respectively	No
6. Huptas et al. (2006)	Both: 10	40 ± 12	Cross-over	10	6	CRP, IL-6	Not reported	CRP: Before (mg/L): 2.90 ± 2.70 After: 3.10 ± 2.90 IL-6: Before (pg/ml): 1.18 ± 0.59 After: 1.59 ± 0.90	CRP: Before: 3.60 ± 3.10 Aft: 5.40 ± 6.80 IL-6: Before: 1.33 ± 1.05 After: 1.29 ± 0.82	No	10 insulin-resistant subjects with metabolic syndrome, Aged 40 ± 9.0, BMI 33.6 ± 5.2 kg/m^2	No
7. Doorn et al. (2006)	F: 30 M: 26	ATOR: 47.1 ± 5.6	Parallel	40	8.57	CRP	Not reported	CRP (mean, 95% CI):	CRP: Before: 2.74	Other group received garlic		No

(*continued on next page*)

Table 1 (*continued*)

Code/Author (yaer)	Subjects and gender	Age range (y) and mean	Design	Medication dosage (mg/day)	Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Any other intervention (from)	Notes about subjects	Adjustment or matching*
								Intervention mean ± SD and number	Control mean ± SD and number			
	Both: 56 ATOR: 30 (17/13) Plb: 26 (13/13)	Plb: 48.8 ± 6.6						Before (mg/L): 2.23 (0.25–16.7) After: 1.71 (1.51–1.93)	(0.49–24.4) After: 2.14 (1.87–2.45)		56 overweight subjects who smoked, aged 40–75 years, BMI > 24.5 kg/m^2	
8. Koh et al. (2008)	F: 33 M: 29 Both: 62 SIM: 30 (16/14) Plb: 32 (17/15)	SIM: 57 ± 2 Plb: 59 ± 2	Parallel	10	8.58	CRP	Latex agglutination	CRP (Median, range): Before (mg/L): 0.64 (0.27, 2.91) After: 0.43 (0.27, 1.01)	CRP: Before: 0.95 (0.46, 2.10) After: 0.90 (0.35, 1.95)	No	62 subjects with hypercholesterolemia, age 57 ± 2 and 59 ± 2 years for SIM and Plb groups, respectively, BMI ≥ 23.0 kg/m^2	2, 3, 4
9. Koh et al. (2008)	F: 34 M: 30 Both: 64 SIM: 32 (17/15) Plb: 32 (17/15)	SIM: 57 ± 2 Plb: 58 ± 2	Parallel	20	8.58	CRP	Latex agglutination	CRP (Median, range): Before (mg/L): 1.05 (0.40, 2.35) After: 0.90 (0.50, 1.95)	CRP: Before: 0.95 (0.46, 2.10) After: 0.90 (0.35, 1.95)	No	64 subjects with hypercholesterolemia, age 57 ± 2 and 59 ± 2 years for SIM and Plb groups, respectively, BMI ≥ 23.0 kg/m^2	2, 3, 4
10. Koh et al. (2008)	F: 34 M: 29 Both: 63 SIM: 31 (17/14) Plb: 32 (17/15)	SIM: 57 ± 2 Plb: 60 ± 2	Parallel	40	8.58	CRP	Latex agglutination	CRP (Median, range): Before (mg/L): 0.73 (0.44, 1.39) After: 0.59 (0.38, 1.44)	CRP: Before: 0.95 (0.46, 2.10) After: 0.90 (0.35, 1.95)	No	63 subjects with hypercholesterolemia, age 57 ± 2 and 59 ± 2 years for SIM and Plb groups, respectively, BMI ≥ 23.0 kg/m^2	2, 3, 4
11. Koh et al. (2008)	F: 33 M: 30 Both: 63 SIM: 31 (16/15) Plb: 32 (17/15)	SIM: 57 ± 2 Plb: 59 ± 2	Parallel	80	8.58	CRP	Latex agglutination	CRP (Median, range): Before (mg/L): 1.52 (0.89, 4.82) After: 0.89 (0.64, 3.05)	CRP: Before: 0.95 (0.46, 2.10) After: 0.90 (0.35, 1.95)	No	63 subjects with hypercholesterolemia, age 57 ± 2 and 59 ± 2 years for SIM and Plb groups, respectively, BMI ≥ 23.0 kg/m^2	2, 3, 4
12. Amudha et al. (2008)	F: 30 M: 26 Both: 56 ATOR: 28 Plb: 28	26.4 ± 4.7	Parallel	80	4	CRP, IL-6	CRP: Immunoturbidimetric Assay IL-6: ELISA	CRP (mean ± SD): Before (mg/L): 3.0 ± 3.9 After: 1.0 ± 1.3 IL-6 (mean ± SD): Before (ng/ml): 0.08 ± 0.20 After: 0.04 ± 0.01	CRP: Before: 2.1 ± 3.7 Aft: 1.8 ± 2.1 IL-6: Before: 0.05 ± 0.02 After: 0.06 ± 0.02	No	56 first-degree relatives of subjects with type 2 diabetes, aged 18–30 years, BMI < 25 kg/m^2	No
13. Clough et al. (2009)	F: 22 M: 17 Both: 39 ATOR: 19 Plb: 20	51.4 ± 9.0	Parallel	40	26	CRP	Not reported	CRP (Median, 95% CI): Before (mg/L): 2.0 (1.31–5.59) After: 0.5 (0.35–4.65)	CRP: Before: 2.0 (1.09, 10.47) After: 3.0 (1.62–6.35)	No	39 subjects with central obesity, age 18–75, BMI 32.1 ± 4.6 kg/m^2	1, 2, 3

(*continued on next page*)

Table 1 (*continued*)

Code/Author (yaer)	Subjects and gender	Age range (y) and mean	Design	Medication dosage (mg/day)	Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Any other intervention (from)	Notes about subjects	Adjustment or matching*
								Intervention mean ± SD and number	Control mean ± SD and number			
14. Liu et al. (2009)	F: 8 M: 32 Both: 40 SIM: 20 (4/16) Plb: 20 (4/16)	SIM: 67.1 ± 8.2 Plb: 64.3 ± 10	Parallel	40	4	CRP	Not Reported	CRP (median, IQR): Before (mg/L): 2.57 (1.49, 3.67) After: 1.52 (1.05, 3.0)	CRP: Before: 2.58 (1.68, 3.66) After: 2.61 (1.66, 3.69)	Simvastatin + Ezetimibe as the third arm.	40 dyslipidemic subjects, age 40–80 years.	5
15. Orr et al. (2009)	F: 15 M: 11 Both: 26 ATOR: 16 (10/6) Plb: 10 (5/5)	54 ± 2 ATOR: 53 ± 2 Plb: 55 ± 3	Parallel	80	12	CRP	Immunometric assay	CRP (Mean, SEM): Before (mg/L): 3.6 ± 0.8 After: 2.1 ± 0.5	CRP: Before: 2.8 ± 0.6 After: 3.0 ± 0.9	No	26 overweight or obese participants, age 40–65, BMI 31.6 ± 0.7 kg/m^2.	No
16. Peters et al. (2010)	F: 397 M: 587 Both: 984 ROS: 702 (281/421) Plb: 282 (116, 166)	ROS: 57 ± 6.2 Plb: 57 ± 6.0	Parallel	40	104.29	CRP	Not Reported	CRP (mean ± SD): Before (mg/L): 3.0 ± 5.8 After: 1.7 ± 2.5	CRP: Before: 2.8 ± 4.2 After: 3.4 ± 10.7	No	984 low-risk subjects, age 45–70 in males and 55–70 in females, respectively.	No
17. Mora et al. (2010)	F: 6801 M: 0 Both: 6801 ROS[8]: 3426 Plb: 3375	Women: 68.0 (65.0–73.0)	Parallel	20	93.86	CRP	Not Reported	CRP (median, IQR): Change (mg/L): −1.8 (-3.6, −0.6)	CRP: Change: −0.6 (-2.2, 0.8)	No	6801 apparently healthy women, age ≥ 60, BMI 28 kg/m^2	No
18. Mora et al. (2010)	F: 0 M: 11,001 Both: 11,001 ROS: 5475 Plb: 5526	Men: 63.0 (58.0–70.0)	Parallel	20	93.86	CRP	Not Reported	CRP (median, IQR): Change (mg/L): −1.7 (-3.4, −0.4)	CRP: Change: −0.8 (-2.5, 0.8)	No	11,001 apparently healthy men, age ≥ 50, BMI 28 kg/m^2	No
19. Krysiak et al. (2010)	Both: 37 ATOR: 19 Plb: 18	Not Reported	Parallel	40	12.86	CRP, IL-6	Not Reported	CRP (Mean, SEM): Before (mg/L): 1.5 ± 0.1 After: 0.8 ± 0.2 IL-6 (Mean, SEM): Before (pg/ml): 8.2 ± 0.8 After: 5.7 ± 0.6	CRP: Before: 1.7 ± 0.3 After: 1.5 ± 0.1 IL-6: Before: 8.2 ± 0.9 After: 8.1 ± 0.5	Fenofibrate as the third arm.	37 subjects with metabolic syndrome.	2, 3

(*continued on next page*)

Table 1 (*continued*)

Code/Author (yaer)	Subjects and gender	Age range (y) and mean	Design	Medication dosage (mg/day)	Duration (wk/d)	Outcomes	Outcome assessment method	Outcome		Any other intervention (from)	Notes about subjects	Adjustment or matching*
								Intervention mean ± SD and number	Control mean ± SD and number			
20. Krysiak et al. (2010)	Both: 117 ATOR: 61 Plb: 56	Not Reported	Parallel	40	12.86	CRP, IL-6	Not Reported	CRP (Mean, SEM): Before (mg/L): 2.5 ± 0.3 After: 1.4 ± 0.3 IL-6 (Mean, SEM): Before (pg/ml): 13.1 ± 0.9 After: 7.7 ± 0.7	CRP: Before: 2.7 ± 0.4 After: 2.4 ± 0.4 IL-6: Before: 12.4 ± 0.3 After: 12.8 ± 0.3	Fenofibrate as the third arm.	117 subjects with metabolic syndrome and prediabetes.	2, 3
21. Millar et al. (2010)	F: 11 M: 9 Both: 20 ATOR: 10 Plb: 10	31 (21–47)	Parallel	80	2	CRP, IL-6	CRP: Ultra high-sensitivity latex turbidimetric immunoassay IL-6: Enzyme immunoassays	CRP (mean ± SD): Before (mg/L): 0.56 ± 0.52 After: 0.54 ± 0.56 IL-6 (mean ± SD): Before (pg/ml): 1.36 ± 1.20 After: 1.66 ± 1.21	CRP: Before: 0.84 ± 0.66 After: 0.90 ± 0.87 IL-6: Before: 1.09 ± 0.98 Aft: 1.58 ± 2.66	No	20 normolipidemic subjects, aged 18–50 years, BMI < 30 kg/m^2	No
22. Loughrey et al. (2013)	F: 18 M: 32 Both: 50 ATOR: 24 (8/16) Plb: 26 (10/16)	49.7 ± 7.1 ATOR: 48.6 ± 7.9 Plb: 50.7 ± 6.3	Parallel	10	6	CRP	Immunoturbidimetry	CRP (mean ± SEM): Before (mg/L): 2.95 ± 0.47 After: 2.83 ± 0.43	CRP: Before: 4.97 ± 1.28 After: 6.76 ± 2.32	No	50 subject with metabolic syndrome, 35–65 years, BMI 32.9 ± 5.0	6
23. Akinkuolie et al. (2016)	F: 4542 M: 7985 Both: 12,527	66	Parallel	20	52.15	CRP	Not reported	CRP (Median, IQR): Change (mg/L): −1.7 (-3.4, −0.5)	CRP: Change: −0.7 (-2.3, 0.7)	No	4542 apparently healthy participants, age 60–71, BMI 24.8 kg/m^2	2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13

Abbreviations: [1]Females, [2]Males, [3]Atorvastatin, [4]Placebo, [5]C – reactive protein, [6]Interleukin-6, [7]Simvastatin, [8]Rosuvastatin.
Abbreviations: 1: Baseline values; 2: Age; 3: Sex; 4: BMI; 5: Changes in LDL; 6: Improvement in lipid profile; 7: Race; 8: Smoking; 9: Blood pressure; 10: Fasting glucose; 11: HDL; 12: Triglycerides; 13: Family history of premature coronary disease.

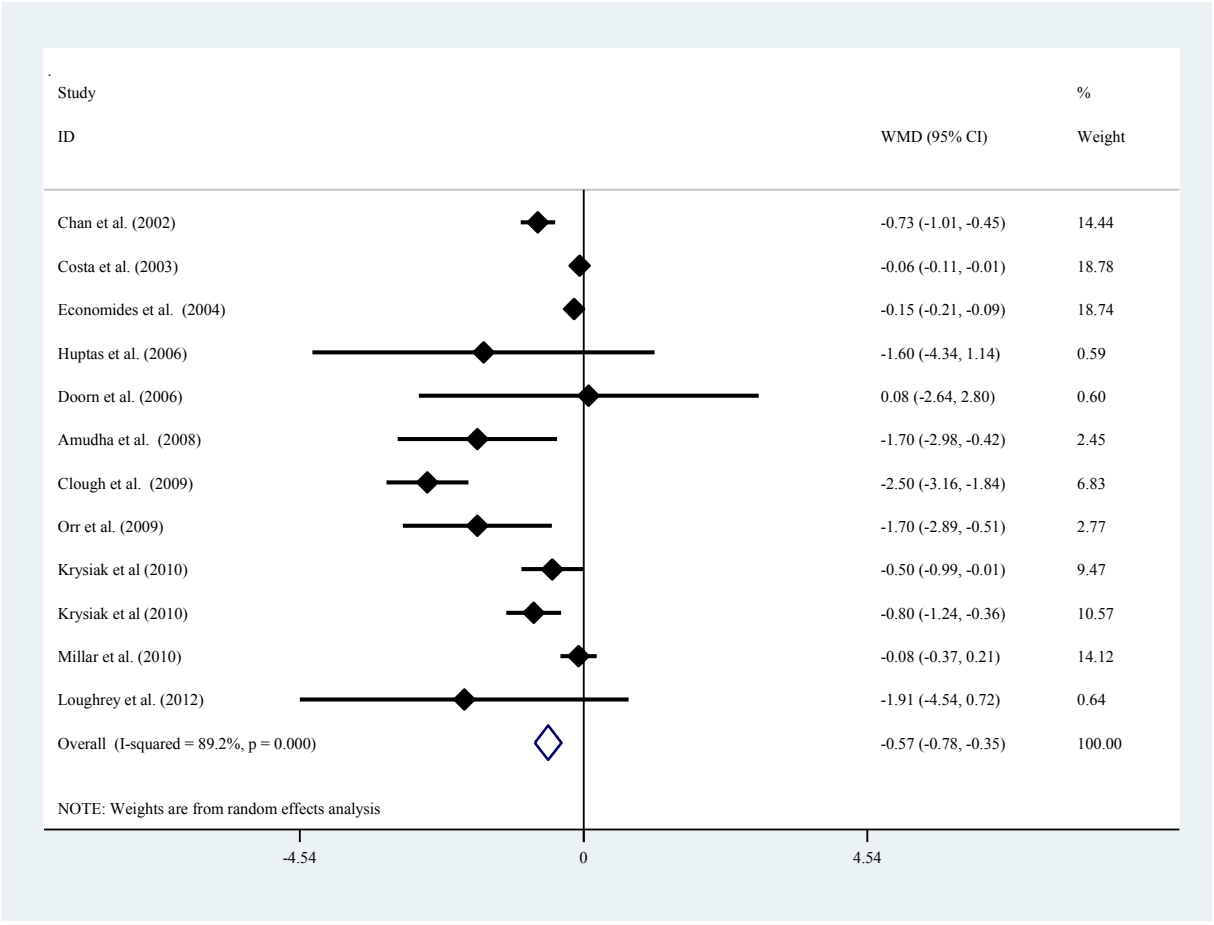

Fig. 2. Forest plot for the effect of Atorvastatin on serum CRP concentrations; expressed as the mean differences between the intervention and the control. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

Table 2
Subgroup analysis for the effect of Atorvastatin on serum concentrations of CRP.

Subgroup	Number of effect sizes	Effect size (95% CI)	I^2	P Within*	P Between*
Overall	12	−0.57 (−0.78, −0.35)	89.2	< 0.001	–
Study duration					0.001
< 8 weeks	5	−0.46 (−0.66, −0.27)	74.6	0.003	
8–12 weeks	3	−0.15 (−0.21, −0.10)	69.3	0.03	
> 12 weeks	4	−0.09 (−0.14, −0.04)	95.4	< 0.001	
Supplement dose					0.46
< 20 mg	3	−0.15 (−0.21, −0.09)	28.4	0.24	
20–40 mg	6	−0.11 (−0.17, −0.06)	94.2	< 0.001	
> 40 mg	3	−0.24 (−0.52, 0.03)	83.3	0.003	
Participants; age					0.76
< 45 years	3	−0.17 (−0.45, 0.11)	71.1	0.03	
≥45 years	9	−0.13 (−0.17, −0.09)	91.6	< 0.001	

* P values were obtained by fixed-effect analysis.

also searched to avoid missing any publication. Unpublished data and grey literature, including patents, congress abstracts, and dissertations were not included in this meta-analysis.

2.2. Inclusion criteria

All placebo-controlled RCTs that examined the effect of statins on pro-inflammatory cytokines in apparently healthy adults or patients with chronic diseases, including those with abnormal glucose tolerance, metabolic syndrome, overweight or obesity, who were not taking medications other than statins, were included. If several publications with the same data set were found, we included only the most complete one.

2.3. Exclusion criteria

Studies with the following criteria were excluded: (1) studies that were conducted on pregnant women, children or elderlies; (2) in vitro studies and those on animal models; (3) studies that did not perform randomized allocation; (4) studies that examined the effect of statins

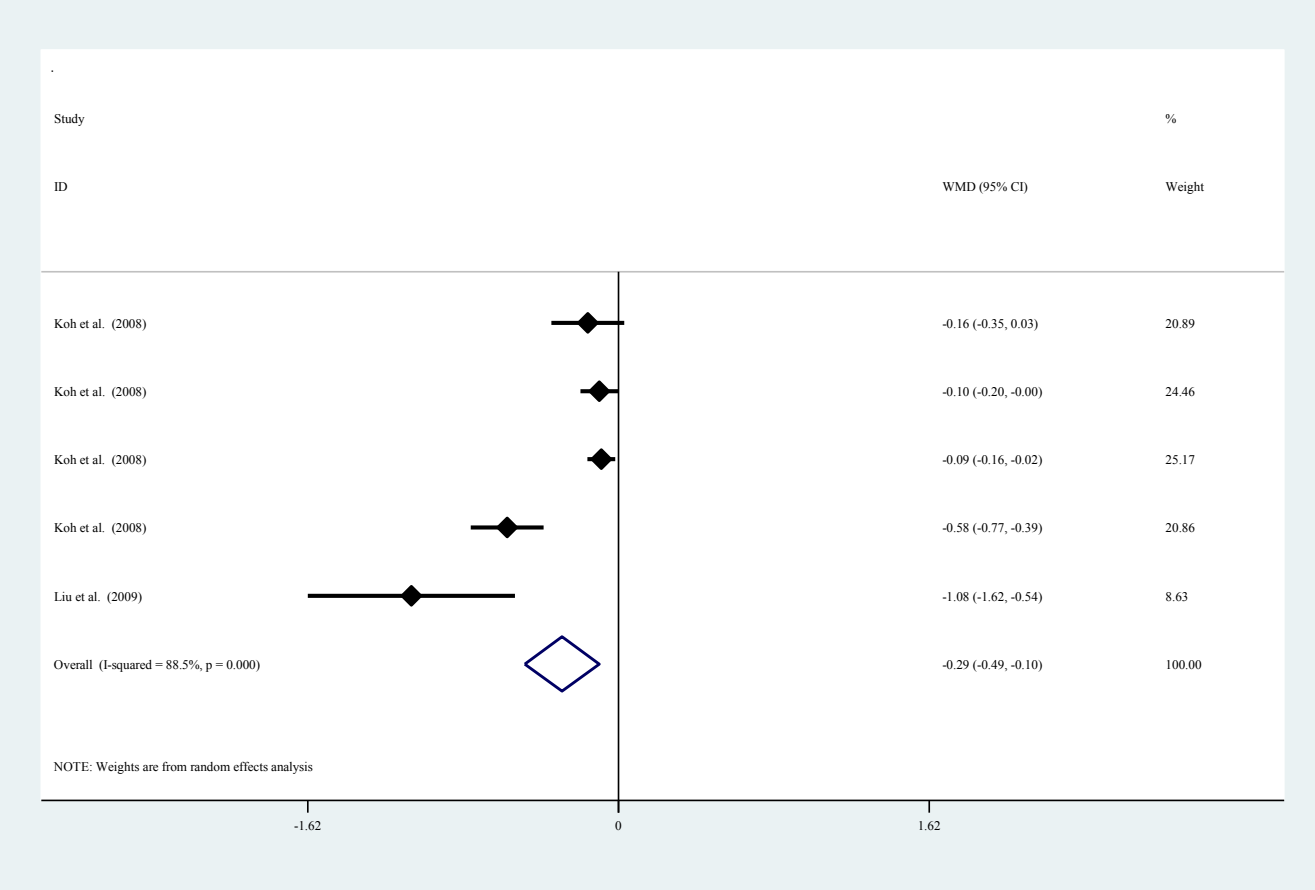

Fig. 3. Forest plot for the effect of Simvastatin on serum CRP concentrations; expressed as the mean differences between the intervention and the control. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

along with other interventions; (5) those without a placebo group or studies that used other medications, instead of placebo, as a comparison; (6) studies that were done on hospitalized individuals; and (7) studies that examined post-operative inflammatory responses.

2.4. Data extraction

The following information were obtained from included studies by two independent reviewers: first author's name, publication year, participants' health condition, study sample size, number of participants in each group, duration of intervention, participants' sex and age, medicine dosage, study design (parallel/cross-over), mean (SD) concentrations of cytokines at study baseline and after intervention in each group or mean (SD) changes of cytokines' concentrations after intervention in each group (when available). We were also interested to know if the included studies did the adjustment for baseline levels of inflammatory biomarkers or not.

2.5. Statistical methods

The overall effect sizes were calculated as mean difference (MD) and SDs of changes of inflammatory biomarkers across the two groups of statins and placebo, using the random-effects model. Standard Errors (SEs), interquartile ranges, and 95% confidence intervals were converted to SDs using appropriate formulas. Serum concentrations of each cytokine were converted to the most frequently used units. Between-study heterogeneity was examined by the Cochran's Q test and I^2 statistic. Subgroup analyses were used to provide some explanation for the between-study heterogeneity. All statistical analyses were done using Stata software, version 14 (Stata Corp, College Station, TX). $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Study characteristics

In general, 18 studies with 23 effect sizes were included in the current systematic review and meta-analysis [16,19–35]. The flow diagram of study selection is shown in Fig. 1. All studies were published between 2002 and 2016. These studies enrolled 32,156 apparently healthy individuals or those with chronic diseases (38% female & 62% male; mean age: 44.79 years). Characteristics of included studies are summarized in Table 1.

All studies had parallel design, except for the study of Huptas et al. which was a cross-over RCT [25]. Atorvastatin [16,20–22,24,25,27,29,30,32,35], Simvastatin [23,26,28,34], and Rosuvastatin [19,31,33] were used as the intervention in the included studies. These medicines were used in dosages of 10, 20, 40, and 80 mg/day. The duration of intervention varied from 4 days to 2 years.

Some included studies had measured serum concentrations of CRP as the outcome [16,19–22,24–33,35], others considered serum levels of IL-6 as the outcome [16,20,23,25,27,30,34]. However, despite our extensive search on all statins and inflammatory factors in apparently healthy individuals or those with chronic diseases, sufficient information were found only about the effect of Atorvastatin on serum CRP and IL-6 concentrations and the effect of Simvastatin and Rosuvastatin on CRP levels. The biomarkers were measured using immunoassay. Some studies did not report methods used for the measurement of study

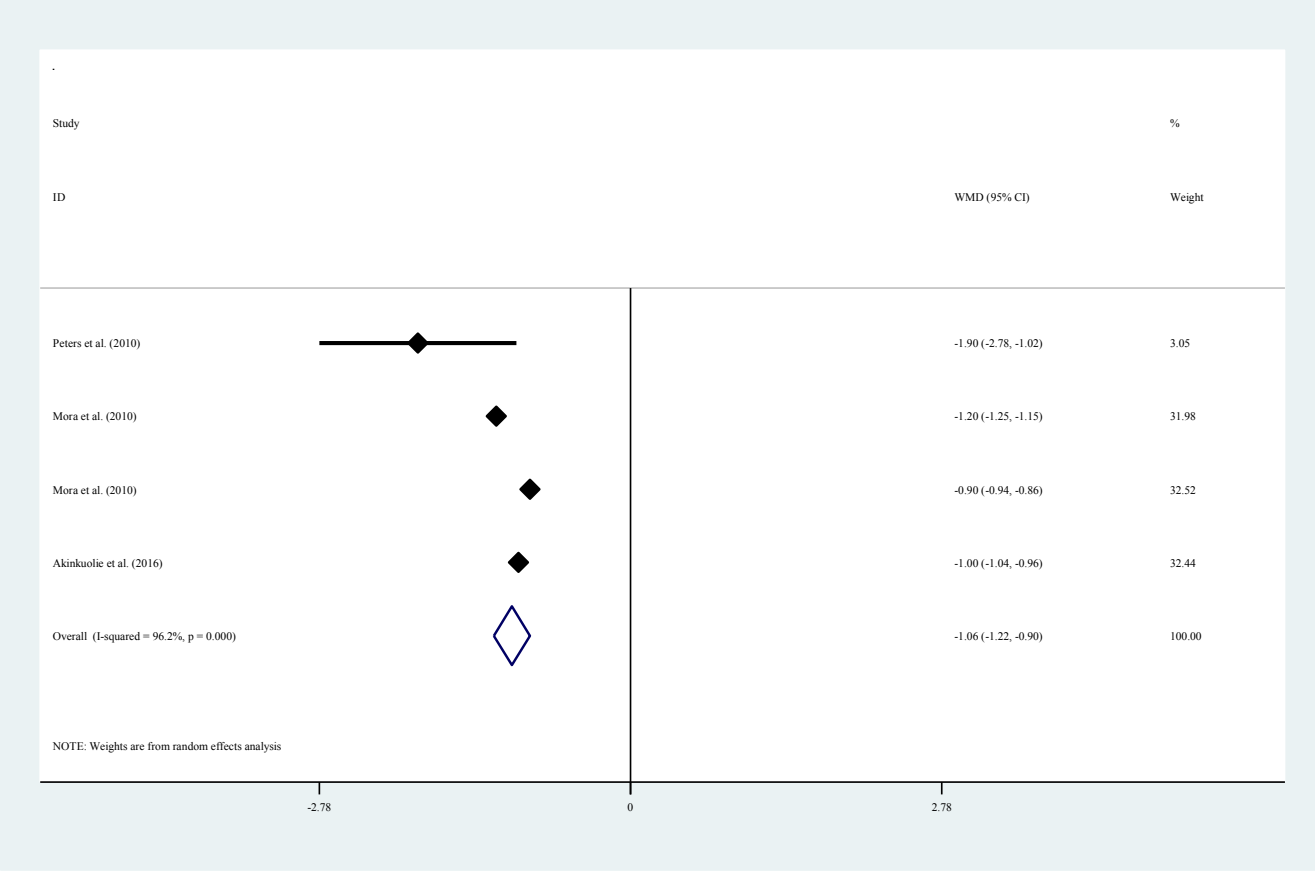

Fig. 4. Forest plot for the effect of Rosuvastatin on serum CRP concentrations; expressed as the mean differences between the intervention and the control. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

outcomes [19,21,22,25,27,28,31,33,35]. Four studies had a third arm intervention along with statin therapy and placebo [20,27,28,35], which were not included in the current meta-analysis. Adjustment for the baseline values of inflammatory biomarkers was done only in two studies [20,21].

3.2. The effect of statins on CRP concentrations

Combining 12 effect sizes from 11 studies, a significant reduction was found in serum CRP concentrations following administration of Atorvastatin [Weighted Mean Difference (WMD): −0.57; 95% CI: −0.78, −0.35] (Fig. 2). Due to a high between-study heterogeneity (I^2 = 89.2%), we conducted subgroup analysis based on participants' age (< 45/≥45 years), as well as medicine dosage (< 20/20–40/ > 40 mg), and duration of intervention (< 8/8–12/ > 12 weeks) (Table 2). The effect of Atorvastatin on serum concentrations of CRP was significant in all subgroups, except for studies that were conducted on patients aged < 45 years (WMD: −0.17; 95% CI: −0.45, 0.11) as well as in studies that used the dosages of > 40 mg/day (WMD: −0.24; 95% CI: −0.52, 0.03). In addition, after excluding the study of Huptas et al. [25], the only available RCT with cross-over design, findings remained unchanged (WMD: −0.56; 95% CI: −0.78, −0.35). Moreover, the exclusion of the study of Pleiner et al. [34], which was exclusively conducted among men, did not influence the findings (WMD: −0.52; 95% CI: −0.73, −0.30). Visual inspection of funnel plot did not provide evidence of publication bias (data were not shown). This finding was approved by the egger regression test (P = 0.70). Moreover, sensitivity analysis showed that no individual study had a great influence on the overall results.

Pooling 5 effect sizes from 2 studies, we found a significant reduction in serum concentrations of CRP following administration of Simvastatin (WMD: −0.29; 95% CI: −0.49, −0.10; I^2 = 88.5%) (Fig. 3). Although between-study heterogeneity was high, we were not able to do subgroup analysis due to limited number of studies. The same findings were reached when we combined 4 effect sizes from 3 studies on the effect of Rosuvastatin on serum CRP levels (WMD: −1.06; 95% CI: −1.22, −0.90; I^2 = 96.2%) (Fig. 4).

In general, when we considered all studies on statins and combined 21 effect sizes from 16 studies to find the effect of whole statins on serum CRP levels, we observed a significant reduction in circulating level of this inflammatory biomarker following administration of statins (WMD: −0.80; 95% CI: −1.05, −0.56) (Fig. 5).

3.3. The effect of Atorvastatin on circulating IL-6 concentrations

Combining 6 effect sizes from 5 studies, we found a significant reduction in serum IL-6 concentrations after Atorvastatin therapy (WMD: −2.13; 95% CI: −3.96, −0.30; I^2 = 98.6%) (Fig. 6). Subgroup analyses were conducted based on participants' age (< 45/≥45 years), medicine dosage (< 40/40–80/≥80 mg), and duration of intervention (< 6/≥6 weeks) (Table 3). The effect of atorvastatin on IL-6 levels was significant in all subgroups, except for studies with a duration of ≥6 weeks (WMD: −0.11; 95% CI: −0.27, 0.05). When we excluded the cross-over study, the significant effect of Atorvastatin on serum concentrations of IL-6 disappeared (WMD: −2.68; 95% CI: −5.40, 0.04). This was also the case when we removed the study that was exclusively done on men (WMD: −2.57; 95% CI: −5.47, 0.32).

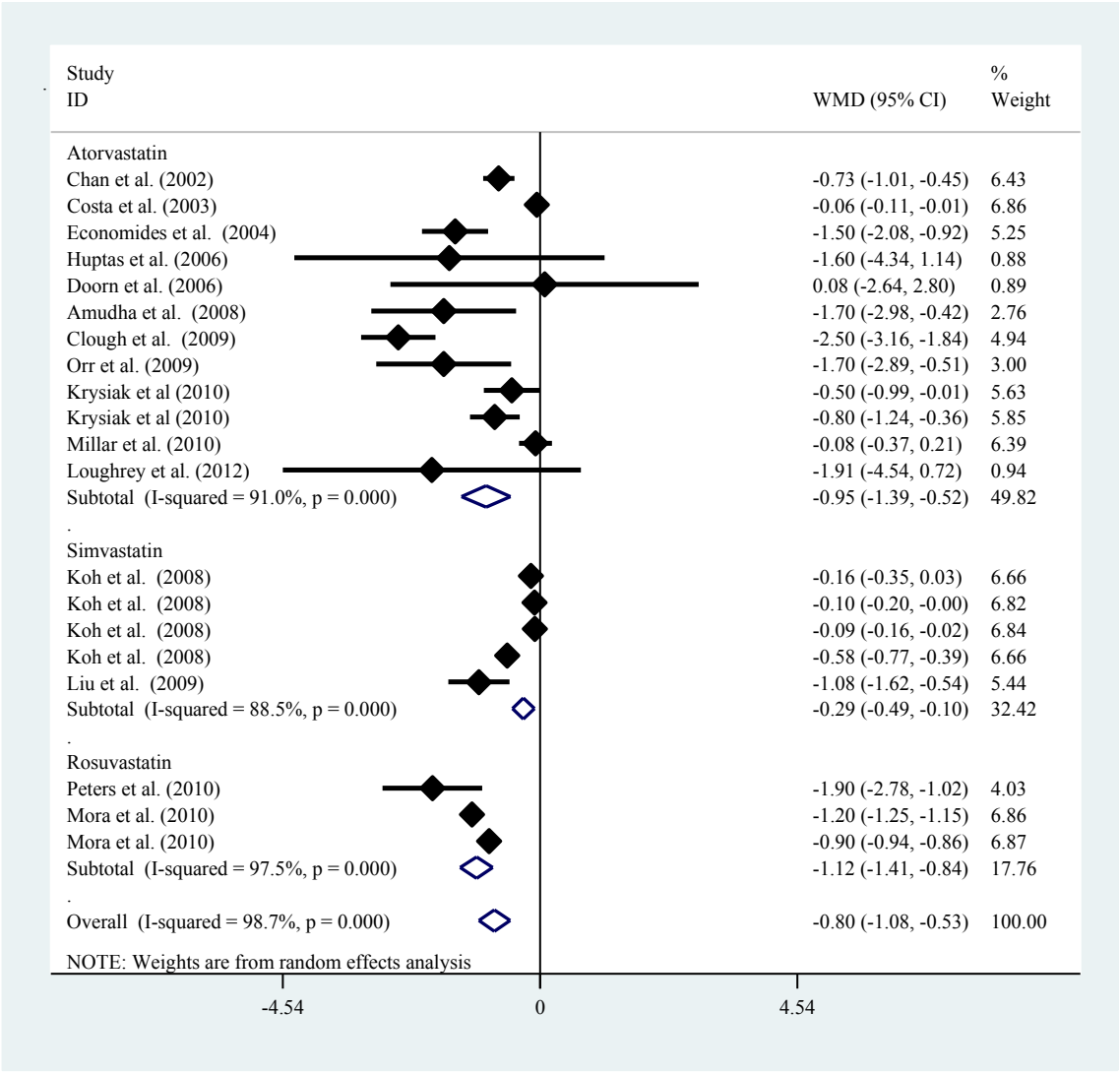

Fig. 5. Forest plot for the effect of whole statins on serum CRP concentrations; expressed as the mean differences between the intervention and the control. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

4. Discussion

A significant reduction was found in serum concentrations of CRP following administration of Atorvastatin, Simvastatin, and Rosuvastatin in apparently healthy individuals or those with chronic diseases. In addition, Atorvastatin therapy resulted in a significant lower concentrations of serum IL-6 in these subjects.

In the current meta-analysis, we found that administration of statins, including Atorvastatin, Simvastatin, and Rosuvastatin reduced CRP concentrations in apparently healthy individuals or those with chronic diseases. Although no previous meta-analysis was done on the effect of statins on serum CRP levels, several meta-analyses are available in non-healthy individuals or those with chronic diseases. For instance, in a meta-analysis of studies on dialysis patients, a significant reduction in serum concentrations of CRP was seen following statins therapy [36]. In addition, administration of Atorvastatin in patients with rheumatoid arthritis significantly reduced serum CRP concentrations [37]. This was also shown in patients with systemic lupus erythematous who received Atorvastatin [38]. However, the effect of Rosuvastatin on CRP levels was not significant in that meta-analysis, which might be due to the low number of included studies. In addition, some other studies also did not find a significant effect of statins on serum levels of CRP [25,29,35]. It should be noted that most of these studies did not consider baseline levels of CRP. In addition, they had mostly used statins at the dosage of 10 mg, which seems too low to influence inflammation. Findings from a previous meta-analysis revealed that preoperative treatment with moderate to high doses of Rosuvastatin, but not low doses, in patients with percutaneous coronary intervention significantly reduced serum levels of CRP [39]. Our subgroup analysis showed that Atorvastatin therapy in low to moderate dosages reduced CRP concentrations, while the effect was not significant in high doses. Lack of finding a significant effect in high dosages might be explained by the limited number of publications in this regard.

In the subgroup analysis, we found that administration of Atorvastatin in individuals aged < 45 years did not affect serum CRP levels. Aging has been reported as a risk factor of inflammation [40]. Animal studies has shown anti-inflammatory effects of statins in aged animal models [41]. Lack of finding a significant of statins on inflammation in young adults might be due to their normal levels of CRP. It seems that elevated levels of inflammation, at least to some extent, is required for statins to influence circulating levels of CRP.

In addition to CRP, we observed that administration of Atorvastatin resulted in reduced concentrations of serum IL-6. To the best of our

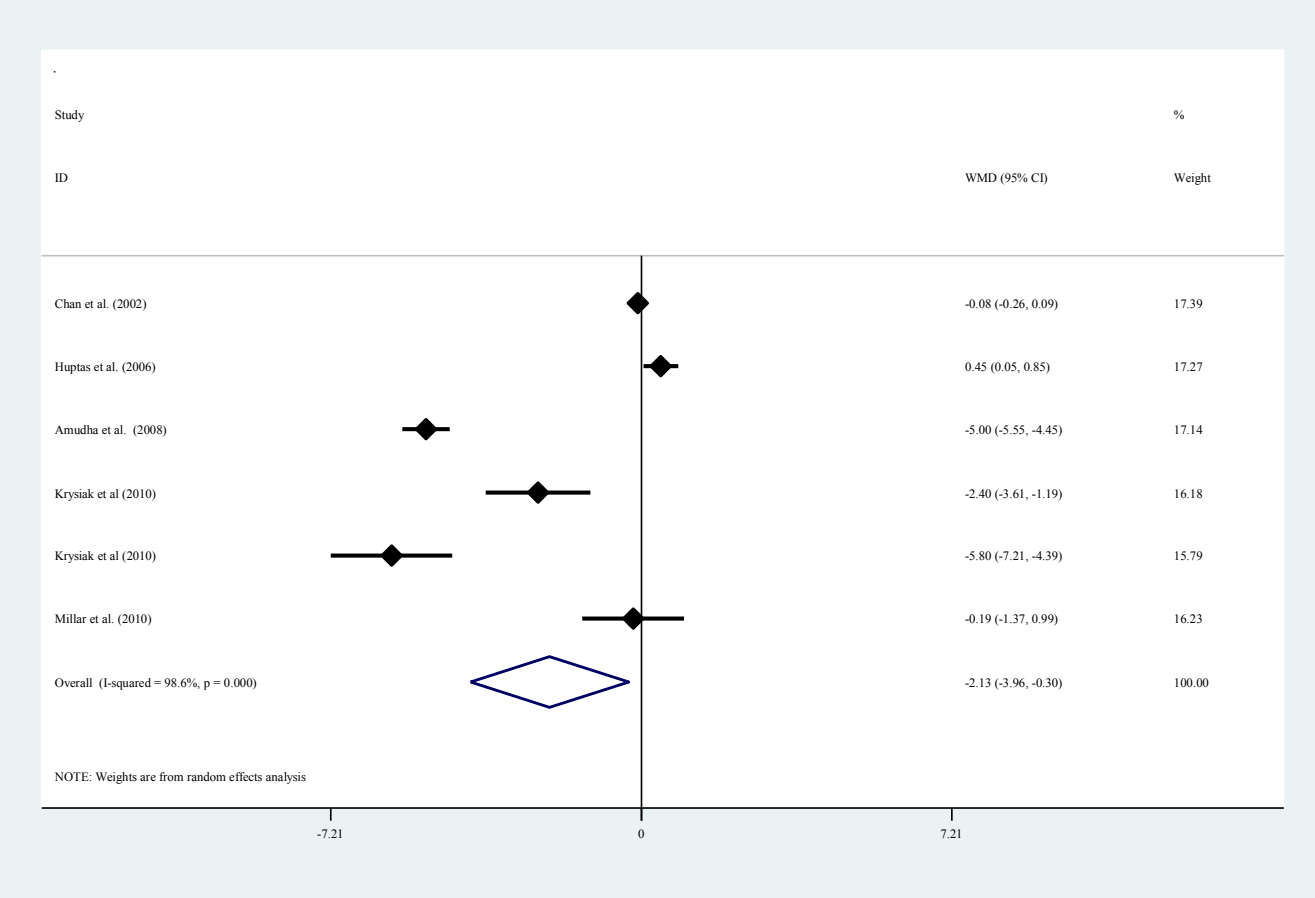

Fig. 6. Forest plot for the effect of Atorvastatin on serum Il-6 concentrations; expressed as the mean differences between the intervention and the control. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

Table 3
Subgroup analysis for the effect of Atorvastatin on serum concentrations of IL-6.

Subgroup	Number of effect sizes	Effect size (95% CI)	I^2	P Within*	P Between*
Overall	6	−2.13 (−3.96, −0.30)	98.6	< 0.001	–
Study duration					< 0.001
< 6 weeks	2	−4.15 (−4.64, −3.65)	98.1	< 0.001	
≥6 weeks	4	−0.11 (−0.27, 0.05)	96.4	< 0.001	
Supplement dose					< 0.001
< 40 mg	1	0.45 (0.05, 0.85)	–	–	
40–80 mg	3	−0.21 (−0.38, −0.04)	97.3	< 0.001	
≥80 mg	2	−4.15 (−4.64, −3.65)	98.1	< 0.001	
Participants; age					< 0.001
< 45 years	3	−1.37 (−1.68, −1.06)	99.2	< 0.001	
≥45 years	3	−0.21 (−0.38, −0.04)	97.3	< 0.001	

* P values were obtained by fixed-effect analysis.

knowledge, no earlier systematic review or meta-analysis has been conducted on the effect of statins on serum IL-6 concentrations. However, several animal studies have reported that Atorvastatin therapy suppressed inflammation at gene levels [42,43]. Suppression of NF-kB signaling pathways by Atorvastatin might decrease secretion of several pro-inflammatory cytokines, including IL-6 [44]. In addition, IL-6 is an important regulator of CRP secretion in the liver [45]. Therefore, changes in these two inflammatory biomarkers are greatly correlated. Although most human studies have reported a significant reduction in serum IL-6 levels following Atorvastatin therapy [16,25,27], some others failed to find such an effect [20,30]. The duration of intervention was mostly short in studies that did not find any significant effect. However, due to limited number of studies, further long-term studies are required to shed light on this issue.

Although the exact mechanisms through which statins might influence serum concentrations of CRP and IL-6 remain unknown, some suggestions can be made. Statins increase PPAR-α and PPAR-γ mRNA expression in hepatocytes and endothelial cells [46], through which they can reduce expression of genes involved in inflammatory responses [47]. Administration of statins can reduce mRNA expression of IL-6 in endothelial cells [48]. The effect of statins on inflammation is considered to be independent of their lipid lowering actions and might be partly related to their role in lowering free fatty acids [49]. Furthermore, administration of statins have also been reported to suppress

immune system enhancers, including Toll-Like Receptors (TLRs) and transcription factors, including NF-kB [50,51].

To the best of our knowledge, this is the first meta-analysis on the effect statins on serum concentrations of CRP and IL-6 in apparently healthy individuals or those with chronic diseases. All included studies were placebo-controlled RCTs. However, some limitations should be taken into account. Sufficient data were available only for few inflammatory biomarkers. This is why we restricted our analysis to CRP and IL-6 concentrations. Further studies, using different types of statins and measuring other inflammatory cytokines, are recommended. Statins were used in different dosages in these studies; however, we took this point into account in our subgroup analysis. Another point is that the duration of intervention and mean age of participants were also different between included studies. We tried to consider them in the subgroup analysis.

In conclusion, combining earlier findings in a meta-analysis, we found that statins administration in apparently healthy people or patients with chronic diseases helps reducing serum CRP concentrations. In addition, Atorvastatin administration resulted in reduced serum IL-6 concentrations in these people.

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None.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

References

[1] K. Speer, D. Upton, S. Semple, A. McKune, Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review, J. Inflammat. Res. 11 (2018) 111.
[2] A. Pradhan, Obesity, metabolic syndrome, and type 2 diabetes: inflammatory basis of glucose metabolic disorders, Nutr. Rev. 65 (suppl_3) (2007) S152–S156.
[3] V. Guarner, M.E. Rubio-Ruiz, Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease, Aging and Health-A Systems Biology Perspective, Karger Publishers, 2015, pp. 99–106.
[4] M. Başaranoğlu, N. Örmeci, Nonalcoholic fatty liver disease: diagnosis, pathogenesis, and management, Turk. J. Gastroenterol. 25 (2014) 127–132.
[5] M. Alturki, I. Beyer, T. Mets, I. Bautmans, Impact of drugs with anti-inflammatory effects on skeletal muscle and inflammation: a systematic literature review, Exp. Gerontol. (2018).
[6] C. Ulivieri, C.T. Baldari, Statins: from cholesterol-lowering drugs to novel immunomodulators for the treatment of Th17-mediated autoimmune diseases, Pharmacol. Res. 88 (2014) 41–52.
[7] S. Van Linthout, A. Riad, N. Dhayat, F. Spillmann, J. Du, S. Dhayat, D. Westermann, D. Hilfiker-Kleiner, M. Noutsias, U. Laufs, Anti-inflammatory effects of atorvastatin improve left ventricular function in experimental diabetic cardiomyopathy, Diabetologia 50 (9) (2007) 1977–1986.
[8] N. Bayat, S. Ebrahimi-Barough, A. Norouzi-Javidan, H. Saberi, M.M.M. Ardakan, A. Ai, M. Soleimannejad, J. Ai, Anti-inflammatory effects of atorvastatin by suppressing TRAF3IP2 and IL-17RA in human glioblastoma spheroids cultured in a three-dimensional model: possible relevance to glioblastoma treatment, Mol. Neurobiol. 55 (3) (2018) 2102–2110.
[9] X. Xu, W. Gao, S. Cheng, D. Yin, F. Li, Y. Wu, D. Sun, S. Zhou, D. Wang, Y. Zhang, Anti-inflammatory and immunomodulatory mechanisms of atorvastatin in a murine model of traumatic brain injury, J. Neuroinflammat. 14 (1) (2017) 167.
[10] J. Sun, Y. Yuan, R. Cai, H. Sun, Y. Zhou, P. Wang, R. Huang, W. Xia, S. Wang, An investigation into the therapeutic effects of statins with metformin on polycystic ovary syndrome: a meta-analysis of randomised controlled trials, BMJ Open 5 (3) (2015) e007280.
[11] J. Deng, Q. Wu, Y. Liao, D. Huo, Z. Yang, Effect of statins on chronic inflammation and nutrition status in renal dialysis patients: a systematic review and meta-analysis, Nephrology 17 (6) (2012) 545–551.
[12] W. Zhang, Y. Zhang, C.-W. Li, P. Jones, C. Wang, Y. Fan, Effect of statins on COPD: a meta-analysis of randomized controlled trials, Chest 152 (6) (2017) 1159–1168.
[13] R.W. Major, C.K. Cheung, L.J. Gray, N.J. Brunskill, Statins and cardiovascular primary prevention in CKD: a meta-analysis, Clin. J. Am. Soc. Nephrol. 10 (5) (2015) 732–739.
[14] A. Oesterle, U. Laufs, J.K. Liao, Pleiotropic effects of statins on the cardiovascular system, Circ. Res. 120 (1) (2017) 229–243.
[15] U. Singh, S. Devaraj, I. Jialal, D. Siegel, Comparison effect of atorvastatin (10 versus 80 mg) on biomarkers of inflammation and oxidative stress in subjects with metabolic syndrome, Am. J. Cardiol. 102 (3) (2008) 321–325.
[16] K. Amudha, A.M. Choy, M.R. Mustafa, C.C. Lang, Short-term effect of atorvastatin on endothelial function in healthy offspring of parents with type 2 diabetes mellitus, Cardiovasc. Ther. 26 (4) (2008) 253–261.
[17] C. Hernandez, G. Francisco, A. Ciudin, P. Chacon, B. Montoro, G. Llaverias, F. Blanco-Vaca, R. Simó, Effect of atorvastatin on lipoprotein (a) and interleukin-10: a randomized placebo-controlled trial, DiabetesMetab. 37 (2) (2011) 124–130.
[18] K. Wang, L. Chen, L. Liu, Y. Cui, X. Zhang, J. Jiang, The effects of atorvastatin on IL-6, CRP, blood lipid and myocardial protection of interventional therapy in patients with acute myocardial infarction, Minerva Med. (2018).
[19] A.O. Akinkuolie, R.J. Glynn, L. Padmanabhan, P.M. Ridker, S. Mora, Circulating N-linked glycoprotein side-chain biomarker, rosuvastatin therapy, and incident cardiovascular disease: an analysis from the JUPITER trial, J. Am. Heart Assoc. 5 (7) (2016) e003822.
[20] D.C. Chan, G.F. Watts, P.H.R. Barrett, L.J. Beilin, T.A. Mori, Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity, Clin. Chem. 48 (6) (2002) 877–883.
[21] G.F. Clough, M. Turzyniecka, L. Walter, A.J. Krentz, S.H. Wild, A.J. Chipperfield, J. Gamble, C.D. Byrne, Muscle microvascular dysfunction in central obesity is related to muscle insulin insensitivity but is not reversed by high-dose statin treatment, Diabetes 58 (5) (2009) 1185–1191.
[22] A. Costa, R. Casamitjana, E. Casals, L. Alvarez, J. Morales, X. Masramon, G. Hernandez, R. Gomis, I. Conget, Effects of atorvastatin on glucose homeostasis, postprandial triglyceride response and C-reactive protein in subjects with impaired fasting glucose, Diabetic Med.: J. Brit. Diabetic Assoc. 20 (9) (2003) 743–745.
[23] S. Devaraj, E. Chan, I. Jialal, Direct demonstration of an antiinflammatory effect of simvastatin in subjects with the metabolic syndrome, J. Clin. Endocrinol. Metab. 91 (11) (2006) 4489–4496.
[24] P.A. Economides, A. Caselli, E. Tiani, L. Khaodhiar, E.S. Horton, A. Veves, The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes, J. Clin. Endocrinol. Metab. 89 (2) (2004) 740–747.
[25] S. Huptas, H.C. Geiss, C. Otto, K.G. Parhofer, Effect of atorvastatin (10 mg/day) on glucose metabolism in patients with the metabolic syndrome, Am. J. Cardiol. 98 (1) (2006) 66–69.
[26] K.K. Koh, M.J. Quon, S.H. Han, Y. Lee, J.Y. Ahn, S.J. Kim, Y. Koh, E.K. Shin, Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients, Diabetes Care 31 (4) (2008) 776–782.
[27] R. Krysiak, A. Gdula-Dymek, R. Bachowski, B. Okopien, Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes, Diabetes Care 33 (10) (2010) 2266–2270.
[28] P.Y. Liu, Y.W. Liu, L.J. Lin, J.H. Chen, J.K. Liao, Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation, Circulation 119 (1) (2009) 131–138.
[29] B.V. Loughrey, A. McGinty, I.S. Young, D.R. McCance, L.A. Powell, Increased circulating CC chemokine levels in the metabolic syndrome are reduced by low-dose atorvastatin treatment: evidence from a randomized controlled trial, Clin. Endocrinol. 79 (6) (2013) 800–806.
[30] J.S. Millar, B. Ky, M.L. Wolfe, L. Pruscino, A. Baer, D.J. Rader, Short-term treatment with high-dose atorvastatin reduces LDL cholesterol but shows no anti-inflammatory effects in normolipidemic subjects with normal CRP levels, Clin. Transl. Sci. 3 (4) (2010) 140–146.
[31] S. Mora, R.J. Glynn, J. Hsia, J.G. MacFadyen, J. Genest, P.M. Ridker, Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials, Circulation 121 (9) (2010) 1069–1077.
[32] J.S. Orr, A.L. Dengo, J.M. Rivero, K.P. Davy, Arterial destiffening with atorvastatin in overweight and obese middle-aged and older adults, Hypertension (Dallas, Tex.: 1979) 54 (4) (2009) 763–768.
[33] S. Peters, M. Palmer, D. Grobbee, J. Crouse III, D. O'Leary, J. Raichlen, M. Bots, C-reactive protein lowering with rosuvastatin in the METEOR study, J. Intern. Med. 268 (2) (2010) 155–161.
[34] J. Pleiner, G. Schaller, F. Mittermayer, S. Zorn, C. Marsik, S. Polterauer, S. Kapiotis, M. Wolzt, Simvastatin prevents vascular hyporeactivity during inflammation, Circulation 110 (21) (2004) 3349–3354.
[35] M.B. van Doorn, S.M. Espirito Santo, P. Meijer, I.M. Kamerling, R.C. Schoemaker, V. Dirsch, A. Vollmar, T. Haffner, R. Gebhardt, A.F. Cohen, H.M. Princen, J. Burggraaf, Effect of garlic powder on C-reactive protein and plasma lipids in overweight and smoking subjects, Am. J. Clin. Nutr. 84 (6) (2006) 1324–1329.
[36] L. Sun, L. Zou, M. Chen, B. Liu, Meta-analysis of statin therapy in maintenance dialysis patients, Ren. Fail. 37 (7) (2015) 1149–1156.
[37] G.-M. Li, J. Zhao, B. Li, X.-F. Zhang, J.-X. Ma, X.-L. Ma, J. Liu, The anti-inflammatory effects of statins on patients with rheumatoid arthritis: a systemic review and meta-analysis of 15 randomized controlled trials, Autoimmun. Rev. (2018).
[38] A. Sahebkar, J. Rathouska, G. Derosa, P. Maffioli, P. Nachtigal, Statin impact on disease activity and C-reactive protein concentrations in systemic lupus erythematosus patients: a systematic review and meta-analysis of controlled trials, Autoimmun. Rev. 15 (4) (2016) 344–353.
[39] M. Liang, S. Yang, N. Fu, Efficacy of short-term moderate or high-dose rosuvastatin in preventing contrast-induced nephropathy: a meta-analysis of 15 randomized controlled trials, Medicine 96 (27) (2017).
[40] M.A. Greene, R.F. Loeser, Aging-related inflammation in osteoarthritis, Osteoarthr. Cartilage 23 (11) (2015) 1966–1971.

[41] X.-K. Tong, N. Nicolakakis, P. Fernandes, B. Ongali, J. Brouillette, R. Quirion, E. Hamel, Simvastatin improves cerebrovascular function and counters soluble amyloid-beta, inflammation and oxidative stress in aged APP mice, Neurobiol. Disease 35 (3) (2009) 406–414.
[42] Y. Yamada, S. Takeuchi, M. Yoneda, S. Ito, Y. Sano, K. Nagasawa, N. Matsuura, A. Uchinaka, T. Murohara, K. Nagata, Atorvastatin reduces cardiac and adipose tissue inflammation in rats with metabolic syndrome, Int. J. Cardiol. 240 (2017) 332–338.
[43] T. Li, D. Wang, Y. Tian, H. Yu, Y. Wang, W. Quan, W. Cui, L. Zhou, J. Chen, R. Jiang, Effects of atorvastatin on the inflammation regulation and elimination of subdural hematoma in rats, J. Neurol. Sci. 341 (1–2) (2014) 88–96.
[44] H. Ajamieh, G.C. Farrell, R.S. McCuskey, J. Yu, E. Chu, H.J. Wong, W. Lam, N.C. Teoh, Acute atorvastatin is hepatoprotective against ischaemia-reperfusion injury in mice by modulating eNOS and microparticle formation, Liver Int. 35 (9) (2015) 2174–2186.
[45] J.G. Bode, U. Albrecht, D. Häussinger, P.C. Heinrich, F. Schaper, Hepatic acute phase proteins–regulation by IL-6-and IL-1-type cytokines involving STAT3 and its crosstalk with NF-κB-dependent signaling, Eur. J. Cell Biol. 91 (6–7) (2012) 496–505.
[46] Y.-W. Qin, P. Ye, J.-Q. He, L. Sheng, L.-Y. Wang, J. Du, Simvastatin inhibited cardiac hypertrophy and fibrosis in apolipoprotein E-deficient mice fed a "Western-style diet" by increasing PPAR α and γ expression and reducing TC, MMP-9, and Cat S levels, Acta Pharm. Sin. 31 (10) (2010) 1350.
[47] E. Rigamonti, G. Chinetti-Gbaguidi, B. Staels, Regulation of macrophage functions by PPAR-α, PPAR-γ, and LXRs in mice and men, Arterioscler. Thromb. Vasc. Biol. 28 (6) (2008) 1050–1059.
[48] A. Rezaie-Majd, T. Maca, R.A. Bucek, P. Valent, M.R. Müller, P. Husslein, A. Kashanipour, E. Minar, M. Baghestanian, Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients, Arterioscler. Thromb. Vasc. Biol. 22 (7) (2002) 1194–1199.
[49] R. Krysiak, A. Gdula-Dymek, B. Okopien, Effect of simvastatin and fenofibrate on cytokine release and systemic inflammation in type 2 diabetes mellitus with mixed dyslipidemia, Am. J. Cardiol. 107 (7) (2011) 1010–1018 e1.
[50] J. Han, Q.H. Yin, Y. Fang, W.Q. Shou, C.C. Zhang, F.Q. Guo, Atorvastatin protects BV-2 mouse microglia and hippocampal neurons against oxygen-glucose deprivation-induced neuronal inflammatory injury by suppressing the TLR4/TRAF6/NF-κB pathway, Mol. Med. Rep. 18 (1) (2018) 1058–1066.
[51] S. Wang, X. Zhang, L. Zhai, X. Sheng, W. Zheng, H. Chu, G. Zhang, Atorvastatin attenuates cognitive deficits and neuroinflammation induced by Aβ 1–42 involving modulation of TLR4/TRAF6/NF-κB pathway, J. Mol. Neurosci. 64 (3) (2018) 363–373.