The impact of statins therapy on disease activity and inflammatory factor in patients with rheumatoid arthritis: a meta-analysis

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Abstract

Objective

Statin is the most widely used as HMG-CoA reductase inhibitor, and contributes to clinically significant vascular risk reduction. However, the role of statins in the rheumatoid arthritis (RA) immunomodulation is debatable. This meta-analysis aimed to determine the efficacy of statins therapy in RA patients.

Methods

A structured literature search was undertaken to identify randomised controlled trials (RCTs) conducted in RA patients receiving either statins or control. A meta-analysis on standardised mean difference (SMD) with a 95% confidence interval (95%CI) was conducted.

Results

We included 15 studies with a total of 992 patients (487 patients allocated to statins therapy). Our data revealed that statins can attenuate disease activity markedly. Overall, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) declined significantly during the treatment (n=12, SMD: -2.222, 95%CI: -2.404, -2.040, p=0.000; n=14, SMD: -3.014, 95%CI: -3.207, -2.821, p=0.000), among which ESR and CRP decreased obviously at 12 months (n=5, SMD: -2.874, 95%CI: -3.224, -2.523, p=0.000; n=7, SMD: -3.970, 95%CI: -4.300, -3.641, p=0.000; respectively). As expected, the tender joint count (TJC) and swollen joint count (SJC) also fell (n=9, SMD: -2.005, 95% CI: -2.216, -1.794; p=0.000; n=10, SMD: -1.76, 95%CI: -1.948, -1.577; p=0.000; respectively). Besides, morning stiffness was attenuated (n=5, SMD: -1.242, 95%CI: -1.474, -1.011, p=0.000), and showed no significant differences between 12 months and 24 months (p=0.205). Notably, statins indeed potently down-regulate inflammatory factors TNF-α (n=7, SMD: -4.290, 95%CI: -4.659, -3.922; p=0.000), IL-1 (n=4, SMD: -1.324, 95%CI: -1.646, -1.003; p=0.000), and IL-6 (n=10, SMD: -1.652, 95%CI: -1.822, -1.482; p=0.000). No publication bias was observed across all studies based on the Begg and Egger test.

Conclusion

This meta-analysis demonstrates the pleiotropic effects of statins on ameliorating RA activity and mediating clinically apparent anti-inflammatory effects in the context of RA autoimmune inflammation, which make it recommended as a potent treatment for RA patients.

Key words

statins, rheumatoid arthritis, disease activity, inflammatory factors, meta-analysis

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Introduction

Statins, HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor, reduced cardiovascular morbidity and mortality. Generally statins work in part via lipid modulation; however current reports indicated statins shared broader properties (1), including modulation of inflammatory conditions (2), suppression of leucocyte cytokine releases (3), and interference with lymphocyte and macrophage cognate interactions (4). Statins also modify apoptosis in smooth muscle and vascular endothelial cells, resulting in impaired vascular function and neovascularisation. These properties offer the potential to modify chronic inflammatory diseases with drugs that show minimal toxic effects in both the short and long term (5).

Rheumatoid arthritis is a chronic inflammatory arthropathy associated with rapid onset of clinically significant functional impairment (6). It is also associated with accelerated vascular risk with attendant early mortality and excess morbidity. Statins suppress inflammation *in vivo* where statins selectively blocked monocyte chemotactic protein-1 expression. Moreover, *in vivo* cytokine release by rheumatoid arthritis synovial mononuclear cells and synovial fibroblasts was also reduced by statins. Similar anti-inflammatory effects of anti-TNF-α therapy have been reported in patients with rheumatoid arthritis (7). Statins therefore have a potential bioactivity profile *in vitro* and *in vivo* that makes them possible therapeutic agents in rheumatoid arthritis to target both vascular risk and synovial inflammation.

However, as yet, no meta-analysis data clearly show that statins modulate autoimmune disease activity in the context of antoimmun inflammation. We therefore undertook a meta-analysis to test the clinical efficacy and laboratory effects of these drugs in rheumatoid arthritis.

Methods

Search methods

An electronic search of PubMed, Medline, Embase database and the Cochrane center was conducted. Online registries including clinicaltrials.gov were also searched. Search terms included the following: "statins", "rheumatoid arthritis [MeSH]", "RCT", "ESR", "CRP", etc. The search was supplemented by reviewing the references of the included studies. If potentially relevant studies included non-published data, primary investigators of the relevant studies were contacted.
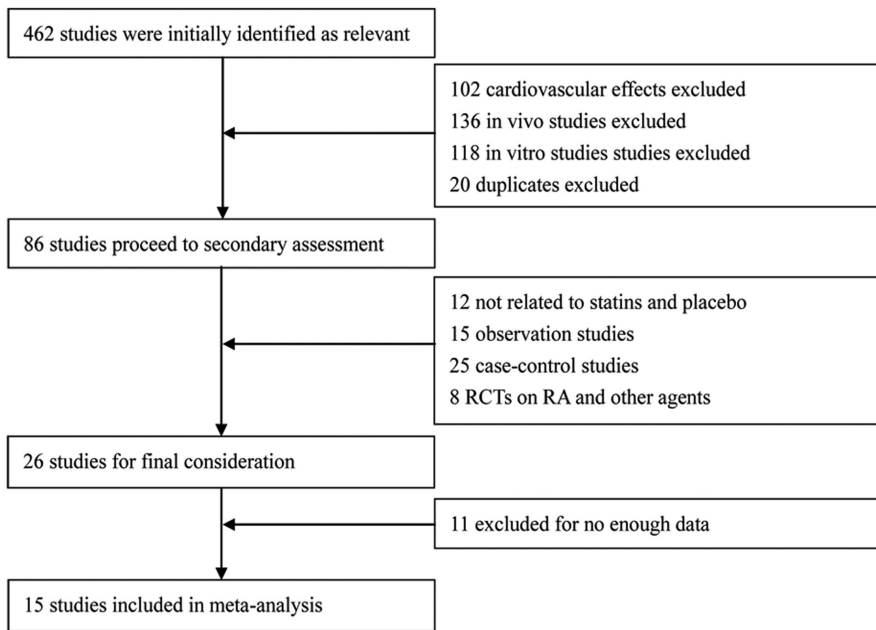
Selection criteria

The study included all randomised controlled trials comparing statins (atorvastatin, rosuvastatin) with control in terms of endpoints (ESR, CRP, TJC and SJC) in rheumatoid arthritis patients. Studies must have been published before July 2014. We excluded RCTs if they did not provide sufficient information to judge their eligibility or relevant outcomes. Rheumatoid arthritis was defined according to consensus criteria developed by American Rheumatism Association criteria for RA.

Data extraction

Two authors independently extracted the following descriptive data from all eligible trials: study design with RCTs, patient characteristics, study methodology (*e.g.* eligibility criteria, method of randomisation, and blinding), intervention (*e.g.* dosage, duration and route of administration), and main outcomes (endpoints). If the data needed clarification or were not presented in the publication, the original authors were contacted by e-mail. Extracted data were verified for accuracy. Any disagreement about inclusion or exclusion was resolved by team discussion and the risk of bias was assessed with the methods recommended by the Cochrane Collaboration (8).

Quality assessment

The study of quality and bias risk of individual studies and across studies was assessed using the Cochrane Collaboration tool (9). The criteria used for assessment were the way in which patients were allocated to treatment groups (sequence generation of allocation, allocation concealment), degree of blinding, the way in which outcomes were reported (selective outcome re-

Fig. 1. Literature search and selection of studies 15 RCT studies were included according to selection criteria.

porting) and any other sources of bias that could be identified. A funnel plot was used to determine publication bias.

Meta-analysis

Analysis was performed using Review Manager, version 5.0 (RevMan, The Cochrane Collaboration, Oxford, UK) and Stata version 11.0. Differences were expressed as SMD with 95% confidence intervals (CIs) for continuous data. All effects were pooled as fixed-effect model, and a random effect model was employed in the case of significant heterogeneity (a *p*-value of Q test <0.10 and/or $I^2 > 50\%$). $p < 0.01$ was considered statistically significant.

Results

Study identification

The primary search generated a total of 462 relevant studies (Fig. 1). Of the
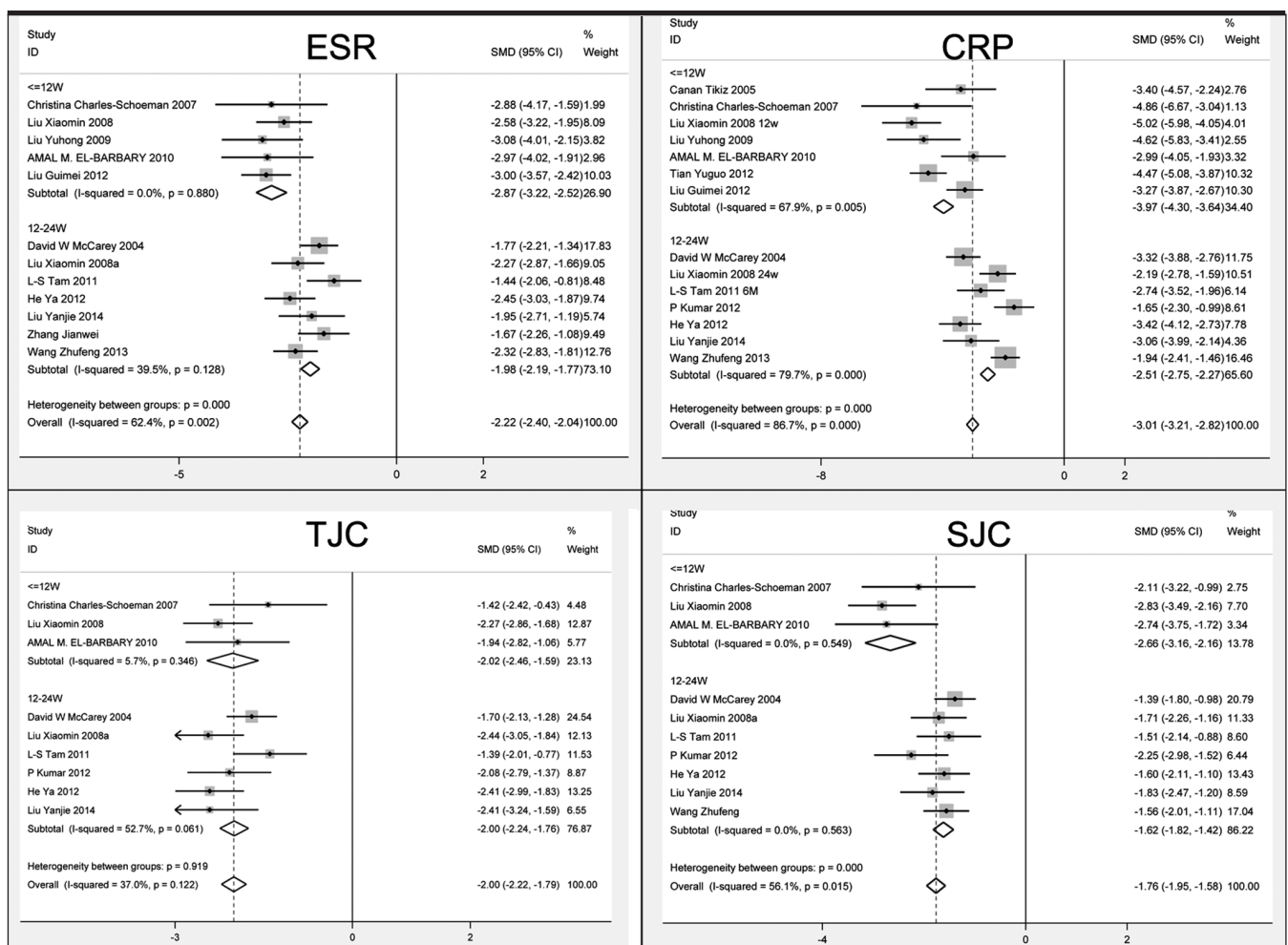
Fig. 2. Pooled SMDs and 95% CIs about the effect of ESR, CRP, TJC and SJC. The boxes are situated in line with the outcome value of the individual studies, and the horizontal lines through the boxes depict the length of the confidence intervals (CIs).The diamond in the graph illustrates the overall result of the meta-analysis.

Table I. Characteristics of included studies.

Study ID	Patients number	Country	Median Age	Gender (women)	Rheum. Factor (+)	Body Mass Index	Disease duration	Intervention	Duration
David W. McCarey 2004 (10)	116	Glasgow	56	100/116	102/116	NA	15.0 y	116 patients with rheumatoid arthritis were randomised in a double-blind placebo-controlled trial to receive 40 mg atorvastatin (n=58) or placebo (n=58) as an adjunct to existing disease-modifying anti-rheumatic drug therapy.	24 w
Frank Hermann 2005 (11)	40	Swiss	57	14/20	15/20	23.8	14.0 y	20 patients were assigned randomly to receive either simvastatin 40 mg/day for four weeks followed by four weeks of matching placebo (n=10).	4 w
Canan Tikiz 2005 (12)	45	Turkey	48	41/45	43/45	26.0	9.0 y	45 patients with long-term RA were randomised into 3 groups to receive 8 weeks of treatment with placebo (n=15), simvastatin (20 mg/day, n=15), or quinapril (10mg/day, n=15) as an adjunct to existing anti-rheumatic drug treatment.	8 w
Christina Charles-Schoeman 2007 (13)	20	USA	56	19/20	16/20	NA	16.0 y	20 subjects with active RA (mean DAS28 5.13 ± 0.92) without dyslipidaemia and history of coronary artery disease were randomised in a double-blind placebo-controlled trial to receive 80 mg of atorvastatin or placebo daily in addition to stable anti-rheumatic drug therapy.	12 w
Liu Xiaomin 2008 (14)	70	China	52	55/70	NA	NA	6.1 y	37 patients with RA treated with simvastatins (40mg/d), leflunomide (20mg/d) and methotrexate (10mg/w). 33 patients with RA treated only leflunomide and methotrexate.	12 w
Liu Yuhong 2009 (15)	40	China	42	35/40	NA	NA	2.6 y	40 patients with active RA were randomised into: (1) Disease modifying anti-rheumatoid drug (DMARD) group; (2) DMARD plus provastatin group (20mg/d).	8 w
Amal M. El-Barbary 2010 (16)	30	Egypt	54	25/30	NA	25.7	NA	Group 1 (n=15) received methotrexate (MTX; 0.2 mg/kg/w; mean total dose 15.5±1.3mg/w) plus prednisone (10mg/d); Group 2 (n=15) received MTX and prednisone with the same dose as Group 1 plus atorvastatin therapy (40mg/d).	4 w
L.-S. Tam 2011 (17)	50	Australia	55	37/50	36/50	NA	12.0 y	50 RA patients were randomised in a double-blind placebo-controlled trial to receive 10mg/d rosuvastatin (n=24) or placebo (n=26).	24 w
P. Kumar 2012 (18)	50	UK	62	27/50	NA	26.0	NA	50 RA patients were randomised in a double-blind placebo-controlled trial to receive either 10 mg/d of rosuvastatin or placebo as an adjunct to existing disease-modifying anti-rheumatic therapy.	24 w
Tian Yuguo 2012 (19)	150	China	42	102/150	NA	NA	NA	75 patients received atorvastatin (20mg/d) and leflunomide (10mg/d); The rest 75 only received leflunomide with the same dose as Group 1.	12 w
He Ya 2012 (20)	80	China	55	62/80	NA	NA	NA	40 patients with RA treated only leflunomide (10mg/w) and (20mg/d); the other 40 patients with RA treated only leflunomide (10mg/w). All patients received NSAID (7.5mg/day).	24 w
Liu Guimei 2012 (21)	100	China	48	84/100	NA	NA	NA	100 RA patients were randomly divided into control drugs group and lovastatin group. Control group (n=50) continued taking the original slow-acting drugs (methotrexate and sulfasalazine); lovastatin group (n=50) received lovastatin (20mg/d) based on the original therapy of control.	12 w
Zhang Jianwei 2013 (22)	60	China	52	33/60	NA	NA	NA	60 RA patients were randomly divided into A and B two groups. A group (n=30) included methotrexate, sulfasalazine, and hydroxychloroquine sulfate; B group (n=30), based on A group, was added with simvastatin (40mg/d).	24 w
Wang Zhufeng 2013 (23)	100	China	51	72/100	NA	NA	NA	100 patients with active RA were randomised into two treatment groups (n=50): simvastatin (20mg/d + methotrexate 6mg/w + chloroquine 250mg/d); the control group (n=50): methotrexate (6mg/w + chloroquine 250mg/d).	24 w
Diana Mazilu 2013 (24)	41	Romania	43	34/41	87.1	NA	NA	41 patients initiating rituximab were included; 17 patients were exposed to the combination of statins and rituximab. Treatment courses were repeated every 6 months for a period of 18 months (3 courses).	24 w

relevant studies, 376 were excluded for 102 cardiovascular effects, 136 *in vivo* studies, 118 *in vitro* studies and 20 duplicates. The remaining 86 underwent secondary evaluation, where additional studies were excluded again for: not relating to statins and control (12), observation (15) or case-control studies (25), RCTs on RA and other agents (8), leaving 26 studies for consideration. Of these, 11 were excluded for insufficient data. Eventually, we determined 15 RCTs studies with a total of 951 patients. Of 15 studies, seven studies were conducted in Asia. The patient sample sizes varied from 20 to 150 patients, and the mean age varied from 42 to 62 years old. Among the 992 partici-

Table II. Pooled SMDs (95%CIs) and heterogeneity about the effects of ESR, CRP, TJC and SJC.

Outcome	Week	Number	SMD	95% CI	Heterogeneity		
					Chi^2	p-value	I^2
ESR	24	12	-2.222	-2.404, -2.040	29.26	0.002	62.4%
	≤12	5	-2.874	-3.224, -2.523	1.19	0.880	0%
	12-24	7	-1.982	-2.195, -1.769	9.92	0.128	39.5%
CRP	24	14	-3.014	-3.207, -2.821	97.57	0.000	86.7%
	≤12	7	-3.970	-4.300, -3.641	18.70	0.005	67.9%
	12-24	7	-2.512	-2.751, -2.274	29.58	0.000	79.7%
TJC	24	9	-2.005	-2.216, -1.794	12.70	0.122	37.0%
	≤12	3	-2.025	-2.463, -1.586	2.12	0.346	5.7%
	12-24	6	-1.999	-2.240, -1.759	0.57	0.061	52.7%
SJC	24	10	-1.763	-1.948, -1.577	20.49	0.015	56.1%
	≤12	3	-2.661	-3.160, -2.162	1.20	0.549	0.0%
	12-24	7	-1.619	-1.818, -1.420	4.85	0.563	0.0%
Morning stiffness	24	5	-1.242	-1.474, -1.011	2.13	0.713	0.0%
	≤12	2	-1.427	-1.869, -0.986	0.11	0.741	0.05%
	12-24	3	-1.173	-1.444, -0.901	1.09	0.579	0.0%

pants, 487 received statins therapy, and the rest were attributed to the placebo or control. Notably, all patients were still under conventional anti-rheumatic drug treatment, and statins were administrated with concomitant stable disease-modifying anti-rheumatic drug (DMARD) in all intervention groups, whereas the individual regimen and baseline characteristics did not differ in the intervention group and control. All patients in the included studies received routine care. The detailed characteristics of the included studies are summarized in Table I.

Effects on different measures of outcome among RA patients
– ESR, CRP, TJC, SJC, and morning stiffness as outcome

As shown in Table II and Figure 2, ESR and CRP data were available on 12 studies and 14 studies respectively. Overall, statins affected ESR and CRP level compared with control. The pooled total SMDs of ESR and CRP of included studies were -2.222 (n=12, 95%CI: -2.404, -2.040, p=0.000), and -3.014 (n=14, 95%CI: -3.207, -2.821, p=0.000), respectively. Thereafter, subgroup analysis revealed both ESR (n=5, SMD: -2.874, 95%CI: -3.224, -2.523) and CRP (n=7, SMD: -3.970, 95%CI: -4.300, -3.641) decreased more obviously at 12 months than that at 24 months (n=7, SMD: -1.982, 95%CI: -2.195, -1.769; n=7, SMD: -2.512, 95%CI: -2.751, -2.274;

respectively), differences were significant by the Z test (ESR: p=0.000; CRP: p=0.000). No between-study heterogeneity was observed within subgroups, despite significant heterogeneity across all studies (p=0.002; p=0.000).

Likewise, reduction in TJC and SJC all remained significant in individuals allocated statins against control (n=9, SMD: -2.005, 95%CI: -2.216, -1.794, p=0·000; n=10, SMD: -1.763, 95%CI: -1.948, -1.577, p=0·000), whereas there was a more statistically significant improvement in either TJC (n=3, SMD: -2.025, 95%CI: -2.463, -1.586) or SJC (n=3, SMD: -2.661, 95%CI: -3.160, -2.162) at 12 weeks than that at 24 months (p<0001; Z test) with little heterogeneity (Table II, Fig. 2).

In addition, there is an obvious improvement in morning stiffness (n=5, SMD: -1.242, 95%CI: -1.474, -1.011, p=0·000), however Z test revealed no significant differences (p=0.205) between 12 months (n=2, SMD: -1.427, 95%CI: -1.869, -0.986) and 24 months (n=3, SMD: -1.173, 95%CI: -1.444, -0.901) as shown in Table II and Figure 3. All the above indicated that statins indeed attenuated the disease activity through decreasing ESR, CRP, TJC, SJC and morning stiffness.

– Inflammatory factors TNF-α and IL-6 as outcome

As the inflammation played an important role in the development of RA (25), in particular, we investigated changes

in inflammatory markers TNF-α, IL-1, and IL-6 in the statins group compared with control. As shown in Table III and Figure 3, there was overall reduction in the serum levels of TNF-α (n=7, SMD: -4.290, 95%CI: -4.659, -3.922; p=0.000), IL-1 (n=4, SMD: -1.324, 95%CI: -1.646, -1.003; p=0.000), and IL-6 (n=10, SMD: -1.652, 95%CI: -1.822, -1.482; p=0.000) when all data were pooled. Meanwhile, it should be noted that serum levels of IL-1 (n=1, SMD: -2.025, 95%CI: -2.566, -1.484) and IL-6 (n=6, SMD: -1.914, 95%CI: -2.138, -1.689) showed more significant reduction with statins therapy at 24 months when compared with 12 months (n=3, SMD: -0.942, 95%CI: -1.342, -0.543; n=4, SMD: -1.302, 95%CI: -1.561, -1.042). No heterogeneity in response was observed within subgroups.

Assessment of risk of bias
Assessment of risk of bias was carried out by RevMan 5.0. Selection bias was mitigated using random sequence generation in all studies, and allocation sequence concealment was adequately conducted in 12 studies, unclear in 3 studies, and no study was inadequately conducted. Participant blinding was adequately conducted in 14 studies, excluding high risk AMAL 2011. Outcome assessment was adequately conducted in 15 studies, which is satisfactory. The number of and reason for withdrawals/dropouts was reported in detail in 9 studies, for 3 studies unclear and Liu 2012 high risk. Of all the studies, eight were defined as free of other bias (Fig. 4).

Publication bias and sensitivity analysis
The Begg and Egger test were used to assess publication bias in this meta-analysis. When all p values were more than 0.05, no statistically significant publication bias was indicated. Here, we concluded the Begg and Egger test of all outcomes as shown in Table IV. No publication bias was observed. In addition, no individual study within each subgroup significantly affected the combined SMDs by sensitivity analysis, suggesting a robust result of this meta-analysis.
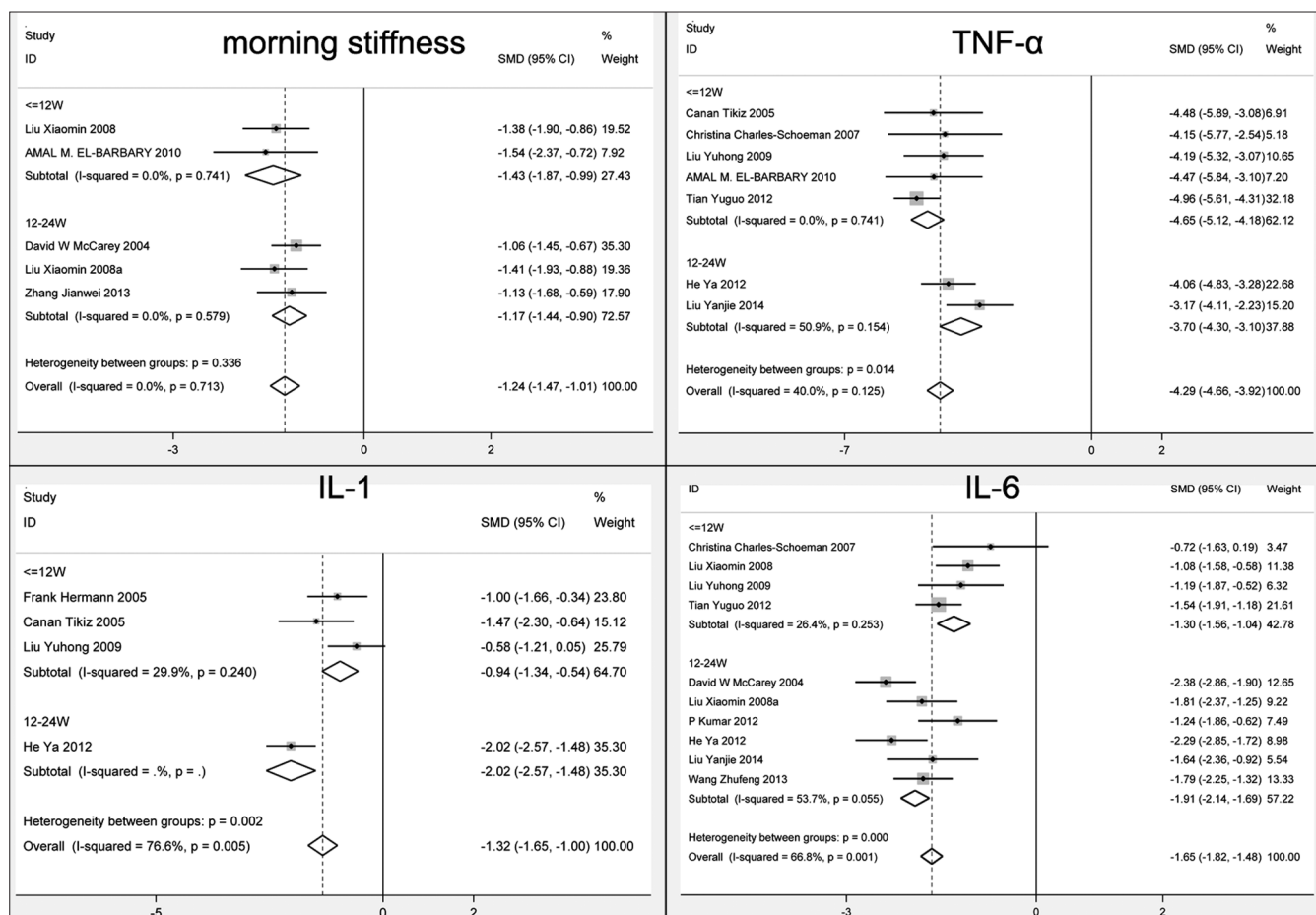
Fig. 3. Pooled SMDs and 95%CIs about the effect of morning stiffness, TNF-α, IL-1 and IL-6. The boxes are situated in line with the outcome value of the individual studies, and the horizontal lines through the boxes depict the length of the confidence intervals (CIs). The diamond in the graph illustrates the overall result of the meta-analysis.

Discussion

Despite the success of statin treatments in improving the quality of life for more patients with cardiovascular diseases, their effects on RA are not fully characterised. Several studies have suggested that statins like rosuvastatin was suggestive of potent immunomodulators (26), however it is still unknown whether such effects on laboratory can be translated to clinical practice. Till now, some RCT trials reported that statins have any clinically useful effect on inflammation and joint disease activity. However, few meta-analyses have identified the precise effects of statins. Thus, it is essential to complete a pooled analysis and systematic evaluation.

We demonstrated that statins significantly suppressed ESR, CRP, TJC and SJC, and then the subgroup analysis also revealed the pooled SMDs of ESR, CRP, TJC and SJC decreased more ob-

Table III. Pooled SMDs (95%CIs) and heterogeneity about the effects of TNF-α, IL-1 and IL-6.

Outcome	Week	Study number	SMD	95% CI	Heterogeneity		
					Chi2	*p*-value	I²
TNF-α	24	7	-4.290	-4.659, -3.922	10.00	0.125	40.0%
	≤12	5	-4.650	-5.117, -4.182	2.04	0.154	50.9%
	12-24	2	-3.701	-4.300, -3.103	1.97	0.741	0.0%
IL-1	24	4	-1.324	-1.646, -1.003	12.79	0.005	76.6%
	≤12	3	-0.942	-1.342, -0.543	2.85	0.240	29.9%
	12-24	1	-2.025	-2.566, -1.484	0.00	NA	NA
IL-6	24	10	-1.652	-1.822, -1.482	27.10	0.001	66.8%
	≤12	4	-1.302	-1.561, -1.042	4.08	0.253	26.4%
	12-24	6	-1.914	-2.138, -1.689	10.80	0.055	53.7%

viously at 12 months than those at 24 months, and differences were significant by the Z test. Actually the pooled SMD values did not represent the absolute changes, according to raw data (data not shown), the absolute values of ESR, CRP, TJC and SJC of patients allocated to statins therapy were significantly decreasing at 24 months than

those at 12 months. These findings suggested that statins efficiently improved the quality of life, which is consistent with attenuation of morning stiffness (27). Additionally, the novel finding of our study was that inflammatory factors IL-1 and IL-6 decreased obviously at 24 months than 12 months. Since the control groups did not receive the
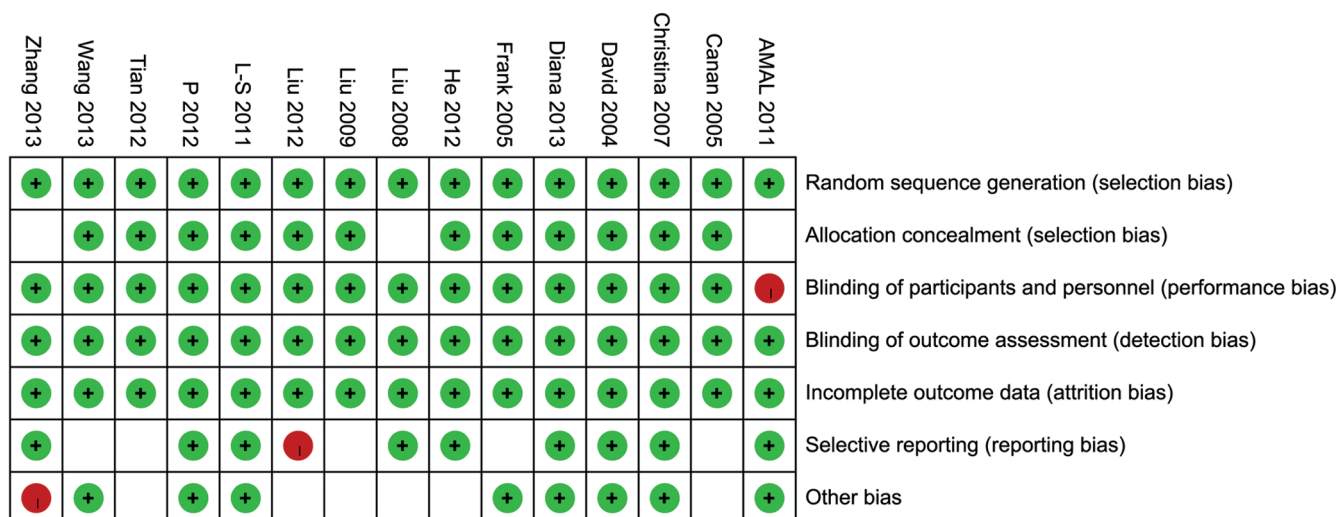
Fig. 4. An overview of assessing risk of bias. The green circle represents low risk; the empty box indicates unclear risk; the red circle is high risk.

Table IV. The Begg and Egger test of all outcomes.

Outcome	Week	Number	Begg p-value	Egger p-value
ESR	≤12	5	0.327	0.707
	12-24	7	0.453	0.965
CRP	≤12	7	0.881	0.693
	12-24	7	0.652	0.385
TJC	≤12	3	0.117	0.206
	12-24	6	0.851	0.356
SJC	≤12	3	0.117	0.426
	12-24	7	0.024	0.021
Morning stiffness	≤12	2	0.317	NA
	12-24	3	0.602	0.538
TNF-α	≤12	5	0.624	0.051
	12-24	2	0.317	NA
IL-1	≤12	3	1.000	0.692
	12-24	1	NA	NA
IL-6	≤12	4	0.174	0.123
	12-24	6	0.348	0.315

statins therapy, no significant changes in IL-1 and IL-6 levels was observed in terms of raw data. These results indeed identified potent anti-inflammatory effects of statins as reported *in vitro* (28). Inflammation is a hallmark of both atherosclerosis and RA, and is responsible for synovial inflammation and subsequent joint destruction (29). In decades, statins, mostly used for lipid modulation, have been reported to improve endothelial vasodilator response in patients with atherosclerosis (30-33). This beneficial effect was attributed to their anti-inflammatory and immunomodulatory properties, which were independent of their cholesterol-lowering function (34).

The present meta-analysis had some limitations. For instances, there were different durations in regimen of statins, lasting from 4 weeks to 24 weeks with doses range from 10 mg/d to 40 mg/d. Second, different agents of statins in all included trials might be different in effectiveness. Third, the baseline in the included trials including rheumatoid factor, disease duration, body mass index (BMI) and concomitant DMARD may need to be considered as the potential source of heterogeneity. However, in this meta-analysis, no individual study significantly affected the combined SMDs within subgroups through sensitivity analysis, suggesting the results were robust.

Publication bias favours the publication of positive results and the rejection of publications with negative results, which can be a major source of bias (35). The language of publication can also potentially contribute to this bias, as this meta-analysis was limited to studies published in English and Chinese. In this study, we evaluated publication bias by Begg and Egger test, which did not reveal significant differences, suggesting low risk of publication bias in this meta-analysis.

Conclusions
The cholesterol-reducing statins therapy could be beneficial for patients with RA, because they efficiently improve clinical outcomes, and reduce inflammation. Besides, these results should be further confirmed by larger scale RCT studies.

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