Statins improve asthma symptoms by suppressing inflammation: a meta-analysis based on RCTs

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Abstract. – OBJECTIVE: Asthma is a chronic airway inflammatory disease caused by high infiltration of multiple inflammatory cells and factors in airway tissues. Statins may inhibit inflammation, hence improve asthma symptoms. This meta-analysis aimed to assess the efficacy of statins in the treatment of asthma patients.

MATERIALS AND METHODS: We searched in PubMed, OVID, Cochrane Library, and Web of Science databases using the following key words: "statin", "atorvastatin", "simvastatin", "pravastatin", "rosuvastatin", "pitavastatin", "fluvastatin", and "asthma". The effects of statins on function, serum biomarkers, sputum mediators, and serum biochemical markers were analyzed from the identified studies.

RESULTS: Twelve articles (613 participants) were included in the meta-analysis. Results showed that statins significantly improved asthma symptoms (ACQ score: MD: -0.43, 95% CI: -0.47 - -0.38, p<0.01; ACT score: MD: 1.96, 95% CI: 1.26-2.67, p<0.01). Furthermore, statins significantly reduced serum hsCRP (MD: -0.50, p=0.02) and cholesterol (MD: -32.76, p<0.01) levels and the proportion of sputum eosinophils (MD: -1.25, p<0.01) and IL6 levels (MD: -64.56, p=0.04) in sputum. However, lung function was not significantly different between the statin and placebo treatment groups.

CONCLUSIONS: Although statins did not change the lung function in patients with asthma, they improved asthma symptoms and reduced the serum hsCRP, sputum eosinophil ratio, and IL6 levels.

Key Words: Statin, Asthma, Inflammation.

Introduction

Asthma is a chronic airway inflammatory disease characterized by airway hyperresponsiveness. It is characterized by high infiltration level of various inflammatory cells and factors in the airway tissues¹. There are more than 300 million asthma patients worldwide based on the 2015 Global Burden of Disease Study analysis, and its prevalence has been increasing yearly². There are many treatments for asthma, including inhaled corticosteroids (ICS) and bronchodilators. Despite these treatments, the inflammatory process worsens in some patients leading to a gradual loss of lung function³.

Statins are 3-hydroxy-3-methylglutaryl-coA reductase inhibitors involved in cholesterol biosynthesis. Currently, statins are widely used as lipid-regulating drugs⁴. Statins participate in immune regulation and have anti-inflammatory, anti-proliferation, anti-fibrosis, and anti-oxidation effects, thus reducing airway response⁵. In a previous study, statins reduced the number of eosinophils in the bronchoalveolar lavage fluid, alleviated inflammatory response, and inhibited the proliferation and contraction of airway smooth muscle in mice models of asthma^{6,7}. Meanwhile, a cross-sectional study on 165 patients with severe asthma showed that the addition of statins to the existing treatment regimen could improve asthma symptoms⁸.

These results demonstrate that statins may control asthma symptoms by suppressing inflammation. In this meta-analysis, we evaluated the role of statins in asthma patients in terms of their effect on lung function, blood, and sputum biochemical indexes.

Materials and Methods

Search Strategy and Eligibility Criteria

This systematic review and meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) and was performed according to a pre-specified protocol. Relevant studies were searched from the PubMed, OVID, Cochrane Library and Web of Science databases, from inception up to 1st March 2022. The following key medical subject headings (MeSH) and Emtree terms were used: "statin", "atorvastatin", "simvastatin", "pravastatin", "rosuvastatin", "pitavastatin", "fluvastatin", and "asthma". The reference lists of selected studies and previous reviews were also searched for potential eligible trials. Two reviewers independently checked the selected RCTs, and any discrepancies were resolved through discussion.

Data Abstraction and End Points

The following data were obtained: name of authors, year of publication, follow-up time, and basic characteristics of the study populations. The endpoints included clinical outcomes, pulmonary function, serum biomarkers, sputum mediators, and serum biochemical markers.

Ouality Evaluation and Statistical Analysis

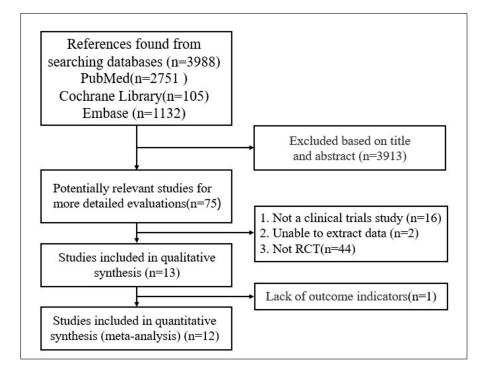
The data extracted from the original literature were expressed as mean±standard deviation^{9,10}.

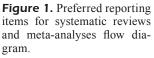
Revman 5.4 software was used for data analysis. The Cochrane risk of bias tool was used to assess the risk of bias. The P values of 25, 50, and 75% represented low, medium, and high degrees of heterogeneity, respectively. If $P \ge 50\%$, the random-effects model was used, otherwise, the fixed-effects model was used. The dichotomous variables were expressed as risk ratios (RR), with a 95% CI, while continuous variables were expressed as mean differences (MD), with a 95% CI. p < 0.05 was considered statistically significant.

Results

Search Results

A total of 3988 relevant articles were obtained. After reading the title and abstract, 75 full-text papers were found to be eligible (Figure 1). At the beginning 13 studies were included, one of the studies¹¹ only provided changes from baseline and was then removed. Finally, 12 articles with 613 participants were included in the analysis (follow-up duration; 4-12 weeks) (Table I). Figure 2 shows the Cochrane randomized trial bias risk scores for the included literature.





Statins improve asthma symptoms by suppressing inflammation

Author year	Drugs and active comparators	Participants (n)	Male (%)	Age (year)	Patients	Follow-up time
Hothersall et al ¹²	Atorvastatin Placebo	54	23 (42.6)	42.5 ± 13.7	Chronic symptomatic atopic asthma	8 weeks
Fahimi et al ¹³	Atorvastatin Placebo	17	9 (52.69)	37.12 ± 12.41	Patients with moderate to severe asthma	4 weeks
Maneechotesuwan et al ¹⁴	Budesonide + simvastatin	22				
	Budesonide + placebo	25	10 (45.45) 7 (28)	46.1 ± 9.40 52.05 ± 12.35	Nonsmoking patients with stable asthma	8 weeks
Cowan et al ¹⁵	Simvastain Placebo	43	14 (33)	45 (20-68)	Patients with stable persistent asthma	7 weeks
Braganza et al ¹⁶	Atorvastatin Placebo	36 32	15 (41.7) 15 (46.9)	40.4 43.0	Cigarette smokers with chronic asthma symptoms	8 weeks
Moini et al ¹⁷	Atorvastatin Placebo	28 29	13 (48.28) 10 (32.14)	40.00 ± 14.47 39.68 ± 12.89	Patients with mild persistent to moderate persistent asthma	4 weeks
Mohammad et al ¹⁸	Atorvastatin Placebo	9 13	/	32.95 ± 10.30	Patients with stable persistent asthma	4 weeks
Badar et al ¹⁹	Atorvastatin Placebo	30 30	17 (56.66) 12 (40)	43.13 ± 10.61 41.73 ± 11.41	Patients diagnosed cases of chronic bronchial asthma	12 weeks
Thomson et al ²⁰	Atorvastatin Placebo	15 24	5 (33.3) 12 (50.0)	37.9 ± 7.8 43.5 ± 10.7	Cigarette smokers with chronic asthma symptoms of more than	8 weeks
Sun et al ²¹	Budesonide and formoterol + simvastatin	41	31 (77.5)	36-72	one year duration Adult-onset obesity with asthma	55 days
	Budesonide and formoterol + placebo	41	29 (72.5)	35-71		
Mehrabi et al ²²	Atorvastatin	40	21 (52.5)	44.8 ± 10.4	Patients diagnosed with asthma	8 weeks
	Placebo	40	16 (40)	43.3 ± 11.6		
Maneechotesuwan et al ²³	Budesonide + simvastatin Budesonide + placebo	22 22	2 (9.09) 10 (45.4)	51.57 ± 4.58 50.53 ± 4.50	Patients with moderate to severe persistent asthma	8 weeks

Table I. Characteristics of studies included in meta-analysis.

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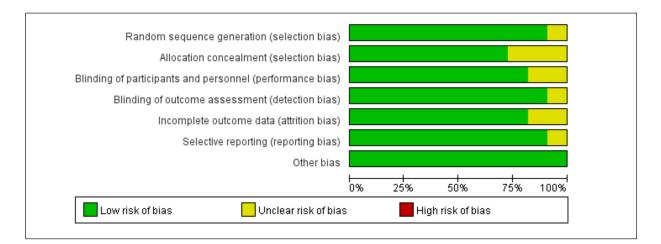


Figure 2. Risk of bias graph.

Clinical Outcomes

Statins significantly improved the symptoms of asthmatic patients. The Asthma Control Test (ACT) score and Asthma Control Questionnaire (ACQ) score were significantly better in the statin-treated group compared with the control group (ACQ score: MD: -0.43, 95% CI: -0.47 – -0.38, p<0.01; ACT score: MD: 1.96, 95% CI: 1.26-2.67, p<0.01) (Figure 3).

not improve the provocation concentration of AMP, causing a 20% fall in FEV1 (PC20AMP) and forced expiratory volume in 1s (FEV1%) in asthmatic patients (PC20AMP: MD: 0.34, p=0.64; FEV1%: MD: 1.82, p=0.25). Moreover, statins did not significantly increase morning or evening peak expiratory flow (PEF) (morning PEF: MD: 7.10, p=0.58 and evening PEF: MD: 5.57, p=0.67) (Figure 4).

Pulmonary Function

Lung function was not significantly different between the statin and placebo groups. Statins did

Serum Biomarkers

Analysis of serological markers showed that the addition of statins significantly reduced the level of serum hypersensitive C-reactive pro-

1.2.1 ACQ score Douglas 2010 0 Georgina(stain) 2011 0 Georgina(stain+ICS)2011 1 Hothersall2008 1	ean SE 0.48 0.84 1.5 0.67 1.38 0.93		<u>Mean</u> 0.74		Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Douglas 2010 C Georgina(stain) 2011 Georgina(stain+ICS)2011 1 Hothersall2008	1.5 0.67		0.74	0 6 0				
Georgina(stain) 2011 Georgina(stain+ICS)2011 1 Hothersall2008	1.5 0.67		0.74	0.60				
Georgina(stain+ICS)2011 1 Hothersall2008		34		0.09	43	2.1%	-0.26 [-0.58, 0.06]	
Hothersall2008	.38 0.93		1.9	0.9	30	1.4%	-0.40 [-0.79, -0.01]	
		33	1.77	1	27	0.9%	-0.39 [-0.88, 0.10]	
	1.4 0.9	54	1.5	0.8	54	2.1%	-0.10 [-0.42, 0.22]	+
Vandana 2014 🛛 🛛 🛛	0.81 0.08	30	1.25	0.11	30	93.4%	-0.44 [-0.49, -0.39]	.
Subtotal (95% Cl)		194			184	100.0%	-0.43 [-0.47, -0.38]	•
Heterogeneity: Chi2 = 5.31, df = 4	4 (P = 0.2	6); I ^z = 2	5%					
Test for overall effect: Z = 17.83	(P < 0.00	001)						
1.2.2 ACT score								
Abdollatif 2011 19	9.85 3.2	28	17.83	4.47	29	12.1%	2.02 [0.01, 4.03]	
Douglas 2010 21	.65 3.83	3 43	21	4.6	43	15.3%	0.65 [-1.14, 2.44]	
Samrad 2021 19	9.88 3.28	3 40	18.6	3.26	40	23.9%	1.28 [-0.15, 2.71]	
Shufang 2017 2	3.4 2.41	40	20.7	2.16	40	48.7%	2.70 [1.70, 3.70]	
Subtotal (95% CI)		151			152	100.0%	1.96 [1.26, 2.67]	-
Heterogeneity: Chi ² = 5.02, df = 3	3 (P = 0.1	7); I ² = 4	0%					
Test for overall effect: Z = 5.50 (F	o < 0.000	D1)						
								-2 -1 0 1 2
Test for subaroup differences: C								Favours (Stain) Favours (Placebo)

Figure 3. The forest chart shows the results of the effect of statins on the clinical outcomes.

		Stain		P	acebo			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
1.5.1 PC20 AMP											
Douglas 2010	33.7	9.59	43	48.32	15.01	43	5.8%	-14.62 [-19.94, -9.30]	+		
Georgina(stain) 2011	4.12	4.86	34	2.93	5	30	28.2%	1.19 [-1.23, 3.61]	•		
Georgina(stain+ICS)2011	5.31	6.2	33	2.31	4	27	24.5%	3.00 [0.40, 5.60]	•		
Hothersall2008	4.75	7.16	54	4.49	6.85	54	23.7%	0.26 [-2.38, 2.90]	•		
Subtotal (95% CI)			164			154	82.3%	0.34 [-1.08, 1.76]			
Heterogeneity: Chi ² = 34.83	df = 3 (P	< 0.0000	1); I ² = 9	91%							
Test for overall effect: Z = 0.4	47 (P = 0.6	64)									
1.5.4 FEV1%											
Abdollatif 2011	93.89	9.73	9	95	12.2	13	2.0%	-1.11 [-10.30, 8.08]	+		
Fanak 2009	86	13	17	86	13	17	2.2%	0.00 [-8.74, 8.74]	+		
Majid 2012	83.46	10.81	28	81.82	13.42	29	4.2%	1.64 [-4.68, 7.96]	+		
Samrad 2021	81.1	9.2	40	78.1	10.5	40	8.9%	3.00 [-1.33, 7.33]	+		
Subtotal (95% CI)			94			99	17.1%	1.82 [-1.29, 4.93]	•		
Heterogeneity: Chi ² = 0.85,	tf = 3 (P =	0.84): 12:	= 0%								
Test for overall effect: Z = 1.											
1.5.5 Morning PEF											
Douglas 2010	415	110	43	408	107	43	0.1%	7.00 [-38.87, 52.87]			
Georgina(stain) 2011		141.63		357.65		30	0.0%	18.74 [-45.70, 83.18]			
Georgina(stain+ICS)2011		123.38		354.64	123.7	27	0.0%	35.87 [-26.97, 98.71]			
Hothersall2008	387	106.5	54	395.3	101	54	0.1%	-8.30 [-47.45, 30.85]			
Subtotal (95% CI)		100.0	164	000.0		154	0.3%	7.10 [-17.74, 31.93]	-		
Heterogeneity: Chi ² = 1.52,	if = 3 (P =	0.68); P	= 0%								
Test for overall effect: Z = 0.			•								
1.5.6 Evening PEF											
Douglas 2010	423	112	43	418	108	43	0.1%	5.00 [-41.50, 51.50]			
Georgina(stain) 2011	384.8	137.1	34	367.4	117.2	30	0.0%	17.40 [-44.91, 79.71]			
Georgina(stain+ICS)2011	400	140.1	33	368.3	130.5	27		31.70 [-36.91, 100.31]			
Hothersall2008	395.3	101	54	403.8	116.3	54	0.1%	-8.50 [-49.58, 32.58]			
Subtotal (95% CI)	000.0		164			154	0.3%	5.57 [-20.04, 31.18]	-		
Heterogeneity: Chi ² = 1.15.	1f = 3 (P =	0.77): 12:									
Test for overall effect: Z = 0.4			0.0								
	10 (1 = 0.0	,									
Total (95% CI)			586			561	100.0%	0.62 [-0.66, 1.91]			
Heterogeneity: Chi ² = 39.48	df = 15 (F	P = 0.000	5); I ² = 6	62%				-	-100 -50 0 50 100		
Test for overall effect: Z = 0.9	95 (P = 0.3	34)							Favours (stain) Favours (placebo)		
Test for subaroup difference	e: Chiž -	113 df-	3 (P -	0 77) 12-	- 0%				Favours (stain) Favours (placebo)		

Figure 4. The forest chart shows the results of the effect of statins on the pulmonary function.

tein (hsCRP) (MD: -0.50, 95% CI: -0.90~-0.09, p=0.02). However, statins did not significantly affect IL6 levels and the proportion of eosinophils (IL6: MD: -1.93, p=0.31; eosinophil%: MD: -0.97, p=0.46) (Figure 5).

Sputum Mediators

The changes in inflammatory mediators in the sputum were also analyzed. Results revealed that statins significantly reduced the proportion of eosinophils in sputum (eosinophil %: MD: -1.25, 95% CI: -2.03 – -0.46, p<0.01) and IL6 levels (IL6: MD: -64.56, 95% CI: -127.57~-1.55, p=0.04). However, statins did not significantly affect the levels of TNFa (p=0.15, 95% CI: -0.51~3.28), IL8 (p=0.31, 95% CI: -0.97~0.31) and IL10 (p=0.13, 95% CI: -2.91~ 21.79) in patients with asthma (Figure 6).

Serum Biochemical Markers

Serum triglyceride and cholesterol levels were significantly lower in the statin-treated group compared with the no-intervention group (triglyceride: MD: -0.24, 95% CI: -0.31~-0.17, p<0.01; cholesterol: MD: -32.76, 95% CI: -34.49~-31.03, p<0.01). However, statins did not significant cause liver damage (ALT: MD: 0.47, p=0.72; AST: MD: 0.53, p=0.57) (Figure 7).

Discussion

The results showed that addition of statins significantly improved the clinical symptoms of asthmatic patients and reduced the serum hsCRP and cholesterol levels. Statins also significantly increased the sputum eosinophil ratio and IL6 level. However, they did not significantly improve lung function in asthma patients.

The ACQ scores are used to predict the level of asthma control. The ACQ score scale assesses asthma control in the past one week with 5/7 equally weighted items²⁴. On the other hand, the

		Stain		Р	lacebo			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl	
1.1.1 hsCRP											
Georgina(stain) 2011	3.1	2.64	31	3.3	3.27	29	7.2%	-0.20 [-1.71, 1.31]			
Georgina(stain+ICS)2011	2.36	2.41	32	2.78	3.23	24	7.0%	-0.42 [-1.96, 1.12]		_ <u>_</u>	
Hothersall2008	0.86	0.77	54	1.39	1.45	54	85.8%	-0.53 [-0.97, -0.09]			
Subtotal (95% CI)			117			107	100.0%	-0.50 [-0.90, -0.09]		•	
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 0.$	18, df=	2 (P =	0.91); l²	= 0%						
Test for overall effect: $Z = 2$.	41 (P = 0	.02)									
1.1.2 IL6											
Georgina(stain) 2011	4.77	8.39	31	9.86	20.12	29	16.5%	-5.09 [-12.99, 2.81]	•		
Georgina(stain+ICS)2011	3.32	6.67	32	8.54	16.55	24	19.6%	-5.22 [-12.23, 1.79]	←		
Hothersall2008	1.74	1.81	54	1.85	2.19	54	63.9%	-0.11 [-0.87, 0.65]			
Subtotal (95% CI)			117			107	100.0%	-1.93 [-5.63, 1.77]			
Heterogeneity: Tau ² = 5.43;	Chi ² = 3.	49, df =	2 (P =	0.17); l ^a	= 43%						
Test for overall effect: Z = 1.	02 (P = 0	.31)									
1.1.3 Eosinophil %											
Douglas 2010	14.47	16.34	43	24.76	18.71	43	9.8%	-10.29 [-17.71, -2.87]	•		
Hothersall2008	1.53	1.9	54	1.64	1.98	43	50.9%	-0.11 [-0.89, 0.67]		-#-	
Samrad 2021	8.3	4.21	40	8.06	5.37	40	39.3%	0.24 [-1.87, 2.35]			
Subtotal (95% CI)			137			126	100.0%	-0.97 [-3.55, 1.60]			
Heterogeneity: Tau ² = 3.24;	$Chi^2 = 7.$	30, df=	2 (P =	0.03); I ²	= 73%						
Test for overall effect: $Z = 0$.	74 (P = 0	.46)									
									+	<u> t_ t_ t_ t_ t_ </u>	
									-10	-5 Ó Ś	1
), I ² = 09					Favours (Stain) Favours (Placebo	

Figure 5. The forest chart shows the results of the effect of statins on the serum biomarkers.

ACT score scale assesses asthma control over the past four weeks by evaluating shortness of breath, frequency of night/early waking, use of salvage medications, overall asthma control, and loss of productive capacity^{25,26}. In this analysis, statins significantly improved ACQ and ACT scores compared with the placebo treatment, indicating that statins can significantly improve asthma symptoms.

Furthermore, statins significantly reduced serum hsCRP levels and improved symptom control in asthma patients. C-reactive protein (CRP) is an acute phase protein synthesized by liver cells in response to inflammatory factors. CRP is involved in various inflammatory and infection processes. It also plays a crucial role in acute and chronic inflammatory responses²⁷. The level of CRP is elevated in asthma patients and is positively correlated with disease severity. Therefore, CRP levels can be used as a diagnostic marker, indicator of treatment efficacy, and a biomarker to evaluate patient prognosis²⁸. For instance, CRP levels can reflect changes in lung function in patients with bronchial asthma. Increased CRP levels indicate decreased lung function²⁹. Statins have been shown to improve symptoms by lowering CRP levels and improving lung inflammation¹².

Asthma is a chronic inflammatory disease affecting the airway tissues caused by T lymphocyte-mediated allergy³⁰. The imbalance of Th1/Th2 ratio contributes to the pathogenesis of asthma. Activated Th2 cells secrete various pro-inflammatory factors, such as IL4, IL5, IL6, IL10, IL17, and TNFa, which increase the number of airway eosinophils and mucus secretion through different mechanisms. This results in bronchial hyper-reactivity³¹. IL6 participates in causing poor lung function and increasing the risk of asthma exacerbation. Elevated IL6 levels indicate an increased susceptibility to asthma exacerbation³². IL6 activates cells through its membrane-bound receptors and GP130 signal sensor glycoproteins. IL6 contributes to the pathogenesis of asthma by regulating the balance between Th1 and Th2, increasing mucus secretion, promoting Th17 differentiation, and inhibiting regulatory T cells³³. Th17 cells can trigger the secretion of $TNF\alpha$, IL1B, IL6, and other inflammatory factors by respiratory epithelial cells and respiratory smooth muscle cells through IL17A, thereby promoting the maturation of neutrophils and respiratory inflammation³⁴. Th17 cells and cytokines are significantly increased in sputum, alveolar lavage fluid, and serum of asthma patients. Moreover, the expression level of Th17 cells and cytokines is positively correlated with respiratory hyper-reactivity and disease severity³⁵.

		Stain		P	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.4.1 TNFα									
Hothersall2008	21.34	30.92	54	49.79	90.33	54	0.5%	-28.45 [-53.91, -2.99]	·
Kittipong 2010	15.36	2.41	22	9.91	1.87	25	30.4%	5.45 [4.20, 6.70]	•
Neil(stain) 2015	0.41	0.57	15	0.58	0.73	15	34.3%	-0.17 [-0.64, 0.30]	•
Neil(stain+ICS) 2015	0.22	0.26	15	0.39	0.52	15	34.7%	-0.17 [-0.46, 0.12]	•
Subtotal (95% CI)			106			109	100.0%	1.39 [-0.51, 3.28]	•
Heterogeneity: Tau ² = 2.67; Chi ² = 80 Test for overall effect: Z = 1.43 (P = 0) (P < 0.0		l² = 96%					
1.4.2 IL6									
Georgina(stain) 2011	168.73	246.83	31	195.45	273.92	29	22.7%	-26.72 [-158.97, 105.53]	
Georgina(stain+ICS)2011	134.56	145.2	32	232.55	381.81	24	15.4%	-97.99 [-258.81, 62.83]	•
Neil(stain) 2015	75.78	80.02	15	157.53	253.44	24	33.3%	-81.75 [-190.93, 27.43]	·
Neil(stain+ICS) 2015		145.99		155.93		24	28.6%	-56.64 [-174.39, 61.11]	•
Subtotal (95% CI)			93			101	100.0%	-64.56 [-127.57, -1.55]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0. Test for overall effect: Z = 2.01 (P = 0		(P = 0.90); I ² = 0	%					
1.4.3 IL8									
Georgina(stain) 2011	1.25	2.19	31	1.68	2.06	29	35.7%	-0.43 [-1.51, 0.65]	•
Georgina(stain+ICS)2011	1.24	2.19	32	1.31	2.18	24	30.9%	-0.07 [-1.23, 1.09]	•
Hothersall2008	1.98	2.36	54	2.45	3.43	54	33.5%	-0.47 [-1.58, 0.64]	•
Subtotal (95% CI)		2.00	117	20			100.0%	-0.33 [-0.97, 0.31]	(
Heterogeneity: Tau ² = 0.00; Chi ² = 0. Test for overall effect: Z = 1.01 (P = 0 1.4.4 IL 10									
	13.7	25.56	31	18.24	12.98	29	15.9%	45411470 5 601	
Georgina(stain) 2011								-4.54 [-14.70, 5.62]	
Georgina(stain+ICS)2011	13.1	17.39	32	11.93	15.97	24		1.17 [-7.61, 9.95]	
Kittipong 2010	72.51	28.31	22	27.59	8.72	22	15.1%	44.92 [32.54, 57.30]	
Kittipong Maneechotesuwan 2021	56.17	10.5	22	25.18	5.81	22	17.3%	30.99 [25.98, 36.00]	
Neil(stain) 2015	3.53	2.48	15	7.04	3.12	24	17.7%	-3.51 [-5.28, -1.74]	-
Neil(stain+ICS) 2015	1.49	0.96	15	10.28	6.91	24	17.6%	-8.79 [-11.60, -5.98]	+
Subtotal (95% CI)			137			145	100.0%	9.44 [-2.91, 21.79]	
Heterogeneity: Tau ² = 223.01; Chi ² = Test for overall effect: Z = 1.50 (P = 0		f=5(P <	0.0000	01); I² = 9	18%				
1.4.5 Eosinophil %									
Douglas 2010	11.14	4.87	43	23.26	5.58	43	7.8%	-12.12 [-14.33, -9.91]	-
Georgina(stain) 2011	0.47	0.78	31	0.51	0.94	29	19.2%	-0.04 [-0.48, 0.40]	1
Georgina(stain+ICS)2011	0.54	0.78	32	0.27	0.47	24	19.7%	0.27 [-0.06, 0.60]	t
Hothersall2008	1.12	0.55	54	1.53	0.57	54	20.1%	-0.41 [-0.62, -0.20]	•
Kittipong 2010	2.94	3.17	22	7.1	7.25	25	4.8%	-4.16 [-7.30, -1.02]	
Kittipong Maneechotesuwan 2021	0.5	0.26	22	0.94	0.42	22	20.2%	-0.44 [-0.65, -0.23]	•
Samrad 2021	8.3	4.21	40	8.06	5.37	40	8.2%	0.24 [-1.87, 2.35]	+
Subtotal (95% CI)	0.3	4.21	244	0.00	5.57		100.0%	-1.25 [-2.03, -0.46]	•
Heterogeneity: Tau ² = 0.78; Chi ² = 13 Test for overall effect: Z = 3.12 (P = 0		6 (P < 0.		; I² = 95%	6	231	100.0%	- 1.25 [-2.05, -0.40]	
									-50 -25 0 25 6
									Favours [Stain] Favours [Placebo]

Figure 6. The forest chart shows the results of the effect of statins on the sputum mediators.

Atorvastatin can inhibit the secretion of cytokines, such as IL6 and IL17 to enhance steroid sensitivity. They can also regulate Th17-mediated diseases ³⁶. In this study, statins significantly reduced IL6 levels in the sputum of asthma patients, suggesting that statins exert anti-inflammatory effects by down-regulating the expression of IL6 and reducing Th17 differentiation.

Eosinophilia is a crucial component of mediated airway type 2 immune response. It is associated with persistent asthma symptoms, decreased lung function, and increased airway reactivity³⁷. Besides secreting various inflammatory factors, eosinophils can also enhance nitrification and oxidative stress response, resulting in oxidative lung damage³⁸. Eosinophils produce reactive oxygen

species when exposed to allergens, releasing eosinophils peroxidase and bromotyrosine amino acids which cause a series of oxidative stress-related airway injuries³⁹. High systemic oxidative stress and serum cholesterol levels in obese patients with asthma increase eosinophils and enhance airway stress response⁴⁰. Statins inhibit stimulus-induced formation of nitric oxide and nitric oxide synthase, reduce inflammatory cytokines and inflammatory cells to suppress airway inflammation and oxidation⁴¹. Statins lower serum cholesterol in obese patients with asthma to reduce lipid-induced asthma exacerbation^{42,43}. Therefore, statins improve asthma symptoms by reducing the proportion of eosinophils in the sputum, serum total cholesterol level, and inflammatory response.

	:	Stain			acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
1.3.1 ALT									
Georgina(stain+ICS)2011	22	14.37	32	24.04	11.7	25	14.2%	-2.04 [-8.81, 4.73]	
Hothersall2008	26.35	12.95	54	22.83	13.71	54	25.8%	3.52 [-1.51, 8.55]	+ - -
Kittipong 2010	19.74	9.71	22	20.79	8.25	25	24.2%	-1.05 [-6.24, 4.14]	
Samrad 2021	15.3	8.8	40	15	10.6	40	35.8%	0.30 [-3.97, 4.57]	+
Subtotal (95% CI)			148			144	100.0%	0.47 [-2.08, 3.02]	◆
Heterogeneity: Chi ² = 2.28, (df = 3 (P =	0.52); F	²=0%						
Test for overall effect: Z = 0.3									
1.3.2 AST									
Hothersall2008	22.65	6.85	54	20	6.09	54	56.0%	2.65 [0.21, 5.09]	-
Kittipong 2010	22.03		22		7.47	25	28.2%	-3.83 [-7.28, -0.38]	
Samrad 2021		11.28	40	17.32	9.66	40	15.8%	0.76 [-3.84, 5.36]	
Subtotal (95% CI)	10.00	11.20	116	17.52	3.00		100.0%	0.53 [-1.30, 2.36]	•
Heterogeneity: Chi ² = 9.04, (df - 2 (P -	0.011					100.070	0.00[-1.00, 2.00]	ſ
Test for overall effect: Z = 0.9			- 70 X	,					
4 0 0 T-1-1									
1.3.3 Triglycerides			~~	4	o 47	~~	40.50		
Abdollatif 2011	1.15		28	1.32	0.47	29	10.5%	-0.17 [-0.39, 0.05]]
Georgina(stain+ICS)2011	1.02		32	1.74	1.29	25	2.0%	-0.72 [-1.24, -0.20]]
Hothersall2008	0.94	0.53	54	1.17	0.61	54	11.4%	-0.23 [-0.45, -0.01]	<u>_</u>
Samrad 2021	1.14	0.25	40	1.38	0.099	40	76.1%	-0.24 [-0.32, -0.16]	
Subtotal (95% CI)			154			148	100.0%	-0.24 [-0.31, -0.17]	
Heterogeneity: Chi ² = 3.66, (² = 18%	•					
Test for overall effect: Z = 6.4	49 (P < 0.)	00001)							
1.3.4 Cholesterol									
Abdollatif 2011	162.85		28	202.65		29		-39.80 [-65.65, -13.95]	•
Georgina(stain+ICS)2011	66.97	14.06	32	98.79	16.65	25		-31.82 [-39.96, -23.68]	
Hothersall2008		4.29	54	94.35	5.15	54		-32.93 [-34.72, -31.14]	
Samrad 2021	134.15	14.06	40	156.9	44	40	1.5%	-22.75 [-37.06, -8.44]	
Subtotal (95% CI)			154			148	100.0 %	-32.76 [-34.49, -31.03]	•
Heterogeneity: Chi ² = 2.25, (Test for overall effect: Z = 37									
									-50 -25 0 25 50

Figure 7. The forest chart shows the results of the effect of statins on the serum biochemical markers.

However, statins did not significantly improve lung function in asthma patients, possibly because most participants had mild to moderate asthma. Also, a longer observational period may be required for accurate assessment since changes in lung function involve airway remodeling.

Study Limitations

The small sample size, short duration of treatment, and lack of classification of asthma severity in most RCT_{s} limit made it difficult to determine the long-term effects of statins use in asthma patients, particularly their effect on airway remodeling. Larger randomized trials with longer durations are, therefore, necessary.

Conclusions

Statins significantly improve ACT and ACQ scores in asthma patients. They also reduce serum hsCRP levels, sputum eosinophils, and IL6 levels thereby controlling inflammatory response

and improving asthma symptoms. However, statins do not significantly improve lung function in asthma patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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None.

Authors' Contribution

Qinxia Zhang, Qinxing Xu contributed to the conception of the study. Haifu Zhang, Xiuting Lu contributed significantly to literature search and data extraction. Qinxia Zhang, Jun Zhao, performed the data analyses and wrote the manuscript. All authors reviewed the manuscript.

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