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# Statin therapy does not improve lung function in asthma: A meta-analysis of randomized controlled trials

Xiao-bei Si,<sup>1</sup> Shuo Zhang,<sup>2</sup> Lin-yu Huo,<sup>3</sup>  
Wen-li Dai<sup>4</sup> and Hai-long Wang<sup>5</sup>

## Abstract

**Objective:** To assess the efficacy of statins in the treatment of asthma.

**Methods:** Electronic databases were searched to identify randomized controlled trials that measured the efficacy of statins in the treatment of asthma, and a meta-analysis of the pooled data was performed.

**Results:** Five trials were identified; four met the inclusion criteria (total number of patients 200). Compared with controls, patients in the statin groups had higher forced expiratory volume in 1 s (FEV<sub>1</sub>) values before inhaled corticosteroids (0.09 l, 95% confidence interval [CI] –0.06, 0.23), higher FEV<sub>1</sub> values after inhaled corticosteroids (0.06 l, 95% CI –0.09, 0.22), and higher morning peak expiratory flow rates (9.87 l, 95% CI –15.66, 35.40). These results were not statistically significant and, furthermore, publication bias was detected.

**Conclusion:** In conclusion, there is currently insufficient evidence to show that statins improve lung function in patients with asthma.

## Keywords

Asthma, lung function, meta-analysis, statins

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<sup>1</sup>Department of Cardiology, Beijing Hospital of the Ministry of Public Health, Beijing, China

<sup>2</sup>Department of Cardiology, Xiangya Hospital, Central-South University, Changsha, Hunan Province, China

<sup>3</sup>Department of Neurology, Xuanwu Hospital, China Capital Medical University, Beijing, China

<sup>4</sup>Department of Internal Medicine, Peking Union Medical College Hospital, Beijing

<sup>5</sup>Department of Epidemiology and Evidence-based Medicine, First Affiliated Hospital, China Medical University, Shenyang, Liaoning Province, China

## Corresponding author:

Dr Hai-Long Wang, Department of Epidemiology and Evidence-based Medicine, First Affiliated Hospital, China Medical University, 155 Nanjing North Street, Heping District, Shenyang 110001, Liaoning Province, China.

Email: whl604@sohu.com

## Introduction

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, and have been proven effective in treating hyperlipidaemia and reducing the risk of cardiovascular disease.<sup>1</sup> Since their introduction for clinical use, statins have revolutionized the treatment of patients with cardiovascular disease.<sup>1</sup> Evidence has also suggested that statins have anti-inflammatory properties and immunomodulatory effects, in addition to their lipid-lowering properties.<sup>2-4</sup> Other evidence suggests their benefits in multiple sclerosis,<sup>5</sup> rheumatoid arthritis,<sup>6</sup> and chronic obstructive pulmonary disease.<sup>7-9</sup> Asthma is an immune-mediated airway disease associated with eosinophilic airway inflammation and a type 2 helper T cell (T<sub>H</sub>2) cytokine functional profile,<sup>10</sup> and preclinical and clinical studies have evaluated its response to statin treatment.<sup>7-9,11-14</sup>

There are several theoretical mechanisms for the benefits of statins against asthma. First, statins inhibit lung parenchymal destruction, peribronchial and perivascular inflammatory cell infiltration,<sup>15</sup> and airway inflammation.<sup>16</sup> Secondly, statins might enhance corticosteroid sensitivity in asthma patients.<sup>17,18</sup> In 2004, McKay et al.<sup>12</sup> reported the positive anti-inflammatory properties of simvastatin in a bronchial asthma murine model, in which asthma was induced using ovalbumin. Subsequent studies have investigated the treatment of asthma.<sup>11,17,19,20</sup>

To date, there have been few published randomized controlled trials on the efficacy of statins in the treatment of asthma, and the number of included cases has ranged between 43 and 64.<sup>11,17,19,20</sup> Moreover, the conclusions of these studies differ. The present meta-analysis of these four randomized controlled trials assessed the efficacy of statins in the treatment of asthma.

## Patients and methods

### Literature Search Strategy

A systemic literature search of articles published up until 16 June 2012 in electronic databases (Medline®, EMBase, Web of Science, China National Knowledge Infrastructure, Wei-Pu, and Wan-Fang) was conducted, using the following key words with the restrictions of 'humans AND randomized controlled trial AND all language' in Medline and 'randomized controlled trial' in EMBase: 'asthma AND (statin OR statins OR atorvastatin OR simvastatin OR fluvastatin)'. A manual review of the reference lists of all identified studies was performed to identify other potentially relevant studies. Titles, abstracts, and citations were independently reviewed by two authors (X.B.S. and S.Z.) to assess their potential relevance for full review. From the full text, both reviewers independently assessed studies and procured the most relevant studies for inclusion, based on the criteria outlined below.

### Study Selection

The following criteria were used for the literature selection and studies that met the criteria were eligible for further meta-analysis: (i) study design consisted of a randomized controlled trial comparing statins against a placebo; (ii) study participants had asthma only; (iii) detailed inclusion and exclusion criteria for the included cases; (iv) baseline data were shown in detail without statistically significant differences between the treatment groups; (v) outcomes of the randomized controlled trial were measured by evaluation of lung function and ideally the results were presented as mean value  $\pm$  variance, but not mean value  $\pm$  95% confidence interval (CI).

## Quality Assessment and Data Abstraction

The methodological quality of each trial was evaluated using the Jadad scale (0, worst; 5, best).<sup>21</sup> The following characteristics were assessed: (i) adequacy of randomization (0 points, not randomized; 1 point, randomized but the methodology of randomization was not mentioned; 2 points, randomized with the methodology of randomization clearly stated); (ii) blinding (0 points, not double-blinded; 1 point, double-blinded but the methodology of blinding not mentioned; 2 points, double-blinded with the methodology of blinding clearly mentioned); (iii) handling of withdrawals and drop outs (0 points, not mentioned; 1 point, mentioned). Articles with 1 or 2 points in total were considered to be low quality; those with 3–5 points in total were considered to be high quality.

## Statistical Analyses

Begg's test and Egger's test were used to analyse the publication bias of included articles using Comprehensive Meta-analysis brand software, version 2.0 (Biostat Inc., Englewood, NJ, USA). The publication bias was considered definite if the Kendall's correlation coefficient of Begg's test was approximate to 1 or the intercept of the Egger's linear regression equation test was approximate to 10. A meta-analysis of the variance between lung-function parameters before and after administration of statins was performed. The meta-analysis was conducted using RevMan software, version 5.0 (Cochrane Collaboration, Oxford, UK). A *P*-value <0.05 was considered statistically significant.

Statistical heterogeneity was assessed by the  $I^2$  statistic.  $I^2$  values  $\geq 50\%$  were considered to indicate a substantial level of heterogeneity.<sup>22</sup> If substantial statistical heterogeneity was present ( $I^2 \geq 50\%$ ), further

exploration of individual study characteristics (and those of subgroups of the main body of evidence) was undertaken. Conversely, the fixed-effect analysis would be used to perform the analysis.

## Results

Initially, 505 studies were identified, including 278 studies published in Chinese and 227 studies published in English. After scanning the titles and abstracts, 500 were excluded and five eligible randomized controlled trials were identified.<sup>11,17,19,20,23</sup> After reading the full texts, one of the five studies was excluded because it used a Wilcoxon test.<sup>23</sup> A total of 200 patients were included over the remaining four trials.<sup>11,17,19,20</sup> The sample size ranged between 43 and 64. There were three trials with a crossover study design.<sup>11,19,20</sup> Two trials compared atorvastatin with placebo<sup>11,20</sup> and two compared simvastatin with placebo.<sup>17,19</sup> Characteristics of the included trials are shown in Table 1.

An analysis of the variation of forced expiratory volume in 1 s (FEV<sub>1</sub>) before and after the administration of inhaled corticosteroids (ICS; salbutamol) was performed using the four trials.<sup>11,17,19,20</sup> There was no significant heterogeneity among the four trials before ( $\chi^2 = 1.29$ ,  $I^2 = 0\%$ ; Figure 1) and after ( $\chi^2 = 0.38$ ,  $I^2 = 0\%$ ; Figure 2) ICS. Compared with the control group, the FEV<sub>1</sub> of the statin group was 0.09 l (95% CI –0.06, 0.23) higher before ICS. Compared with the control group, the FEV<sub>1</sub> of the statin group was 0.06 l (95% CI –0.09, 0.22) higher after ICS. These differences between the control and statin groups were not statistically significant. The Kendall's correlation coefficients in Begg's test for FEV<sub>1</sub> before and after ICS were 0.4 and 0.8, respectively. The intercepts of Egger's linear regression equation were 3.1817 and

**Table 1.** Characteristics of the four randomized controlled trials included in the current meta-analysis of the efficacy of statins in the treatment of asthma

| Author                               | Year | Country     | Patients                               | N (S/C)                        | Study design                                       | Intervention                                             | Follow-up            | Jadad score <sup>21</sup> |
|--------------------------------------|------|-------------|----------------------------------------|--------------------------------|----------------------------------------------------|----------------------------------------------------------|----------------------|---------------------------|
| Hothersall et al. <sup>11</sup>      | 2008 | UK          | Adults with atopic asthma              | 46                             | Double-blind randomized controlled crossover trial | 40 mg/day atorvastatin or placebo with crossover         | 8 weeks for each arm | 5                         |
| Maneechotesuwan et al. <sup>17</sup> | 2010 | UK          | Nonsmoking patients with stable asthma | 47 (25/22)                     | Double-blind randomized controlled trial           | 10 mg/day simvastatin or placebo without crossover       | 8 weeks              | 4                         |
| Cowan et al. <sup>19</sup>           | 2010 | New Zealand | Patients with stable persistent asthma | 43                             | Double-blind randomized controlled crossover trial | 40 mg/day simvastatin or placebo with crossover          | ≥ 1 month            | 5                         |
| Braganza et al. <sup>20</sup>        | 2011 | UK          | Smokers with mild-to-moderate asthma   | 64 (arm 1: 34/30;arm 2: 33/27) | Double-blind randomized controlled crossover trial | 40 mg atorvastatin or placebo twice daily with crossover | 8 weeks for each arm | 4                         |

S/C, statin group/control group.

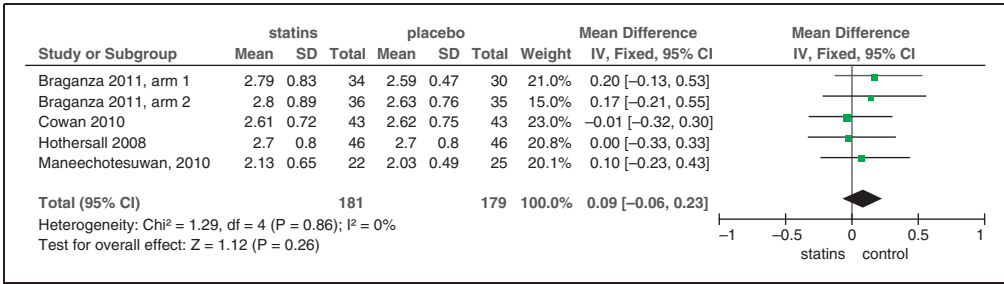


**Figure 1.** Meta-analysis of the forced expiratory volume in l s before the administration of inhaled corticosteroids (salbutamol) in the statin and control groups. IV, increase value; CI, confidence interval, in four trials<sup>13,17,19,20</sup>.

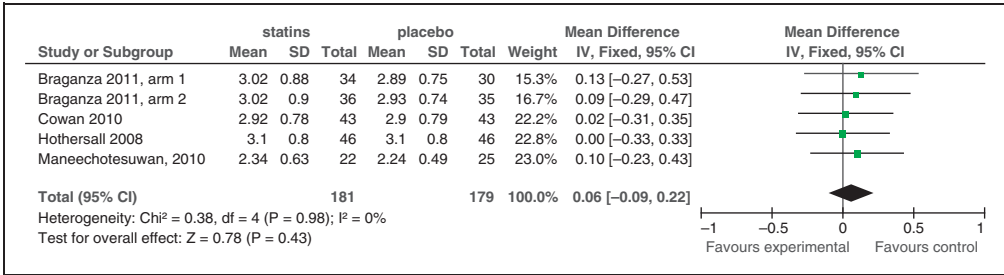


**Figure 2.** Meta-analysis of the forced expiratory volume in l s after the administration of inhaled corticosteroids (salbutamol) in the statin and control groups. IV, increase value; CI, confidence interval in four trials<sup>13,17,19,20</sup>.

2.0664 for FEV<sub>1</sub> before and after ICS, respectively. These results indicated the presence of publication bias.

An analysis of the variations of morning peak expiratory flow (PEF) rate among three of the included trials was performed.<sup>11,19,20</sup> There was no significant heterogeneity among the three trials ( $\chi^2 = 1.43$ ,  $I^2 = 0\%$ ; Figure 3). Compared with the control group, the morning PEF was 9.87 l (95% CI -15.66, 35.40) higher in the statin group, but it was not significantly different. The Kendall's correlation coefficient in Begg's test for morning PEF was 0.7 and the intercept of the Egger's linear regression equation test was 6.0480, again indicating publication bias.

## Discussion

Since their discovery in 1973, statins have become widely accepted and are considered to have revolutionized the care of patients with heightened cardiovascular risk or hyperlipidaemia.<sup>24</sup> Furthermore, statins have now been recognized to have anti-inflammatory and immunomodulatory properties,<sup>12</sup> although the mechanisms of these properties remain unclear.<sup>11,17</sup> The first clinical trial regarding these effects was published in 2007,<sup>23</sup> and at the time of the present meta-analysis, only five randomized controlled trials have been published, two reporting positive<sup>11,20</sup> and three reporting negative<sup>17,19,23</sup> conclusions.

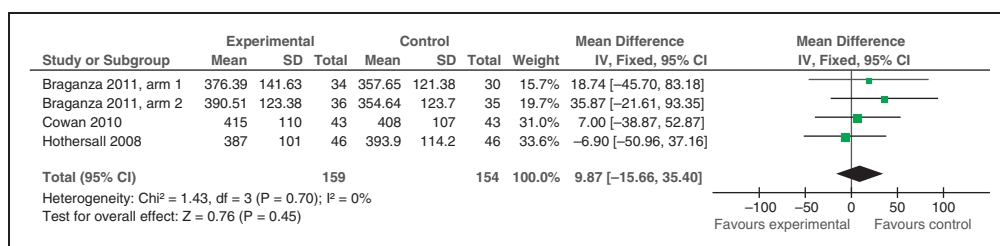


**Figure 3.** Meta-analysis of morning peak expiratory flow values of the statin and controls groups. IV, increase value; CI, confidence interval in four trials<sup>13,17,19,20</sup>.

There were four randomized controlled trials included in the present meta-analysis, each exploring the effects of statin therapy on lung function in asthma patients.<sup>11,17,19,20</sup>

The present meta-analysis indicated that lung function may be improved after statin use, but the finding was not statistically significant. The results from recent clinical trials further the debate over these benefits. In 2007, when the effects of simvastatin on lung function in patients with asthma were first studied,<sup>23</sup> there was no significant difference in the changes in lung function between the statin and control groups; although, compared with the control group, the statin group showed reduced exhaled nitric oxide and methacholine hyper-responsiveness. A 1-year retrospective study showed that there was a significant worsening of FEV<sub>1</sub> at every time point for the statin group compared with the controls.<sup>25</sup> At 6 months, more patients in the statin group needed increased maintenance medications, used albuterol more frequently, had more nocturnal awakenings and visited the clinic more frequently for acute asthma symptoms.<sup>25</sup> In contrast, a population-based study in 3965 patients using the Taiwan National Health Insurance Database indicated that statins may have contributed to reduced hospitalization rates due to asthma attacks, in patients with asthma.<sup>26</sup>

Rates of adverse events and side-effects associated with the use of statin medications

in asthma patients has been another controversial subject. Two articles included in the present study reported adverse events, but neither article showed a significant variance between the treatment groups;<sup>11,20</sup> the adverse events recorded included back pain, oral candidiasis, neck pain and worsening asthma. A population-based study reported a higher prevalence of coronary artery disease, diabetes mellitus, hypertension, dysrhythmia and chronic kidney disease in patients who used statins compared with those who did not use statins.<sup>26</sup> The benefits of statin medications for asthma were thought to be dose-dependent, which may account for the apparently conflicting data in murine studies that tested the effects of statins at various doses.<sup>18,25</sup> A low dose of statins may inhibit chemotaxis of type 1 helper T cells, which cause proliferation and aggregation, whereas large doses of statins may inhibit cell death of dendritic cells that differentiate to T<sub>H</sub>2 cells.<sup>13,25</sup> These hypotheses have been tested and verified in mice.<sup>12,13</sup> Mascitelli et al.<sup>14</sup> presented the hypothesis that statins may promote an increase in the number and function of regulatory T cells, but noted that statins may also inhibit antitumour immunity to some degree, which may increase the risk of tumours.

Other diverging viewpoints have also been raised, based on the clinical trials available to date. It has been maintained that statins are not useful in treating patients

with asthma.<sup>27</sup> ICS are sufficient to limit the acute exacerbations of asthma, while the anti-inflammatory effect of statins was not conclusive or apparent.<sup>27</sup> In contrast, it has been argued that although asthma may be controlled by ICS, the long-term use of ICS carries the risk of side-effects such as adrenal suppression, growth inhibition, and osteoporosis.<sup>18</sup> Statins may help improve the results of long-term ICS treatment and prevent the above-mentioned side-effects. An experiment was undertaken to verify whether statins could prevent and improve airway remodelling, according to regulation of the proliferation of goblet cells and the production of profibrogenic mediators; the authors concluded that statins should be used for asthma.<sup>28</sup> Murine models of asthma induced with ovalbumin have been widely used in many experimental protocols, but some doubt has been expressed regarding the validity of these models, because the pathophysiological processes are quite dissimilar those known to be involved in humans.<sup>14</sup>

There were several limitations to the current meta-analysis. First, as far as it was possible to ascertain, there have been only five published randomized controlled trials concerning the effects of statin therapy on lung function in patients with asthma.<sup>11,17,19,20,23</sup> Four of these, which included a total of 200 patients, fulfilled the inclusion criteria but showed publication bias.<sup>11,17,19,20</sup> Secondly, because the FEV<sub>1</sub> and morning PEF values were the common indices in the four included randomized controlled trials, it was not possible to perform further analyses using other lung-function parameters, therefore it was not possible to present thoroughly the overall status of the patients' lung function. Thirdly, the types of statins and ICS medications tested among the included trials were different.

In conclusion, this meta-analysis found no evidence that statins improve lung

function in patients with asthma. At present, the study of statins in the treatment of asthma is in the early stages. Additional randomized controlled trials will be needed to verify or refute any conclusions. To the best of the authors' knowledge, this is the first meta-analysis to address this issue, and should be viewed as a preliminary examination of this subject.

### Declaration of Conflicting Interest

The Authors declare that there is no conflict of interest.

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