



The effect of statins for asthma. A systematic review and meta-analysis

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Abstract

Objective: To assess the effects of statins on asthma by systematically reviewing and conducting a meta-analysis on all clinical studies, including randomized controlled trials (RCTs) and observational studies, that examined the effects of statins on asthma.

Methods: PubMed, EMBASE databases, and Cochrane reviews were searched to identify RCTs and observational studies, conducted through June 16, 2020, that assessed the effect of statins as a treatment for asthma. A meta-analysis was conducted using the following main outcomes: asthma control test (ACT), asthma control questionnaire (ACQ), pre- and post-bronchodilator forced expiratory volume in one second (FEV1), peak flow (PEF), and asthma exacerbation (asthma-related emergency department (ED) visits and hospitalization).

Results: Our search revealed 11 RCTs and 8 observational studies that met the inclusion criteria. A meta-analysis demonstrated that statin treatment significantly improved ACT scores (mean difference: 1.61, $P < 0.001$) and ACQ scores (mean difference: -0.38, $P < 0.001$) compared to a placebo. Furthermore, statin treatment significantly reduced asthma-related ED visits (hazard ratio [HR], 95% confidence interval [CI], 0.83 [0.75-0.92], $P < 0.001$, number needed to treat [NNT], 5.9). However, statin treatment did not improve pulmonary function (FEV1 and PEF).

Conclusion: Our results suggest that statins have the potential to improve asthma control and reduce asthma exacerbation without any improvement in pulmonary function.

Introduction

Asthma is a disease characterized by chronic airway inflammation and variable airflow limitation; it affects approximately 2.7 billion people worldwide.¹ Widespread use of inhaled corticosteroids (ICS) has reduced mortality rates, but asthma is still difficult to cure and many patients have poorly controlled asthma symptoms.^{2,3}

Over the years, many drug candidates have been examined for the treatment of asthma, and novel therapeutics have shown promise. Statins, which act as HMG-CoA reductase inhibitors, are lipid-lowering drugs used primarily for the prevention of cardiovascular disease.⁴ Interestingly, statins have pleiotropic effects, including anti-inflammatory properties, which might be effective against a variety of diseases, including asthma.⁵ Indeed, animal and cellular experiments using statins have reported the inhibitory effects on airway inflammation and remodeling in asthma.^{6,7} However, previous small randomized controlled trials (RCTs) have yielded conflicting results regarding the benefits of statins for asthmatic patients. Further, a meta-analysis of four RCTs reported in 2013 demonstrated no improvement in pulmonary function after statin treatment.⁸ In contrast, recent observational studies have reported beneficial effects of statins on asthma exacerbation, evidenced by reduced asthma-related emergency department (ED) visits.⁹ However, most of these observational studies did not assess the effect of statins on pulmonary function. Thus, it remains unclear whether statins are an effective treatment option for asthma.

In this study, we aimed to assess the effects of statins on asthma by systematically reviewing and conducting a meta-analysis on all clinical studies, including RCTs and observational studies, that examined the effects of statins on asthma.

Methods

Search strategies

A systemic literature search of articles published through June 16, 2020 in scientific databases (Medline and EMBASE) was conducted using disease-specific search terms such as “asthma” AND “statin” OR “statins” OR “HMG-CoA reductase inhibitor” OR “HMG-CoA reductase inhibitors” OR “3-hydroxy-3-methylglutaryl coenzymes A reductase inhibitor” OR “3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors” OR “atorvastatin” OR “lovastatin” OR “simvastatin” OR “fluvastatin” OR “pravastatin” OR “rosuvastatin” OR “pitavastatin”. We also searched reference lists of the relevant Cochrane review articles to identify additional studies.¹⁰ We performed the search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ Two investigators (KS and HK) reviewed all the articles and judged selection, comparability, and outcomes independently. When the two investigators disagreed, the third author (TK) was asked to make a decision independently.¹² The risk of bias was evaluated using the risk of bias in randomized trials (RoB2) for RCTs and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) for observational studies (eFigure 1, 2).^{13, 14}

Study inclusion criteria

Included studies met the following criteria: (1) studies were published in peer-reviewed journals, (2) they compared asthmatic patients who received statins with those who did not receive statins, and (3) the studies reported at least one of the following clinical outcomes: asthma control test (ACT), asthma control questionnaire (ACQ), pre- and post-bronchodilator forced expiratory volume in one second (FEV1), peak flow (PEF), and asthma exacerbation (i.e. asthma-related ED visits and hospitalization). ACT scores

range from 5 (poor control) to 25 (complete control), based on five questions that are related to the frequency of asthma symptoms and rescue medication use during the previous 4 weeks. ACQ scores are similar tools to assess asthma control with scores between 0 (totally controlled) and 6 (severely uncontrolled), including 7 questions. The mean clinically important differences (MCID) are 3 points for the ACT scores and 0.5 points for the ACQ scores in adults, respectively.¹⁵ Studies conducted *in vitro* or in animal models were not included in this analysis.

Data analysis

For each study, relevant data were directly extracted from the selected articles, including patient demographic data, the type of study, duration of treatment, and outcome assessment. To evaluate the effect of statins on asthma, the data were categorized and analyzed based on each outcome. The Review Manager (RevMan Version 5.4; Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) software was used to calculate pooled hazard ratios (HRs) with 95% confidence intervals (CIs). In addition, we calculated the mean differences (MD) as follows: first, we extracted changes (from baseline to post-treatment) in continuous data of both the statin and control groups from each study; second, generated MDs (with 95% CIs) between the changes of the statin and control groups (otherwise, extracted MDs directly from each study); finally, the MDs were pooled in a random-effects model using the Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ, USA). Missing standard deviations and changes from baseline to post-treatment were imputed according to the Cochrane Handbook.¹⁶ The random-effects model was used in each outcome regardless of the heterogeneity among studies as it allowed for a more conservative assessment of the pooled effect size.

145 Significant heterogeneity was considered to be present when the I^2 index was over 50%
146 or the P-value for heterogeneity was <0.05 .

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Results

Study selection and results

Figure 1 summarizes the results of our systematic literature search, which initially yielded 1350 potentially relevant articles (215 articles from PubMed and 1339 articles from EMBASE), and a total of 1333 articles were excluded. We added four articles from the Cochrane review articles,¹⁰ hence a total of 21 articles underwent full-text assessment.¹⁷⁻³⁷ Two articles were excluded as they did not assess the effect of statin treatment in asthmatic patients.^{36,37} Finally, our research identified 19 studies (11 RCTs and 8 observational studies). The characteristics and outcome measures of the included studies are shown in Table 1. The RCTs included a small number of patients (up to 54 patients in the statin group) and a short intervention period (up to 12 weeks), while observational studies had a large number of patients (up to 19866 patients in the statin group) and longer observational periods (up to 4.6 years). Most RCTs assessed the ACT, ACQ, or pulmonary function, while observational studies evaluated asthma-related ED visits and hospitalizations as primary outcomes (Table 1).

Statins improved asthma control

Both the ACT and ACQ are validated tools for assessing asthma control, and some studies used only the ACT, while others used only the ACQ for assessing asthma control. Three RCTs and one observational study evaluated asthma control using the ACT in the statin and placebo groups (Fig 2A).¹⁷⁻²⁰ Our meta-analysis of these studies assessed the difference in the ACT scores after statin treatment versus the placebo and showed that statin treatment significantly improved ACT scores (mean difference [MD]: 1.61, $P < 0.001$) without heterogeneity (I^2 : 0%, $P = 0.510$). Similarly, four RCTs

assessed asthma control using the ACQ (Fig 2B) and showed that statin treatment significantly improved ACQ scores compared to the placebo (MD: -0.38, $P < 0.001$) without heterogeneity (I^2 : 28%, $P = 0.28$).²⁰⁻²³ Collectively, these results indicated that statin treatment significantly improved asthma control although the differences between statin and the placebo group were less than the MCID.

Statins did not improve pulmonary function

Reversible airflow obstruction is a hallmark of asthma, and pulmonary function tests are used as outcome measures in many studies. However, it is not appropriate to combine and analyze all studies together due to the lack of absolute values and multiple methods of assessment (before and after administration of a bronchodilator).^{24, 31, 33} Three RCTs evaluated pre-bronchodilator FEV1 (Fig 3A), and our meta-analysis assessed the difference in FEV1 changed by statin treatment or the placebo, which showed that statin treatment did not improve pre-bronchodilator FEV1 compared to the placebo (MD: 0.061, $P = 0.059$) without heterogeneity (I^2 : 8.6%, $P = 0.340$).²¹⁻²³ Similarly, three RCTs and one observational study reported post-bronchodilator FEV1 (Fig 3B), and statin treatment did not improve post-bronchodilator FEV1 compared to the placebo (MD: 0.015, $P = 0.440$) with heterogeneity (I^2 : 51.0%, $P = 0.110$).^{19, 21-23} Furthermore, four RCTs and one observational study reported PEF (Fig 3C), and meta-analysis revealed that statin treatment did not improve PEF compared to the placebo (MD: 2.088, $P = 0.49$) with heterogeneity (I^2 : 60.5%, $P = 0.038$).^{19, 21-24} Thus, the effect of statins on pulmonary function was variable across studies, and we found no significant effects in the meta-analysis.

Statins reduced asthma exacerbation

Some studies have shown that statins improved asthma control. However, previous RCTs have not directly assessed the frequency of asthma exacerbation because it requires a large number of patients to assess asthma exacerbation. In contrast, recent observational studies have often assessed asthma exacerbation. Four observational studies evaluated asthma-related ED visits in asthmatic patients who were exposed to statins and those who were not (Fig 4A).²⁵⁻²⁸ One study divided asthmatic patients using ICS, and in all studies, except for ICS non-users, statin exposure was independently associated with a reduction in asthma-related ED visits, as indicated by multivariate analysis. Our meta-analysis revealed that patients exposed to statins had a significantly lower risk of experiencing asthma-related ED visits compared with control patients (HR [95% CI]: 0.83 [0.75-0.92], $P < 0.001$, NNT: 5.9) (Fig 4A) without heterogeneity (I^2 : 21%, $P = 0.280$).

Furthermore, five observational studies assessed asthma-related hospitalization (Fig 4B).²⁵⁻²⁹ The patients exposed to statins had a lower risk of asthma-related hospitalization than the control patients, but this effect was not statistically significant (HR [95% CI]: 0.93 [0.78-1.04], $P = 0.160$) with heterogeneity (I^2 : 77%, $P < 0.001$). However, four observational studies assessed outcomes that combined asthma-related ED visits and hospitalization (Fig 4C)^{25,26,28,30}, and the patients who received statins had a significantly lower risk of asthma-related ED visits and hospitalization than the control patients (HR [95% CI]: 0.87 [0.77-0.99], $P = 0.030$, NNT: 7.7) (Fig 4C) with heterogeneity (I^2 : 77%, $P < 0.001$). Collectively, statin treatment significantly reduced asthma exacerbation, particularly asthma-related ED visits.

Discussion

We conducted a systematic review and meta-analysis of studies that investigated the effects of statins on asthma. A meta-analysis revealed that statins improved asthma control and reduced asthma exacerbation, although there were no significant effects on pulmonary function. These results indicate that statins may be effective for the treatment of asthma.

Statins, HMG-CoA inhibitors, are generally used for primary and secondary prevention of cardiovascular disease through the improvement of dyslipidemia. Interestingly, previous reports using animal or cell culture models, have suggested that statins exert their beneficial effects on asthma function through various mechanisms, including anti-inflammatory effects, reduction of oxidative stress, inhibition of inflammatory cells, and induction of apoptosis.³⁸ In mouse models of asthma, statins have been reported to suppress airway inflammation and remodeling by decreasing inflammatory cells and type-2 cytokines, including IL-4, IL-5, and IL-13.^{6,7} Furthermore, statins inhibit the proliferation and differentiation of airway smooth muscle cells and epithelial cells. In cellular experiments, it has been shown that statins inhibit the proliferation of T-cells via reduction in ATP production, since statins suppress the glycolytic pathway initiated by acetyl-CoA, an upstream metabolite of the mevalonic acid pathway.^{39,40} Based on these data, statins are expected to be useful as a treatment option for asthma.

However, previous RCTs and meta-analyses had conflicting conclusions regarding the benefit of statin treatment for asthma. Our meta-analysis showed that statins improved asthma control, but not pulmonary function. The reasons for this include: (1) small sample size (e.g., 16–54 patients in the statin group), (2) short-term

intervention (e.g., for 4–12 weeks in RCTs), and (3) mixed phenotype and severity of asthma. Since asthma is a heterogeneous disease, the effectiveness of drugs varies greatly from patient to patient. Therefore, it is important that clinical trials be appropriately stratified and organized such that patients with a certain severity and phenotype of asthma are recruited. For example, anti-IL-5 antibodies were found to be effective in a clinical trial targeting only eosinophilic asthma after the failure of generalized trials targeting patients with all types of asthma.⁴¹ In addition, with respect to lung function, a longer observation period may be required to properly assess the impact on airway remodeling. Therefore, to clarify the effect of statins on asthma, large-scale, well-designed RCTs with a long treatment schedule are required.

In contrast to the RCTs, recent observational studies, which included a large number of patients (several hundred to 19 866 patients in the statin group) with yearly observation periods, consistently showed new evidence of the beneficial effect of statins (i.e. a reduction in asthma exacerbation). Asthma exacerbation has been incorporated as an important outcome in many clinical trials. However, a large number of patients and long-term observational periods are required to properly assess asthma exacerbation. Therefore, this outcome was not included in the results of previous RCTs. Our results suggest that the assessment of asthma exacerbation is valuable for future RCT studies on the effects of statin treatment.

In recent years, several studies have focused on particular characteristics of patients with asthma which are especially responsive to statin treatment. Basic research data and pharmacological characteristics indicate that statins may be particularly effective for individuals with asthma who smoke or are obese. Braganza et al. included patients who were currently smoking and with asthma, and found a significant

improvement in the ACQ after statin treatment.²² Furthermore, Zeki et al. examined the effect of statins in patients with severe asthma, whose BMI was more than 30 kg/m², and showed that statin treatment significantly improved ACT scores.¹⁹ Since there is a lack of effective drugs for non-type-2 asthma, such as for asthmatic patients who are smokers or obese, statins may be a promising treatment option for them. Another study reported a difference in the effect of statins depending on the single nucleotide polymorphisms in the HLA-G gene.³⁶ Although our data showed that there were small effects in clinical scores which may not be clinically significant for all patients with asthma, it may be possible to identify patients with asthma who would benefit from statin treatment, by identifying specific phenotypes or genetic testing.

This study has several limitations. First, the number of studies examining the effects of statins on asthma is limited. Also, some studies, especially observational studies, had a certain bias. In this study, we combined and analyzed all studies to exclude selection bias although it is desirable that a meta-analysis is performed based on high quality RCTs. Second, individual patient data were not available to us, and our interpretations were limited by the available summary data from already published studies. Third, patients had variable backgrounds, such as different patient populations and comorbidities, which had the potential to confound our results. Furthermore, this analysis was performed without stratification because this would have reduced the number of cases. In order to identify patients who respond better to statin treatment, it is recommended to increase the number of cases and conduct stratified studies in future research.

In conclusion, statins are potentially beneficial for improving asthma symptoms and reducing ED visits. Although statins have not been shown to improve lung function

290 in previous small RCTs, the effects of statins need to be fully and properly investigated
291 in large-scale clinical trials.

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References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018; **392**:1789-1858.
2. Barnes PJ, Pedersen S, and Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med*. 1998; **157**:S1-S53.
3. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43**:343-373.
4. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999; **282**:2340-2346.
5. Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation*. 2015; **132**:1224-1233.
6. Liang L, Hur J, Kang JY, Rhee CK, Kim YK, Lee SY. Effect of the anti-IL-17 antibody on allergic inflammation in an obesity-related asthma model. *Korean J Intern Med*. 2018; **33**:1210-1223.
7. Wu S, Yang R, Wang G. Anti-asthmatic effect of pitavastatin through aerosol inhalation is associated with CD4⁺ CD25⁺ Foxp3⁺ T cells in an asthma mouse model. *Sci Rep*. 2017; **7**:6084.

- 314 8. Si XB, Zhang S, Huo L, Dai W, Wang H. Statin therapy does not improve lung
315 function in asthma: a meta-analysis of randomized controlled trials. *J Int Med Res.*
316 2013; **41**:276-283.
- 317 9. Wardzyńska A, Kubsik B, Kowalski ML. Comorbidities in elderly patients with
318 asthma: Association with control of the disease and concomitant treatment. *Geriatr*
319 *Gerontol Int.* 2015; **15**:902-909.
- 320 10. Naing C, Ni H. Statins for asthma. *Cochrane Database Syst Rev.* 2020; **7**:
321 CD013268.
- 322 11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al.
323 The PRISMA statement for reporting systematic reviews and meta-analyses of studies
324 that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.*
325 2009; **151**:W65-W94.
- 326 12. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral
327 anticoagulation for patients with atrial fibrillation on long-term hemodialysis. *J Am Coll*
328 *Cardiol.* 2020; **75**:273-285.
- 329 13. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe N, Boutron I, et al. RoB 2: a
330 revised tool for assessing risk of bias in randomized trials. *BMJ.* 2019; **366**:14898.
- 331 14. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen S, Hahn S, et al. Testing a tool for
332 assessing the risk of bias for nonrandomized studies showed moderate reliability and
333 promising validity. *J Clin Epidemiol.* 2013; **66**:408-414.
- 334 15. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braidò F, Caminati M, et al.
335 Minimal clinically important difference for asthma endpoints: an expert consensus
336 report. *Eur Respir Rev.* 2020; **3**:29.

16. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; **45**:769–773.
17. Moini A, Azimi G, Farivar A. Evaluation of atorvastatin for the treatment of patients with asthma: a double-blind randomized clinical trial. *Allergy Asthma Immunol Res.* 2012; **4**:290-294.
18. Sun S, Han W, Hao W. Clinical studies of simvastatin in treatment of adult-onset obesity with asthma. *Biomedical Research.* 2017; **28**:6514-6517.
19. Zeki AA, Oldham J, Wilson M, Fortenko O, Goyal V, Last M, et al. Statin use and asthma control in patients with severe asthma. *BMJ Open.* 2013; **3**:e003314.
20. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Simvastatin in the treatment of asthma: lack of steroid-sparing effect. *Thorax.* 2010; **65**:891-896.
21. Badar VA, Navale S, Deshmukh S, Munje R, Badar A. The effect of atorvastatin on lung function and sputum cell count in chronic asthma patients. *International Journal of Pharmacological Research.* 2014; **4**:194-198.
22. Braganza G, Chaudhuri R, McSharry C, Weir CJ, Donnelly I, Jolly L, et al. Effects of short-term treatment with atorvastatin in smokers with asthma--a randomized controlled trial. *BMC Pulm Med.* 2011; **11**:16.
23. Hothersall EJ, Chaudhuri R, McSharry C, Donnelly I, Lafferty J, McMahon AD, et al. Effects of atorvastatin added to inhaled corticosteroids on lung function and sputum cell counts in atopic asthma. *Thorax.* 2008; **63**:1070-1075.
24. Fahimi F, Salamzadeh J, Jammati H, Sohrabi S, Fakharian A, Mohammadtaheri Z. Do statins improve lung function in asthmatic patients? A randomized and double-blind trial. *Iran J Pharm Sci.* 2009; **5**:13-20.

25. Lokhandwala T, West-Strum D, Banahan BF, Bentley JP, Yang Y. Do statins improve outcomes in patients with asthma on inhaled corticosteroid therapy? A retrospective cohort analysis. *BMJ Open*. 2012; **2**:e001279.
26. Tse SM, Li L, Butler MG, Fung V, Kharbanda EO, Larkin EK, et al. Statin exposure is associated with decreased asthma-related emergency department visits and oral corticosteroid use. *Am J Respir Crit Care Med*. 2013; **188**:1076-1082.
27. Tse SM, Charland SL, Stanek E, Herrena V, Goldfarb S, Litonjua AA, et al. Statin use in asthmatics on inhaled corticosteroids is associated with decreased risk of emergency department visits. *Curr Med Res Opin*. 2014; **30**:685-693.
28. Wang JY, Yao TC, Tsai YT, Wu AC, Tsai HJ. Increased dose and duration of statin use is associated with decreased asthma-related emergency department visits and hospitalizations. *J Allergy Clin Immunol Pract*. 2018; **6**:1588-1595.e1.
29. Huang CC, Chan WL, Chen YC, Chen TJ, Chou KT, Lin SJ, et al. Statin use in patients with asthma: a nationwide population-based study. *Eur J Clin Invest*. 2011; **41**:507-512.
30. Wardzyńska A, Kubsik B, Kowalski ML. Comorbidities in elderly patients with asthma: Association with control of the disease and concomitant treatment. *Geriatr Gerontol Int*. 2015; **15**:902-909.
31. Menzies D, Nair A, Meldrum KT, Fleming D, Barns M, Lipworth BJ. Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. *J Allergy Clin Immunol*. 2007; **119**:328-335.
32. Maneechotesuwan K, Ekjitrakul W, Kasetsinsombat K, Wongkajornsilp A, Barns PJ. Statins enhance the anti-inflammatory effects of inhaled corticosteroids in asthmatic

- 383 patients through increased induction of indoleamine 2, 3-dioxygenase. *J Allergy Clin*
384 *Immunol.* 2010; **126**:754-762.e1.
- 385 33. Mohammad MM, Fahimi F, Fakharian A, Gamishan MK, Sistanizad M, Fayazi N,
386 et al. Methacoline challenge test as an evaluator of response to statins in bronchial
387 hyperresponsiveness. *Iran J Pharm Res.* 2012; **11**:969-977.
- 388 34. Thomson NC, Charron CE, Chaudhuri R, Spears M, Ito K, McSharry C.
389 Atorvastatin in combination with inhaled beclometasone modulates inflammatory
390 sputum mediators in smokers with asthma. *Pulm Pharmacol Ther.* 2015; **31**:1-8.
- 391 35. Ostroukhova M, Kouides RW, Friedman E. The effect of statin therapy on allergic
392 patients with asthma. *Ann Allergy Asthma Immunol.* 2009; **103**:463-468.
- 393 36. Naidoo D, Wu AC, Brilliant MH, Deny J, Ingram C, Kitchner TE, et al. A
394 polymorphism in HLA-G modifies statin benefit in asthma. *Pharmacogenomics J.* 2015;
395 **15**:272-277.
- 396 37. Afshar M, Wu D, Durazo-Arvizu R, Aguilar FG, Kalhan R, Davis SM, et al.
397 Association of serum lipids and obstructive lung disease in Hispanic/Latino adults of
398 diverse backgrounds. *J Pulm Respir Med.* 2017; **7**:419.
- 399 38. So JY, Dhungana S, Beres JJ, Criner GJ. Statins in the treatment of COPD and
400 asthma-where do we stand? *Curr Opin Pharmacol.* 2018; **40**:26-33.
- 401 39. Gruenbacher G, Gander H, Rahm A, Dobler G, Drasche A, Troppmair J, et al. The
402 human G protein-coupled ATP receptor P2Y₁₁ is associated with IL-10 driven
403 macrophage differentiation. *Front Immunol.* 2019; **10**:1870.
- 404 40. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van de Heijden CDCC, Li Yang,
405 et al. Metabolic induction of trained immunity through the mevalonate pathway. *Cell.*
406 2018; **172**:135-146.e9.

41. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al.
Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind,
placebo-controlled trial. Lancet. 2012; **380**:651-659.

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