PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to Thorax but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Open. The paper was subsequently re-reviewed at BMJ Open before being accepted for publication.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Do statins improve outcomes in patients with Asthma on inhaled corticosteroid therapy? A Retrospective cohort analysis |
|---|---|
| AUTHORS | Tasneem Lokhandwala, Donna West-Strum, Benjamin F Banahan, John P Bentley and Yi Yang |

VERSION 1 – REVIEW (AT THORAX)

| REVIEWER | Bruce K. Rubin MEngr, MD, MBA, FRCPC  
Jessie Ball duPont Distinguished Professor and Chair, Dept. of Pediatrics  
Professor of Biomedical Engineering  
Virginia Commonwealth University School of Medicine  
Physician in Chief, Children’s Hospital of Richmond at VCU ; USA |
|---|---|
| GENERAL COMMENTS | There have been several studies that have suggest that statin medications have anti-inflammatory properties. There are conflicting data from well controlled, prospective randomized clinical trials evaluating the use of statins for the treatment of asthma. Larger retrospective cohort studies tend to suggest a modest decrease in symptoms of asthma in subjects taking concomitant statin therapy. In this study the authors provide confirmatory evidence in another, smaller, retrospective cohort study limited to Medicaid claims data from a decade ago in the American state of Mississippi. The analytic methods are robust and the manuscript well written, however these results only provide confirmatory data of earlier published studies.

1. I was unable to identify an abstract
2. On page 4 line 54 the authors describe a washout period. How is it possible to have a washout in a retrospective observational study?
3. It would have been most interesting to evaluate changes in hospital admissions, emergency department visits, and asthma prescriptions filled in those subjects taking statin therapy comparing data from the year before statin therapy was initiated to the first year of statin therapy. |
**GENERAL COMMENTS**

**General comments**

Recent pre-clinical data suggest that in addition to lowering circulating blood cholesterol levels statins may have anti-inflammatory properties that could be of benefit in the treatment of inflammatory airway diseases including asthma. Short-term clinical trials of statins in asthma have produced inconclusive finding on efficacy. Using a retrospective cohort design involving analysis of the US Medicaid beneficiary data for a 3 year period the investigators examined the effects of statins on asthma outcomes. The main finding was a significant reduction in the odds of hospitalization and ER visits due to asthma was associated with statin use. The observation is of interest although the possibility of a difference in severity of asthma between the unexposed and exposed groups requires further consideration.

**Main comments**

1. **Confounding factors**

The main concern about the findings is that statin use is an indicator of a confounding factor(s) that explains the reduction in the odds of hospitalization and ER visits due to asthma. The authors have tried to control for these, but the unexposed compared to the exposed group may have had more severe asthma e.g. oral steroid use (31% unexposed versus 17% exposed, Table 2); fewer ER visits in previous 6 months prior to the index date (0.02 ± 0.14) vs. 0.06 (0.29), table 3). Although this later difference was adjusted for there remains the concern that the unexposed group had more severe asthma. Could the authors include previous oral steroid use in a re-analysis of the data? In addition this issue of a possible difference in severity between the unexposed and exposed groups requires further discussion.

2. **Abstract:** Omitted from manuscript; please include.

**Minor comments**

1. **Page 2, line 5:** Consider revising sentence to: ‘A randomized double-blind crossover placebo-controlled trial was investigated the effect of oral atorvastatin on measures of asthma control and airway inflammation’.

2. **Additional clinical study:** Include reference to a recently published study of atorvastatin in smokers with asthma Braganza et al. Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial. BMC Pulm Med 2011;11:16
There have been several studies that have suggest that statin medications have anti-inflammatory properties. There are conflicting data from well controlled, prospective randomized clinical trials evaluating the use of statins for the treatment of asthma. Larger retrospective cohort studies tend to suggest a modest decrease in symptoms of asthma in subjects taking concomitant statin therapy. In this study the authors provide confirmatory evidence in another, smaller, retrospective cohort study limited to Medicaid claims data from a decade ago in the American state of Mississippi. The analytic methods are robust and the manuscript well written, however these results only provide confirmatory data of earlier published studies.

4. I was unable to identify an abstract

Authors’ response: The abstract was submitted separately in the submission system. However, it has now been included in the main document of the manuscript.

5. On page 4 line 54 the authors describe a washout period. How is it possible to have a washout in a retrospective observational study?

Authors’ response: The term ‘washout period’ in the article has been used to refer to the 6 month window from January 1, 2002 to June 31, 2002. This period was used to track the prior 6 month prescription records of subjects identified at the beginning of the ‘identification window’. This enabled us to compute the additional covariates, namely, adherence to ICS, average number of short-acting β agonists per subject, prior hospitalizations, ER visits, office, and laboratory visits due to asthma controlled for in the final analyses. This has been explained in the manuscript. We understand the reviewer’s concerns as it does not refer to ‘the period allowed for the entire administered drug to be eliminated from the body’ as it usually does in a clinical trial.

6. It would have been most interesting to evaluate changes in hospital admissions, emergency department visits, and asthma prescriptions filled in those subjects taking statin therapy comparing data from the year before statin therapy was initiated to the first year of statin therapy.

Authors’ response: The study design we used did not identify statin naïve patients. Our study design involved identifying patients diagnosed with asthma and adherent to statins (‘exposed’), comparing their asthma outcomes to patients diagnosed with asthma but not on concurrent statin therapy (‘unexposed’). The ‘exposed’ and ‘unexposed’ subjects were matched on their propensity to be on statins, and additional covariates were controlled for in the analyses. We believe this study design accounts for confounding effects within the limitations of using observational data. The reviewer has suggested an alternate methodology, i.e. comparing the asthma outcomes of a patient prior to initiation of statin therapy versus their asthma outcomes post statin therapy initiation. Using the suggested methodology here has 2 caveats:

i. We had 3 years of Medicaid data from January 1, 2002 to December 31, 2004. Leaving a year prior to initiation and post initiation of statin therapy for comparison of asthma outcomes, would leave only a year for identifying asthma adults initiating statin therapy. We believe this would considerably reduce our sample size from the 589 ‘exposed’ subjects currently in the study.

ii. Many aeroallergens appear in seasonal patterns, asthma exacerbations, particularly those requiring emergency treatment, show analogous seasonal cycles. Comparing the asthma outcomes prior to initiation of statin therapy versus asthma outcomes post statin therapy initiation does not account for these seasonal effects. Our study design involved matching...
‘exposed’ subjects to corresponding subjects from the ‘unexposed’ group; following which the ‘unexposed’ subjects were assigned the index date of the ‘exposed’ subjects they were matched to. The asthma outcomes were then compared during the same one year period, beginning on the same index date. This should account for seasonal effects.

**REVIEWER: 2**

**Comments to the Author**

**General comments**

Recent pre-clinical data suggest that in addition to lowering circulating blood cholesterol levels statins may have anti-inflammatory properties that could be of benefit in the treatment of inflammatory airway diseases including asthma. Short-term clinical trials of statins in asthma have produced inconclusive finding on efficacy. Using a retrospective cohort design involving analysis of the US Medicaid beneficiary data for a 3 year period the investigators examined the effects of statins on asthma outcomes. The main finding was a significant reduction in the odds of hospitalization and ER visits due to asthma was associated with statin use. The observation is of interest although the possibility of a difference in severity of asthma between the unexposed and exposed groups requires further consideration.

**Main comments**

1. Confounding factors

   The main concern about the findings is that statin use is an indicator of a confounding factor(s) that explains the reduction in the odds of hospitalization and ER visits due to asthma. The authors have tried to control for these, but the unexposed compared to the exposed group may have had more severe asthma e.g. oral steroid use (31% unexposed versus 17% exposed, Table 2); fewer ER visits in previous 6 months prior to the index date (0.02 [± 0.14] vs. 0.06 [0.29], table 3). Although this later difference was adjusted for there remains the concern that the unexposed group had more severe asthma. Could the authors include previous oral steroid use in a re-analysis of the data? In addition this issue of a possible difference in severity between the unexposed and exposed groups requires further discussion.

**Authors’ response:** We appreciate the concerns put forth by the reviewer. We believe this study design accounts for the confounding effects of asthma severity within the limitations of using observational data.

   Our literature review section discusses the mechanisms that have been put forth in previous studies that offer explanations as to why statins may be potentially beneficial in asthma management.

   Our discussion section acknowledges the fact that a higher proportion of the unexposed subjects were on additional asthma controller therapy. However, as mentioned in the manuscript it is interesting to note that despite them being on additional controller medications for asthma, they still have higher number of asthma hospitalization events. Therefore, their asthma is not being managed despite additional controller medications. Hence, our study implies that perhaps addition of statins to inhaled corticosteroid therapy might help.

   Additionally we have controlled for the average number of short-acting β agonist prescriptions in the six months prior to the observation period, in addition to controlling for adherence to ICS, prior hospitalizations, ER visits, office, and laboratory visits due to asthma which should control for their asthma severity.

2. Abstract: Omitted from manuscript; please include.
Authors’ response: The abstract was submitted separately in the submission system. However, it has now been included in the main document of the manuscript.

Minor comments

1. Page 2, line 5: Consider revising sentence to: ‘A randomized double-blind crossover placebo-controlled trial was investigated the effect of oral atorvastatin on measures of asthma control and airway inflammation’.

Authors response: The sentence has been revised to: ‘A randomized double-blind crossover placebo-controlled trial investigated the effect of oral atorvastatin on measures of asthma control and airway inflammation’.

2. Additional clinical study: Include reference to a recently published study of atorvastatin in smokers with asthma Braganza et al. Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial. BMC Pulm Med 2011;11:16

Authors’ response: We thank the reviewer for pointing out the omission of a relevant and recent study by Braganza et al (2011). Thorax has a limit on the number of references, which lead us to include only the most relevant articles. However, this study has now been included in the literature review section.

VERSION 2 – REVIEW (AT BMJ OPEN)

REVIEWER
Bruce K. Rubin MEng, MD, MBA, FRCPC
Jessie Ball duPont Distinguished Professor and Chair, Dept. of Pediatrics
Professor of Biomedical Engineering
Virginia Commonwealth University School of Medicine
Physician in Chief, Children’s Hospital of Richmond at VCU; USA

No competing interests

REVIEW RETURNED
13/04/2012

THE STUDY
Asthma control and severity is assessed using several different methods

GENERAL COMMENTS
This is a fairly small retrospective observational study using the Mississippi Medicaid database to address the question of statins as potential add on therapy for the treatment of asthma in older patients. The paper is well written and the study well conducted. The results are consistent with previously published work.

The authors acknowledged that there are conflicting data in the literature including data that suggests that statins can be pro-inflammatory. Because of this I strongly recommend that they remove the term “the anti-inflammatory statins” in the opening sentence of the objectives.

VERSION 2 – AUTHOR RESPONSE

REVIEWER: 1
Comments to the Author
Q: ‘Is the outcome measure clear?’
Reviewer comment: Asthma control and severity is assessed using several different methods
This is a fairly small retrospective observational study using the Mississippi Medicaid database to address the question of statins as potential add on therapy for the treatment of asthma in older patients. The paper is well written and the study well conducted. The results are consistent with previously published work.

The authors acknowledged that there are conflicting data in the literature including data that suggests that statins can be pro-inflammatory. Because of this I strongly recommend that they remove the term “the anti-inflammatory statins” in the opening sentence of the objectives.

Authors’ response: Asthma exacerbations were the outcome of interest and have been measured using hospitalizations and emergency room visits due to asthma only. In order to eliminate bias due to the ‘unexposed’ having a higher severity of disease, this was controlled for. The ‘exposed’ and ‘unexposed’ were matched on propensity scores computed using age, gender, race, regions of Mississippi and Charlson Comorbidity Index. Additionally, we have controlled for the average number of short-acting β agonist prescriptions, adherence to ICS, hospitalizations, ER visits, office, and laboratory visits due to asthma in the six months prior to the observation period, in order to control for asthma severity. We believe this study design accounts for the confounding effects of asthma severity within the limitations of using observational data.

We thank the reviewer for pointing out the controversial use of the term ‘the anti-inflammatory statins’ in the objectives. The sentence on page 2, paragraph 1 has been revised to ‘Animal studies and clinical trials have examined the potential benefits of statins in asthma management with contradictory results.’

Additionally, on page 8, we have added titles for the two figures in the study.